Population pharmacokinetic analysis of datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate

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Introduction

- Datopotamab deruxtecan (Dato-DXd) is a trophoblast cell surface antigen 2 (TROP2)-directed antibody-drug conjugate (ADC) in clinical development for the treatment of advanced or metastatic NSCLC and other tumor types. The released drug, MAAA-1181a (DXd), inhibits DNA topoisomerase I leading to the inhibition of cell replication and promotes apoptosis of the target tumor cells.
- TROPION-PanTumor01 (TP01) is an ongoing, phase 1 study of Dato-DXd that evaluated a dose range of 0.27 mg/kg to 10 mg/kg administered once every 3 weeks (Q3W) in patients with advanced solid tumors (210 NSCLC and 85 BC subjects). The Dato-DXd 6 mg/kg Q3W dose was selected for late-stage development in TROPION-Lung01 (TL01) and TROPION-Lung05 (TL05) to determine the benefit-risk profile of Dato-DXd in patients with advanced NSCLC.
- The pivotal phase 3 study TL01 demonstrated a statistically significant improvement of progression-free survival (PFS) over docetaxel in patients with advanced NSCLC treated with at least one prior line of therapy. The present analysis is to characterize the population PK of Dato-DXd and DXd based on these three studies.

Objectives

- To establish a population PK model describing the PK characteristics of Dato-DXd and DXd.
- To assess the impact of intrinsic and extrinsic covariates on the PK of Dato-DXd and DXd.

Conclusions

- Population PK model adequately described PK data of Dato-DXd and DXd. The linear clearance was the major elimination pathway for Dato-DXd doses of 4 mg/kg and above, whereas nonlinear clearance was necessary for satisfactory description of PK at doses of less than 4 mg/kg.
- Body weight was the most influential covariate on Dato-DXd and DXd exposures. Other covariates had no clinically meaningful impact on PK. Dose adjustments based on the tested covariates or for special populations are not recommended.
- Model-based simulation revealed Dato-DXd and DXd exposures increased with the body weight but were overlapped significantly across the weight groups at the proposed dose of 6 mg/kg Q3W, supporting a body weight-normalized regimen is appropriate for Dato-DXd.

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Methods

Population PK analysis datasets

- The population PK analysis was performed using 9036 and 9012 plasma concentration values for Dato-DXd and DXd from 729 subjects in Studies TL01 (N=297), TL05 (N=137), and TP01 (N=295).

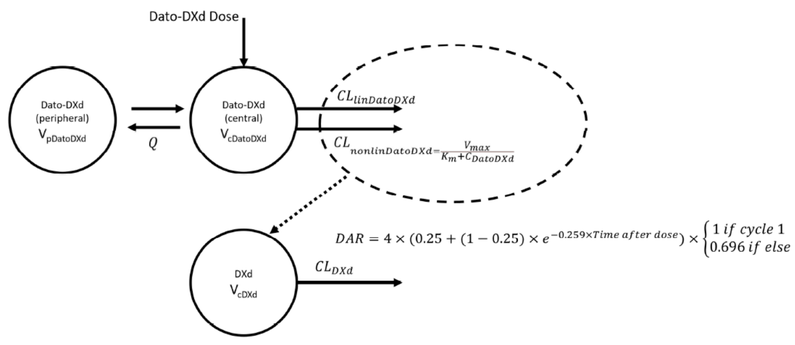
Development of a population PK model for Dato-DXd and DXd

- Dato-DXd and DXd model was established with improved model structures from a legacy model [1]. This model was updated to describe DXd by using individual post hoc PK parameters from the Dato-DXd model as the input.
- Potential covariate-parameter relationships were evaluated using the stepwise covariate model building procedure (SCM) with adaptive scope reduction denoted SCM+ [2]. The evaluated covariates included age, body weight, albumin, sex, race, country/region, creatinine clearance, hepatic function, ECOG, tumor size, last prior line of therapy including IO agent (LPIO), number of prior lines of therapy (NPLT), tumor type, histology, tumor membrane TROP2 protein expression, actionable genomic alterations status (AGA), anti-drug antibody status (ADA), drug product, and smoking status.
- The impact of covariates on Dato-DXd and DXd exposures at steady state (AUC3) was illustrated using forest plots.
- Body weight-based dosing regimen of Dato-DXd was evaluated by performing model-based simulations across the relevant body weight range.

Results

- The final model diagram of Dato-DXd and DXd and covariate – PK relationships are presented below.
- Population PK of Dato-DXd was best described by a two-compartment model with parallel linear and nonlinear clearance.
- Population PK of DXd was best described by a one-compartment model with linear clearance. The release rate of DXd was the sum of linear and nonlinear elimination rate of Dato-DXd.
- The Drug-to-Antibody ratio (DAR) changed with time within and between cycles as previously described for other ADCs [3,4].

Dato-DXd and DXd final population PK model diagram



Dato-DXd

$$CL_{linDatoDXd} = 0.386 \times \left(\frac{WT}{66}\right)^{0.750} \times \left(\frac{ALB}{38}\right)^{-0.788} \times \left(\frac{AGE}{62}\right)^{-0.306} \times \begin{cases} 1\ if\ male \\ 1 - 0.263\ if\ female \end{cases} \times \begin{cases} 1\ if\ not\ Japan\ country \\ 1 - 0.219\ if\ Japan\ country \end{cases}$$

$$V_{cDatoDXd} = 3.06 \times \left(\frac{WT}{66}\right)^{0.415} \times \begin{cases} 1\ if\ male \\ 1 - 0.160\ if\ female \end{cases}$$

$$V_{pDatoDXd} = 2.88 \times \left(\frac{WT}{66}\right)^{0.311}$$

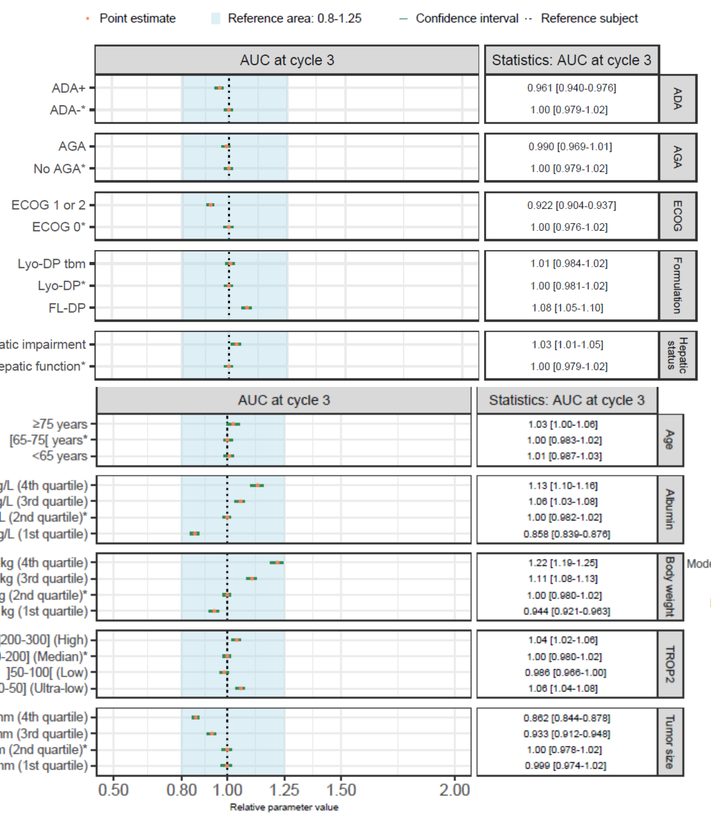
$$V_{max} = 8410 \times \left(\frac{Tumor\ size}{66}\right)^{0.125}$$

DXd

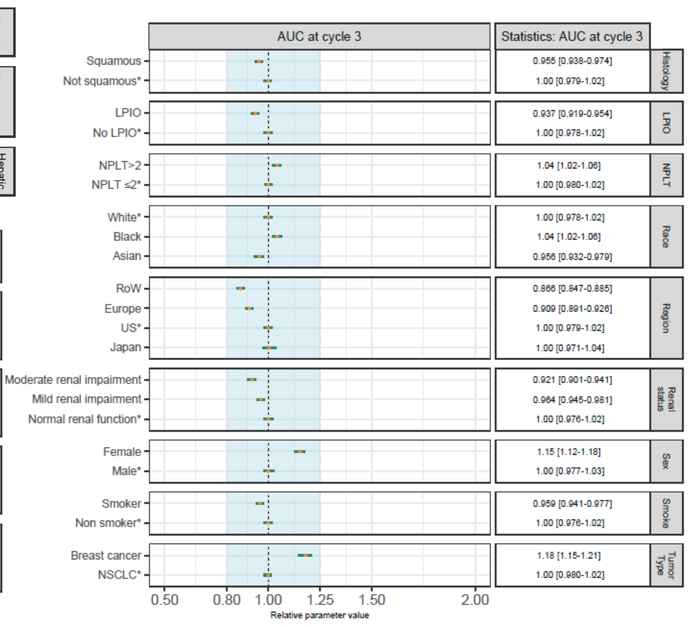
$$CL_{DXd} = 2.66 \times \left(\frac{WT}{66}\right)^{0.298} \times \left(\frac{ALB}{38}\right)^{0.343} \times \left(\frac{AST}{22}\right)^{-0.154} \times \left(\frac{TBIL}{0.4}\right)^{-0.139} \times \begin{cases} 1\ if\ US\ or\ Japan\ country \\ 1 + 0.240\ if\ Europe\ countries \\ 1 + 0.196\ if\ Rest\ of\ the\ World\ countries \end{cases}$$

$$V_{cDXd} = 25.1 \times \left(\frac{WT}{66}\right)^{0.530} \times \begin{cases} 1\ if\ male \\ 1 - 0.185\ if\ female \end{cases}$$

Covariates evaluated had no clinically meaningful effects on Dato-DXd and DXd PK except higher values of body weight

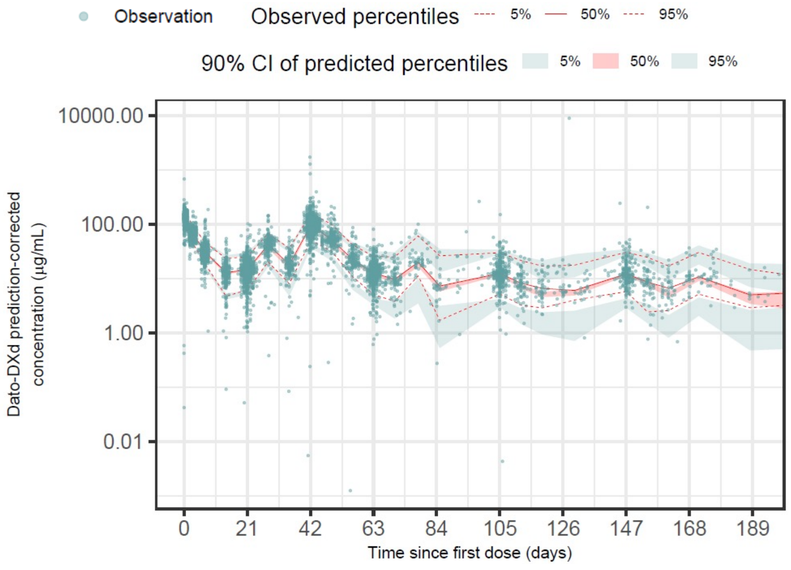


- Empirical forest plot illustrating the association of the predicted Dato-DXd steady-state exposure (AUC3) and continuous covariates. Asterisks (*) denotes the reference subgroups.
- Empirical forest plot of DXd is not shown. The ratio of DXd AUC3 in the weight group of ≥77 kg was 1.34 [90%CI:1.30-1.37] compared to DXd AUC3 in the reference group [57-66) kg. The remaining covariates had no clinically meaningful effect on DXd AUC3.

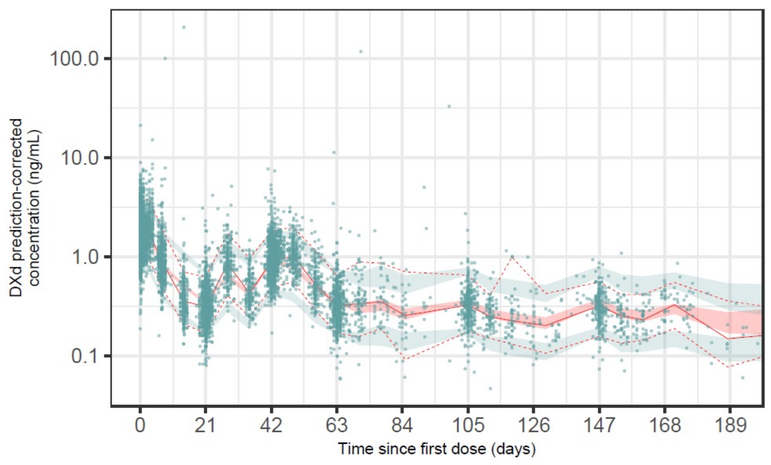


pcVPCs show the model adequately captured the central tendency and variability

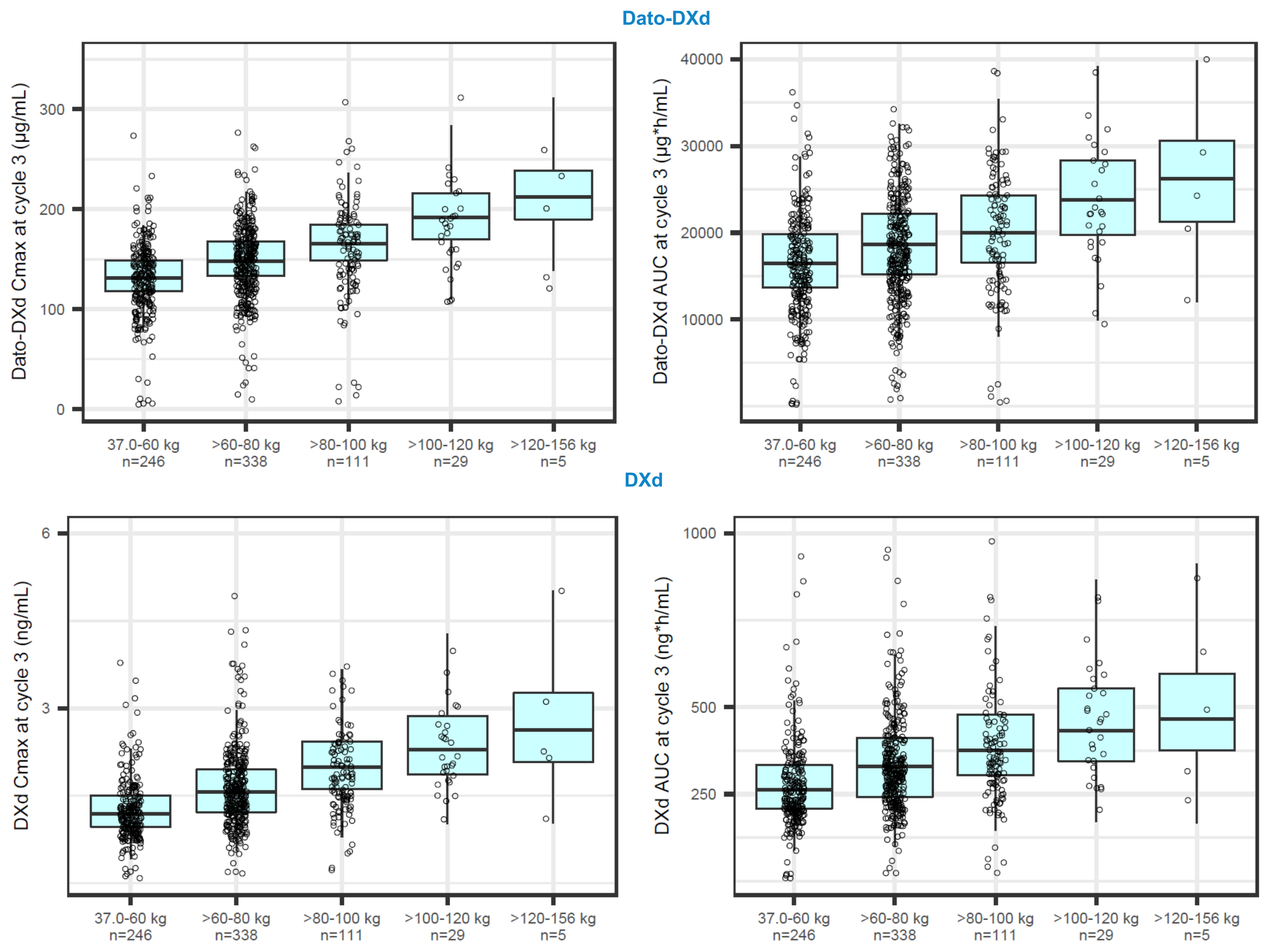
Dato-DXd



DXd



Significant overlap of Dato-DXd and DXd exposure was observed across body weight groups, supporting the body weight-based dosing regimen is appropriate for Dato-DXd



Simulated Dato-DXd and DXd Cmax3 and AUC3 (represented as boxplot) using a body weight-based dosing of 6 mg/kg administered as an IV infusion Q3W across body weight groups. A total of 500 virtual subjects per body weight category were simulated. Overlaid black open circles represent the individual observed Dato-DXd and DXd Cmax3 and AUC3. The sample size on the x-axis indicates the number of subjects in the population PK dataset.

References

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