IK-930 is a Novel TEAD Inhibitor for the Treatment of Cancers Harboring Mutations in the Hippo Signal Transduction Pathway

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Disclosure Information

Jeffrey Ecsedy
I have the following relevant financial relationships to disclose:
   Employee of: Ikena Oncology
   Consultant for: Cytoimmune Sciences
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Hippo Signal Transduction Pathway in Cancer

- Multiple activating signals drive YAP/TAZ nuclear localization $\rightarrow$ TEAD binding $\rightarrow$ gene expression of proliferation / pro-survival pathways

- TEAD transcription dysregulated in many cancers
  Numerous tumor suppressor / oncogenes lead to TEAD activation
  Increased nuclear YAP1/TAZ, TEAD activity associated with poor outcome

- Key mechanism of therapeutic resistance
Genetic Alterations in Hippo Signal Transduction Pathway Drive Oncogenesis in Patients Across Multiple Indications

- **Meningioma**
  - High frequency of NF2 deficiency
  - Most common CNS tumor, accounting for ~one-third of primary CNS tumors

- **Soft Tissue Sarcoma**
  - ~90% of epithelioid hemangioendothelioma, or EHE, have TAZ-CAMTA1 fusions
  - 10% of EHE have YAP1-TFE3 fusions

- **Non-small Cell Lung Cancer**
  - ~6% YAP1 and 29% TAZ amplification
  - Drives resistance to EGFR therapies

- **Malignant Mesothelioma**
  - ~40% have NF2 loss of function mutations
  - Associated with poor patient prognosis
  - In both epithelioid and sarcomatoid/byphasic

~125,000 Newly Diagnosed Cancer Patients (US Only / Year) with Deregulated Hippo Pathway
Translational Data to Drive Indication Selection

Bioinformatics Analyses

NF2, YAP1, TAZ, LATS1/2, MST1/2, BAP1 Alterations

YAP1/TAZ Activity Score

Indications of Interest

MESO, HNSCC, CHOL, NSCl.C, Pancreatic

YAP/TAZ Nuclear Localization

High YAP1 nuclear protein expression indicative of pathway activation in select indications

<table>
<thead>
<tr>
<th></th>
<th>%YAP1 +2 +3</th>
<th>%TAZ +2 +3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>76</td>
<td>8</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>NSCLC</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>Pancreas</td>
<td>70</td>
<td>4</td>
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<tr>
<td>Thymoma</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Liver/Hepatocellular</td>
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*Signature derived from Pham et al 2021
IK-930 is an Oral, Selective, Potent TEAD Inhibitor

Binding the Central Lipid Pocket of TEAD

Potent TEAD Inhibition

Robust Inhibition
TEAD Target Gene Expression

Selective Activity in Hippo-Mutated Cells
IK-930 Demonstrated Anti-Tumor Activity in Tumor Models with Hippo Pathway Mutations

Potential for Monotherapy Across Genetic Mutations
IK-930 has Favorable ADME/PK Profile

Cyp, hERG and Safety Panel Profiling Suggest Low Risk for Drug-drug Interaction

<table>
<thead>
<tr>
<th>CYP Inhibition, IC₅₀</th>
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<tbody>
<tr>
<td>Cyp1A2</td>
<td>&gt;10 uM</td>
</tr>
<tr>
<td>Cyp2B6</td>
<td>&gt;10 uM</td>
</tr>
<tr>
<td>Cyp2C9</td>
<td>&gt;10 uM</td>
</tr>
<tr>
<td>Cyp2C19</td>
<td>7.6 uM</td>
</tr>
<tr>
<td>Cyp2D6</td>
<td>&gt;10 uM</td>
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<tr>
<td>Cyp3A4-M</td>
<td>9.0 uM</td>
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<tr>
<td>Cyp3A4-T</td>
<td>&gt;10 uM</td>
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</table>

<table>
<thead>
<tr>
<th>Nonclinical PK Summary</th>
<th></th>
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<tbody>
<tr>
<td>Mouse</td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>1.6 h</td>
</tr>
<tr>
<td>Vd</td>
<td>2.7 L/kg</td>
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<tr>
<td>Oral bioavailability</td>
<td>55%</td>
</tr>
<tr>
<td>Rat</td>
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</tr>
<tr>
<td>T1/2</td>
<td>1.7 h</td>
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<tr>
<td>Vd</td>
<td>2.8 L/kg</td>
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<tr>
<td>Oral bioavailability</td>
<td>56%</td>
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<tr>
<td>Dog</td>
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<tr>
<td>T1/2</td>
<td>1.8 h</td>
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<tr>
<td>Vd</td>
<td>3.1 L/kg</td>
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<td>Oral bioavailability</td>
<td>52%</td>
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<td>Monkey</td>
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<tr>
<td>T1/2</td>
<td>2.2 h</td>
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<tr>
<td>Vd</td>
<td>2.8 L/Kg</td>
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<tr>
<td>Oral bioavailability</td>
<td>49%</td>
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- Highly selective across a receptor, enzyme, ion channel safety panel (> 50 fold over H226 IC₅₀)
- Minimal inhibition of hERG in automated patch clamp assay (IC₅₀ > 200 fold over H226 IC₅₀)
- Minimal Cyp inhibition - low potential to drug-drug-interactions
- Not a substrate of P-gp or BCRP transporters
- Moderate and similar plasma protein binding across species
- Very good oral bioavailability in mouse, rat, dog, and monkey
- Brain penetrant
Role of Hippo Pathway in Therapeutic Resistance; Multiple Opportunities for Combination with IK-930

Screens identifying Hippo-mediated resistance

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Condition</th>
<th>Hit</th>
<th>Format</th>
<th>Reference</th>
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<tr>
<td>Melanoma</td>
<td>BRAFi</td>
<td>NF2</td>
<td>CRISPR</td>
<td>Shalem, O. et al. (2014) Science, 343, 84</td>
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<td>PDAC</td>
<td>Kras KO</td>
<td>YAP amp</td>
<td>GEMM</td>
<td>Kapoor, A. et al. (2014) Cell, 158,185</td>
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<td>NSCLC</td>
<td>EGFRi</td>
<td>TEAD Gene signature</td>
<td>RNASeq</td>
<td>Kurppa, K et al. (2020) Cell, 37 (104-22)</td>
</tr>
</tbody>
</table>

* EMICERI*: Increase MOB38 (component of MST1/2 and LATS1/2 inhibitor complex) expression

Combined TEAD and RTK or KRAS / MAPK inhibition synthetically lethal in BRAF- and KRAS mutant tumors

MEK Inhibitor Induces YAP1 Nuclear Localization and TEAD Dependent Transcription

HCT116 cells (KRAS G13D)

Vehicle

Trametinib (5 nM)

DAPI

YAP1

DAPI/YAP1

TEAD-Luciferase

Cell Viability

Trametinib Log(nM)

Cell Viability (%Max)

Vehicle

Trametinib (5 nM)

TEAD-Luciferase (%Max)

IK930 (μM)

Vehicle

Trametinib (5 nM)

Cell Viability (%)
IK-930 Enhances Apoptosis in MEK Inhibitor -Treated KRAS Mutant Cells

HCT116: KRAS G13D CRC Model
Apoptosis Induction (HCT116)

LOVO: Human KRAS G13D CRC Model
Apoptosis Induction (LoVo)

A549: KRAS G12S NSCLC Model
Apoptosis Induction (A549)

Calu-1: KRAS G12C NSCLC Model
Apoptosis Induction (Calu-1)
Increased Anti-Tumor Effect of IK-930 in Combination with MEK Inhibitor in KRAS Mutant Tumors In Vivo

Impact Across Tumor Models for KRASm CRC and NSCLC

<table>
<thead>
<tr>
<th>Model</th>
<th>HCT116</th>
<th>A549</th>
<th>Lovo</th>
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<tbody>
<tr>
<td>In vivo TGI Combination</td>
<td>83% (1mg/kg MEKi)</td>
<td>78% (0.5mg/kg MEKi)</td>
<td>75% (1mg/kg MEKi)</td>
</tr>
</tbody>
</table>
Developing First-in-Class TEAD Inhibitor for Genetically Altered Cancers and Therapeutic Resistance

Monotherapy strategy focused on NF2-deficient orphan indications including NF2 deficient MPM, EHE and other solid tumors with prevalent NF2 and YAP/TAZ fusion genes.

Combination strategy to explore multiple with targeted agent combos to reverse mechanism of resistance in broader indications.

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