Selective IDO1 Inhibition: Pharmacodynamic and Antitumor Activity of INCB24360

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The following relationships exist related to this presentation:

Incyte Corporation: Employee
All inflammatory and immune responses are accompanied and limited by the generation of feedback inhibition.

**Major players:**
- Tregs
- Immunosuppressive cytokines
  - IL-10 and TGFβ
- Metabolic Enzymes
  - Arginase and IDO

Many tumors appear to have subverted these mechanisms to suppress immunity.
IDO1 – A Tryptophan Catabolizing Enzyme

• Converts tryptophan into kynurenine and other metabolites
  – Two other family members: TDO and IDO2

• Upregulated in response to IFN-γ during infection and tissue inflammation

• Predominantly expressed by antigen presenting cells
  – Tissue expression highest in gut, thymus, lung, placenta

• Plays an important role in the negative regulation of T cell responses
  – Low levels of tryptophan and high levels of kynurenine metabolites limit the proliferation of T cells
  – High IDO expression is associated with the induction of Tregs
  – Significant role in allogeneic fetal tolerance
Overview of Tryptophan Biochemistry

Diagram:
- Protein
- Food
- Recycling
- Trp-tRNA
- Tryptophan
- O2
- Kynurenine
- Quinolinic acid
- NAD

IDs: IDO1 IDO2 TDO
Overview of Tryptophan Biochemistry

IDO1, IDO2, TDO

INCB24360, 1MT, 680C91

Protein → Food

Recycling

Trp-tRNA → Tryptophan

O₂ → 5-hydroxytryptophan → Serotonin

Kynurenine → Quinolinic acid → NAD

TPH
# IDO Expression in Various Tumor Types

<table>
<thead>
<tr>
<th>Tumor</th>
<th>IDO+ Tumor Samples</th>
<th>&gt;50% IDO+ Cells</th>
<th>10-50% IDO+ Cells</th>
<th>&lt;10% IDO+ Cells</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>11/11</td>
<td>7</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Colorectal</td>
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<td>5</td>
<td>3</td>
<td>2</td>
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<td>Pancreatic</td>
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<td>1</td>
<td>1</td>
<td>7</td>
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<tr>
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<tr>
<td>Renal Cell</td>
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<td>1</td>
<td>4</td>
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<tr>
<td>Melanoma</td>
<td>11/25</td>
<td>0</td>
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<td>11</td>
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</tbody>
</table>

Elevated kynurenine levels in urine of patients with breast, prostate, bladder cancer and leukemia

IDO1 Is A Marker Of Poor Prognosis

IDO1 expression in human tumors is associated with decreased survival:
- Ovarian
- Melanoma
- Colon
- Pancreatic
- Endometrial
- Oral squamous cell carcinoma

Kaplan-Meier survival curves in ovarian cancer based on IDO staining

IDO1 Inhibitor Identification Strategy

Through a directed medicinal chemistry effort, identify a potent, selective, orally bioavailable IDO1 inhibitor that would:

• Reduce kynurenine levels both *in vitro* and *in vivo*
• Not impact TDO metabolic activity
• Allow for enhanced activation of the immune system
• Control the growth of tumors, alone and in combination regimens
• Meet ADME and safety criteria to allow safe dosing in humans

**INCB24360 identified as the clinical candidate**
INCB24360: A Potent and Highly Selective IDO1 Inhibitor

INCB24360 (10 μM) exhibits little activity against a panel of 50 GPCRs, ion channels, transporters and enzymes.

Liu et al Blood 2010
IDO1 Inhibition By INCB24360 Modulates T Cell Responses in vitro

- IDO1+ dendritic cells block T cell proliferation in vitro
- INCB024360 treatment reverses inhibition and dose-dependently promotes T cell proliferation
  - Similar effects on proliferation observed in CD4+, CD8+ and NK cells
  - Results in significant increases in IFN-γ production

**T cell proliferation assay**

- IL-2 + anti-CD3 and IFN-γ + LPS
- INCB024360 IC50 = 18 nM (n = 2)

Liu et al Blood 2010
INCB24360 Reduces Kyn Levels In Wild Type Mice To Levels Present In IDO1\(^{-/-}\) Mice

Kyn inhibition observed in multiple species

In tumor-bearing mice, decreased kyn levels observed in plasma, tumor and LN

Koblish et al Mol Can Ther 2010
INCB24360 Controls CT26 Tumor Growth Only In Immunocompetent Mice

Balb/c mice

Balb/c nu/nu mice

Associated with increased T cell percentages and activity and decreased percentage of Tregs

Koblish et al Mol Can Ther 2010
INCB24360 Enhances Doxorubicin Activity In CT26 Tumors

Similar data have been obtained with gemcitabine and cisplatin.
Chemotherapy induced Kyn generation correlates with enhanced efficacy in combination studies

24 hours, naïve mice
Basic study design

- Non-randomized, open-label, single agent dose escalation in advanced cancers (all tumor types) to assess safety and tolerability and to determine the maximum tolerated dose
- Safe Starting Dose of 960 mg, first cohort received 50 mg
- Endpoints to include:
  - Characterization of the pharmacokinetics of INCB24360
  - Analysis of PD markers
    - IDO whole blood assay and plasma tryptophan/kynurenine ratio
    - Markers of immune cell activation
    - Markers of inflammation
    - Correlation of effects with IDO1 expression in primary biopsy
  - Evidence of anti-tumor activity
INCB24360 inhibits Kyn generation in patients

**Day 15 PD:**
- Dose dependent PD effect
- Consistent PD profile observed in all subjects in a cohort
- PD effects are consistent with the PK profile
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