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.
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

First Generation MEK Inhibitors: Limited Activity in RAS Mutant Patients

Ikena Aims to Overcome the Limitations and Challenges of Currently Available MEK Inhibitors

Challenges

**Efficacy**
- CRAF mediated pathway rebound

**Tolerability**
- Narrow TI

**Patient**
- Limited clinical benefit

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**MEK/CRAF complex inhibition**
- Tuning PK allowing for breaks in normal tissues
- Fast to PoC RAS/RAF altered cancers

Ikena

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AACR SPECIAL CONFERENCE: TARGETING RAS
IK-595 Stabilizes MEK-RAF Complex in an Inactive Conformation

AlphaLISA Biochemical Assay

IK-595

MEK-BRAF (active)
IK-595-MEK-BRAF (Inactive)

αC-helix “in” (active)
αC-helix “out” (inactive)
“Inhibitory turn”

Activation segment

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

Compounds treated at IC90

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*

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>VS-6766</td>
<td>7</td>
</tr>
<tr>
<td>IK-595</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Compounds were dosed at IC$_{90}$

Classic 1$^{st}$ 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

In vitro ERK1/2 Phosphorylation (HCT116 cells)

*N*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

Correlates with the described CRAF dependency: RASmut > RASwt

<table>
<thead>
<tr>
<th>CRAF Alteration</th>
<th>Percent Inhibition (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRASmut</td>
<td>★★★★★</td>
</tr>
<tr>
<td>KRASmut</td>
<td>★★★★★★</td>
</tr>
<tr>
<td>BRAFV600</td>
<td>★★★★</td>
</tr>
<tr>
<td>Non-BRAFV600</td>
<td>★★</td>
</tr>
<tr>
<td>PI3K-PTENmut</td>
<td>★</td>
</tr>
<tr>
<td>EGFRmut</td>
<td>★★</td>
</tr>
</tbody>
</table>

IK-595

Jones, 4th RAS-Targeted Drug Development Summit 2022
IK-595 Demonstrates Robust Anti-tumor Efficacy Across Multiple RAS/RAF Altered CDX Models

- **KRAS G12D**
  - Pancreatic

- **KRAS G12C**
  - Lung

- **CRAF amp**
  - Bladder

- **NRAS Q61L**
  - AML

**AsPC-1**
- Days of Treatment vs. Mean tumor volume (mm$^3$) +/- SEM
  - Vehicle
  - IK-595 3 mg/kg

**NCI-H2122**
- Days of Treatment vs. Mean tumor volume (mm$^3$) +/- SEM
  - Vehicle
  - IK-595 3 mg/kg

**5637**
- Days of Treatment vs. Mean tumor volume (mm$^3$) +/- SEM
  - Vehicle
  - IK-595 3 mg/kg

**OCI-AML-3**
- Days of Treatment vs. Mean tumor volume (mm$^3$) +/- SEM
  - Venetoclax resistant
  - Venetoclax 100 mg/kg
  - Vehicle
  - IK-595 3 mg/kg
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

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

- Superior Synergy with G12Ci
- Strong Synergy across Multiple Key Mechanisms

**Sos1 Inhibitor**
- BI-3406

**PI3Kα Inhibitor**
- Inavolisib

**SHP2 Inhibitor**
- RMC-4550

**EGFR mAb**
- Cetuximab
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:

- 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\textsubscript{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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