IK-595, a best-in-class MEK-RAF molecular glue, drives broad and potent anti-tumor activity across RAS/MAPK pathway-altered cancers as a monotherapy and in combination

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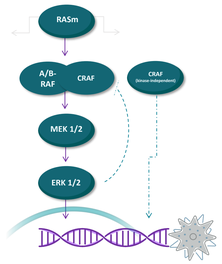
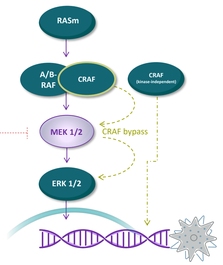
Background

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
- ERK-dependent negative feedback triggers CRAF-mediated pathway reactivation
- CRAF has kinase-independent anti-apoptotic activities that will be missed by 1st gen MEK inhibitors
- **CRAF plays a critical role in the therapeutic resistance of approved MEK inhibitors in RAS mutant cancer patients**

Large Unmet Medical Need Drives Development of Next-Gen MEK-RAF Inhibitors

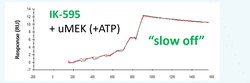
With broad activity in cancers with KRAS, NRAS, RAF, and NF1 mutations and RAF fusions

With optimized PK profile allowing for improved therapeutic index and intra- and inter-pathway combination opportunities

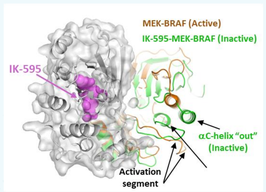
An Effective Next-Gen MEK-RAF Inhibitor Could be Broadly Impactful in the RAS/RAF-Altered Patient Population

Results

IK-595, a Potential Best-In-Class Next-Gen Inhibitor, Stabilizes MEK-RAF Complex in an Inactive Conformation



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



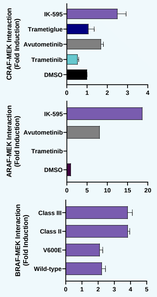


Figure 1. A) IK-595 has a slow off-rate to unphosphorylated MEK1 as measured by SPR. B) Crystal structure of IK-595 in complex with BRAF and MEK. IK-595 induces an αC-helix "out" inactive conformation in BRAF protein. C) (Top) Quantification of Western blots of MEK-CRAF co-immunoprecipitations in HCT-116 (KRAS G13D) cells treated with IK-595, trametinib, avutometinib, or trametiglue for 4 hours. (Middle) Mass spectrometry of MEK immunoprecipitants demonstrates MEK-ARAF interaction in AsPC-1 (KRAS G12D) cells treated for 4 hours with DMSO, IK-595, trametinib, or avutometinib. (Bottom) Quantification of Western blots of MEK-BRAF co-immunoprecipitations following 4 hours of IK-595 treatment in HCT-116 (BRAF Wild-Type), HT-29 (BRAF V600E), NCI-H1755 (BRAF Class II), and NCI-H1666 (BRAF Class III) cells. All compounds were treated at their respective IC_{50} concentration.

IK-595 Demonstrates Prolonged and Robust Pathway Inhibition

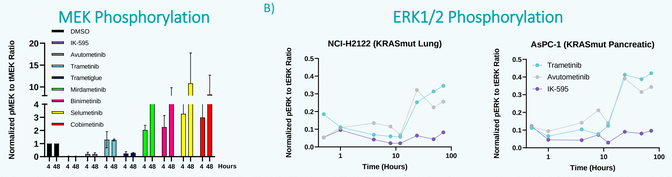


Figure 2. Quantification of MEK phosphorylation in HCT-116 cells (KRAS G13D) (A) and ERK1/2 phosphorylation (B) western blots in NCI- H2122 (KRAS G12C), or AsPC-1 (KRAS G12D) cells demonstrates that IK-595 blocks MEK phosphorylation for at least 48 hours and has reduced rebound in ERK phosphorylation for at least 96 hours compared to other MEK inhibitors. All compounds were treated at their respective IC_{90} concentration.

Intermittent Dosing of IK-595 is Efficacious with Superior Tolerability

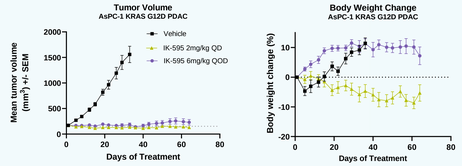


Figure 3. (Left) IK-595 demonstrates similar efficacy in AsPC-1 (KRAS G12D) CDX model when dosed on a QD or QOD regimen. (Right) Improved tolerability as measured by percent body weight change observed in groups treated with QOD regimen compared to QD dosing.

IK-595 Demonstrates Robust Anti-Tumor Activity Across RAS/MAPK-Altered *In Vivo* Models Demonstrating Potential Breath of Applicability

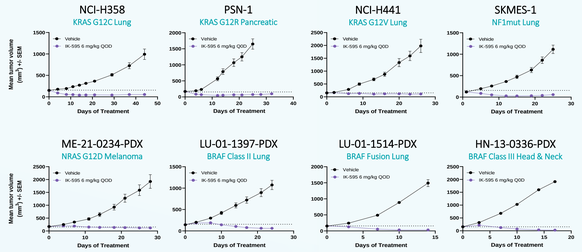


Figure 4. IK-595 drives tumor regressions in KRAS, NRAS, BRAF, and NF1 mutant tumors regardless of tumor indication.

IK-595 Combinations Broaden Clinical Opportunities

RAS Inhibitors (In-Pathway Combination)	Other In-Pathway Combinations	Alternate Signaling Nodes	Standard of Care Chemotherapy

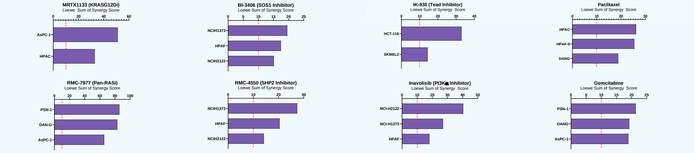


Figure 5. IK-595 synergizes with MRTX1133 (KRASG12Di), RMC-7977 (Pan-RASi), BI-3406 (SOS1i), RMC-4550 (SHP2i), IK-930 (TEAD1i), inavolisib (PI3Kαi), paclitaxel and gemcitabine. All Loewe Sum of Synergy scores were calculated from a 5-day CellTiter Glo assay using the Combenefit software. Values to the right of the red dashed line are considered to be synergistic.

IK-595 is an Optimal KRASG12C Inhibitor Combination Partner

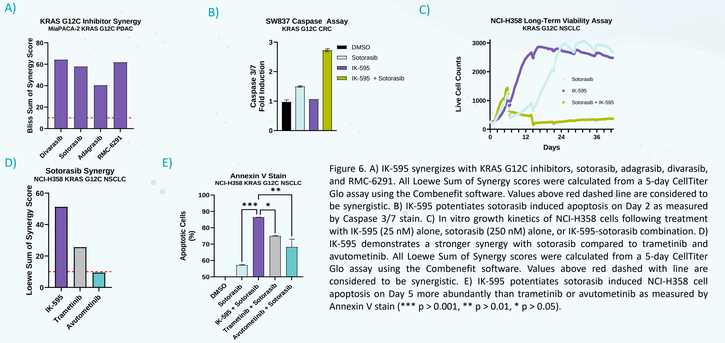


Figure 6. A) IK-595 synergizes with KRAS G12C inhibitors, sotorasib, adagrasib, divarasib, and RMC-6291. All Loewe Sum of Synergy scores were calculated from a 5-day CellTiter Glo assay using the Combenefit software. Values above red dashed line are considered to be synergistic. B) IK-595 potentiates sotorasib induced apoptosis on Day 2 as measured by Caspase 3/7 stain. C) In vitro growth kinetics of NCI-H358 cells following treatment with IK-595 (25 nM) alone, sotorasib (250 nM) alone, or IK-595-sotorasib combination. D) IK-595 demonstrates a stronger synergy with sotorasib compared to trametinib and avutometinib. All Loewe Sum of Synergy scores were calculated from a 5-day CellTiter Glo assay using the Combenefit software. Values above red dashed with line are considered to be synergistic. E) IK-595 potentiates sotorasib induced NCI-H358 cell apoptosis on Day 5 more abundantly than trametinib or avutometinib as measured by Annexin V stain (*** $p > 0.001$, ** $p > 0.01$, * $p > 0.05$).

IK-595 Exhibits Anti-Tumor Activity in KRASG12Ci Resistant Models

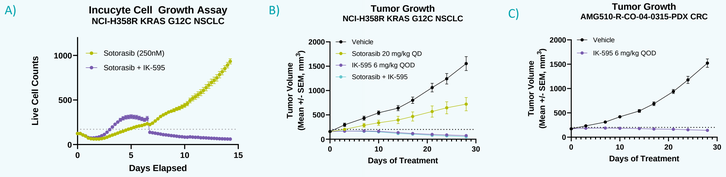
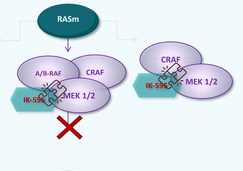


Figure 7. A) In vitro growth kinetics of NCI-H358 cells resistant to sotorasib (250 nM) following treatment with sotorasib (250 nM) alone or IK-595-sotorasib combination. B) In vivo tumor growth of NCI-H358-R cells treated with Vehicle, sotorasib 20 mg/kg QD, IK-595 6 mg/kg QOD or the IK-595-sotorasib combination. C) In vivo tumor growth of sotorasib-resistant PDX model AMG510-R-CO-04-0315 treated with vehicle or IK-595 at 6 mg/kg QOD.

Conclusion

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



IK-595 has potential to be a best-in-class inhibitor that could broadly impact the RAS therapeutic space

- ✓ Inhibits MEK mediated ERK1/2 phosphorylation
- ✓ Prevents MEK phosphorylation by RAF
- ✓ Alleviates therapeutic resistance through CRAF mediated bypass and pathway reactivation
- ✓ Robust and broad efficacy in RAS/MAPK pathway-altered tumors
- ✓ PK profile enables targeting IC_{90} plasma concentrations and allowing recovery effectively widening the therapeutic window
- ✓ Combines synergistically with therapies targeting RAS or other compensatory pathways, including KRAS G12C inhibitors

For information regarding the IK-595 clinical trial