Applying a quantitative system pharmacology (QSP) model to inform KRAS^{G12C} covalent inhibitors' PK driver level needed for efficacy in patients with non-sma cell lung cancer (NSCLC)

Poster I-28

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INTRODUCTION

KRAS mutation occur in 30% of all human cancers [1], however, this target is known to be undruggable until recently with approvals of KRAS^{G12C} covalent inhibitors sotorasib [2] and adagrasib [3] for NSCLC indication. In patients, occurrence of KRAS nucleotide cycling equilibrium between unbound KRAS^{G12C}, KRAS^{G12C} bound with GDP and KRAS^{G12C} bound with GTP forms was found [1]. Among them, KRAS^{G12C} with GTP form, elicits oncogenic signals [4]. As a treatment, the KRAS^{G12C} inhibitors bind covalently with mutated GDP-bound form of KRAS^{G12C} at switch II pocket (SIIP) for inhibition to disrupt the KRAS oncogene equilibrium state and thereby its KRAS^{G12C} signaling pathway [1]. We developed a QSP model describing the covalent binding kinetics of KRAS^{G12C} inhibitors in tumor, tumor KRAS^{G12C} target occupancy rate (TOR), phosphorylated extracellular-signal-regulated kinase (pERK) downstream effect, and tumor growth inhibition (TGI) in H358 tumor-bearing mice. The model informed the physchem properties of a KRAS covalent inhibitor to be potent, the PK driver for efficacy, and the level of PK driver needed for efficacy of preclinical candidates in patients with NSCLC.

OBJECTIVES

- **Develop a QSP model of KRAS^{G12C} using in vitro data and in vivo PK/PD/efficacy data in H358 tumor-bearing mice**
- **Validate the model prediction with the reported minimum effective plasma exposure from adagrasib**
- **Estimate the level of PK driver of KRAS^{G12C} inhibitors needed for efficacy of the preclinical candidates in patients with NSCLC**

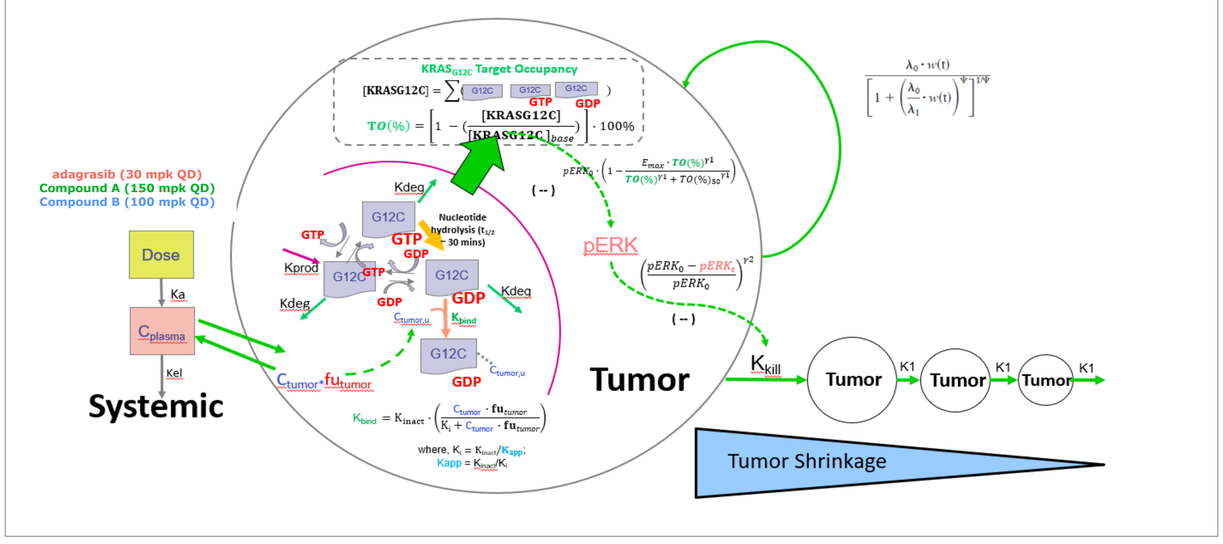
METHODS

Serial sampling of plasma and tumor PK, tumor TOR, pERK/ERK, and TGI (Tumor growth Inhibition) in H358 tumor-bearing mice model following daily dosing (30, 100, 150 mg/kg [mpk]) of KRAS^{G12C} inhibitors (adagrasib, and two preclinical candidates [Compounds A and B]) for either 3 or 10 days. The model development was performed using Stochastic Approximation Expectation Maximization (SAEM) in Monolix version 2020 (Lixoft®). The simulations were performed using R-based Monolix Suite Simulx version 2020 (Lixoft®).

RESULTS

The model constituted of a one-compartmental model for KRAS^{G12C} inhibitors plasma PK with a tumor penetration model [5] adapted from Wittrup et al. [6, 7, 8]. In the tumor, the nucleotide cycling model [1] was adopted and free KRAS^{G12C} inhibitors assumed to engage covalently with KRAS^{G12C} GDP form, depicted by a covalent binding model which consists of initial reversible binding followed by formation of covalent bond [9]. The key binding parameters, reversible binding equilibrium (K_i) and first-order constant of the chemical step (K_{inact}) were fixed with estimations from in vitro assays. In the model, different forms of KRAS^{G12C} were used to calculate TOR that links with downstream signal of pERK/ERK using a Emax inhibition model and followed by the link with TGI model [10] via a power function (***Figure 1***).

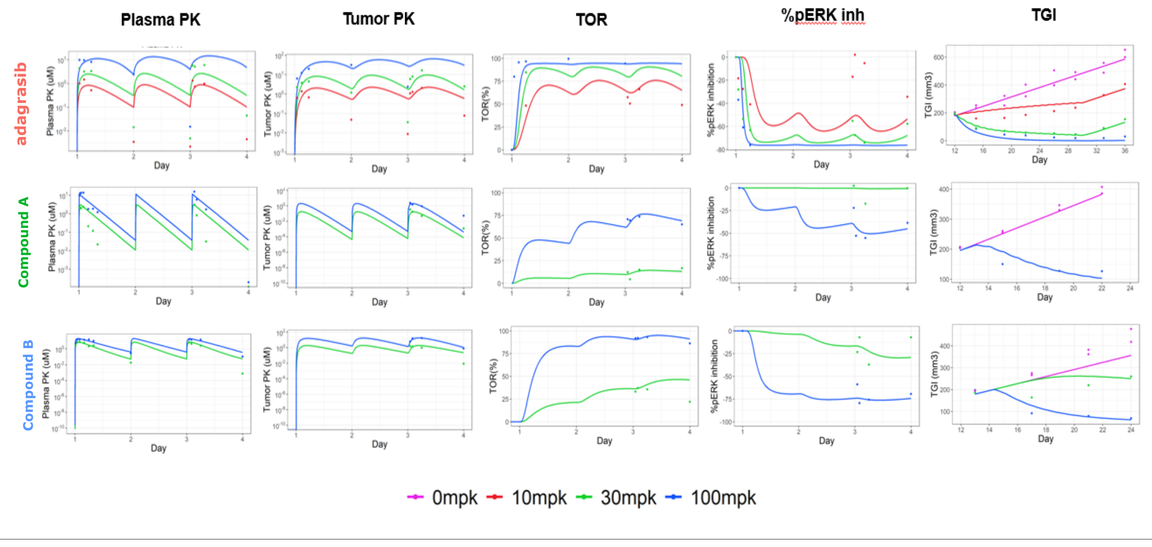
Figure 1: Model Structure



The model successfully fitted PK/PD/efficacy data of adagrasib, compounds A, and B for all the tested doses in mice (***Figure 2***).

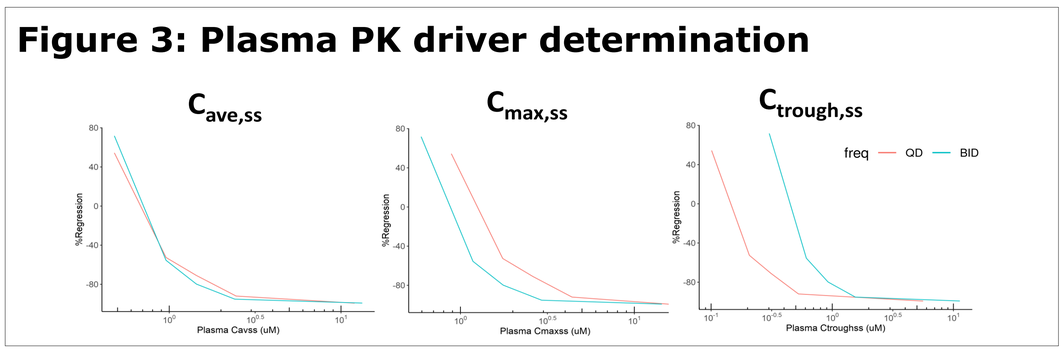
Figure 2: Model fits validation with PK/PD/Efficacy data from in H358 tumor-bearing mice

Solid lines denotes predicted PK/PD/Efficacy profiles
Dots denotes observed PK/PD/Efficacy



- The model predicted average total plasma concentration at steady-state (Cave,ss) as the PK driver. The superposition of the relationship between %tumor regression against plasma Cave,ss following QD and BID dosing (***Figure 3***), indicating Cave,ss is the PK driver, regardless of dosing frequency.

Figure 3: Plasma PK driver determination



- By defining 70% of tumor regression in mice as the target of efficacy in tumor-bearing mice, we predicted a consistent adagrasib Cave,ss needed for efficacy in NSCLC patients as compared to reported value (predicted 1.4 µM vs. 1.6 µM [11]) [***Figure 4 and Table 1***].
- Our precandidates, compounds A and B were predicted requiring 3x and 6x higher total plasma Cave,ss for efficacy than adagrasib for achieving 70% tumor regression, despite similar average free tumor concentrations (***Figure 4 and Table 1***).

Figure 4: Predicted total and free tumor PK needed for 70% tumor regression

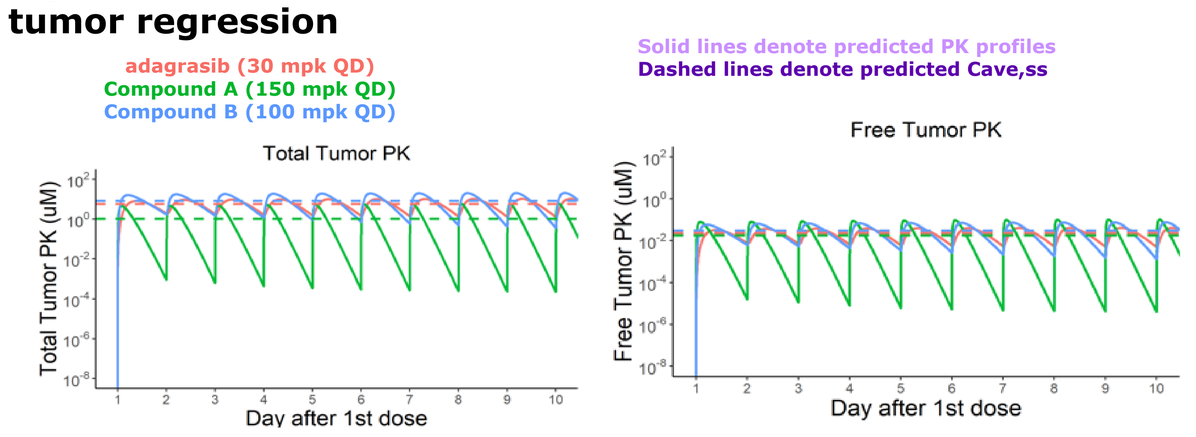


Table 1: Predicted and plasma & tumor exposure needed for 70% tumor regression

	QD Dose (mpk)	Cave,ss (µM)			Fold-change of Dose or Cave,ss relative to adagrasib			
		Plasma	Tumor		QD Dose	Plasma	Tumor	
		Total	Total	Free		Total	Total	Free
adagrasib	**30**	1	5.75	0.02	1	1	1	1
Compound A	**150**	3	1.02	0.02	5	3	0.2	1
Compound B	**100**	6	8.04	0.03	3	6	1.4	1.5

DISCUSSION

- Model predicted similar average free tumor concentrations for all the molecules suggested that a candidate with a higher fraction unbound in tumor would be favorable for its potency, which is warranted to be confirmed.

CONCLUSIONS

- **The model development in mice for KRAS^{G12C} covalent inhibitors was well validated to predict exposure needed in patients using clinically validated molecule adagrasib. It informed the level of Cave,ss needed for efficacy to project the active dose of preclinical candidates in patients with NSCLC.**

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