Activity of IMM-1-104 Alone or in Combination with Chemotherapy in RAS-altered Pancreatic Cancer Models

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Introduction

Addiction to the MAPK pathway drives a large proportion of cancers, and pancreatic tumors almost universally display activation of the MAPK pathway and most commonly by way of RAS mutations. IMM-1-104, a once-daily oral treatment being evaluated in a Phase 1/2a trial for RAS-mutant solid tumors [NCT05585320], offers a novel deep cyclic inhibition (DCI) approach in disrupting the MAPK pathway at MEK. Traditionally, MAPK-targeted drugs inhibit the pathway chronically and are associated with serious class-effect toxicities and limited durability. In contrast, IMM-1-104 was uniquely designed to drive deep pulsatile inhibition of MEK, with the goal of improving tolerability and durability in MAPK-driven tumors. Recently released top-line results from the Phase 1 portion of the Phase 1/2a trial included the following observations: IMM-1-104 was well-tolerated, 100% suppression of acquired RAS mutations and ≥1 target lesion regressions in over half of patients treated with IMM-1-104 at 240 or 320 mg QD.

Experimental Procedures

IMM-1-104 responses in humanized 3D tumor growth assays (3D-TGA), which better predict *in vivo* tumor response relative to 2D culture[1,2], were combined with NGS data using machine learning (ML) to refine a pharmacogenomic response model. Evaluation of databases such as AACR Project GENIE enabled prediction of patient alignment of preclinical models based on genomic profile, identification of patient populations displaying MAPK pathway addiction and projected sensitivity to IMM-1-104 mono- or combination therapy. To test combinations with approved chemotherapy agents, IMM-1-104, gemcitabine (GEM) and nab-paclitaxel (PAC) and 5-fluorouracil (5-FU) were evaluated in 3D-TGA and in a pancreatic tumor xenograft model with drugs alone or across multiple combinations.

Projecting MAPK Pathway Biomarker Sensitive Populations

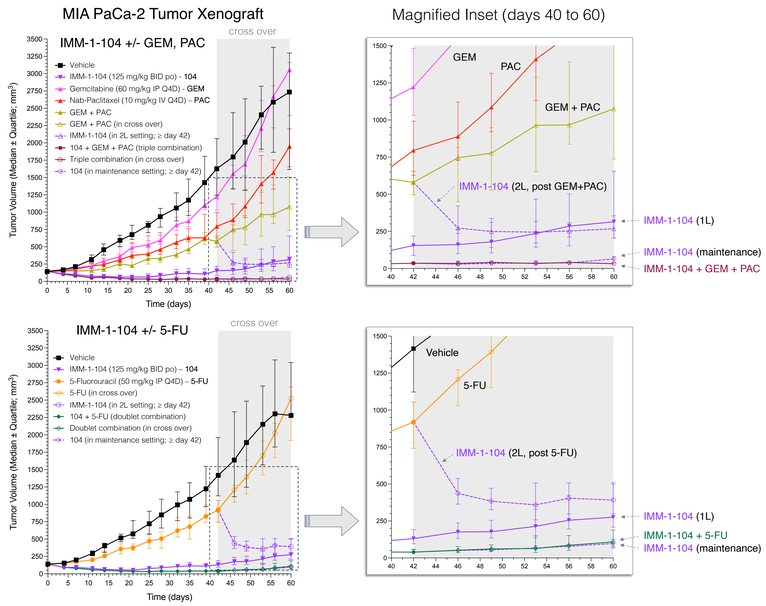
By examining cell line 3D-TGA response data using in-house whole exome sequencing that was further supported by emergent Phase 1 clinical ctDNA data, a machine learning model was further refined (v.2.0) to predict IMM-1-104 sensitivity. A starting set of gene features, defined by alteration frequency ≥ 5% in the GENIE 15.0 database[3] within the indications of pancreatic adenocarcinoma, colorectal adenocarcinoma, lung adenocarcinoma, and melanoma, was filtered for representation in the dataset and prioritized using ordinal regression. Model-projected responses were then calculated for GENIE patient profiles in select solid tumor indications. Mutation patterns observed in GENIE patients were also compared with those observed in cell lines to identify preclinical models that better resemble real-world patients. The goal of this effort is to increase the translational fidelity of specific tumor models, aiming to translationally identify patient populations more likely to benefit from IMM-1-104 treatment[4]. Here, we focus on model refinement in pancreatic cancer to better understand MAPK pathway addiction vs. utilization.

Figure 1. Model-predicted MAPK pathway dependence in PAAD: AACR GENIE v15.0

MAPK signaling pathway in pancreatic adenocarcinoma (PAAD), and its projected therapeutic sensitivity profile based on a ML model. Shown is a kernel density plot of the probability of response to therapeutic disruption of the MAPK by IMM-1-104. Consistent with high RAS mutation rates, pancreatic cancer displays a strong MAPK biomarker (+) subset, where 91% present with some level of MAPK pathway susceptibility in this dataset of > 4500 PAAD patients in GENIE v15.0. However, additional model features on the v2.0 testing panel suggest diversity of patient tumor addiction (i.e., ideal for monotherapy) versus utilization (i.e., ideal for combination therapy).

IMM-1-104 Combinations with Chemotherapy in Pancreatic Cancer

Figure 2. IMM-1-104 +/- chemotherapy in MIA PaCa-2 pancreatic xenograft model



MIA PaCa-2 Pancreatic ($KRAS^{G12C}$) xenograft tumor models in athymic nude mice. Gemcitabine (antimetabolite), nab-paclitaxel (taxane) and 5-fluorouracil (5-FU; antimetabolite) were commercially purchased. All studies started with 12 animals, per group. Mice within specific groups randomized for cross-over of treatments (≥ day 42). IMM-1-104 + GEM (doublet combination) similar but slightly inferior to triple combination (104 + GEM + PAC) – data not shown.

Table 1. Bliss Combination Index (CI) and Synergy Score (SS) of IMM-1-104 in combination *in vivo* from above MIA PaCa-2 Tumor Xenograft Efficacy studies

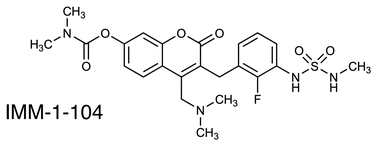
Comparison	AUC Combination Index (CI) +/- 95% Confid. Int.		AUC Synergy Score (SS) +/- 95% Confid. Int.		Synergy Call	
	Day 39	Day 60	Day 39	Day 60	Day 39	Day 60
75 mg/kg PO BID IMM-1-104 + 50 mg/kg IP Q4D 5-FU	0.30 [0.17 - 0.51]	0.34 [0.07 - 1.40]	8.60 [3.7 - 16.0]	2.50 [-1.00 - 6.40]	Synergistic	Additive
125 mg/kg PO BID IMM-1-104 + 50 mg/kg IP Q4D 5-FU	0.30 [0.20 - 0.46]	0.47 [0.17 - 1.20]	3.00 [1.30 - 5.90]	0.41 [-0.09 - 1.20]	Synergistic	Additive

Comparison	AUC Combination Index (CI) +/- 95% Confid. Int.		AUC Synergy Score (SS) +/- 95% Confid. Int.		Synergy Call	
	Day 39	Day 60	Day 39	Day 60	Day 39	Day 60
60 mg/kg IP Q4D Gemcitabine + 10 mg/kg IV Q4D nab-Paclitaxel	0.72 [0.43 - 1.10]	0.53 [0.16 - 1.30]	10.0 [-3.50 - 26.0]	9.9 [-4.60 - 26.0]	Additive	Additive
75 mg/kg PO BID IMM-1-104 + 60 mg/kg IP Q4D Gemcitabine	0.21 [0.14 - 0.30]	0.28 [0.14 - 0.57]	12.0 [7.30 - 19.0]	4.00 [1.40 - 8.50]	Synergistic	Synergistic
125 mg/kg PO BID IMM-1-104 + 60 mg/kg IP Q4D Gemcitabine	0.18 [0.12 - 0.27]	0.12 [0.042 - 0.36]	4.50 [2.60 - 7.70]	1.00 [0.39 - 2.10]	Synergistic	Synergistic
75 mg/kg PO BID IMM-1-104 + 60 mg/kg IP Q4D Gemcitabine + 10 mg/kg IV Q4D nab-Paclitaxel	0.23 [0.14 - 0.39]	0.22 [0.06 - 0.96]	4.40 [2.00 - 8.40]	0.83 [0.02 - 2.80]	Synergistic	Synergistic
125 mg/kg PO BID IMM-1-104 + 60 mg/kg IP Q4D Gemcitabine + 10 mg/kg IV Q4D nab-Paclitaxel	0.41 [0.21 - 0.77]	0.83 [0.21 - 3.60]	1.20 [0.28 - 2.90]	0.04 [-0.21 - 0.47]	Synergistic	Additive

Twelve pancreatic tumor models were evaluated (3D-TGA model) in combinations of IMM-1-104 with either gemcitabine, paclitaxel or 5-FU. 9 of 12 (75%) of the models showed additivity as assessed by ZIP synergy scores between -10 and +10 for each treatment. Additive models: MIA PaCa-2, PA-TU-8988S, CFPAC-1, HPAF-II, Panc 03.27, PSN-1, Panc 10.05, Capan-1, HPAC. Capan-2, PANC-1 and AsPC-1 failed to reach additive cutoffs with only 5-FU.

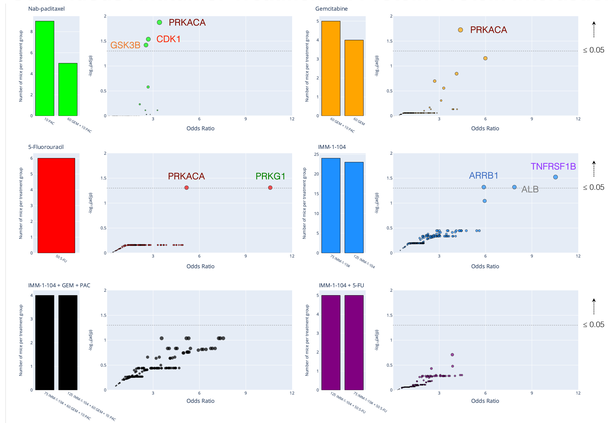
Figure 3. IMM-1-104, a Potent MEK Inhibitor that Drives Deep Cyclic Inhibition (DCI)

An orally bioavailable, selective, potent inhibitor of MEK that promotes Deep Cyclic Inhibition (DCI) of the MAPK pathway at MEK



Treatment-Acquired Mutations Show Distinct Mechanisms of Adaptation

Figure 4. Enrichment Analysis of Recurrently-Mutated Genes Under Continuous Antitumor Treatment in Protein-Protein Interaction Hubs



PRKACA activates MAPK signaling via RAF; with 5-FU treatment or combination therapy using Nab-paclitaxel + Gemcitabine, tumors may exhibit increased reliance on MAPK for survival and proliferation. Notably, this enrichment is absent in IMM-1-104 monotherapy or combinations. CDK1 mediates paclitaxel resistance[5], while GSK3B acts as a compensatory mechanism in paclitaxel treatment; co-treatment with a GSK3 inhibitor enhances paclitaxel efficacy[6]. PRKG1 gene set itself is likely not a driver of resistance, but its component gene BRAF signals through MAPK. TNFRSF1B regulates PI3K-Akt, a MAPK-independent pro-survival pathway. ARRB1 facilitates ERK auto-phosphorylation in the absence of MEK.[7]

Conclusions

While pancreatic tumors display near universal activation of the RAS/MAPK pathway, not all tumors are addicted to this pathway alone. A goal of combination therapy is to drive deeper, more durable antitumor responses, and IMM-1-104 showed promising combination effects with GEM, PAC and 5-FU in multiple 3D-TGA pancreatic cancer models. Further, IMM-1-104 alone showed greater tumor growth inhibition (TGI) head-to-head versus single or combination chemotherapy in MIA PaCa-2 tumor xenografts. Combinations of IMM-1-104 plus standard-of-care chemotherapies demonstrated synergy *in vivo* and resulted in near complete responses in a majority of animals.

The ongoing Phase 2a clinical trial includes five arms, three of which focus on pancreatic cancer, where IMM-1-104 is being evaluated as both monotherapy and in combination with approved GEM and 5-FU containing chemotherapy combinations. These new *in vitro, in vivo* and ML modeling data further support an advancing translational roadmap for IMM-1-104 in pancreatic cancer.

References

1. D. Onion, et al. 2016 Mol Cancer Ther 15(4):753-763
2. B. Hall, et al. 2022 J Clin Oncol 40 (suppl 16; abstr e15084)
3. GENIE v15.0: The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through An International Consortium, Cancer Discov. 2017 Aug;7(8):818-831
4. P. Nair, et al. 2023 Cancer Res 83 (7_Supplement): 4265
5. T. Bae, et al. 2015 Carcinogenesis 36(12):1561-1571
6. P. Duda, et al. 2020 Cells 9(5):1110
7. A. Kahsai, et al. 2023 PNAS 120(43):e2303794120

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