Poster 7180

Tumour Growth Inhibition Modeling and Simulation to Support Dose Justification of Datopotamab deruxtecan (Dato-DXd) in HR-positive, HER2-negative Breast Cancer Patients

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Objective

- Describe the relationship between Dato-DXd pharmacokinetics (PK) and tumour growth inhibition (TGI) in HR-positive/HER2-negative breast cancer patients.
- Further demonstrate 6 mg/kg every three weeks (Q3W) is the optimal dose for Dato-DXd clinical development.

Conclusions

- The tumour size data in a total of 39 patients with HR-positive/HER2-negative breast cancer was well-described by the TGI model.
- Simulations based on the TGI model suggested greater tumour size reduction at Dato-DXd 6 mg/kg compared to 4 mg/kg in HR-positive/HER2-negative breast cancer patient population.

Plain language summary

Why did we perform this research?

Dato-DXd is a TROP2-directed antibody-drug conjugate. A dosing regimen of 6 mg/kg every three weeks (Q3W) has been proposed as the optimal schedule based on phase I data in patients with non-small cell lung cancer (NSCLC) who received Dato-DXd 0.27 mg/kg Q3W – 10 mg/kg Q3W[1]. MTD established at 8 mg/kg Q3W.

A single dose level at 6 mg/kg Q3W was evaluated in multiple tumour types and pivotal trials, including TROPION-Breast01. Supporting analyses were needed to further demonstrate the superiority of 6 mg/kg compared to lower dose level levels.

How did we perform this research?

A tumour growth inhibition model was developed based on tumour size data from HR-positive/HER2-negative breast cancer patients who received 6 mg/kg Dato-DXd Q3W in a Phase I study (TROPION-PanTumor01)

What were the findings of this research?

Simulations based on the tumour growth inhibition model suggested greater tumour size reduction at Dato-DXd 6 mg/kg compared to 4 mg/kg in HR-positive/HER2-negative breast cancer patient population.

What are the implications of this research?

This research further supported Dato-DXd 6 mg/kg Q3W as optimal dose for the treatment of adult patients with HR-positive/HER2-negative breast cancer.

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: ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03401385

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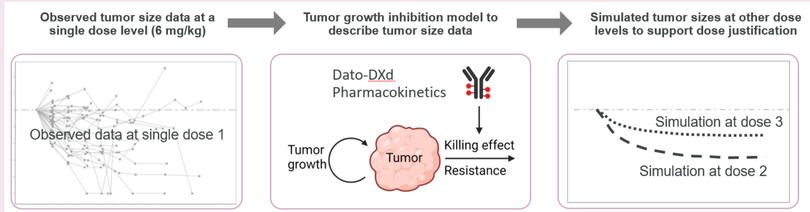
Introduction

- Dato-DXd, a TROP2-directed antibody-drug conjugate, has demonstrated efficacy and a manageable safety profile in multiple tumour types. Recently, Dato-DXd demonstrated statistically significant and clinically meaningful improvement in PFS compared with investigator's choice of chemotherapy (ICC) in patients with HR-positive/HER2-negative breast cancer (BC) in TROPION-Breast01.
- An optimal dose at 6 mg/kg every three weeks (Q3W) was selected for Dato-DXd late phase development based on data from advanced or metastatic non-small cell lung cancer (NSCLC) patients in a Phase I study TROPION-PanTumor01[1]. The optimal dose at 6 mg/kg Q3W was evaluated as the single dose level in multiple tumour types and Dato-DXd pivotal trials, including TROPION-Breast01.
- A tumour growth inhibition (TGI) model was developed to support dose justification at 6 mg/kg in HR-positive/HER2-negative BC patients (**Figure 1**).

Methods

- A previously-developed PopPK model for Dato-DXd was updated with TROPION-PanTumor01 breast cancer PK data to derive individual PK metrics for tumour growth inhibition (TGI) model development. A TGI model was developed based on tumour size data from HR-positive/HER2-negative BC patients who received 6 mg/kg Dato-DXd Q3W in TROPION-PanTumor01 (N = 39, Data cutoff July 2022).
- The TGI model described the tumour size as the result of an exponential tumour growth, a tumour shrinkage that was driven by Dato-DXd cycle-specific AUC, and a resistance term suggesting that the shrinkage effect by Dato-DXd decreases over time. Cycle-specific Dato-DXd AUC was derived based on the AUC and time at each cycle for each individual.
- Simulations were conducted using the TGI model to compare tumour size change from baseline at 4, 6, and 8 mg/kg in HR-positive/HER2-negative breast cancer patients, with consideration of dropouts.

Figure 1. Tumour Growth Inhibition Modelling and Simulation Schematic

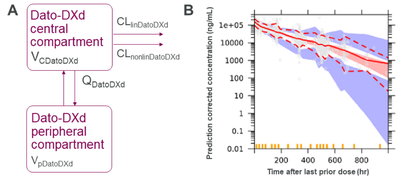


Results and interpretation

Population pharmacokinetic model (PopPK) model:

- A total of 295 patients from TROPION-PanTumor01, including 210 NSCLC patients and 85 BC patients were included in the analysis. Clinical study design was described elsewhere[2].
- A two-compartment model with parallel linear ($CL_{linDatoDXd}$) and nonlinear Michaelis-Menten clearance ($CL_{nonlinDatoDXd}$) from the central compartment well-described the Dato-DXd PK data (**Figure 2**). Inter-individual variability (IIV) was characterized on $CL_{linDatoDXd}$, $V_{cDatoDXd}$, $V_{pDatoDXd}$, $Q_{DatoDXd}$, and V_{max}. The model included the following covariate-parameter relationships: Baseline body weight (WT); baseline albumin (ALB), region, and sex on $CL_{linDatoDXd}$, and WT on $Q_{DatoDXd}$, $Vc_{DatoDXd}$, and $Vp_{DatoDXd}$;

Figure 2. PopPK Model



A. Schematic of PopPK model. **B.** pcVPC suggested that the model well-described Dato-DXd PK data. The solid and dashed lines = the median, 5th, and 95th percentiles of the observations; the shaded red and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model CI = confidence interval, pcVPC = prediction-corrected visual predictive check.

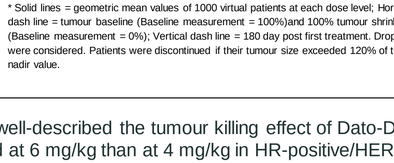
Table 1. Parameter Estimates of the PopPK Model*,†

Parameter	Estimate	RSE (%)	95% CI
$CL_{linDatoDXd}$, L/d	0.396	3.24	[0.35 ; 0.43]
$Vc_{DatoDXd}$, L	2.78	1.46	[2.7 ; 2.86]
$Q_{DatoDXd}$, L/d	0.435	2.34	[0.39 ; 0.48]
$Vp_{DatoDXd}$, L	2.91	2.44	[2.66 ; 3.12]
V_{max}, µg/d	6934	2.36	[5534 ; 8940]
K_m, ng/mL	3076	3.58	[1846 ; 5009]
ALB ~ $CL_{linDatoDXd}$	-0.757	8.33	[-1.1 ; -0.5]
Sex (Female) ~ $CL_{linDatoDXd}$	-0.230	11.7	[-0.3 ; -0.15]
Region (Japan) ~ $CL_{linDatoDXd}$	-0.174	18.9	[-0.26 ; -0.1]
IIV RUV	0.555	4.02	[0.47 ; 0.64]
IIV $CL_{linDatoDXd}$	0.261	5.39	[0.21 ; 0.3]
IIV $Vc_{DatoDXd}$	0.197	4.41	[0.17 ; 0.22]
IIV $Q_{DatoDXd}$	0.402	5.16	[0.32 ; 0.46]
IIV $Vp_{DatoDXd}$	0.349	5.24	[0.3 ; 0.4]
IIV V_{max}	0.296	6.4	[0.23 ; 0.36]
RUV	0.117	4.2	[0.11 ; 0.13]

*WT on $CL_{linDatoDXd}$ and $Q_{DatoDXd}$ were fixed to 0.75; WT on $Vc_{DatoDXd}$ and $Vp_{DatoDXd}$ were fixed to 1.
†Shrinkage (SD based) was 0%, 11.1%, 2%, 10.7%, 10.1%, 14.3% and 1.4% for variance of IIV RUV, IIV $CL_{linDatoDXd}$, IIV $Vc_{DatoDXd}$, IIV $Q_{DatoDXd}$, IIV $Vp_{DatoDXd}$, IIV V_{max}, and RUV.
$CL_{linDatoDXd}$, linear clearance; IIV, interindividual variability; K_m, concentration associated with a half V_{max}; $Q_{DatoDXd}$, intercompartmental clearance; RSE, relative standard error; $Vc_{DatoDXd}$, central volume; V_{max}, maximum of nonlinear clearance; $Vp_{DatoDXd}$, peripheral volume. RUV = Additive component for Dato-DXd; RSE = relative standard error.

- Dato-DXd PK profiles of 1000 virtual patients were simulated at 4, 6, and 8 mg/kg to derive PK metrics. At 6 mg/kg, majority of observed PK data were captured by 2.5th – 97.5th percentiles of simulated PK profiles of 1000 virtual patients (**Figure 3**). No observed PK data at 4 or 8 mg/kg was available from HR-positive/HER2-negative BC patients.

Figure 3. PopPK model well-described observations

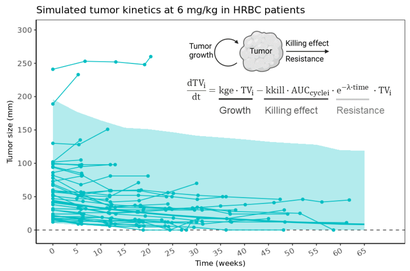


Simulated vs. observed Dato-DXd PK profiles of HR-positive/HER2-negative BC patients at 6mg/kg. Black dots = observed PK data from HR-positive/HER2-negative BC patients in TROPION-PanTumor01 study. Solid lines and shadow areas = geometric mean value and 2.5th – 97.5th percentiles of 1000 virtual patients at 6 mg/kg.

Tumour Growth Inhibition (TGI) model:

- A total of 195 tumour size observations from 39 HR-positive/HER2-negative BC patients were included in the modelling dataset. All patients received Dato-DXd at 6 mg/kg Q3W.
- The TGI model described the tumour size as the result of an exponential tumour growth and shrinkage that was driven by Dato-DXd cycle-specific AUC. The model included a resistance term suggesting that the shrinkage effect by Dato-DXd decreases over time (**Figure 4**). No statistically significant covariates were identified. Parameters were estimated with reasonable precision (**Table 2**). Goodness-of-fit plots showed that the data were appropriately described by the model. TGI model recapitulated observed tumour sizes in HR-positive/HER2-negative BC patients (**Figure 4**).

Figure 4. TGI model well-described observations



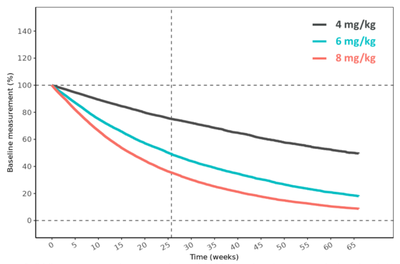
Simulated tumour size data vs. observed tumour size data. In the simulation patients were discontinued if their tumour size exceeded 120% of the nadir value. Points = observed tumour size data from HR-positive/HER2-negative BC patients in TROPION-PanTumor01 study. Solid lines and shadow areas = individual tumor size data and 5th – 95th percentiles of 1000 virtual patients at 6 mg/kg.

Table 2. Parameter Estimates of the TGI Model*,†

Parameter	Estimate	RSE (%)
TS0, mm	45.9	12.68
kge, day^{-1}	0.000802	43.64
kkill, day^{-1}	0.00000514	24.55
λ, day^{-1}	0.00593	64.46
IIV TS0	0.777	12.15
IIV kge	1.24	26.26
IIV kkill	0.732	22.19
IIV λ	1.95	48.92
Additive Error	4.67	7.44

*Shrinkage (%) for IIV TS0, IIV kge, IIV kkill, and IIV λ were -1.34, 6.03, 3.6, and -6.73%. †TS0: Initial tumour size; kge: Exponential tumour growth rate; kkill : linear tumour growth inhibition rat; λ: Resistance appearance.

Figure 5. Simulated Tumour Size Data at 4, 6, and 8 mg/kg*,†



* Solid lines = geometric mean values of 1000 virtual patients at each dose level; Horizontal dash line = tumour baseline (Baseline measurement = 100%)and 100% tumour shrinkage (Baseline measurement = 0%); Vertical dash line = 180 day post first treatment. Dropouts were considered. Patients were discontinued if their tumour size exceeded 120% of the nadir value.

- TGI model simulation suggested a deeper tumour shrinkage profile for Dato-DXd at the dose level of 6 mg/kg compared to 4 mg/kg in HR-positive/HER2-negative BC patients.
- At 180 days post the first treatment, geometric mean values of tumour shrinkage from baseline were -25%, -51%, and -65% at 4, 6, and 8 mg/kg, respectively (**Figure 5**).
- The current TGI model and simulation supported Dato-DXd 6 mg/kg administered as an intravenous infusion Q3W (21-day cycle) offers an optimal benefit: risk ratio for the treatment of adult patients with unresectable or metastatic HR-positive/HER2-negative BC who have received prior systemic therapy.
- Similarly, a TGI model was also developed for NSCLC patients from TROPION-PanTumor01 at 0.27 – 10 mg/kg (N = 187, DCO 8 Jan 2021). The simulated maximum tumour size reductions at 4, 6, and 8 mg/kg were greater at higher Dato-DXd dose levels. The maximum tumour shrinkage from baseline in NSCLC patients was predicted to be 30% with 4 mg/kg, 37% with 6 mg/kg, and 41% with 8 mg/kg[3].

TROPION-Breast01

…Phase III trial demonstrated that Dato-DXd significantly extended progression-free survival vs. chemotherapy in patients with HR-positive, HER2-low or negative breast cancer

Positive results from the pivotal TROPION-Breast01 Phase III trial showed that Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to investigator's choice of chemotherapy (median PFS: 6.9 months vs. 4.9 months, HR 0.63 [95% CI 0.52–0.76]; p<0.0001) in patients with inoperable or metastatic HR-positive, HER2-low or -negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and at least one systemic therapy[4-6]

Project Optimus

…FDA Oncology Center of Excellence (OCE) initiative

Project Optimus is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development (https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus).

Tumour Growth Inhibition Model

…A powerful modelling tool to support Project Optimus

"…dose selection decision making can be supported by modeling of population PK and tumour size in combination with exposure-response modeling. Such modeling approaches are intended to characterize the relationship between drug exposure and rate of reduction in tumour size and are used to support initial dosages selected for investigation in expansion cohorts, …" [7,8]

The tumour growth inhibition model well-described the tumour killing effect of Dato-DXd. Simulation suggested a more suitable tumour inhibition profile by Dato-DXd at 6 mg/kg than at 4 mg/kg in HR-positive/HER2-negative breast cancer patients.

Abbreviations

PK: Pharmacokinetics. PopPK: Population pharmacokinetic model. GOF: Goodness-of-fit

Acknowledgements

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Disclosures

YP, SL, and YH are employees of Daiichi Sankyo, Inc, and disclose holding Daiichi Sankyo, Inc, stocks and options. **ZT, YJ, HY, DD, CG, LI, SR, AP, and DZ** are employees of AstraZeneca, and disclose AstraZeneca, stocks and options.

References

[1]Lu, Yasong, et al. CPT: Pharmacometrics & Systems Pharmacology 13.1 (2024): 23-28 [2]ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03401385. [3]ACoP13 2022. [4]https://www.annalsofoncology.org/article/S0923-7534(23)04159-5/fulltext. [5]ESMO 2023. [6]ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05104866. [7]Al-Huniti, Nidal, et al. CPT: pharmacometrics & systems pharmacology 9.8 (2020): 419-427. [8]Fourie Zirkelbach, Jeanne, et al. Journal of Clinical Oncology 40.30 (2022): 3489-3500