Preliminary Clinical Data from a Phase 1 Trial with CPI-818, A Selective ITK Inhibitor that Preferentially Blocks the Growth of T Lymhoma Cells

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BACKGROUND

ITK is a sykine kinase crucial to T cell receptor (TCR) signaling. Overexpression of its gene has been reported in cutaneous T lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Genetic analyses have demonstrated the contribution of aberrant TCR signaling in the pathogenesis of T-cell lymphoma (TCL). ITK is a closely related kinase, is co-expressed with ITK in T and NK cells, and is partially functionally redundant with ITK signaling. Selective inhibition of ITK, but not other signal transduction components such as RLK, may be an effective strategy to treat TCL while preserving normal T and NK cell functions.

CPI-818 is an orally bioavailable, covalent inhibitor of ITK with >100-fold selectivity over RLK and BTK (Figure 1). It was well tolerated and exhibited ant-tumor activity in canine dogs with spontaneous TCL (2019 AACR Annual Meeting Abstract #3131). A Phase 1/2 trial with CPI-818 in human TCL has been initiated (NCT03520787). Here we present preclinical evidence that CPI-818 inhibits the proliferation of malignant TCL cells with relative sparing of normal lymphocytes, and we report early results from the clinical trial.

CPI-818 TREATS T-CELL LYMPHOPROLIFERATIVE DISEASE AND AUTOIMMUNITY IN MRL/lpr MICE

In animals with established disease, CPI-818 treatment led to marked regression of lymphadenopathy with minimal effect on normal CD4+ and CD8+ T cells, and prevented autoimmune glomerulonephritis.

Figure 1. CPI-818 Specifically Inhibits ITK and Downstream Signaling

CPI-818 is a covalent, selective ITK inhibitor that results in sustained occupancy of ITK and thus preferential inhibition of T-cell proliferation. This selective inhibition results in minimal effect on CD4+ and CD8+ T cells, and prevents autoimmune glomerulonephritis.

CLINICAL STUDY

Peripheral Blood B, and NK Cell Counts

Increased normal CD8+ cells in 3 patients (A), one of which has an activated, memory phenotype

CONCLUSIONS

- CPI-818 is a covalent, selective ITK inhibitor that results in sustained blockade of ITK.
- CPI-818 treatment led to marked regression of lymphoproliferative disease in MRL/lpr mice, with minimal impact on normal CD4+ and CD8+ T cells, and no effect on other immune cells.
- CPI-818 prevented autoimmune nephritis in MRL/lpr mice.
- In vitro studies showed that malignant Sézary cells were more sensitive to the antiproliferative effect of CPI-818 than normal T cells.
- The initial two dose-escalation cohorts of the Phase 1/2 trial have been enrolled. No DLTs or treatment-related grade 3-4 AEs have been reported. Treatment of 2 out of 3 patients in the second cohort is ongoing. Occupancy studies revealed significant but incomplete ITK inhibition.
- Consistent with preclinical data, CPI-818 did not decrease normal T, B, or NK cell counts. Normal CD8+ T cells increased in 3 patients.

ACKNOWLEDGMENTS

- Contributed to the design and execution of the preclinical studies.
- Co-authored and contributed to the study.
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Figure 5. Pharmacokinetic analysis of patient whole blood (A) or pleural effusion (B) in one subject treated in the Phase 1/2 trial.

Figure 6. Demonstration of selective antiproliferative effect on Sézary cells (A) and reduction in serum levels of IL-2 and IL-15 (B) in Sézary cell line.

Figure 7. BID dosing achieved significant but incomplete ITK inhibition that persisted after drug clearance.

Figure 8. Study design for the extension of the Phase 1 trial in patients with TCL and PTLD.

Figure 9. Progression-free survival and overall survival in patients with PTLD.

Figure 10. Kaplan-Meier curves showing incidence of adverse events in patients with PTLD treated with CPI-818.