Immuneering

Deep Cyclic Inhibition of MEK

A transformational approach aimed for durable and safe combinations in RAS-mutant cancers

Brett Hall, PhD
Chief Scientific Officer

September 17, 2025

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 atebimetinib (formerly known as IMM-1-104); the design, enrollment criteria and conduct of the Phase 1/2a clinical trial for atebimetinib; the ability of interim clinical data to de-risk atebimetinib and be confirmed as the trial progresses, including the safety, tolerability, pharmacokinetics, pharmacodynamics and potential efficacy of atebimetinib, alone or in combination with modified gemcitabine/nab-paclitaxel ("mGnP"); the potential advantages and effectiveness of the Company's clinical and preclinical candidates; the timing of additional trial updates; the timing of the initiation and completion of a pivotal trial of atebimetinib in combination with mGnP, including trial design, the timing and substance of FDA feedback on the pivotal trial; the filing with, and approval by, regulatory authorities of the Company's 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 related to the Company's projected cash runway, current operating plans and ability to continue as a going concern; and the plans and objectives of Company management for future operations, including with respect to the planning and execution of additional combination or potential pivotal clinical trials.

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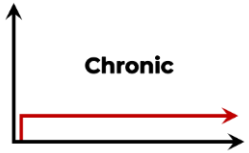
Unless otherwise specified, all clinical data of atebimetinib in the following slides is based on an interim data collection from the intent-to-treat population of 34 patients dosed at the 320 mg once-daily dose level of atebimetinib in combination with modified gemcitabine/nab-paclitaxel (mGnP), as of May 26, 2025,. This represents the same cohort of patients from the Company's June 2025 data release, the primary Phase 2 population enrolled as part of the Simon two-stage design from the ongoing Phase 1/2a trial of atebimetinib. All data remains subject to follow-up and database updates.

Disclosures

Brett M. Hall, Ph.D.

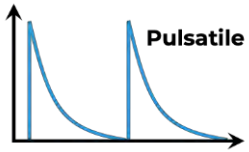
- I have the following financial relationships to disclose:
  - Stockholder in Immuneering Corporation
  - Employee of Immuneering Corporation
- I will not discuss off label use and/or investigational use in my presentation.

Deep Cyclic Inhibition (DCI) of MEK



- **Historical Paradigm**:
  - Chronic target engagement → Prioritizes fast/deep RECIST tumor shrinkage beyond -30% (surrogacy for OS?)

- **Challenges**:
  - High toxicity, adaptive/acquired resistance, limited durability



- **Alternative Approach**:
  - Pulsatile MEK inhibition (Deep Cyclic Inhibition - DCI) → designed to break tumor addiction + spare healthy tissues

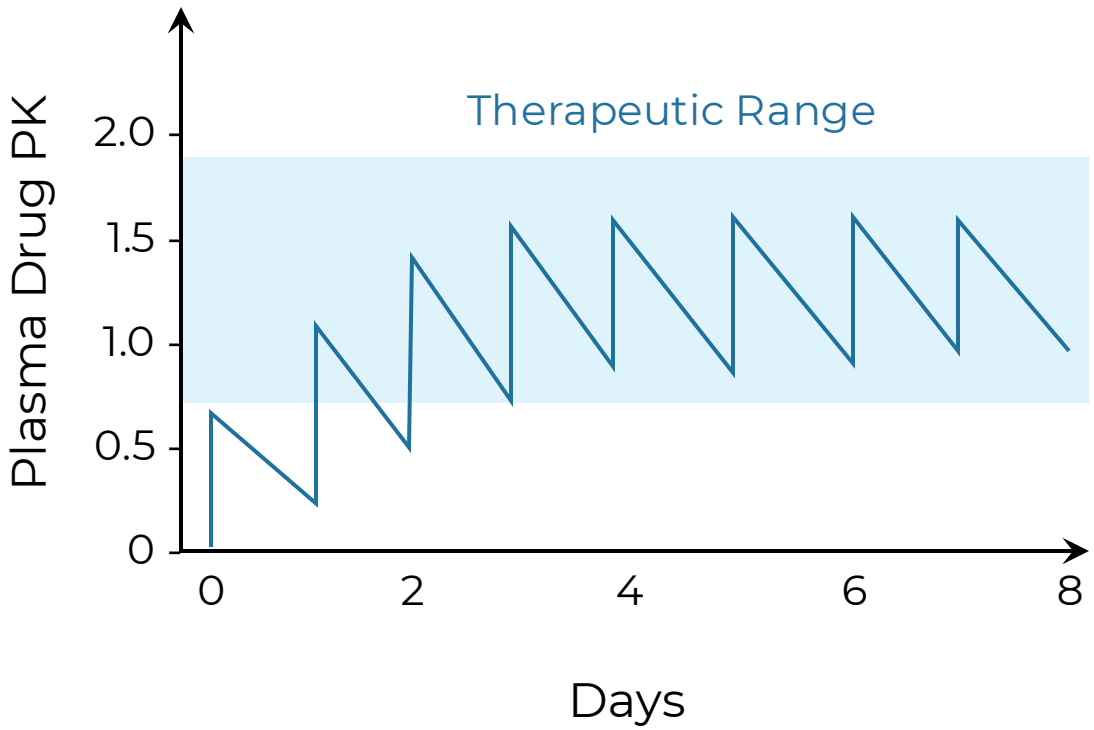
- **DCI Validation**:
  - Observed favorable safety, clinical activity, strong 1L PDAC outcomes, combination potential (durability and tolerability)

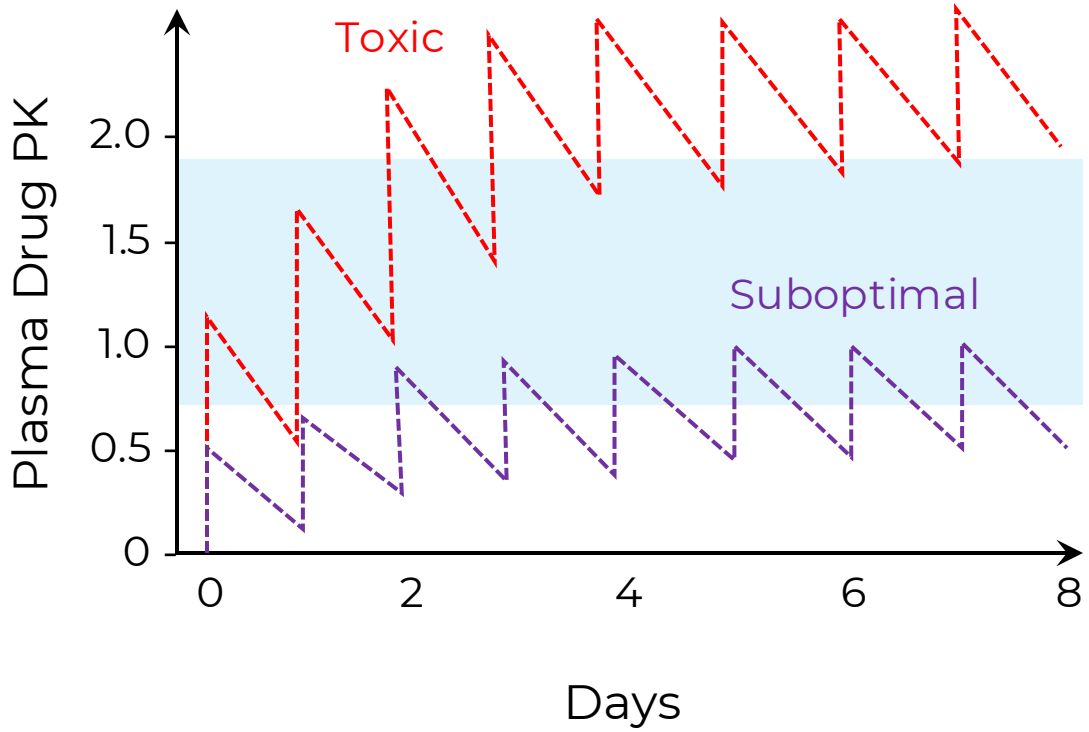
Historical Paradigm:

Chronic Target Engagement

- **Rationale**: sustained inhibition required to break oncogenic addiction
- **Challenges**: toxicity, resistance, limited durability/combinability

Optimizing Dose/Schedule: Chronic Pathway Inhibition





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

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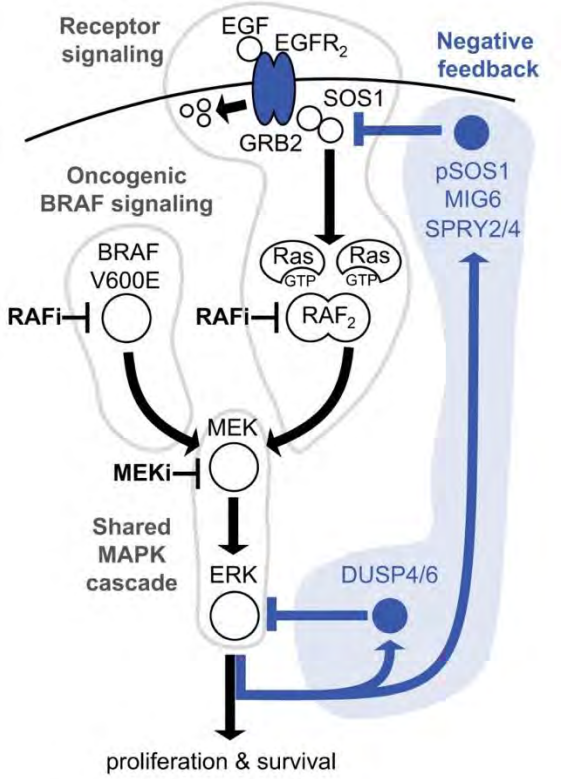
Challenges with Chronic MAPK Pathway Inhibition

Limited response, short durability and toxicity contribute to limited clinical utility

Loss of Negative Regulators

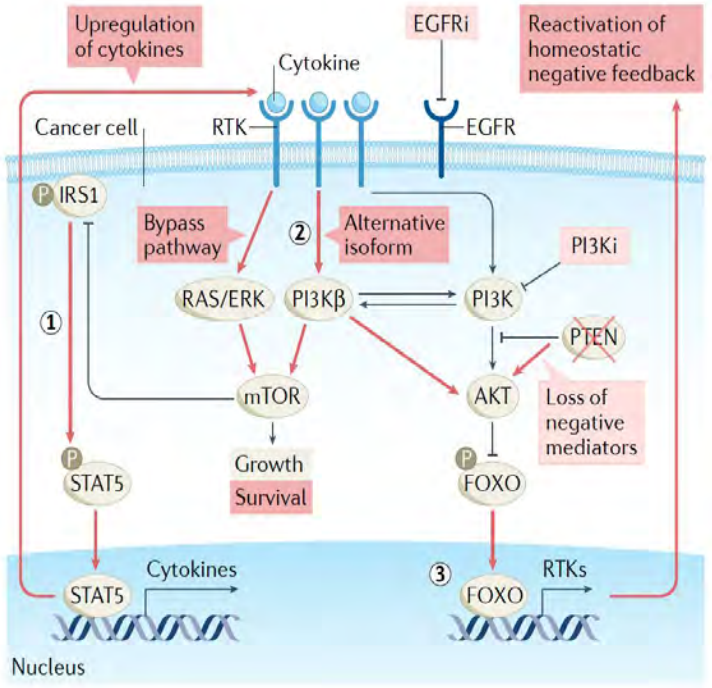
- Loss of MAPK Pathway Control -



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

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

Summary of Phase 3 NEMO study of Binimetinib as reported in Lancet (c.2017)

	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

>50% increased toxicity

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

Over 2x improvement in ORR

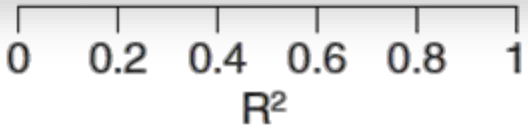
NRAS Status	Binimetinib 2:1	Dacarbazine
	N = 269	**N = 133**
Q61K	100 (37%)	51 (38%)
Q61L	32 (12%)	17 (13%)
Q61R	137 (51%)	64 (48%)
Wildtype	0	1 (1%)

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

RECIST ORR: a Poor Surrogate for Overall Survival

Objective response rate (ORR) as a surrogate of overall survival

Studies	N Studies	N Subjects	R^2 (95% CI)	p(Het)
All	**535**	**276,635**	**0.10 (0.05 to 0.15)**	
Experimental Arm				**< 0.001**
Chemotherapy	146	66,249	0.25 (0.13 to 0.37)	
Immunotherapy	101	57,728	0.19 (0.05 to 0.33)	
Targeted	272	145,022	0.07 (0.01 to 0.13)	poor surrogacy



"…growing evidence of the **lack of strong surrogacy for ORR and PFS for OS** across tumor groups and treatments. This has significant implications for regulatory agencies such as FDA and EMA…"

Shahnam, et al 2024 Eur J Cancer 198:113503

Alternative Approach:

Deep Cyclic Inhibition (DCI)

- **Rationale 1**: pulsatile inhibition designed to disrupt oncogenic addiction
- **Rationale 2**: improve safety, quality of life and combinability

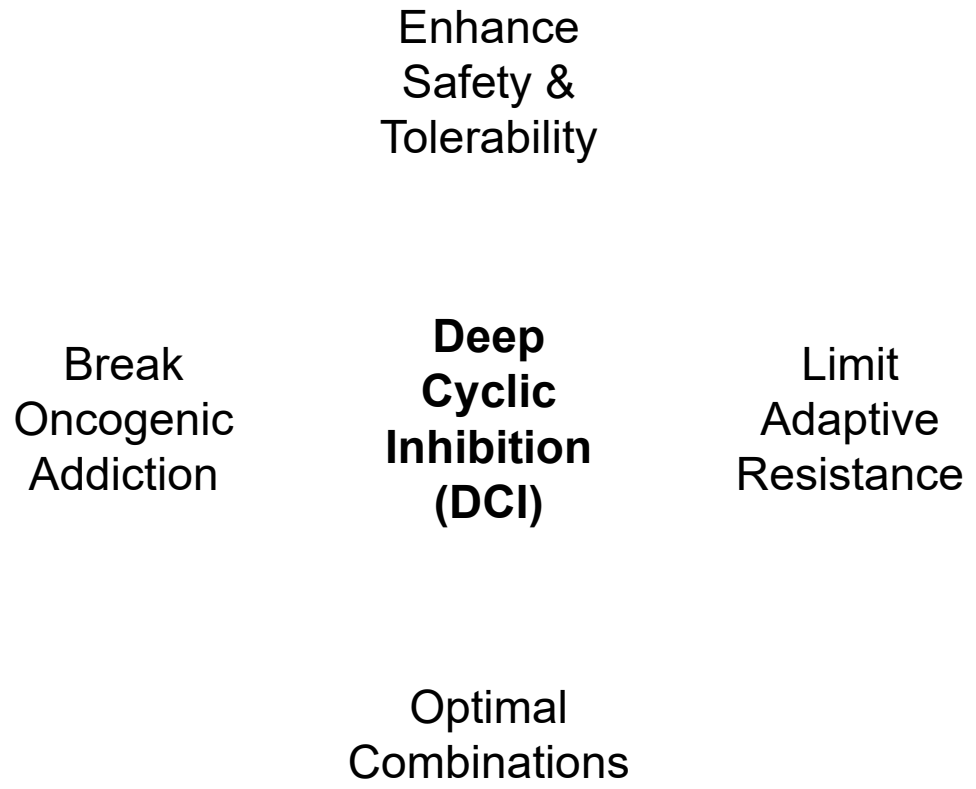
- **Challenges**: innovation resistance, legacy endpoints (surrogacy)

Atebimetinib (IMM-1-104) Goal: Deep Cyclic Inhibition (DCI) of MEK

Deep Cyclic Inhibition (Thesis)

Pulsatile inhibition of MEK designed to:

1. Disrupt MAPK pathway addiction
2. Reduce adaptive resistance
3. Improve safety & tolerability
4. Expand therapeutic combinations



November 2024 ACoP (Phoenix, AZ) – de Jong, et al. [W-019]; DCI = Deep Cyclic Inhibition

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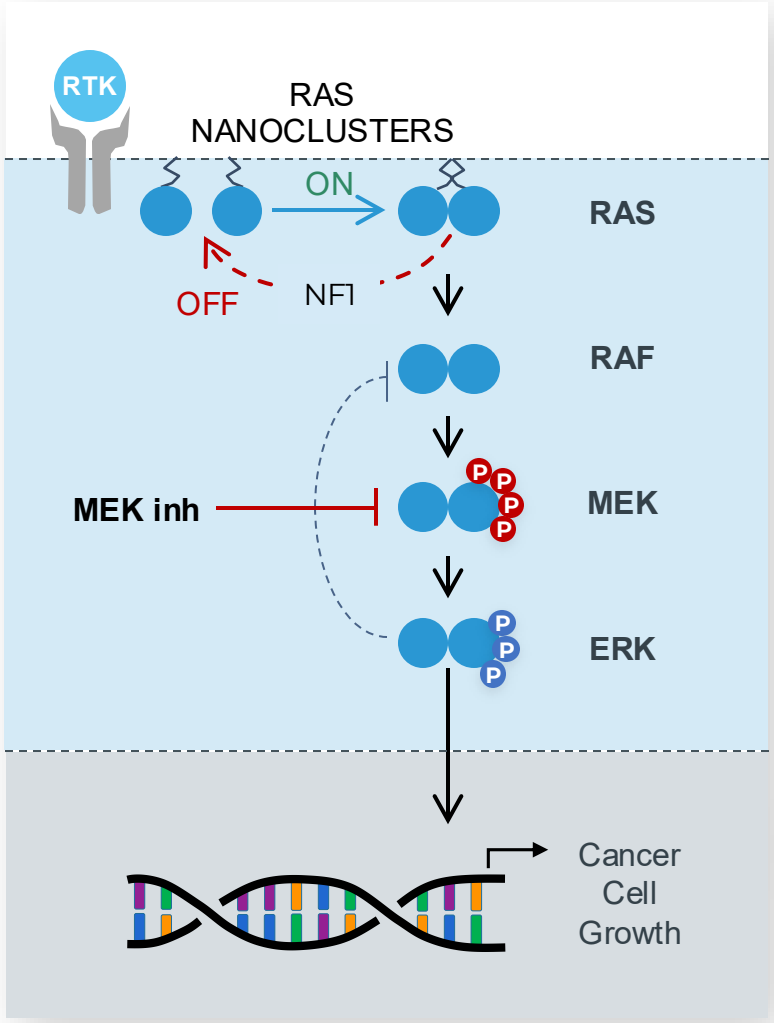
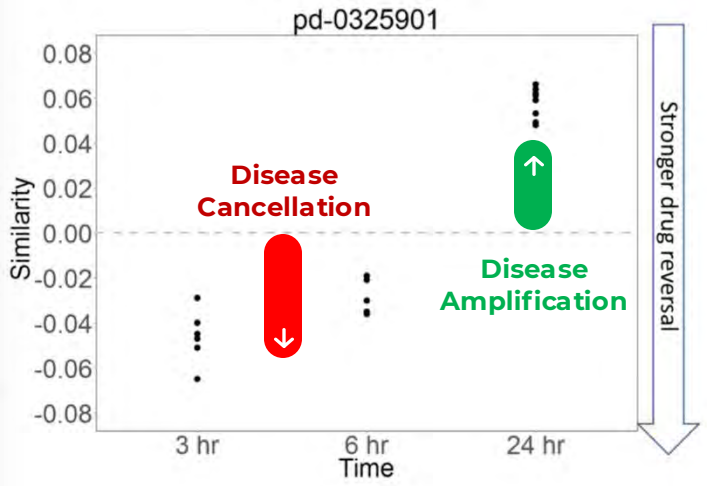
Our Platform Suggested an Opportunity for Cyclic Inhibition

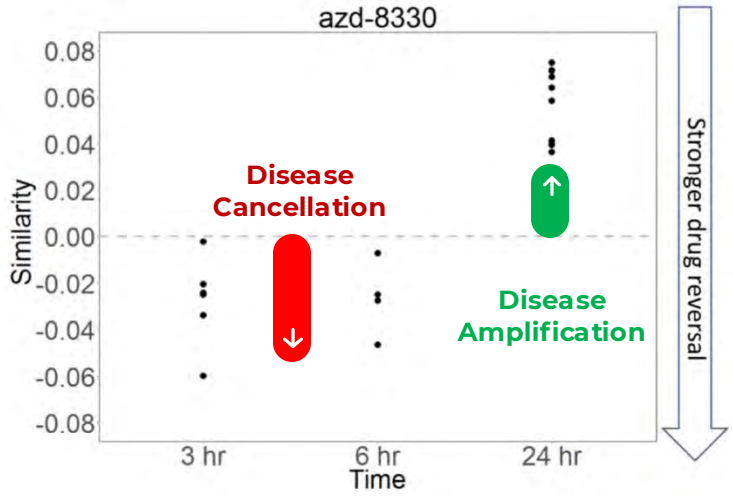
Goal: achieve **broader activity** and **better tolerability** in RAS/MAPK pathway activated disease



1st generation MEKi



1st generation MEKi



Note: dots are representative of various concentrations

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

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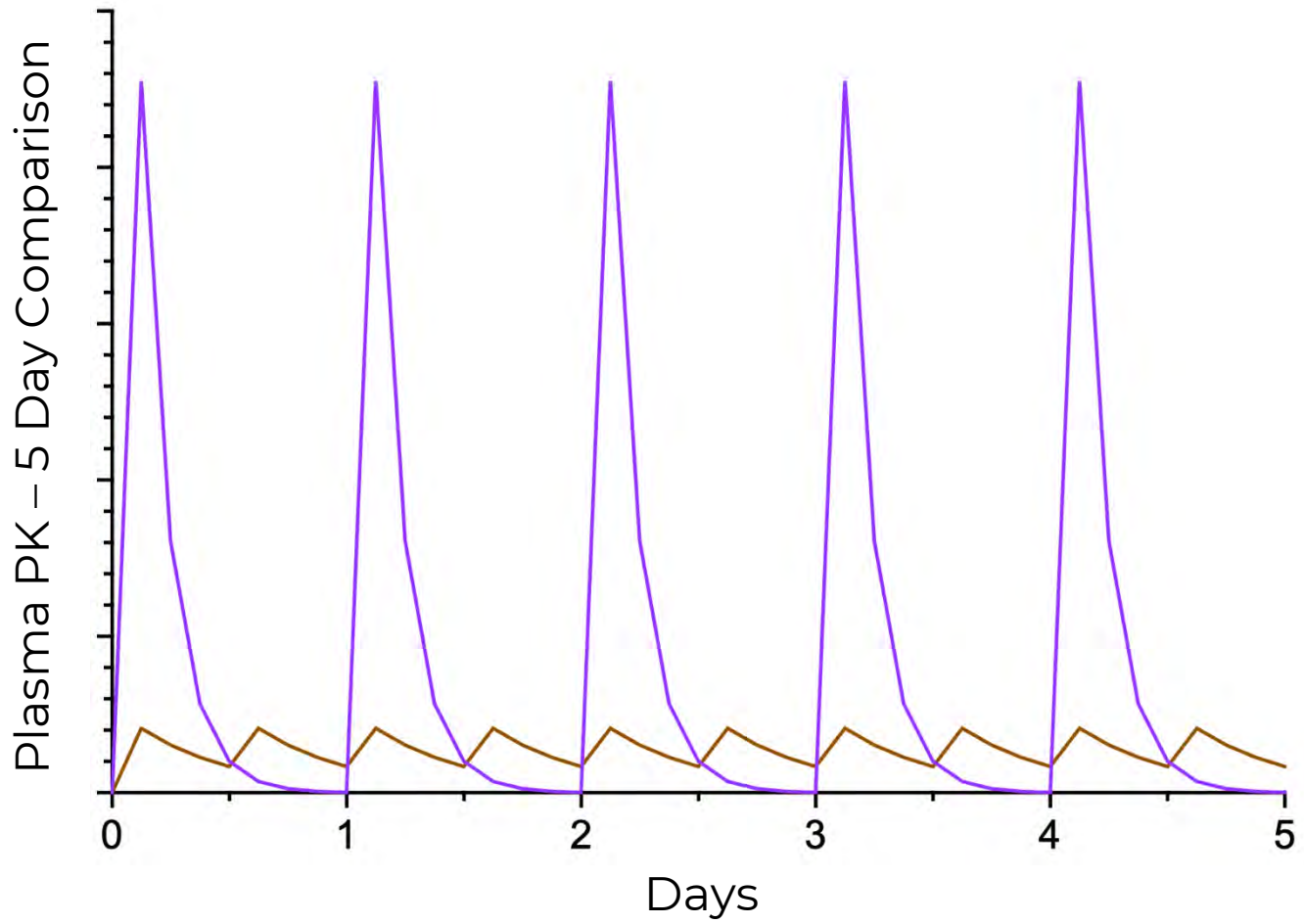
Atebimetinib's Deep Cyclic Inhibition of MEK is designed to improve tolerability and broaden activity vs. chronic inhibition of MEK



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

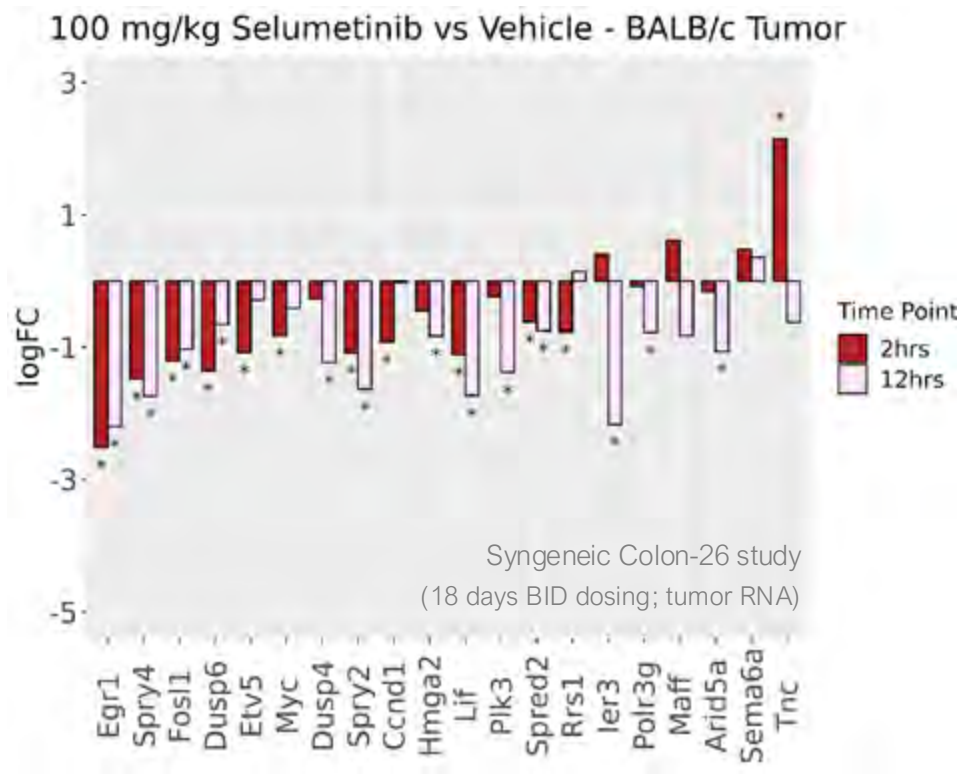
GOAL: Short plasma half-life to improve tolerability and limit adaptive resistance, so **every day is a drug holiday**

MoA Target Engagement

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

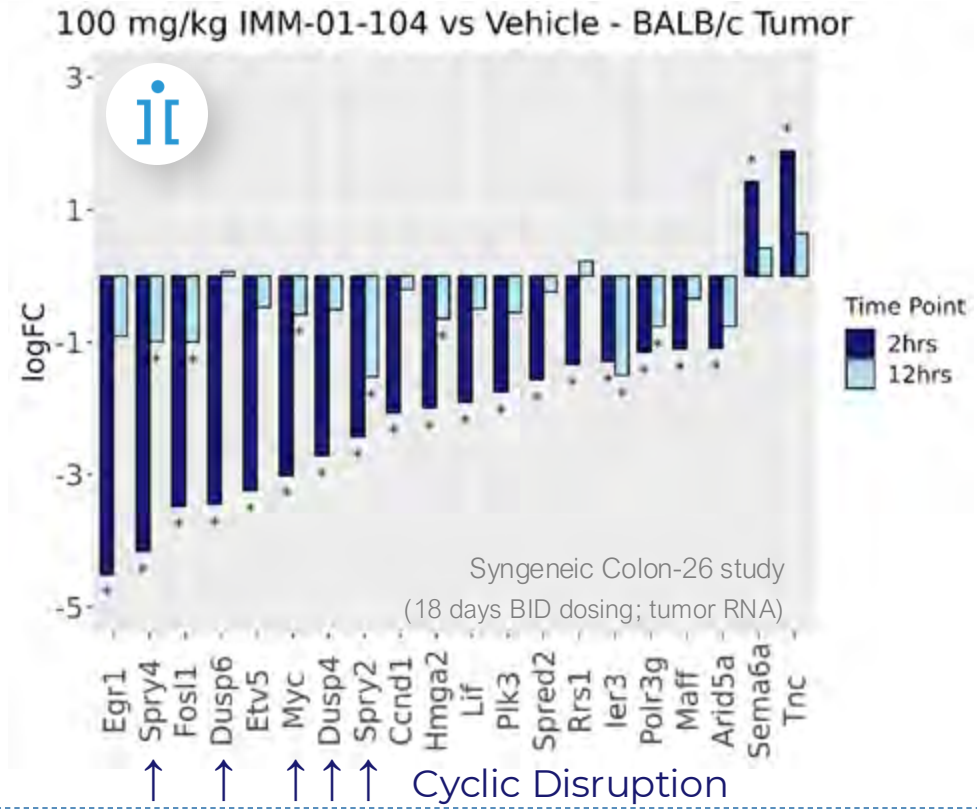
Deep Cyclic Inhibition Confirmed Using Transcriptomics

Traditional Approach



Chronic Suppression → TOXICITY

Signaling Dynamics



Cyclic Disruption → TOLERABILITY

Skolitz, et al. 2021 AACR-NCI-EORTC (virtual)

Atebimetinib (IMM-1-104)

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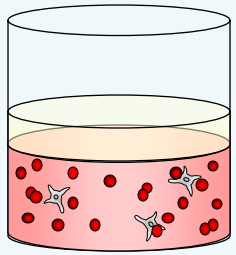
Atebimetinib Demonstrated Universal-RAS Potential

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 atebimetinib 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)

Emergent Atebimetinib Monotherapy and Combinations

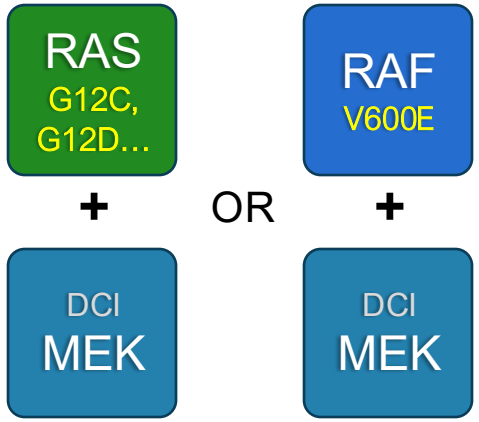
Monotherapy

Pulsatile MAPK Pathway Inhibition

Ideal: In patients with broad MAPK pathway addiction

Vertical Combinations

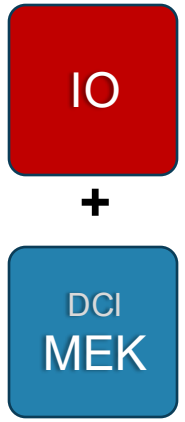
Selective Vertical Drug Combinations



Goal: Greater Depth & Durability of Response

Immune Modifying Combinations

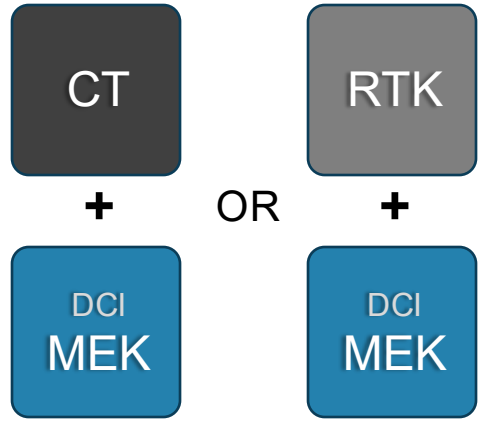
Dual-targeting of Tumor & Immune System



Goal: Break MAPK Addiction; Enhance Antitumor Immunity

Orthogonal MoA Combinations

Non-overlapping Mechanism of Action Combinations



Goal: Expand & Improve Overall Antitumor Response

Activity along with DCI MEKi safety & tolerability expand combination opportunities

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

Head-to-Head NRAS-Q61R Melanoma Xenograft Study:

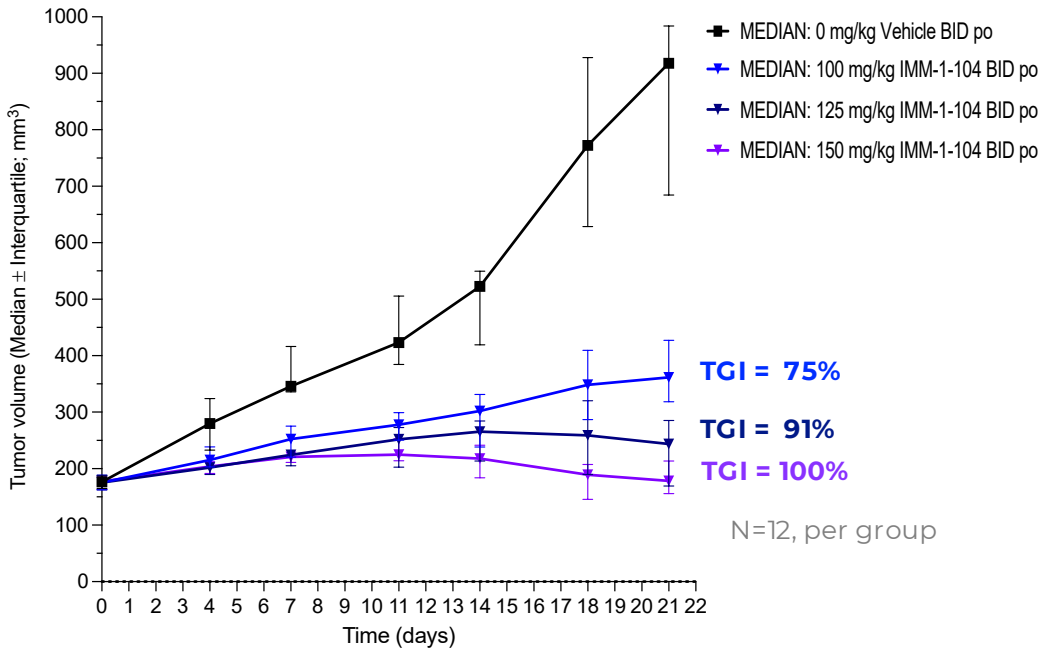
Binimetinib vs. atebimetinib in SK-MEL-2

Atebimetinib as compared to binimetinib monotherapy demonstrated greater tumor growth inhibition (TGI)

DCI MEK

Atebimetinib (IMM-1-104)

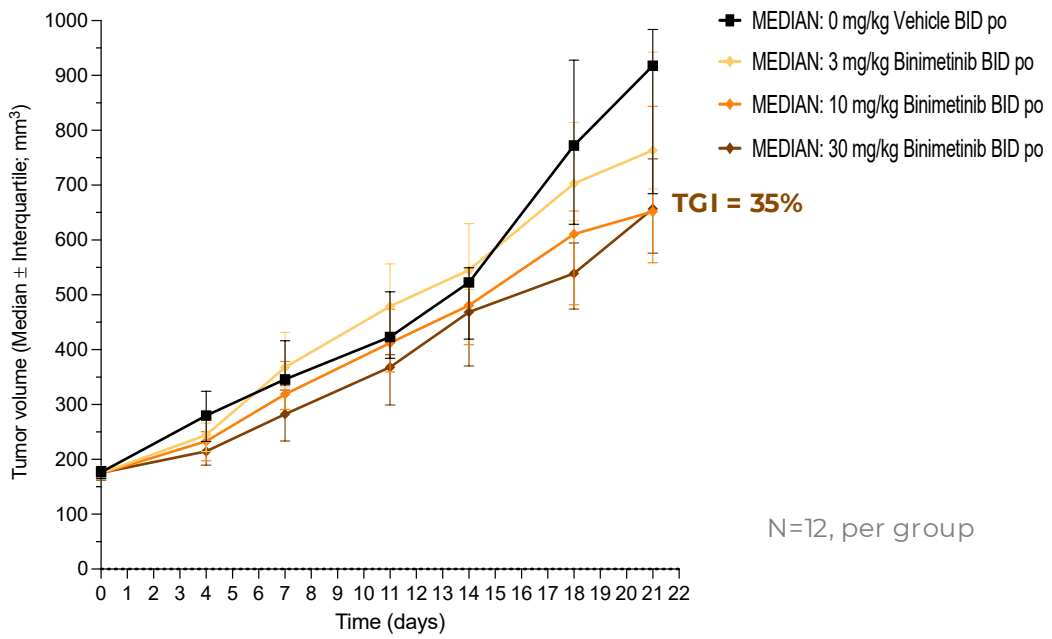
(100-125-150 mg/kg BID p.o.)



Chronic MEK

Binimetinib

(3-10-30 mg/kg BID p.o.)



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

King, et al. 2022 AACR Special Conference: Targeting RAS (Lake Buena, FL)

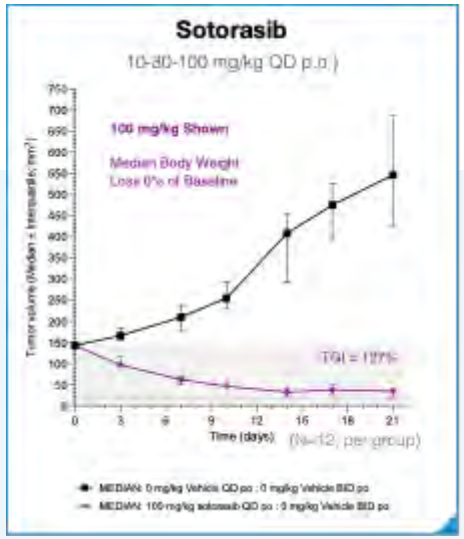
Binimetinib was commercially purchased

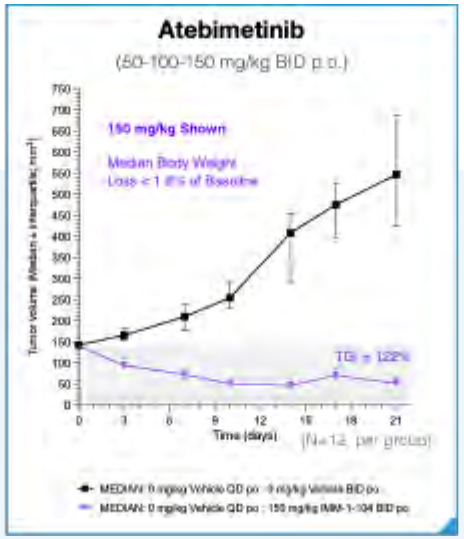
Head-to-Head Comparison of Atebimetinib +/- Sotorasib in KRAS^{G12C} PANC

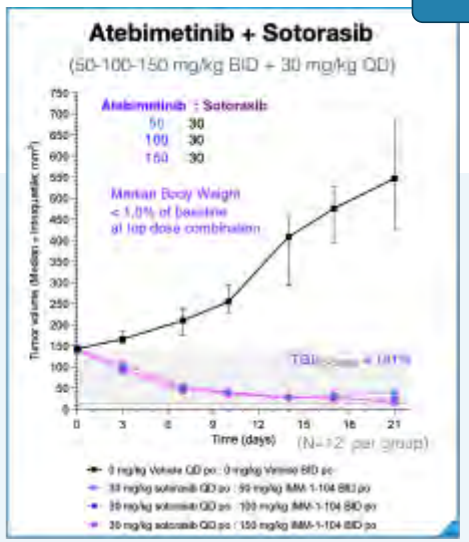
Atebimetinib plus sotorasib demonstrated deeper, more durable tumor regressions with insignificant BWL

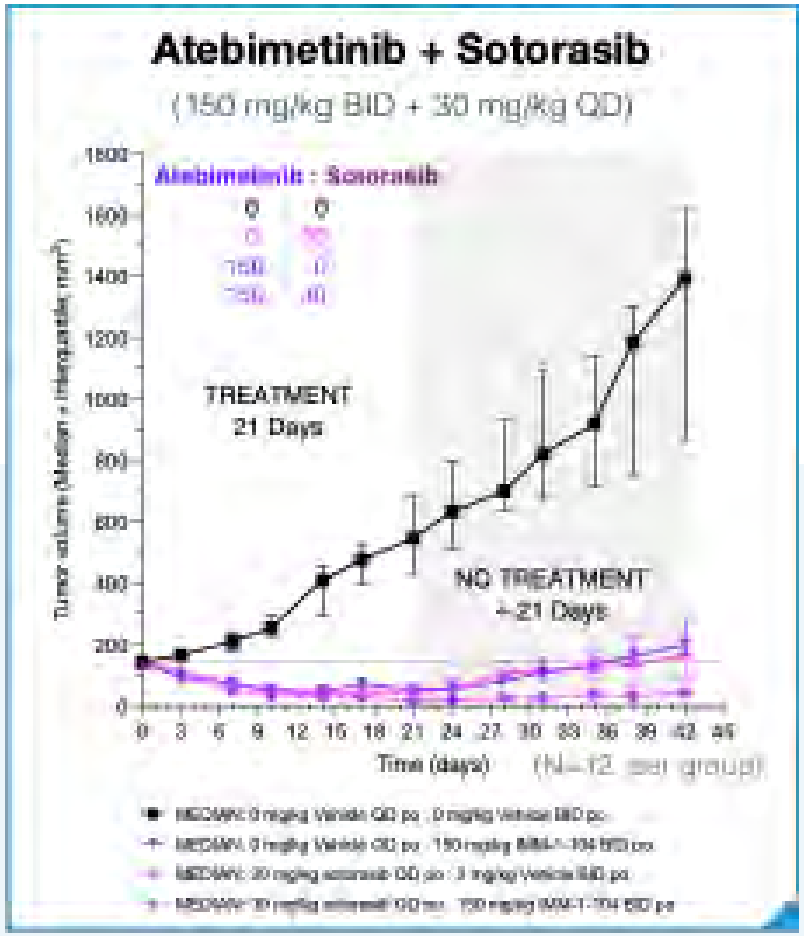
KRAS^{G12C} PANC

RAS G12C + DCI MEK









› 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)

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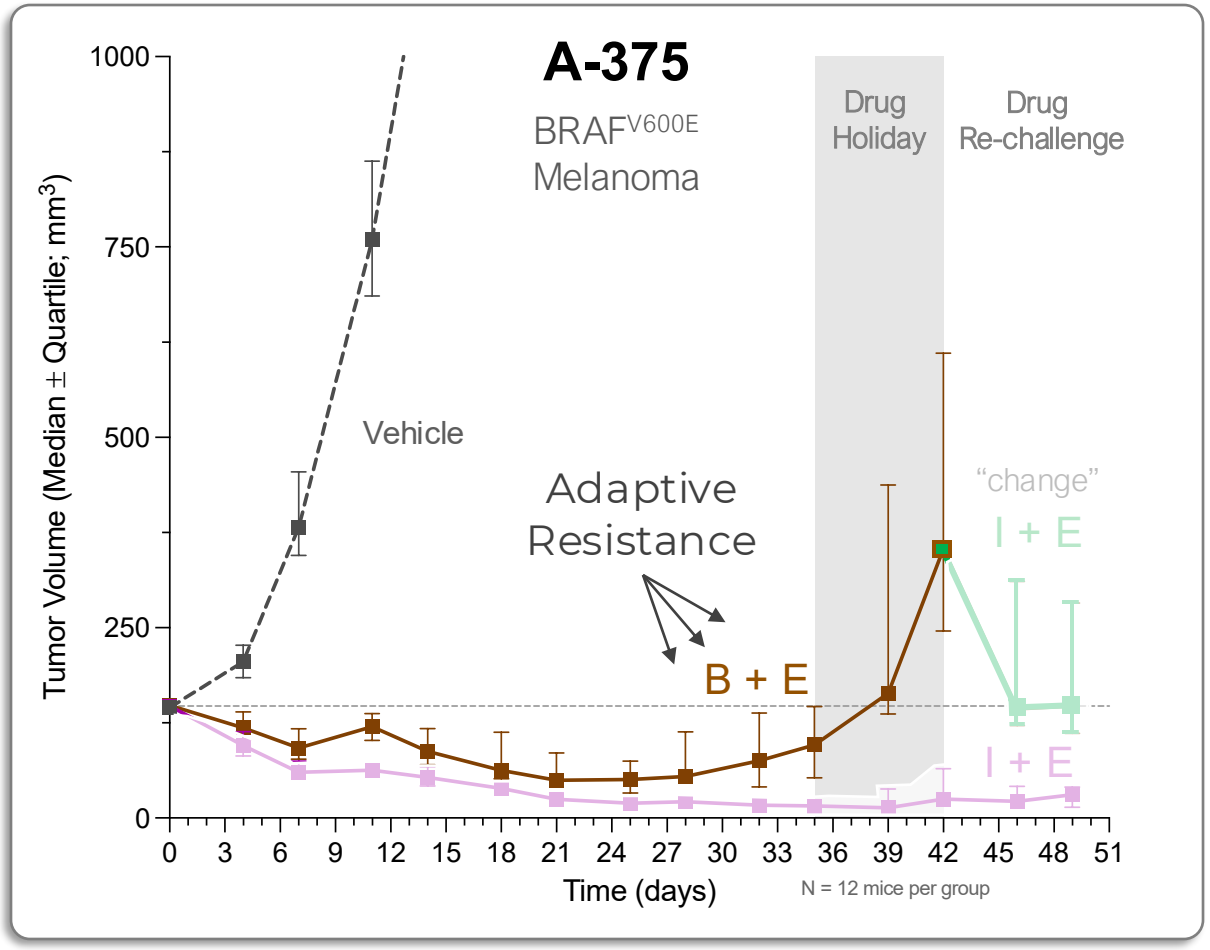
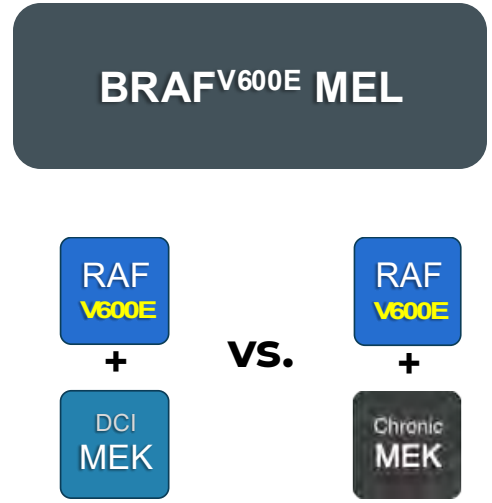
DCI MEKi (I) + BRAFi (E) Drives Deeper More Durable Response than Chronic MEKi (B) + BRAFi (E) in BRAF-Mutant Melanoma Model





- Vehicle
- (B) 3.5 mg/kg BID PO + (E) 60 mg/kg QD PO
- (I) 180 mg/kg BID PO + (E) 60 mg/kg QD PO
- Replace → I+E after holiday → (I) 180 mg/kg BID PO + (E) 60 mg/kg QD PO

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.

Travesa, et al. 2023 AACR: EORTC (Boston, MA); IMM-6-415 = DCI MEKi

Bedside-to-Bench for DCI-MEKi

Rationale Combination Design

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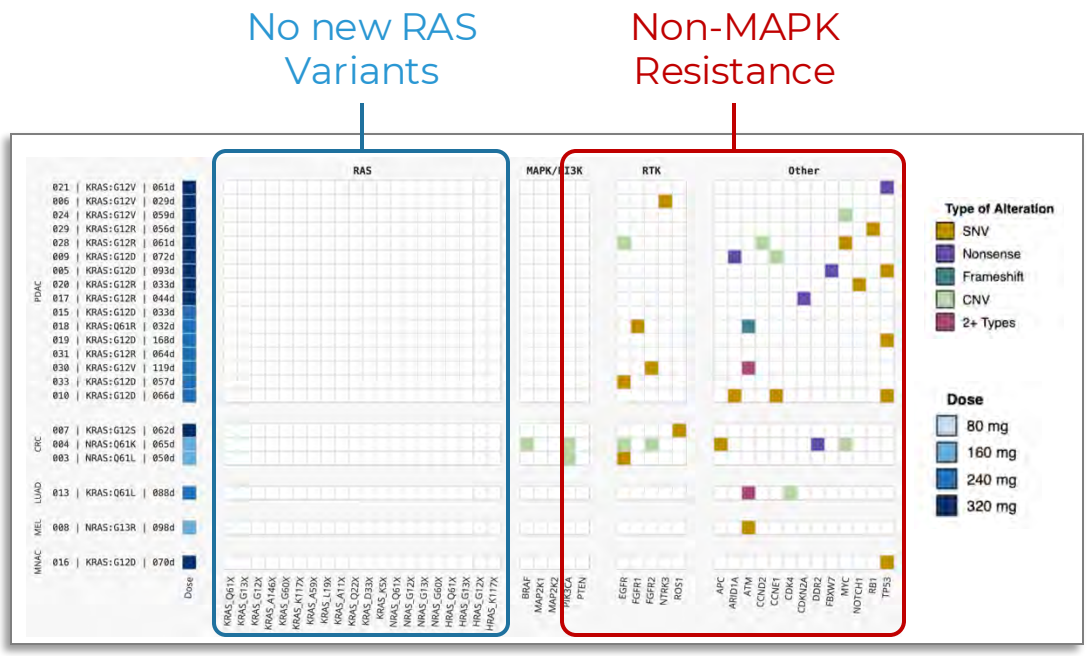
Deep, Durable Responses: Atebimetinib with Gemcitabine + nab-Paclitaxel

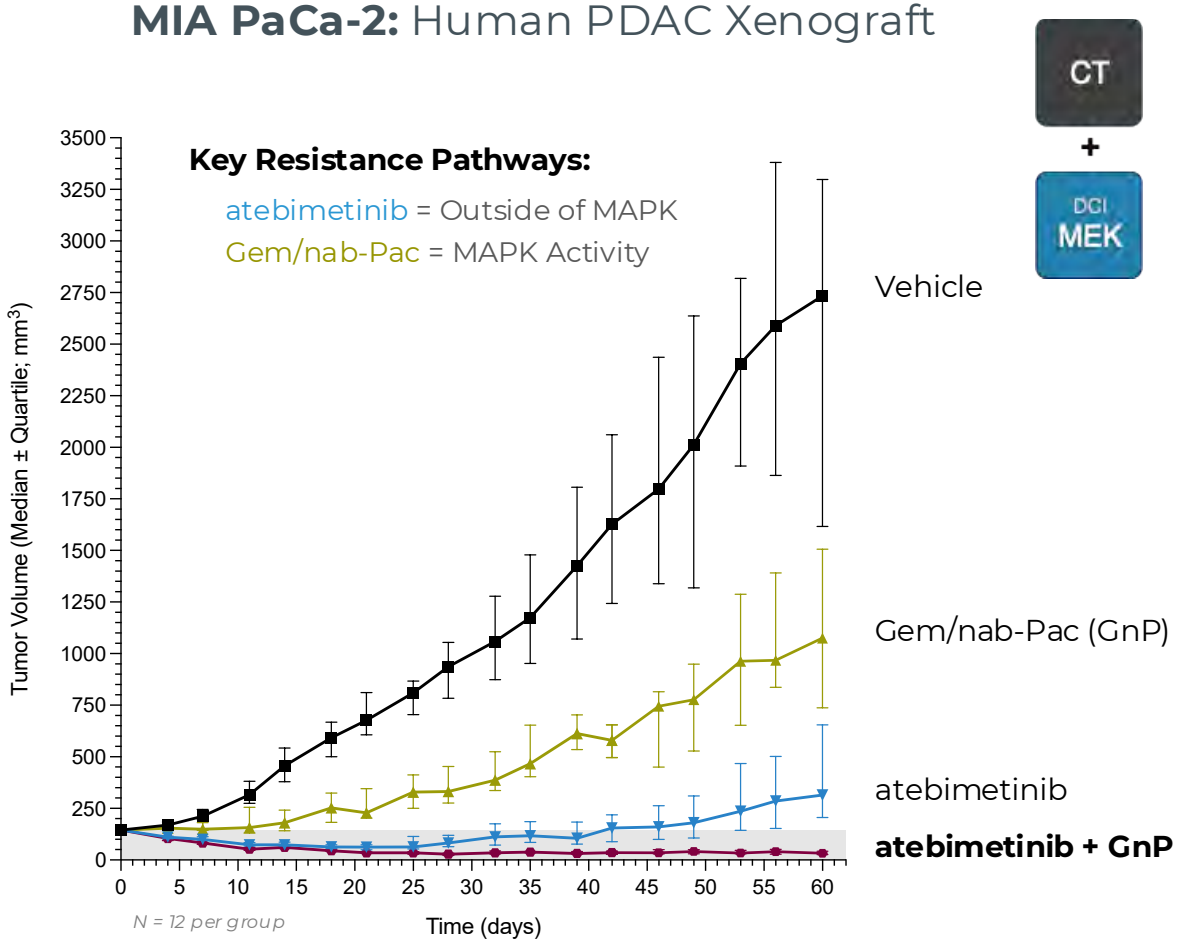
Translational rationale for combination

Phase 1: ctDNA Monotherapy atebimetinib



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

MIA PaCa-2: Human PDAC Xenograft



2024 AACR King, et al.

(104) atebimetinib = 125 mg/kg BID PO
(G) gemcitabine = 60 mg/kg IP Q4D
(P) nab-Paclitaxel = 10 mg/kg IV Q4D

Immuneering

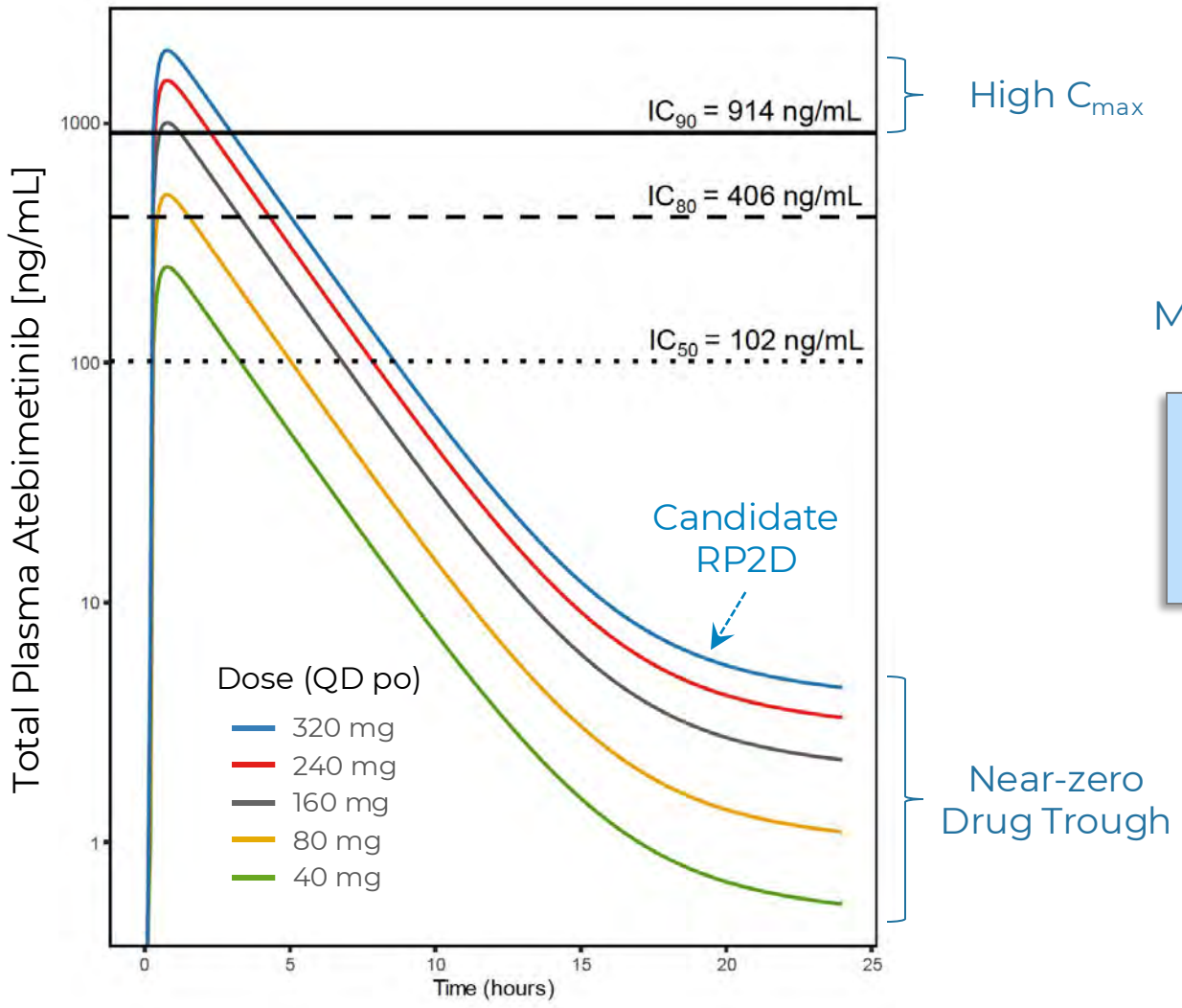
DCI-MEKi Clinical Translation:

Atebimetinib PK/PD (Phase 1)

Immuneering

Atebimetinib Inhibits the MAPK Pathway >90%

Topline PK/PD Data for atebimetinib



High C_{max}

Near-zero Drug Trough

Deep Cyclic Inhibition (DCI) Profile Maximized at 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 atebimetinib plasma concentrations (ng/mL) versus time (h) on a semilogarithmic scale for the 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 IC90 at 320 mg (4.0 hr) vs. 240 mg (3.3 hr)

EDC Snapshot as of 20FEB24: PK/PD Patient Profiles (IMM1104-101 trial)

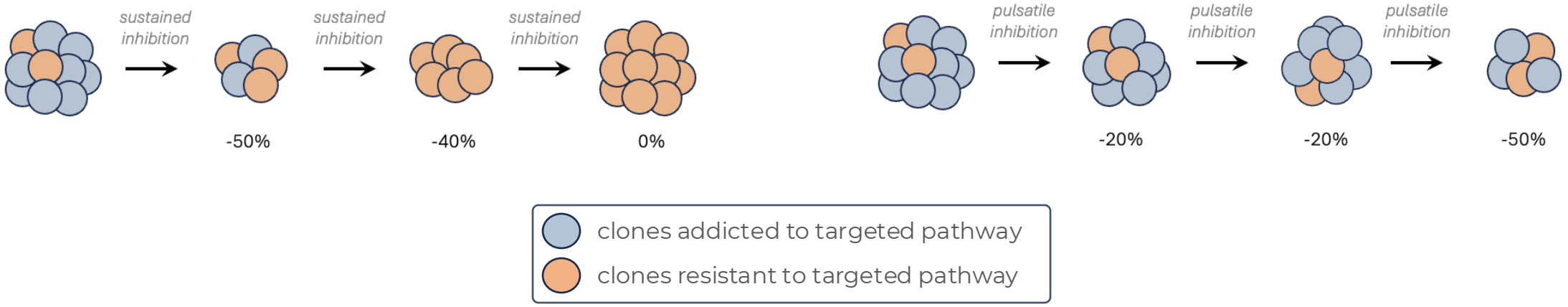
November 2024 ACoP (Phoenix, AZ) – de Jong, et al. [W-019]; DCI = Deep Cyclic Inhibition

Immuneering

Atebimetinib: achieving durability by outpacing cancer

Most therapies are designed for **sustained inhibition**, driving cancer to adapt and develop resistance; tumors shrink **quickly but temporarily**

Our therapies are designed for **deep cyclic inhibition**, pulsing faster than cancer can adapt; tumors shrink **slowly but durably**



1. *Gatenby, et al. 2009 Can Res – Adaptive Therapy – 1;69(11):4894*
2. *Seyedi (Maley), et al. 2024 Can Res – Resistance Management – 84(22):3715*

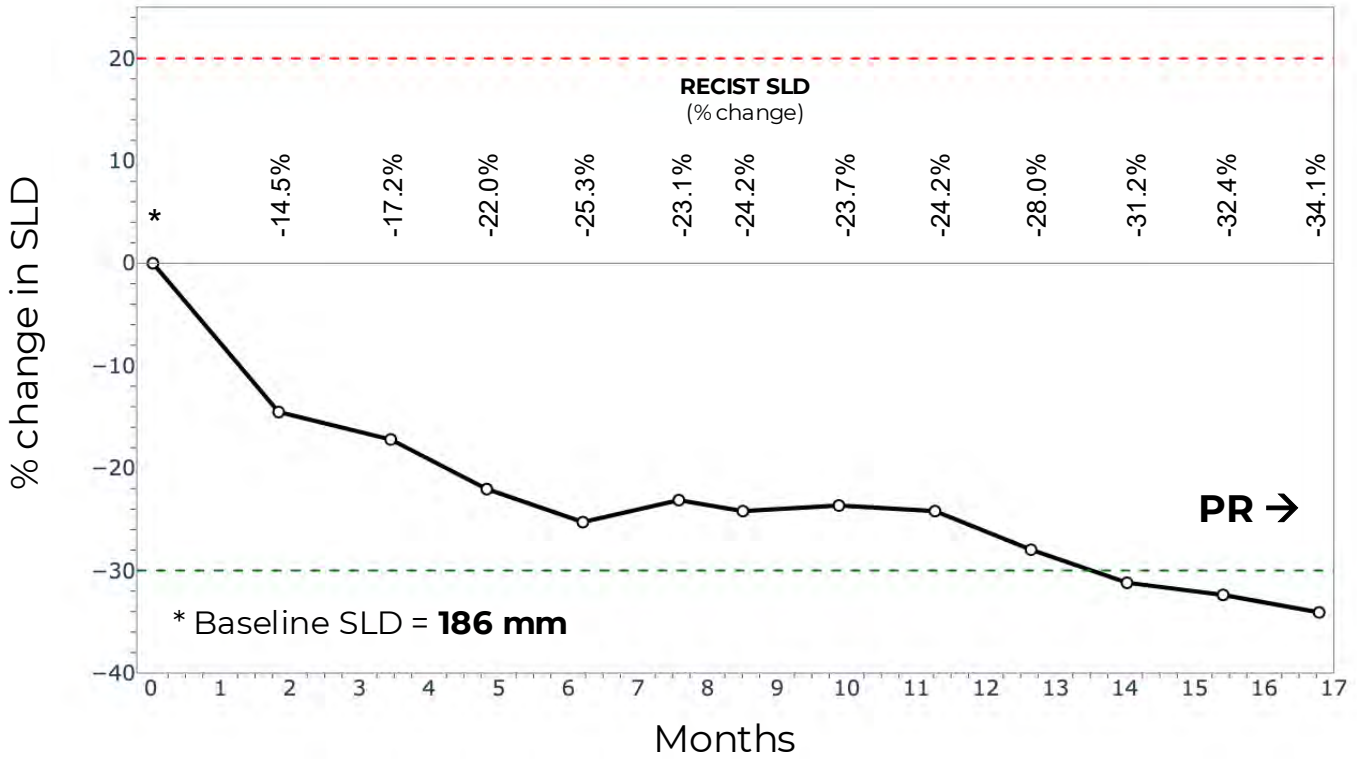
Immuneering

Atebimetinib Monotherapy Case Study Shows Durability and Tolerability with Complete Resolution of Bone Lesion

Case Study (3L Metastatic PDAC)

- 1st Line (1L): FOLFIRINOX (**BOR = PD**)
- 2nd Line (2L): Gem/Cis/nab-Pac (**BOR = PD**)
- 3rd Line (3L): atebimetinib (**BOR = PR**)
  - 70-year-old male; 240 mg QD p.o.
  - ≳18 mo. on atebimetinib
    - on treatment as of data cutoff
  - Improved QoL (PRO Instrument)
  - Weight gain (+16%)
  - Reduction in $KRAS^{G12D}$ ctDNA
  - 96% reduction in peak CA 19-9 levels
  - Complete resolution of bone lesion

Atebimetinib Monotherapy (3L PDAC; Phase 1)



Data based on interim data collection from Phase 1 dose expansion as of August 7, 2025, from an ongoing Phase 1/2a trial of atebimetinib. Data subject to follow-up and database updates. August 2025 Immuneering Corporate Deck

Immuneering

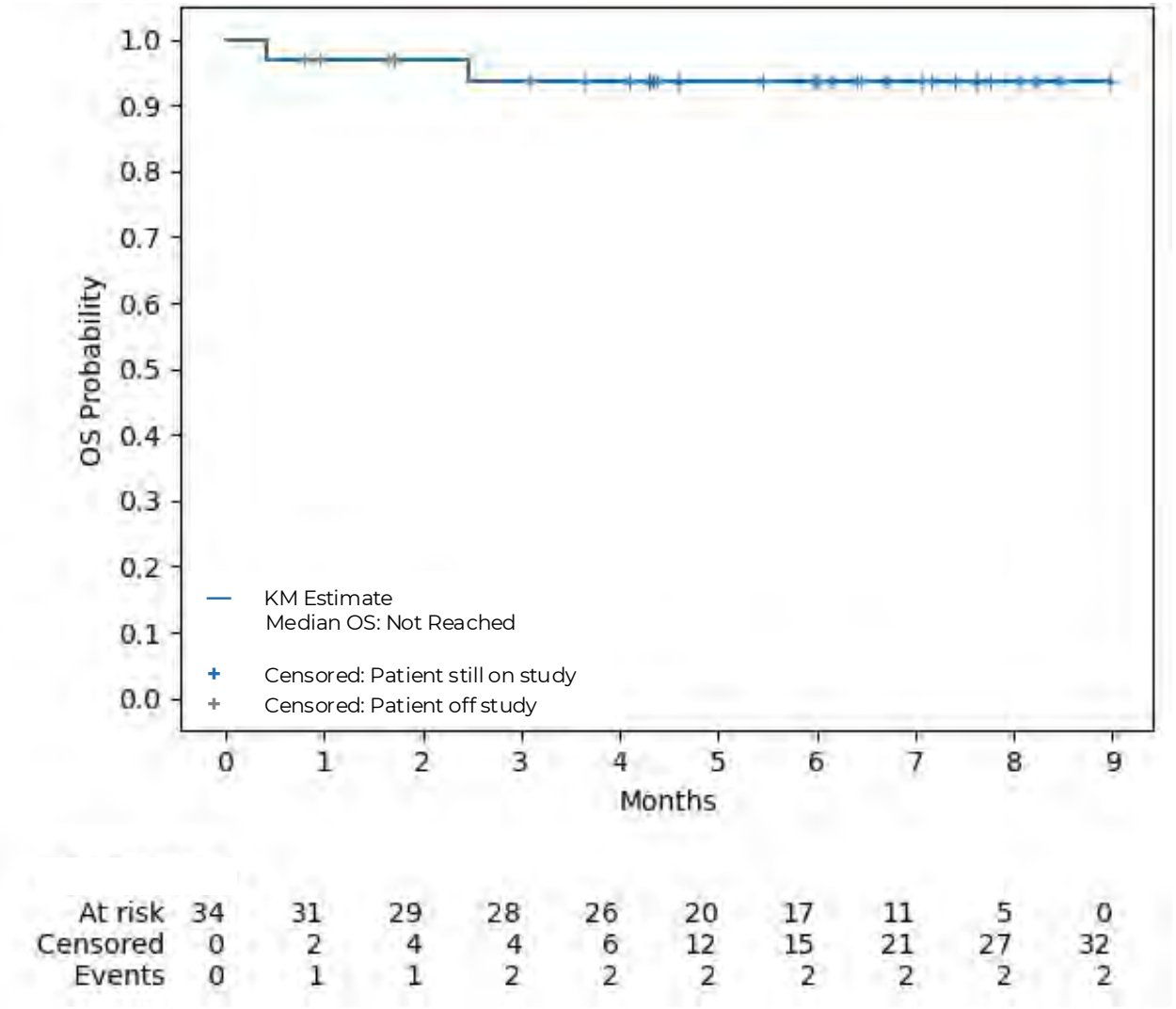
Clinical Impact of DCI MEKi:

Atebimetinib + chemotherapy (1L PDAC)

Immuneering

Exceptional Overall Survival (OS) Observed For Atebimetinib + mGnP in 1L PDAC

Atebimetinib (320 mg QD) + mGnP OS, N=34



First Line (1L) Pancreatic Cancer

	Atebimetinib + mGnP (320 mg atebi-; N=34)
6-month OS	**94%** [77, 98]

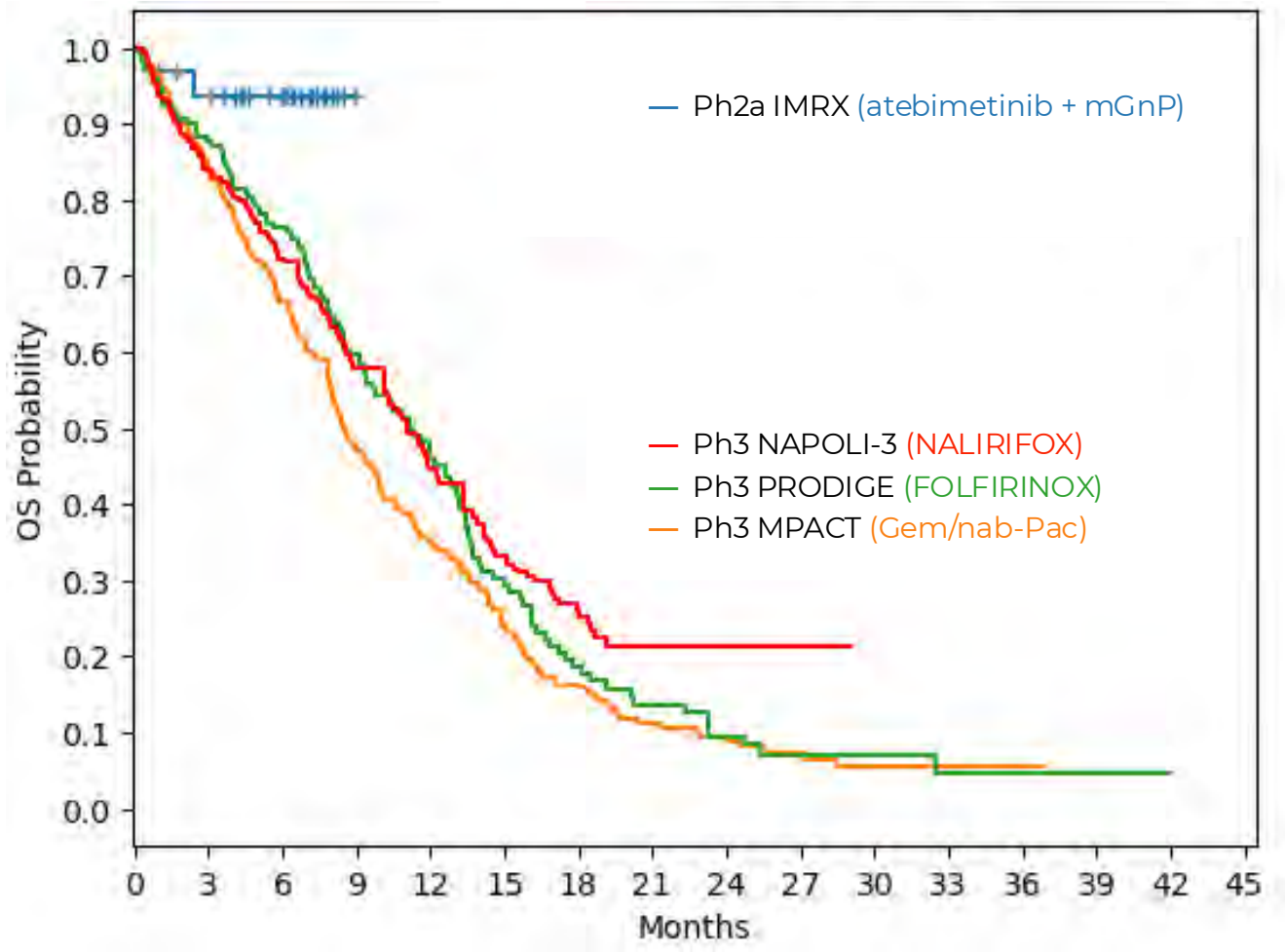
Median follow-up time: 6.0 months

Unless otherwise specified, all atebimetinib data based on interim data collection from the 320mg intent-to-treat population (N=34), as of May 26, 2025, from an ongoing Phase 1/2a trial of atebimetinib. Data subject to follow-up and database updates. mGnP = 1,000 mg/m2 (Gem) + 125 mg/m2 (nab-Pac) days 1 & 15, every 4 weeks

Immuneering

Exceptional OS Observed For Atebimetinib + mGnP in 1L PDAC

Atebimetinib (320 mg QD) + mGnP OS, N=34



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6-month OS	**94%** [77, 98]

Median follow-up time: 6.0 months

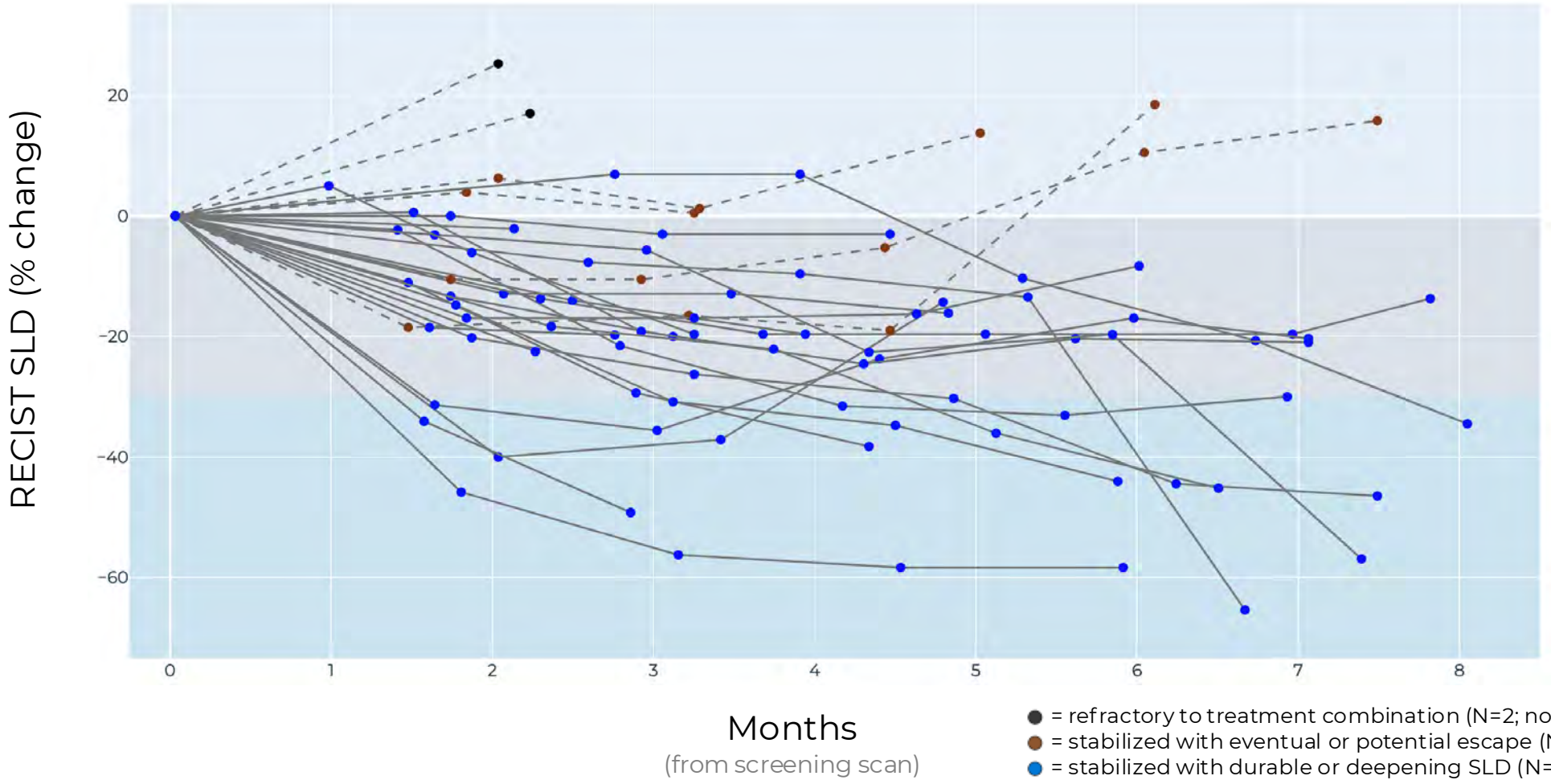
Reconstructed Kaplan-Meier (KM) Plots of Pivotal Ph3 Studies per 2024 JAMA Nichetti, et al. 7(1):e2350756

Pivotal Studies [6 mo OS]: (1.) MPACT 2013 NEJM (PMID: 24131140) N=431 [67%], (2.) PRODIGE 4 / ACCORD 11 2011 NEJM (PMID: 21561347) N=171 [76%], (3.) NAPOLI 3 2023 LANCET (PMID: 37708904) N=383 [72%]

FOR ILLUSTRATIVE PURPOSES ONLY: No head-to-head clinical trial has been conducted evaluating atebimetinib and other candidates or products. Differences exist between trial designs, subject characteristics and other factors, and caution should be exercised when comparing data across studies.

Deepening Tumor Responses Over Time Aligned With DCI MoA

Atebimetinib (320 mg QD) + mGnP in First Line Pancreatic Cancer



In the above graph, N=29, consisting of response evaluable patients who also had ≥ 1 matched RECIST-evaluable post-baseline scan. Color coded categorization based on Company's initial assessment. Data subject to follow-up and database updates. SLD = RECIST sum of longest diameter for target lesions.

Immuneering

Foundation for Durable, Safe and Combination-ready Oncology

Advancing DCI: Building a Robust Treatment Platform

- Mechanistic Boundaries of DCI:
  - Map adaptive resistance timing
  - Molecular limits for DCI PK/PD for safety & durability
- DCI Combination Strategies:
  - Tumor-specific sensitivity signatures
  - Utilization vs. toxicity trade-offs in non-tumor cells
- Pipeline Expansion:
  - Optimize DCI MEKi + RASi, RAFi, IO, chemo, RTKi
  - Develop new DCI programs for MAPK and beyond

Thank you!

Immuneering

Special thanks to patients and caregivers who make this research possible;
To investigators and clinical teams for their dedication;
To my colleagues for their collaboration and insights;
To the event organizers for the invitation to speak today.