Phase 1 Interim Population PK/PD Modeling and Recommended Phase 2 Dose Exploration for IMM-1-104, A Novel Concept Oral Deep Cyclic Inhibitor of MEK

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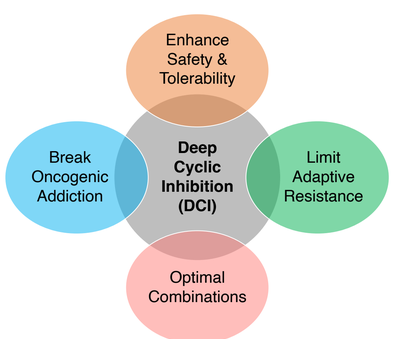
Introduction

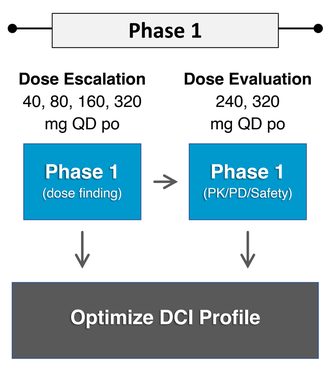
Activating RAS mutations are present in a third of all cancers. Approved MEK inhibitors are designed to chronically inhibit the downstream signaling of RAS-RAF-MEK-ERK, causing significant toxicity.

IMM-1-104 was designed to have high oral bioavailability, a short half-life and a near-zero drug trough, which drives Deep Cyclic Inhibition (DCI). The first-in-human Study IMM1104-101 recently completed Phase 1 dose expansion (1,2), and the current PK/PD analysis was aimed at identifying Phase 2 dosing regimens that achieve the desired DCI pattern in targeted patient populations (advanced solid tumors with high prevalence of RAS mutations, e.g., pancreatic, lung, melanoma).

Deep Cyclic Inhibition (Thesis)

- Pulsatile inhibition of MEK
- Improve safety & tolerability
- Reduce adaptive resistance
- Disrupt MAPK pathway addiction
- Expand therapeutic combinations





Objectives

To provide dose justification and inform on IMM-1-104 efficacy in patients, by developing a population PK model of IMM-1-104 that describes the relationship between IMM-1-104 exposure and phosphorylated mitogen-activated protein kinase (p-MEK) and extracellular signal-regulated kinase (p-ERK).

Data/Methods

- PK sampling (fasted) C1D1 + C1D15: pre-dose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 h post-dose
- PD sampling C1D1 + C1D15: pre-dose, 1, 2, 4, 6, 8 and 24 h post-dose
- Ex-vivo surrogate PD endpoint was the inhibition of MEK and (downstream) ERK phosphorylation in the A549 (KRAS-G12S) cell line, expressed as the ratio of phosphorylated/total kinase
- The population modelling analyses of the IMM-1-104 PK and PD (i.e., phosphorylated (p)-ERK/total (t)-ERK and p-MEK/t-MEK) data were performed using NONMEM version 7.5.3
- IMM-1-104 PK: To establish the base model, several absorption models were tested, and WT was added as a mechanistic covariate. Then, exploratory covariates (demographic, disease manifestation and severity, co-medication, etc) were investigated
- p-ERK/t-ERK and p-MEK/t-MEK: population models describing the effect of IMM-1-104 exposure on p-ERK/t-ERK and on p-MEK/t-MEK were developed. The final models were used to simulate p-ERK/t-ERK or p-MEK/t-MEK response (with median and 90% prediction interval (PI)) for different dose groups to evaluate the time from nadir returning to 20% maximum phospho-protein reduction

IMM-1-104 Phase 1 Data Visualization, PK & PD

Figures 1-2 (IMM-1-104 PK): plasma concentration values were available for 45 subjects (1 at 40 mg, 1 at 80 mg, 3 at 160 mg, 19 at 240 mg and 21 at 320 mg), the majority of whom have metastatic pancreatic cancer. Profiles of individual observations versus time suggest a rapid, complex and highly variable absorption profile. The exposure appears not to increase proportionally with dose, as shown with dose-normalized concentrations.

Caveat: IMM-1-104 dissolution is sensitive to stomach pH. While use of acid-reducing agents was restricted, there were some unusually low PK exposures that may have influenced modelling assessments.

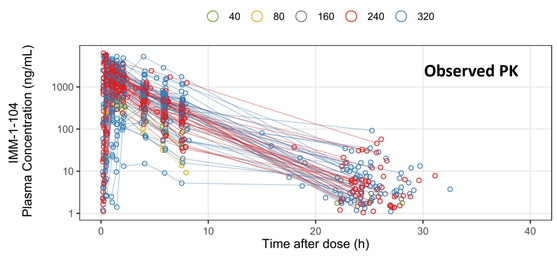


Figure 1 – Individual observed IMM-1-104 plasma concentrations versus time after dose (semi-logarithmic scale).

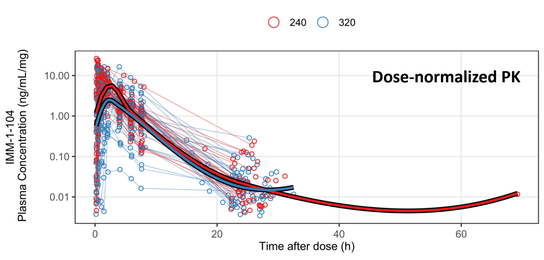


Figure 2 – Dose-normalized individual observed IMM-1-104 plasma concentrations versus time after dose after 240 or 320 mg (semi-logarithmic scale). Thick lines represent the GAM smooth of the data in each dose level.

Figures 3-4 (p-ERK/t-ERK): observations were available for 45 subjects (1 at 40 mg, 1 at 80 mg, 3 at 160 mg, 19 at 240 mg and 21 at 320 mg). Profiles of individual observations versus time suggest a rapid and direct exposure–effect relationship.

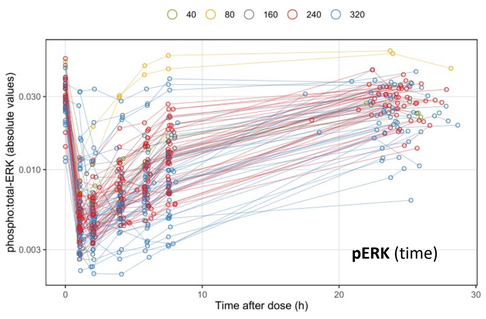


Figure 3 – Individual observed (absolute value) versus time after dose (semi-logarithmic scale).

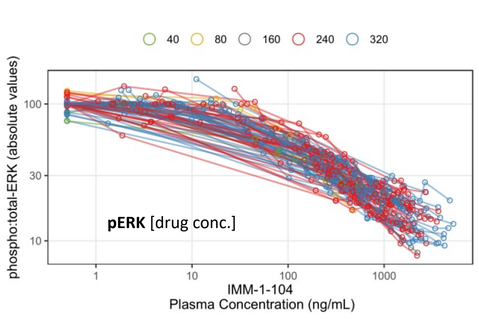


Figure 4 – Individual observed versus individual observed IMM-1-104 plasma concentrations (logarithmic scale).

Figures 5-6 (p-MEK/t-MEK): observations were available for 12 patients (1 at 40 mg, 1 at 80 mg, 3 at 160 mg, 3 at 240 mg and 4 at 320 mg). Profiles of individual observations versus time suggest a rapid and direct exposure–effect relationship.

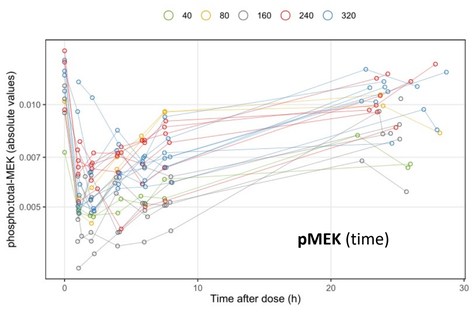


Figure 5 – Individual observed (absolute value) versus time after dose (semi-logarithmic scale).

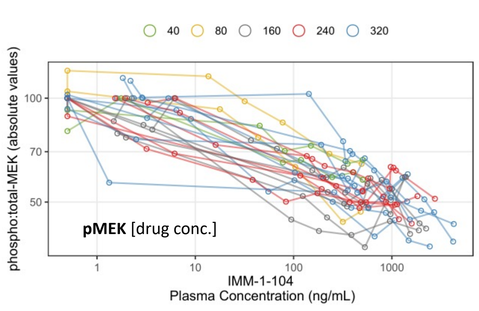
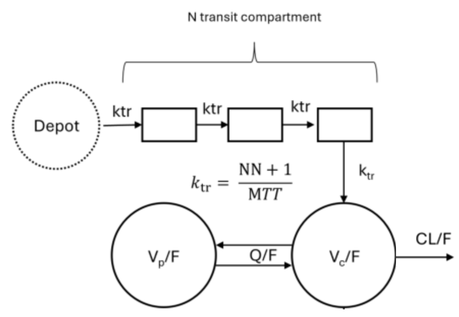


Figure 6 – Individual observed versus individual observed IMM-1-104 plasma concentrations (logarithmic scale).

Population PK Modeling

Figure 7 (Population Pharmacokinetics):

- Two-compartment model
- Absorption transit compartments
- Weight-based allometric scaling applied to clearance and distribution volume parameters
- Dose effect on bioavailability to account for tentative less than dose proportional increase in exposure



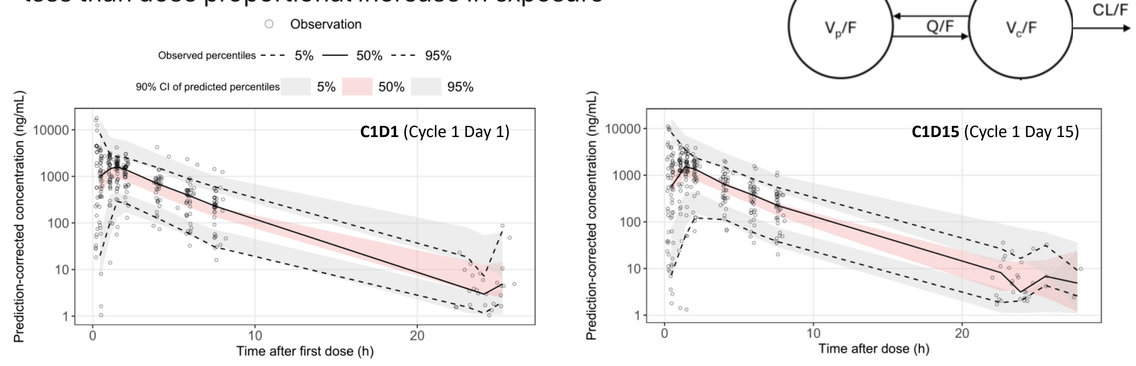


Figure 7 – Prediction-corrected visual predictive check of IMM-1-104 PK plasma concentrations vs time after Dose, C1D1 (left), C1D15 (right); semi-logarithmic scale.

PK/PD Modeling

Figures 8-10 (Pharmacokinetics/Pharmacodynamics):

- Maximal inhibition (target engagement) achieved mostly at 1 h (note: 1st PD time point), returning to baseline p-ERK or p-MEK levels between 8 and 24 h
- Direct model, with a proportional inhibitory effect (on baseline)
- Informed by observed plasma concentrations

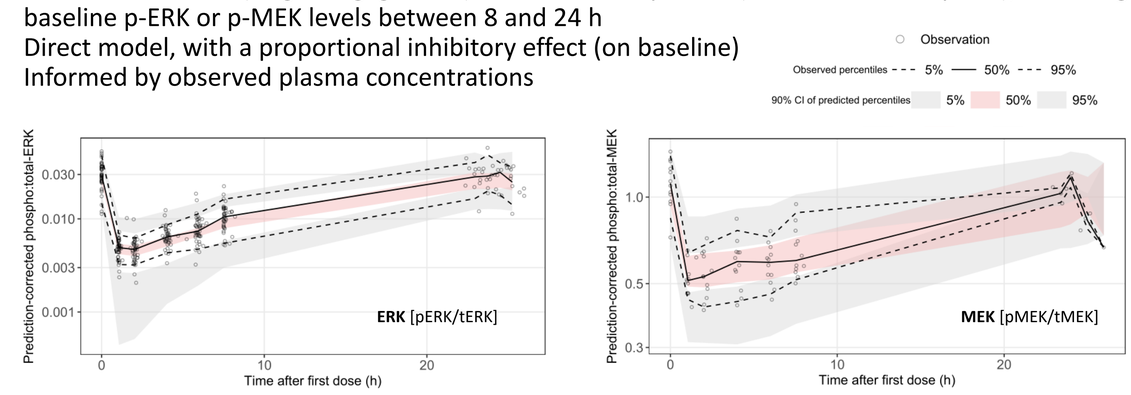
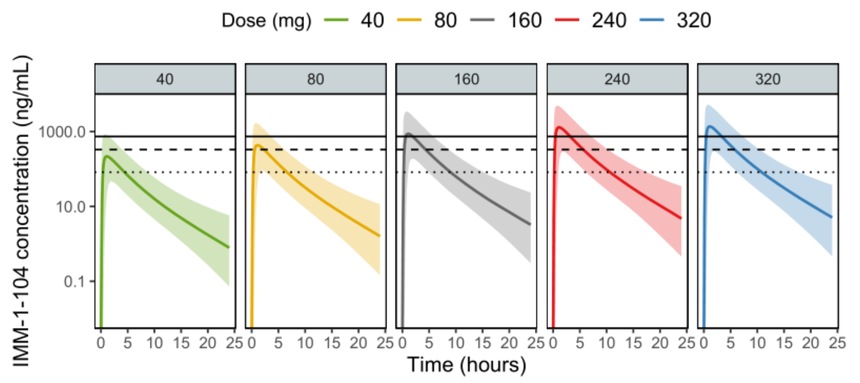
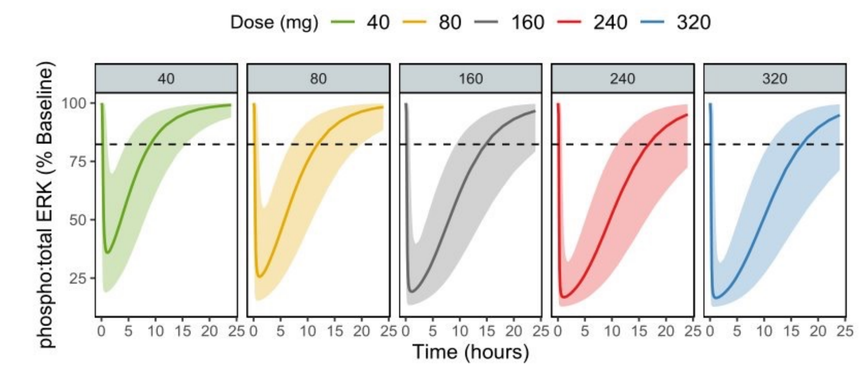


Figure 8 – Prediction-corrected visual predictive check of p-ERK/t-ERK (left) and p-MEK/t-MEK (right) versus time after Dose, at C1D1 (semi-logarithmic scale).



Parameter	40 mg	80 mg	160 mg	240 mg	320 mg
Median time above IC_{50} [h] (90% PI)	3.9 (0-8.1)	6.2 (2.4-11.2)	8.7 (4.5-14.8)	10.3 (5.9-17.0)	10.6 (6.0-17.0)
Median time above IC_{80} [h] (90% PI)	0 (0-3.4)	1.8 (0-5.6)	3.9 (0-8.2)	5.2 (1.6-9.7)	5.4 (1.6-10.0)
Median time above IC_{90} [h] (90% PI)	0 (0-1.1)	0 (0-3.0)	1.5 (0-5.2)	2.7 (0-6.5)	2.8 (0-6.7)
$IC_{50/80/90}$: Concentration at 50%, 80% and 90% of maximum reduction, PI: prediction interval					

Figure 9 – Populations simulations of IMM-1-104 plasma concentrations (ng/mL) versus time (h). Solid lines show the median concentration and shaded areas the 90% prediction interval. The dotted, dashed and solid black lines represent the IC_{50}, IC_{80} and IC_{90}, at 82.2 ng/mL, 329 ng/mL and 740 ng/mL, respectively.



Parameter	40 mg	80 mg	160 mg	240 mg	320 mg
Median nadir of p-ERK/t-ERK [% Baseline] (90% PI)	31.3 (17.5-58.8)	22.7 (14.6-43.6)	17.5 (13.0-31.0)	15.6 (12.6-25.3)	15.3 (12.5-24.9)
Median time to nadir [h] (90% PI)	0.9 (0.2-3.0)	0.9 (0.2-3.1)	0.9 (0.2-3.0)	0.9 (0.2-3.0)	0.9 (0.2-3.0)
Median time from nadir back to 20% of maximum inhibition [h] (90% PI)	7.6 (3.2-14.0)	10.3 (5.6-17.7)	13.6 (7.8-21.0)	15.3 (9.3-21.8)	15.4 (9.4-21.8)
% of subjects getting back to 20% of maximum inhibition	99.8	98.9	94.4	89.8	88.1

Figure 10 – Populations simulations of phospho:total ERK (% baseline) versus time (h) on a linear scale for the different dose groups. Solid lines are colored by treatment group. The dashed black line represents 20% of maximum reduction.

Conclusions

- For both 240 and 320 mg candidate doses explored per FDA Optimus guidance, the plasma concentrations are predicted to be above the pERK IC_{90} for on average 2.7 and 2.8 h, respectively (Fig. 9)
- Vast majority of subjects (90% and 88% at 240 and 320 mg QD, respectively) are predicted to have less than 20% of maximum inhibition at the daily drug trough (Fig. 10)
- PK/PD modeling combined with Phase 1 safety and activity data suggests that 240 and 320 mg are viable doses that promote DCI of the MAPK pathway

References/Acknowledgement

1. A Phase 1/2a Study of IMM-1-104 in Participants with Previously Treated, RAS-Mutant, Advanced or Metastatic Solid Tumors - NCT05585320
2. V Chung et al, Preliminary phase 1 safety and activity of IMM-1-104, an orally dosed universal RAS inhibitor that drives deep cyclic inhibition of the MAPK pathway at MEK, in patients with advanced unresectable or metastatic solid tumors - ESMO 2024, Barcelona, Spain

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