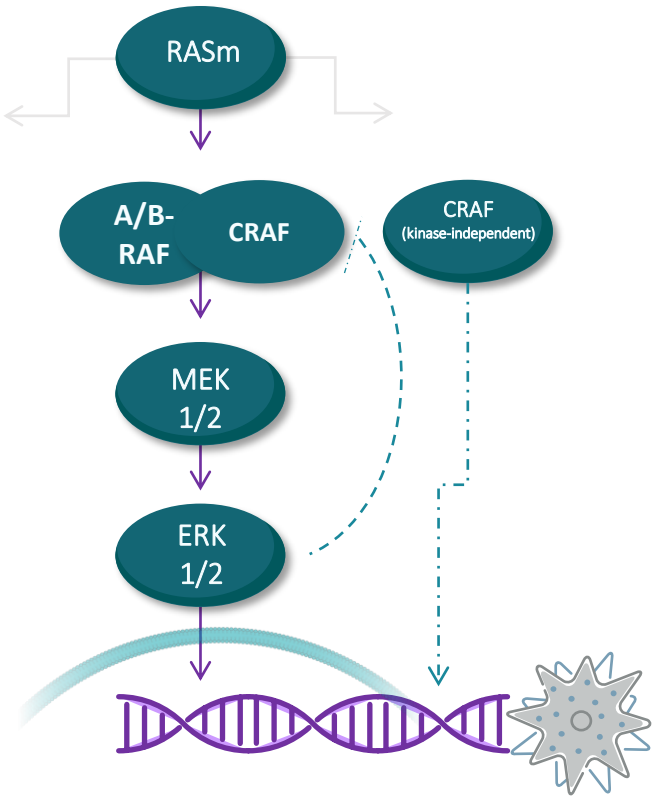
IK-595: A MEK/RAF Complex Inhibitor

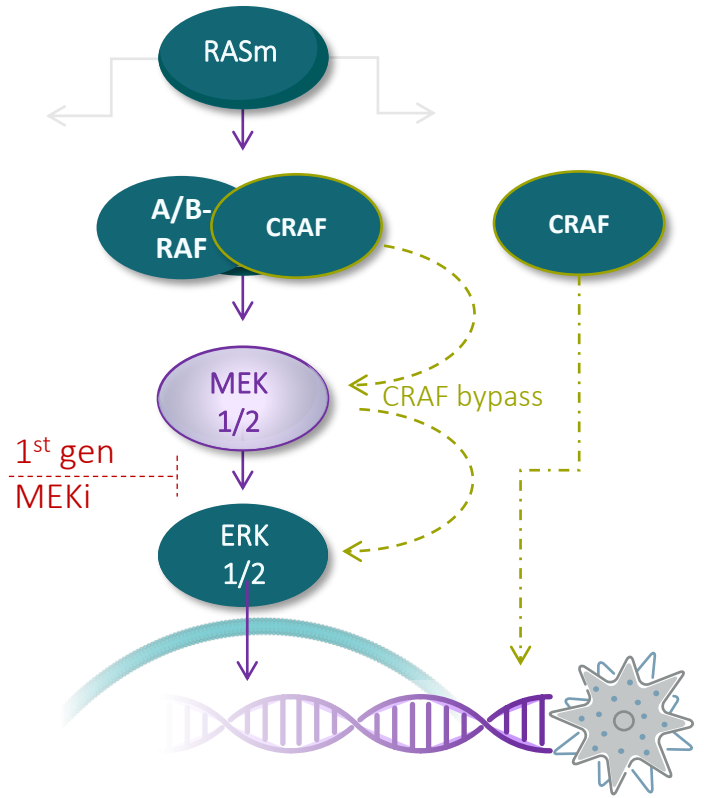
September 2023

First Generation MEK Inhibitors: Limited Activity in RAS Mutant Patients

MEK's role in driving ERK-mediated tumor growth



First gen MEK inhibitors trigger CRAF mediated pathway reactivation



Approved MEK inhibitors block MEK kinase activity

Feedback in the pathway triggers CRAF activation

Cancer's survival mechanism utilizes CRAF to reactivate the pathway and bypass inhibition

Additionally, approved inhibitors miss blocking kinase-independent CRAF function that can promote tumor growth

Leads to incomplete pathway inhibition

Lito *et al.* Cancer Cell 2014; Venkatanarayan *et al.* Cell Reports 2022; Sanclemente *et al.* Cancer Cell 2021; Nolan *et al.* Genes 2021.

Ikena Aims to Overcome the Limitations and Challenges of Current MEK Inhibitors

Challenges

Efficacy

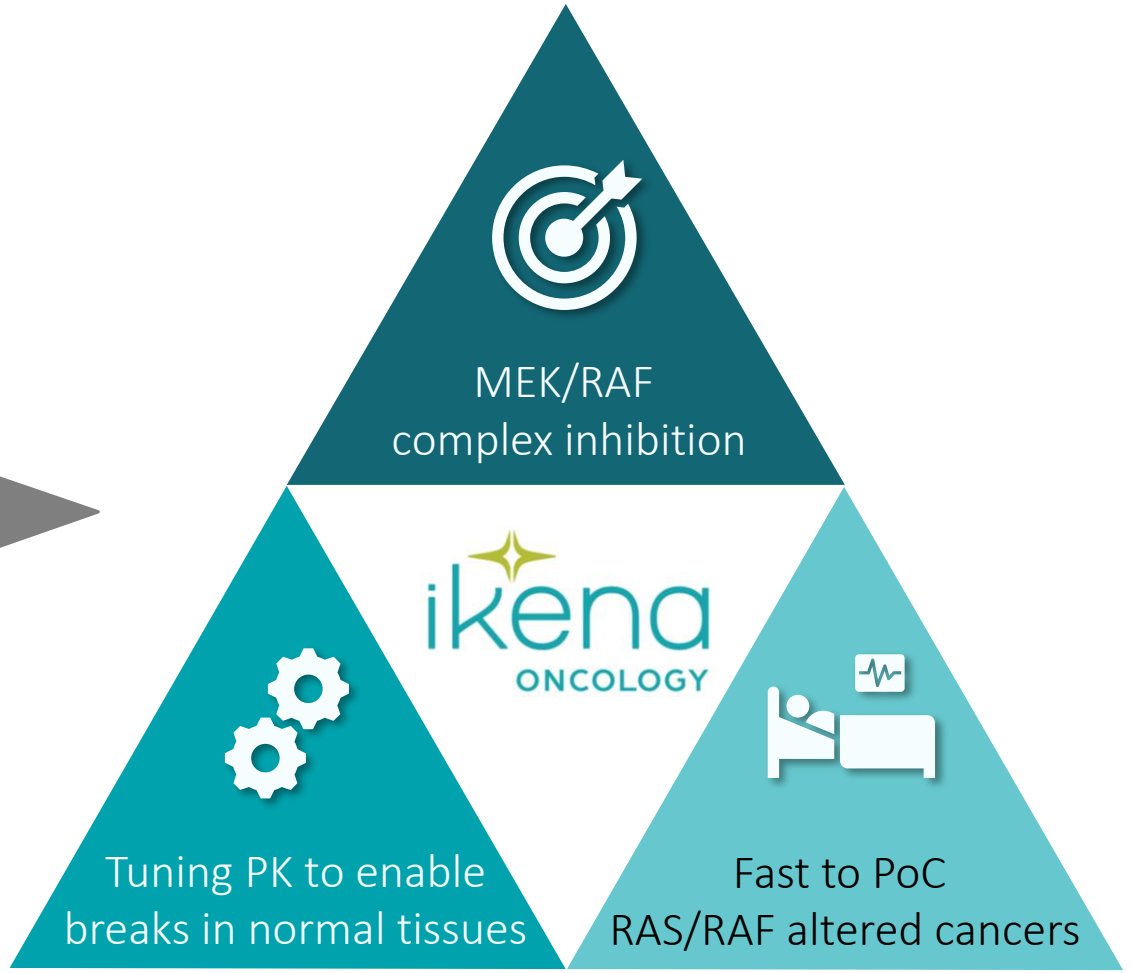
CRAF mediated pathway rebound

Tolerability

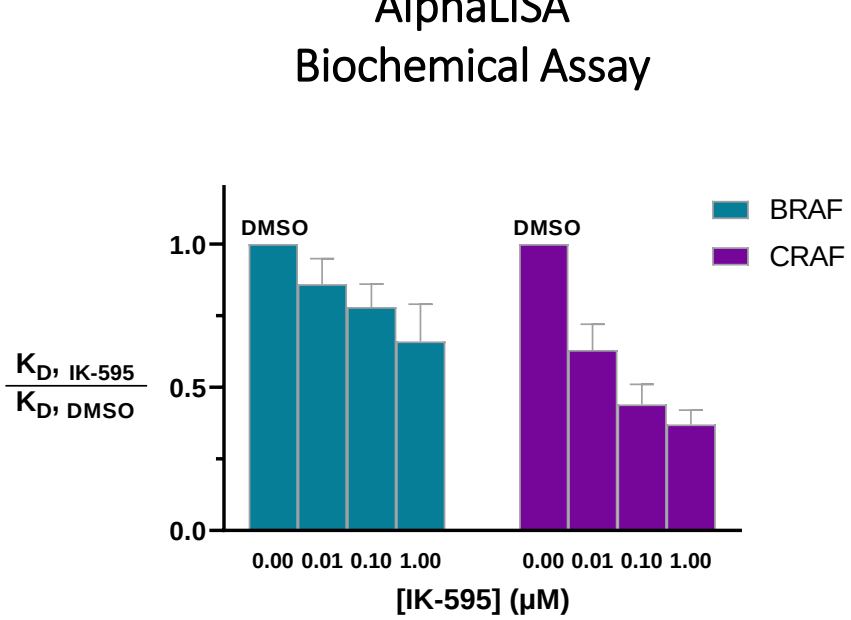
Narrow TI

Utility

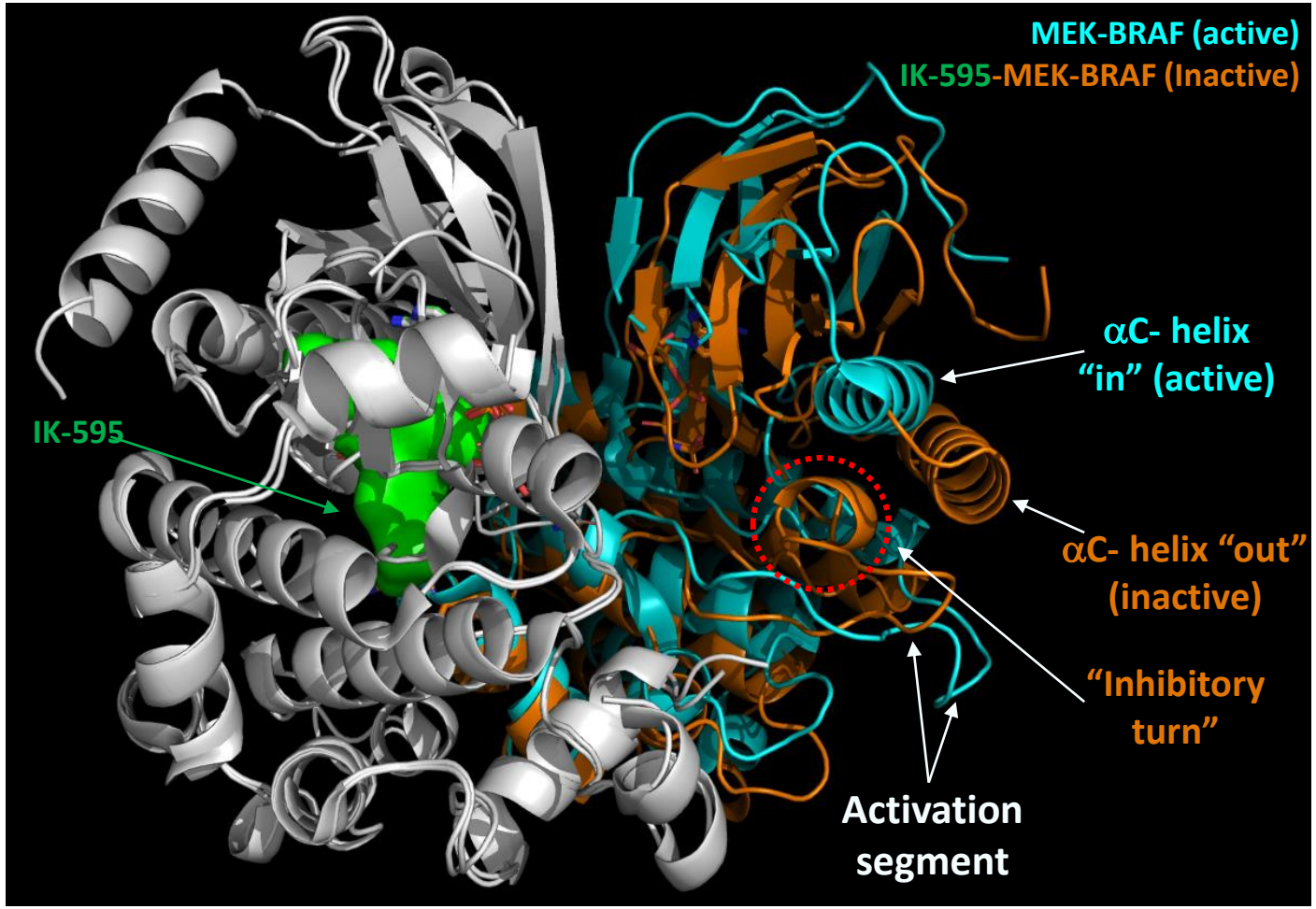
Limited clinical benefit



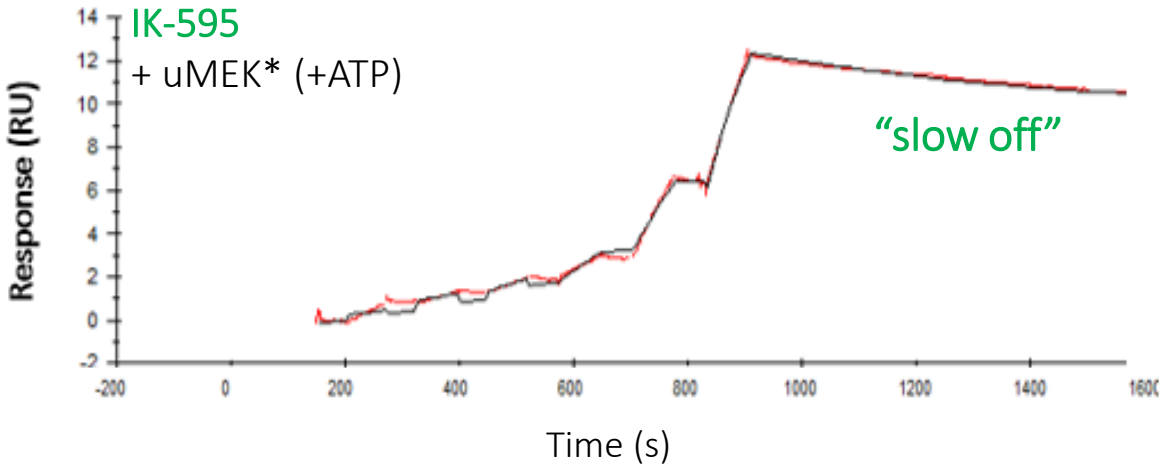
IK-595 Stabilizes MEK-RAF Complexes in an Inactive Conformation, Locking the αC-Helix in an Inactive Form



MEK-BRAF: $K_{D,\ DMSO}$ = 16.3 nM
MEK-CRAF: $K_{D,\ DMSO}$ = 5.9 nM



IK-595 Binds to MEK with Very Slow Off-Rate Kinetics

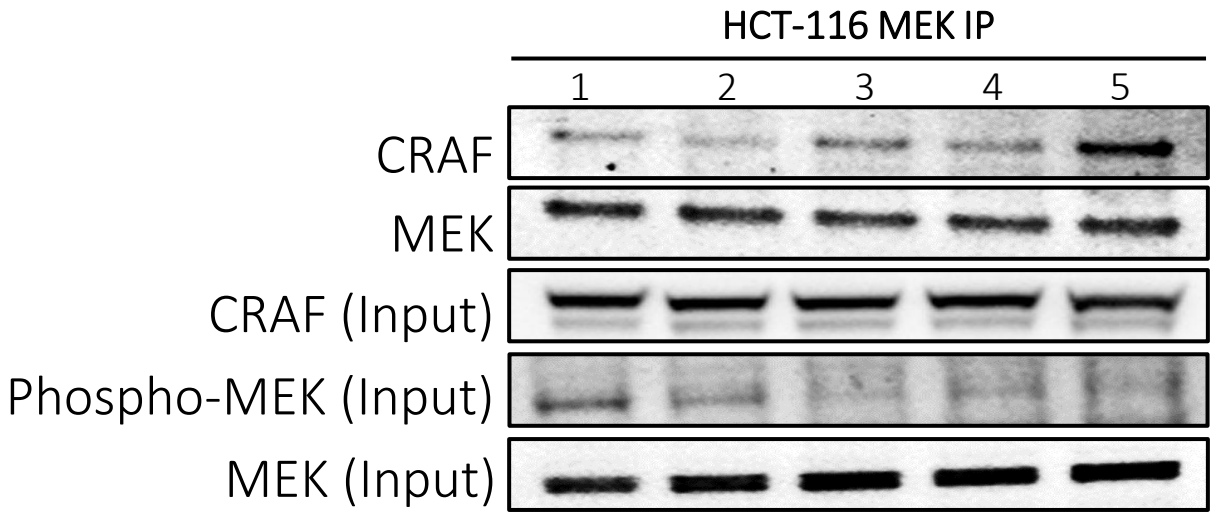


SPR Single Cycle Kinetics

MEK	$k_{on}(M^{-1}s^{-1})$	$k_{off}(s^{-1})$	K_D (nM)
IK-595 (to MEK)	8.24 E+04	6.09 E-04	7.39

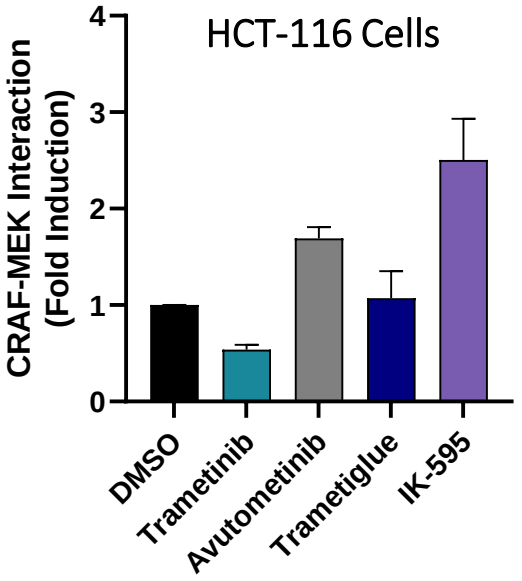
*uMEK: unphosphorylated MEK

IK-595 Stabilizes MEK-CRAF, MEK-BRAF and MEK-ARAF Complexes in Cells

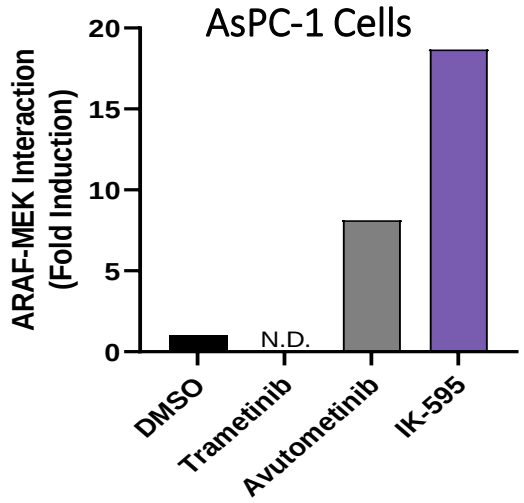


Compounds treated at IC90

1- DMSO
2- Trametinib
3- Avutometinib
4- Trametiglue
5- IK-595

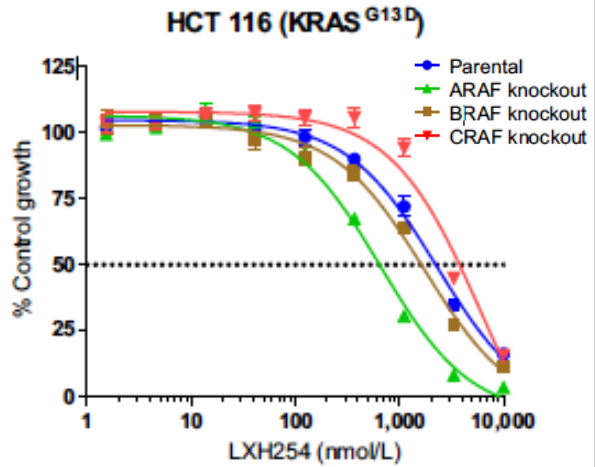


MassSpec data from HCT116 and AsPC1 pulldown demonstrates that IK-595 stabilizes MEK interactions with ARAF, BRAF and CRAF

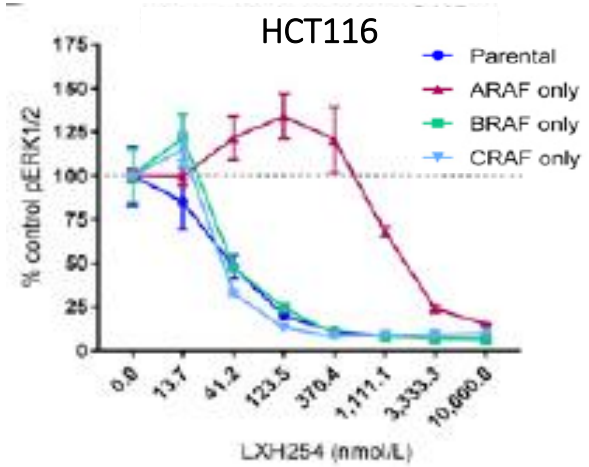


ARAF Plays a Critical Role in Resistance to Pan-RAF Inhibitors in KRASm Cancer Cells

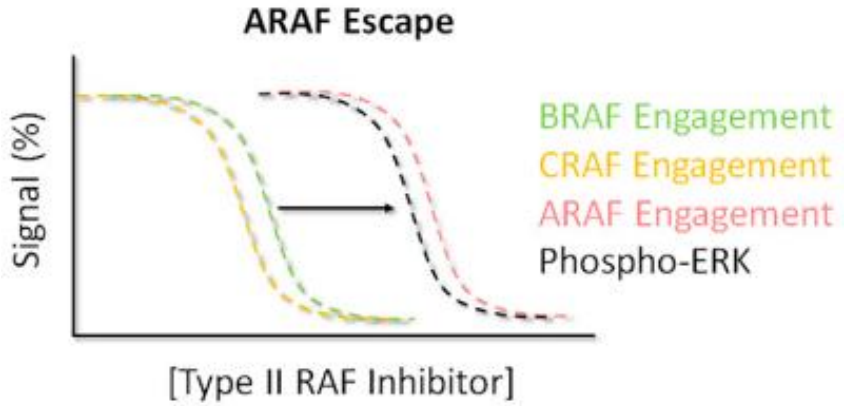
Loss of ARAF expression sensitizes KRASm cell lines to LXH254



KRASm cells expressing only ARAF are resistant to LXH254



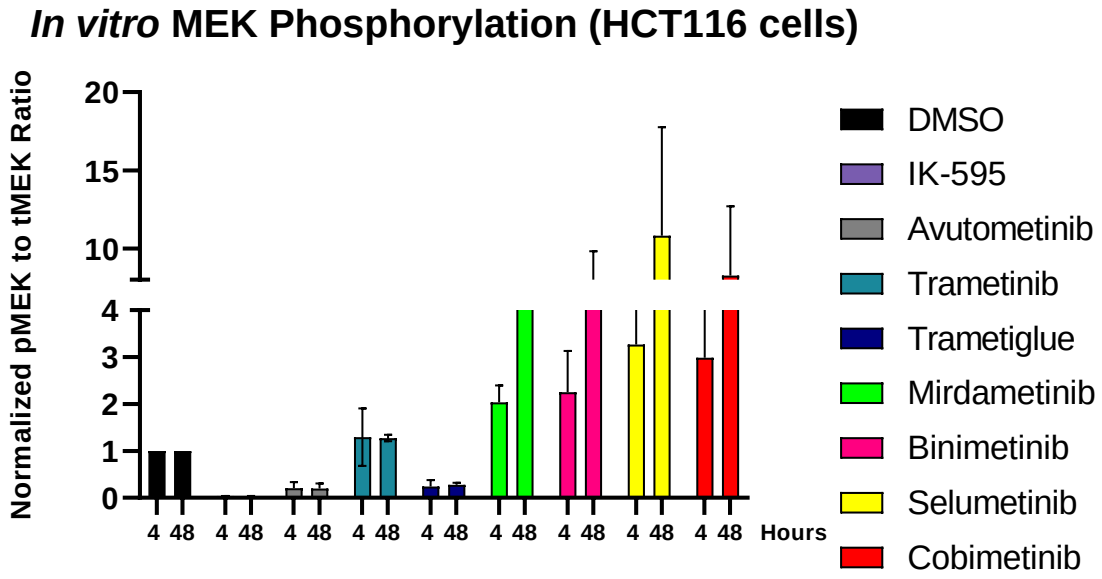
Clinical stage pan-RAF inhibitors escape ARAF inhibition in KRASm cells



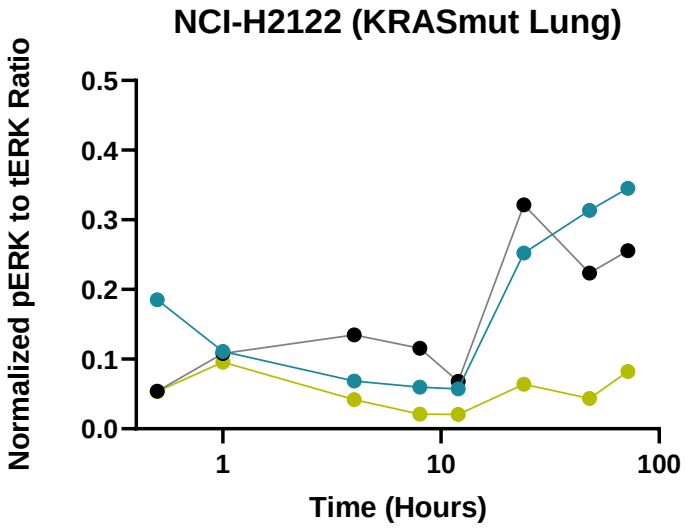
Potential MoA advantage of IK-595 over RAFi + MEKi

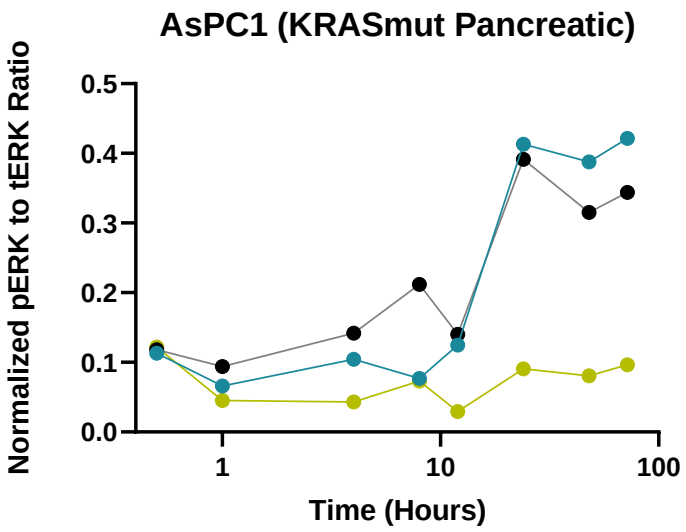
Monaco, K., et al., Clin Cancer Res (2021); Venkatanarayan, A., et al., Cell Reports (2022); Tkacik, E., et al., J Biol Chem (2023); Vasta, J., et al., Cell Chem Biol (2023)

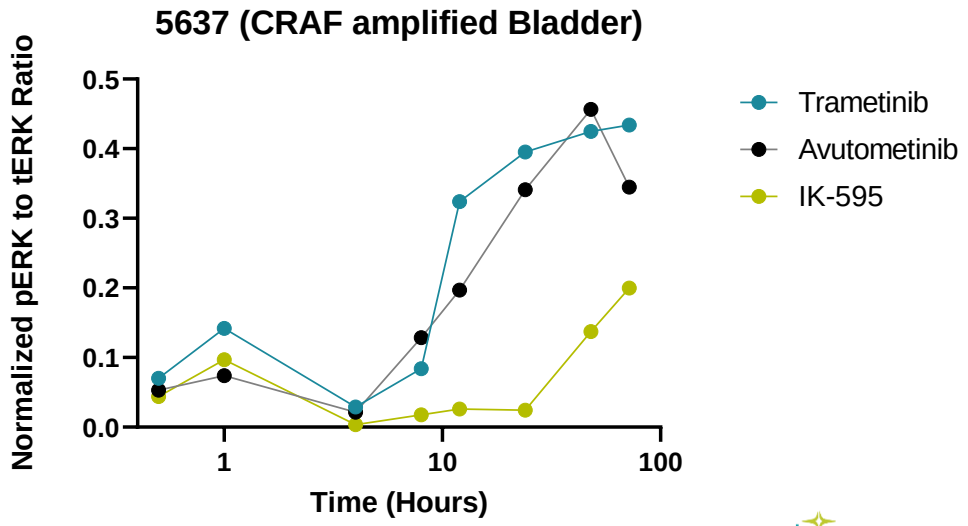
IK-595 Demonstrates Robust and Prolonged pMEK and pERK Inhibition



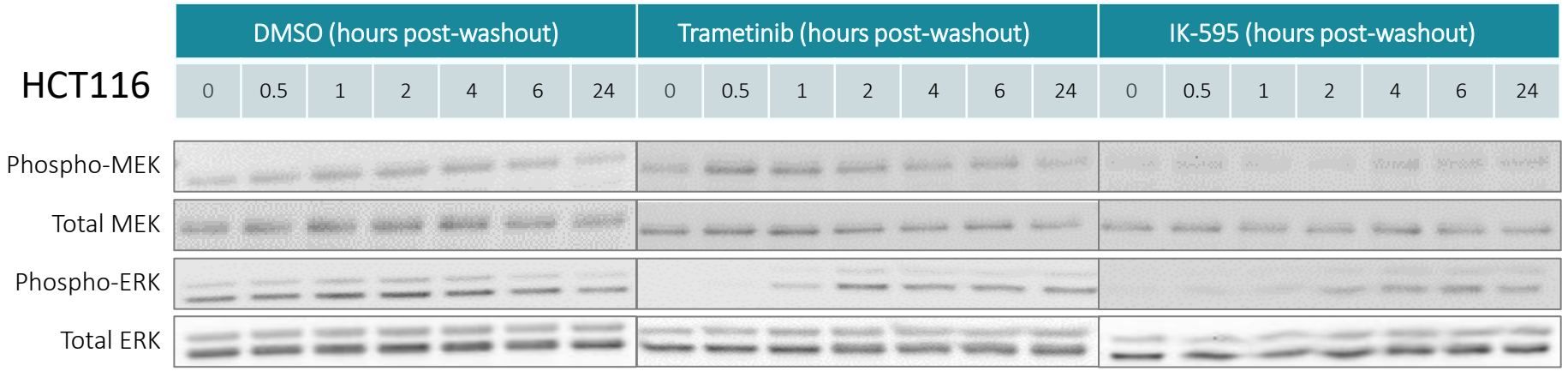
*Compounds were dosed at pERK IC_{90}

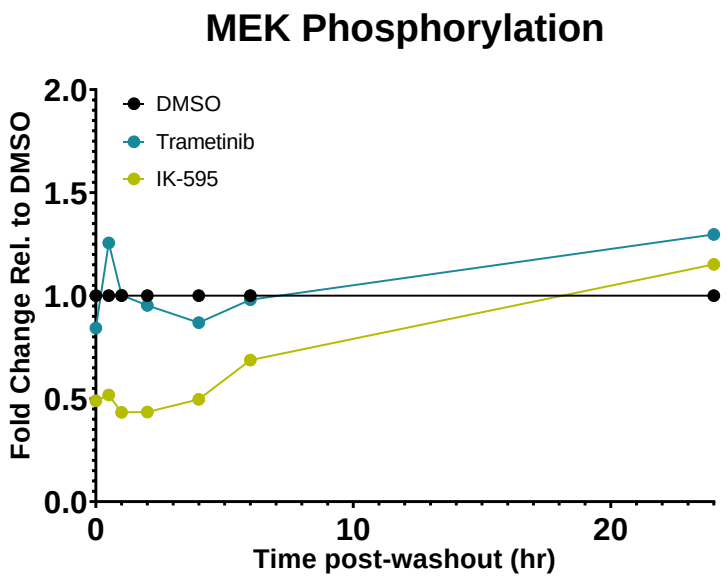


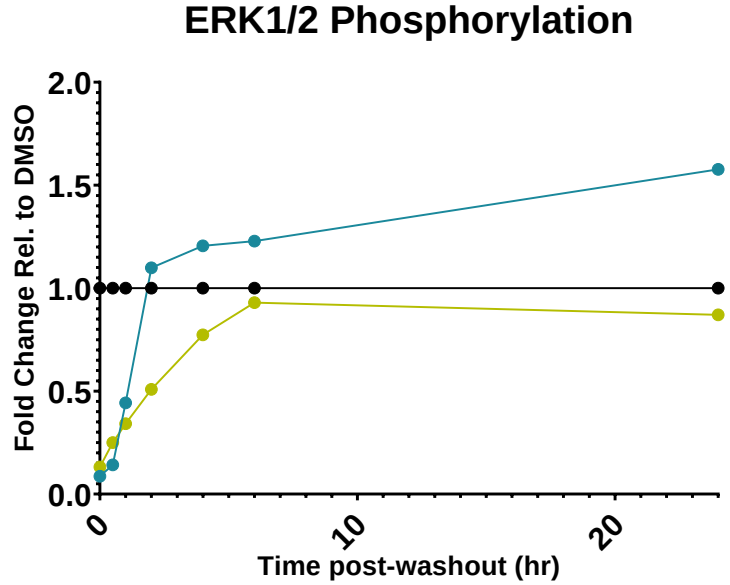




Inhibition of MEK/ERK Phosphorylation by IK-595 Persists Following Washout





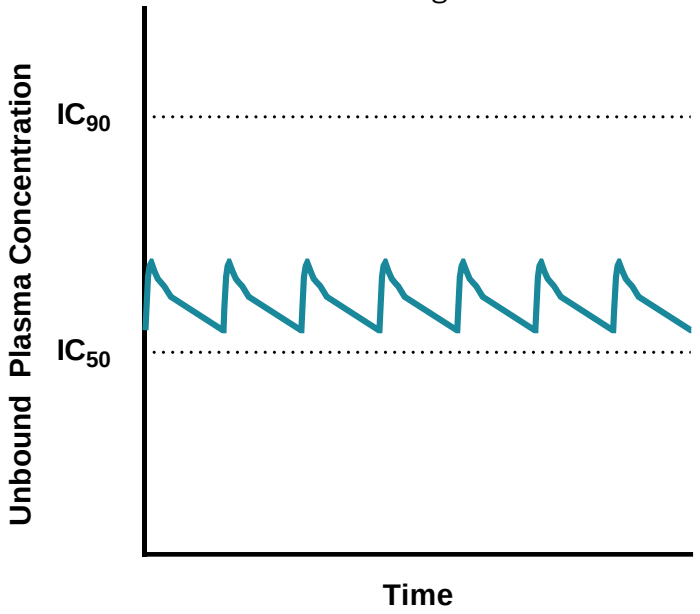


Compounds were dosed at pERK IC_{90} for 1hr before washout

IK-595 is Designed to Have a PK that Enables Dosing Schedules where Concentrations Above IC_{90} Are Projected to Be Achieved in Human

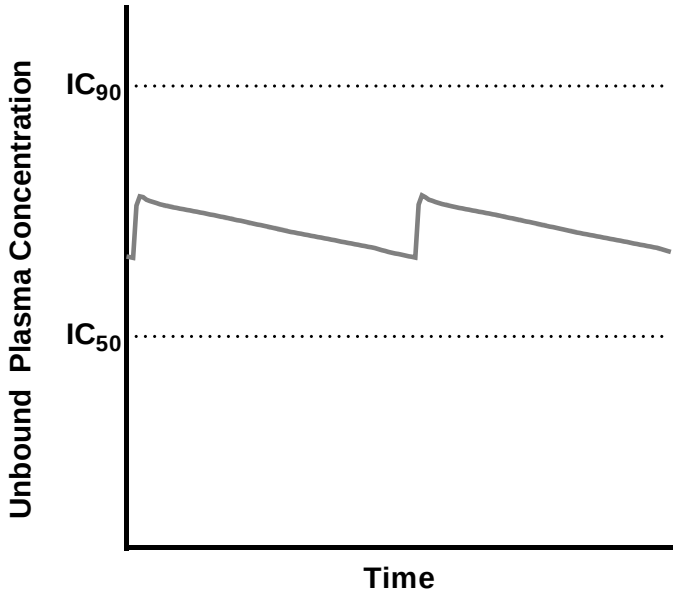
Trametinib[1]

Clinical PK
2 mg QD



Avutometinib[2]

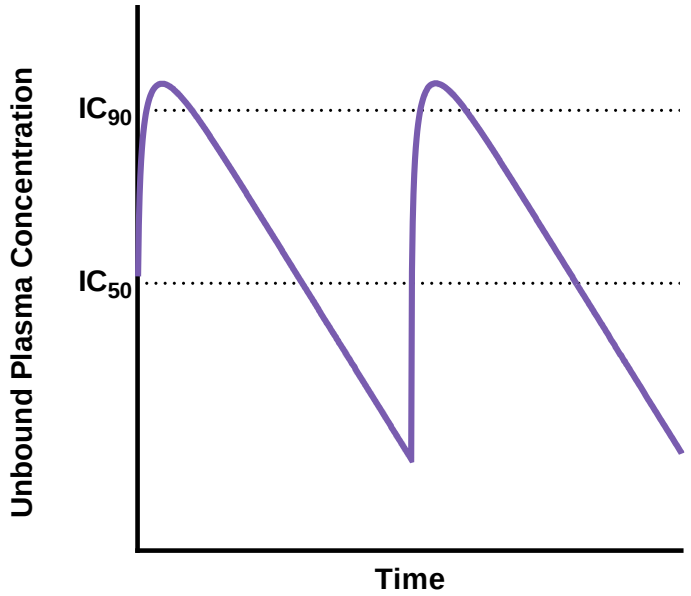
Clinical PK
3.2 mg twice/week



Clinical doses of trametinib and avutometinib do not reach plasma concentrations above IC_{90} due to the very long human $T_{1/2}$ of trametinib (72-120 hrs) and avutometinib (60-100 hrs)

IK-595

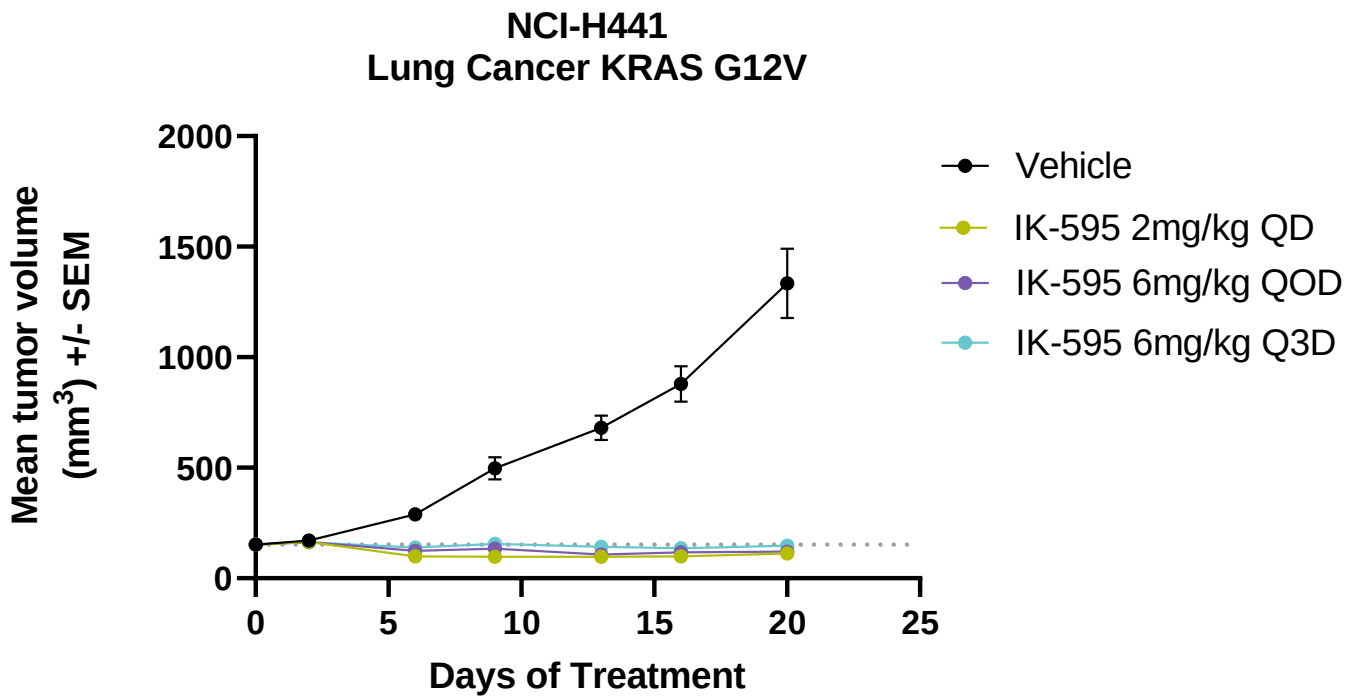
Human Predicted PK

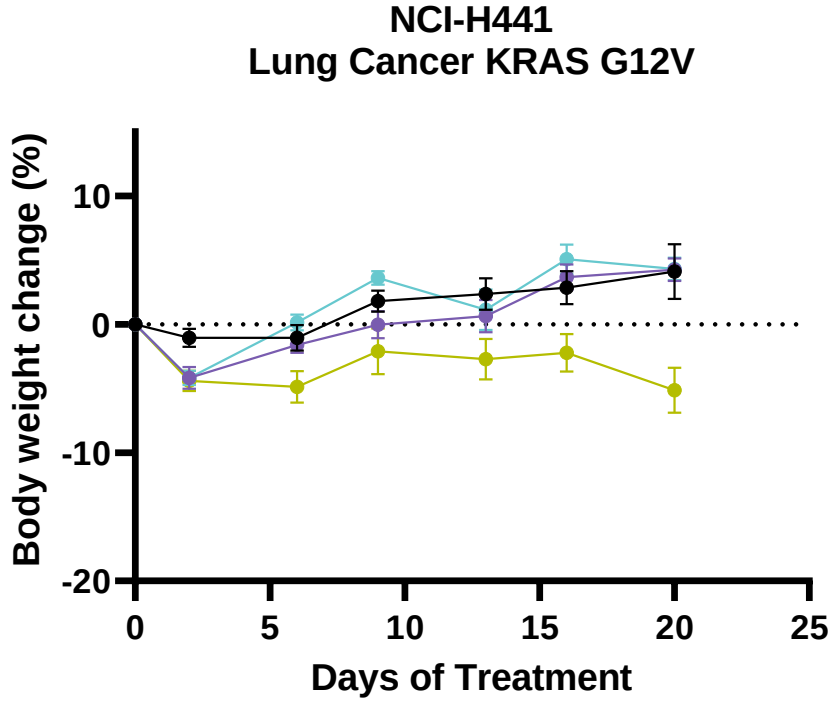


The predicted human PK of IK-595 allows flexibility in dosing schedules, and enables transient plasma concentrations above IC_{90} and allows for recovery before next dose

1. Infante et al. The Lancet Oncology 2012
2. Martinez-Garcia et al. Clin Cancer Res 2012

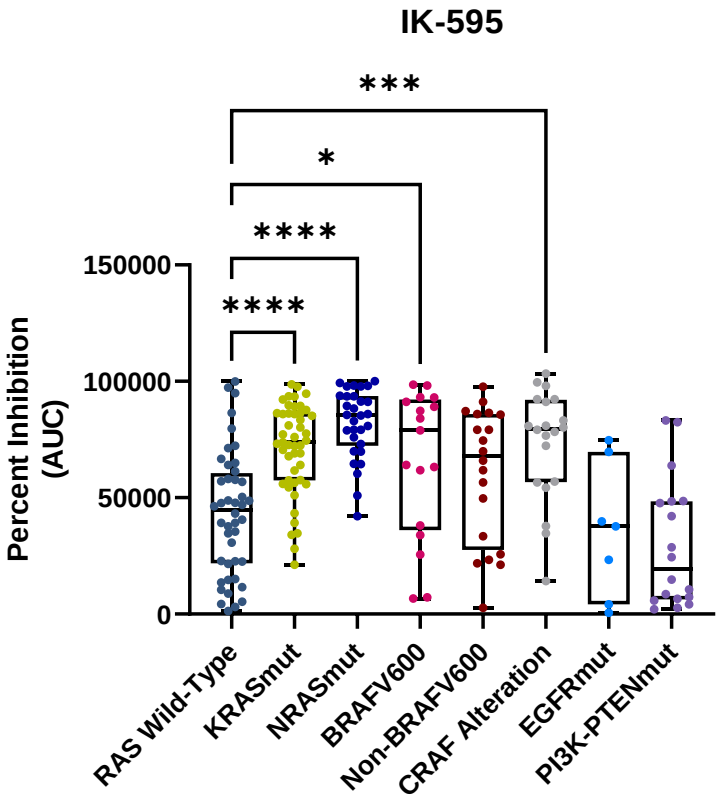
In Vivo Efficacy Demonstrated Following Intermittent Dosing of IK-595

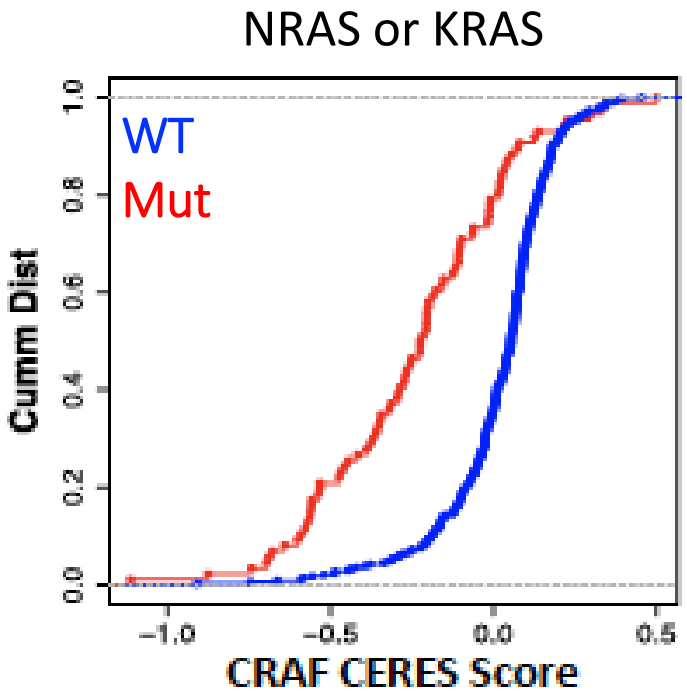




QD, QOD, and Q3D dosing show equivalent efficacy in multiple CDX models with better tolerability for intermittent schedules

NRAS/KRAS-Mutant and CRAF-altered Cell Lines Are More Sensitive to IK-595 than RAS^{WT} Cells



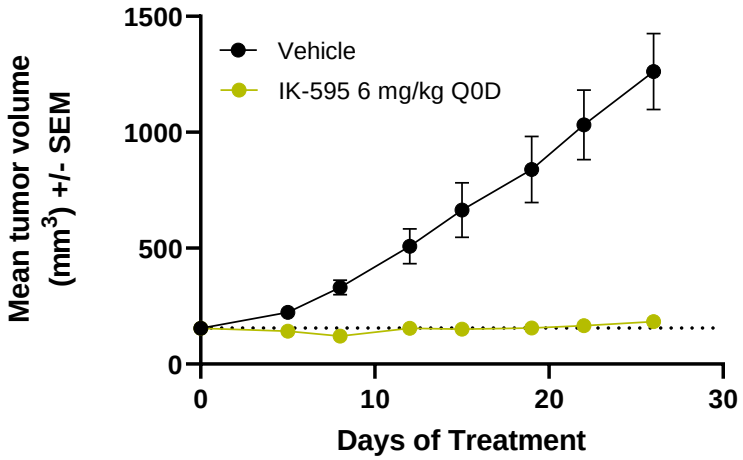


Jones, 4th RAS-Targeted Drug Development Summit 2022

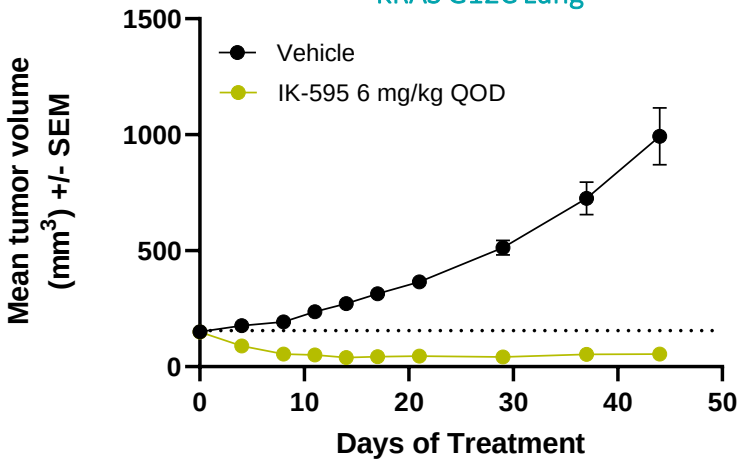
Correlates with the described CRAF dependency: RASmut > RASwt

Tumor Regressions Are Observed with IK-595 Across Multiple Genetically-driven Tumors

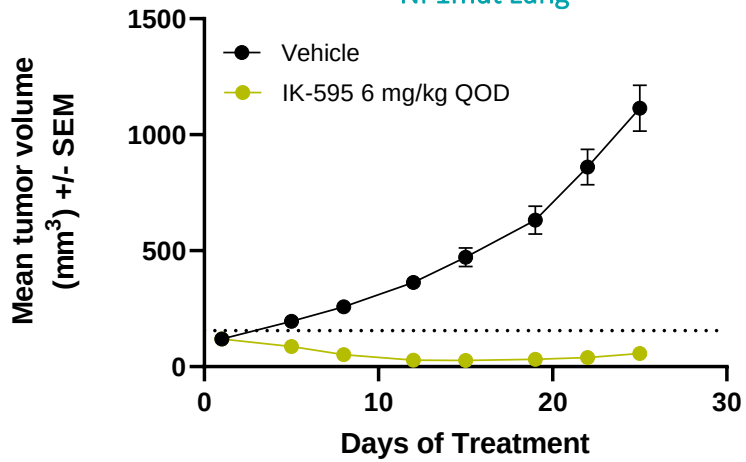
AsPC1
KRAS G12D Pancreatic



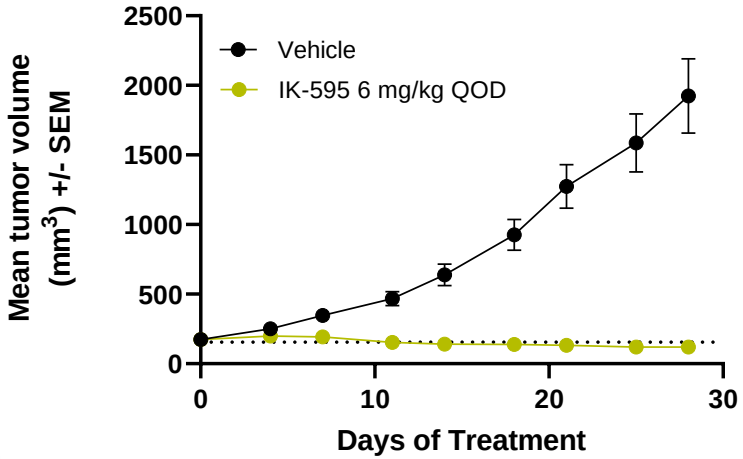
NCI-H358
KRAS G12C Lung



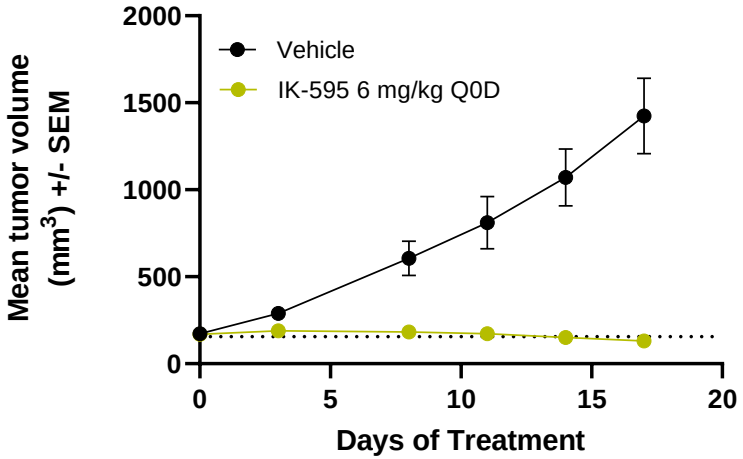
SKMES-1
NF1mut Lung



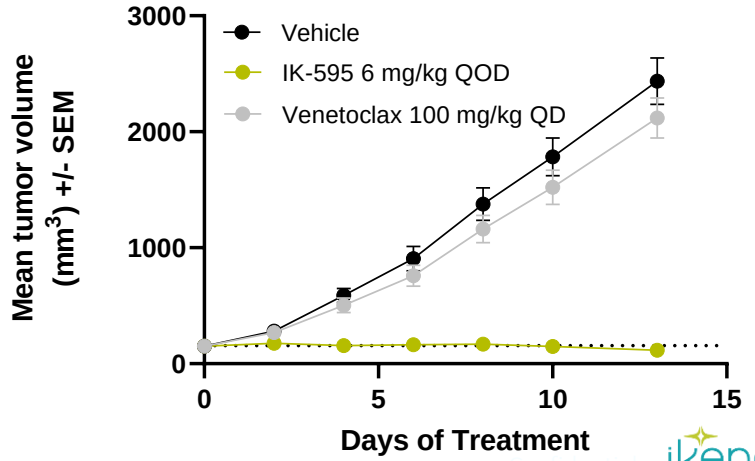
ME-21-0234-PDX
NRAS G12D Melanoma



Hs-936T
NRAS Q61L + BRAF Class III Melanoma



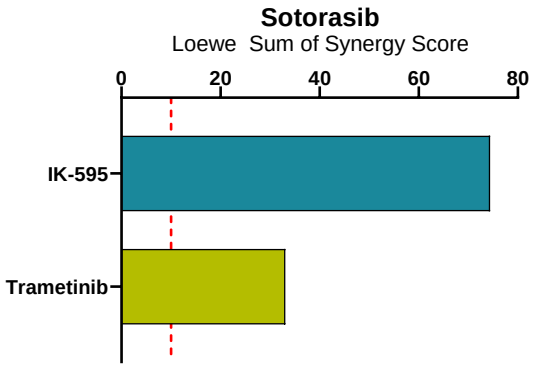
OCI-AML3
NRAS Q61L AML

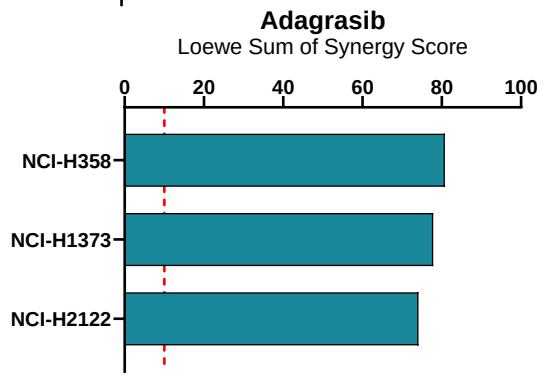


Synergy of IK-595 with Multiple Combination Agents Provides Expansion Opportunities Beyond Monotherapy

G12C Inhibitors (In-Pathway Combination)

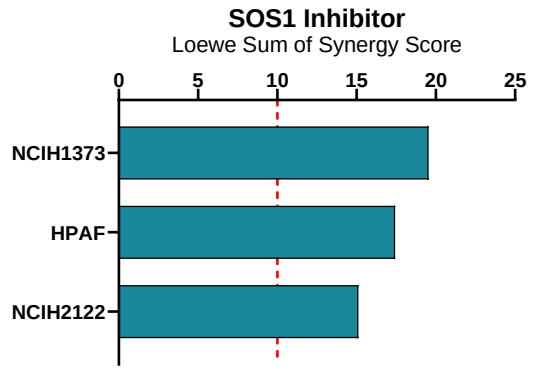
MEK reactivation is a known common resistance mechanism to G12C inhibitors

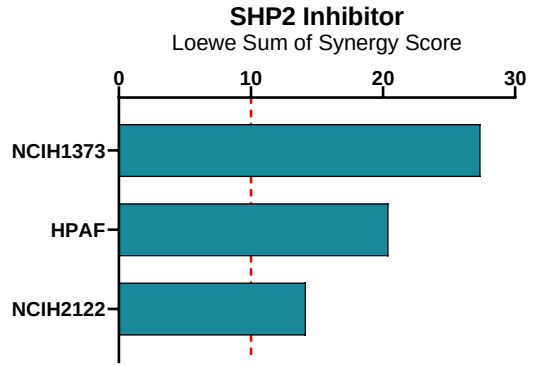




Other In-Pathway Combinations

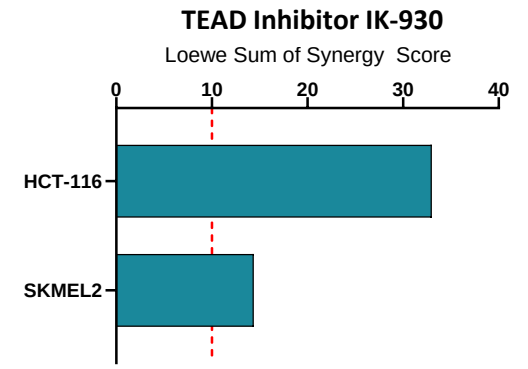
Simultaneous targeting of multiple RAS pathway nodes enhances pathway inhibition and response

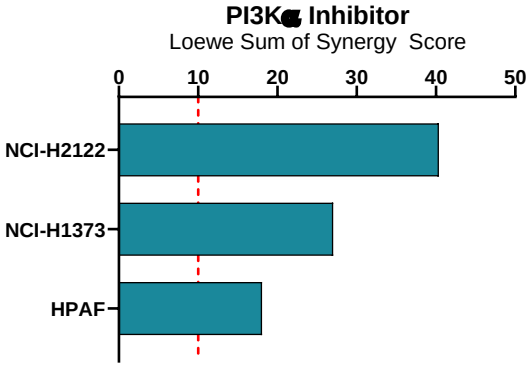




Alternate Signaling Nodes

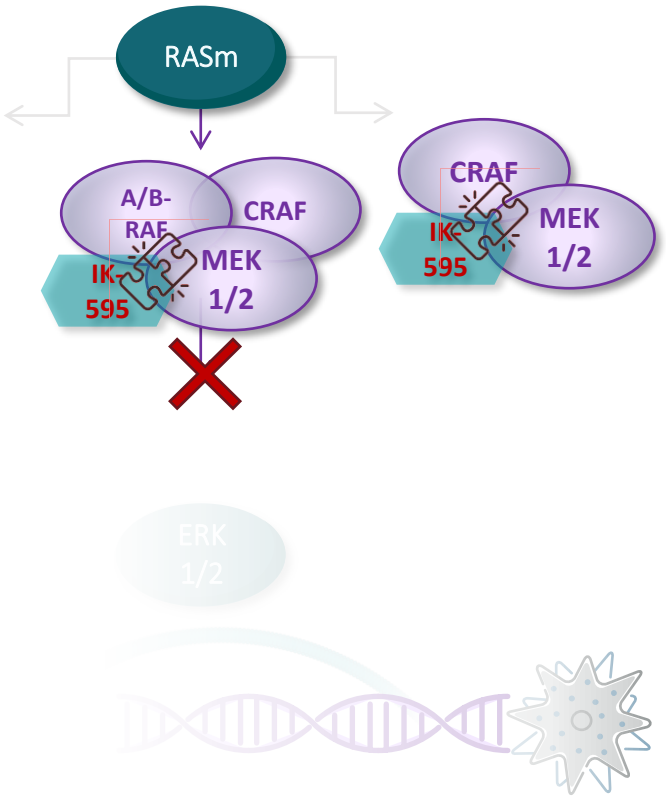
Co-targeting MEK and alternate signaling nodes potentiates induction of cell death and anti-tumor response





IK-595: A Potentially Best-in-Class Dual MEK-RAF Complex Inhibitor

IK-595 traps MEK & RAF in an inactive complex to prevent CRAF bypass and kinase-independent CRAF function

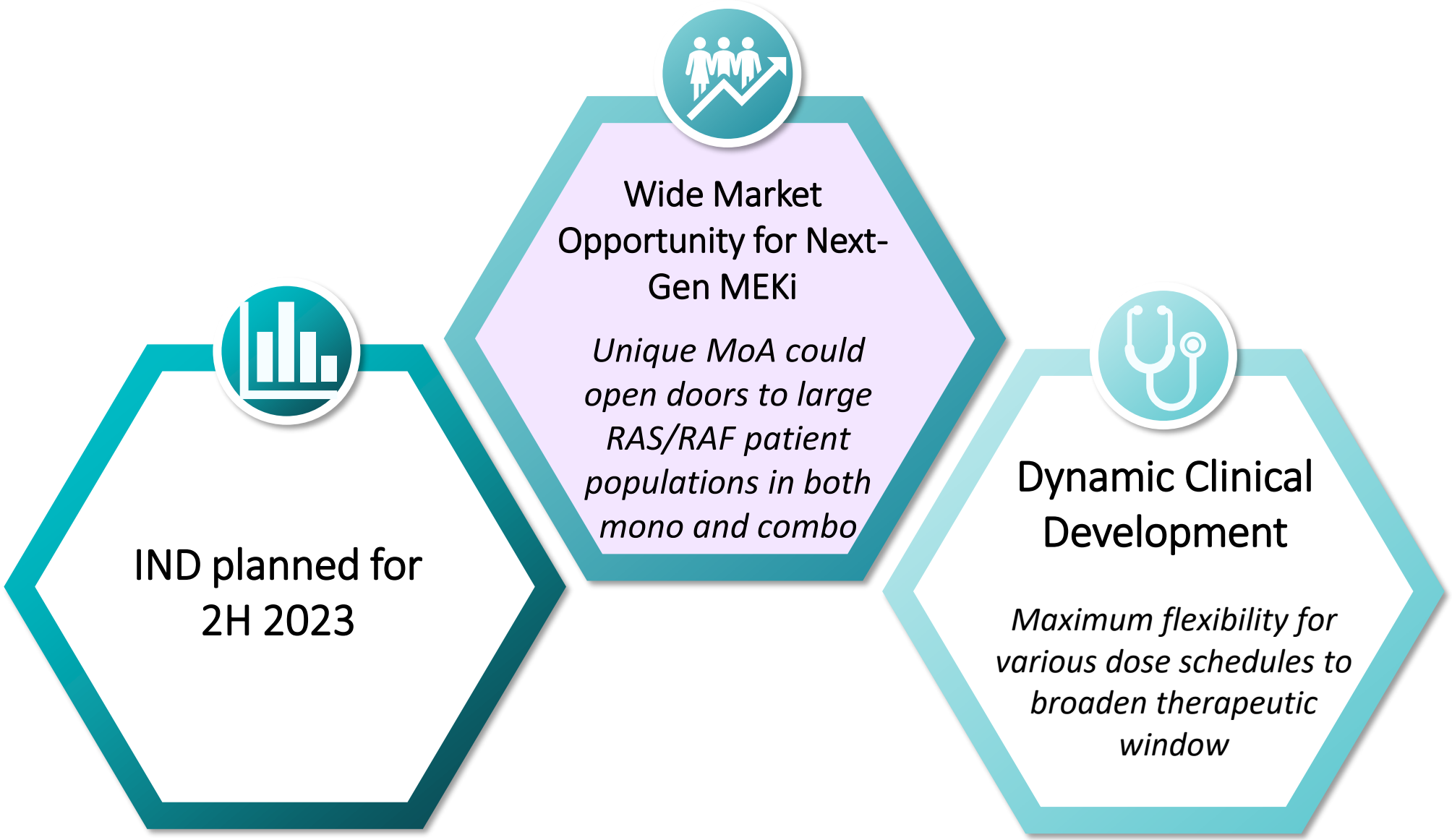


Summary

IK-595 is designed to and has shown preclinical evidence of superior profile compared with first generation and in-development MEK inhibitors

- ✓ Inhibits MEK mediated ERK1/2 phosphorylation
- ✓ Prevents MEK phosphorylation by RAF
- ✓ Alleviates therapeutic resistance through CRAF mediated bypass and pathway reactivation
- ✓ PK profile enables targeting IC_{90} plasma concentrations and allowing recovery effectively widening the therapeutic window
- ✓ Brain penetrant with demonstrated brain tumor PD
- ✓ Combines synergistically with therapies targeting RAS or other compensatory pathways

IK-595 Has Unique Opportunity to Access Patients Across the RAS/RAF Landscape



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Ao Yang

Clinical

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Thank you