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CPI-818, an Oral Interleukin-2-Inducible T-Cell Kinase Inhibitor, is Well-tolerated and Active in Patients with T-Cell Lymphoma

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Disclosures

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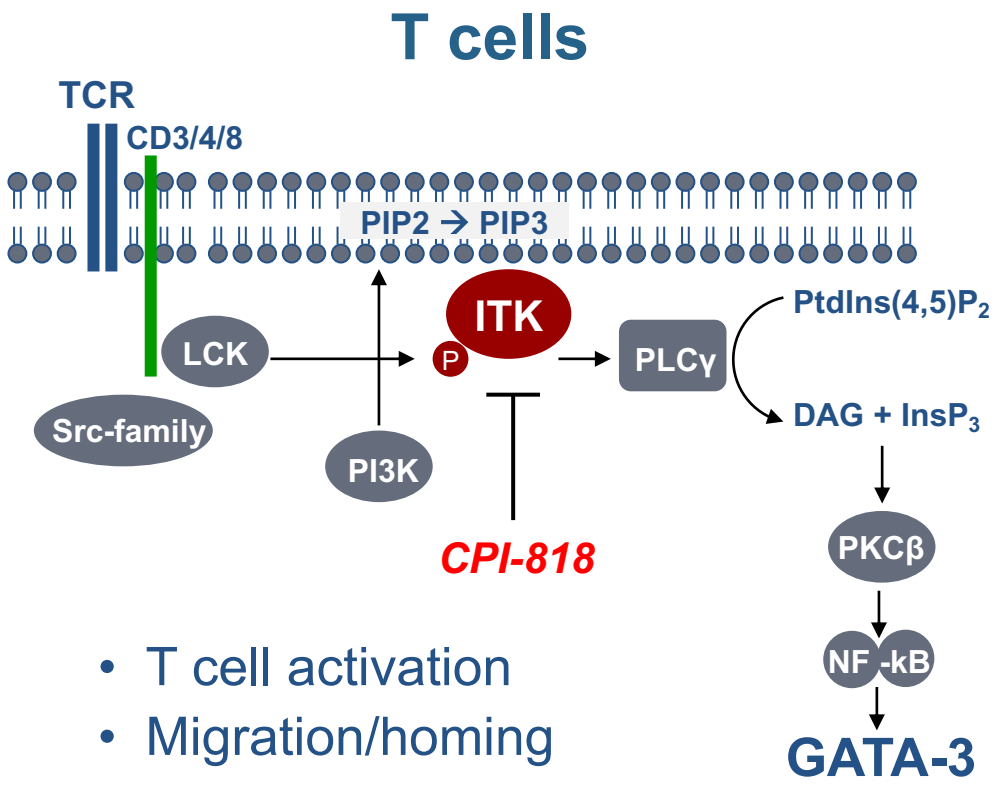
Seattle Genetics – Member of Advisory Board

Rationale for Targeting ITK for T Cell Lymphoma

- TCR signaling is maintained in most T cell lymphomas
- Analogous to BCR and B cell lymphomas; ITK is the T cell homologue of BTK and is widely expressed in T cell malignancies
- Activation of ITK drives NF-κB which drives GATA-3 and survival
- CTCL and certain PTCLs are thought to be T_H2-driven malignancies

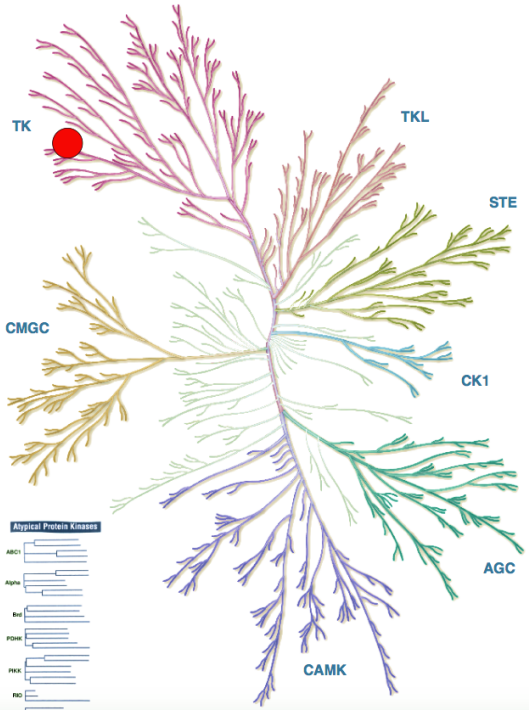


- T cell activation
- Migration/homing
- Proliferation

CPI-818 Covalently and Selectivity Inhibits ITK

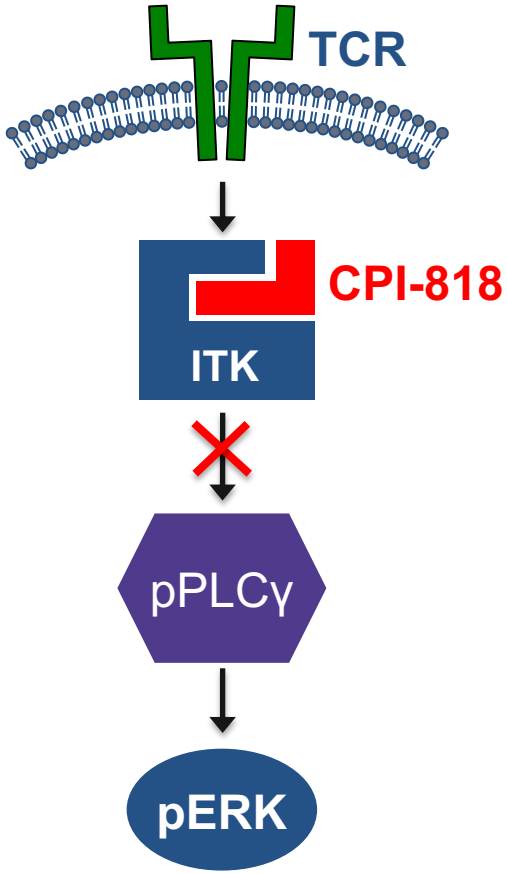
Blocks T Cell Receptor Signaling Pathway

Kinome Profile and Kinases with Cys-442

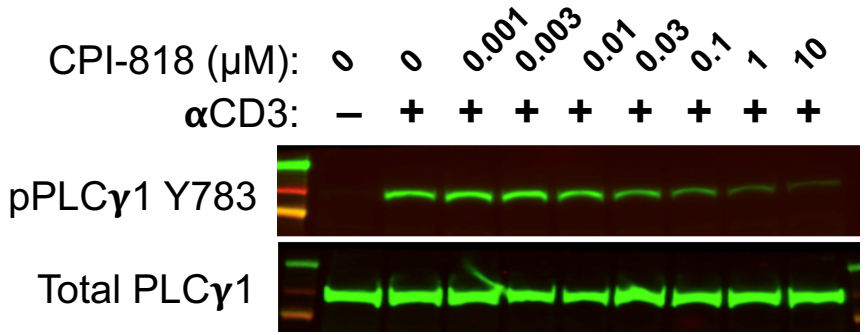


K_i < 10 nM
468 Kinases Profiled

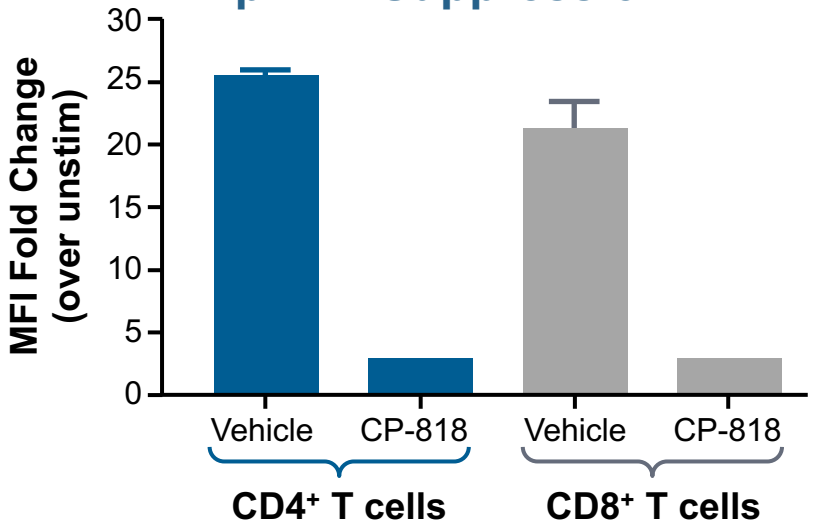
	CPI-818 Kd in nM
ITK	2.5
BLK	4700
BMX	9100
BTK	1200
EGFR	>10000
ERBB2	>10000
ERBB4	>10000
JAK3	2800
MKK7	>10000
TEC	540
RLK	2700



pPLCγ1 Suppression

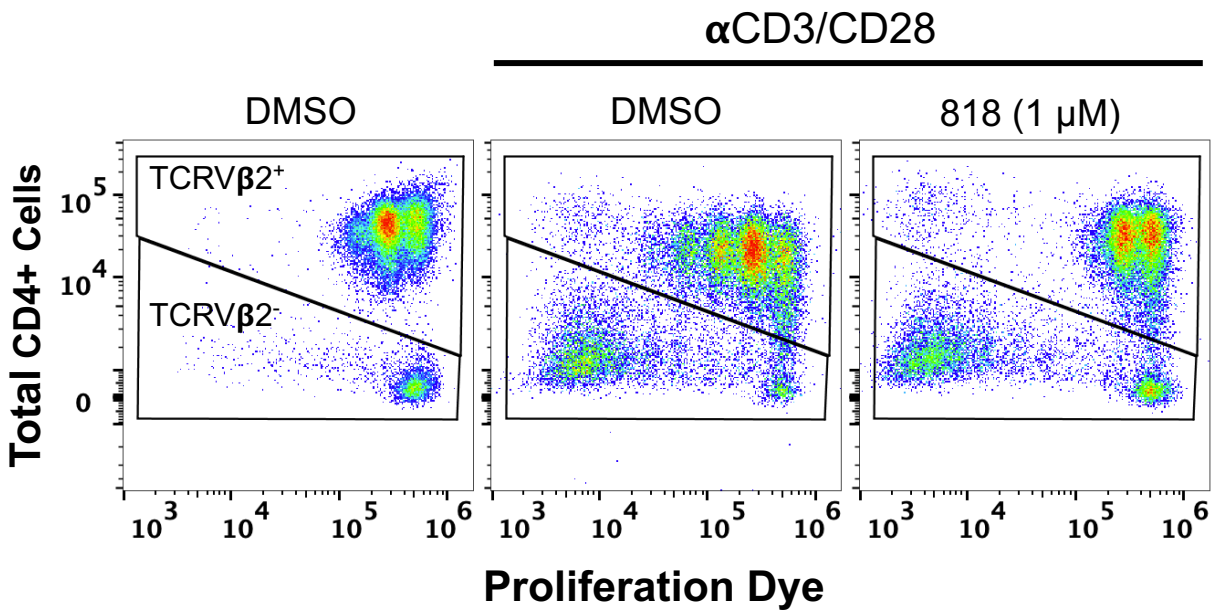


pERK Suppression

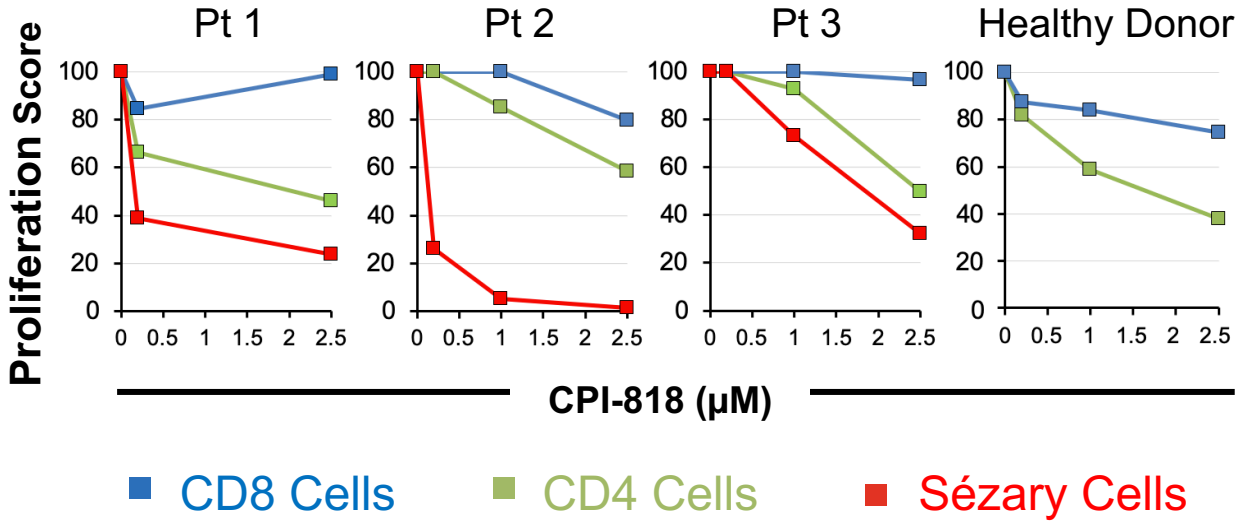


CPI-818 Preferentially Inhibits Sézary Cells

Gating Strategy



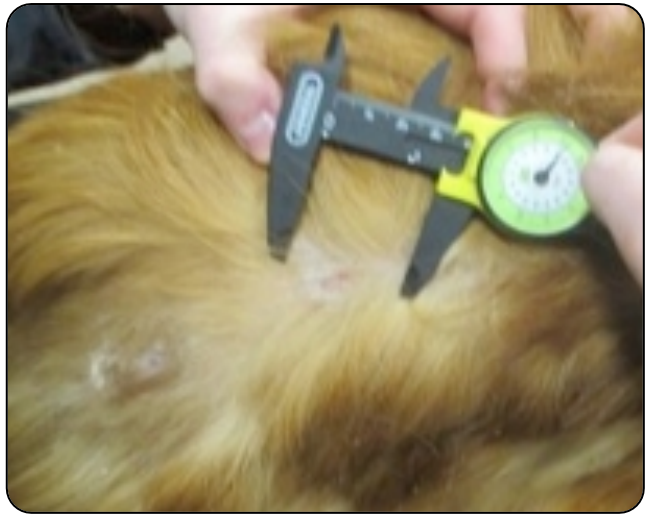
Inhibition of Cell Division



Sézary cells were more sensitive than normal CD4+ or CD8+ T cells to the anti-proliferative effect of CPI-818

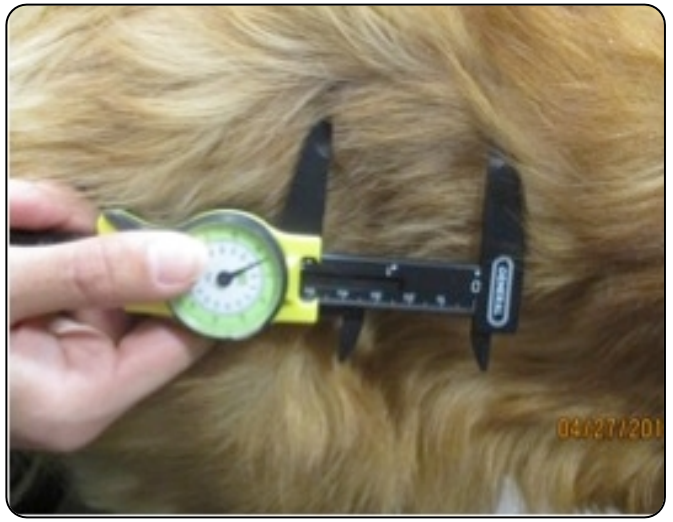
Spontaneous T Cell Lymphoma in Companion Animals

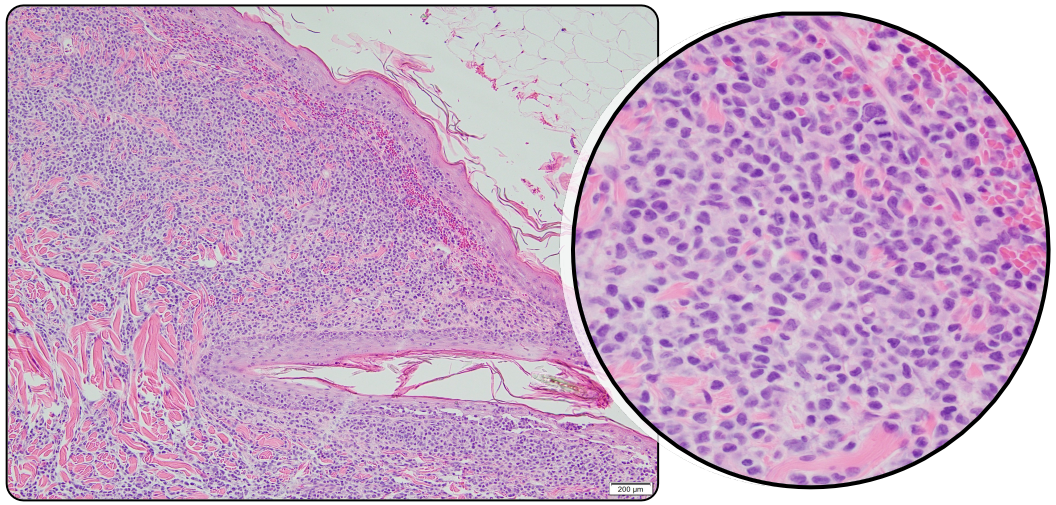
Evaluation of CPI-818 in a dog achieving CR

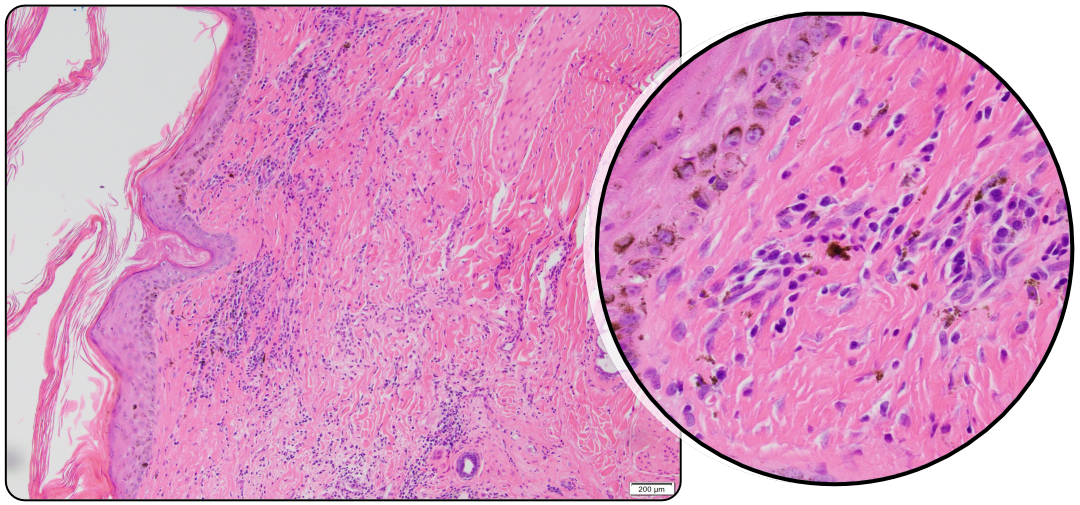


CTCL Patient
11 year old, Male
Golden Retriever

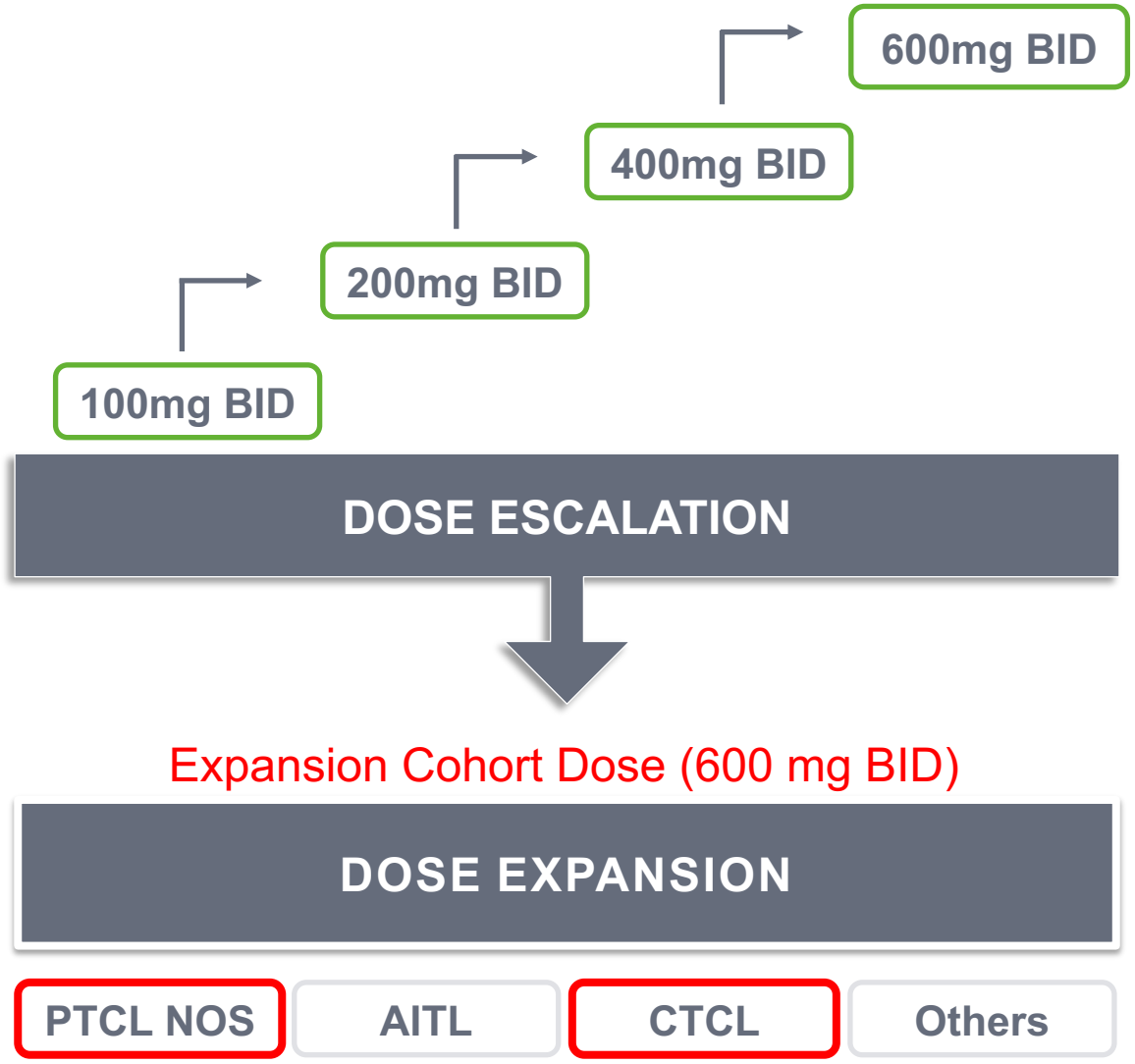
4 months







CPI-818 Ph 1/1b Clinical Trial Design in T cell Lymphomas



Design

- Dose escalation with 3+3 (+ optional 3) design
- Ascending dose levels of CPI-818
- Enroll patients with various types of T-cell lymphoma (PTCL and CTCL) who have progressed on, refractory to, relapsed, or intolerant to at least 2 standard therapies
- Patients will receive CPI-818 orally BID continuously up to sixteen 21-day cycles, until progression or unacceptable toxicity
- Expansion focused on PTCL-NOS and CTCL

Objectives

- Primary: To establish Safety / tolerability and determine MTD or MAD, as well as Expansion Cohort Dose
- Secondary: PK/PD, biomarkers and efficacy

CPI-818-001 Study
Patient Characteristics

	CPI-818 100mg BID (N=4)	CPI-818 200mg BID (N=3)	CPI-818 400mg BID (N=5)	CPI-818 600mg BID (N=13)	Total (N=25)
Age (yrs), median (range)	51 (29, 75)	59 (57, 60)	69 (42, 80)	62 (34, 84)	62 (29,84)
Gender, male N (%)	3 (75%)	0 (0%)	3 (60%)	6 (46.2%)	12 (48%)
No. of prior therapies, median (range)	3 (2, 4)	3 (2, 6)	7 (3, 12)	5 (1,9)	4 (1,12)
Histologies	**N**	**N**	**N**	**N**	
Angioimmunoblastic T cell lymphoma	1	1	0	0	2
Anaplastic large cell lymphoma	1	0	0	0	1
Adult T cell leukemia/lymphoma	1	0	0	0	1
CTCL (Mycosis fungoides)	0	0	1	5	6
CTCL (Sézary syndrome)	0	1	4	1	6
PTCL- NOS	1	1	0	7	9

*Data cut off date: 05Oct2020

Most Common Adverse Events (≥ 2 patients)

Adverse Events N (%)	100mg (N=4)	200mg (N=3)	400mg (N=5)	600mg (N=13)	Total (N=25)
Subjects with any TEAE	4 (100.0)	3 (100.0)	4 (80.0)	11 (84.6)	22 (88.0)
Fatigue	0 (0.0)	1 (33.3)	3 (60.0)	3 (23.1)	7 (28.0)
Pruritus	1 (25.0)	2 (66.7)	2 (40.0)	2 (15.4)	7 (28.0)
Pyrexia	0 (0.0)	1 (33.3)	1 (20.0)	3 (23.1)	5 (20.0)
Nausea	1 (25.0)	1 (33.3)	1 (20.0)	0 (0.0)	3 (12.0)
Actinic keratosis	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (8.0)
Fall	0 (0.0)	0 (0.0)	1 (20.0)	1 (7.7)	2 (8.0)
Headache	0 (0.0)	1 (33.3)	0 (0.0)	1 (7.7)	2 (8.0)
Hypercalcaemia	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)
Hyperuricemia	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (8.0)
Musculoskeletal pain	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	2 (8.0)
Oedema peripheral	0 (0.0)	0 (0.0)	1 (20.0)	1 (7.7)	2 (8.0)
Rash	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	2 (8.0)
Vomiting	1 (25.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (8.0)

- No DLTs observed and MTD not reached
- Majority of AEs Grade 1-2, no increase in AEs as a function of dose
- Grade 3 AE reported in 7 patients
  - All assessed as not-related to study drug (due to underlying disease or progression)
- No reports of opportunistic infections

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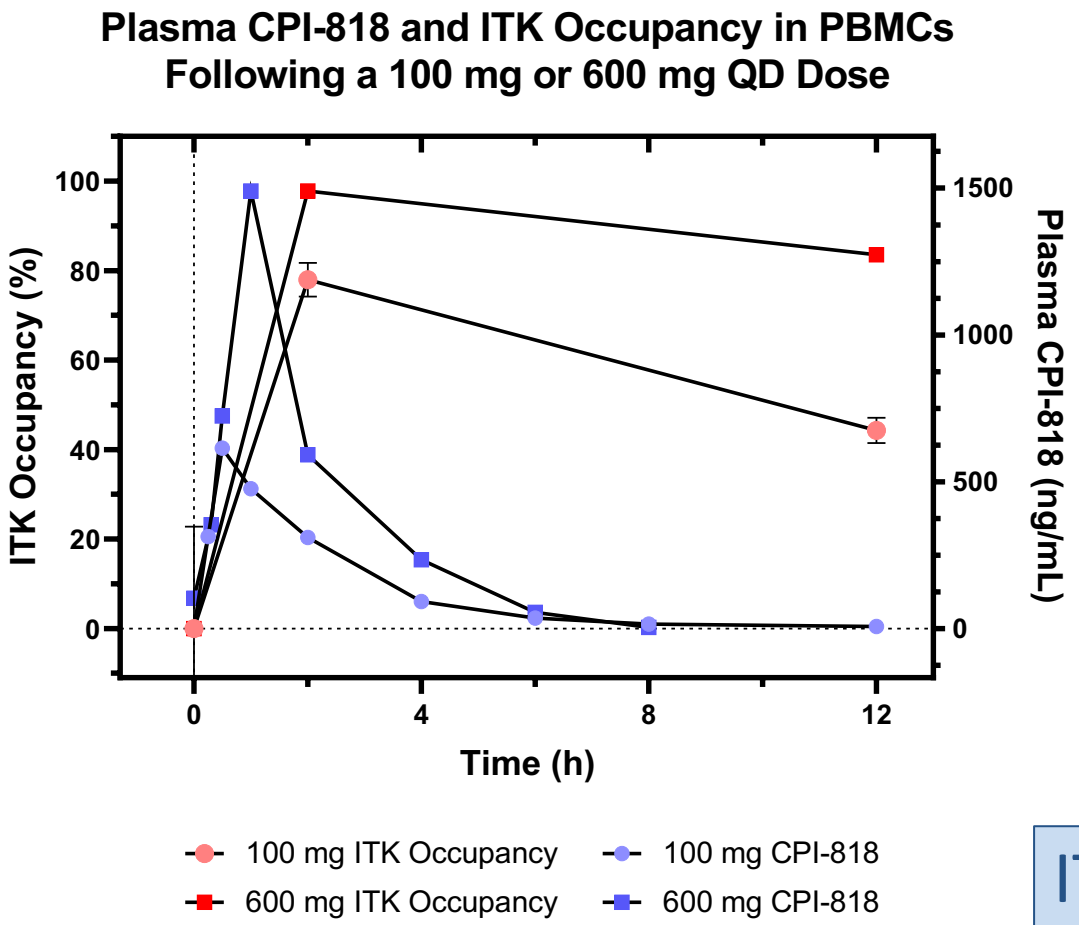
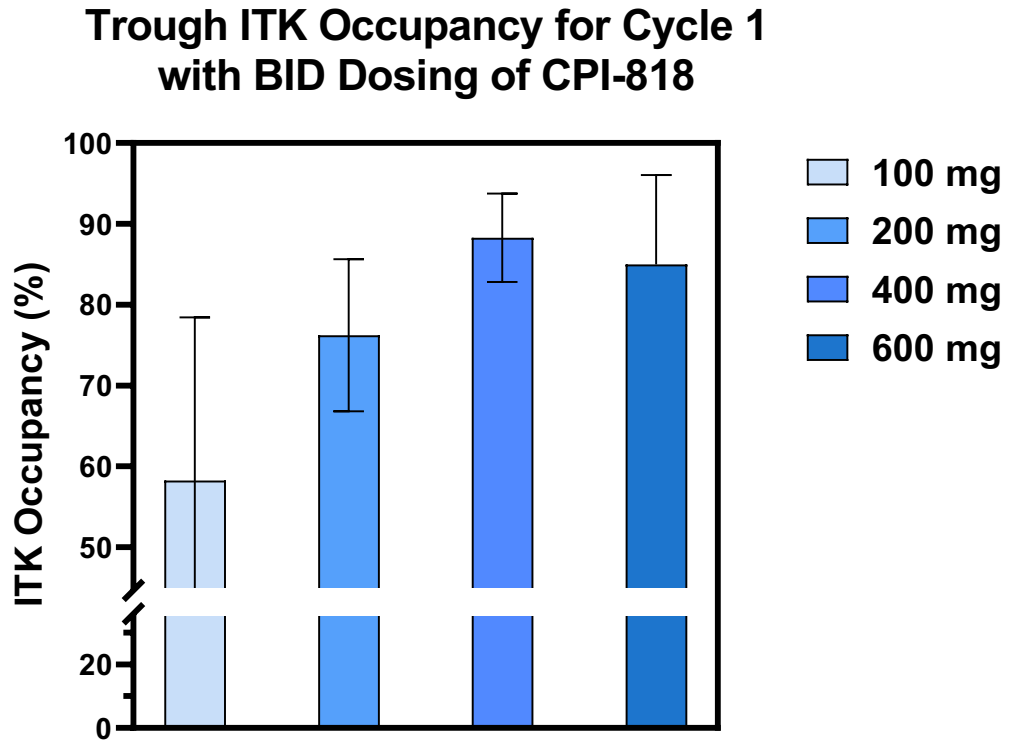
PK and Occupancy Summary from Cohorts 1, 2, 3 and 4

Occupancy is increasing as a function of dose, BID Dosing Required

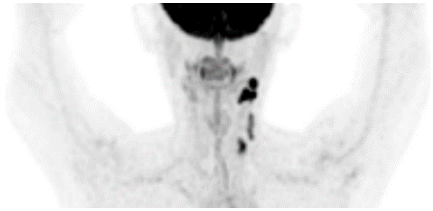




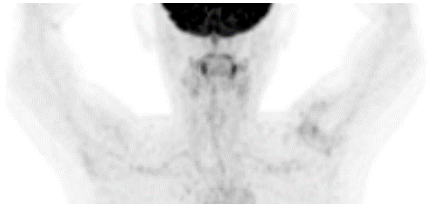
ITK biosynthesis rate dictates BID dosing
>75% trough occupancy at doses ≥ 200 mg

Summary from the Escalation and Ongoing Expansion in the PTCL-NOS Cohort

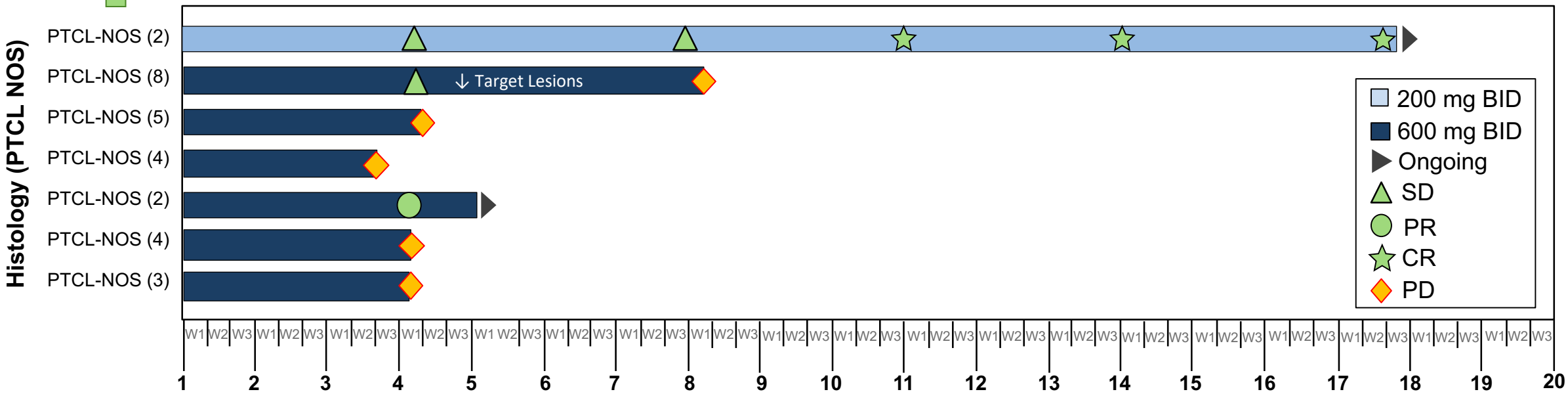
Baseline PET



Week 30 PET

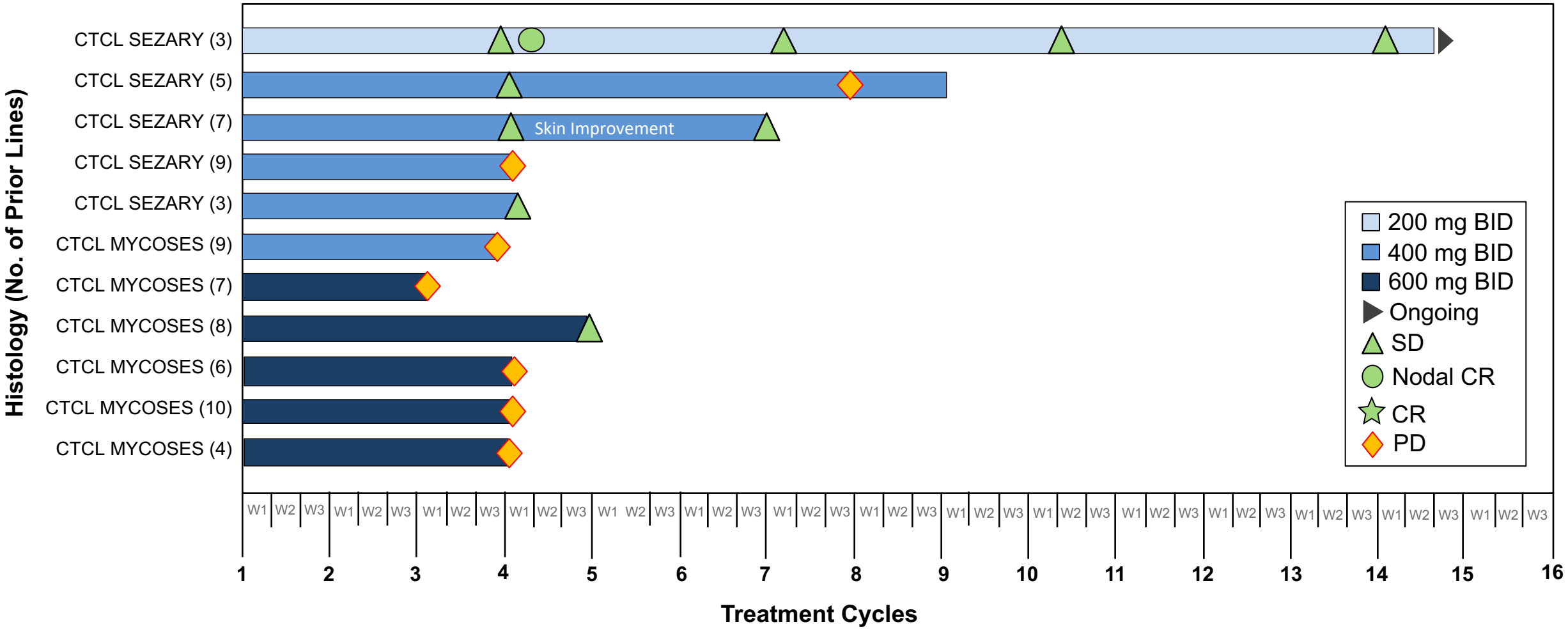


ORR: 1CR, 1PR out of 7 evaluable at doses of ≥ 200 to 600 mg BID



*Data cut off date: 05Oct2020

Summary from the Escalation and Ongoing Expansion in the CTCL Cohort



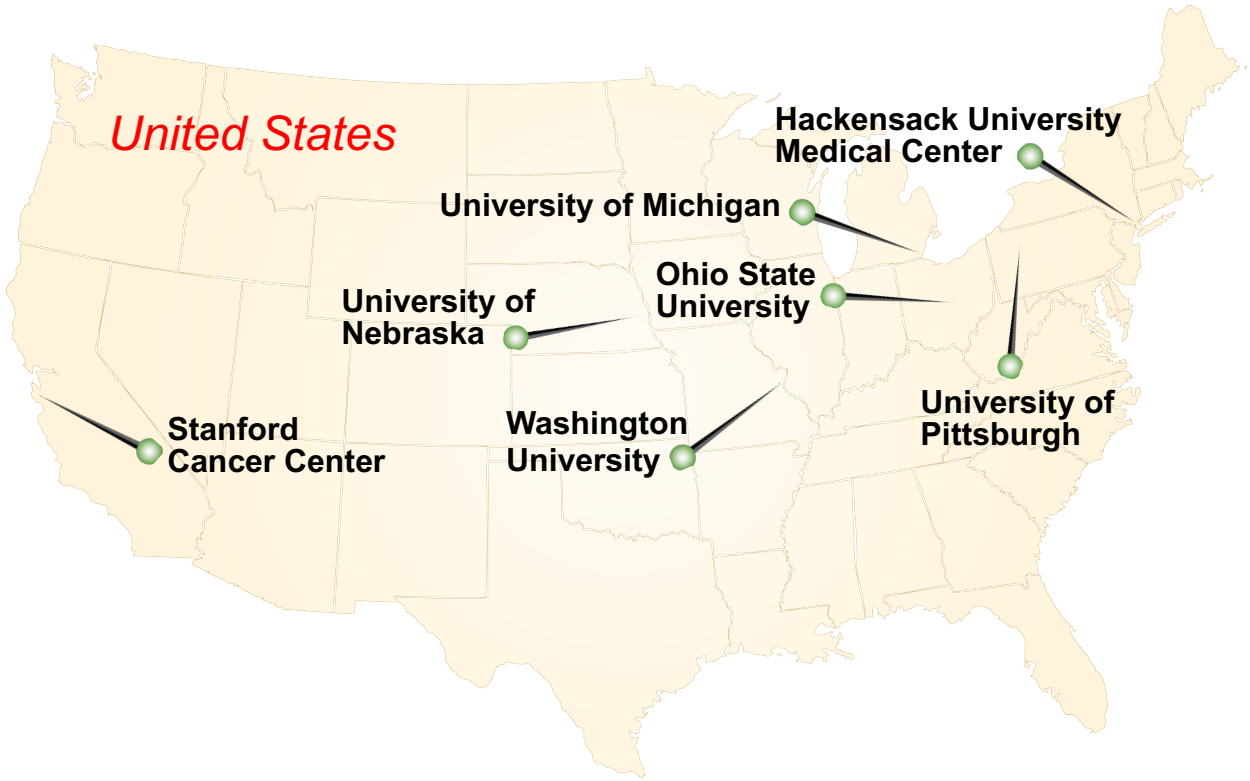
*Data cut off date: 05Oct2020

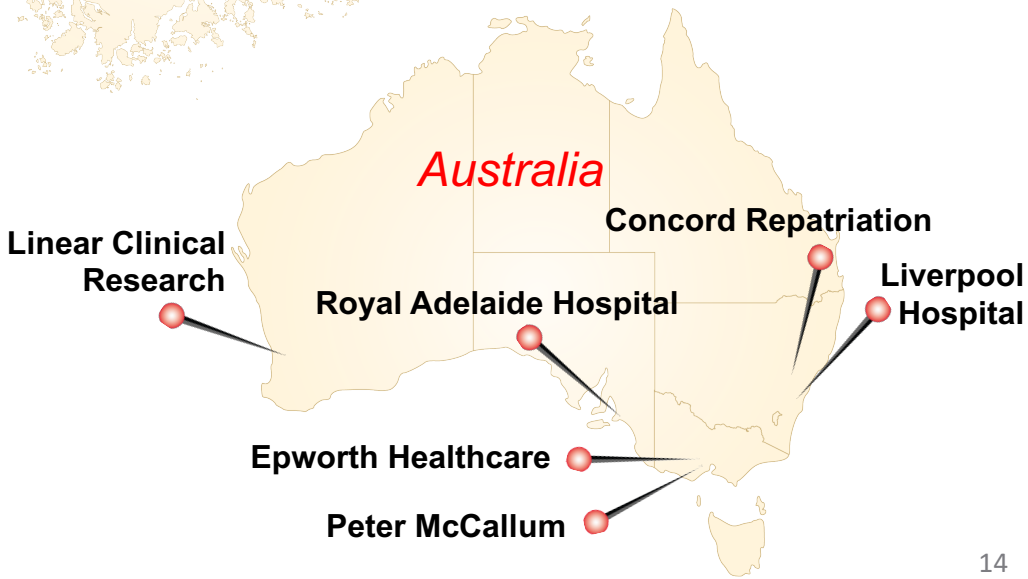
Conclusion

- CPI-818 is a selective, covalent inhibitor of ITK (sparing RLK and BTK) that blocks signal transduction in endpoints downstream of T-cell activation
- The dose-escalation part of the CPI-818-001 trial demonstrated that the 100, 200, 400 and 600 mg BID doses are well tolerated.
- 600 mg BID which yields near maximal ITK inhibition was selected as expansion cohort dose.
- At doses which yield good ITK inhibition, clinical activity was observed in PTCL-NOS and CTCL including 2/7 objective response (1 CR and 1 PR) in PTCL-NOS.
- Disease specific expansion cohorts for PTCL-NOS and CTCL are enrolling patients at a dose of 600 mg BID.

Acknowledgements

- **Participating Centers and Investigators**:





We thank the patients and their families.