Exposure–response analysis of datopotamab deruxtecan (Dato-DXd) in combination with pembrolizumab with or without platinum chemotherapy in patients with advanced or metastatic non-small cell lung cancer

T-100

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BACKGROUND

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC. It has received regulatory approval for the treatment of adult patients with previously treated, unresectable or metastatic HR+/HER2− breast cancer, and for patients with previously treated metastatic NSCLC harboring *EGFR*-activating mutations. The cytotoxic payload (DXd) is an exatecan derivative and a potent DNA topoisomerase I inhibitor. Once released inside target tumor cells, the payload induces DNA damage and apoptosis of tumor cells
- Dato-DXd demonstrated prolonged PFS as monotherapy compared to docetaxel in previously treated patients with a/m NSCLC lacking actionable genomic alterations in the TROPION-Lung01 trial.[1] It is currently being further evaluated in phase 3 studies as a first-line combination therapy with anti-PD-1 with or without platinum-based chemotherapy in patients with a/m NSCLC
- TROPION-Lung02 is an ongoing phase 1b study evaluating Dato-DXd + pembrolizumab ± platinum chemotherapy in patients with a/m NSCLC without actionable genomic alterations. It has demonstrated encouraging antitumor activity and tolerable safety in 142 patients (first-line, second-line, and beyond) who received Dato-DXd at 4 or 6 mg/kg Q3W in combination with pembrolizumab (doublet) or pembrolizumab and platinum chemotherapy (triplet).[2,3] Here we report the exposure–response analysis based on TROPION-Lung02 data

OBJECTIVES

- To characterize the exposure–response of Dato-DXd for tumor size (TS) response and best overall response of complete response or partial response in patients with NSCLC receiving the doublet or triplet regimen
- To assess the potential influence of the baseline patient characteristics and dosing regimen (i.e., doublet vs. triplet) on the antitumor response of Dato-DXd

METHODS

Population pharmacokinetics

- A previously developed population PK model[4] was used to derive exposure metrics for Dato-DXd. Briefly, Dato-DXd PK was best described by a two-compartment model with parallel linear and nonlinear clearance. The DXd PK was modeled using the total elimination rate of Dato-DXd (incorporating time-dependent drug-to-antibody ratio decline) as input, with DXd disposition characterized by a one-compartment model with linear clearance

Exposure–response for tumor size

- Longitudinal TS data were used to develop a TGI model (**Figure 1**), in a nonlinear mixed-effects modeling framework using NONMEM 7.5. Both exposure-dependent (Eq. 1) and exposure-independent (Eq. 2) models were tested for the combined multiplicative drug effect component. The differential equation defining the TGI dynamics (Eq. 3) was solved to develop the closed-form Eq. 4, which was used for modeling purposes (using $PRED) to ensure numerical stability
- Covariates were evaluated using a full model-based approach. Since all treatment arms included both Dato-DXd and pembrolizumab, informative priors ($PRIOR in the first order conditional estimation with interaction method) were used for E_{Dato} and E_{Pembro}

Exposure–response for BOR of CR/PR

- Logistic regression analysis was performed to characterize the probability of BOR being CR/PR (ORR). Competing models with several exposure metrics of cycle 1 (AUC_1, C_{max1}, C_{min1}) and exposure structures (linear, log-linear, E_{max}, sigmoidal E_{max}) were evaluated for base model selection. A full modeling approach was used to estimate the covariate effects
- Model fitting was carried out in a Bayesian framework using weakly informative proper priors. Posterior samples were obtained using Markov Chain Monte Carlo sampling

RESULTS

Patient characteristics

- The TS dataset had 844 repeated post-baseline measurements of TS from 141 patients (out of 142) who also had corresponding baseline TS records. Among the 142 patients, 52 patients (36.6%) and 90 patients (63.4%) received the 4 mg/kg and 6 mg/kg dose of Dato-DXd, respectively; 70 patients (49.3%) and 72 patients (50.7%) received the doublet and triplet regimen, respectively; 96 patients (67.6%) and 46 patients (32.4%) had zero and ≥1 PLT, respectively
- Among the 46 patients who received ≥1 PLT, 18 patients (39.1%) had their last PLT with an immuno-oncology drug (LPIO). PD-L1 expression levels (locally tested) were <1% in 58 patients (40.8%), 1–49% in 52 patients (36.6%), ≥50% in 31 patients (21.8%), and missing in 1 patient (0.7%)

Full models

- The exposure-dependent drug effect model accounting for Dato-DXd AUC_τ on TGI (Eq 1) had a convergence issue, possibly because of the saturation of the drug effect at the first exposure quartile. Therefore, the exposure-independent drug effect model (Eq. 2) was chosen to avoid over-parameterization (**Table 1**). The probability of BOR (CR/PR) was best predicted by a log-linear drug effect model with Dato-DXd AUC_1 (**Table 2**). Both models performed well upon visual comparison with the observed data (**Figure 2**)

Model inference

- Univariate analyses of the TGI and ORR model revealed that higher PD-L1 expression (1–49% and ≥50%), no PLT (i.e., treatment-naïve), or LPIO had an overall significant and positive influence on TS reduction and probability of BOR being CR/PR (**Figure 3**). The highest influence was seen in treatment-naïve patients, in whom the estimated median percent change in TS at nadir (%TS_{nadir}) was 21.5% [95% CI: 6.58%, 35.3%] and the odds ratio was 3.82 [95% CI: 1.37, 11.4]
- Dato-DXd exposure had an effect on ORR, as evident from the estimated odds ratio varying from 0.78 [95% CI: 0.358, 1.70] to 1.30 [95% CI: 0.567, 2.99] between the 5th and 95th percentiles of Dato-DXd AUC_1
- The triplet regimen achieved an ORR comparable to that of the doublet regimen (odds ratio: 0.822; 95% CI: 0.328, 1.90), supporting the evaluation of both regimens in the ongoing phase 3 TROPION-Lung07 study

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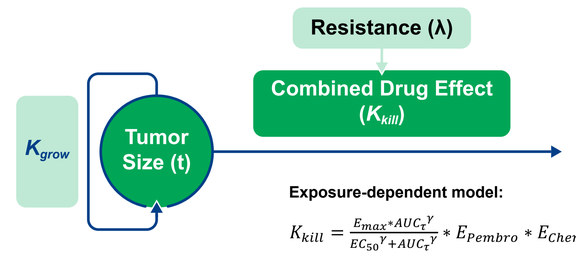
Figure 1. Schematic diagram of the TGI model



Exposure-dependent model:

$$K_{kill} = \frac{E_{max} * AUC_\tau^{\gamma}}{EC_{50}^{\gamma} + AUC_\tau^{\gamma}} * E_{Pembro} * E_{Chemo} \quad \textbf{(Eq.1)}$$

Exposure-independent model:

$$K_{kill} = E_{Dato} * E_{Pembro} * E_{Chemo} \quad \textbf{(Eq.2)}$$

Differential equation defining TS dynamics:

$$\frac{d(TS)}{dt} = K_{grow} * TS - K_{kill} * e^{-\lambda * t} * TS \quad \textbf{(Eq.3)}$$

Closed-form equation defining TS dynamics:

$$TS(t) = Baseline\ TS * e^{\left[\frac{K_{kill} * (e^{-\lambda * t} - 1)}{\lambda} + K_{grow} * t\right]} \quad \textbf{(Eq.4)}$$

E_{Chemo} was separately estimated as effect of carboplatin (E_{Carbo}) and cisplatin (E_{Cis}). λ, resistance to drug effect; AUC_τ, cycle-wise area under the curve of Dato-DXd; K_{grow}, first-order rate constant for tumor growth; K_{kill}, first-order rate constant for combined multiplicative drug effect of Dato-DXd (E_{Dato}), pembrolizumab (E_{Pembro}), and platinum chemotherapy (E_{Chemo}).

Table 1. Parameter estimates of the full model for TGI

Parameter	Unit	Covariate[a]	Estimate[a]	95% CI
	1/day	–	0.00335	0.00281, 0.00400
	–	Treatment-naïve	2.01	1.40, 2.88
	–	Last line IO	1.66	0.978, 2.82
E_{Dato}	–	Squamous histology	0.884	0.620, 1.26
	–	Female	1.08	0.775, 1.50
	–	ADA+ without NAb	0.643	0.412, 1.00
	–	ADA+ with NAb	1.23	0.790, 1.92
	–	PD-L1 <1%	1.00 FIXED[b]	–
E_{Pembro}	–	PD-L1: 1–49%	1.70	1.20, 2.40
	–	PD-L1 >50%	1.51	1.01, 2.26
E_{Carbo}	–	–	0.947	0.663, 1.35
E_{Cis}	–	–	1.51	0.981, 2.34
λ	1/day	–	0.0118	0.00844, 0.0164
	1/day	–	0.000631	0.000213, 0.00187
	–	Former smoker	2.53	1.08, 5.91
	–	Current smoker	1.47	0.449, 4.81
K_{grow}[c]	–	Liver metastasis	1.96	1.01, 3.78
	–	Bone metastasis	1.01	0.497, 2.04
	–	Brain metastasis	0.642	0.302, 1.37
	–	ECOG PS=1	0.817	0.441, 1.51
	–	Asian	0.415	0.236, 0.730

[a]Covariate effects are shown as fold-change of the respective parameter estimate.
[b]Fixed because the estimate was close to null in PD-L1 ≤1%.
[c]Box-Cox shape parameter [95% CI] for K_{grow} was –0.387 [–0.547, –0.226].

The variances (CV) of E_{Dato}, λ, and K_{grow} were 114%, 109%, and 1730%, respectively, with respective shrinkage of 18.7%, 30.5%, and 34.1%. Corr(E_{Dato}, K_{grow}) = –0.0236, Corr(K_{grow}, λ) = –0.318, and Corr(E_{Dato}, λ) = 0.583. Additive error = 1.48 mm; proportional error (CV) = 7.22%.

Table 2. Parameter estimates of the full logistic regression model for ORR

Parameter	Predictor[a]	Estimate[a]	95% CI[c]
Baseline probability of BOR (CR/PR)	–	0.0910	0.0277, 0.265
	Log (AUC_1 of Dato-DXd)	1.17[b]	0.707, 1.95
	Age	0.564[b]	0.356, 0.850
	ECOG=1	2.64	1.15, 6.16
	Treatment-naïve	3.82	1.37, 11.4

[a]A predictor effect represents the odds ratio compared to the baseline probability.
[b]Effect size corresponds to one SD increase in the predictor.
[c]95% credible interval of the posterior distribution; predictors are reported only if the 95% CI did not include the null value (except exposure).

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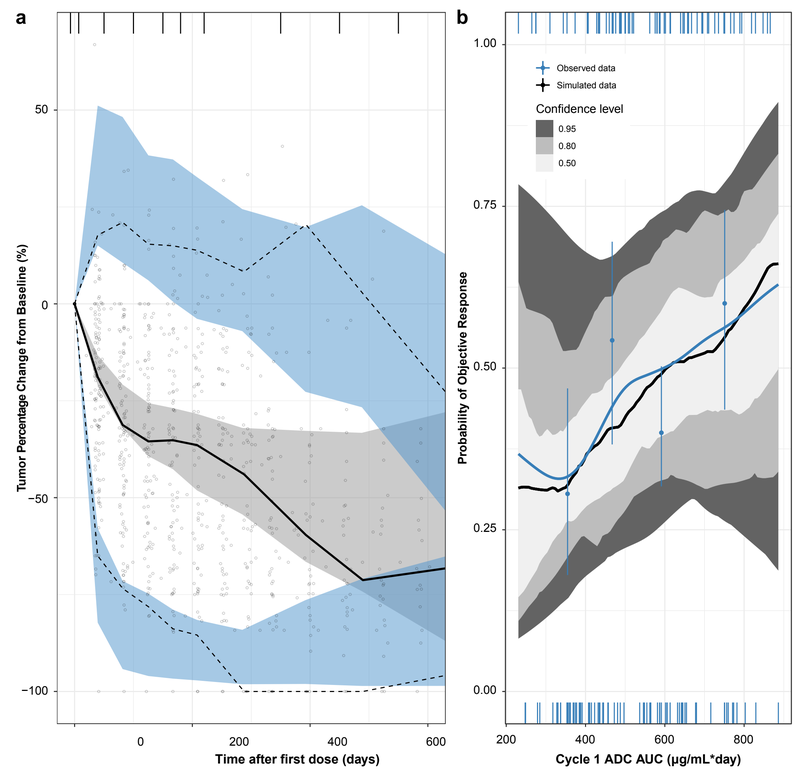
ABBREVIATIONS

ADA, antidrug antibodies; ADC, antibody–drug conjugate; a/m, advanced/metastatic; AUC, area under the curve; AUC_τ, cycle-wise area under the curve; BOR, best overall response; CI, confidence interval; C_{max}, maximum concentration; C_{min}, minimum concentration; CR, complete response; CrI, credible interval; CV, coefficient of variation; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*m, epidermal growth factor receptor-mutated; Eq, equation; ER, exposure–response; HER2−, human epidermal growth factor receptor-negative; HR+, hormone receptor-positive; IO, immune-oncology treatment; LPIO, last prior line of therapy with an IO; NAb, neutralizing antibodies; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PLT, prior line of therapy; Q3W, every 3 weeks; SD, standard deviation; TGI, tumor growth inhibition; TROP2, trophoblast cell surface antigen 2; TS, tumor size.

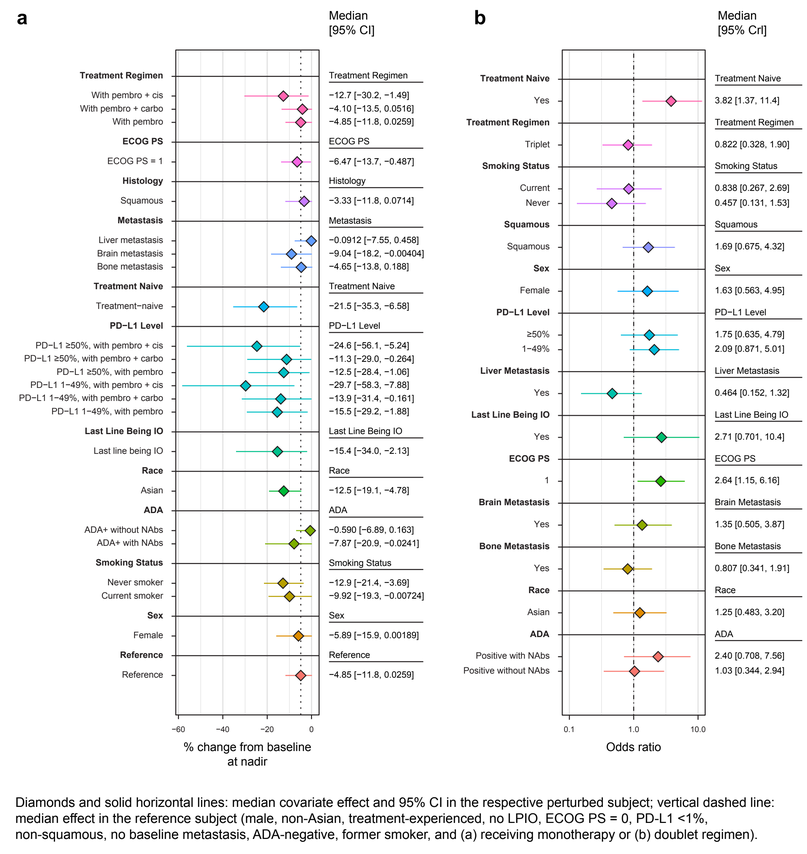
Figure 2. Graphical evaluation of the full TGI (a) and ORR (b) models



(a) Visual predictive check of the final TGI model. Open circles: observed data; solid and dashed lines: 50th, 2.5th, and 97.5th percentiles of the observed data, respectively. Shaded areas: 95% CI of the simulated percentiles; tick marks along the top of each plot represent the boundaries between time bins.

(b) Posterior predictive check of the full ORR model. Black and blue lines: mean of generalized additive model fits of the simulated (n=200) and observed data, respectively; gray bands: 50%, 80%, and 95% credible intervals of the simulations; blue points and error bars: observed mean response and Wilson's 95% CI, respectively, within each exposure quartile; blue ticks on the top and bottom of the panel represent the responders and non-responders, respectively.

Figure 3: Univariate analysis of covariate effects on the (a) percent change in TS from baseline at nadir (%TS_{nadir}) and (b) the odds ratio of the BOR of CR/PR



Diamonds and solid horizontal lines: median covariate effect and 95% CI in the respective perturbed subject; vertical dashed line: median effect in the reference subject (male, non-Asian, treatment-experienced, no LPIO, ECOG PS = 0, PD-L1 <1%, non-squamous, no baseline metastasis, ADA-negative, former smoker, and (a) receiving monotherapy or (b) doublet regimen).

CONCLUSIONS

- Tumor size response was characterized by a TGI model incorporating the multiplicative combination effects. The model indicated that the combination of Dato-DXd + pembrolizumab ± platinum chemotherapy continued to elicit durable tumor size reduction and improved ORR with the increase of Dato-DXd exposure in patients with a/m NSCLC
- Models predicted greater tumor size reduction and a higher ORR in treatment-naïve patients compared to treatment-experienced patients, supporting the evaluation of Dato-DXd + pembrolizumab ± platinum chemotherapy in the 1L setting in the ongoing pivotal phase 3 TROPION-Lung07 and TROPION-Lung08 studies
- Key baseline patient characteristics associated with antitumor response were identified and warrant further evaluation in ongoing phase 3 studies of Dato-DXd in these combination regimens
- Limitations: TROPION-Lung02 was a nonrandomized study and effect of covariates (including regimen effect and PD-L1 status) could not be estimated with a high degree of confidence due to the limited sample sizes

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