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TARGETING RAS
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AACR American Association for Cancer Research®

IK-595, a MEK-RAF complex inhibitor, obviates CRAF mediated resistance resulting in superior RAS/MAPK pathway inhibition and anti-tumor activity in RAS/RAF altered cancers

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I am a full-time employee and member of the executive team at Ikena Oncology.

First Generation MEK Inhibitors: Limited Activity in RAS Mutant Patients

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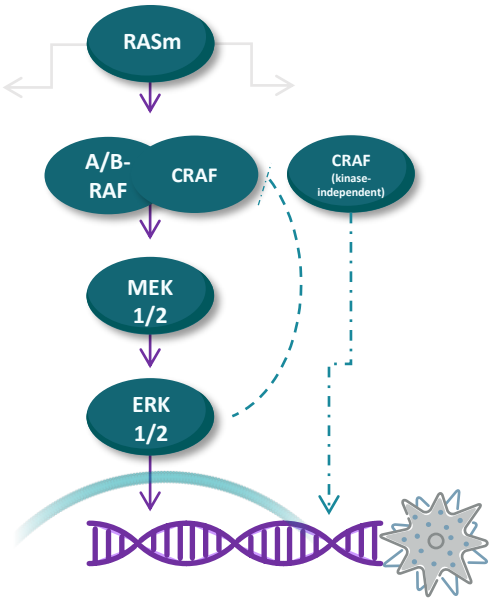
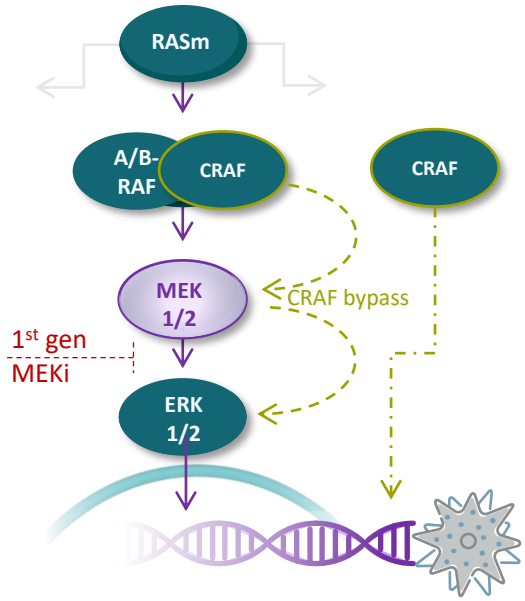
MEK's role in driving ERK-mediated tumor growth



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 Currently Available MEK Inhibitors

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Challenges

Efficacy

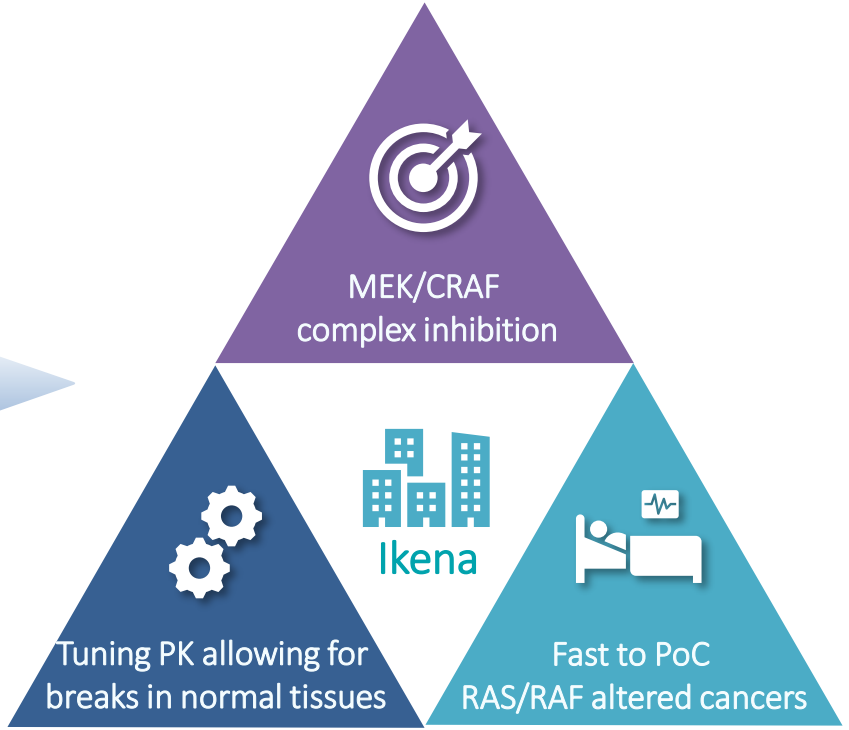
CRAF mediated pathway rebound

Tolerability

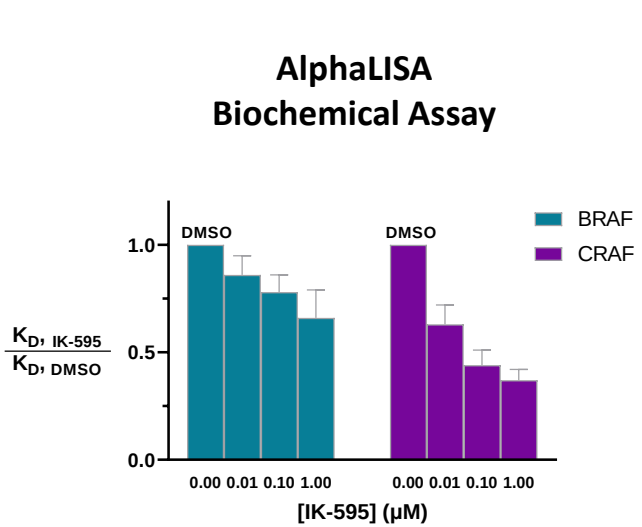
Narrow TI

Patient

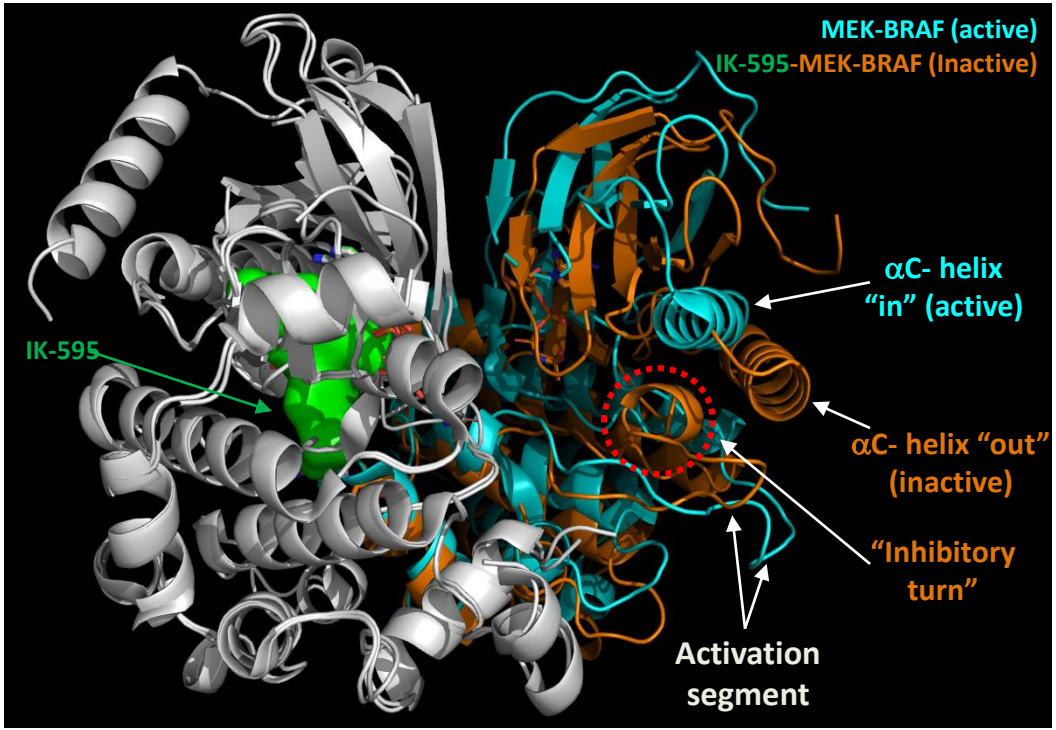
Limited clinical benefit



IK-595 Stabilizes MEK-RAF Complex in an Inactive Conformation



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



IK-595 stabilizes MEK-CRAF, MEK-BRAF and MEK-ARAF complexes in cells

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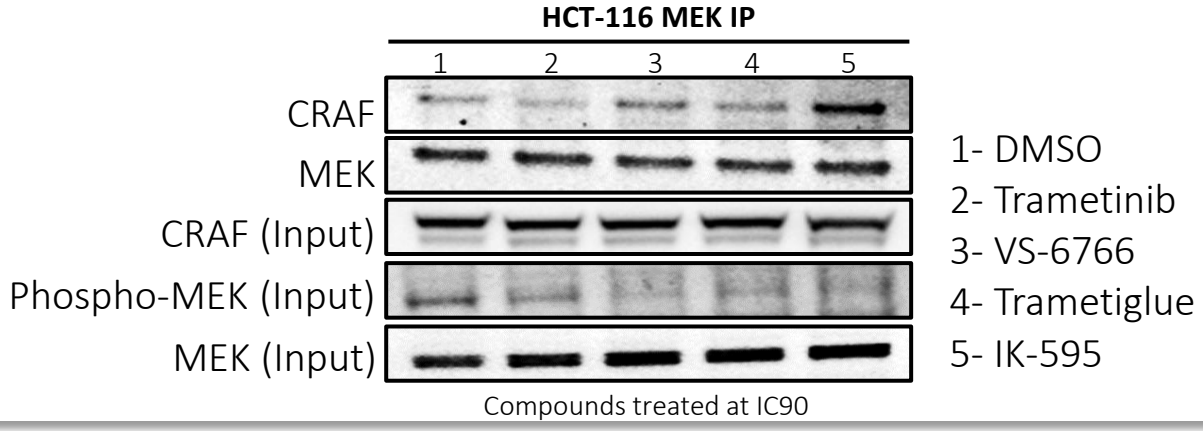
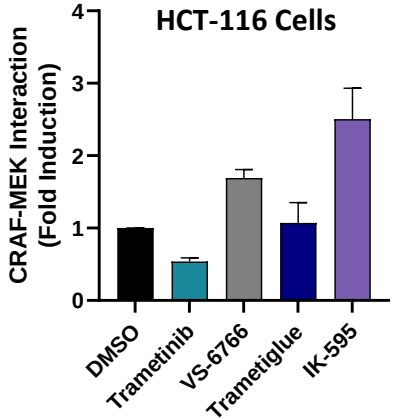
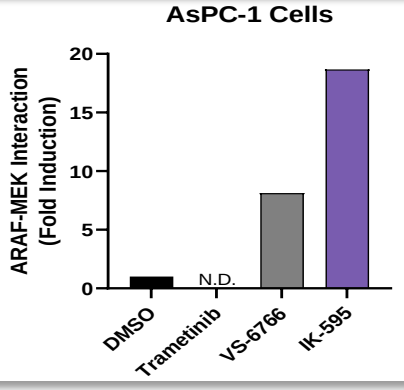




MassSpec data from HCT116 and AsPC1 pulldown demonstrates that IK-595 stabilizes MEK interactions with ARAF, BRAF and CRAF



IK-595 Potently Blocks MEK Phosphorylation *In Vitro*

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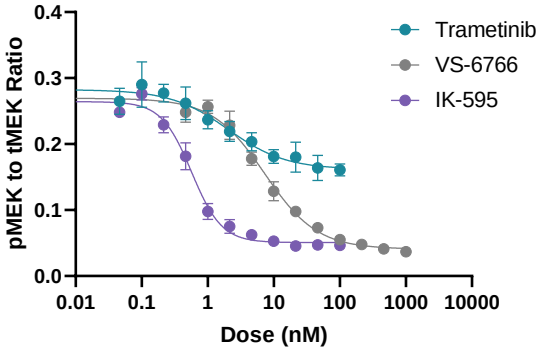
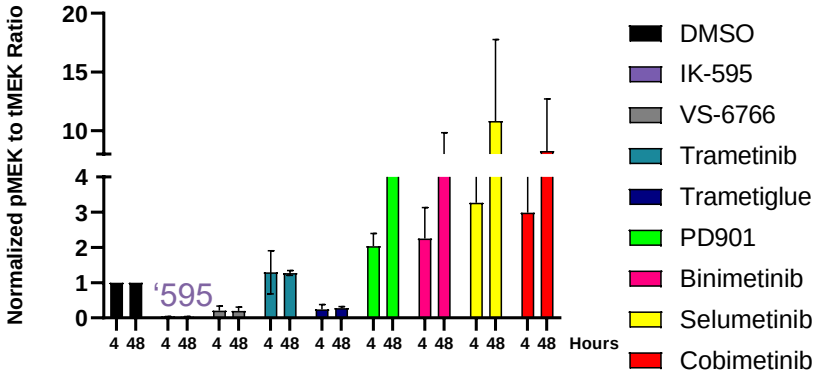
***In vitro* MEK Phosphorylation (AsPC-1 cells)**



Compound	IC_{50} (nM)
Trametinib	> 100
VS-6766	7
IK-595	0.6

***In vitro* MEK Phosphorylation (HCT116 cells)**



*Compounds were dosed at IC_{90}

Classic 1st gen MEK inhibitors induce strong MEK phosphorylation and activation

Trametinib has minimal or no effect on MEK phosphorylation

IK-595 Demonstrates Robust and Prolonged pERK Inhibition

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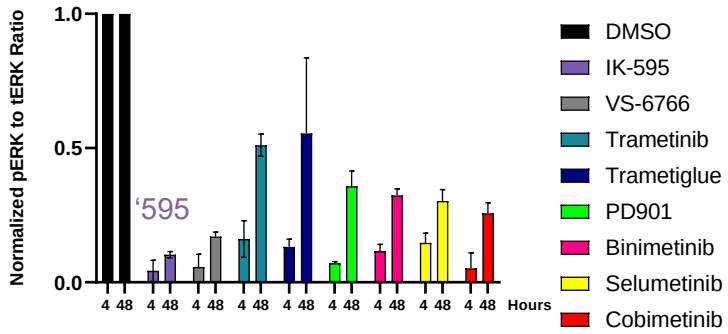
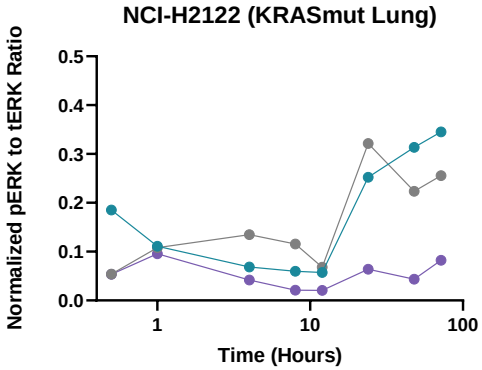
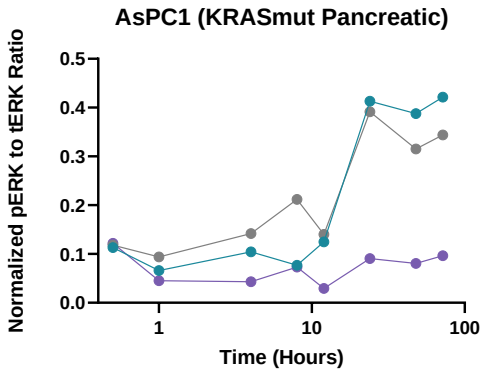
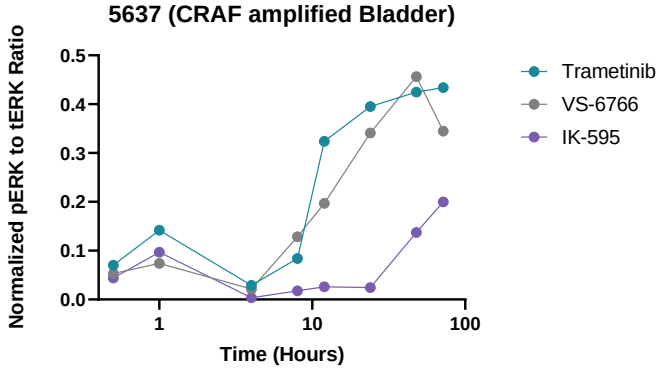
***In vitro* ERK1/2 Phosphorylation (HCT116 cells)**



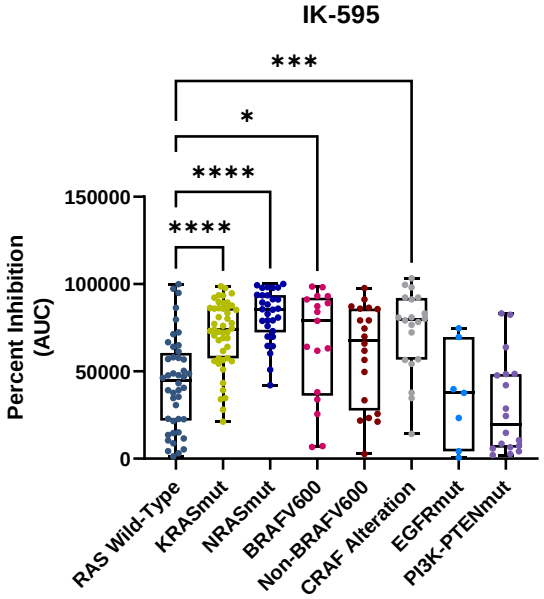
*Compounds were dosed at pERK IC_{90}

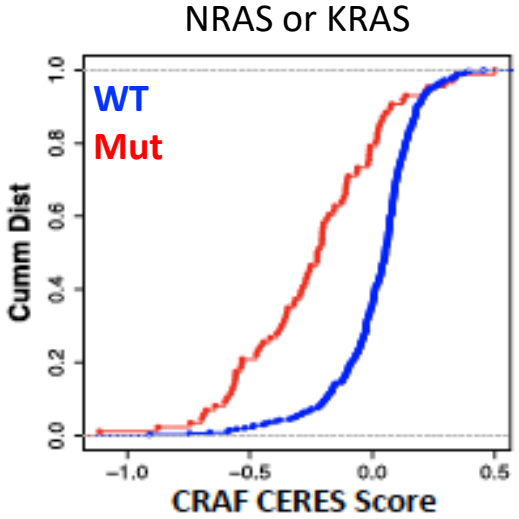






NRAS/KRAS Mutant and CRAF Altered Cell Lines are More Sensitive to IK-595 than RAS WT Cells





Jones, 4th RAS-Targeted Drug Development Summit 2022

Correlates with the described CRAF dependency: RASmut > RASwt

IK-595 Demonstrates Robust Anti-tumor Efficacy Across Multiple RAS/RAF Altered CDX Models

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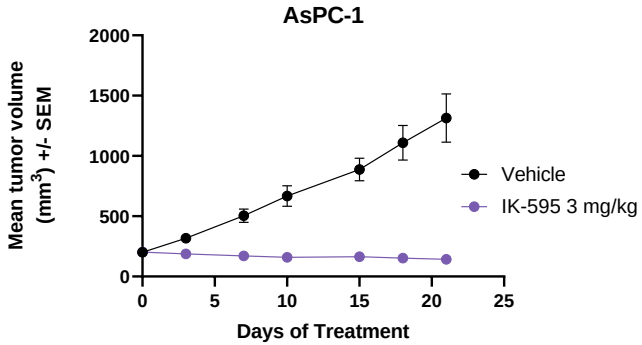
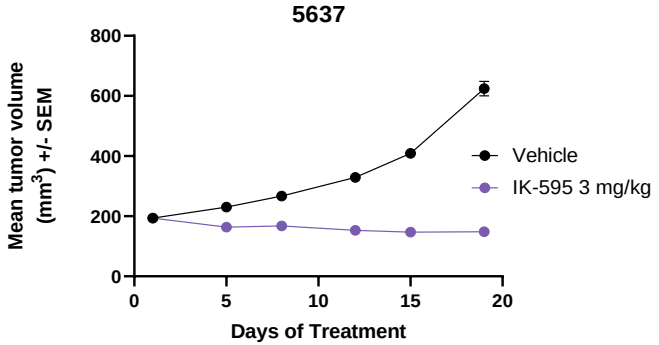
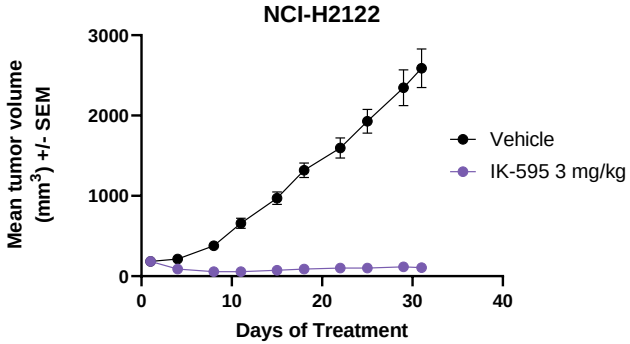
KRAS G12D pancreatic



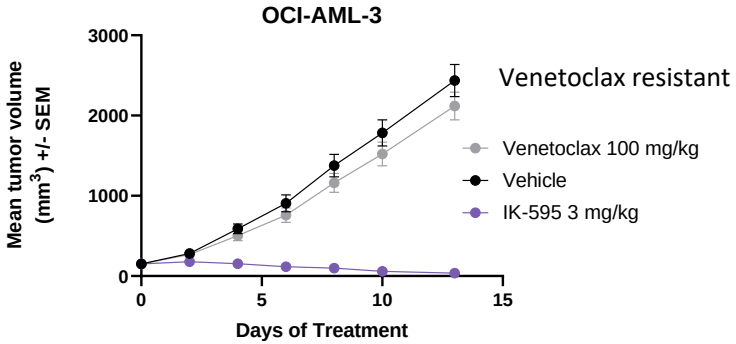
CRAF amp bladder



KRAS G12C lung



NRAS Q61L AML



IK-595 Designed to have a $T_{1/2}$ that Enables Dosing Schedules where Concentrations Above IC_{90} are Projected to be Achieved in Human

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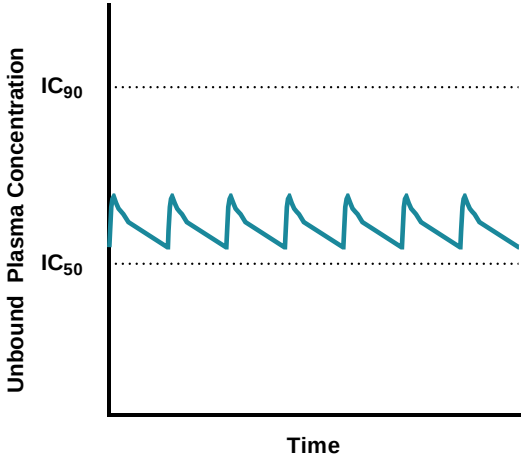
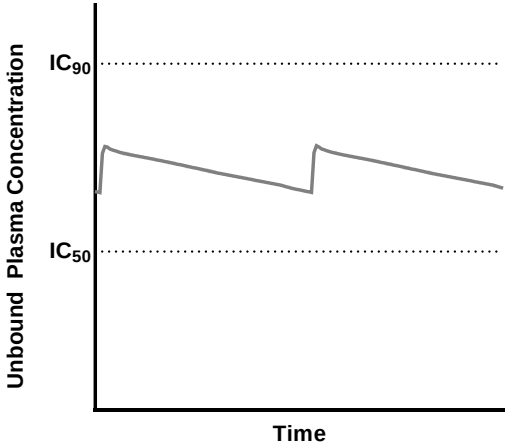
Trametinib[1]

Clinical PK - 2 mg QD



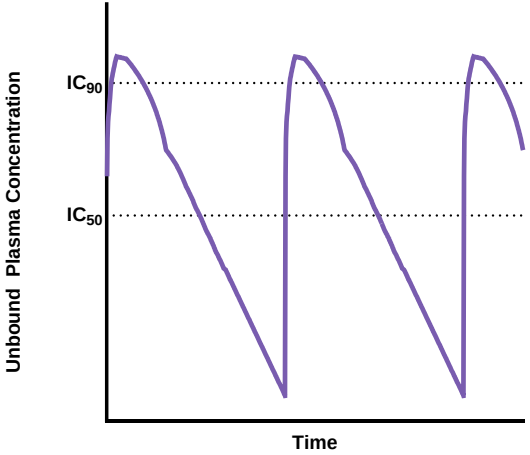
VS-6766[2]

Clinical PK
3.2 mg twice/week



IK-595

Human Predicted PK



Clinical doses of trametinib and VS-6766 do not reach plasma concentrations above IC_{90} due to the very long human $T_{1/2}$ of trametinib (72-120 hrs) and VS-6766 (60-100 hrs)

The predicted much shorter human $T_{1/2}$ 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

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

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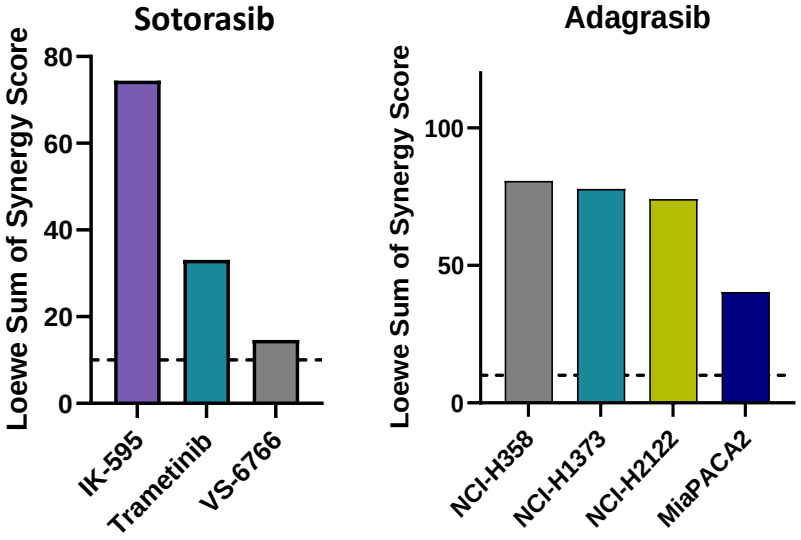
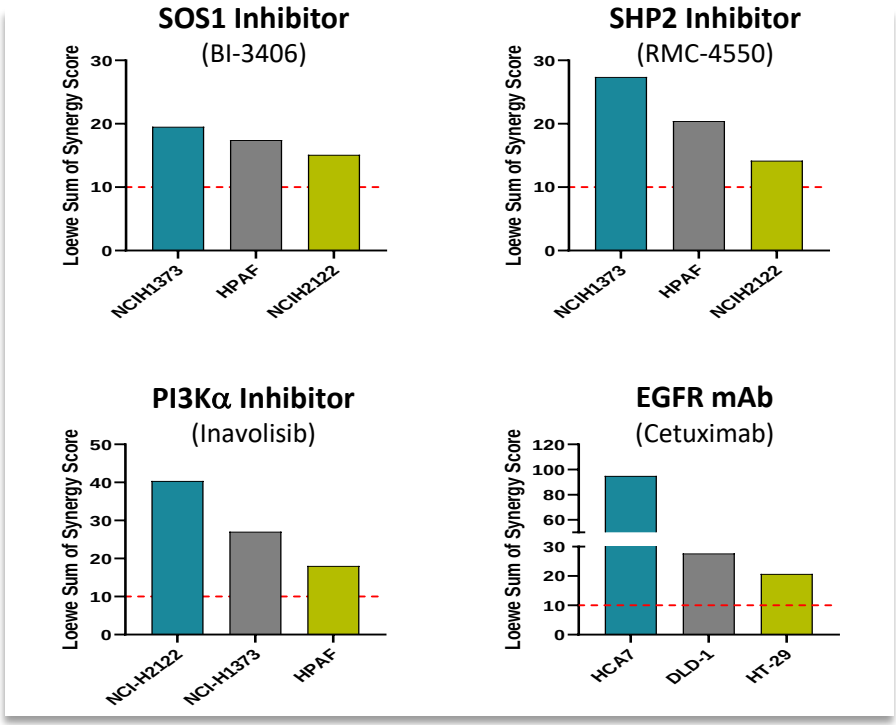


Superior Synergy with G12Ci



Strong Synergy across Multiple Key Mechanisms

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

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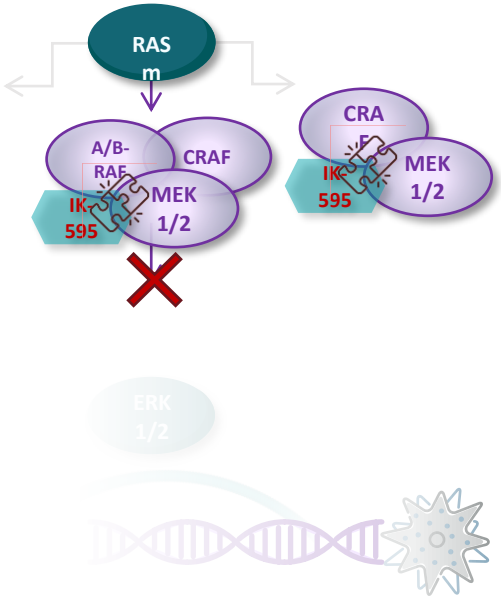
IK-595 traps MEK & RAF in an inactive complex to prevent CRAF bypass and kinase-independent CRAF function



Summary

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

- ✓ Inhibit MEK mediated ERK1/2 phosphorylation
- ✓ Prevent MEK phosphorylation by RAF
- ✓ Alleviate therapeutic resistance through CRAF mediated bypass and pathway reactivation
- ✓ Optimized PK profile to target IC_{90} plasma concentrations widening the therapeutic window
- ✓ Combine synergistically with therapies targeting RAS or other compensatory pathways
- ✓ IND submission targeted in 2H 2023
- ✓ FiH study planned to target selected subsets of CRAF dependent, NRASm and KRASm tumors with significant unmet medical need for monotherapy and combination opportunities

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