

MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 7-10, 2021



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IMM-1-104: a novel, oral, selective dual-MEK inhibitor that displays broad antitumor activity and high tolerability across RAS and RAF mutant tumors in vivo

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I have the following financial relationships to disclose:

Stockholder in Immuneering Corporation

Employee of Immuneering Corporation

I will not discuss off label use and/or investigational use in my presentation.

Key Limitations for U.S. FDA Registered MEK Inhibitors

- Safety and tolerability (on-target toxicity)
- Limited durability (limited combinations)
- Restricted mainly to RAF mutant tumors

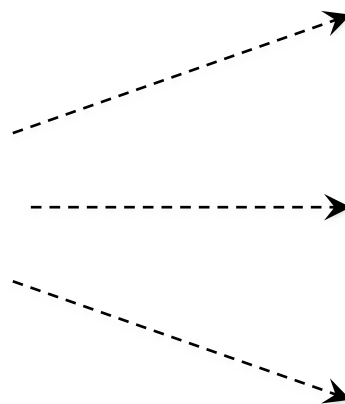
Chronic Suppression of
Homeostatic Pathway

Accelerated Selection of
Escape Variants

RAS-mutant Tumors with
High CRAF-bypass

Preclinical Attributes of IMM-1-104, a Novel Dual-MEK Inhibitor

- Improved safety (cyclic inhibition)
- Depth and durability of tumor response
- Active in RAS and RAF mutant tumors



Cyclic Suppression of
Tumor Addicted Pathway

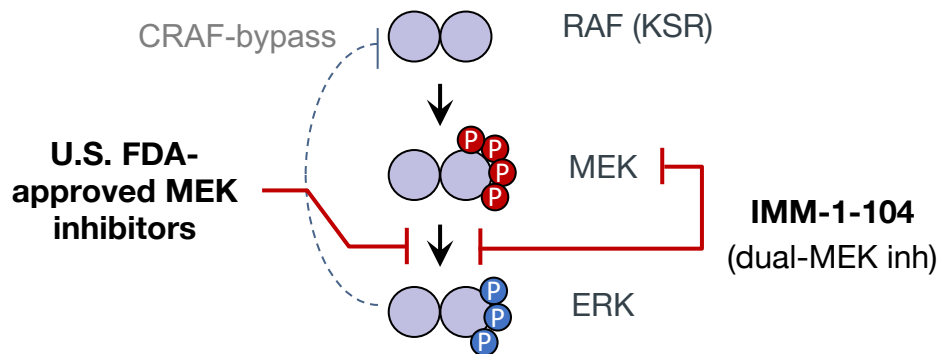
Greater Opportunity for
Drug-Drug Combinations

Resistant to CRAF-bypass
in RAS Mutant Tumors

IMM-1-104 Inhibits Phosphorylation of Both MEK and ERK (Dual-MEK inhibitor)

CRAF-bypass Mechanism

1. Allosteric inhibition of MEK kinase function
2. Reduction of cellular pERK pools
3. Loss of CRAF feedback suppression
4. Increased pMEK (for non-resistant drugs)



A549 NSCLC	Trametinib	Cobimetinib	Binimetinib	Selumetinib	IMM-1-104
pERK (2 hr)	> 70% inh	> 70% inh	> 70% inh	> 70% inh	> 70% inh
pMEK (2 hr)	+ 24%	+ 546%	+ 196%	+ 145%	44% inh

A549 (KRAS^{G12S}) lung tumor model; 2-hours drug exposure at 100 nM; Δ pERK:tERK and pMEK:tMEK; (Protein Simple® - Jess)

U.S. FDA-Approved MEK inhibitors: Trametinib, Cobimetinib, Binimetinib, Selumetinib; Commercially purchased

1. **Binding Mechanism** = Dual-MEK (resistant to bypass mechanisms)

- MEK1/2 engagement lowers both pERK and pMEK activation
- Designed to disrupt activation of MEK by RAF and KSR

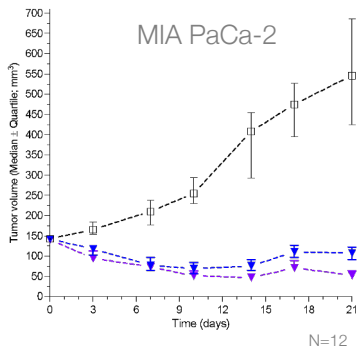
2. **Short Half Life** = Deep, Cyclic Inhibition

- Plasma half life in mice = 1.3 hours (see Poster 240; Peter King)
- Deep, cyclic inhibition of pERK transcriptome (see Poster 254; Sarah Kolitz)

IMM-1-104 Demonstrates Broad Activity in RAS and RAF Mutant Tumor Models In Vivo

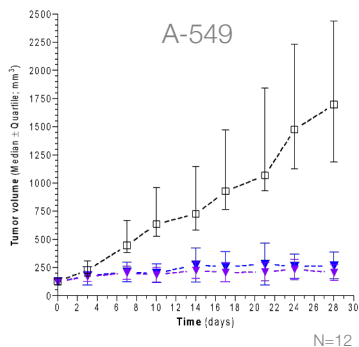
See Poster: P240

IMM-1-104 KRAS^{G12C} PANC

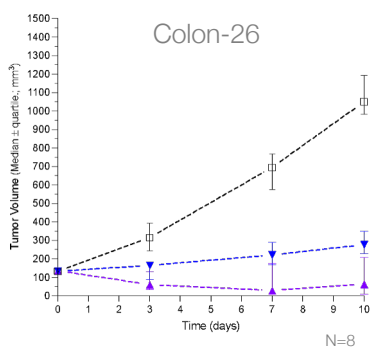


See Poster: P254

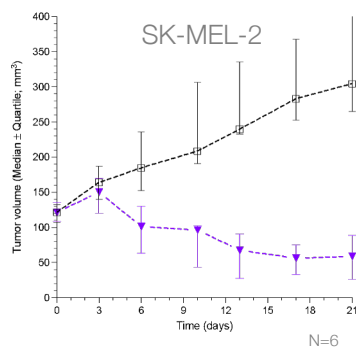
IMM-1-104 KRAS^{G12S} NSCLC



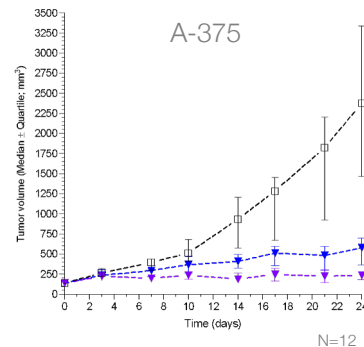
IMM-1-104 KRAS^{G12D} CRC



IMM-1-104 NRAS^{Q61R} MEL



IMM-1-104 BRAF^{V600E} MEL



□ MEDIAN Vehicle 0 mg/kg BID po
▼ MEDIAN 100 mg/kg IMM-01-00104 BID po
▼ MEDIAN 150 mg/kg IMM-01-00104 BID po

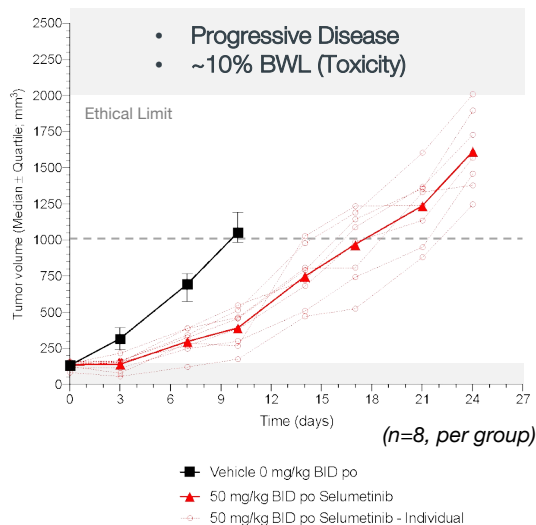
Goal: decouple therapeutic activity and tolerability; demonstrate **broader activity** in RAS mutant disease setting

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; MEL = melanoma; PANC = pancreatic cancer

Head-to-Head Comparison of IMM-1-104 Against Selumetinib and Binimetinib in a KRAS^{G12D} CRC Model Colon-26

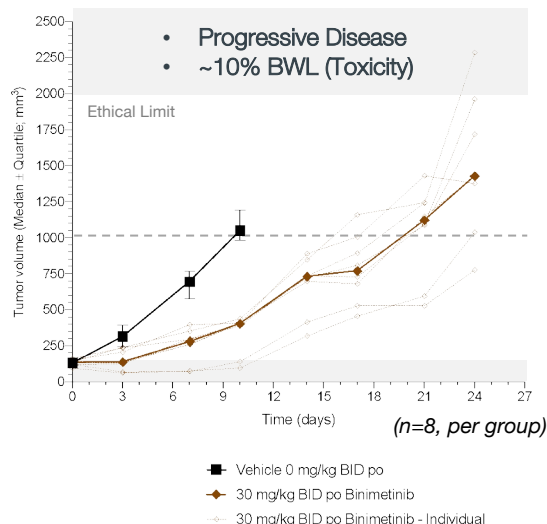
Selumetinib

(FDA-approved APR-2020)



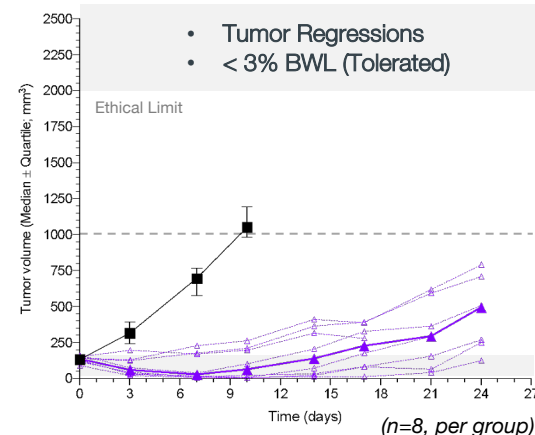
Binimetinib

(FDA-approved JUN-2018)



IMM-1-104

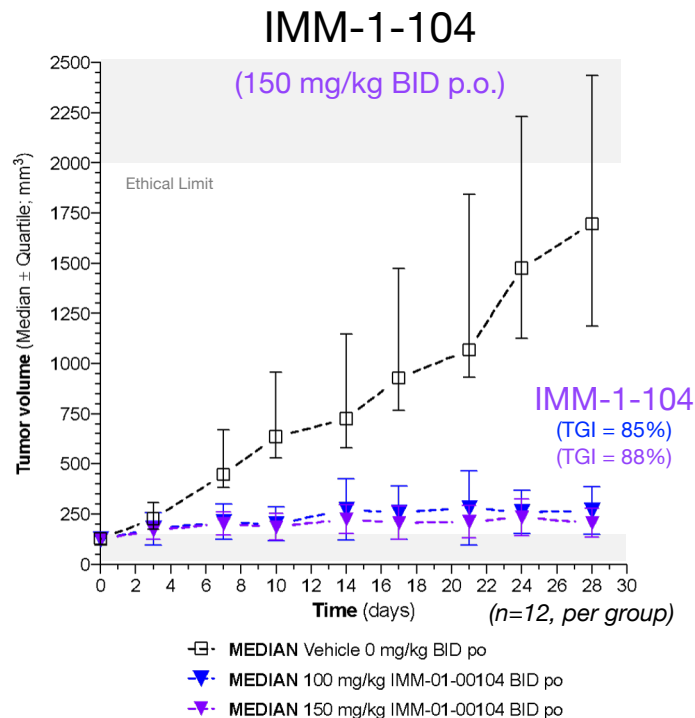
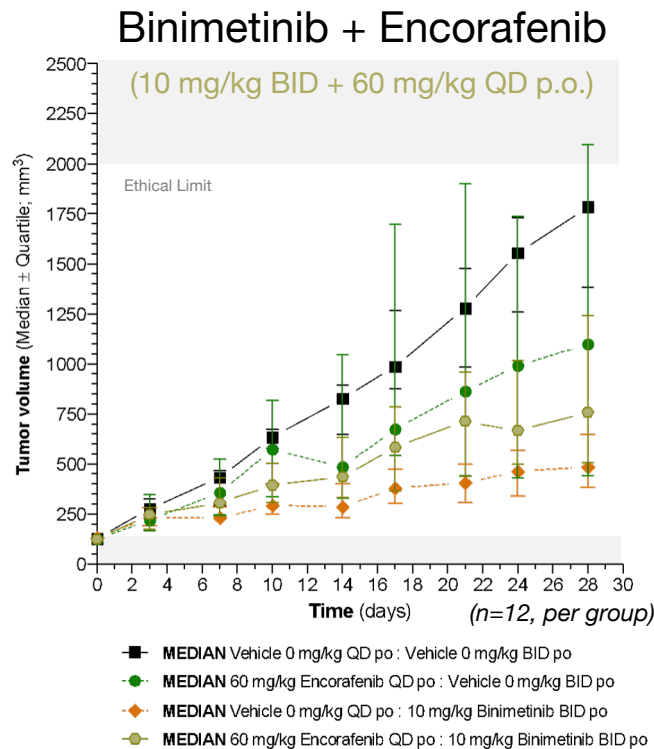
(IND-Enabling)



Colon-26 (KRAS^{G12D}) BALB/c Syngeneic Colorectal Tumor Model

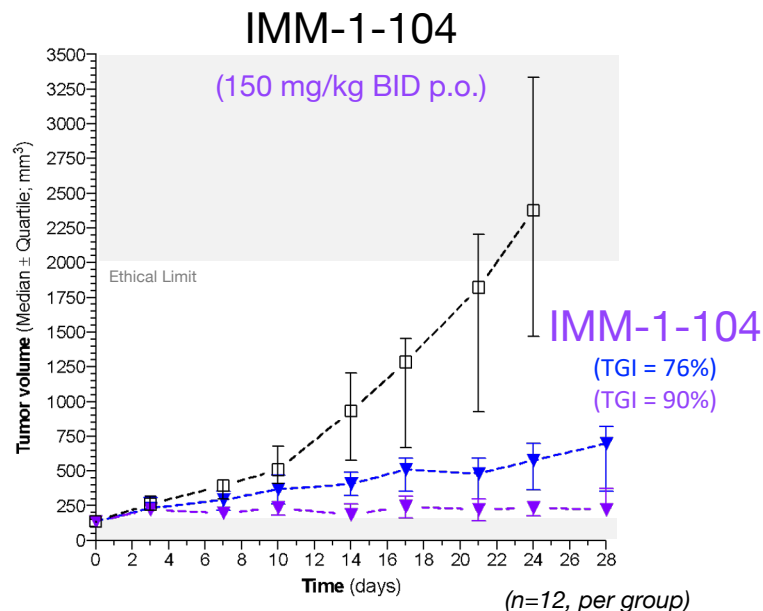
Colon-26 (KRAS^{G12D}) Syngeneic Colorectal Cancer (CRC) Tumor Model in Immune Competent Mice; Selumetinib and Binimetinib were commercially purchased

Head-to-Head Comparison of IMM-1-104 Against Binimetinib and Encorafenib in a KRAS^{G12S} Lung Cancer Model A549

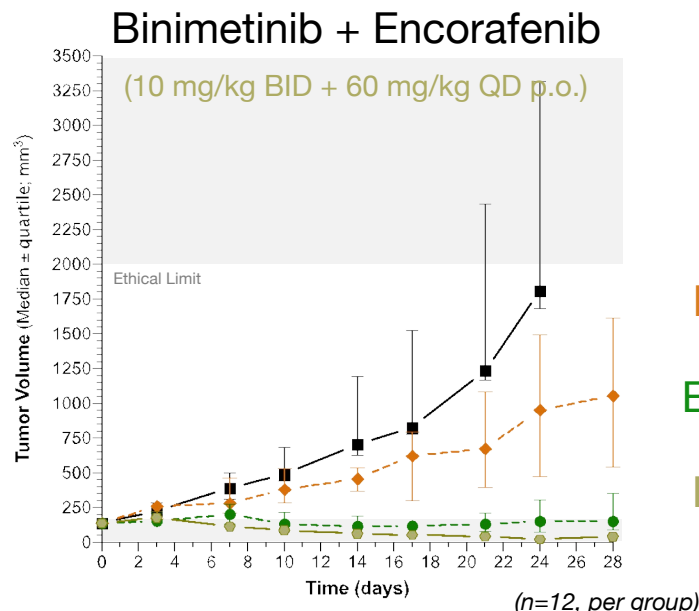


A549 (KRAS^{G12S}) NSCLC Xenograft Tumor Model in Athymic Nude Mice; Binimetinib and Encorafenib were commercially purchased

Head-to-Head Comparison of IMM-1-104 Against Binimetinib and Encorafenib in a BRAF^{V600E} Melanoma Model A375



- MEDIAN Vehicle 0 mg/kg BID po
- ▼ MEDIAN 100 mg/kg IMM-01-00104 BID po
- ▼ MEDIAN 150 mg/kg IMM-01-00104 BID po



- MEDIAN Vehicle 0 mg/kg QD po : Vehicle 0 mg/kg BID po
- MEDIAN 60 mg/kg Encorafenib QD po : Vehicle 0 mg/kg BID po
- ◆ MEDIAN Vehicle 0 mg/kg QD po : 10 mg/kg Binimetinib BID po
- MEDIAN 60 mg/kg Encorafenib QD po : 10 mg/kg Binimetinib BID po

A375 (BRAF^{V600E}) MEL Xenograft Tumor Model in Athymic Nude Mice; Binimetinib and Encorafenib were commercially purchased

Immuneering Oncology



7 Precision Oncology Programs Enabled by Signaling Dynamics

- **Initial Focus:** MAPK and mTOR pathways, which are inappropriately activated in **more than half of all cancers**
- **Existing Options:** chronically suppress the pathways with either elevated toxicity or limitation to specific mutations.
- **Our Approach:** Using our platform, we design product candidates with short half-lives that potentially break tumor addiction through deep cyclic disruption of these pathways. We aim to maximize therapeutic activity in **broad patient populations** and improve tolerability.

IMM-1-104 (Dual MEK inhibitor)



A Lead Product Candidate For RAS Mutant Solid Tumors

- **IMM-1-104:** a dual MEK inhibitor that is potentially differentiated from FDA-approved MEK inhibitors
- **Insights from preclinical studies:**
 - Broad activity in RAS/RAF tumor models*
 - Synergy with reduced-dose of AMG-510¹*
 - Greater anti-tumor activity and improved tolerability vs selumetinib, binimetinib¹*
 - Broad activity across a wide range of 3D tumor models*

¹As demonstrated in head-to-head studies versus IMM-1-104 in certain tumor models (also see Poster 240)

Thank You for Your Attention!

bhall@immuneering.com

Please see additional posters for IMM-1-104 listed below:

- **P240** "Benchmarking the novel dual-MEK inhibitor, IMM-1-104, head-to-head and in combination with sotorasib (AMG-510) in the MIA PaCa-2 (KRAS-G12C) pancreatic cancer xenograft model"
- **P254** "Transcriptional effects in C26 tumor highlight mechanistic aspects of a novel dual MEK inhibitor, IMM-1-104"

MOLECULAR TARGETS AND CANCER THERAPEUTICS

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Abstract P252



Background: Inappropriate activation of the MAPK pathway, often stemming from mutations in RAS or RAF, represents one of the most common oncogenic events in human cancer. Therefore, MEK1 and MEK2 (MEK), which lie downstream of RAS and RAF but upstream of ERK, have represented an attractive drug target for over two decades. Unfortunately, first generation MEK inhibitors have been limited by pathway reactivation events and serious on-target drug toxicities that restrain clinical utility, especially in patients with RAS mutant tumors. We sought to develop a new approach to MEK inhibition that would be more effective in RAS mutant tumors and with improved tolerability. IMM-1-104 is a novel dual-MEK inhibitor that is designed to disrupt phosphorylation of MEK and subsequently prevent activation of ERK1 and ERK2 (ERK). IMM-1-104's dual-MEK mechanism resists RAF activation of MEK, and its short drug half-life allows for chronic dosing while maintaining a near-zero drug trough for improved tolerability.

Materials & Methods: IMM-1-104 was profiled across a series of preclinical experiments to assess its physicochemical and drug-like properties. Cell-free and cell-based in vitro as well as in vivo characteristics were evaluated, including four independent in vivo pharmacology rodent studies in lung, colon and skin tumor models.

Results: IMM-1-104 is a highly selective, orally bioavailable, non-ATP competitive, allosteric dual-MEK inhibitor. At drug exposures up to 1 micromolar (μM) in cell-free and in situ kinome screens, thermodynamic interactions and altered activity levels were observed for MEK1 and MEK2. At higher drug exposures up to 10 μM , IMM-1-104 also thermodynamically interacted with RAF1 (CRAF) and prompted reduction of KSR1 and KSR2 activation markers. IMM-1-104 displayed dual-MEK activity (i.e., RAS mutant tumor cell reductions in both ERK and MEK phosphorylation) across multiple human tumor cell-based models including A549 (KRAS-G12S) lung, A375 (BRAF-V600E) and SK-MEL-2 (NRAS-Q61R) melanoma. Pharmacokinetic studies in rodent models revealed a drug plasma half life for IMM-1-104 of approximately 1.3 hours. In vivo tumor pharmacology studies in A549 and A375 achieved tumor stasis (i.e., 85% to 95% Tumor Growth Inhibition) with regressions observed in Colon-26 and SK-MEL-2.

Conclusions: The dual-MEK mechanism and short half-life of IMM-1-104 has proven to be broadly active and well-tolerated in multiple RAS and RAF mutant preclinical tumor models in rodents. IMM-1-104 drives deep, cyclic inhibition of the MAPK pathway (improving tolerability) while resisting pathway bypass mechanisms (improving activity). Our collective data suggest that RAS and RAF mutant tumor cells are not able to tolerate periods of deep but cyclic MAPK pathway inhibition. Overall, these results are consistent with on and off signaling events that can significantly impact cell fate decisions (i.e. signaling dynamics).