Predicting activity of IMM-1-104 as single agent and in combination for patients with RAS or RAF mutant tumors

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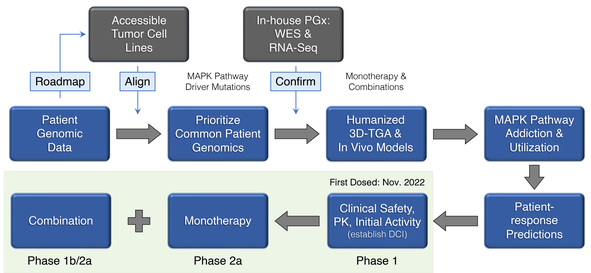
Introduction

Many tumors are addicted to MAPK pathway activation, including the > 20% of human tumors with mutations in RAS or RAF[1]. IMM-1-104 is an oral once-daily treatment currently in Phase 1 patients with advanced or metastatic RAS-mutant solid tumors [NCT05585320]. To date, drugs disrupting the MAPK pathway have done so chronically, leading to dose-limiting toxicities (DLTs) and poor response durability. In contrast, IMM-1-104 was designed to provide deep cyclic inhibition (DCI) of the MAPK pathway via features including a unique pharmacokinetic (PK) profile with high peak plasma drug levels and a near zero, daily drug trough. This promotes pulsatile inhibition of MEK, depriving tumors of sustained signaling of a critical oncogenic pathway while limiting toxicity and durability issues associated with chronic MEK inhibition. In Phase 1a dose escalation, no DLTs were observed, the plasma drug half-life was approximately 2-hours, and pharmacodynamic (PD) data were consistent with DCI.

Experimental Procedures

Using cancer-specific, patient-aligned cell lines, IMM-1-104 activity was characterized in the humanized 3D-Tumor Growth Assay (3D-TGA), which more accurately replicates human tumor biology and better predicts *in vivo* tumor responses versus 2D culture[2,3]. Antitumor activity of IMM-1-104 was evaluated in over 190 tumor models spanning 20 distinct tumor types in the humanized 3D-TGA (**Fig. 1**). Pharmacogenomic data were used to generate a model predictive of response to IMM-1-104 and identify biomarker-aligned patient subpopulations.[4] Selected model predictions were then tested in specific tumor xenograft models in female BALB/c nude mice.



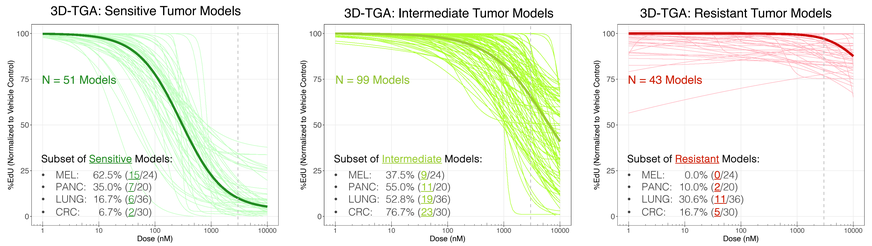
NCT05585320 (Phase 1/2A)

IMM-1-104 Phase 1 Trial Summary:

- Drug Plasma Half-life: ~2 hours
- Plasma C_{max} Free-fractions: ~1-3 uM
- Near Zero Drug Trough: YES
- pERK inhibition over 90%: YES
- RP2D Evaluation: 240 or 320 mg QD
- Planning multiple monotherapy trials
- Planning initial drug combination trials

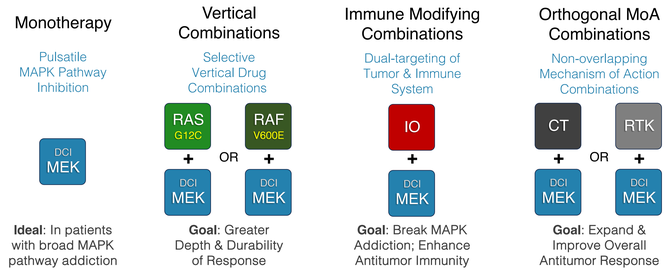
Expanded Benchmarking of IMM-1-104 Responses in the Humanized 3D-TGA

Figure 1: 3D-TGA IMM-1-104 Dose Responses (N = 193 Models; > 20 Tumor Types)



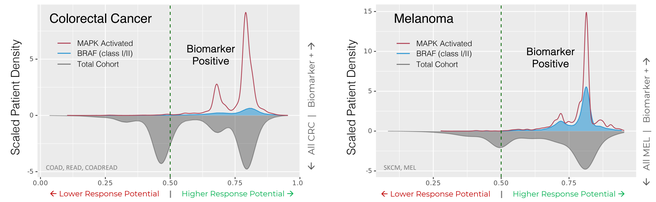
Cell lines tested in 3D-TGA (N=193) were assigned response of sensitive (IC50 < 1uM), intermediate (IC50 ≥ 1 and >25% reduction at 10uM), and resistant otherwise
The dark line on each plot represents the median of the individual curves; Dotted vertical line matches C_{max} IMM-1-104 drug free-fraction levels achieved at 320 mg QD p.o.
Major tumor types with activation mutation in the MAPK pathway upstream of MEK (Biomarker Positive): MEL (23/24), PANC (19/20), LUNG (33/36), CRC (28/30)

Figure 2. Emergent IMM-1-104 Monotherapy and Combinations



DCI = Deep Cyclic Inhibition of the MAP Kinase pathway is a core feature of Immuneering's Dual MEK inhibitor, IMM-1-104
[IO = immune oncology; CT = Cytotoxic Therapy; RTK = Receptor Tyrosine Kinase]

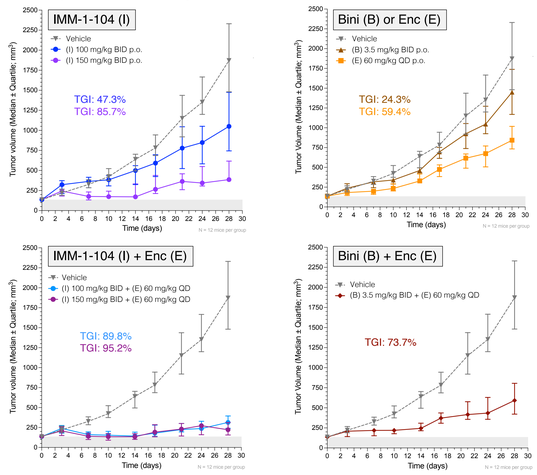
Figure 3. Mapping BRAF Variant Subsets in GENIE® 13.1



Shown for each indication: kernel density plot of probability of predicted response
for entire cohort (projected onto the negative y-axis), and biomarker+ subset (positive y-axis)

Vertical Combination of IMM-1-104 with BRAF Inhibitor

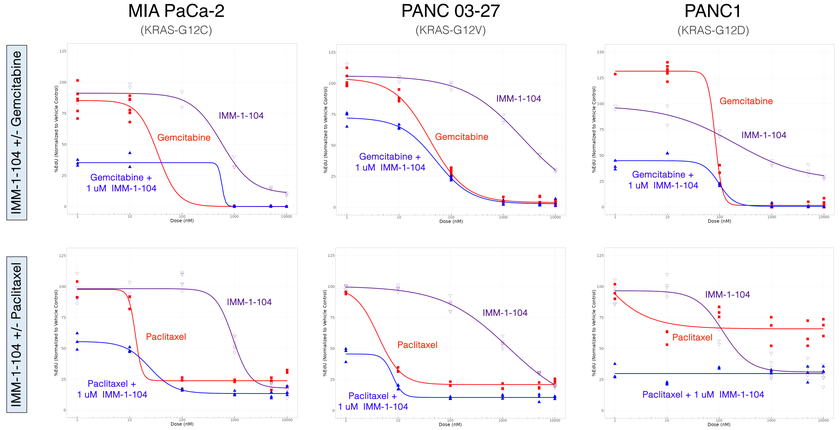
Figure 4. Superior Activity of IMM-1-104 in HT-29 (BRAF^{V600E} CRC)



HT-29 BRAF^{V600E} Colorectal Cancer (CRC) xenograft tumor model in athymic nude mice. Binimetinib (MEK inhibitor) and encorafenib (BRAF inhibitor) were commercially purchased. Tumor Growth Inhibition (TGI) % = [1-(Ti-To)/(Ci-Co)]x100%. No median body weight loss was noted.

IMM-1-104 Orthogonal Combinations with Cytotoxic Agents in Pancreatic Cancer

Figure 5. Enhanced Antitumor Activity of IMM-1-104 with Gemcitabine and Paclitaxel



IMM-1-104 ± CT dose response curves in the humanized 3D Tumor Growth Assay (3D-TGA)[2,3]. Three human pancreatic cancer cell models were selected based on patient alignment scores, where each model's mutational profile mapped to three distinct subsets of GENIE v13.1 patients categorized as pancreatic adenocarcinoma. Gemcitabine and paclitaxel (CT agents commonly used for treatment of pancreatic cancer) were commercially purchased.

Conclusions

IMM-1-104 is a short-lived dual MEK inhibitor (MEKi) that works through Deep Cyclic Inhibition (DCI) and is currently under evaluation in early clinical development with an initial focus on advanced RAS mutant solid tumors (NCT05585320). Expanded preclinical and translational modeling support broad potential as monotherapy and in combination for MAPK-pathway mutations upstream of MEK. Assessment of IMM-1-104 in over 190 patient-aligned 3D tumor models demonstrated diverse responses across a wide range of MAPK-driven tumor types, including those with RAS or RAF mutations. In addition to RAS, these and prior data support potential for IMM-1-104 treatment in RAF-mutant disease. Here, IMM-1-104 was tested alone and in a vertical combination with encorafenib (HT-29 colorectal BRAF^{V600E} xenograft tumor model). The *in vivo* DCI MEKi combination of IMM-1-104 with encorafenib resulted in deeper regressions and superior durability in a head-to-head comparison versus binimetinib plus encorafenib. In an orthogonal combination, 3D modeling revealed IMM-1-104 combination potential with cytotoxic agents in pancreatic tumor models (*in vivo* combination studies are underway). Immuneering's integrated translational platform with integrated bioinformatics utilizes patient-aligned model systems to identify key factors that help predict response to IMM-1-104 and its unique DCI profile. A logical extension to this workstream is development of rational drug-drug combination opportunities that may aid in future clinical development strategies.

References

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