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# Deep Cyclic Inhibition of MEK in RAS-mutant Tumors:

## Constraining MAPK-Axis Escape and Preserving Combination Optionality

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September 8, 2026

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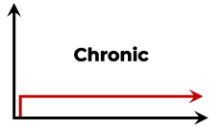
Unless otherwise specified, all clinical data in the following slides is based on an interim data collection from the intent-to-treat population of 55 patients dosed at the 320 mg once-daily dose level of atebimetinib in combination with modified gemcitabine/nab-paclitaxel ("mGnP" = 1,000 mg/m2 (Gem) + 125 mg/m2 (nab-Pac) days 1 & 15, every 4 weeks) in the Company's ongoing Phase 1/2a clinical trial, as of April 24, 2026. The median follow-up for overall survival (OS) was estimated by the reverse Kaplan–Meier method. All data remains subject to follow-up and database updates.

# Disclosures

**Praveen Nair, 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 the MAPK pathway at MEK

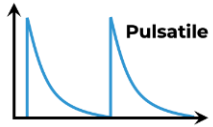



## PREVAILING PARADIGM

Chronic target engagement → prioritizes fast, deep RECIST shrinkage beyond -30% (surrogate for OS?)

## CHALLENGES

- High toxicity from continuous pathway suppression (esp. pan-RAS, pan-MAPK)
- Adaptive and acquired resistance; limited durability of response
- **Limited combination optionality → little room left for partner agents**




## ALTERNATIVE APPROACH

- Pulsatile MEK inhibition (Deep Cyclic Inhibition, DCI)
- Break tumor addiction and constrain resistance while sparing healthy tissue
- **Designed to combine: synergy and durability over monotherapy RECIST ORR**

## DCI VALIDATION: PROMISING PHASE 2 DATA & ENROLLING PHASE 3

- Encouraging overall survival, safety, activity in 1L PDAC to date
- Definitive tests come with randomized phase 3 readouts



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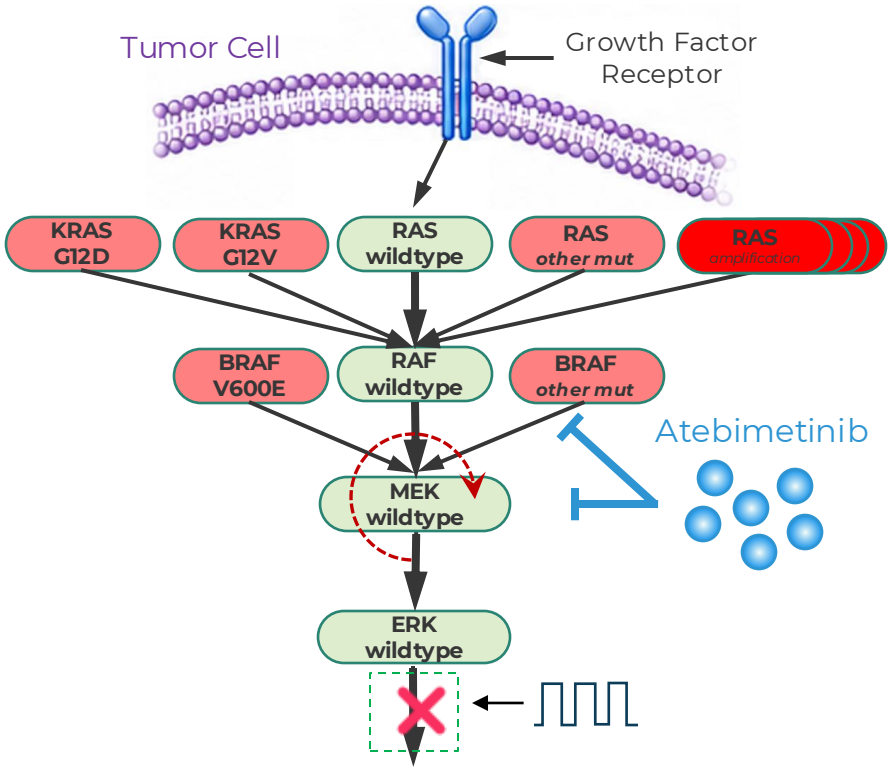
# Atebimetinib Could Unlock the Full Potential of MEK Inhibition

## Immuneering's First Target: MEK

*Pulsatile ≥$IC_{90}$ Inhibition with Once-Daily Oral Dosing*




**Healthy Cells = Intermittent**

**Cancer Cells = Continuous**

## **Goal:** Optimize Combination Durability & Tolerability

| | **Liabilities** | | **Strengths** | |
|---|---|---|---|---|
| **1st Generation MEK Inhibitors** | Ineffective in cancers driven by **RAS** | Poorly tolerated | Effective in cancers driven by **RAF** | Counters Cachexia to preserve body mass |
| | corrected | improved | retained | retained |
| **Atebimetinib** | **Block** RAF-mediated MEK phosphorylation | **Immuneering's Deep Cyclic Inhibitor (DCI) Technology** | | |





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# Prevailing Paradigm:

## Chronic Target Engagement

- **Rationale**: sustained inhibition required to break oncogenic addiction
- **Challenges**: toxicity, resistance, narrow window, limited combinability
- **Scope**: chronic MEK, mutant-selective- and pan-RAS inhibitors

# Widening RAS Blockade Does Not Close the Escape Route

Adaptive and acquired escape converges on RAS/MAPK reactivation - whatever the scope of blockade

## MUTANT-SELECTIVE RAS INHIBITORS

(e.g., KRAS G12C(OFF): sotorasib, adagrasib)

**SCOPE**

Narrow/focused, allele-defined patient subsets

**RESISTANCE**

Allele-specific and mutational: secondary KRAS mutations, plus NRAS, BRAF, MAP2K1, NF1 loss, RTK amplification (MET, EGFR, ERBB2, FGFR2); often multiple per patient

**TOXICITY**

Normal tissue largely spared; mutant protein is dispensable in healthy cells

**COMBINATION LOGIC**

Vertical pairing makes sense: atebimetinib (DCI MEKi) covers the MAPK node that escape runs through, without stacking chronic toxicity

## PAN- / MULTI-RAS INHIBITORS

(e.g., RAS(ON) multi-selective: daraxonrasib)

**SCOPE**

Broad coverage across multiple RAS alleles

**RESISTANCE**

Amplification-driven: emergent RAS-pathway alterations in 59% at end of treatment; mutant-KRAS amplification 36%, MAPK 25%, RTK 9%, PI3K 9%; no secondary KRAS mutations

**TOXICITY**

Wild-type RAS engagement: rash 86%, diarrhea 58%, stomatitis 53%; 36% dose reduced

**COMBINATION LOGIC**

Vertical pairings are constrained: wild-type RAS toxicity and broad pathway inhibition already restricts combination opportunities

Kim et al., AACR 2026 #1873; Aronchik et al., Nat Med 2026; O'Reilly et al., NEJM 2026 (RASolute 302); Ebright et al. 2025; Tanaka et al. 2021





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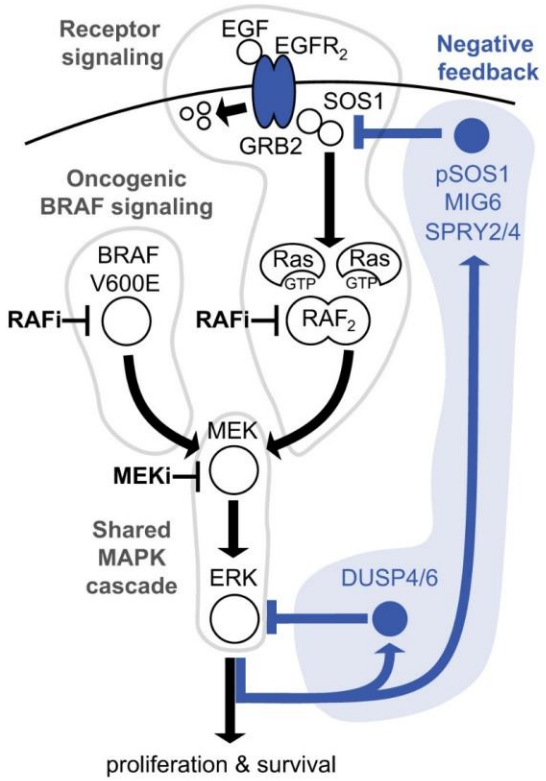
# Chronic MEK Inhibition: Feedback Loss, Resistance, Toxicity

The same MAPK-reactivation exit plus a toxicity ceiling that has restricted wider combinations

## Loss of Negative Regulators

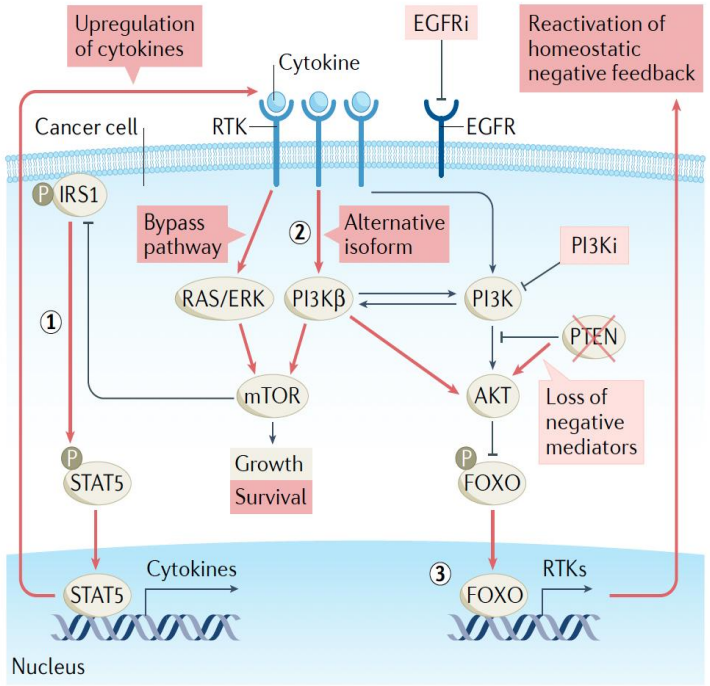
- RAF bypass: pMEK accumulates, pERK rebounds -




Gerosa et al, Cell Systems, 2020

## Increased Adaptive Resistance

- Adaptive escape precedes acquired resistance -




2022 Nat Rev Can p.323

## Increased Risk of MEK Toxicities

- Narrow window limits dose and combinations -

| 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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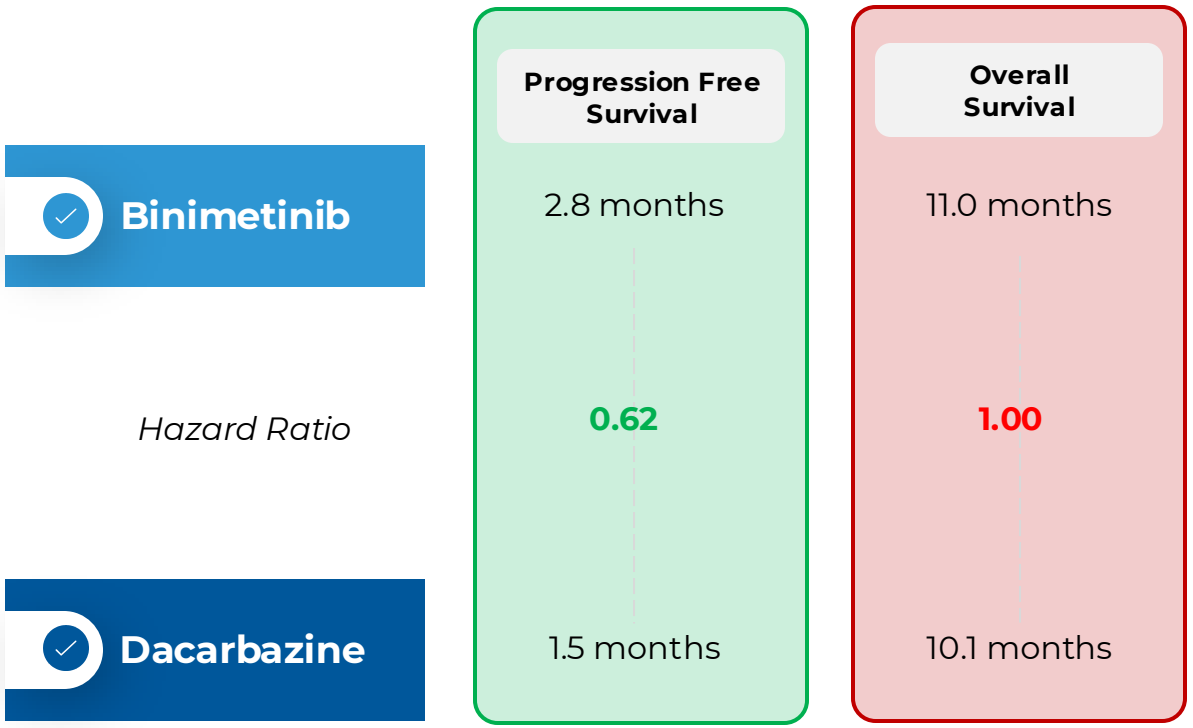
# NEMO Phase 3: Binimetinib vs. Dacarbazine (NRAS$^{mut}$ melanoma)

Better ORR and PFS, no OS benefit — dose reductions 61% vs 16%, discontinuations 20% vs 5%




| 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%) |

>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

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





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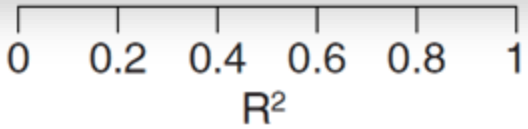
# RECIST ORR: a Poor Surrogate for Overall Survival

## Targeted therapy: ORR–OS correlation $R^2$ = 0.07 (95% CI 0.01–0.13)

| 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
- (PDAC) Makris, et al. 2017 Ann Surg Oncol 24:2371



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# Alternative Approach:

## Deep Cyclic Inhibition (DCI)

- **Rationale 1**: constrain MAPK-axis escape (deep pulse with daily reset)
- **Rationale 2**: combination optionality → tolerability headroom to combine

- **Challenges**: innovation resistance, legacy endpoints (surrogacy), historical limitations of chronic MEK inhibitors

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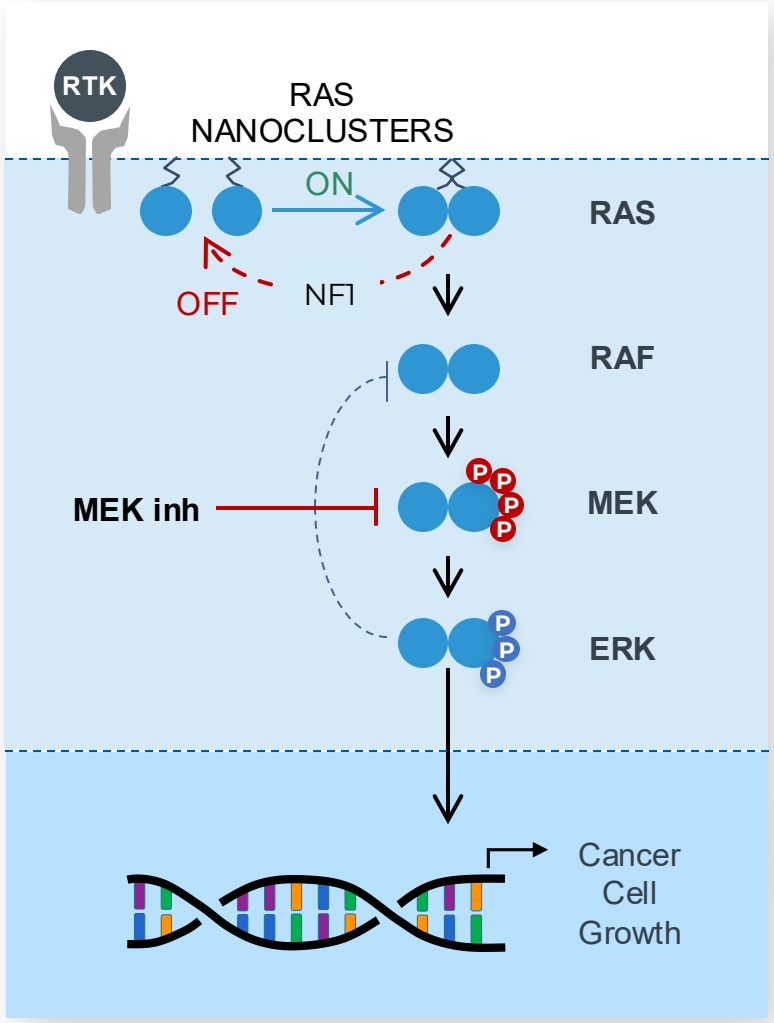
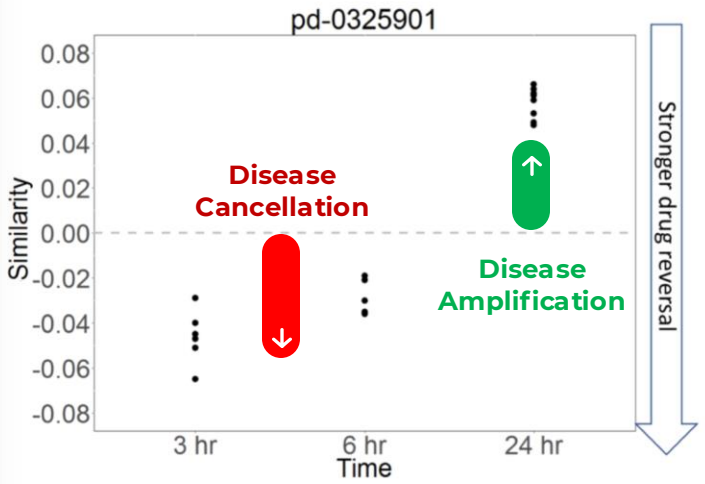
# Signaling Dynamics Pointed to the Pulse, Not the Plateau

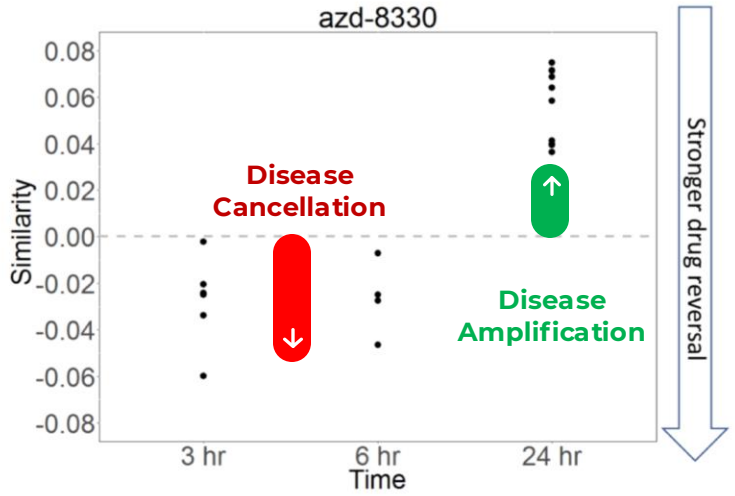
**Design goal:** achieve **broader activity** and **better tolerability** in RAS/MAPK pathway activated disease




**1st generation MEKi**




**1st generation MEKi**




Note: dots are representative of various concentrations

**Atebimetinib's dual-MEK binding resists CRAF bypass; its short half-life delivers the pulse first-generation MEKi cannot.**

*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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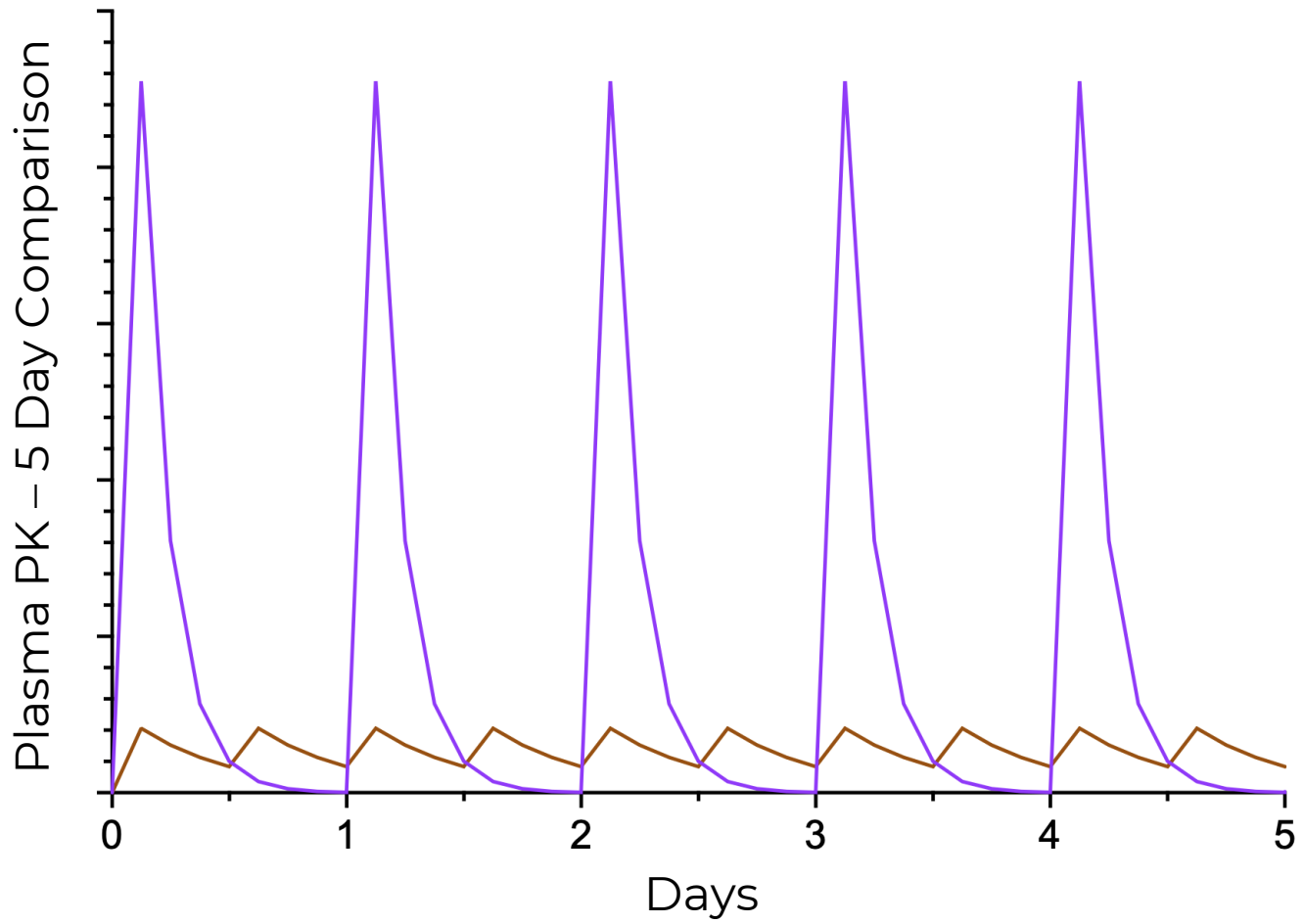
# Deep Cyclic Inhibition Requires: A Deep Pulse and a Daily Reset




*Conceptual illustration of deep cyclic inhibition (purple) vs. chronic inhibition (brown) | de Jong et al., ACoP 2024 (W-019)*

**Deep Pulse Above IC90**
**GOAL**: many-fold higher Cmax free-fraction to break tumor addiction

**Near-Zero Trough**
**GOAL**: short 2-3 h half-life, so every day includes a drug holiday

**Bypass-Resistant MoA**
**GOAL**: prevent RAF-mediated MAPK bypass; broaden RAS-mutant activity

**Combination Headroom**
**GOAL**: improved tolerability to add vertical and orthogonal partners



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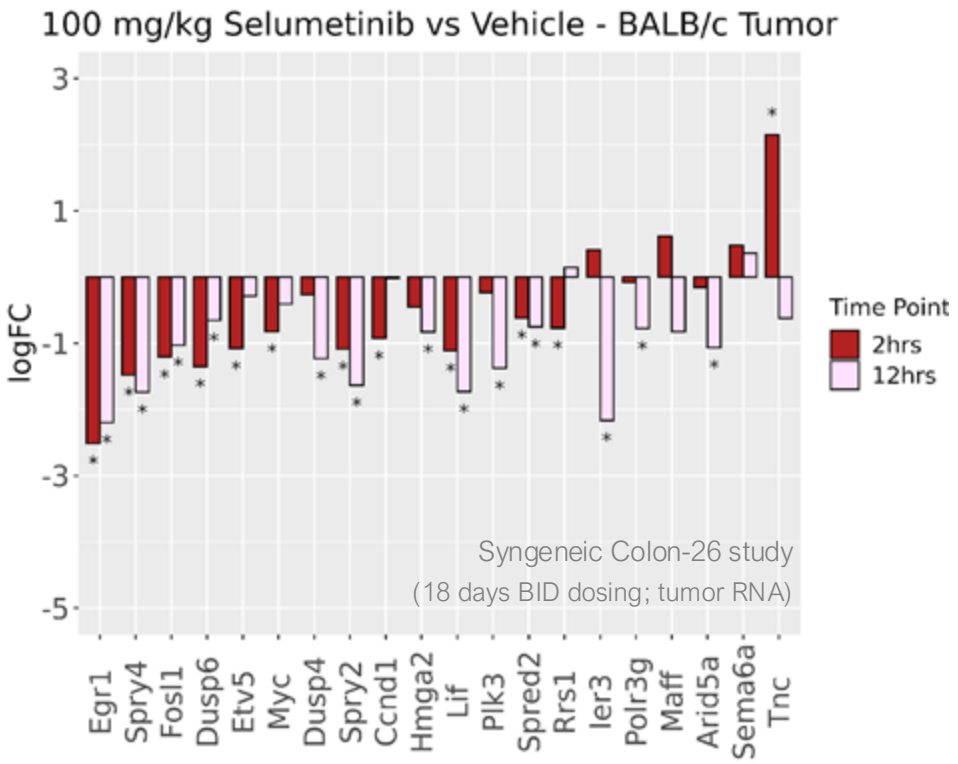
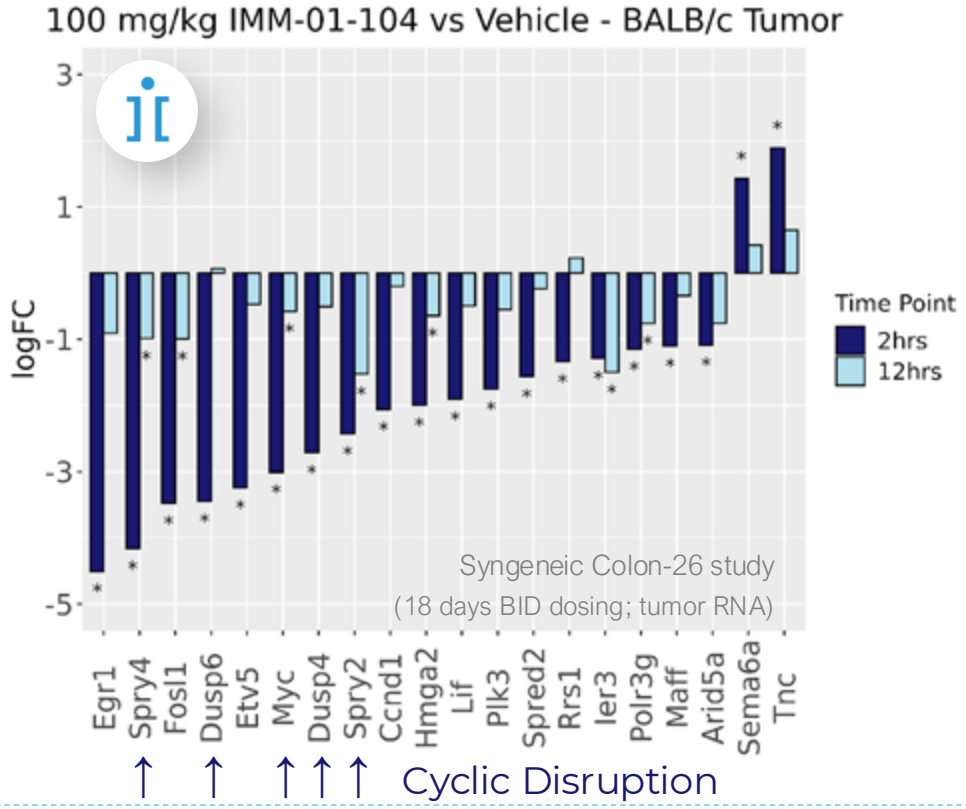
# Pathway Recovers Daily: Cyclic Disruption, Not Chronic Suppression

## Chronic MEK Inhibition




Sustained suppression → unrelenting selective pressure + TOXICITY

## Deep Cyclic Inhibition




Daily reset → pressure released + TOLERABILITY

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



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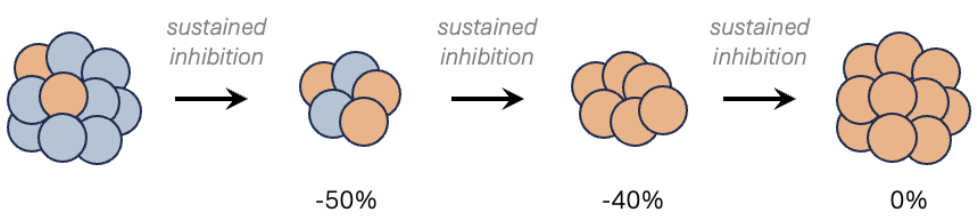
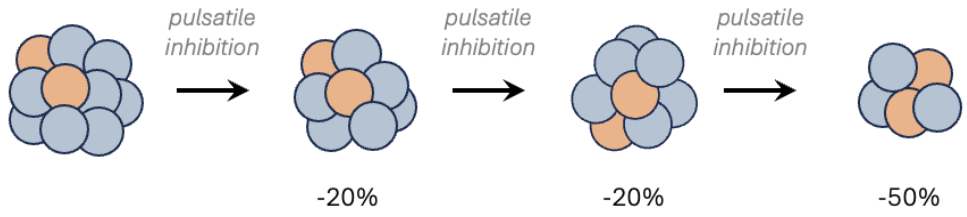
# Outpacing Adaptation: Slower Shrinkage, Longer Control

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**




clones addicted to targeted pathway

clones resistant to targeted pathway


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*



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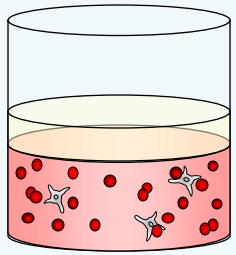
# Breadth at the MEK Node: 157 of 211 Models Responsive

## 211 Tumor Models

124 = RAS Mutant

32 = RAF Mutant



Humanized 3D-TGA

Nair, et al. 2023
AACR EORTC
Boston, MA

| Tissue | Response # | Non-Response # |
|---|---|---|
| **Pancreatic †** | **18** | **3** |
| **Melanoma †** | **24** | **0** |
| **Lung †** | **28** | **13** |
| **CRC** | **25** | **10** |
| Thyroid | 9 | 2 |
| Cholangiocarcinoma | 7 | 0 |
| AML | 10 | 0 |
| Uveal Melanoma | 4 | 1 |
| Multiple Myeloma | 4 | 4 |
| Soft Tissue | 3 | 2 |
| Breast | 3 | 6 |
| Gastric | 4 | 2 |
| Ovary | 4 | 3 |
| Prostate | 1 | 2 |
| Fibrosarcoma | 1 | 0 |
| Liver | 4 | 2 |
| Neuroblastoma | 1 | 1 |
| Other (BLA, UTE, ESO, HNSQ) | 7 | 3 |
| **Total** | **157** (74.4%) | **54** (25.6%) |

| RAS, RAF mutation | Response # | Non-Response # |
|---|---|---|
| NRAS G12 | 4 | 0 |
| NRAS G13 | 1 | 0 |
| NRAS Q61 | 23 | 4 |
| KRAS A146 | 2 | 1 |
| KRAS G12 | 54 | 12 |
| KRAS G13 ^ | 4 | 3 |
| KRAS Q61 | 5 | 2 |
| HRAS G12 | 2 | 1 |
| HRAS G13 * | 1 | 0 |
| HRAS Q61 | 5 | 0 |
| BRAF (Class I or II) | 26 | 5 |
| **Total** | **127** (81.9%) | **28** (18.1%) |

| RAS, RAF mutation | Response # | Non-Response # |
|---|---|---|
| Not Present | 34 | 25 |
| **Total** | **34** (57.6%) | **25** (42.4%) |

^ 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)







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# Bedside-to-Bench for DCI-MEKi

## Rational Combination Design

- **Rationale**: ctDNA points escape away from MAPK; so, combine orthogonally
- **Design**: chemotherapy combination first, then immunotherapy and vertical partners

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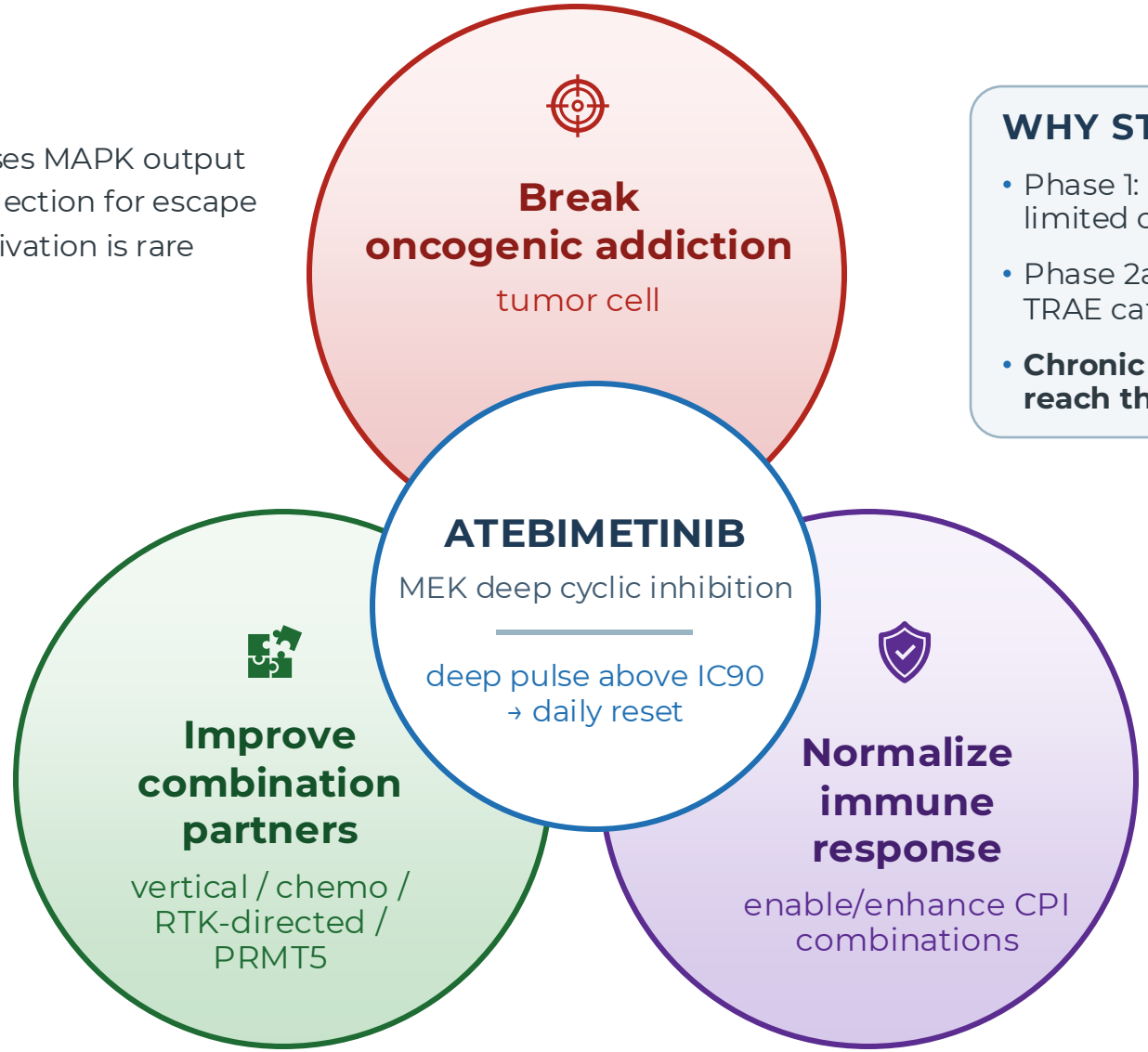
# Atebimetinib Combination Potential: Stacking MoA's

- Pulse ≥ IC90 collapses MAPK output
- Daily reset limits selection for escape
- ctDNA: MAPK reactivation is rare




**WHY STACKING CAN WORK**

- Phase 1: deep suppression at peak, limited cumulative toxicity
- Phase 2a 1L PDAC: only two grade 3+ TRAE categories at ≥10%
- **Chronic MEKi and pan-RASi agents reach the toxicity cap first**

- Prevents MAPK node RASi and RAFi reactivation
- Reduces chemoresistance and non-MAPK escape
- Blunts RTK-driven MAPK rebound
- Enhance synthetic lethality (internal data)

- Reverses MAPK-driven immune escape in the TME
- Spares the T-cell compartment
- Rationale for CPI combinations (NSCLC in clinic)

Kolitz et al. 2026; King et al. 2024; Nair et al. 2023; Choi et al., Cell Rep 2019; Kim et al., AACR 2026 #1873

# Combination Optionality: Vertical, Immune, Orthogonal

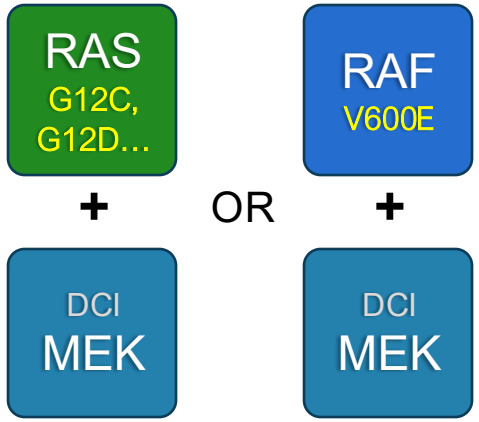
## Monotherapy

Pulsatile MAPK Pathway Inhibition


**Ideal**: In patients with broad MAPK pathway addiction

## Vertical Combinations

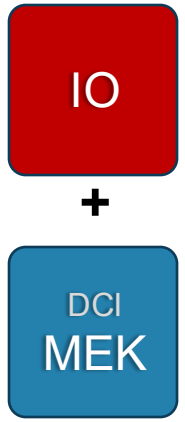
Selective Vertical Drug Combinations




**Goal**: Greater Depth & Durability of Response

## Immune Modifying Combinations

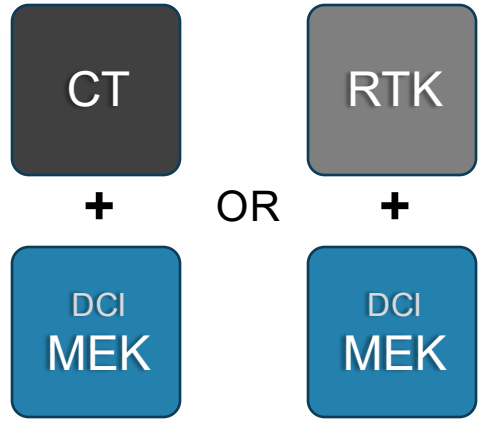
Dual-targeting of Tumor & Immune System




**Goal**: Break MAPK Addiction; Enhance Antitumor Immunity

## Orthogonal MoA Combinations

Non-overlapping Mechanism of Action Combinations




**Goal**: Expand & Improve Overall Antitumor Response

Tolerability headroom is what makes these pairings feasible

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





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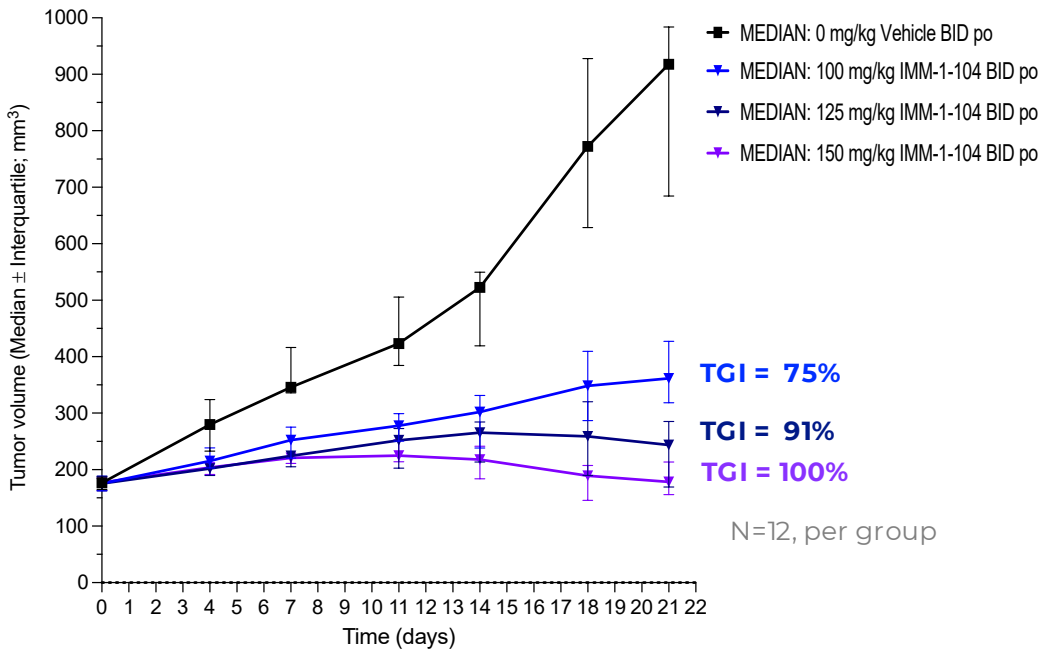
# The DCI Pulse Is Not a Compromise: Atebimetinib vs. binimetinib in NRAS-Q61R SK-MEL-2 melanoma

Deep cyclic MEK inhibition reached TGI of 100% vs. 35% for chronic binimetinib

DCI MEK

## Atebimetinib (IMM-1-104)

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

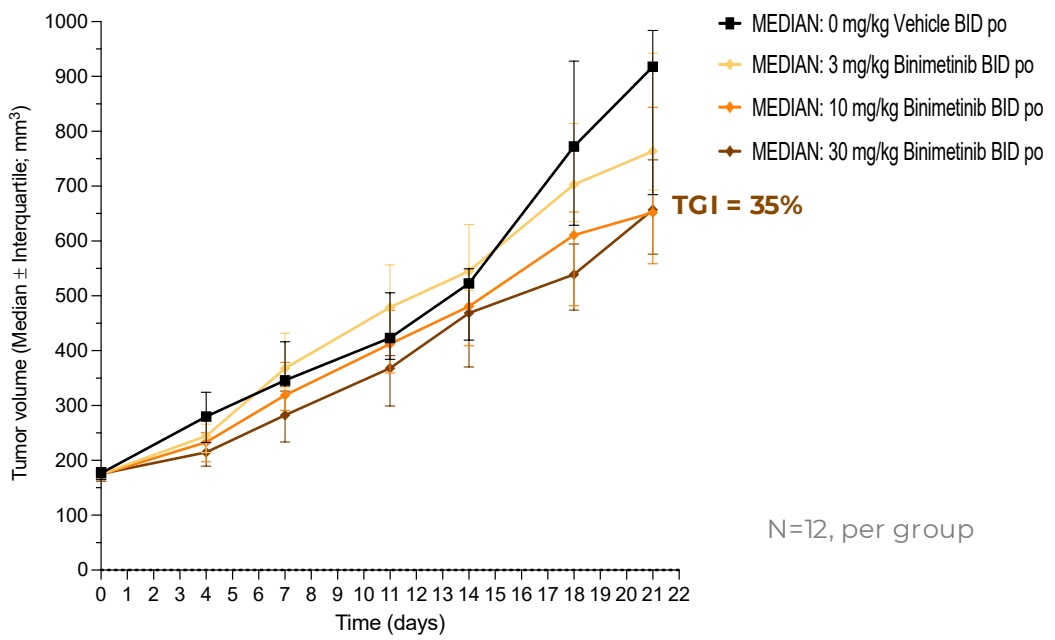



N=12, per group

Chronic MEK

## Binimetinib

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




N=12, per group

**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)

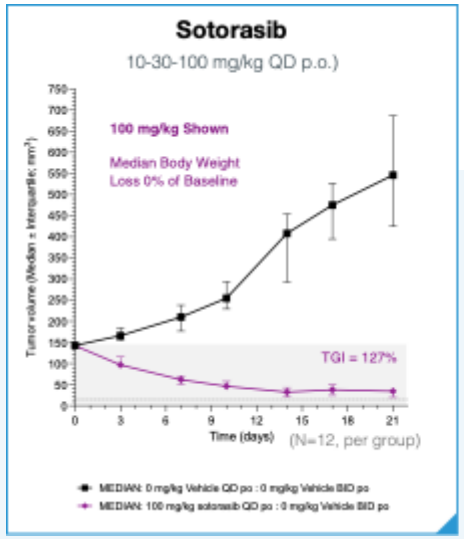
*Binimetinib was commercially purchased*

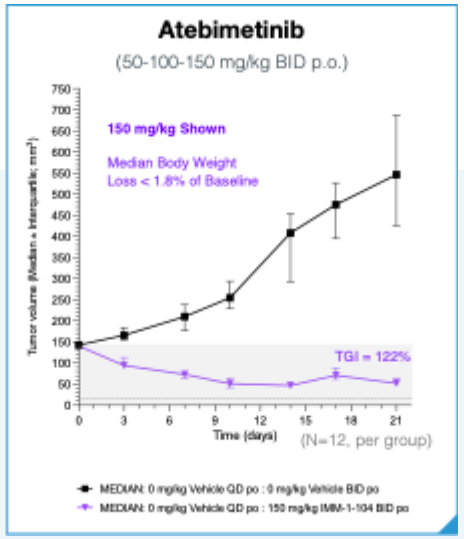
# Vertical Combination, Proven: Atebimetinib + Sotorasib

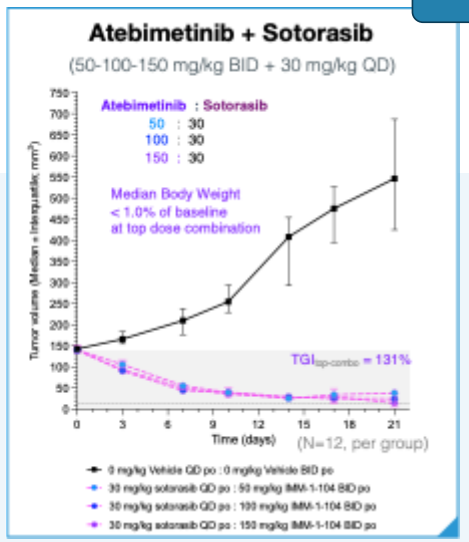
Deeper, more durable regressions than either agent alone, with minimal body-weight loss

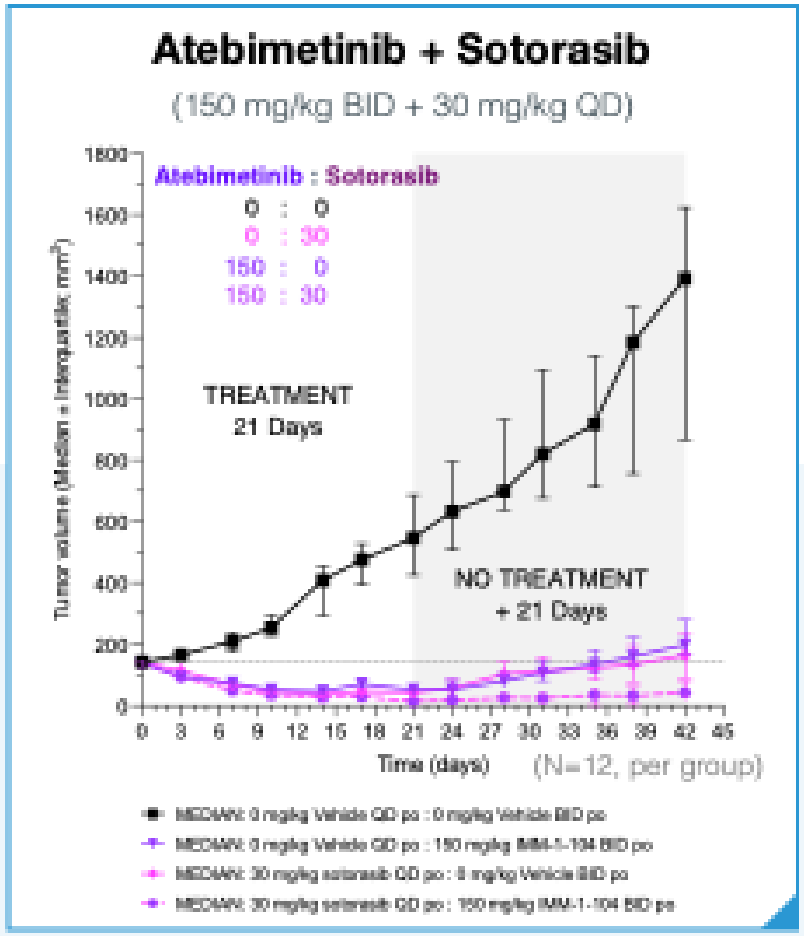
**KRAS$^{G12C}$ PANC**

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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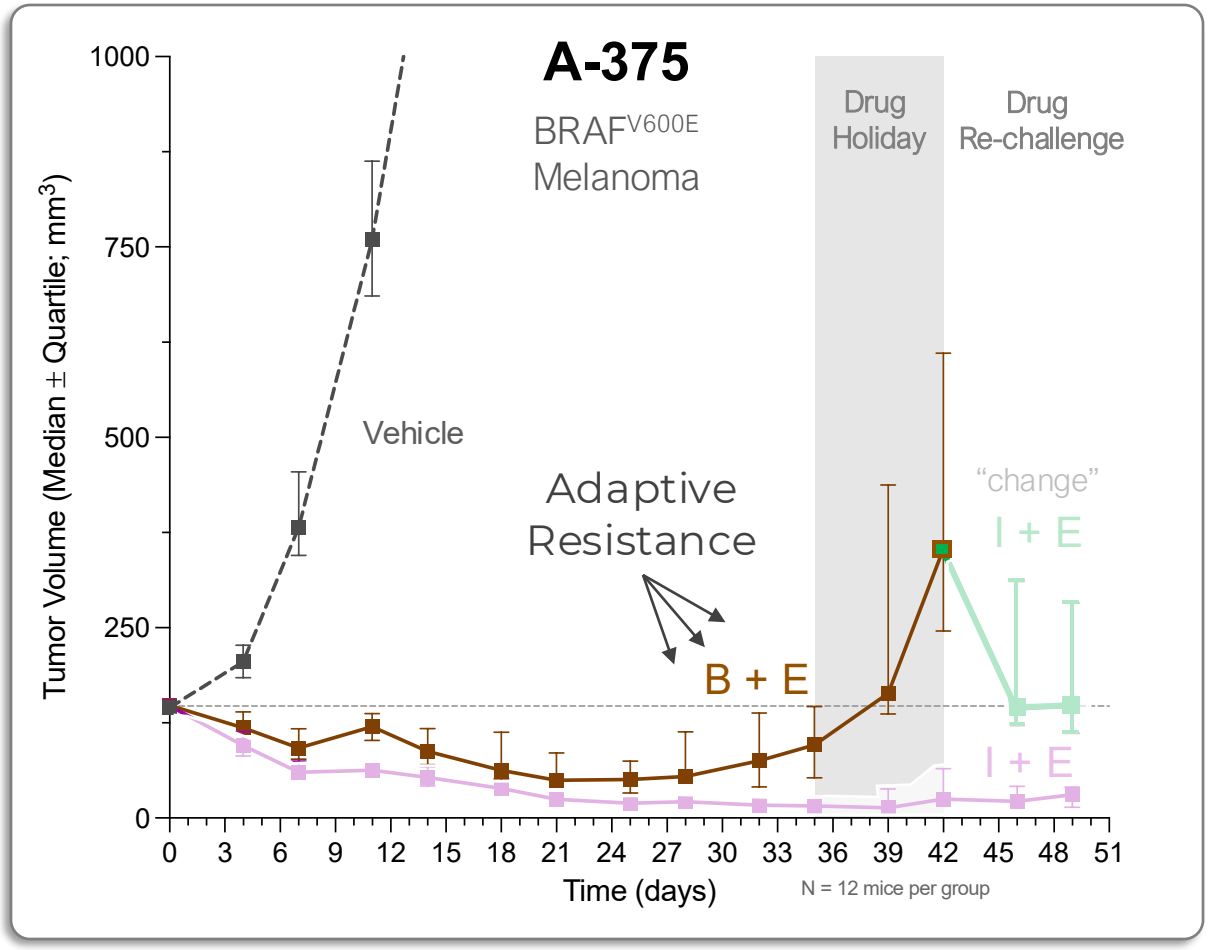
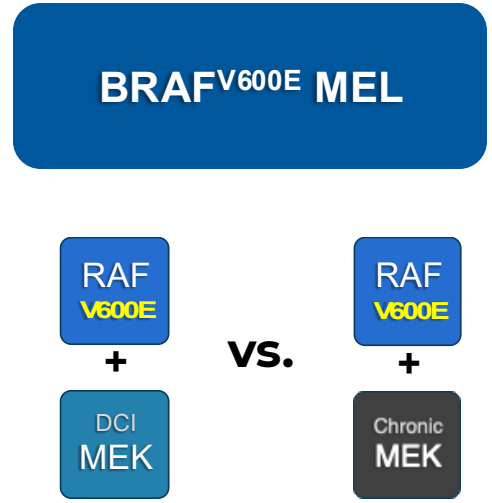
# Vertical Combination, Proven: DCI MEKi + BRAFi Outperforms Chronic MEKi + BRAFi in BRAF-Mutant Melanoma




- 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

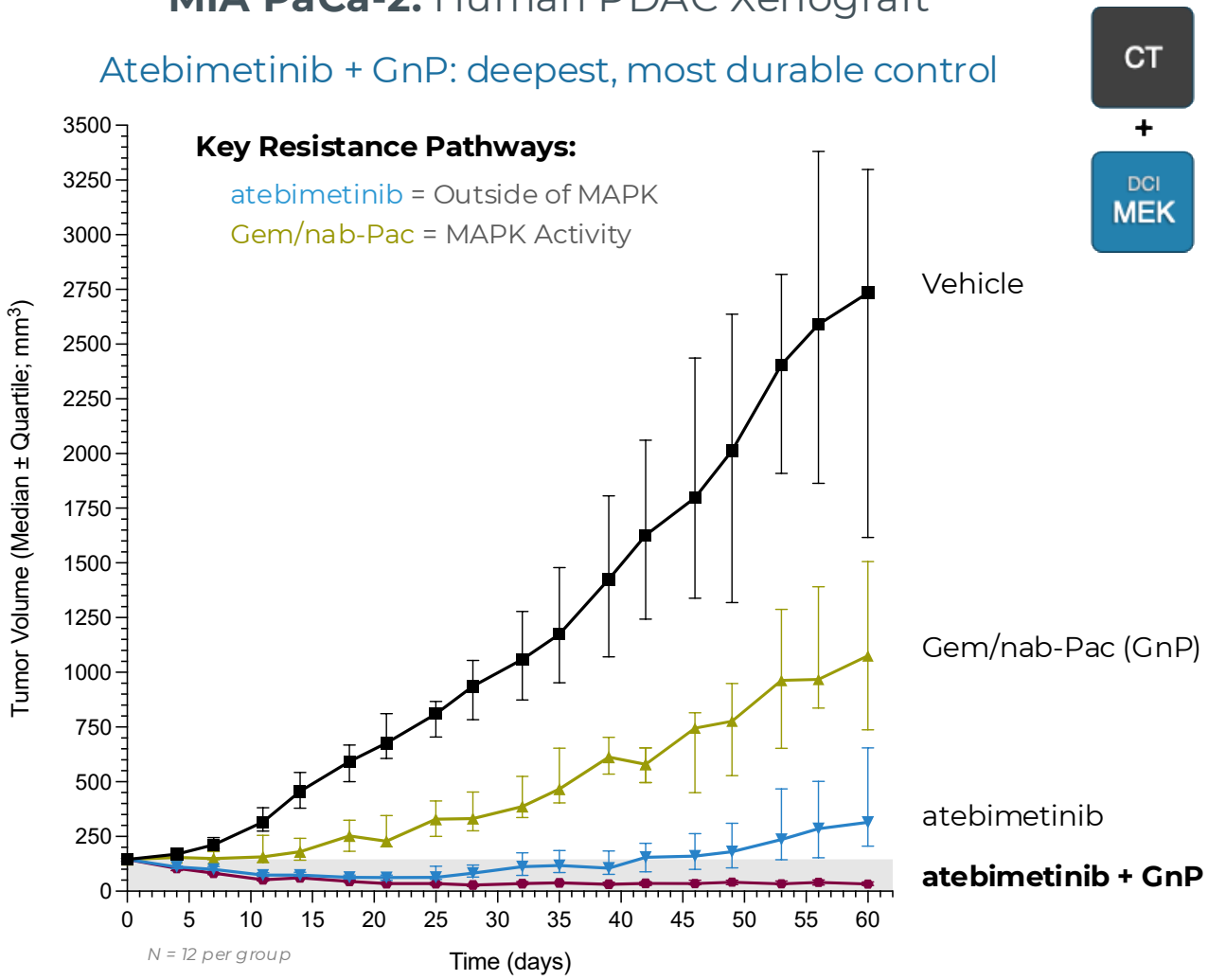
A-375 Melanoma BRAF$^{V600E}$ xenograft tumor models in athymic nude mice. Binimetinib (MEK inhibitor) and encorafenib (BRAF inhibitor) were commercially purchased. Tumor Growth Inhibition (TGI) % = [1-(Ti-To)/(Ci-Co)]x100%. No median body weight loss was noted.

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

# Deep, Durable Responses: Atebimetinib + Gem/nab-Pac

**MIA PaCa-2:** Human PDAC Xenograft

Atebimetinib + GnP: deepest, most durable control




*King et al., AACR 2024 — near-complete responses in most animals*

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





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# DCI-MEKi Clinical Translation

## Atebimetinib PK/PD (Phase 1)

- **Question**: does the pulse reach ≥IC90 and clear in patients?
- **Readout**: time above pERK IC90, trough depth, tolerability

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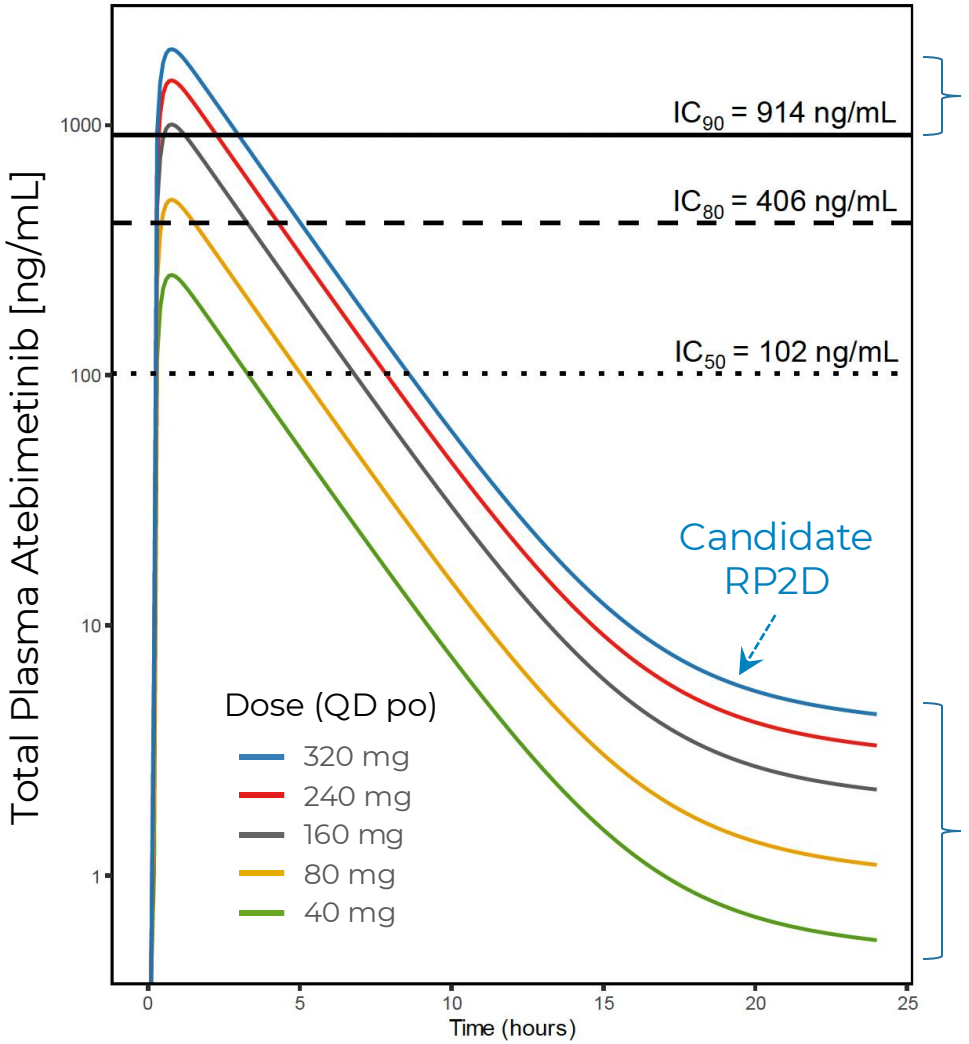
# The DCI Pulse: >90% Inhibition, Near-Zero Trough

## 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

**Both DCI requirements met in patients: a deep pulse above $IC_{90}$, then daily clearance**

*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)*

*November 2024 ACoP (Phoenix, AZ) – de Jong, et al. [W-019]; DCI = Deep Cyclic Inhibition PK/PD Patient Profiles (IMM1104-101 trial)*





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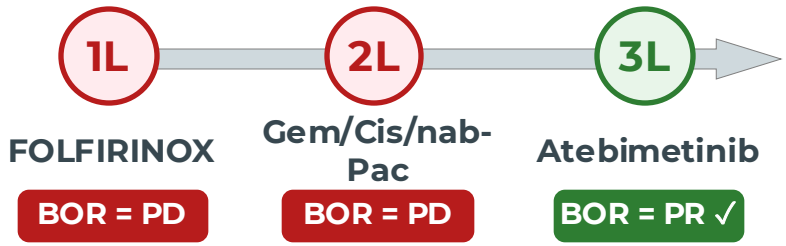
# 27+ Months PFS on Atebimetinib Monotherapy (3L PDAC)
# Durability without a single grade 3+ event; the DCI thesis in one patient

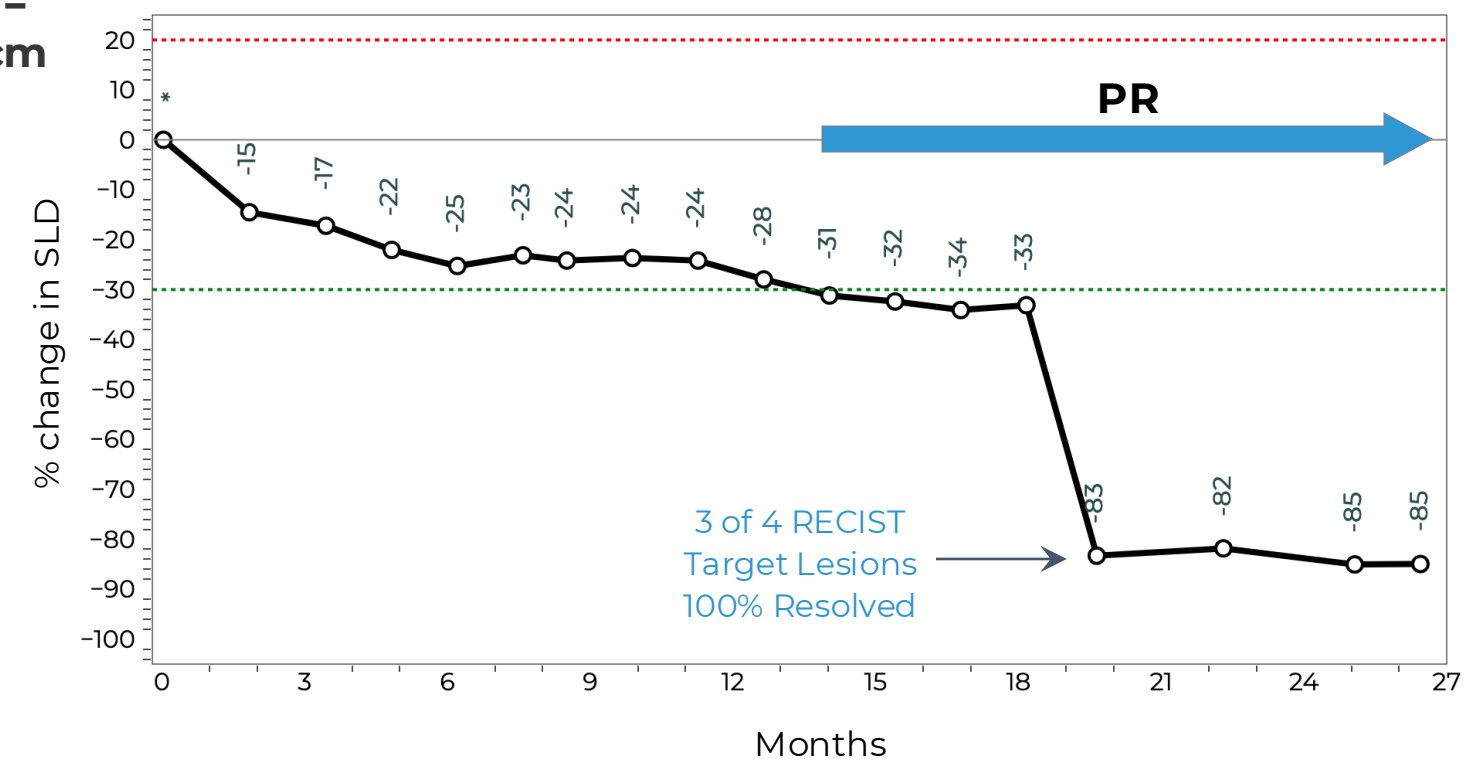



**Baseline SLD = 18.6 cm**

KEY CLINICAL OUTCOMES

| | |
|---|---|
| **27 months** on treatment at data cutoff | **−85%** Ongoing tumor burden reduction |
| **3** of 4 target lesions fully resolved (1 bone + 2 liver) | **+14% Weight** + 23 lb / QoL Improved on PRO instrument |

***No Grade 3+ Adverse Events***




70 year old male patient with KRAS G12D mutant tumor treated at 240 mg QD p.o. Based on interim data collection from Phase 1 dose expansion as of May 5, 2026 from an ongoing Phase 1/2a trial of atebimetinib. In addition to the 3 target lesions, one non-target lesion in the pancreas has fully resolved. Data subject to follow-up and database updates.



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# Clinical ctDNA: Under DCI, MAPK Reactivation Is Uncommon

Serial ctDNA in 86 patients on atebimetinib monotherapy and 37 on first-line PDAC combination therapy

## ATEBIMETINIB (DCI MEKi)

pulsatile MEK inhibition with daily reset

RTK | RAS | RAF | **MEK** | ERK

**Pathway output CONSTRAINED at MEK**

- On-treatment variants infrequent, with little early enrichment for canonical RAS/MAPK resistance
- No dominant MAPK-reactivation signature: no enriched RAS pathways in PDAC monotherapy or combination
- Acquired events heterogeneous, skewing to cell-cycle/DDR, MYC and TERT/PLK3 biology

## CHRONIC RAS-DIRECTED THERAPY

pan-, multi- and mutant-selective agents

**RTK** | **RAS** | **RAF** | MEK | ERK

**Pathway output RESTORED upstream of MEK**

- Emergent alterations converge on RAS/MAPK restoration
- KRAS secondary mutations and amplification, NRAS, BRAF, MAP2K1, NF1 loss, RTK amplification
- Escape is recurrent and convergent across agent classes
- Daraxonrasib: RAS-pathway alterations in 59% of patients at end of treatment

**IMPLICATION:** with the MAPK exit constrained, combination optionality stays open; vertical (mutant-selective RAS or RAF) and orthogonal (chemotherapy, immunotherapy, RTK-directed)

Kim et al., AACR 2026 #1873 (Figures 1–4); Phase 1/2a NCT05585320; Aronchik et al., Nat Med 2026. Single-arm data for atebimetinib





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# Clinical Impact of DCI MEKi

## Atebimetinib + chemotherapy (1L PDAC)

- **Question**: does tolerability headroom convert into combination benefit?
- **Readout**: OS, PFS, ORR/DCR against Gem/nab-Pac benchmarks

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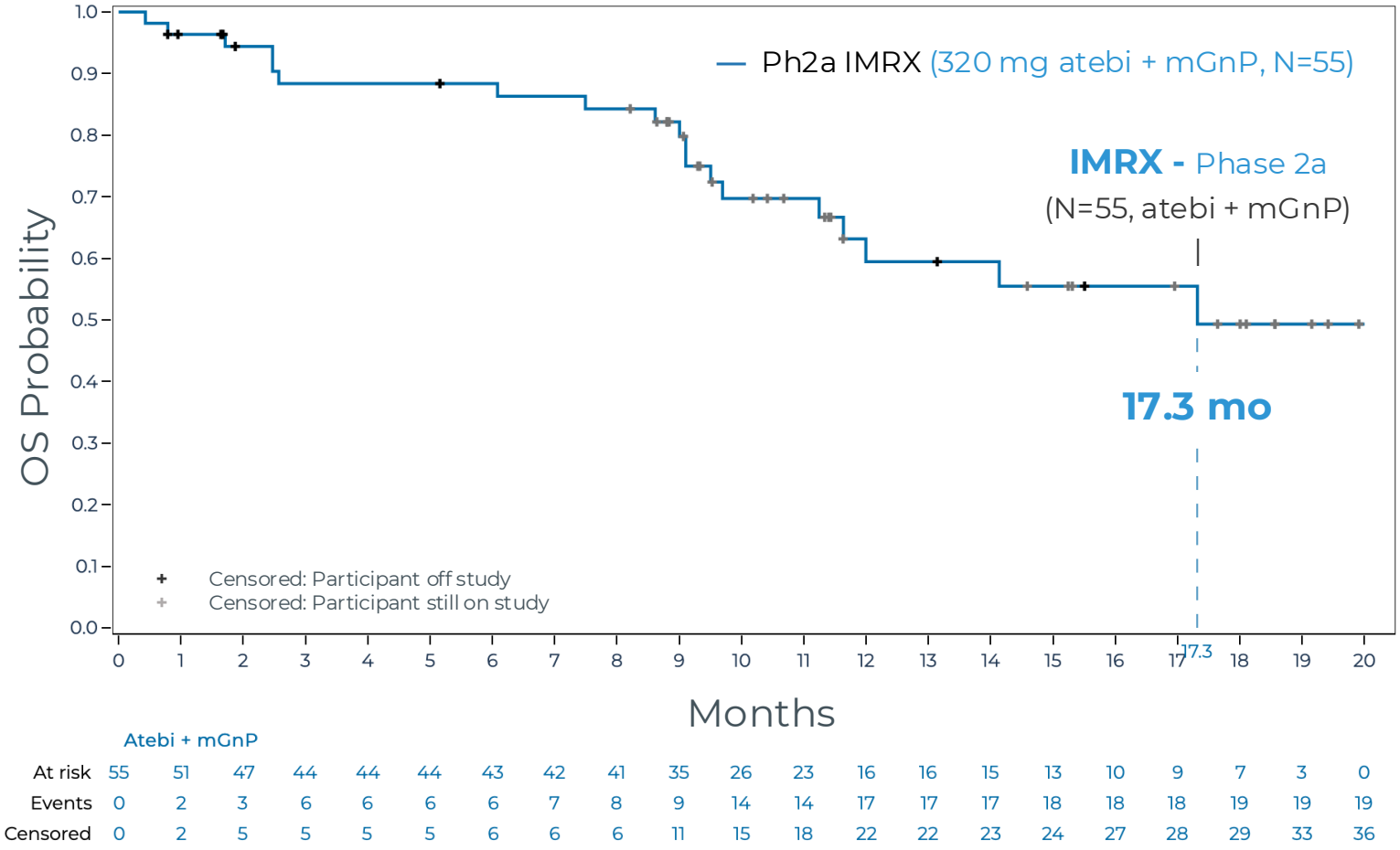
# Compelling Survival and Tolerability in First Line Pancreatic Cancer

## Phase 2a | Atebimetinib + mGnP: OS 17.3 vs 8.5 mo (GnP), **N=55**




| **Median OS** (months) | |
|---|---|
| **Atebimetinib + mGnP** (N=55) | **17.3** |

Only 2 categories of TRAE grade ≥3 in ≥10% of participants, both chemotherapy related

MAPKeeper 301

Phase 3 Now Recruiting, NCT07562152

As of the April 24, 2026 data cutoff, the median follow-up was 11.6 months (N=55) as estimated by the reverse Kaplan–Meier method.

**ASCO 2026 Chung, Vu, et al.**





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# Separation from Gem/nab-Pac Benchmarks Across Every Endpoint

| | **Atebimetinib + mGnP** (N = 55) | **GnP** (MPACT) |
|---|---|---|
| **Median OS** (months) | **17.3** [11.2, NR] | 8.5 |
| **Median PFS** (months) | **8.3** [5.9, 9.6] | 5.5 |
| **ORR*** | **36%** | 23% |
| **DCR*** | **82%** | 48% |
| **Participants weight stable or gained weight at 3 months**** | **84%** | NR |

Primary Endpoint for Phase 3 trial is Overall Survival (OS). Secondary endpoints include progression-free survival (PFS), disease control rate (DCR), overall response rate (ORR) and Quality of Life (QoL).

* N=50 of response evaluable patients. Atebimetinib dosed at 320 mg. Scans occur approx. every 6 weeks. Patients that progressed without complete radiographic scans are not presented in graph but are counted in ORR/DCR analyses. Patients with baseline and at least one on-treatment assessment were considered evaluable.
** Weight observations from participants with weight data at ~3 mo and C1D1; weight stable defined as within 5%.

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. Pivotal Ph3 Study MPACT 2013 NEJM (PMID: 24131140)



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# MAPKeeper 301: Global Randomized Phase 3 Pivotal Trial Underway

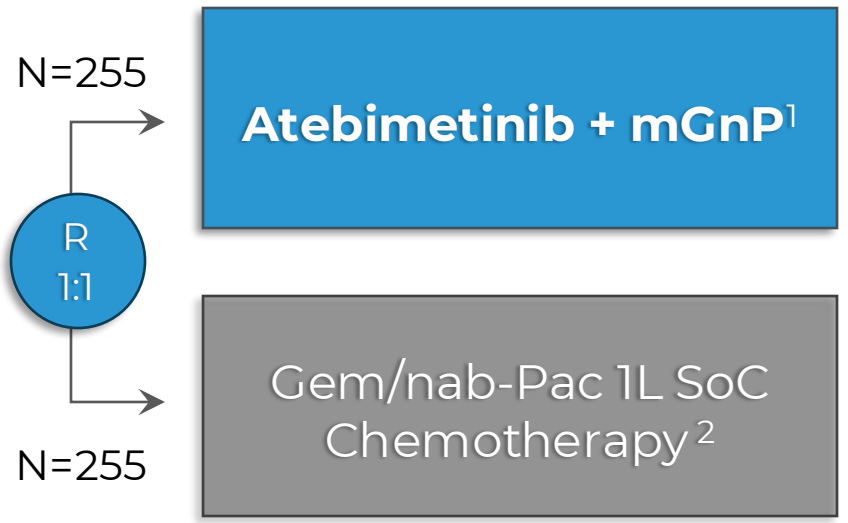
NCT07562152 | recruiting

*A definitive randomized test of the DCI hypothesis in 1L metastatic PDAC*

## Participant Population: First-line (1L) metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

MAPKeeper 301

- First line (1L) PDAC
- Metastatic setting
- ECOG PS 0-1




| Primary Endpoints |
|---|
| OS |
| **Secondary Endpoints** |
| PFS |
| DCR |
| ORR |
| QoL |

(R) = Randomization Stratification Factors: (1.) Geography (US vs. ROW), (2.) Liver Metastasis (present vs. absent), (3.) ECOG PS: 0 vs. 1, (4.) Denovo vs Recurrent Metastatic

SOC chemotherapy options: full schedule Gemcitabine + nab-Paclitaxel. SOC = standard of care; R = randomize; PFS = progression-free survival; OS = overall survival; ORR = overall response rate; DCR = disease control rate; QoL = Quality of Life

(1) mGnP = 1,000 mg/m2 (Gem) + 125 mg/m2 (nab-Pac) days 1 & 15, every 4 weeks

(2) SOC chemotherapy = full schedule Gemcitabine + nab-Paclitaxel (3 wk on/ 1 wk off)





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# DCI: Foundation for Durable, Safe and Combination-ready Oncology

## Constraining MAPK Escape, Preserving Combinability

- **What the data support:**
  - Any scope of chronic RAS blockade leads to escape by convergence on MAPK reactivation
  - In contrast, DCI delivers pulsatile MAPK pathway inhibition at MEK and rare MAPK escape
  - Tolerability headroom converted: 17.3 vs. 8.5 months median OS in 1L PDAC
- **What remains to be tested:**
  - MAPKeeper 301 randomized readout (NCT07562152) vs. standard of care
  - Pulsatile PK vs. dual-MEK binding as the causal drivers
  - Non-MAPK escape routes: PI3K/AKT, YAP/TAZ, FGFR
- **Where DCI is heading next:**
  - Vertical (RASi, RAFi) and orthogonal (chemo, IO, RTKi) combinations
  - DCI at other pathway nodes, and tumor-specific sensitivity signatures

# Thank you!


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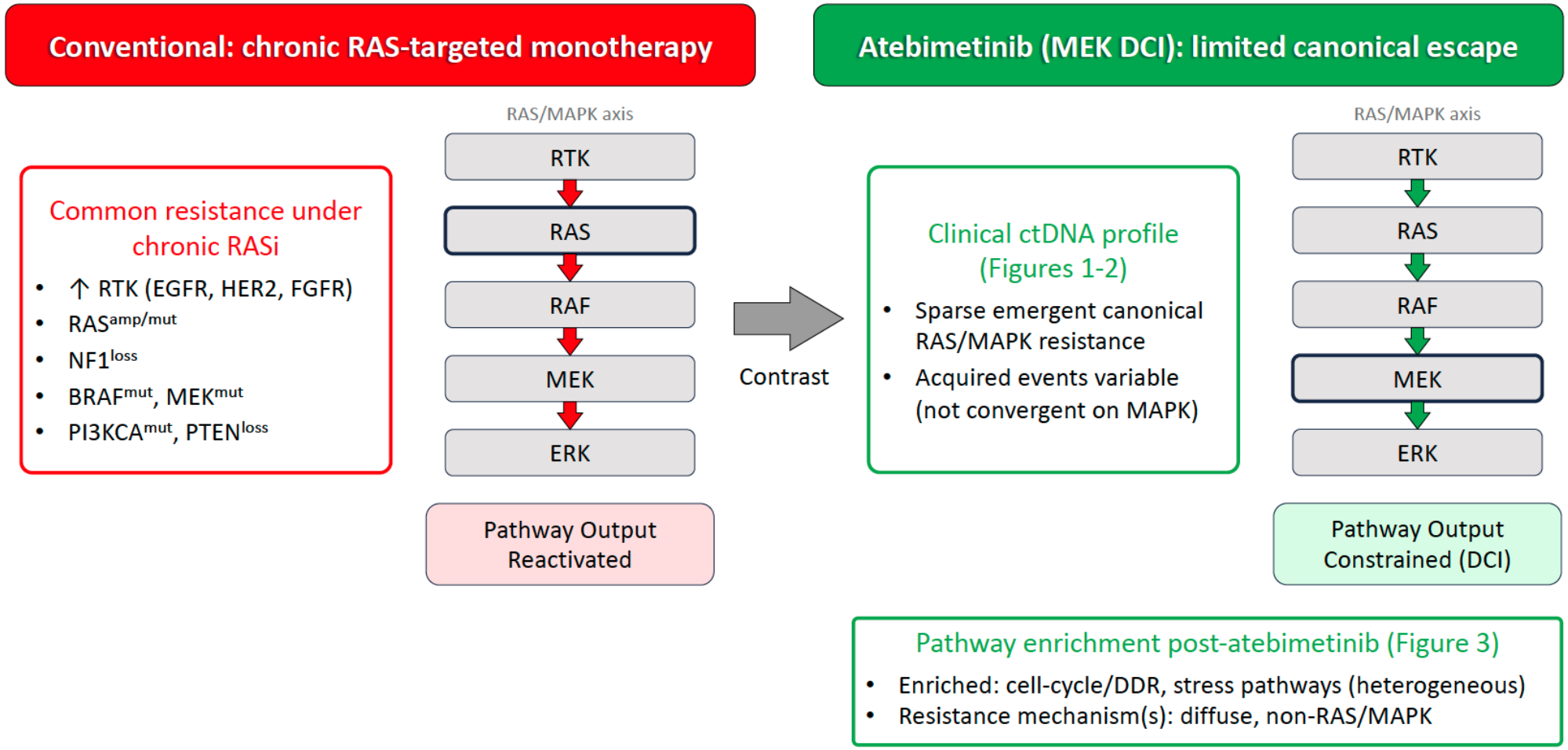
**Special thanks to patients and caregivers** who make this research possible;
To investigators and clinical teams for their dedication;
To my colleagues for their collaboration and insights;
To the event organizers for the invitation to speak today.

# Appendix: Treatment-Acquired Mutation Patterns

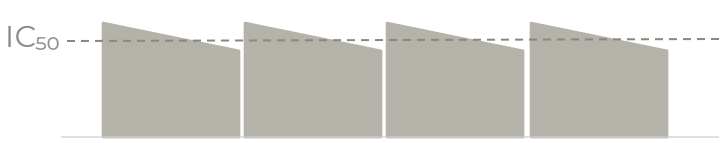



**Implication**: Deep Cyclic Inhibition (DCI) of MEK preserves opportunity for optimized combinations

J. Kim, et al 2026 AACR (San Diego, CA) #1873

# Immuneering's Deep Cyclic Inhibitor Technology: Engineering for Longer Survival with Fewer Tradeoffs

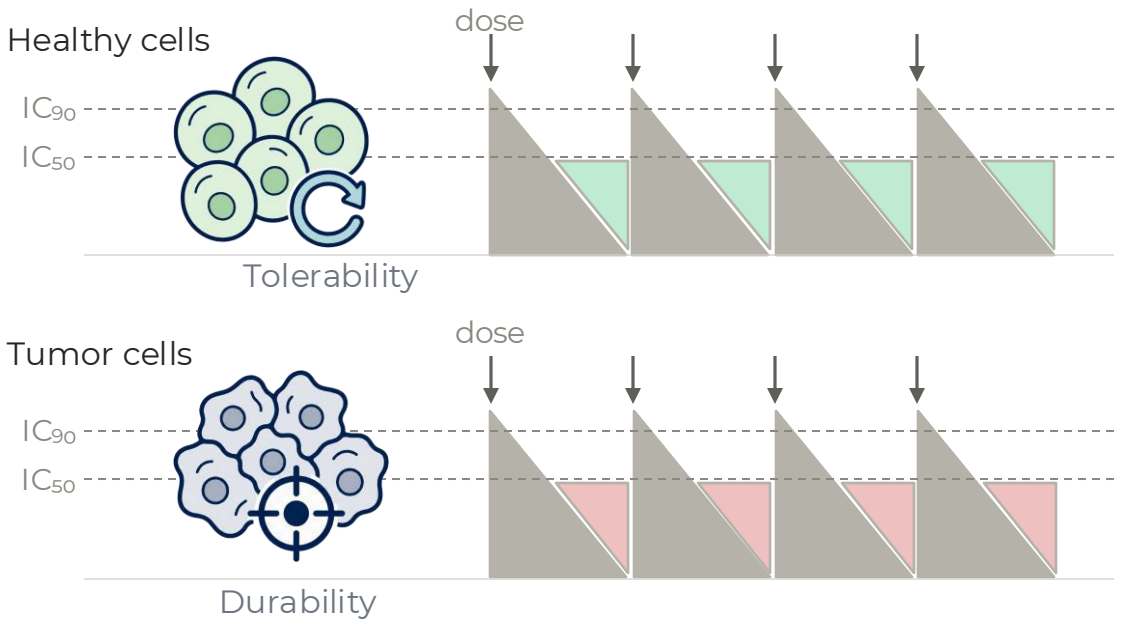
## Conventional Wisdom: Chronic Inhibitors




**All cell signaling suppressed**
= toxicity, resistance

## Immuneering's Deep Cyclic Inhibitor Technology

*Pulsatile ≥$IC_{90}$ Inhibition with Once-Daily Oral Dosing*




*High Free-Fraction CMax, Fast Off Rate, Short Half Life (~2 hours)*

### 1. Tolerability

Provides Recovery Window for Healthy Cells

### 2. Durability

Limits Adaptive and Acquired Resistance





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