Itk inhibitor induces Th1 skewing and host anti-tumor response mediated by CD8+ TEMRA cells in refractory T cell lymphoma patients

N. Ding[1], Y. Xie[1], J. Reneau[2], R. Miller[3], S. Mahabhashyam[3], L. Hsu[3] , Y. Guo[4], K. C. Li[4], T. Du[1], L. Mi[1], N. Lin[1], J. Cao[1], D. Hu[1], D. Wang[1], Y. Li[1], Z. Li[1], J. Zhu[1], Y. Song[1]

[1]Peking University Cancer Hospital, Department of Lymphoma, Beijing, China; [2]The Ohio State University and Wexner Medical Center, Columbus, Ohio, United States of America; [3]Corvus Pharmaceuticals Inc., Burlingame, California, United States of America; [4]Angel Pharmaceuticals Co., Ltd., Jiaxing, China

BACKGROUND

ITK is involved in both T cell receptor (TCR) signaling and differentiation of helper T cells. ITK-/- mice have defects in Th2 differentiation resulting in skewing toward Th1 cells that secrete IFN-γ. CPI-818 is a selective covalent inhibitor of ITK (Kd 2.5nM). Its activity was assessed in several murine tumor models and demonstrated anti-tumor activity by increasing infiltration of normal CD8+ T cells in the tumors, findings that are consistent with Th1 skewing. CPI-818 is now being evaluated in an ongoing Phase 1/1b trial in refractory T cell lymphoma (TCL). An optimum dose of 200 mg po BID has been identified based on the demonstration of target occupancy and maximum induction of Th1 skewing.

METHODS

- EL4, A20 and CT26 tumors were grown in syngeneic mice. Animals with established tumors received CPI-818 orally by gavage or in chow. In depletion experiments animals received treatment with anti-CD8, anti-CD4, and anti-NK antibodies. Immunohistochemistry was performed on tumor samples to evaluate T cell infiltration. RNA expression was measured using Nanostring.
- Flow cytometry and single-cell RNA-seq were used to measure Th1 and T effector cells in blood and tumor biopsies from patients.
- A Phase 1/1b clinical trial was conducted in patients with relapsed/refractory TCLs. Patients received CPI-818 in successive cohorts using doses of 100, 200, 400, and 600 mg BID. The 200 mg dose was selected for cohort expansion.

NON-CLINICAL RESULTS

CPI-818 INHIBITS TUMOR GROWTH IN SEVERAL MODELS

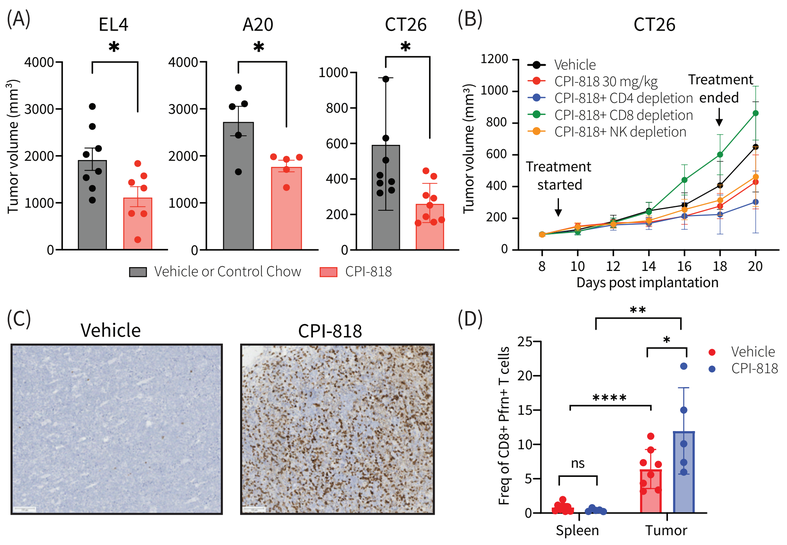

Fig 1. (A) Doses of CPI-818 30 mg/kg daily for 7-8 days (EL4 [T cell lymphoma] & CT26 [colon cancer]) and 130 mg/kg daily for 13 days (A20 [B cell lymphoma]) leads to tumor regression. (B) Growth inhibition was reduced by normal CD8 cell depletion in CT26. (C) Treatment was associated with tumor infiltration of normal CD8 cells in EL4. (D) CD8+ cells infiltrating CT26 tumor showed increased perforin expression. These results demonstrate induction of anti-tumor immunity by CPI-818.

ITK INHIBITION BY CPI-818 SYNERGIZES WITH CHECKPOINT INHIBITORS, REDUCES AND REVERSES T CELL EXHAUSTION

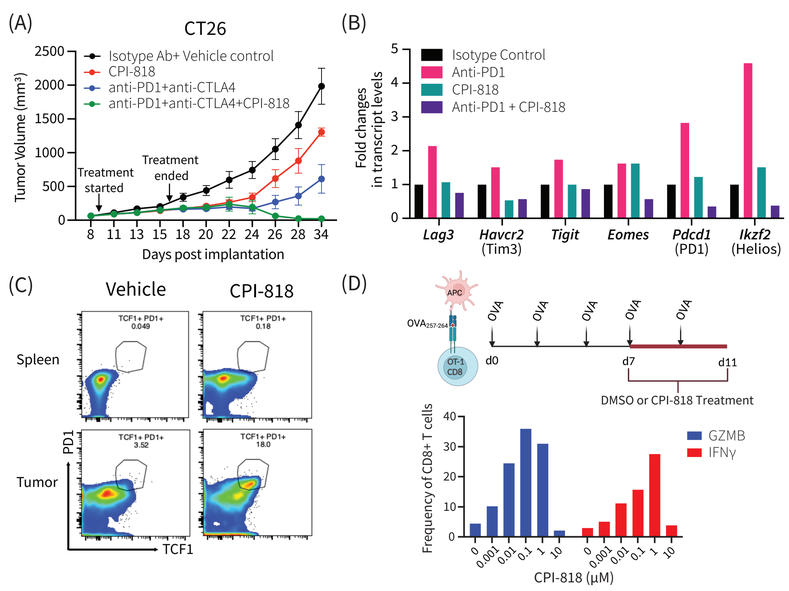

Fig 2. (A) CPI-818 treatment 30 mg/kg daily for 7 days leads to tumor inhibition which is increased by combining with sub-therapeutic doses of anti-PD1 and/or anti-PD1 + anti-CTLA4. (B) T cell exhaustion markers are increased in anti-PD1 treated tumors. CPI-818 reduces expression of T cell exhaustion markers. (C) T cells in CT26 treated animals show increased stemness (TCF1+). (D) Ovalbumin-specific T cells from DO.11 mice repeatedly stimulated in vitro become exhausted. Exposure of exhausted T cells to CPI-818 results in reinvigoration of cytolytic T cells that express granzyme B and interferon gamma at concentrations up to 1 μM. A hook effect is seen at higher concentrations.

PHASE 1 TRIAL RESULTS WITH 200 MG BID DOSE

PATIENT CHARACTERISTICS

	200 mg BID *(N=30*)*
Age (yrs.), median (range)	60 (29, 81)
Gender, male N (%)	13 (43.3)
No. of prior therapies, median (range)	3 (1, 18)
HISTOLOGIES	
PTCL-NOS	13
AITL	4
ALCL	3
CTCL Sézary syndrome	2
CTCL Mycosis fungoides	5
Other	3

**20 patients evaluable at this time*

SAFETY SUMMARY

- Most common (≥ 10%; all causality) AEs: anemia, diarrhea, nausea, pyrexia, Covid-19, upper respiratory tract infection, bilirubin increased, neutrophil count decreased, platelet count decreased, WBC decreased, hypokalemia, pruritus and rash.
  - Most common (≥ 2 patients; all causality) Grade 3+ AEs: neutrophil count decreased.

ANTI-TUMOR ACTIVITY AT OPTIMAL DOSE OF 200 MG BID

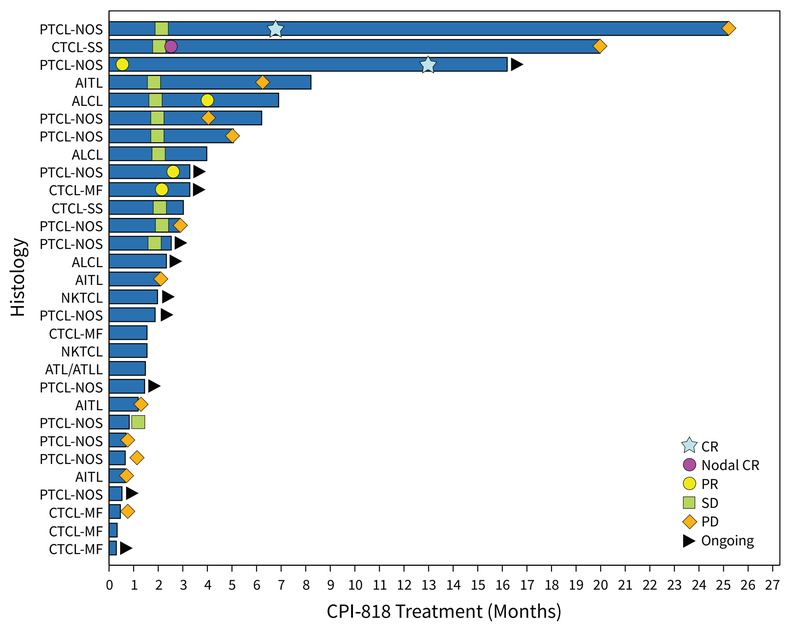

Fig 3. The swimmer plot shows duration of treatment and tumor response in patients treated with 200 mg BID. This dose results in maximum Th1 skewing.

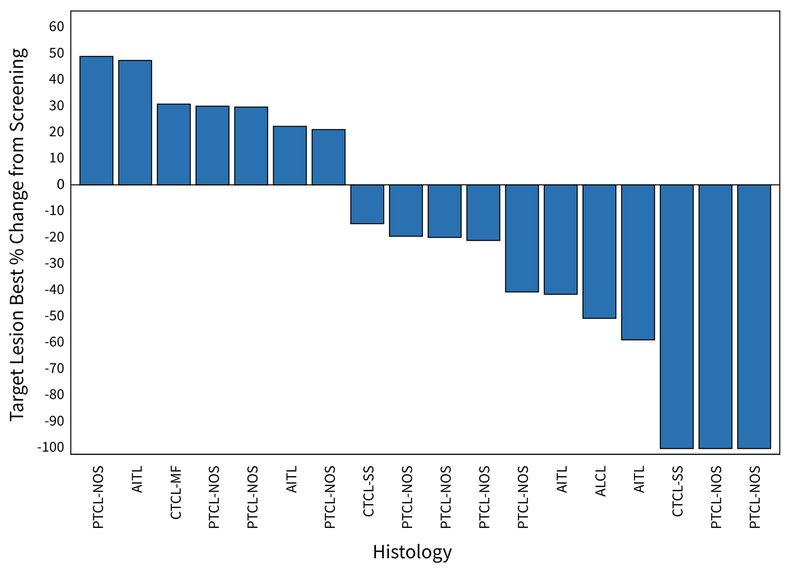

Fig 4. The waterfall plot shows best tumor response in treated patients.

BASELINE ABSOLUTE LYMPHOCYTE COUNT PREDICTS BENEFIT WITH CPI-818

Disease Assessment	ALC <900/mm³ *(N=6)*	ALC ≥900/mm³ *(N=14)*
Number Objective Response	0	6
Number Disease Control (CR, PR, SD)	2	12

ANTI-TUMOR ACTIVITY SEEN ACROSS HISTOLOGIES

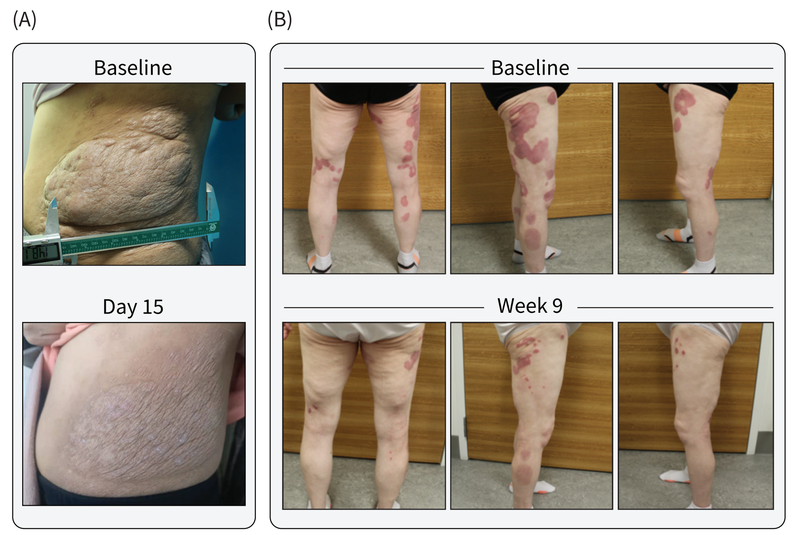

Fig 5. Tumor response in patients with relapsed/refractory PTCL-NOS (A) and CTCL large cell transformation (B).

ANALYSIS OF BLOOD AND TUMOR IN RESPONDING PATIENT

CD4+ TH1 AND CD8+ TEMRA CELLS ARE ELEVATED IN TUMOR TISSUE AND PERIPHERAL BLOOD

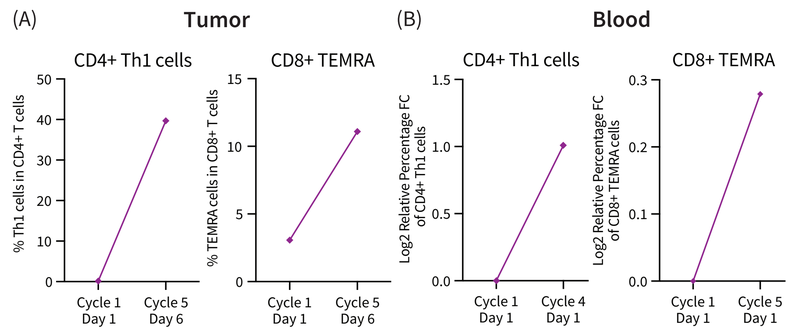

Fig 6. The percentage of CD4+ Th1 cells (CD3+/CD4+/CD8-/CD183+/CD196-) and CD8+ TEMRA cells (CD3+/CD4-/CD8+/CD197-/CD45RA+) were analyzed by flow cytometry in the tumor tissue (A) and in the peripheral blood (B) in PTCL-NOS patient from Figure 5.

CYTOTOXIC SIGNATURE RELATED GENES ARE ELEVATED IN TUMOR TISSUE CD8+ T CELLS

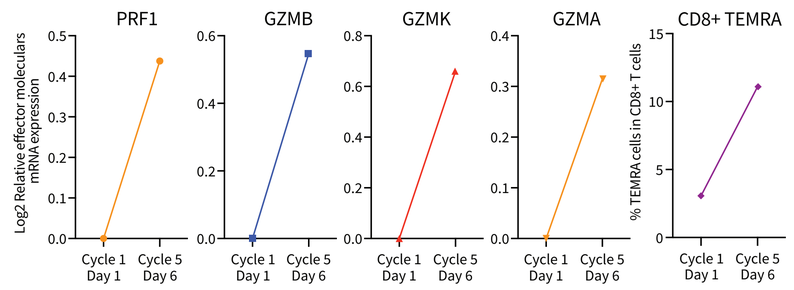

Fig 7. The mRNA expression of cytotoxic signature related genes were analyzed in tumor microenvironment infiltrated normal CD8+ T cells using single-cell RNA-seq in PTCL-NOS patient from Figure 5.

CONCLUSIONS

- CPI-818 is a covalent, selective ITK inhibitor that spares RLK resulting in Th2 blockade and Th1 skewing.
- CPI-818 monotherapy is active in several murine tumor models such as EL4 (T cell lymphoma), A20 (B cell lymphoma), and CT26 (colon cancer).
- CPI-818 mechanism of action involves increased CD8+ cytotoxic T lymphocyte infiltration, increased cytolytic capacity and reduction in T cell exhaustion.
- In an ongoing Phase 1/1b trial in relapsed/refractory peripheral T cell lymphoma, an RP2D of 200 mg BID was identified; this dose produces maximum Th1 skewing.
- Minimum absolute lymphocyte count of 900 was identified as predictive for response with ORR of 6/14 including 3 CRs.
- Paired tumor biopsies in a responding patient demonstrated treatment-associated increase in Th1 cells; increase in T cells producing effector molecules; and reduction of T cell exhaustion.
- These data demonstrate that selective ITK blockade may represent a novel approach to therapy for lymphoma and solid tumors.