**ABSTRACT**

**Background:** ITK is a non-receptor tyrosine kinase that modulates TCR signaling (August et al. 2012). In T-cell lymphoproliferative disorders, expression of the TCR and its downstream components are maintained suggesting malignant T cells may exploit this pathway for growth and survival. Profound antigens presenting cells (APCs), abundant in the lymphoma microenvironment, may provide antigens to drive TCR signaling through ITK, which is consistently expressed in a variety of T-cell lymphomas including peripheral T-cell lymphomas (PTCL), cutaneous T-cell lymphomas (CTCL), and angio-immunoblastic T-cell lymphoma (Agostinelli et al., 2014). In addition, activation of ITK in malignant T cells has been shown to up-regulate GATA-3, a transcription factor that drives Th2 differentiation and is overexpressed in PTCL with poor overall survival (Briand et al. 2014, Iqbal et al. 2014, Wilson et al. 2014) suggesting that selective pharmacological inhibition of ITK, sparing RLK, may be necessary to inhibit Th2 response without affecting Th1 dependent immunity.

**Methods:** We report the discovery and characterization of CPI-818, an irreversible inhibitor of ITK.

**Results:** CPI-818 irreversibly inhibited ITK (IC₅₀ 2.3 nM) with >100-fold selectivity over RLK and BTK (430 nM) and BTK (850 nM). The mechanism of ITK inhibition involves covalent binding to CYS-442 demonstrated using an active site competitive probe. In cellular assays, CPI-818 inhibited anti-CD3/28-induced phosphorylation of ERK (T202/Y204) and IL-2 secretion in Jurkat cells (IC₅₀ 76 nM). CPI-818 demonstrated dose-dependent inhibition of TCR-induced proliferation of malignant T-cells from Sézary syndrome patients. In mice orally treated with CPI-818 an increase in the ratio of CD4⁺/CD8⁺ was confirmed using the probe assay. Evidence of anti-tumor activity was confirmed by mass spectrometry. Irreversible inhibition of ITK in vitro and in vivo was demonstrated using an active site competitive probe. In cellular assays, CPI-818 inhibited anti-CD3/28-induced phosphorylation of ERK (T202/Y204) and IL-2 secretion in Jurkat cells (IC₅₀ 76 nM). CPI-818 demonstrated dose-dependent inhibition of TCR-induced proliferation of malignant T-cells from Sézary syndrome patients.

**Conclusions:** CPI-818 is a selective, covalent inhibitor of ITK (sparking RLK and BTK) that is well tolerated with evidence for clinical responses in PTCL patients with T cell malignancies.

**REFERENCES and FOOTNOTES**

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**INTRODUCTION**

Antigen Presenting Cell

Normal Immune Response

Normal Proliferation

Impaired Growth, Survival

Chemo-Resistance

**RESULTS**

**CPI-818 is a potent ITK inhibitor and selective versus the "cytokinome"**

Inhibition of signal transduction and cytokine production by CPI-818

**CPI-818 promotes IFNγ production (Th1 biasing)**

**REFERENCES**

5. Plan jjanc@corvuspharma.com

**CONCLUSIONS**

- CPI-818 is a selective, covalent inhibitor of ITK (sparking RLK and BTK)
- CPI-818 blocks signal transduction in proximal (pERK) and distal endpoints (IL-2 secretion) downstream of T-cell activation
- Through selective ITK inhibition, CPI-818 promotes IFNγ production in an OTI adoptive T-cell transfer model
- BID dosing of CPI-818 at 20 mg/kg in dogs provides durable ITK inhibition
- In a companion animal study in dogs with PTCL and CTL, CPI-818 was well tolerated with evidence for clinical responses
- A Fh study of CPI-818 is planned in FL, ATL, PTCL-Nos and CTL

**CLINICAL PLAN**

Plan for phase 1/2b clinical trial for CPI-818 in humans

**BASELINE CHARACTERISTICS OF COMPARISON ANIMALS WITH PTCL AND CTCL**

<table>
<thead>
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<th>Cohort</th>
<th>Study Dosing</th>
<th>MTU</th>
<th>PBMCs Throughout</th>
<th>Dose (mg/kg) Administered</th>
<th>Lesion</th>
<th>Change in measurable lesion diameters</th>
<th>Baseline</th>
<th>Cohort 2</th>
<th>Cohort 1</th>
<th>Cohort 3</th>
<th>Cohort 2</th>
<th>Cohort 1</th>
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<td>12.2</td>
<td>CTL, CTCL</td>
<td>CR</td>
<td>2.2</td>
<td>-</td>
<td>n = 11</td>
<td>n = 17</td>
<td>n = 11</td>
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</tbody>
</table>

**RESULTS (Cont)**

**Pharmacodynamic assessment of ITK inhibition by CPI-818 in vivo**

**Change in sums of measurable lesion diameters in COR-001 Patients.**

- A: Photographs of COR-002-001 before treatment (left) and 14 days after CPI-818 initiation (right).
- B: Photographs of COR-002-002 between day 1 (left) and 2 (right).
- C: Change in the ratio of CD4⁺/CD8⁺ was confirmed using the probe assay.

For PI Patients

**ACKNOWLEDGMENTS**

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