PI-038

Reverse-Translational Findings for Datopotamab Deruxtecan (Dato-DXd) Human Efficacious Dose Prediction Based on Mechanistic PK/Tumor Growth Inhibition Analysis for Patient-Derived and Cancer Cell Line-Derived Xenograft Mice

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Background

- Trophoblast cell surface antigen 2 (TROP2) is broadly expressed in solid tumors and is highly expressed in non-small cell lung cancer (NSCLC), hormone receptor positive breast cancer (HR+BC), and triple negative breast cancer (TNBC)[R1], supporting the therapeutic potential of TROP2-directed therapies in these tumor types.
- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed antibody-drug conjugate (ADC) with a tumor-selective cleavable linker and potent topoisomerase I inhibitor payload (DXd)[R2]. It has been approved in the US, EU, and Japan for the treatment of adult patients with unresectable or metastatic HR+, human epidermal growth factor receptor 2 (HER2) negative (IHC 0, IHC 1+, or IHC 2+/ISH-) BC who have received prior endocrine-based therapy and chemotherapy.
- Dato-DXd has shown encouraging antitumor activity and a manageable safety profile in patients with NSCLC, HR+BC and TNBC as monotherapy and in combination with immunotherapy or other targeted therapy.

Objective

- To describe pharmacokinetics (PK)/ pharmacodynamic (PD) relationship in patient-derived xenografts (PDX) and cancer cell line-derived xenografts (CDX) mice models using tumor growth inhibition (TGI) as a PD index following intravenous (IV) administration of Dato-DXd.
- To compare efficacious concentration estimated from preclinical studies with clinical human PK profiles (TROPION-PanTumor-01: TP01 [NCT03401385]) in patients with NSCLC and BC as part of reverse-translational research.

Results

- The mean tumor static concentration (TSC), which represents the plasma concentration of Dato-DXd that leads to equal rates of tumor growth and death in the xenograft models, was 12.2 μg/mL for BC PDX (6 models) and 10.1 μg/mL for NSCLC PDX (6 models). Lung CDX provided the similar TSC (8.27 μg/mL in 4 models: Calu-3, EBC-1, HCC827, and NCI-H2170) to those estimated from PDX models from patients with NSCLC.
- The overall mean TSC in all preclinical models tested was 10.0 μg/mL (25 models in total). In patients with NSCLC and BC receiving 6 mg/kg of Dato-DXd, the plasma concentration of Dato-DXd at steady state mostly remained around or above the TSCs (10.0 – 12.2 μg/mL) estimated in the respective preclinical models.

Disclosure of COI

All authors are employees of Daiichi Sankyo or AstraZeneca.

Acknowledgement

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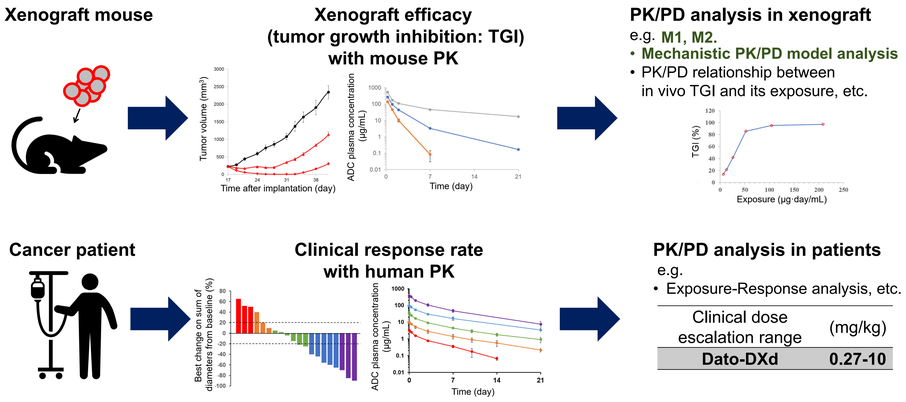
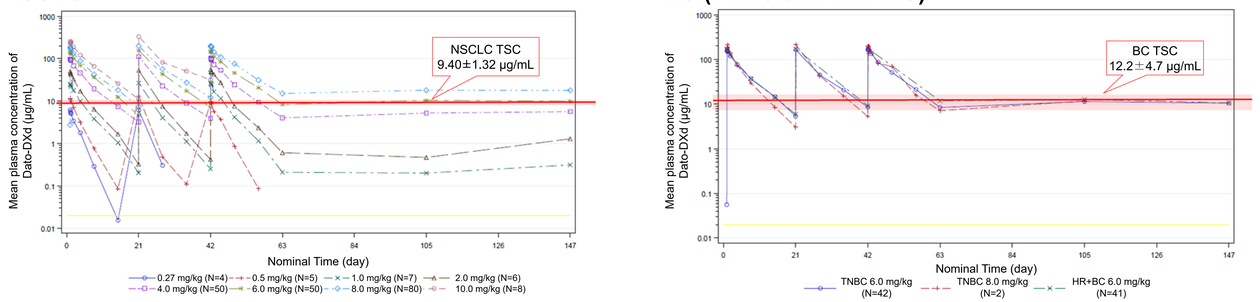
Preclinical PK/TGI analysis is a reliable way to estimate the clinically efficacious concentration of Dato-DXd in patients with NSCLC and BC, thereby supporting 6 mg/kg as the optimal dose of Dato-DXd for clinical study design

How do key PK parameters for efficacy in mice correspond with clinical PK in patients?



M3. *Comparison between preclinical mouse TSC and clinical PK profiles in patients with NSCLC, TNBC and HR+ BC*



In patients with NSCLC and BC, the plasma concentration of Dato-DXd at steady state, when administered at the optimal dose (6 mg/kg), mostly remained around or above the TSCs estimated in the respective preclinical models.

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below:
https://bit.ly/DSASCPT2025

Reference

R1. Liu X, et al. Pharmacol Ther 2022; 239:108296
R2. Okajima D, et al. Mol Cancer Ther 2021; 20: 2329-40
R3. Simeoni M, et al. Cancer Res 2004; 64: 1094-101

M1. PK model analysis was adopted to describe the plasma concentration-time profile of Dato-DXd in NCI-N87 (a gastric cancer cell line) xenograft mice.[R2]

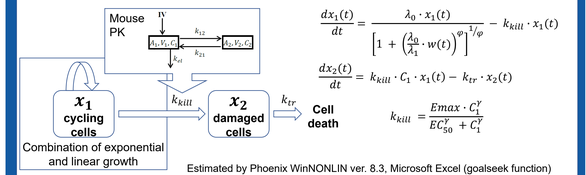
M2. Mechanistic PK/TGI model analysis was conducted to estimate TSC

M3. The preclinical TSCs were compared to clinical human PK profiles in patients with NSCLC and BC following multiple IV dosing of Dato-DXd (0.27-10 mg/kg; TP01) to evaluate the relevance of preclinical TSC to clinical optimal dose (6 mg/kg).

Monotherapy clinical trial: TP01 [NCT03401385], TROPION-Lung05 [NCT04484142], TROPION-Breast01 [NCT05104866], TROPION-Breast02 [NCT05374512]

TSC estimation: mouse PK/TGI model analysis for PDX and CDX

Mechanistic PK/TGI model analysis modified from Simeoni et al.[R3] was adopted for TSC estimation. The number of transit compartment (zero or one) was optimized.



Estimated by Phoenix WinNONLIN ver. 8.3, Microsoft Excel (goalseek function)

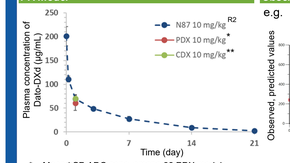
TSC is the concentration where tumor growth and death rates are equal, and tumor volume remains unchanged. → Tumor growth rate is zero ($\because dx_1(t)/dt = 0$):

$$Emax \cdot TSC^{\gamma} / (EC_{50}^{\gamma} + TSC^{\gamma}) = \lambda_0 / [1 + (w(0) \cdot \lambda_0 / \lambda_1)^{\varphi}]^{1/\varphi}$$

$w(0) = initial\ tumor\ volume\ before\ dosing$, $\varphi = 20$[R3]

M1, M2. *Preclinical Dato-DXd mouse PK/TGI modeling*

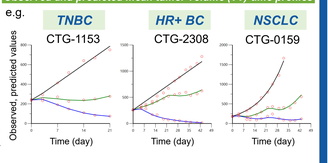
PK model



* Mean±SD ADC conc. among 38 PDX models
** Mean±SD ADC conc. among 6 CDX models
SD: standard deviation

PK difference among xenograft models appeared to be limited. Assumption: Linear PK of Dato-DXd in mice was applied in this analysis.

Observed and predicted mean tumor volume (TV)-time profiles



This PK/TGI model fits the data well!

TSC estimates for PDX and CDX mice after IV administration of Dato-DXd

	Model No.	Tumor type	TSC (μg/mL)	Mean	SE	Indication mean	Indication SE
PDX	CTG-1017	TNBC	12.3	6.49	2.45	**12.2**	**4.7**
	CTG-0437		7.28				
	CTG-1153		6.00				
	CTG-1408		0.376				
	CTG-1705	HR+ BC	33.8	23.6	-		
	CTG-2308		13.3				
PDX	CTG-0159	NSCLC	9.78	**10.1**	**2.2**	**9.40**	**1.32**
	CTG-0165		4.47				
	CTG-1444		19.9				
	CTG-2143		6.55				
	CTG-2539		9.98				
	CTG-2669		10.2				
CDX	Calu-3	Lung	9.64	**8.27**	**0.82**		
	EBC-1		9.20				
	HCC827		5.98				
	NCI-H2170		8.27				
PDX	CTG-0411	Pancreatic	0.812	-	-	1.21	-
CDX	CFPAC		1.59				
PDX	CTG-0294	Cholangiocarcinoma	1.00	5.31	-		
	CTG-1210		9.61				
	CTG-0406	Colorectal	1.00	7.12	-		
	CTG-1235		1.65				
	CTG-1510		18.7				
	CTG-0776	Head and Neck	43.2	24.8	-		
	CTG-0820		6.47				
Overall mean			**10.0**				
Overall Standard Error (SE)			**2.0**				

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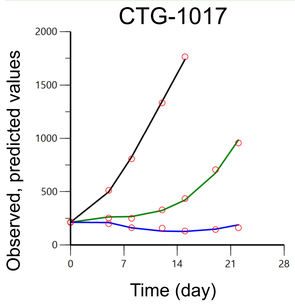
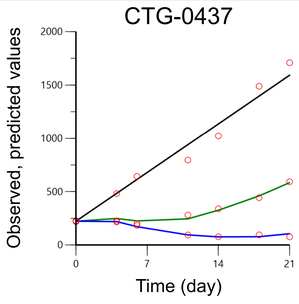
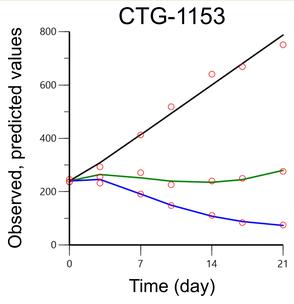
Observed and predicted mean tumor volume (TV)-time profiles

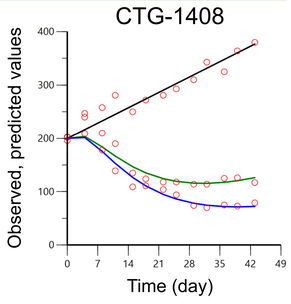
PDX

TNBC

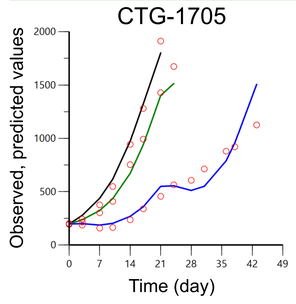


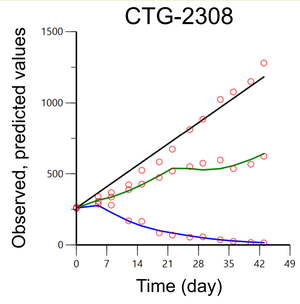




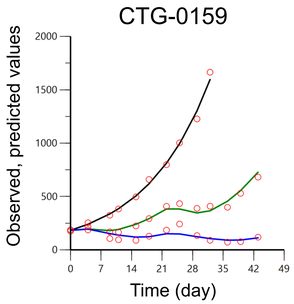


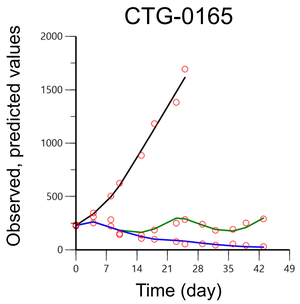
HR+ BC

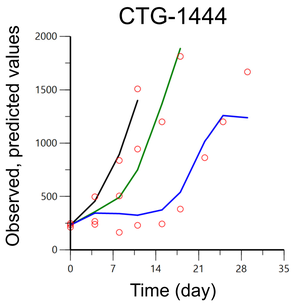


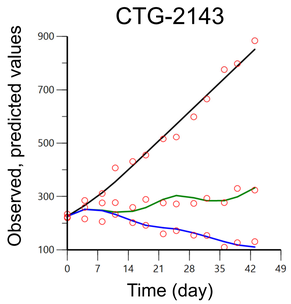


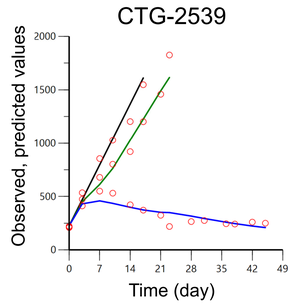
NSCLC

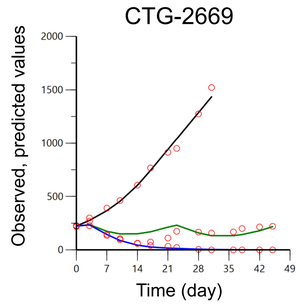




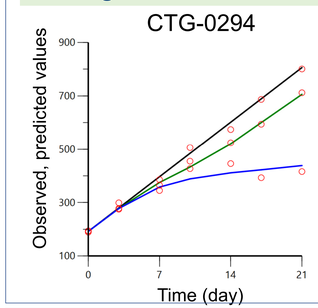


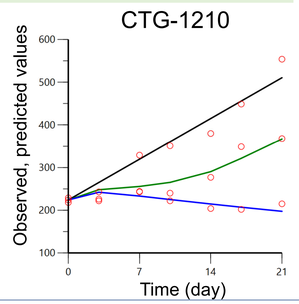




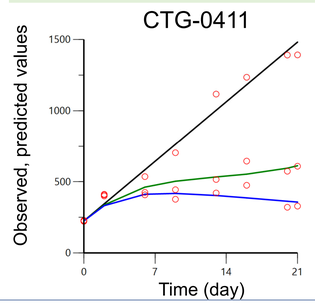


Cholangiocarcinoma

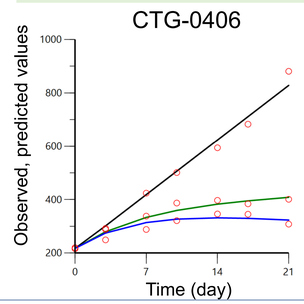


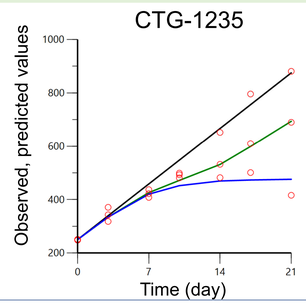


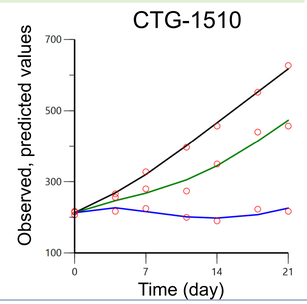
Pancreatic



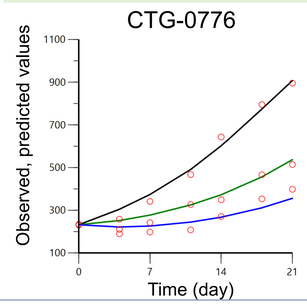
Colorectal

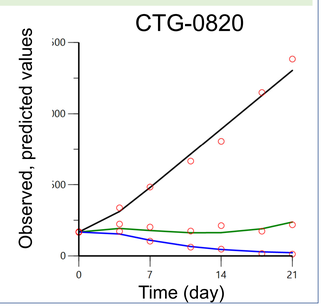






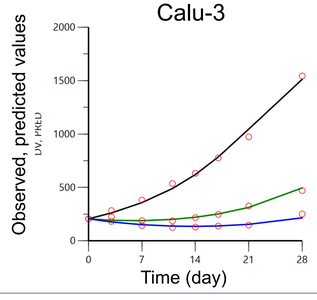
Head and Neck

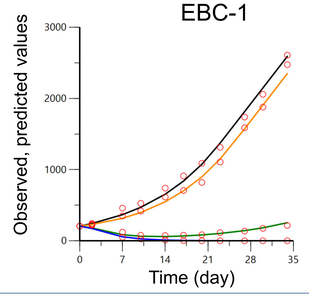


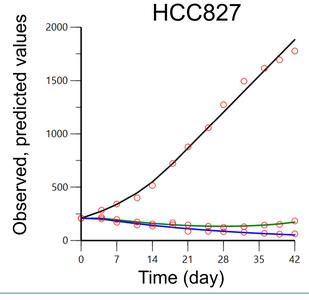


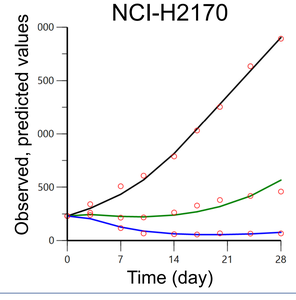
CDX

Lung

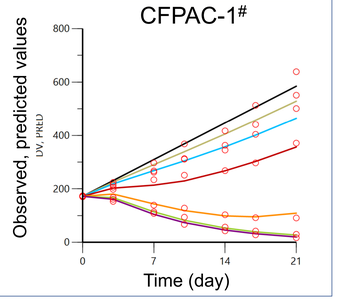








Pancreatic



○: **Observed mean TV**

Predicted mean TV-time profiles

-: Control

-: Dato-DXd 1 mg/kg q3w

-: Dato-DXd 3 mg/kg q3w

-: Dato-DXd 10 mg/kg q3w

Dato-DXd
0.125, 0.25, 0.5, 1, 2, and 4 mg/kg q3w