IK-595: A MEK/RAF Complex Inhibitor

September 2023
First Generation MEK Inhibitors: Limited Activity in RAS Mutant Patients

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

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

**MEK/RAF complex inhibition**

- Tuning PK to enable breaks in normal tissues
- Fast to PoC RAS/RAF altered cancers
IK-595 Stabilizes MEK-RAF Complexes in an Inactive Conformation, Locking the αC-Helix in an Inactive Form

MEK-BRAF: $K_D, \text{DMSO} = 16.3$ nM
MEK-CRAF: $K_D, \text{DMSO} = 5.9$ nM
IK-595 Binds to MEK with Very Slow Off-Rate Kinetics

**SPR Single Cycle Kinetics**

<table>
<thead>
<tr>
<th>MEK</th>
<th>$k_{on}$ $(M^{-1}s^{-1})$</th>
<th>$k_{off}$ $(s^{-1})$</th>
<th>$K_D$ $(nM)$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IK-595 (to MEK)</strong></td>
<td>8.24 E+04</td>
<td><strong>6.09 E-04</strong></td>
<td>7.39</td>
</tr>
</tbody>
</table>

*uMEK: unphosphorylated MEK*
IK-595 Stabilizes MEK-CRAF, MEK-BRAF and MEK-ARAF Complexes in Cells

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

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

Potential MoA advantage of IK-595 over RAFi + MEKi

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

<table>
<thead>
<tr>
<th>HCT116</th>
<th>DMSO (hours post-washout)</th>
<th>Trametinib (hours post-washout)</th>
<th>IK-595 (hours post-washout)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Phospho-MEK

Total MEK

Phospho-ERK

Total ERK

MEK Phosphorylation

ERK1/2 Phosphorylation

Compounds were dosed at pERK IC₉₀ 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

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)

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
*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\textsuperscript{WT} Cells

Correlates with the described CRAF dependency: RAS\textsuperscript{mut} > RAS\textsuperscript{wt}

Jones, 4th RAS-Targeted Drug Development Summit 2022
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*

**Sotrasib**
Loewe Sum of Synergy Score

IK-595
Trametinib

**Adagrasib**
Loewe Sum of Synergy Score

NCI-H358
NCI-H1373
NCI-H2122

**Other In-Pathway Combinations**

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

**SOS1 Inhibitor**
Loewe Sum of Synergy Score

NCI-H1373
HPAF
NCI-H2122

**SHP2 Inhibitor**
Loewe Sum of Synergy Score

NCI-H1373
HPAF
NCI-H2122

**Alternate Signaling Nodes**

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

**TEAD Inhibitor IK-930**
Loewe Sum of Synergy Score

HCT-116
SKMEL2

**PI3K Inhibitor**
Loewe Sum of Synergy Score

NCI-H2122
NCI-H1373
HPAF
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\textsubscript{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

CRAF
RAS\textsubscript{m}
ERK\textsubscript{1/2}
A/B-RAF
MEK\textsubscript{1/2}
IK-595 traps MEK & RAF in an inactive complex to prevent CRAF bypass and kinase-independent CRAF function

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

IND planned for 2H 2023

Dynamic Clinical Development
Maximum flexibility for various dose schedules to broaden therapeutic window

Wide Market Opportunity for Next-Gen MEKi
Unique MoA could open doors to large RAS/RAF patient populations in both mono and combo
Acknowledgment

Program Lead
Sabine K. Ruppel

Biology/Translational
Eric Haines (Lead)
Rachel Catterall
Sarah R. Wessel
Grace Werosta
Oksana Zavidij
Lan Xu

Chemistry
Michael Burke (Lead)

ADME/PK
Joseph D. Manna

Biochem/Biophysics
Bin Li
Ao Yang
Aravind Basavapathruni

In Vivo Pharmacology
George Punkosdy
Victor De Jesus
Sheila Newhouse
Jill Cavanaugh

Structural Biology
Ao Yang

Clinical
Sergio Santillana
Thank you