Dose Selection by a Model-Informed Drug Development (MIDD) Approach for Naporafenib and Trametinib Combination in Patients with Melanoma

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Background

- Naporafenib is a potent and selective adenosine triphosphate (ATP)-competitive inhibitor of the wild-type CRAF and BRAF protein kinases and mutant BRAF V600E. Naporafenib has been evaluated in combination with trametinib, a MEK inhibitor, as a treatment for patients with solid tumors.
- Multiple combination dosages of naporafenib (mg BID) + trametinib (mg QD) (i.e., 100/1, 200/0.5, 200/1. 400/0.5, 400/1, and 400/1 2 weeks on/2 weeks off), along with naporafenib monotherapy (100 to 1200 mg QD or 200 to 800 mg BID) and trametinib monotherapy (2 mg QD), were evaluated across 5 clinical trials (CLXH254X2101, CLXH254X2102, CLXH254C12201, SEACRAFT-1 and SEACRAFT-2)[1-4], to inform dose selection.

Objectives

- To recommend the combination dosage of naporafenib + trametinib for subsequent clinical development using a Model Informed Drug Development (MIDD) strategy.

Methods

- An MIDD framework, including population PK (PopPK) modeling, exposure-response (ER) analyses, and PK/PD modeling were used to integrate PK, safety, and efficacy data from multiple clinical trials and relevant PK/PD data from nonclinical pharmacology studies.
- A PopPK model was developed to characterize naporafenib PK and evaluate the effect of potential intrinsic and extrinsic covariate(s) on PK variability.
- With naporafenib efficacious concentration (C_{eff}) derived from PK/PD modeling of mouse xenograft models, popPK simulations were performed to predict target coverage at doses of interest for naporafenib.
- The potential ER relationships for the selected safety endpoints (e.g., Grade ≥ 3 (G3+) AEs or severe adverse events (SAEs), adverse events (AEs) leading to dose modifications, skin-related AEs) were evaluated using logistic regression.
- The potential ER relationships for the efficacy endpoints (objective response rate (ORR), clinical benefit rate (CBR), and maximum change in tumor size from baseline) were evaluated using logistic regression or linear regression, as appropriate.
- As an orthogonal assessment, trametinib PopPK modeling and ER analyses were also performed. The trametinib PopPK model was based on a published model[5]. The trametinib ER analyses were performed by including trametinib exposure metrics and naporafenib exposure quartile as potential covariates.

References:

[1] Filip Janku, et al. First-in-human study of naporafenib (LXH254) with or without spartalizumab in adult patients with advanced solid tumors harboring MAPK signaling pathway alterations, European Journal of Cancer, 196, 0959-8049(2024)

[2] Filippo de Braud et al. Initial Evidence for the Efficacy of Naporafenib in Combination With Trametinib in NRAS-Mutant Melanoma: Results From the Expansion Arm of a Phase Ib, Open-Label Study. J Clin Oncol 41, 2651-2660(2023).

[3] David Planchard, et al. A phase Ib study of the combination of naporafenib with rineterkib or trametinib in patients with advanced and metastatic KRAS- or BRAF-mutant non-small cell lung cancer. Lung Cancer, 197, 0169-5002 (2024),

[4] Alexander I. Spira et al. An open-label study to assess the safety and efficacy of naporafenib (ERAS-254) administered with trametinib in previously treated patients with locally advanced unresectable or metastatic solid tumor malignancies with RAS Q61X mutations (SEACRAFT-1). J Clin Oncol 42, TPS3178-TPS3178(2024).

[5] Ouellet D, Kassir N, Chiu J, et al. Population pharmacokinetics and exposure-response of trametinib, a MEK inhibitor, in patients with BRAF V600 mutation-positive melanoma. Cancer Chemother Pharmacol,77(4):807-17(2016).

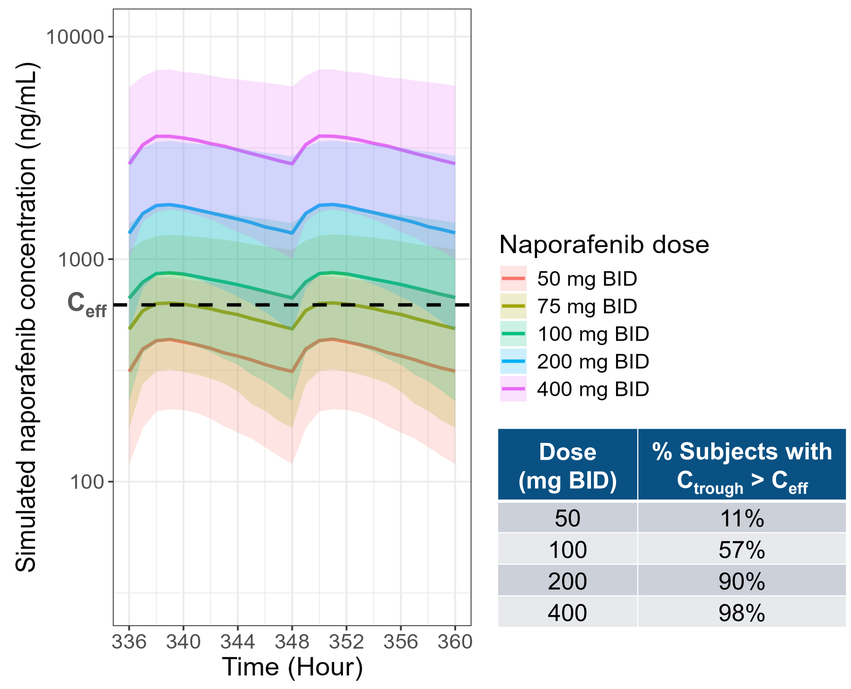
Results

- Naporafenib PK was adequately described by a two-compartment model with first-order absorption and elimination. Body weight and baseline albumin were evaluated using power models and were identified as statistically significant covariates for CL/F and Vc/F **(Table 1)**.
- PopPK-based target coverage simulations suggested naporafenib dosages of 200 and 100 mg BID will result in steady-state trough concentrations exceeding the target C_{eff} in 90% and 57% of subjects, respectively **(Figure 1)**.
- Safety ER analyses suggested that naporafenib exposure and trametinib dose positively correlated with the probability of G3+ AEs or any grade SAEs, and AEs leading to dose reduction/interruption. Higher trametinib dose, instead of naporafenib exposure, was found to be associated with increased risk for developing any grade skin-related AEs. No significant ER relationships were identified for other prespecified safety endpoints **(Figure 2)**.
- In the efficacy ER analyses, the final ER models included an interaction term (naporafenib exposure × trametinib dose) as an additional predictor besides naporafenib exposure and trametinib dose, given preclinical evidence of pharmacologic synergy between naporafenib and trametinib. This interaction term showed a statistically significant positive association with all three efficacy endpoints. **(Figure 3)**
- Findings from orthogonal trametinib-based ER analyses were generally consistent with naporafenib-based ER analyses.

Table 1. Parameter Estimates of the Naporafenib PopPK Model

Parameters	Estimates	RSE(%)
CL/F (L/hr)	10.3	2.32
Vc/F (L)	289	3.96
Ka (1/hr)	0.795	5.98
ALAG (hr)	0.376	0.728
Q/F (L/hr)	2.12	37.6
Vp/F (L)	282	15.9
Between subject variability (%)		
CL/F	42.90	11.1
Vc/F	55.68	12.3
Ka	82.58	14.1
Covariate Effect		
Albumin effect on CL/F	1.34	15.4
Albumin effect on Vc/F	0.746	35.3
Body weight effect on CL/F	0.560	18.2
Body weight effect on Vc/F	0.585	22
Residual Error		
Additive error	2.5 Fix	–
Proportional error (%)	35.0	2.14

Figure 1. Naporafenib Target Coverage Simulations



Dose (mg BID)	% Subjects with $C_{trough} > C_{eff}$
50	11%
100	57%
200	90%
400	98%

Figure 2. Naporafenib Safety ER Analysis for ≥ Grade 3 AEs or SAEs

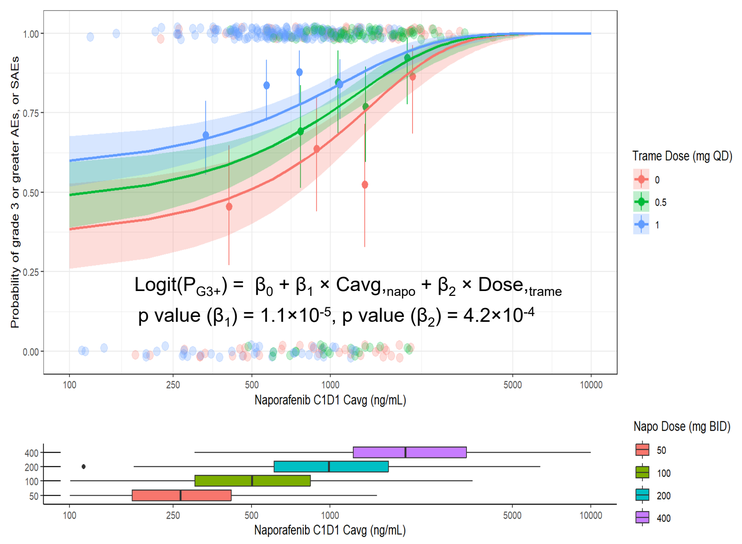
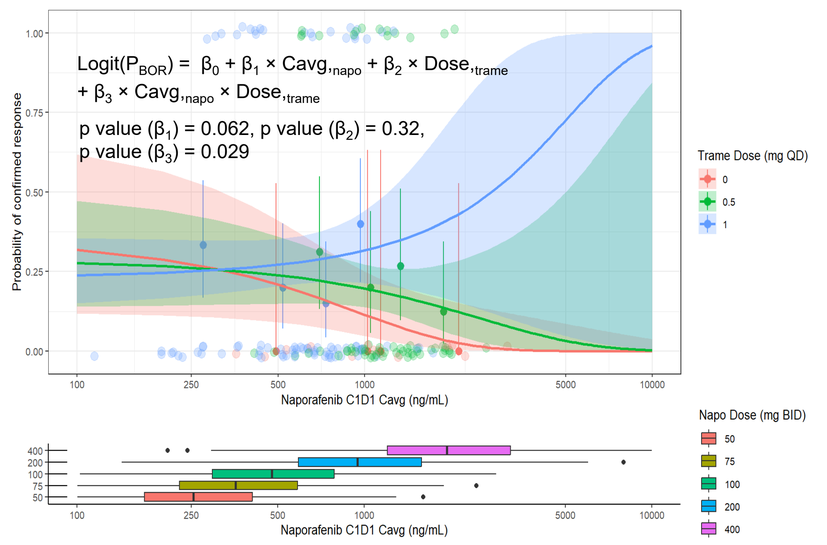


Figure 3. Naporafenib Efficacy ER Analysis for Confirmed Best Overall Response



Conclusions

- The application of MIDD provided rationale and justification for selection of the naporafenib + trametinib combination dose.
- Target coverage simulations suggested that naporafenib 200 mg BID provides optimal target coverage, while the 100 mg BID represents a minimum effective dose. The efficacy ER analyses revealed that higher doses of both agents are expected to achieve greater combination benefit, as evidenced by the significant interaction term identified. The safety ER analyses suggested that dose modifications may help to manage and improve safety and tolerability.
- Collectively, the integrated modeling and simulation supported selecting naporafenib 200 mg BID + trametinib 1 mg QD (200/1) for subsequent clinical development. The 200/1 dose is expected to have the most favorable benefit/risk profile and preserve opportunities to further improve safety and tolerability through dose reduction while maintaining anticipated clinical benefit.