Investor Presentation

Immuneering

Nasdaq: IMRX

April 2024

FORWARD-LOOKING STATEMENTS AND OTHER DISCLAIMERS

This presentation contains forward-looking statements, including within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements including, without limitation, statements regarding: Immuneering Corporation's (the "Company") plans to develop, manufacture and commercialize its product candidates; the treatment potential of its product candidates, including IMM-1-104 and IMM-6-415; the design, enrollment criteria and conduct of the Phase 1/2a clinical trials for IMM-1-104 and IMM-6-415; initial signs of clinical activity of IMM-1-104; the translation of preclinical data into human clinical data; the ability of initial clinical data to de-risk IMM-1-104 and / or IMM-6-415 and be confirmed as the trials progress, including the safety, tolerability, pharmacokinetics, pharmacodynamics and potential efficacy of IMM-1-104 and / or IMM-6-415; the potential advantages and effectiveness of the company's clinical and preclinical candidates; the timing of additional trial updates; the Company's recommended IMM-1-104 phase 2 dose; the indications to be pursued by the Company in the Phase 2a portions of the trials and timing to results;; the filing with, and approval by, regulatory authorities of our product candidates; the sufficiency of funds to operate the business of the Company; statements regarding the Company's ability to advance its pipeline and further diversify its portfolio and make progress towards its longstanding goal of creating better medicines for cancer patients; the Company's cash needs and availability, including our projected cash runway and current operating plans; and the plans and objectives of management for future operations.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, without limitation: our limited operating history; our history of operating losses; our ability to raise the substantial additional capital that will be required to finance our operations; the difficulty of obtaining regulatory approval for any of our current or future product candidates; our ability to submit an Investigational New Drug application ("IND"), or IND amendments or comparable documents in foreign jurisdictions in order to commence clinical trials on the timelines we expect; our limited experience in designing and conducting clinical trials; the timing of the initiation, progress and potential results of our ongoing and planned preclinical studies and clinical trials and our research programs, including our Phase 1/2a clinical trials; our ability to successfully complete our Phase 1/2a clinical trials, or any planned or future clinical trials and for those trials to produce positive results; the risk of substantial delays in completing, if at all, the development and commercialization of our current or future product candidates; risks related to adverse events, toxicities or other undesirable side effects caused by our current or future product candidates; the risk of delays or difficulties in the enrollment and/or maintenance of patients in clinical trials; our substantial reliance on the successful development of our current and future product candidates, as well as our platform, including our proprietary technologies such as DCT and Fluency; risks related to competition in our industry; the market opportunity for our product candidates, if approved; risks related to manufacturing; risks related to our reliance on third parties; risks related to our intellectual property; and risks related to ongoing and / or future pandemics.

These and other important factors discussed under the caption "Risk Factors" in the Company's Annual Report on Form 10-K for the annual period ended December 31, 2023 filed with the SEC and its other reports filed with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While the Company may elect to update such forward-looking statements at some point in the future, other than as required by law it disclaims any obligation to do so, even if subsequent events cause its views to change. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of that data or undertake to update such data after the date of this presentation.

Data of trametinib, cobimetinib, binimetinib, selumetinib, encorafenib, AMG-510 (now known as sotorasib) and / or other therapeutic agents as compared to IMM-1-104 presented in this presentation is based on head-to-head studies where these therapies have been purchased from commercial sources rather than the pharmaceutical company commercializing or developing, as applicable, the compound.

Immuneering

Differentiated Approach

- Targeting broad **Universal-RAS/RAF** patient population vs. single mutations
- Aim to **improve tolerability** and to **increase durability** vs. chronic inhibition
- **Deep Cyclic Inhibition:** a counterintuitive approach deeply rooted in data
- **IMM-1-104:** First Deep Cyclic Inhibitor of MAPK pathway. QD oral. Unique profile includes:
  - **Manyfold higher C_{MAX}**
  - **Shorter half-life**
- **IMM-6-415**: Deep Cyclic Inhibitor of MAPK pathway. BID oral.

IMM-1-104: Phase 1/2a Clinical Study In Progress

- **Positive Topline Phase 1 data reported March 2024 and Phase 2a underway at 320 mg QD p.o.**
- **Phase 2a: monotherapy arms**
  - PDAC 1L or 2L
  - RASmut Melanoma 2L or 3L post-IO, or 1L*
  - RASmut NSCLC 2L-3L
- **Phase 1b/2a combination arms**
  - 1L PDAC IMM-1-104 + mFOLFIRINOX
  - 1L PDAC IMM-1-104 + mGem/nab-Pac

Key Inflection Points Expected in Near Term

- **IMM-104 initial data from multiple Phase 2a arms expected in 2024**
- **IMM-6-415: Initial PK/PD and safety data from Phase 1 portion of Phase 1/2a trial expected in 2024**
- **Active discovery pipeline**
- **Cash runway** projected **into 2H 2025**

*1L Melanoma for patients who are not candidates for existing therapies

Development Pipeline

Wholly Owned Product Portfolio Differentiated by Molecule Design, Indication, Half-life, Combination Potential

PROGRAM	INDICATION	DISCOVERY	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	ANTICIPATED MILESTONES
IMM-1-104	Universal-RAS	Once-Daily (QD)					Initial data from multiple Phase 2a arms expected in 2024
IMM-6-415	Universal-RAS/RAF	Twice-Daily (BID)					Initial PK/PD and safety data from Phase 1 portion of Phase 1/2a trial expected in 2024
Multiple additional programs in discovery phase							

Cash, cash equivalents and marketable securities as of December 31, 2023 of $85.7M projected to fund operations projected into 2H 2025

IMM-1-104

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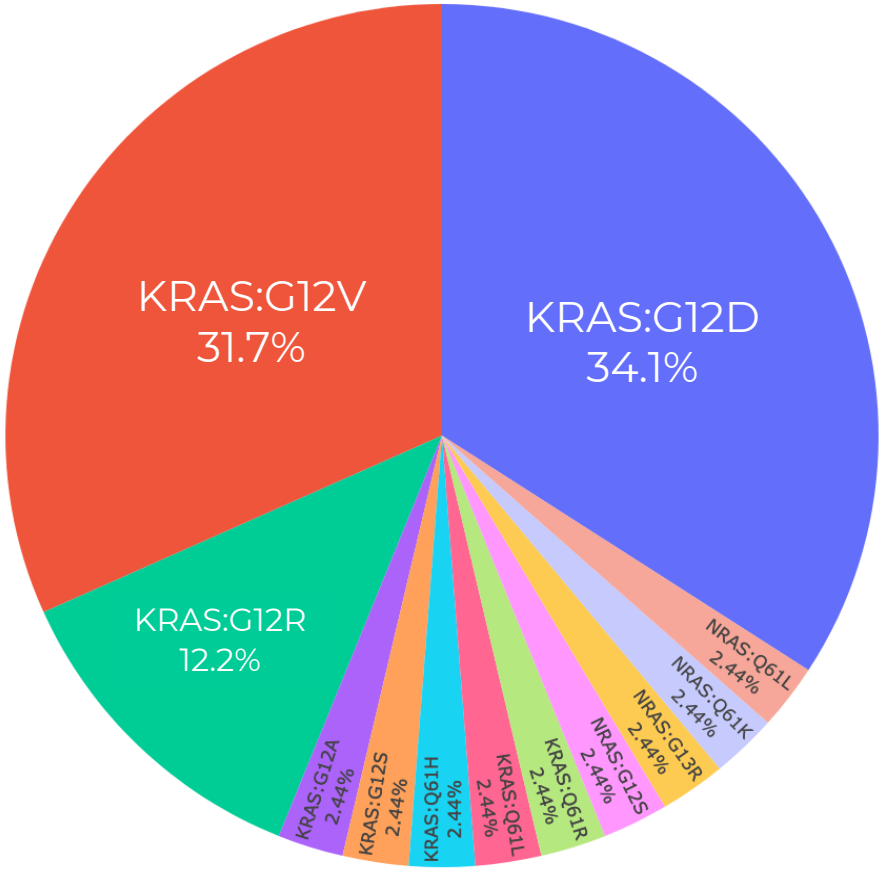
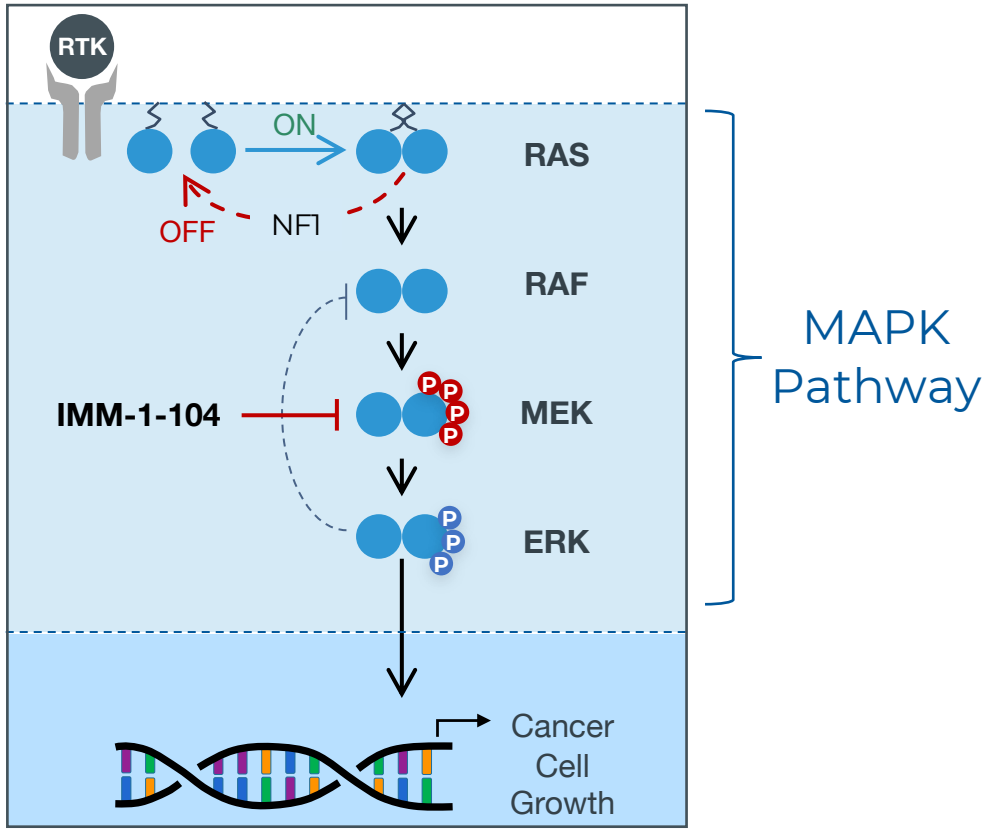
IMRX's Goal: Medicines for Broad Populations of Cancer Patients

IMM-1-104 Phase 1 Enrolled a Broad, Universal-RAS Patient Population



RAS mutation reported at enrollment (N=41)

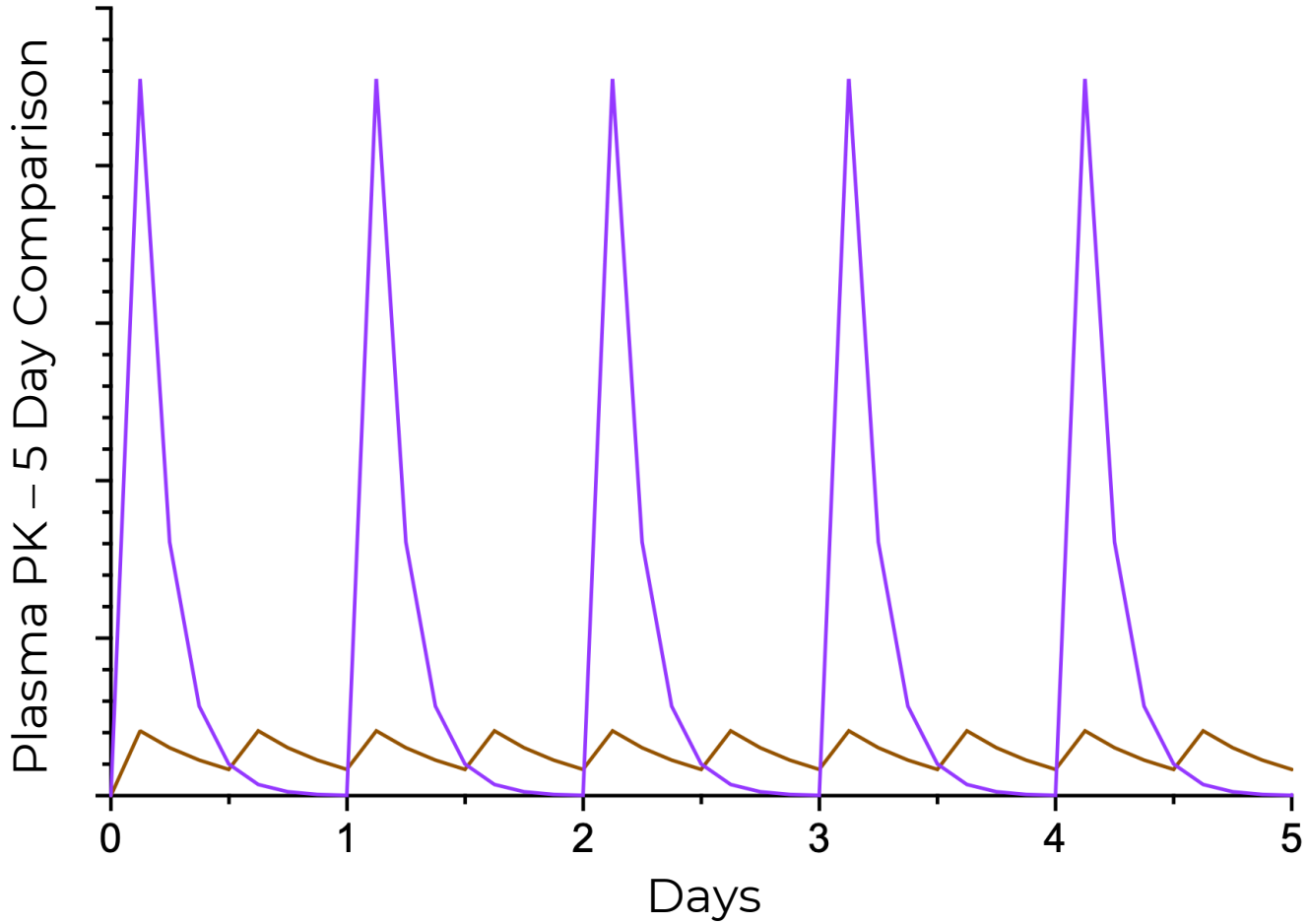
IMM-1-104 is a Deep Cyclic Inhibitor of MEK in the MAPK Pathway



Chronic inhibitors of MEK have been poorly tolerated, limited mainly to RAF mutant disease

Electronic Data Capture (EDC) Snapshot as of February 20, 2024

IMM-1-104's Deep Cyclic Inhibition of MEK is designed to improve tolerability and broaden activity vs. chronic inhibition of MEK



Conceptual illustration of deep cyclic inhibition (purple) vs. chronic inhibition (brown)

Dramatic PK C_{MAX} Pulse

GOAL: Achieve many fold higher drug free fraction C_{MAX} to **break tumor addiction**

Near-Zero Drug Trough

GOAL: Short plasma half-life to improve tolerability and limit adaptive resistance, so **every day is a drug holiday**

MoA Target Engagement

GOAL: Prevent MAPK-pathway bypass events, for **expanded activity into RAS mutant setting**

IMM-1-104 Phase 1 Overview

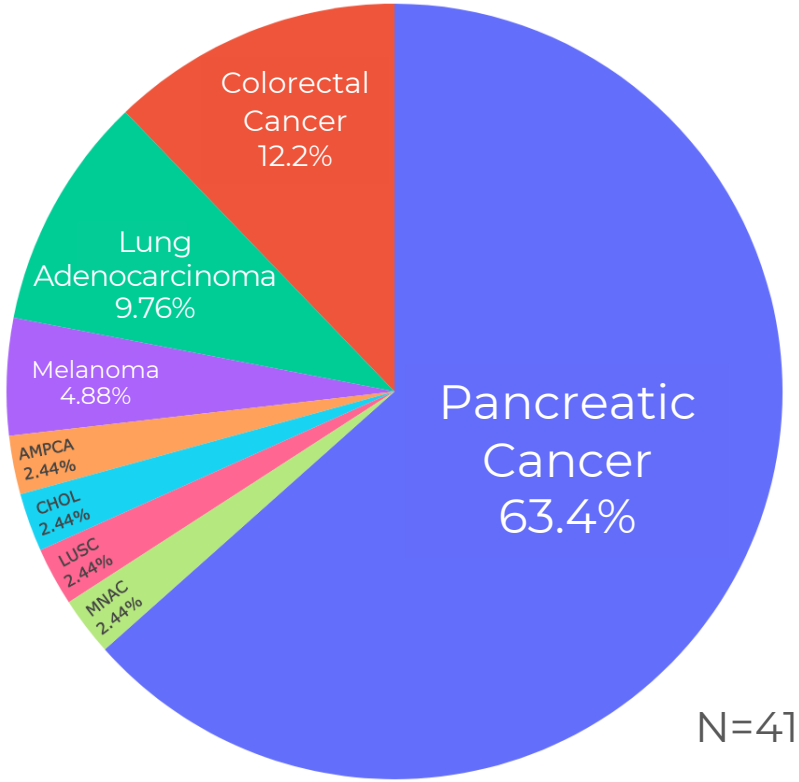
Objectives & Endpoints:

Primary
Safety (Adverse Events)
Tolerability (Dose Limiting Toxicities)
Recommendation for Phase 2 Dose (RP2D)

Secondary
Pharmacokinetics (PK)

Exploratory Objectives:
Pharmacodynamic (PD) & blood-based biomarkers, initial activity…

Key Patient Demographics:



- **82% never had a PR or CR to any prior therapy**
- **~2/3^{rds} treated with IMM-1-104 in ≥ 3rd line, up to 7th line**

- EDC snapshot as of February 20, 2024: 41 patients total, including 26 pancreatic ductal adenocarcinoma (PDAC), 5 colorectal cancer (CRC), 4 lung adenocarcinoma (LUAD), 2 melanoma (MEL), 1 lung squamous cell carcinoma (LUSC), 1 ampulla of vater carcinoma (AMPCA), 1 mesonephric adenocarcinoma (MNAC), 1 cholangiocarcinoma (CHOL).
- 34 patients with prior treatment history, of which only 6 are known to have had a partial response (PR) and none are known to have had a complete response (CR), in response to any prior treatment for metastatic disease (excludes adjuvant), IMM-1-104 treatment was the median third line of therapy (range 2nd-7th line)

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IMM-1-104 Phase 1: Summary of Treatment-Related Adverse Events

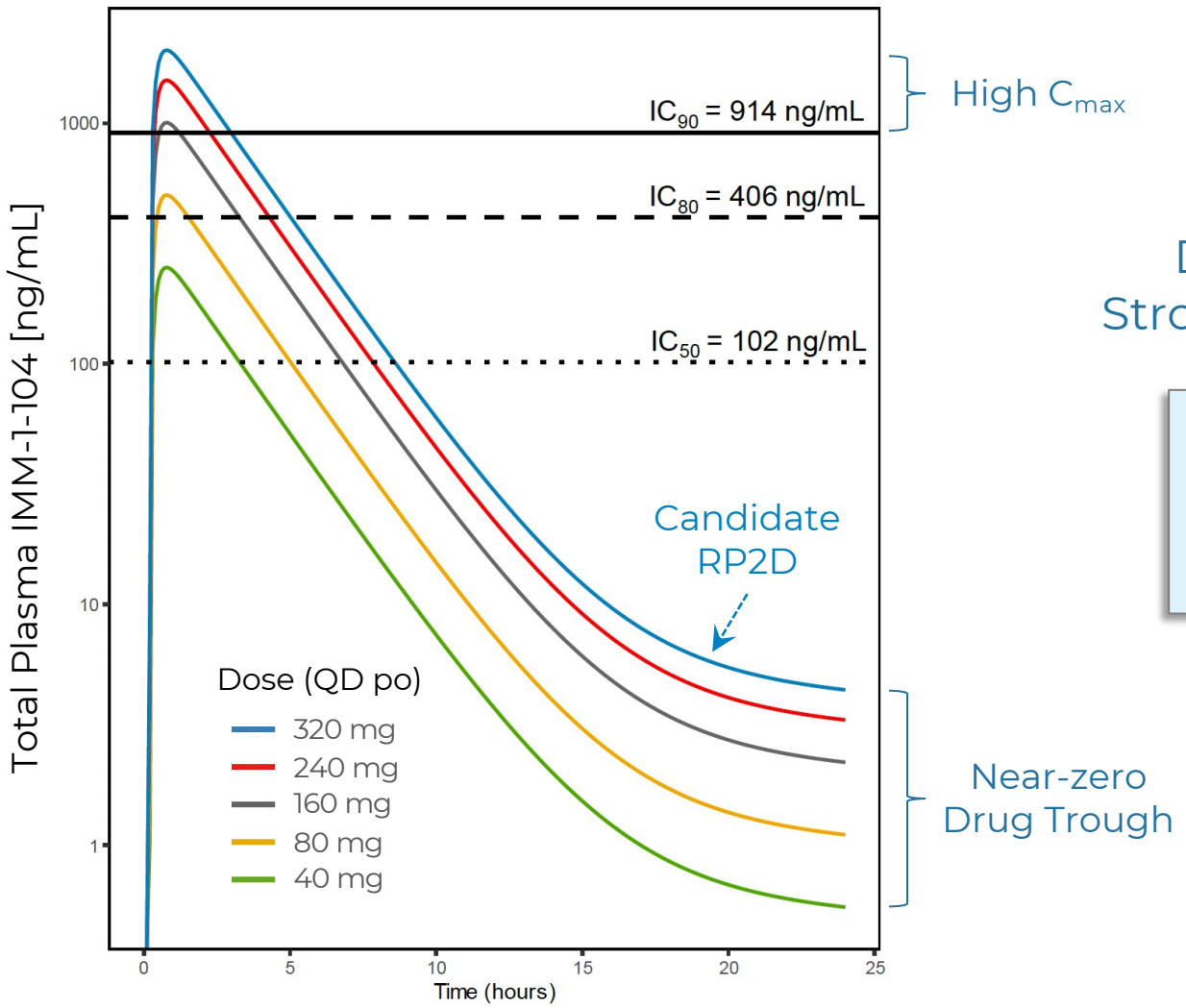
Topline Phase 1 Safety (N = 41)

Maximum Severity of TRAEs:	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs observed in ≥10.0% of patients, n(%)					
1. Diarrhea	8 (19.5%)	3 (7.3%)	0	0	11 (26.8%)
2. Nausea	8 (19.5%)	0	0	0	8 (19.5%)
3. Fatigue	5 (12.2%)	3 (7.3%)	0	0	8 (19.5%)
4. Vomiting	5 (12.2%)	2 (4.9%)	0	0	7 (17.1%)
5. Rash Maculopapular	3 (7.3%)	2 (4.9%)	1 (2.4%)	0	6 (14.6%)
6. Oedema Peripheral	3 (7.3%)	2 (4.9%)	0	0	5 (12.2%)

- *As of February 20, 2024, EDC snapshot: No IMM-1-104 treatment-related adverse events (TRAEs) were deemed serious; No DLTs reported in dose escalation, evaluated at oral doses of 40, 80, 160 and 320 mg QD.*
- *Note 36 of 41 patients received a once-daily oral dose of IMM-1-104 at 240mg (N=17) and 320mg (N=19).*

IMM-1-104 Inhibited the MAPK Pathway at pERK > 90%

Topline PK/PD Data for IMM-1-104



Deep Cyclic Inhibition (DCI) Profile Strongest for Candidate RP2D of 320 mg

- Longer time above pERK IC_{90} at 320 mg (2.7 hr) vs. 240 mg (1.9 hr)
- Lower variance in PD (p-ERK) profiles at 320 mg vs. 240 mg

Modeled typical profiles based on 19 patients of IMM-1-104 plasma concentrations (ng/mL) versus time (h) on a semilogarithmic scale for different dose groups. Direct measure of time above PD IC_{level} does not consider k_{off} PD shadow. Approximately dose linear from 40 to 320 mg PO QD; no drug accumulation. Tight relationship observed between plasma concentrations and phosphorylated ERK (p-ERK) to total ERK (t-ERK) ratios; Longer time above pMEK IC_{90} at 320 mg (4.0 hr) vs. 240 mg (3.3 hr)

EDC Snapshot as of February 20, 2024: PK/PD Patient Profiles (IMM1104-101 trial)

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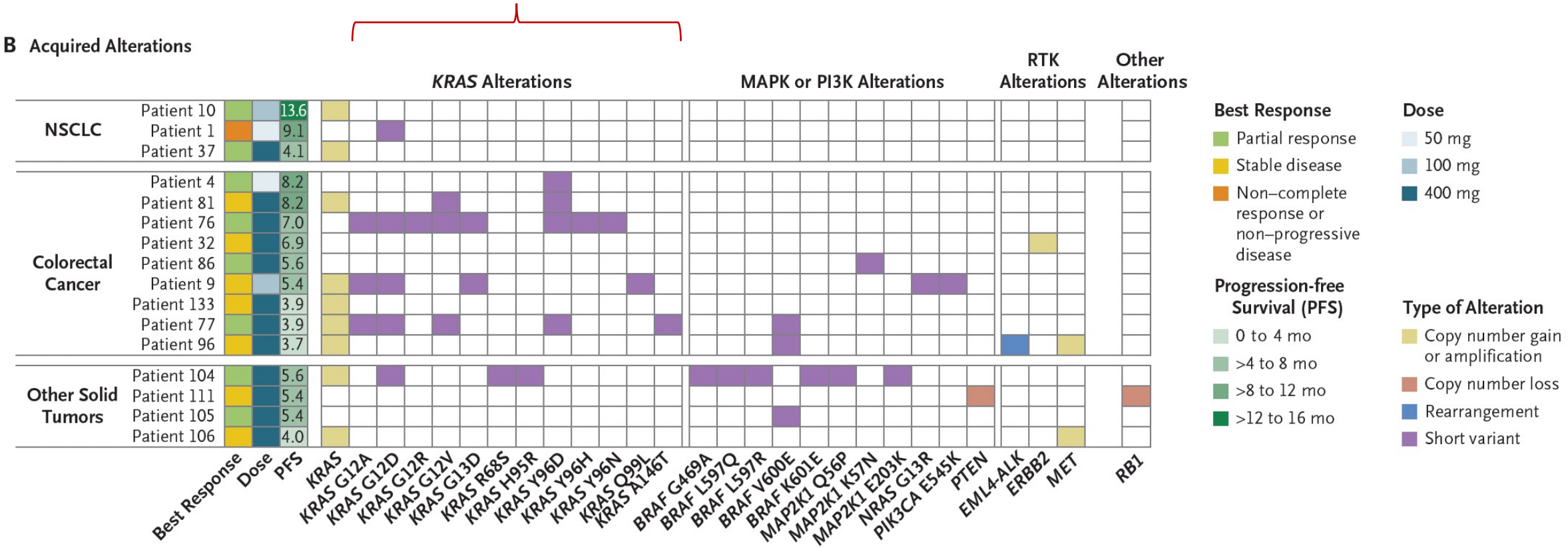
Divarasib (KRAS-G12Ci): Many Acquired Alterations in RAS (ctDNA)

New RAS alterations observed



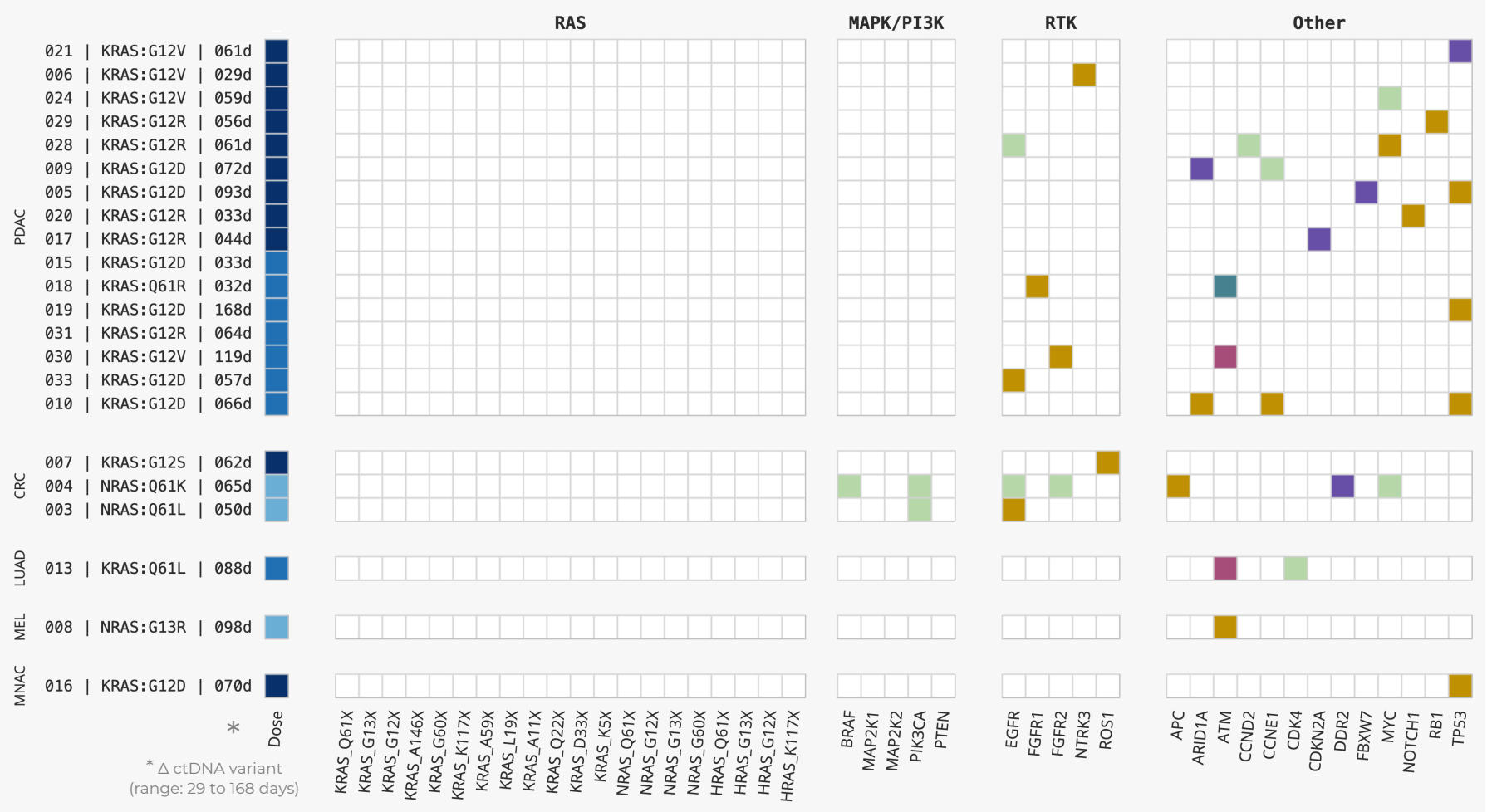
New RAS alterations help to circumvent KRAS-G12C inhibitors

2023 NEJM Sacher, et al. 389(8):710

IMM-1-104 Phase 1: No Acquired Alterations in RAS (ctDNA)

No new RAS alterations observed

Acquired Alterations:



Newly arising variants detected by Guardant Health circulating tumor DNA (ctDNA) test on ~day 28 or end of treatment (EoT)

Data received by February 20, 2024

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Initial Signs of Clinical Activity

IMM-1-104 observed to shrink at least one target lesion in ~half of patients

- **Best individual lesion regressions: -35.7%** at 320mg in 2L (vs. -11.4% at 240mg)
- **Best RECIST SLD: -18.9%** at 320mg in 2L (vs. -7.1% at 240mg)
- **Longest duration on therapy: 162 days (5+ months)** at 240mg; no TRAEs
- **53% of patients had ≥ 1 target lesions regress** at 320mg or 240mg

All data as of February 20, 2024, EDC snapshot. 11 patients with post-baseline scans at 320mg, 6 patients with post-baseline scans at 240mg, 3 patients with scans at lower doses, 7 patients have started treatment but not yet scanned, 5 patients are pending data entry and 8 patients progressed before they could receive a post-baseline scan, and 1 was not evaluable. 6 of 20 (30%) patients with completed RECIST scans, showed best sum of longest diameters (SLD) of 0% to -18.9%, and 4 of 20 (20%) showed best SLD less than zero. (Note: 2 patients at 320 mg with -35.7% as best individual lesion regression, both in 2L).

IMM-1-104: Phase 1/2a Clinical Trial:

Topline Phase 1 Observations

- **Well-tolerated,** potential for **differentiated safety profile**
- 100% suppression of acquired RAS alterations, **supporting goal of Universal-RAS activity**
- Candidate RP2D of 320 mg supported by tolerability, PK/PD, ctDNA results & initial activity
- **Individual target lesion regression in approximately half of patients**

Phase 2a (Active)

Phase 2a monotherapy* & combination arms (N≈150)

Monotherapy	Combination
PDAC 1L† or 2L (N≈30 pts)	**1L PDAC** IMM-1-104 + mFOLFIRINOX (N≈30 pts)
RAS^{mut} Melanoma 2L, 3L post-IO or 1L† (N≈30 pts)	**1L PDAC** IMM-1-104 + mGem/nab-Pac (N≈30 pts)
RAS^{mut} NSCLC 2L-3L (N≈30 pts)	
Candidate RP2D Expansion	*Safety Lead-in 1b → 2a*

* Simon 2-Stage or Similar Design
† For patients who are not candidates for existing therapies

- RP2D = Recommended Phase 2 Dose
- PGx = Pharmacogenomics (e.g., ctDNA)

All data as of February 20, 2024, EDC snapshot

Emergent IMM-1-104 Monotherapy and Combinations

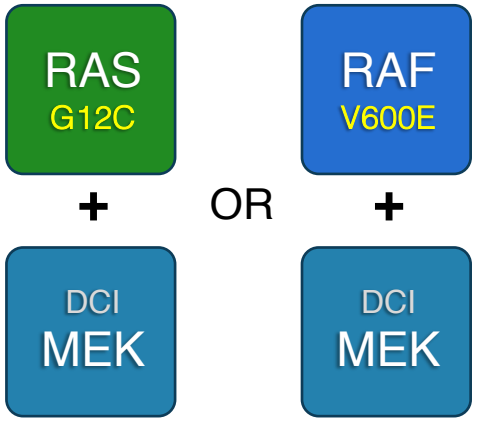
Monotherapy

Pulsatile MAPK Pathway Inhibition

Ideal: In patients with broad MAPK pathway addiction

Vertical Combinations

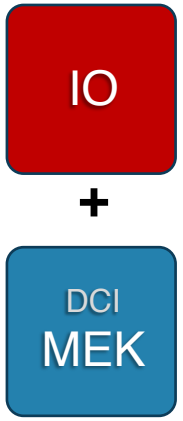
Selective Vertical Drug Combinations



Goal: Greater Depth & Durability of Response

Immune Modifying Combinations

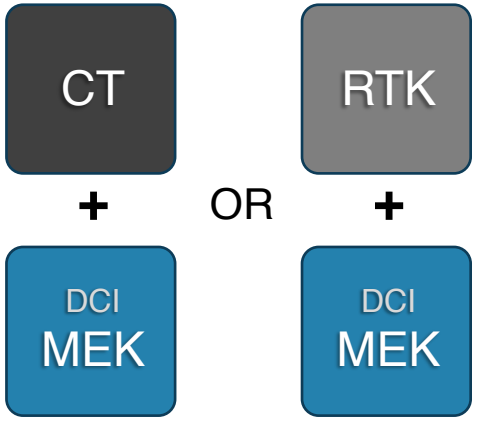
Dual-targeting of Tumor & Immune System



Goal: Break MAPK Addiction; Enhance Antitumor Immunity

Orthogonal MoA Combinations

Non-overlapping Mechanism of Action Combinations

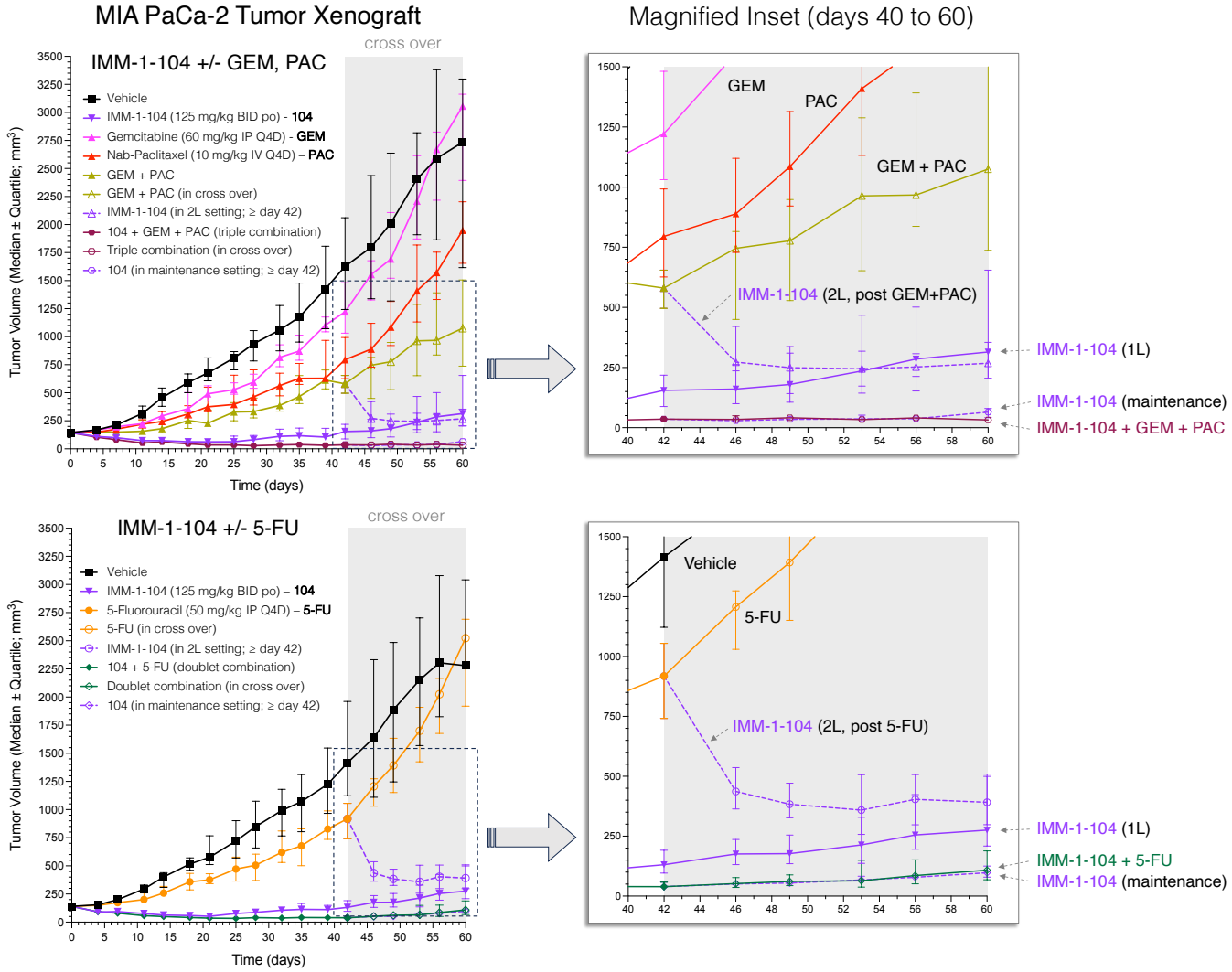


Goal: Expand & Improve Overall Antitumor Response

Nair, et al. 2023 AACR: EORTC (Boston, MA)

IMM-1-104 Combinations with Chemotherapy in Pancreatic Cancer

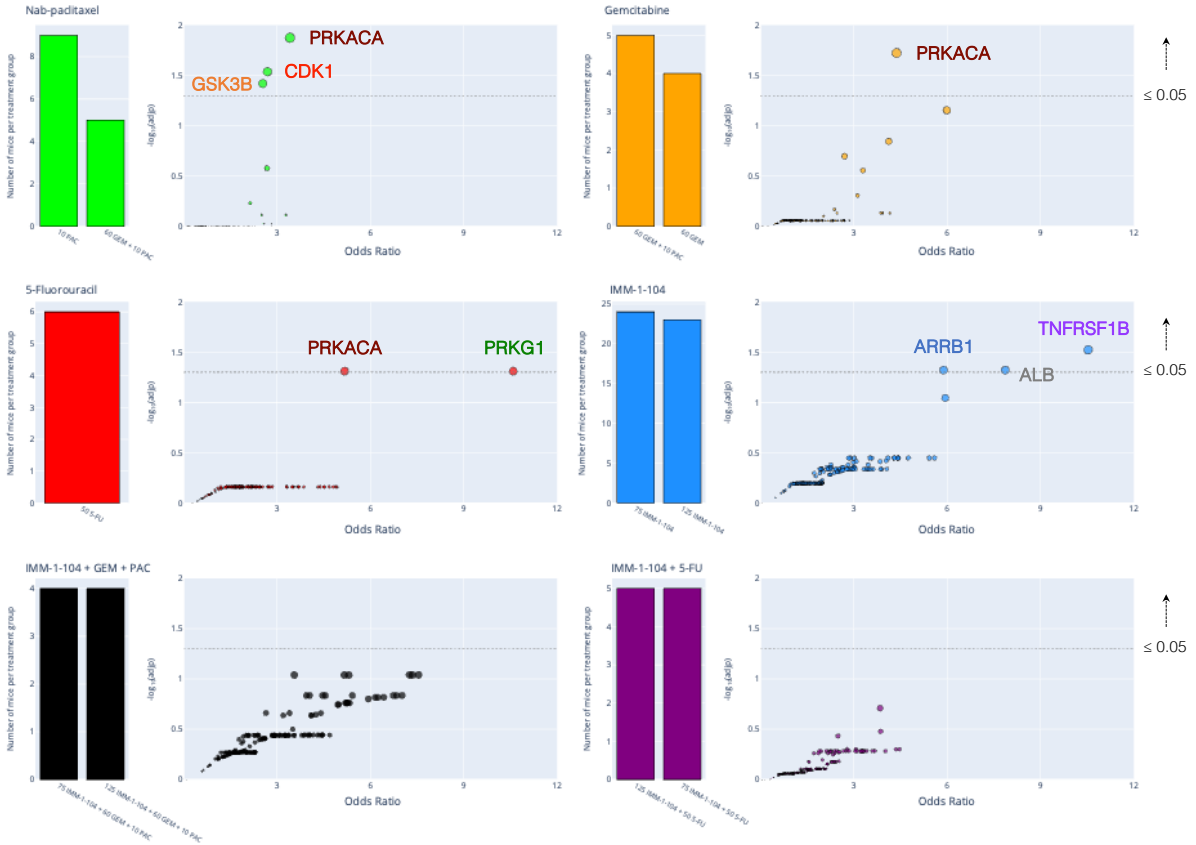
IMM-1-104 +/- chemotherapy in MIA PaCa-2 pancreatic xenograft model



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.

Treatment-Acquired Mutations Show Distinct Mechanisms of Adaptation

Enrichment Analysis of Recurring-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]

IMM-6-415

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IMM-6-415: Phase 1/2 Clinical Trial Plan

First Time in Humans

Phase 1: Dose Escalation & Evaluation

IMM-6-415
(2x/daily, oral, DCI for RAS/RAF mutant solid tumors)

First patient dosed March 2024

Dose Escalation Phase 1a*

Bayesian Design (mTPI-2) escalation

Dose Evaluation Phase 1b

Dose Evaluation and Candidate RP2D**

Phase 2a

Tumor specific cohorts

Phase 1 endpoints: safety, tolerability, PK & PD

* Solid tumor, all comer with evidence of RAF, KRAS, NRAS or HRAS mutation.
**RP2D = Recommended Phase 2 Dose

IMM-6-415: Monotherapy Activity in RAF and RAS Mutant Tumors

NRAS^{Q61R} MEL — SK-MEL-2

BRAF^{V600E} MEL — A-375

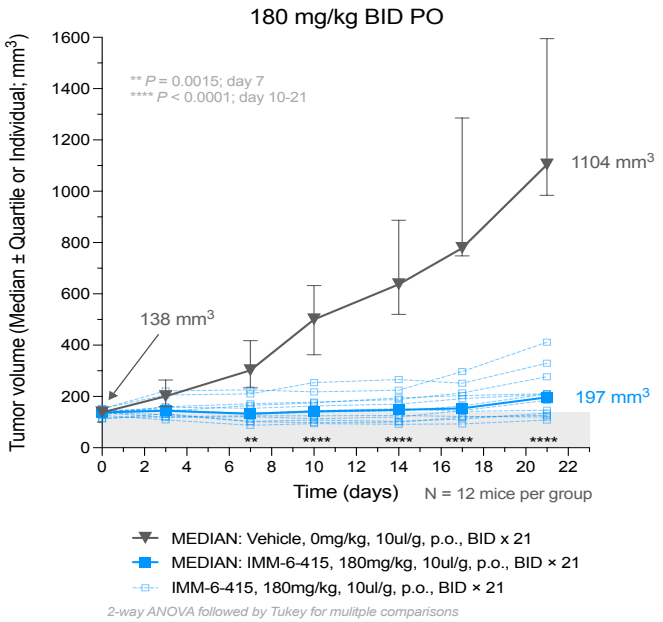
BRAF^{V600E} MEL — SK-MEL-28

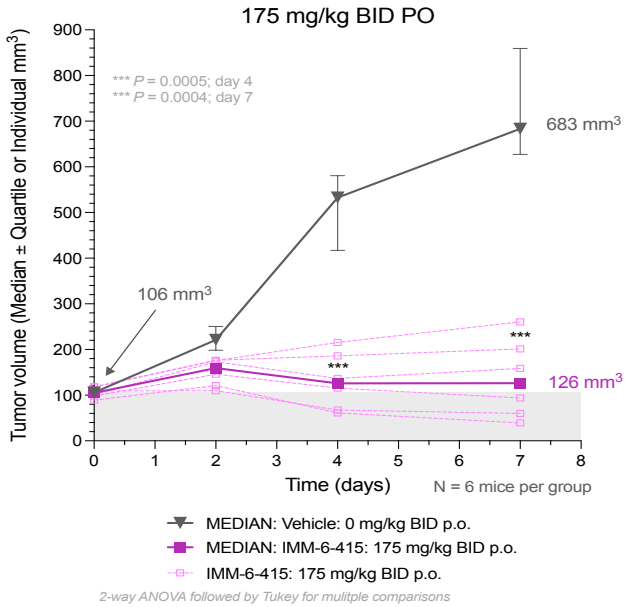
KRAS^{G12S} NSCLC — A-549

KRAS^{G12D} CRC — Colon-26

Model	HRAS	NRAS	BRAF	NF1	3D-TGA
SK-MEL-2		p.Q61R			
MM127		p.G13R	p.G464E		n.t.
MM415		p.Q61L			n.t.
MEL-JUSO	p.G13D	p.Q61L			n.t.
SK-MEL-30		p.Q61K			n.t.
Hs852T		p.G12V			n.t.
MeWo				LoF	n.t.
A375			p.V600E		
SK-MEL-28			p.V600E		

3D-Tumor Growth Assay (3D-TGA) sensitivity (green)





Well Tolerated up to Maximum Monotherapy Effective Dose Range of 150 to 180 mg/kg

SITC 2022 Presentation: Maximum Effective Dose Range in Mice (**plasma $t_{1/2}$ = 0.3 to 0.4 hours**): 150-180 mg/kg BID

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

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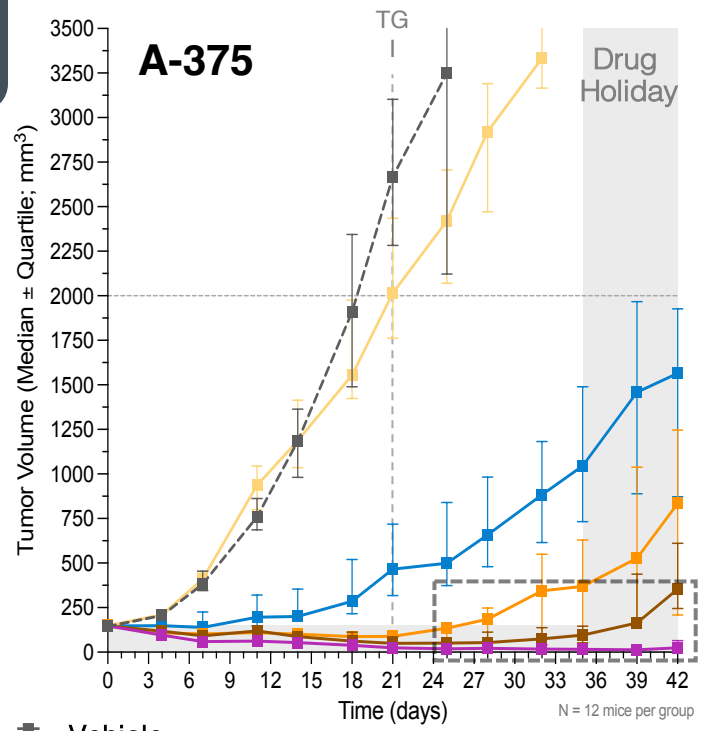
IMM-6-415 (I) ± Encorafenib (E) vs Binimetinib (B) ± Encorafenib in A-375

BRAF^{V600E} MEL

RAF V600E + DCI MEK



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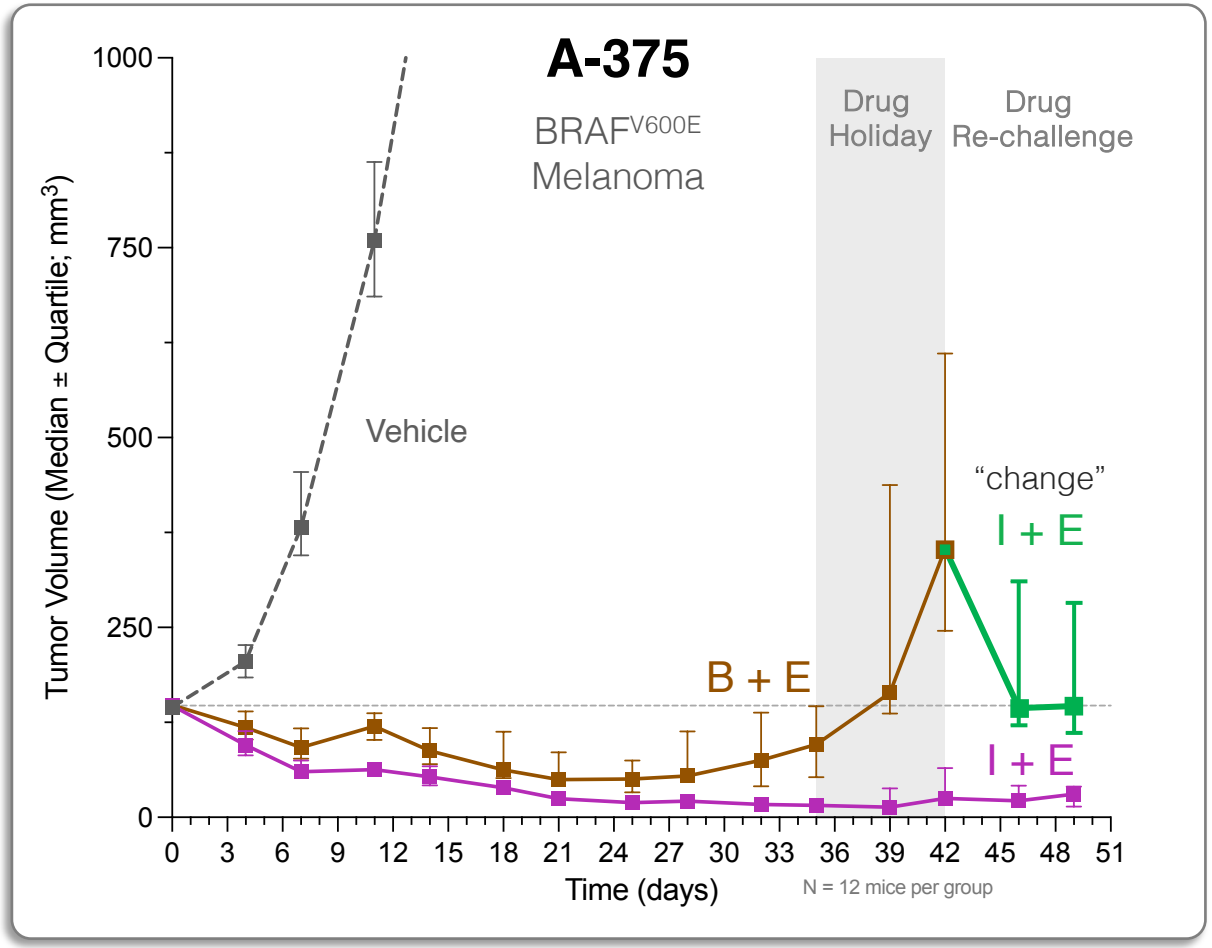

A-375 Melanoma BRAF^{V600E} xenograft tumor models in athymic nude mice. Binimetinib (MEK inhibitor) and encorafenib (BRAF inhibitor) were commercially purchased. Tumor Growth Inhibition (TGI) % = [1-(Ti-To)/(Ci-Co)]x100%. No median body weight loss was noted.

Corporate

Immuneering

Finance & Intellectual Property

Finance

- Cash, cash equivalents and marketable securities as of December 31, 2023: **$85.7M**
- **Cash runway projected into 2H 2025** supports:
  - IMM-1-104:
    - Multiple data readouts from Phase 1/2a trial
  - IMM-6-415:
    - Phase 1/2a clinical trial
  - Research in additional oncology programs

Intellectual Property*

Patents issued/pending:

- Pending U.S. and ex-U.S. applications relating to IMM-1-104
- Pending U.S. provisional and PCT applications relating to IMM-6-415
- Issued U.S. patent and pending application relating to DCT
- Pending U.S. applications to Fluency

Patent term on lead asset (excluding patent term adjustments, etc.) expected until at least 2041

*As reported in the Company's most recent Annual Report on Form 10-K filed with the SEC

Milestones

Program	Milestone	Expected Timing
IMM-1-104	Phase 1 topline data (tolerability, candidate RP2D, PK/PD, ctDNA and initial clinical activity)	**COMPLETE**
IMM-1-104	First Patient Dosed in Phase 2a	**COMPLETE**
IMM-1-104	Initial Data from Multiple Arms of the Phase 2a	2024
IMM-6-415	First Patient Dosed in Phase 1/2a	**COMPLETE**
IMM-6-415	Initial Phase 1 PK/PD and safety data	2024

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- **Active discovery pipeline**
- **Cash runway** projected **into 2H 2025**

*1L Melanoma for patients who are not candidates for existing therapies

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- Nasdaq: IMRX

Appendix

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Nasdaq: IMRX

≥ 3 Line PDAC: No benchmarks, increased lesion-to-lesion heterogeneity

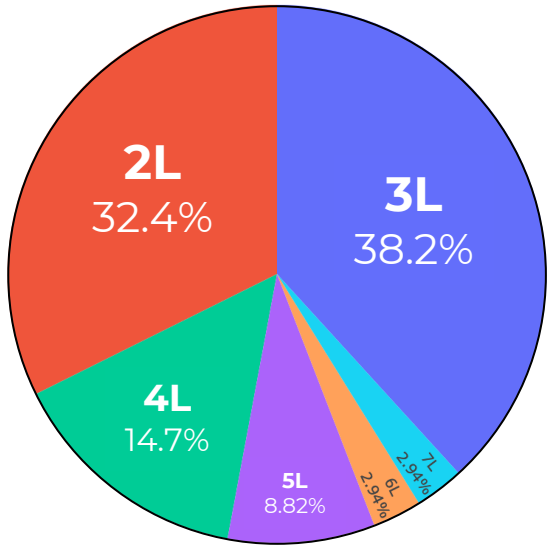
Pancreatic Cancer Benchmarks

Trial	Treatment	Line of Treatment	ORR
[a] **Phase III MPACT**	Gemcitabine	**1st Line**	**7%**
[a] **Phase III MPACT**	Gemcitabine + nab-paclitaxel	**1st Line**	**23%**
[b] **Phase III PRODIGE/ACCORD 11**	FOLFIRINOX	**1st Line**	**32%**
[c] **Phase III NAPOLI-3**	NALIRIFOX	**1st Line**	**42%**
[d] **Phase III NAPOLI-1**	nal-IRI + FU/LV	**2nd Line**	**17%**
[e] **Phase III MPACA-3**	mFOLFIRINOX	**2nd Line**	**15%**

[a] Phase III MPACT trial (link)
[b] Phase III PRODIGE/ACCORD 11 trial (link)
[c] Phase III NAPOLI-3 trial (link)
[d] Phase III NAPOLI-1 trial (link)
[e] Phase III MPACA-3 trial (link)

Phase 1 Patients

IMM-1-104 treatment line



Topline EDC snapshot as of February 20, 2024 (IMM-1-104) 34 patients with prior treatment history

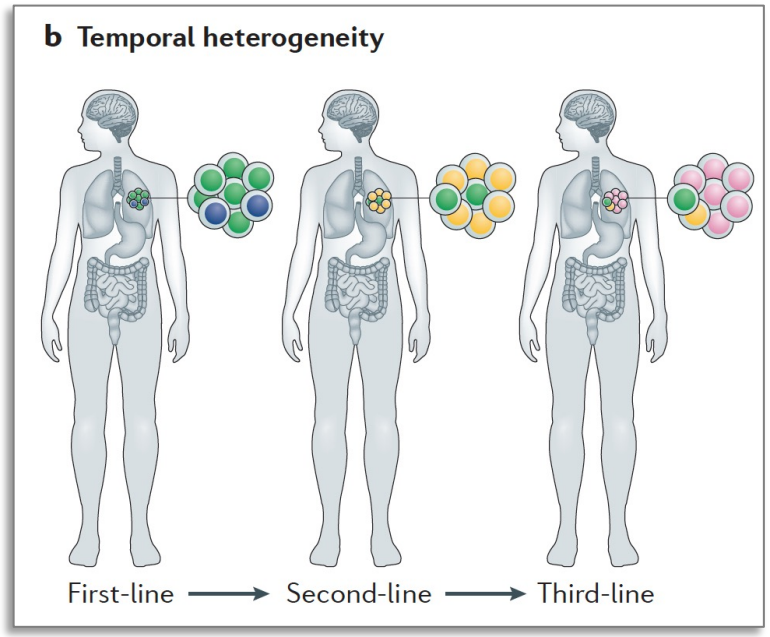
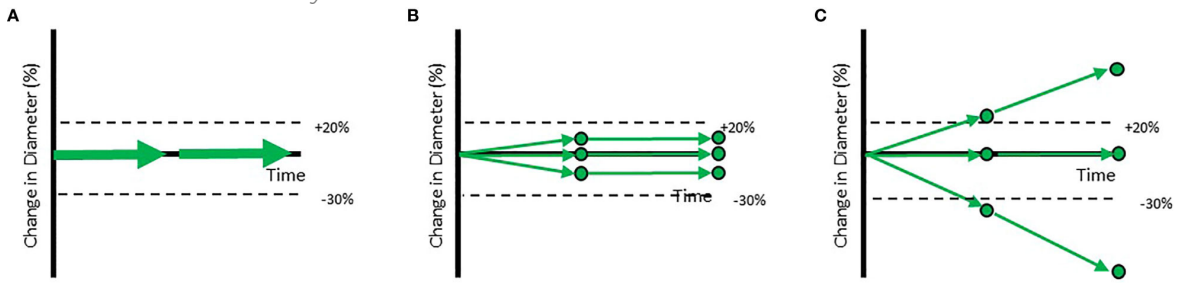


Figure from: 2018 Nat. Rev. Clin. Onc. 15:81



"...patient response evaluation with an appreciation of lesion-to-lesion heterogeneity can potentially improve decision-making at the early stage of oncology drug development..." [Kumar, et al. 2023]

Figure from: https://doi.org/10.3389/fimmu.2023.1173546

Immuneering

Patient Status Summary for IMM-1-104 (as reported at AACR April 2023)

#	Patient	RAS Mutation	Dose Level	Dose	C1D1 ($t_{1/2}$)	C1D15 ($t_{1/2}$)	Mean ($t_{1/2}$)	DLT Window
1.	PANCREATIC	KRAS-G12D	I	40 mg QD p.o.	1.82 hours	2.10 hours	**1.96 hours**	Cleared
2.	COLORECTAL	KRAS-G12V	II	80 mg QD p.o.	1.41 hours	1.43 hours	**1.42 hours**	Cleared
3.	COLORECTAL	NRAS-Q61L	III	160 mg QD p.o.	2.04 hours	1.83 hours	**1.94 hours**	Cleared
4.	COLORECTAL	NRAS-Q61K	III	160 mg QD p.o.	1.91 hours	1.97 hours	**1.94 hours**	Cleared
5.	PANCREATIC	KRAS-G12D	IV	320 mg QD p.o.	2.31 hours	2.46 hours	**2.38 hours**	Cleared
6.	PANCREATIC	KRAS-G12V	IV	320 mg QD p.o.	2.04 hours	2.27 hours	**2.16 hours**	Cleared
7.	COLORECTAL	KRAS-G12S	IV	320 mg QD p.o.	1.45 hours	2.27 hours	**1.86 hours**	Cleared

BLUE = Clinical data timeline reported through April 10th, 2023 (i.e., ~20 weeks since first patient dosed)
GRAY = Data subsequent to AACR that are part of phase 1a dose escalation and have cleared the DLT window

Represents a variety of tumor types, RAS mutations and covers four dose levels

Additional patient enrolled at 160 mg QD p.o. (NRAS-G13R Melanoma); independent of DLT dose escalation

IMM-1-104 Demonstrated Universal-RAS Potential

193 Tumor Models

114 = RAS Mutant

33 = RAF Mutant

Humanized 3D-TGA

Nair, et al. 2023
AACR EORTC
Boston, MA

Tissue	Response #	Non-Response #
Pancreatic †	**18**	**2**
Melanoma †	**24**	**0**
Lung †	**25**	**11**
CRC	**25**	**5**
Thyroid	9	2
Cholangiocarcinoma	7	0
AML	9	0
Uveal Melanoma	4	1
Multiple Myeloma	4	4
Soft Tissue	4	2
Breast	2	6
Gastric	4	2
Ovary	2	3
Prostate	1	2
Fibrosarcoma	1	0
Liver	4	2
Neuroblastoma	1	1
Other (BLA, UTE, ESO, HNSQ)	5	1
Total	**149** (77.2%)	**44** (22.8%)

RAS, RAF mutation	Response #	Non-Response #
NRAS G12	5	0
NRAS G13	1	0
NRAS Q61	23	3
KRAS A146	2	1
KRAS G12	54	10
KRAS G13 ^	4	1
KRAS Q61	5	3
HRAS G12	1	0
HRAS G13 *	1	0
HRAS Q61	2	0
BRAF (Class I or II)	29	5
Total	**126** (84.7%)	**23** (15.3%)

RAS, RAF mutation	Response #	Non-Response #
Not Present	25	19
Total	**25** (56.8%)	**19** (43.18%)

^ 1 model also bearing KRAS Q61 /// * 1 model also bearing NRAS Q61

Response to IMM-1-104 based on 3D-TGA and other preclinical modeling. Parallel translational efforts are focused on projecting patient-aligned molecular profiles or 'Targetability'.

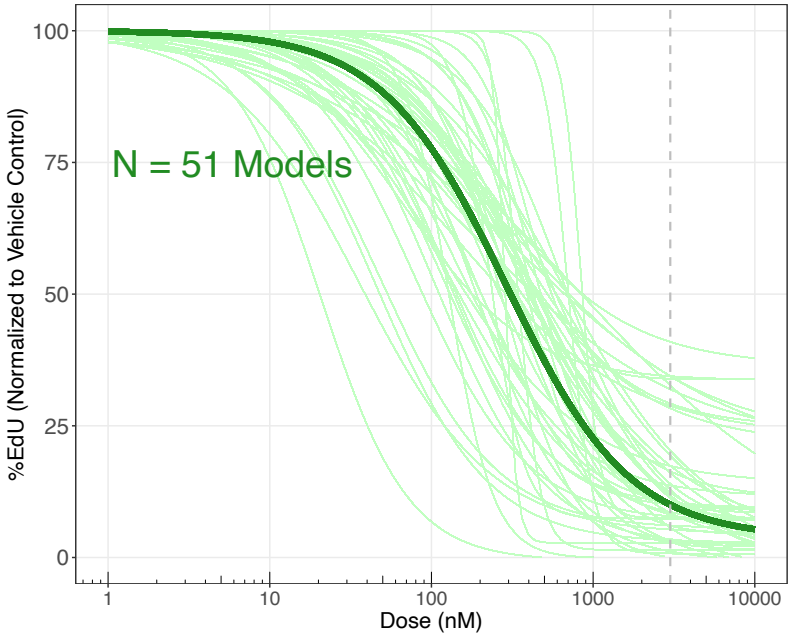
Models tested in 3D-TGA were assigned responsive if dose response IC50 < 1uM (sensitive) or IC50 ≥ 1 with >25% reduction at 10uM (intermediate), and non-responsive otherwise (resistant)

† Select 3D-TGA models: (1.) Pancreatic MIA PaCa-2 (sensitive/responsive), (2.) Pancreatic Capan-2 (intermediate/responsive), (3.) Melanoma SK-MEL-2 (sensitive/responsive), (4.) Lung A549 (intermediate/responsive)

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

Attaining Clinical Free Fraction C_{max} of ~1-3 uM; Aligns with 3D-TGA Response Categorization

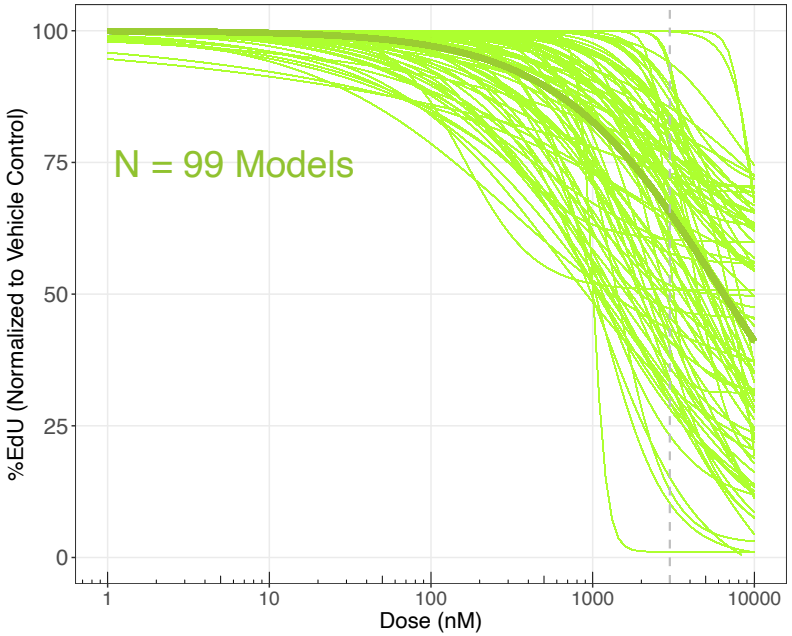
3D-TGA: Sensitive Tumor Models



Subset of Sensitive Models:

- MEL: 62.5% (15/24)
- PANC: 35.0% (7/20)
- LUNG: 16.7% (6/36)
- CRC: 6.7% (2/30)

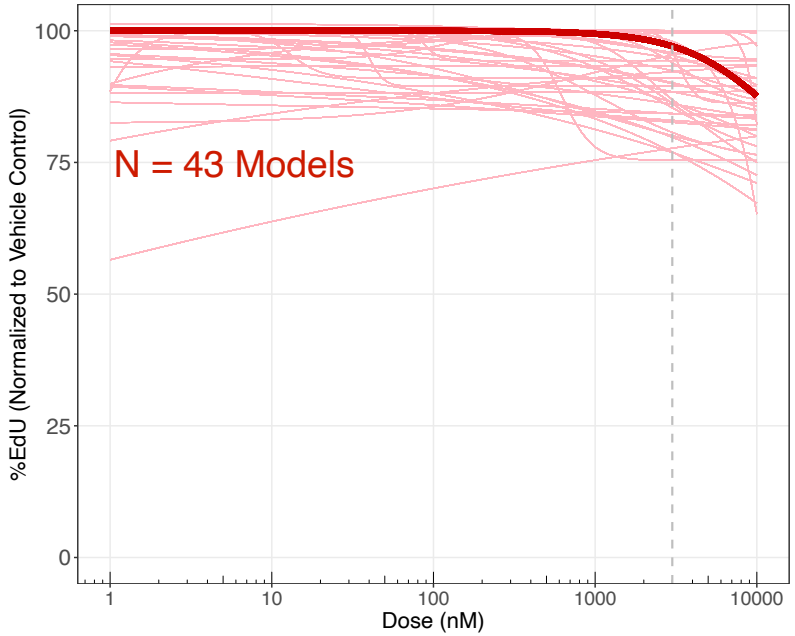
3D-TGA: Intermediate Tumor Models



Subset of Intermediate Models:

- MEL: 37.5% (9/24)
- PANC: 55.0% (11/20)
- LUNG: 52.8% (19/36)
- CRC: 76.7% (23/30)

3D-TGA: Resistant Tumor Models



Subset of Resistant Models:

- MEL: 0.0% (0/24)
- PANC: 10.0% (2/20)
- LUNG: 30.6% (11/36)
- CRC: 16.7% (5/30)

- 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)

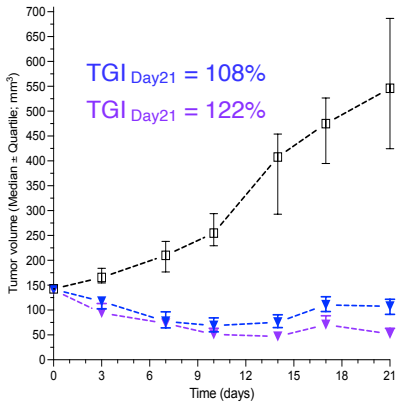
Nair, et al. 2023, AACR EORTC, Boston, MA

IMM-1-104 Demonstrated Universal-RAS Potential

IMM-1-104 demonstrated significant and consistent Tumor Growth Inhibition (TGI)

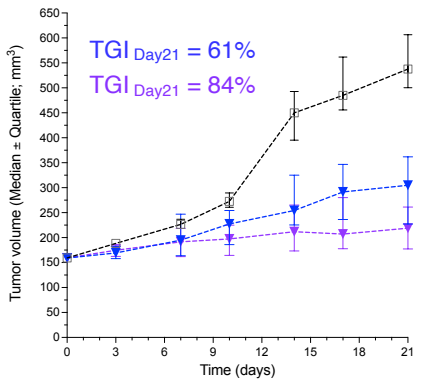
DCI MEK

$KRAS^{G12C}$ PANC	$KRAS^{G12V}$ PANC	$NRAS^{Q61R}$ MEL	$KRAS^{G12S}$ NSCLC	$KRAS^{G12D}$ CRC
MIA PaCa-2	Capan-2	SK-MEL-2	A-549	Colon-26



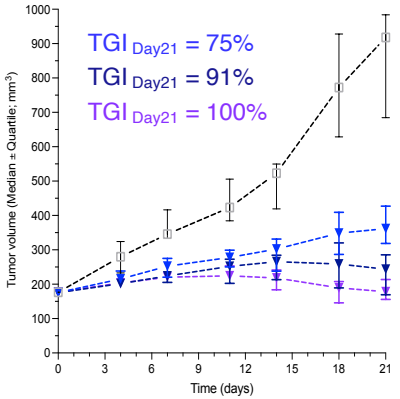
N=12

- **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



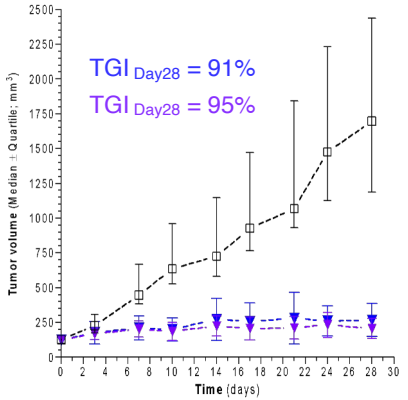
N=12

- **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



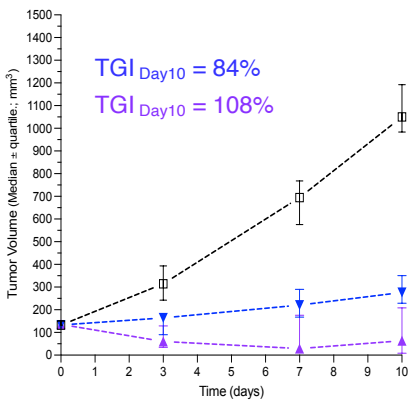
N=12

- **MEDIAN:** 0 mg/kg Vehicle BID po
- **MEDIAN:** 100 mg/kg IMM-1-104 BID po
- **MEDIAN:** 125 mg/kg IMM-1-104 BID po
- **MEDIAN:** 150 mg/kg IMM-1-104 BID po



N=12

- **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



N=8

- **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

Well Tolerated: Median Body Weight Loss ≤ 3-6%* of baseline at top doses

Maximum Effective Dose Range in Mice (plasma $t_{1/2}$ = 1.3 hours) is 100 mg/kg to 150 mg/kg BID po

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

Tumor Growth Inhibition (TGI) % = [1 – (Ti – T0)/(Ci – C0)]x100 ; T = treatment groups ; C = control groups
*Well-tolerated at top doses with no more than 3-6% median body weight loss (BWL)
**Capan-2 PANC model, as reported at ASCO 2022 (0% TGI for sotorasib and adagrasib at top doses)

Immuneering

Head-to-Head Comparison of IMM-1-104 +/- Sotorasib in KRAS^{G12C} PANC

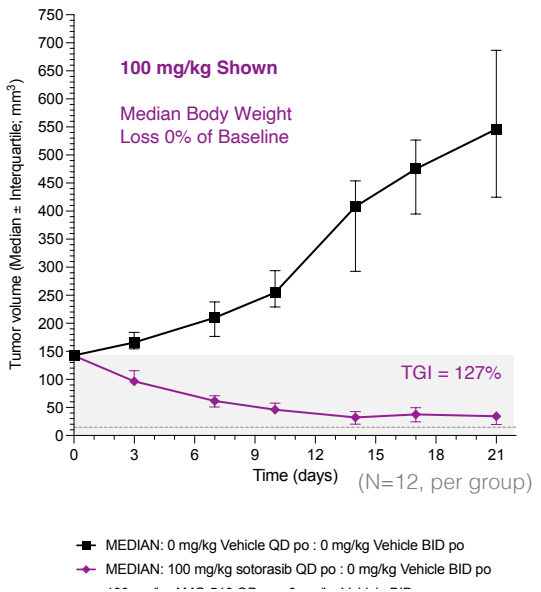
IMM-1-104 as compared to sotorasib demonstrated tumor regression, both with insignificant BWL

KRAS^{G12C} PANC

RAS G12C + DCI MEK

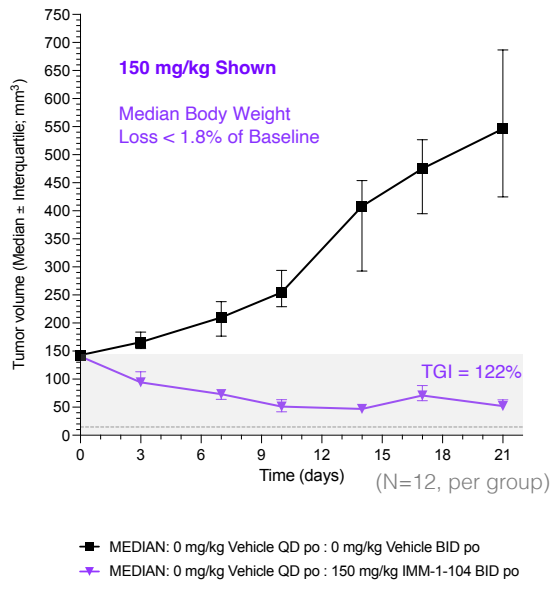
Sotorasib

10-30-100 mg/kg QD p.o.



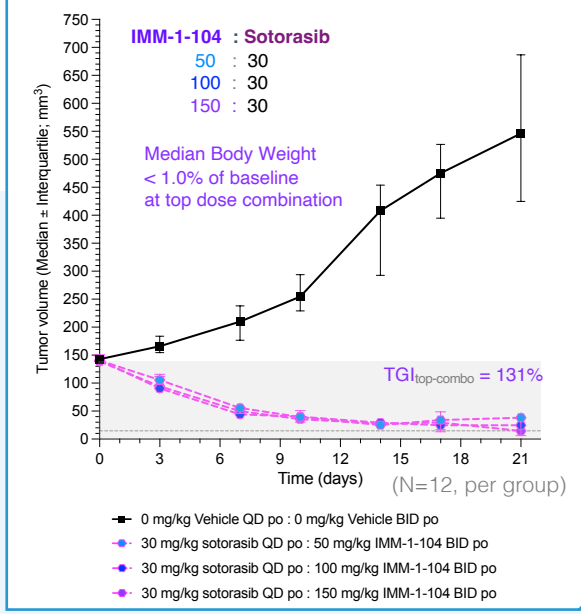
IMM-1-104

(50-100-150 mg/kg BID p.o.)



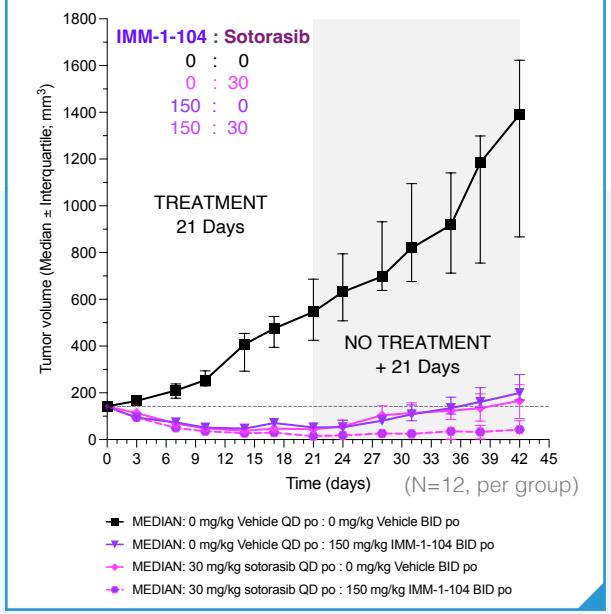
IMM-1-104 + Sotorasib

(50-100-150 mg/kg BID + 30 mg/kg QD)



IMM-1-104 + Sotorasib

(150 mg/kg BID + 30 mg/kg QD)



› MIA PaCa-2 (KRAS^{G12C}) Pancreatic Xenograft Tumor Model in Athymic Nude Mice

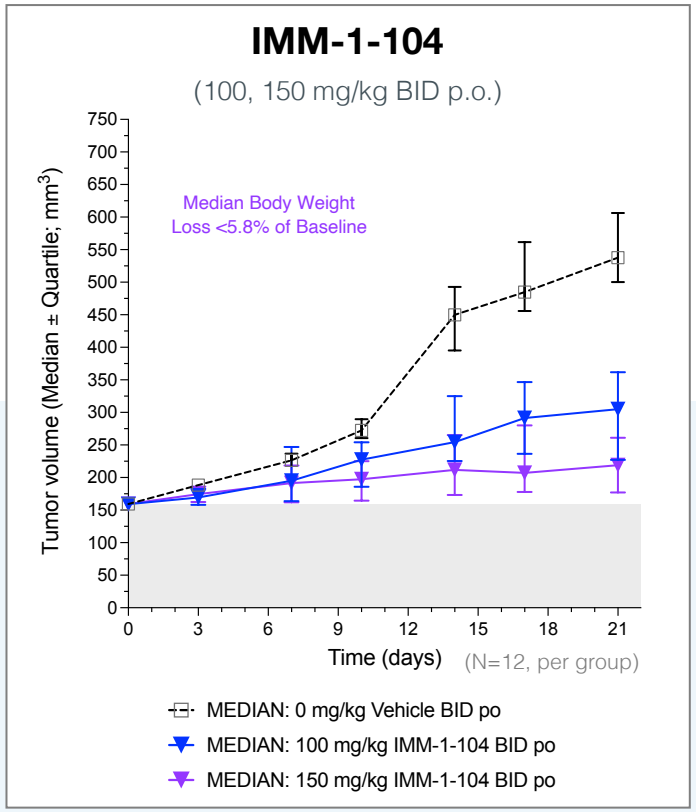
› *Sotorasib was commercially purchased*

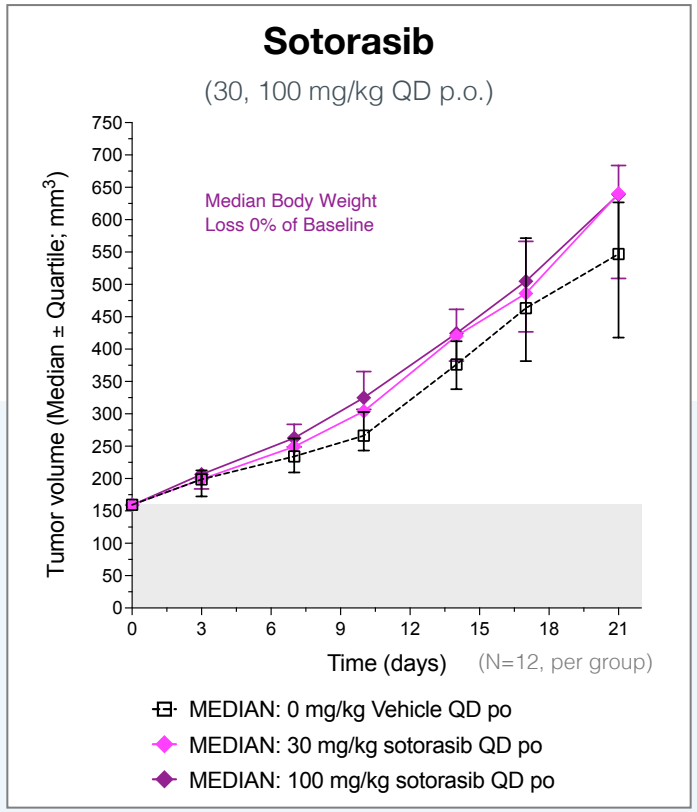
Tumor Growth Inhibition (TGI) % = [1 – (T_i – T_0)/(C_i – C_0)]x100%; Expanded TGI formula vs. previous 1-[T/C]x100% method

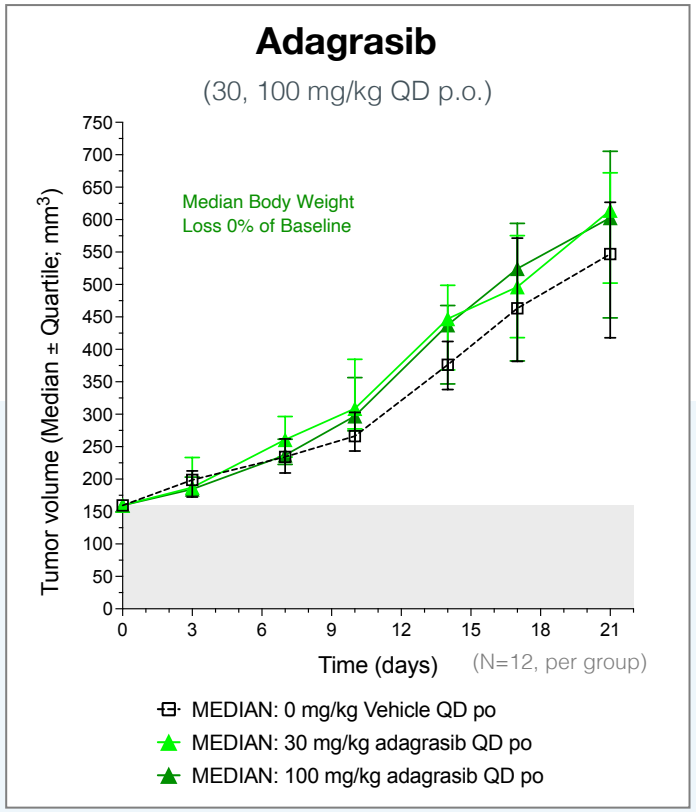
King, et al. 2021 AACR: EORTC (Philadelphia, PA)

Pancreatic: Head-to-Head Comparison of IMM-1-104 vs. Sotorasib and Adagrasib in a KRAS-G12V Pancreatic Tumor Model

IMM-1-104 demonstrated tumor regression as compared to no reduction with sotorasib or adagrasib, with insignificant BWL







› Capan-2 ($KRAS^{G12V}$) Pancreatic Xenograft Tumor Model in Athymic Nude Mice

› *Sotorasib and adagrasib were commercially purchased*

Tumor Growth Inhibition (TGI) % = $[1 – (T_i – T_0)/(C_i – C_0)]x100\%$; Expanded TGI formula vs. previous 1-[T/C]x100% method

Immuneering

Melanoma: Phase 3 NEMO Study: Binimetinib vs. Dacarbazine (NRAS^{mut} Melanoma)

Summary of Phase 3 NEMO study of Binimetinib as reported in Lancet (c.2017) - ***a potential opportunity for IMM-1-104***

	Progression Free Survival	Overall Survival
Binimetinib	2.8 months	11.0 months
Hazard Ratio	**0.62**	**1.00**
Dacarbazine	1.5 months	10.1 months

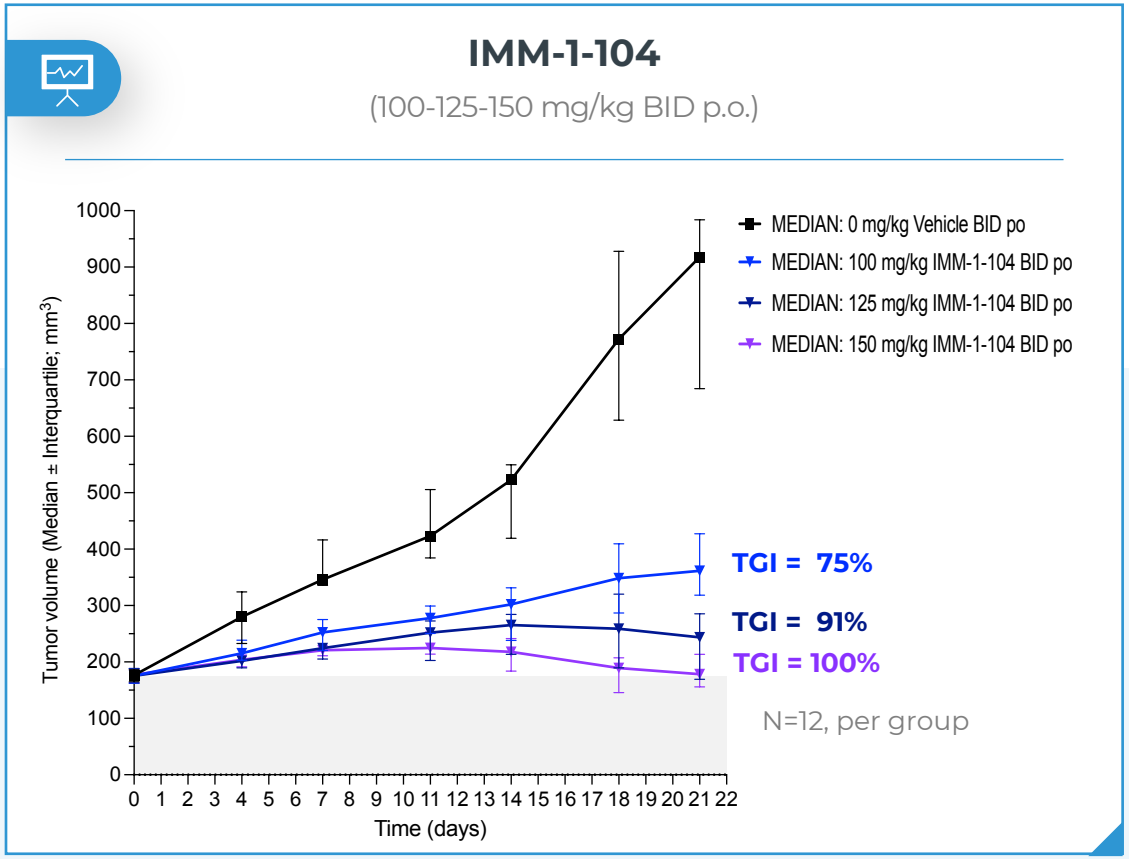
NRAS Status	Binimetinib 2:1	Dacarbazine
	N = 269	**N = 133**
Q61K	100 (37%)	51 (38%)
Q61L	32 (12%)	17 (13%)
Q61R	137 (51%)	64 (48%)
Wildtype	0	1 (1%)

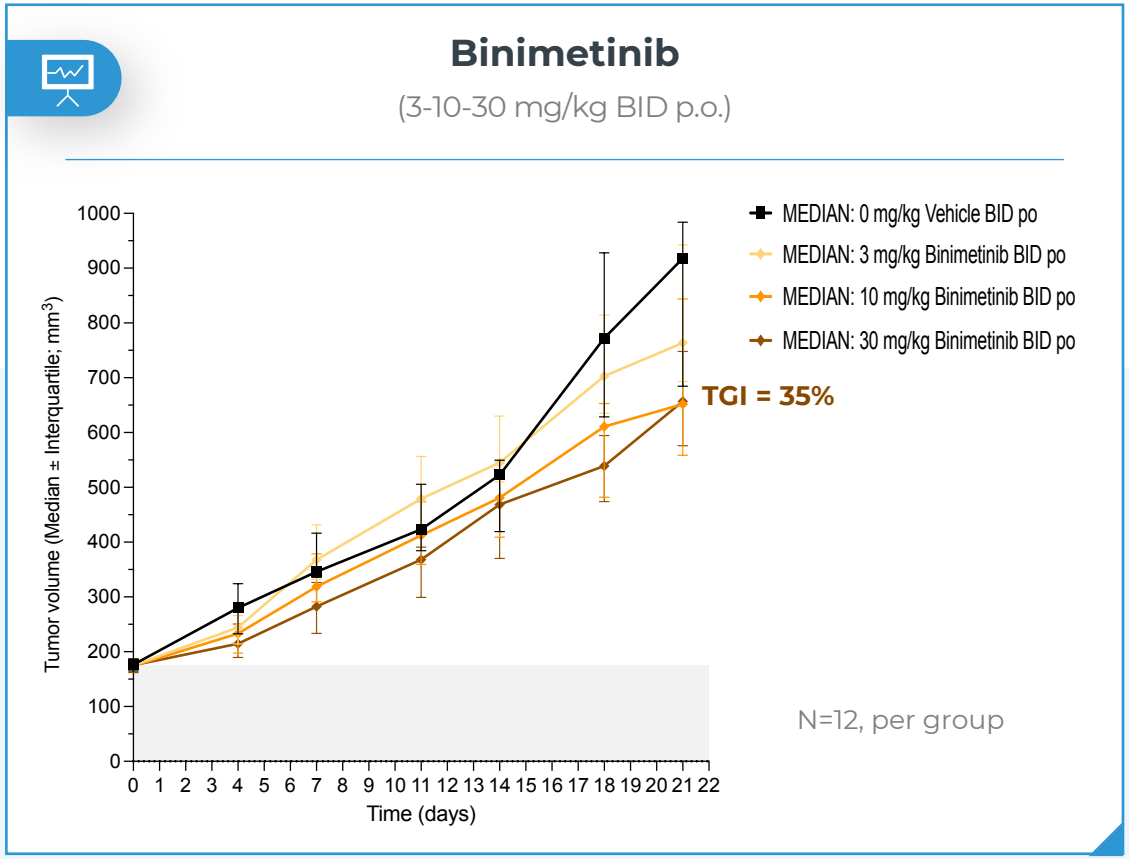
- Serious Adverse Events (34% binimetinib vs. 22% dacarbazine)
- Overall Response Rate (ORR: 15% binimetinib vs. 7% dacarbazine)

Dummer, et al 2017 Lancet S1470-2045 (17) 30180-8

Melanoma: Head-to-Head NRAS-Q61R Melanoma Xenograft Study: Binimetinib vs. IMM-1-104 in SK-MEL-2

IMM-1-104 as compared to binimetinib monotherapy demonstrated greater tumor growth inhibition (TGI)





SK-MEL-2 (NRAS-Q61R) Melanoma Xenograft Tumor Model in Athymic Nude Mice

Binimetinib was commercially purchased

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

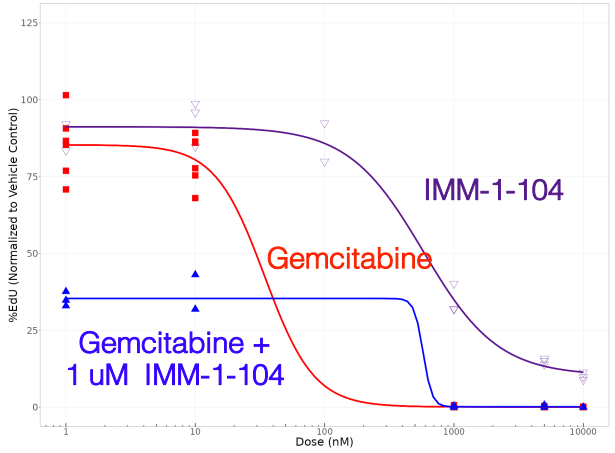
RAS^{mut} PANC

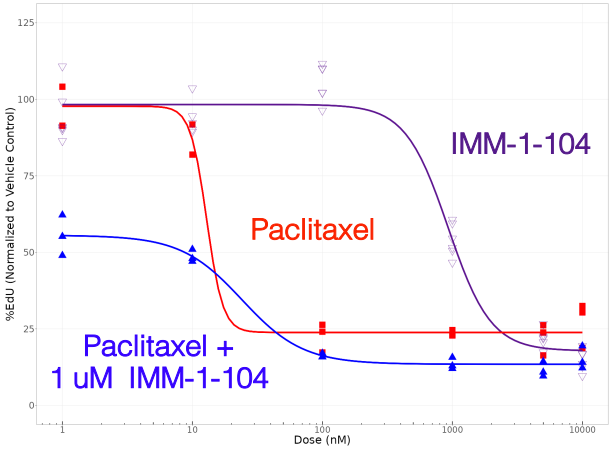
CT + DCI MEK

IMM-1-104 +/- Gemcitabine

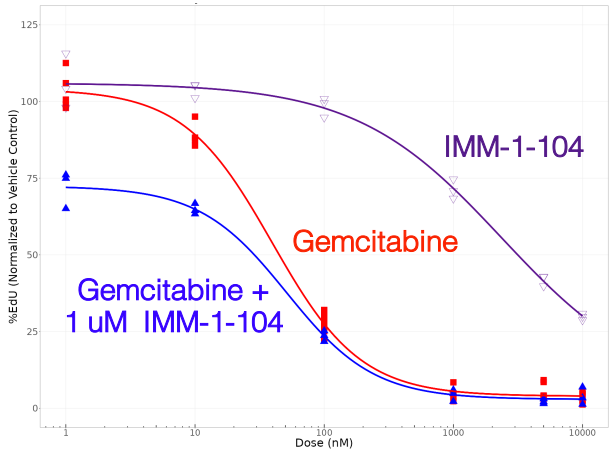
IMM-1-104 +/- Paclitaxel

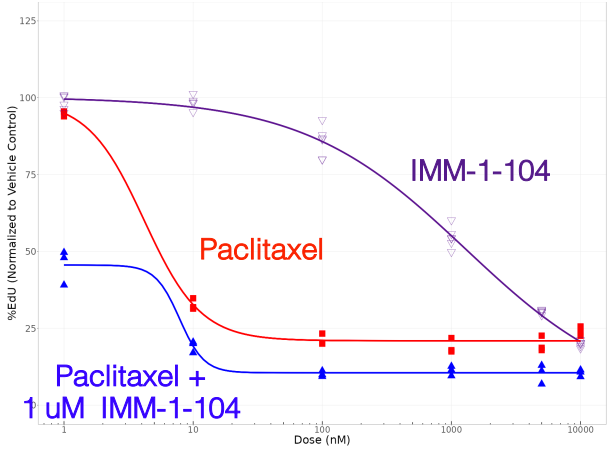
MIA PaCa-2 (KRAS-G12C)



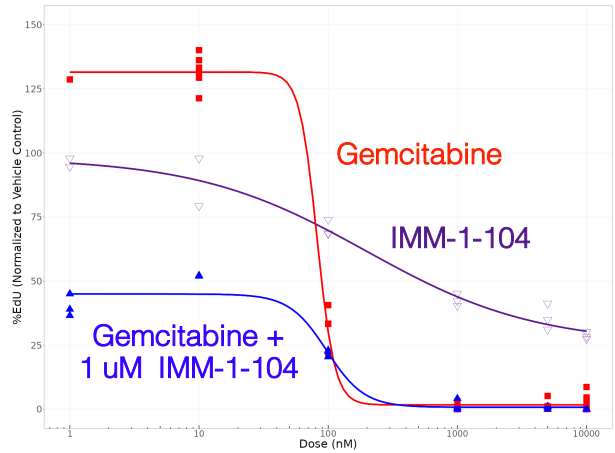


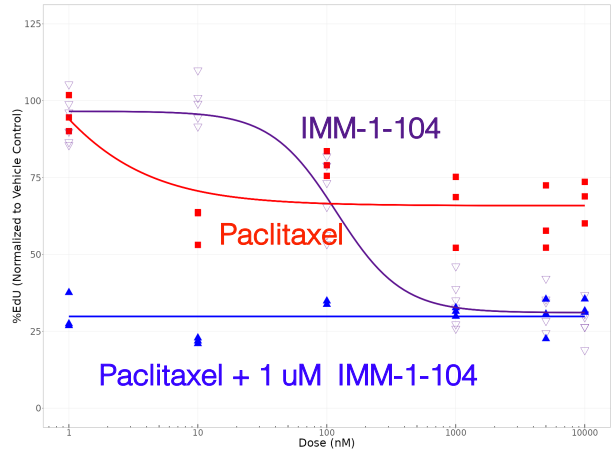
PANC 03-27 (KRAS-G12V)





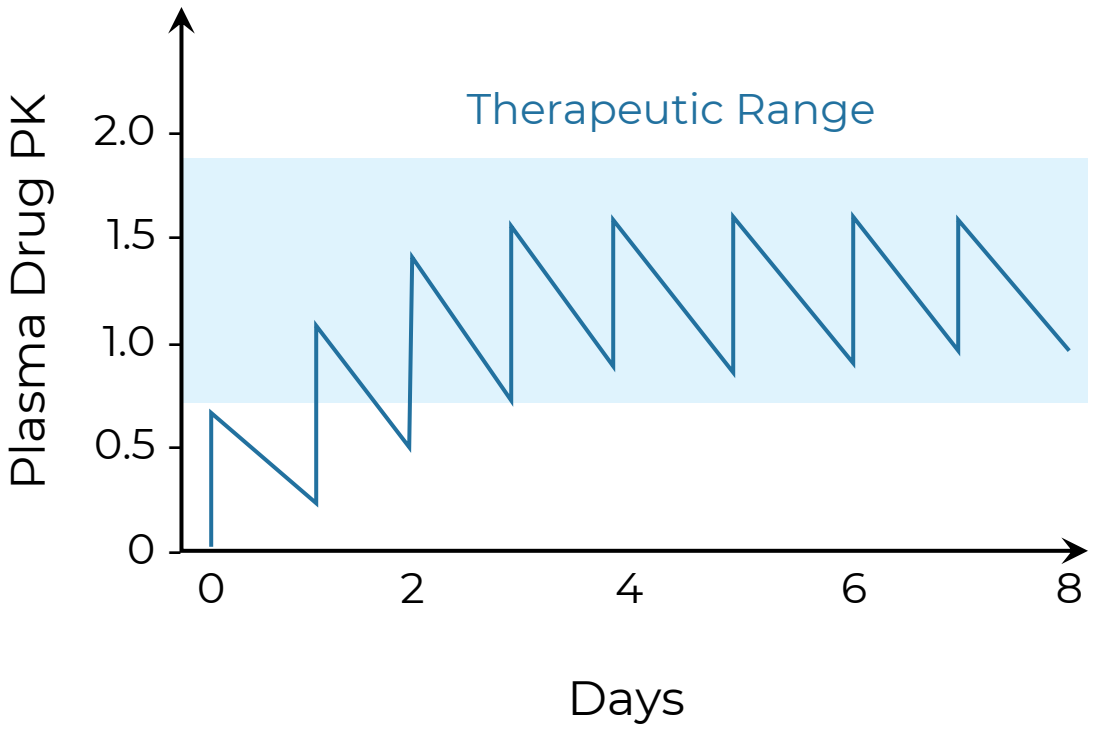
PANC1 (KRAS-G12D)

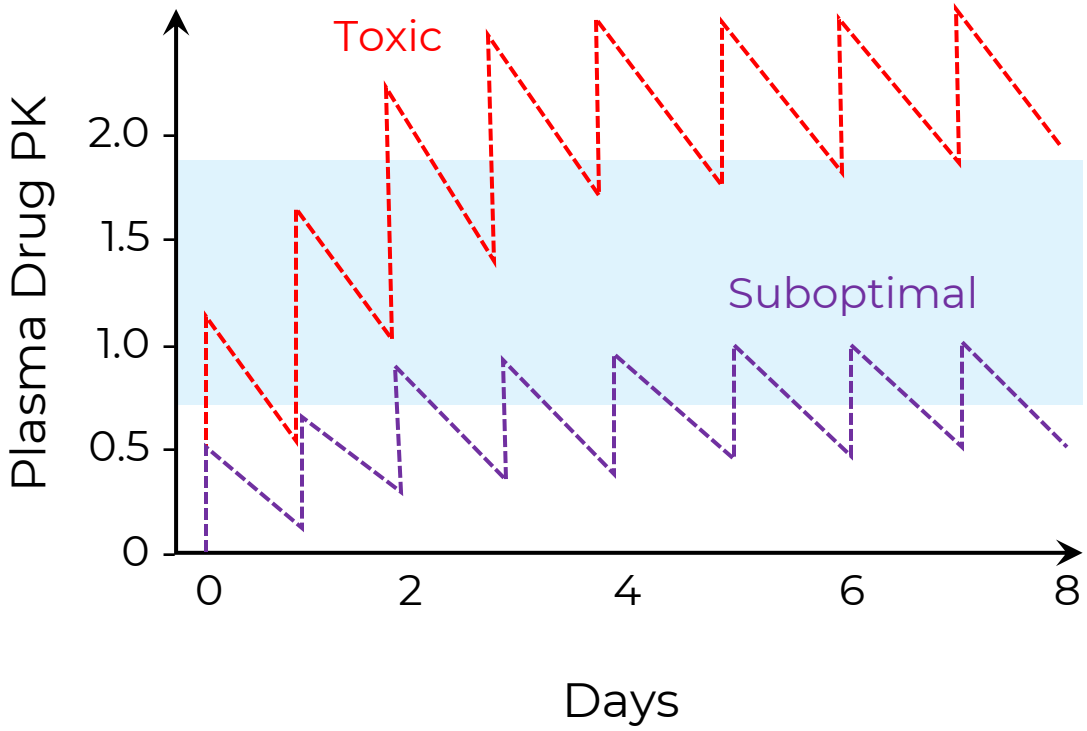




IMM-1-104 ± CT dose response curves in the humanized 3D Tumor Growth Assay (3D-TGA)[2,3]. Three human pancreatic cancer cell models were selected based on patient alignment scores, where each model's mutational profile mapped to three distinct subsets of GENIE v13.1 patients categorized as pancreatic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

Chronic Pathway Inhibition in Targeted Oncology





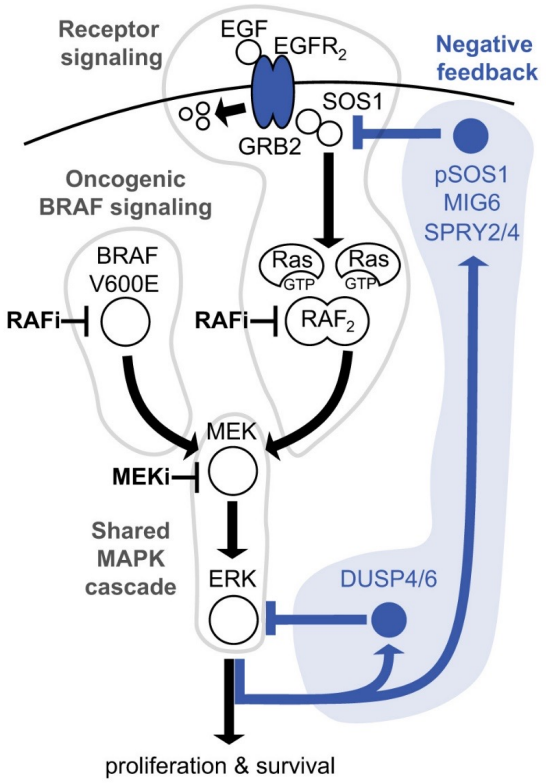
Common approach for therapeutic dosing (**chronic drug exposures**)

Challenges with Chronic Pathway Inhibition

Limited response, short durability, toxicity and limited clinical utility

Loss of Negative Regulators

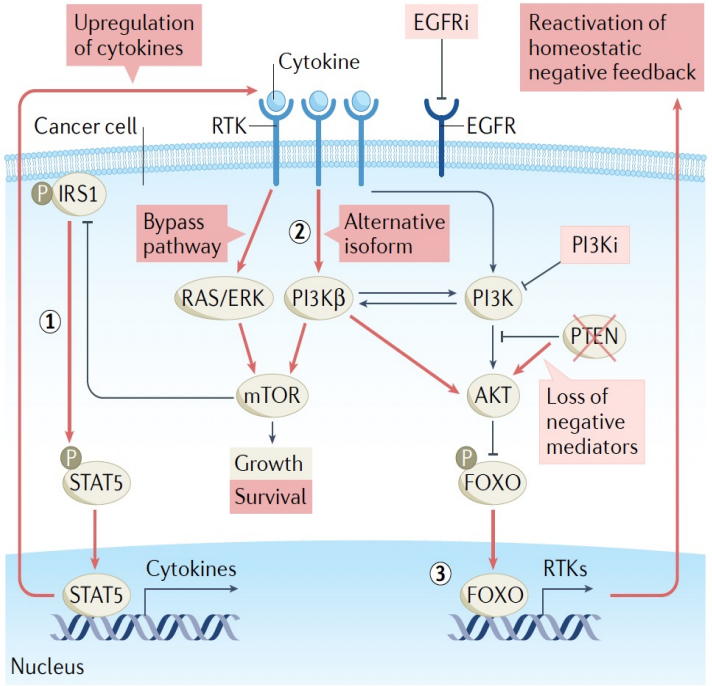
- Loss of MAPK Pathway Control -



Gerosa et al, Cell Systems, 2020

Increased Adaptive Resistance

- Gateway to acquired resistance -



2022 Nat Rev Can p.323

Increased Risk of MEK Toxicities

- Loss of key homeostatic pathway -

Clinical Scenario		V+C	D+T	E+B
Gastrointestinal disease	Diarrhea			
	Vomit			
	Anorexia	-	-	-
Liver disease	↑ AST			
	↑ ALT			
Cardiovascular disease	↓ Ejection fraction			-
	Hypertension			
Rheumatological disease	Arthralgia			
Dermatological disease	Skin rash			
Hematological disease	Anemia			

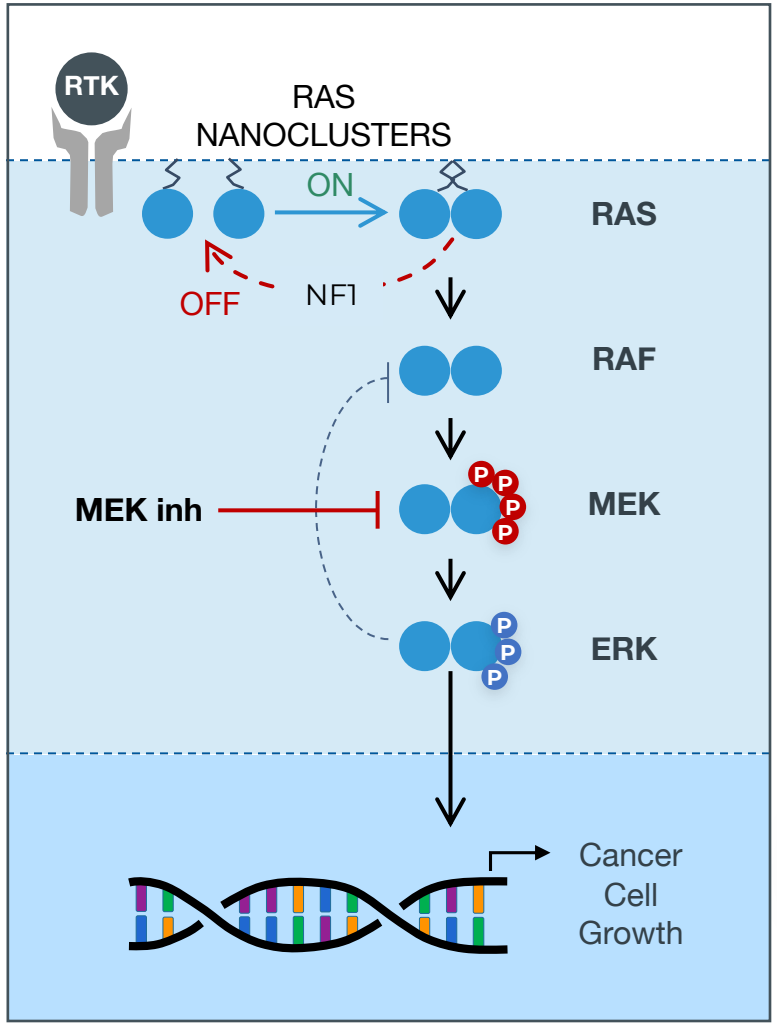
Grade 3, 4, 5 Events

I ≥ 10%
5% ≤ I < 10%
I < 5%

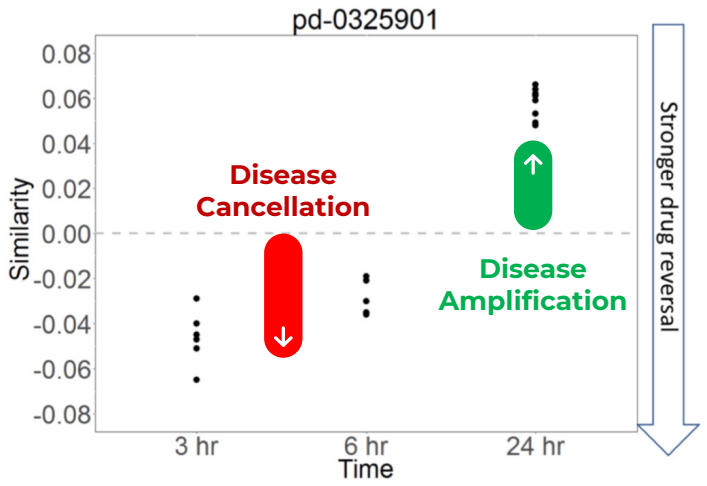
2019 ESMO Open p.e000491
2023 Cancers 15:141

Our Platform Converts Gene Expression to Counterintuitive Insights

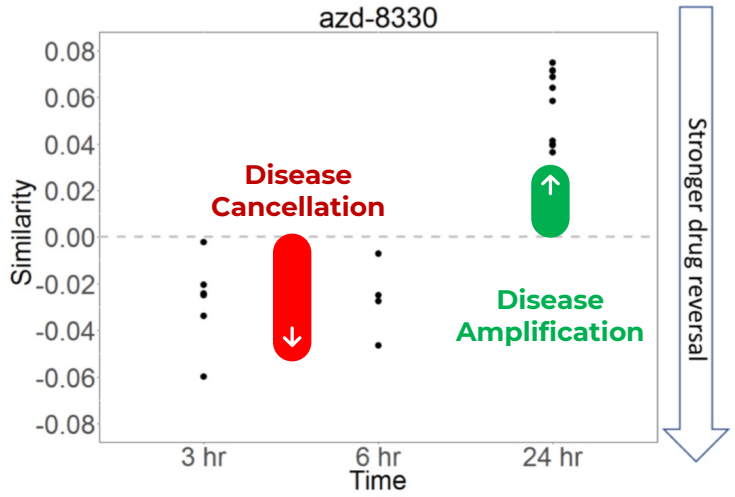
Goal: achieve **broader activity** and **better tolerability** in RAS and beyond mutant disease



1st generation MEKi



1st generation MEKi



Note: dots are representative of various concentrations

› *IMRX Disease Cancelling Technology - US Patent 11,043,305*

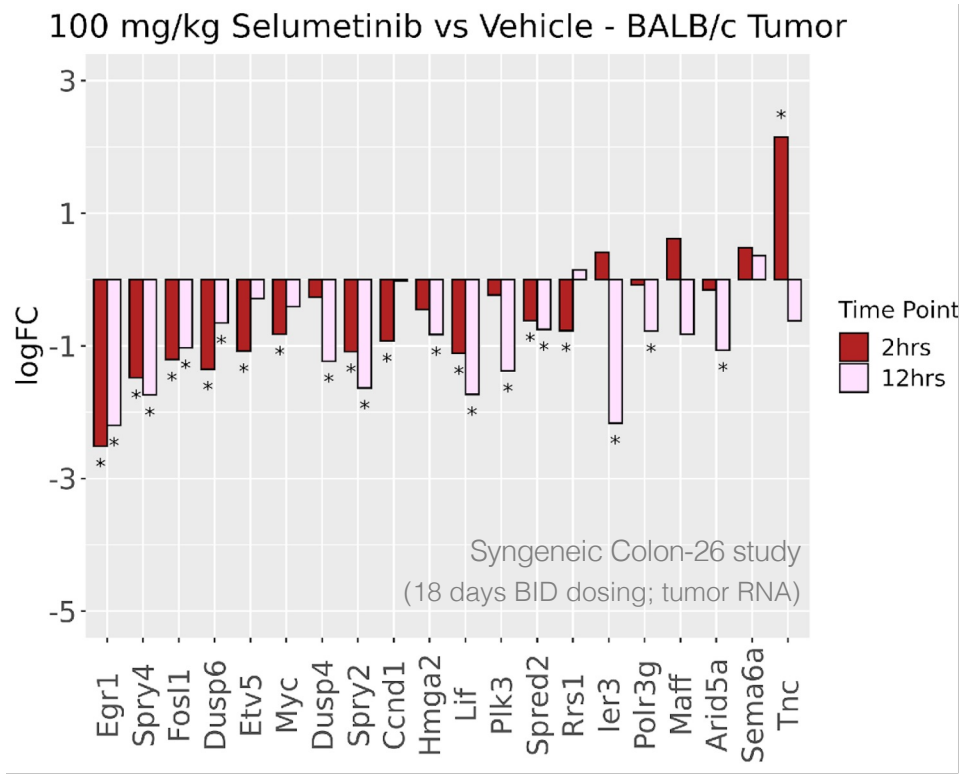
Unlike first generation MEK inhibitors, IMM-1-104 is designed to prevent RAF- and KSR-mediated activation of MEK (i.e., CRAF-bypass) and displays a short plasma half-life to potentially drive deep cyclic inhibition of the pathway.

Data-driven Identification and Optimization of New Medicines to Cancel Cancer Cachexia
Presented by Ben Zeskind at the 12th International Conference of Cachexia, Sarcopenia & Muscle Wasting (SCWD) in Berlin, Dec. 6-8, 2019

Immuneering

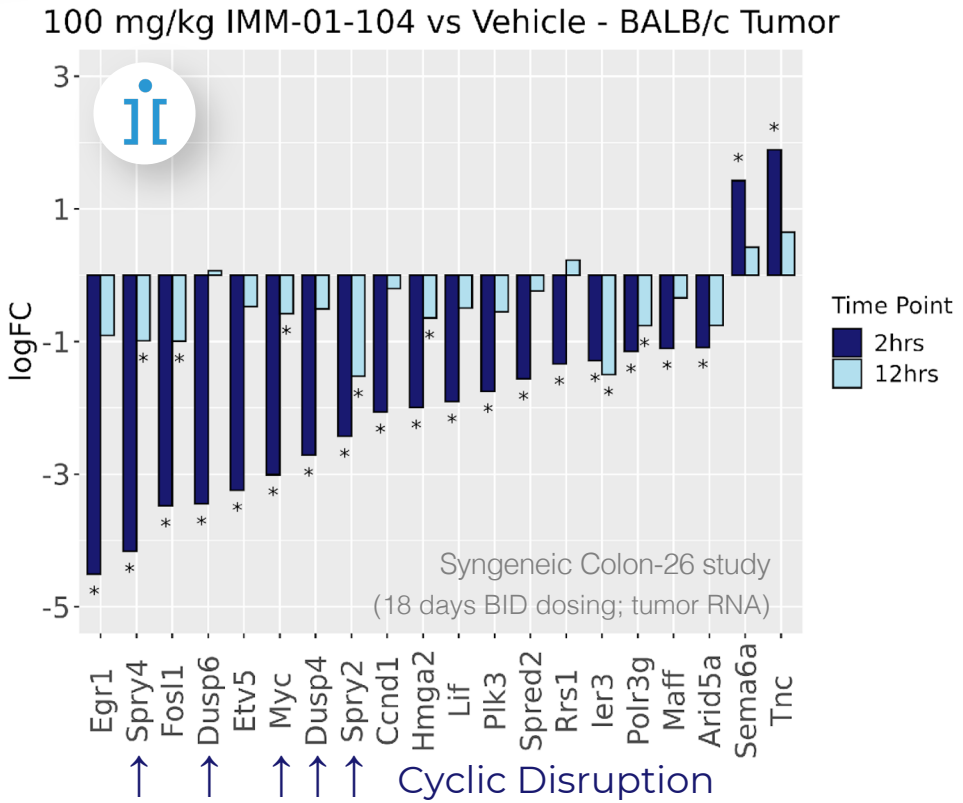
Deep Cyclic Inhibition Confirmed Using Transcriptomics

Traditional Approach



Chronic Suppression → TOXICITY

Signaling Dynamics



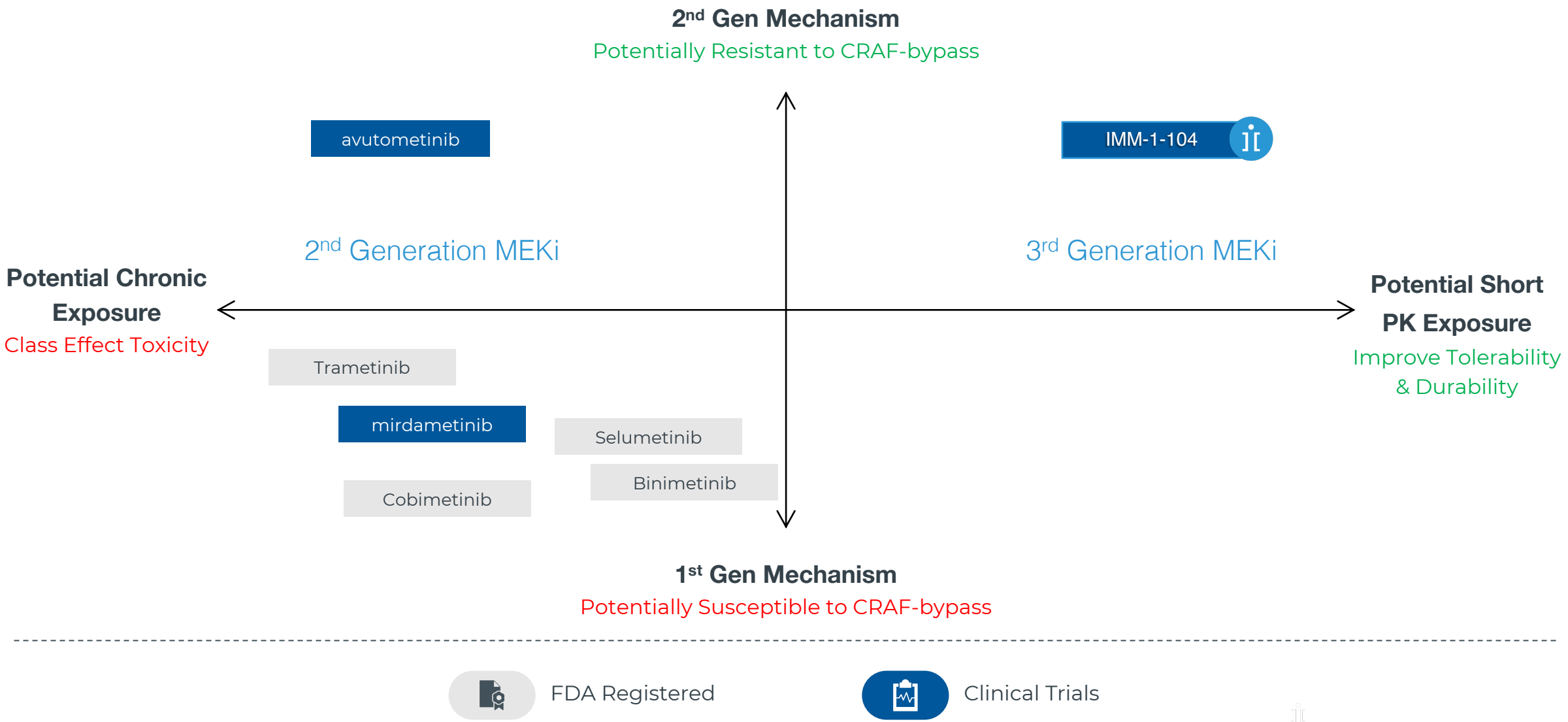
Cyclic Disruption → TOLERABILITY

Metastatic PDAC (mPDAC): Key Clinical Benchmarks

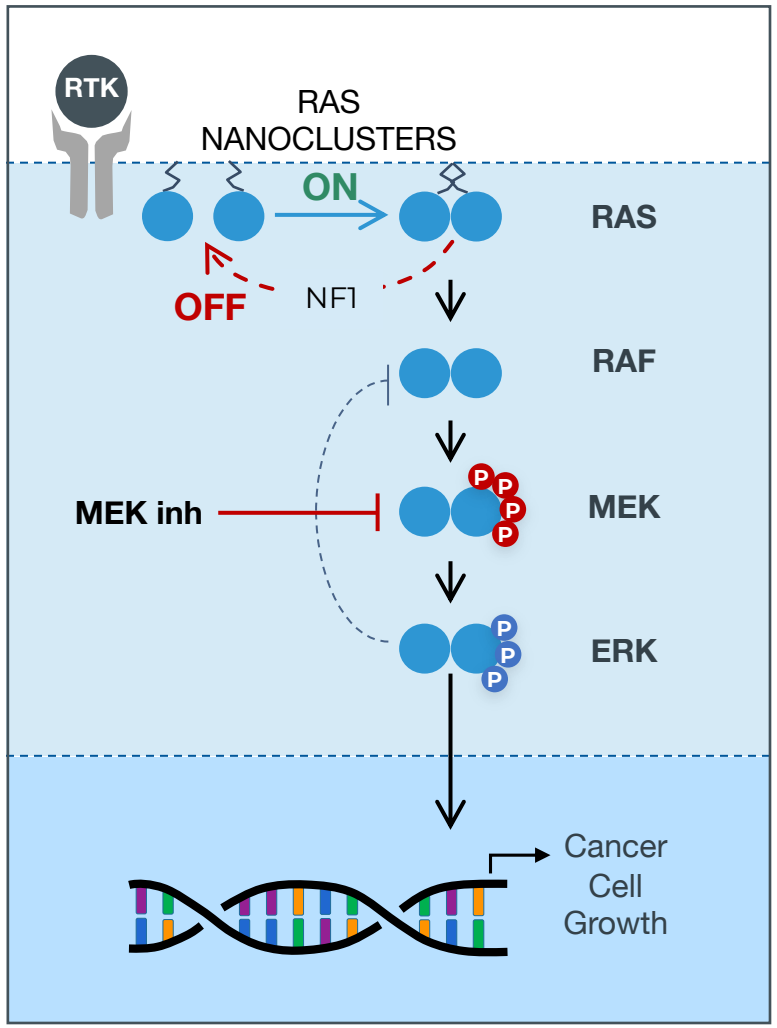
Trial	Treatment	Line of Treatment	PS	OS (months)	ORR	PFS (months)	CR (%)	PR (%)	SD (%)
[a] **No Treatment**	None	-	-	< 6.0	-	-	-	-	-
[b] **Phase III MPACT**	Gemcitabine	**1st Line**	0-1	6.7	**7%**	**3.7**	0	**7.2**	28.4
[b] **Phase III MPACT**	nab-paclitaxel + Gemcitabine	**1st Line**	0-1	8.5	**23%**	**5.5**	0.2	**22.7**	27.4
[c] **Phase III PRODIGE/ACCORD 11**	FOLFIRINOX	**1st Line**	0-1	11.1	**32%**	**6.4**	0.6	**31.0**	38.6
[d] **Phase III NAPOLI-3**	NALIRIFOX	**1st Line**	0-1	11.1	**42%**	**7.4**	0.6	**41.5**	25.8
[e] **Phase III NAPOLI-1**	nal-IRI + FU/LV	**2nd Line**	0-1	6.2	**17%**	**3.1**	0	**17**	32
[f] **Phase III MPACA-3**	mFOLFIRINOX	**2nd Line**	0-1	9.2	**15%**	**5.2**	0	**15**	50

[a] Metastatic PDAC clinical review reference (link)
[b] Phase III MPACT trial (link)
[c] Phase III PRODIGE/ACCORD 11 trial (link)
[d] Phase III NAPOLI-3 trial (link)
[e] Phase III NAPOLI-1 trial (link)
[F] Phase III MPACA-3 trial (link)

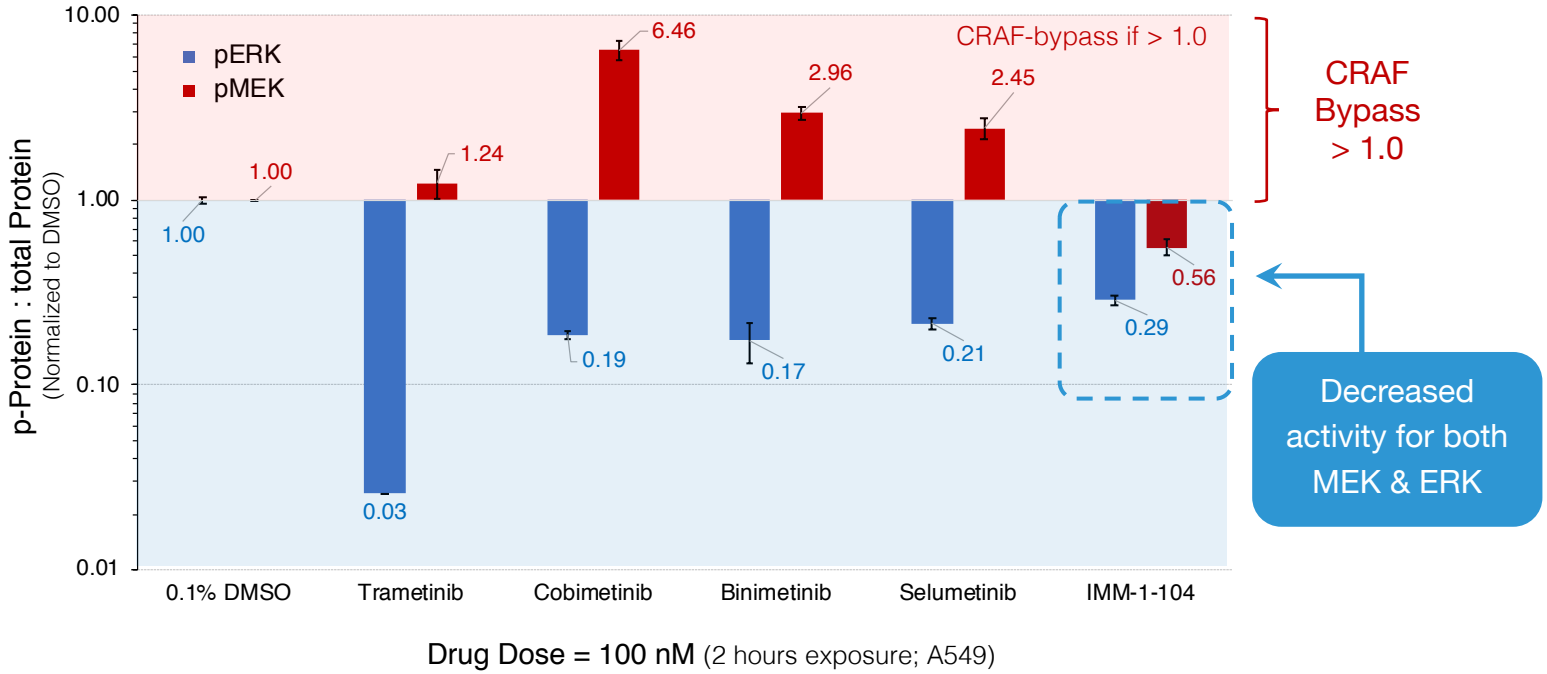
Clinical Stage MEK Inhibitors: Insights & Limitations



Head-to-Head Comparison of IMM-1-104 Against FDA-Approved MEK Inhibitors: CRAF-Bypass Resistance



A549KRAS-mut Lung Cancer: pERK and pMEK



Drug Dose = 100 nM (2 hours exposure; A549)

- ***FDA-Approved MEK inhibitors:*** *Trametinib, Cobimetinib, Binimetinib, Selumetinib commercially purchased*

Decades of drug discovery and development experience

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