



# A Phase I Dose Escalation Study of the Btk Inhibitor PCI-32765 in Relapsed and Refractory B Cell Non-Hodgkin Lymphoma



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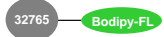
## INTRODUCTION

- B cell receptor (BCR) activation stimulates multiple downstream tyrosine kinases
- Signaling through the BCR sustains B-cell malignancies; inhibition of tonic activation of signaling through the BCR may induce apoptosis
- Bruin's tyrosine kinase (Btk) is activated by signaling through the BCR. Functional null mutations of Btk leads to X-linked agammaglobulinemia, characterized by a lack of mature B cells.
- PCI-32765 is a potent and selective covalent inhibitor of Btk that targets Cys-481 in the enzyme active site
- PCI-32765 inhibits BCR signaling, induces apoptosis in lymphoma cell lines and inhibits disease in multiple animal models of lymphoma

## STUDY DESIGN

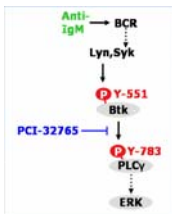
- Phase I, multicenter, open-label trial of PCI-32765 for patients with relapsed/refractory B-cell lymphoma
- Each cycle equals 28 daily treatments followed by a 7-day rest
- Six-patient cohorts receive escalating oral doses (1.25, 2.5, 5.0, 8.3, 12.5, 17.5 mg/kg) until maximum tolerated dose (MTD) established
- Dose limiting toxicity (DLT): Grade  $\geq 3$  non-hematologic toxicity despite symptomatic therapy; Grade  $\geq 3$  QTc prolongation; Grade 4 neutropenia or thrombocytopenia; Dosing delay due to toxicity for  $>7$  days
- Dose Escalation: If  $<2$  DLT observed per cohort, dose escalation will proceed as planned; if  $\geq 2$ , MTD will be prior cohort
- Response assessments performed after cycles 2, 4 and 6
- Blood samples collected on dosing day 1 for determination of plasma concentrations of PCI-32765
- Pharmacodynamic samples collected on Days 1, 2, and 8
  - Basophil assay determines inhibition of anti-IgE stimulated degranulation, a process dependent upon Btk
  - Phospho-ERK assay determines inhibition of signaling downstream of the BCR, as ERK pathway is critical for B cell survival and function

### A Novel Pharmacodynamic Probe Assay



- Consists of PCI-32765, spacer and fluorophore
- Covalently binds Btk; can be detected by fluorescent scanning
- Assays occupancy of the active site of Btk by the drug in PBMCs

### Btk and BCR Signaling



## Patient Characteristics

N=16
Cohort 1 = 7; Cohort 2 = 9
Median Age = 65 (49-82)
Gender
Male = 9; Female = 7
Disease Subtypes
Follicular lymphoma (FL) (N= 7)
Diffuse Large B-Cell Lymphoma (DLBCL) (N= 3)
Mantle Cell Lymphoma (MCL) (N= 3)
Chronic lymphocytic leukemia (CLL/SLL) (N=3)
Prior Therapies
Median number of prior therapies= 3 (range 1-4)
Prior Rituximab= 14/16
Prior CHOP= 11/16
Prior Autologous Stem Cell Transplantation= 2/16
Prior Fludarabine= 4/16
Prior Radioimmunotherapy= 1/16
Prior Bortezomib= 2/16

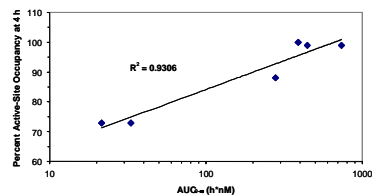
CHOP=cyclophosphamide, adriamycin, vincristone, prednisone

## Pharmacokinetics

N	Dose Level (mg/kg/d)	C <sub>max</sub> <sup>a</sup> (nM)	T <sub>max</sub> (h)	AUC <sub>0-∞</sub> (nM·h)	t <sub>1/2</sub> (h)
7	1.25	82.0 (85%) <sup>b</sup>	1.14 (33%)	302 (83%)	4.92 (66%)

<sup>a</sup> LLOQ was 0.114 nM  
<sup>b</sup> Mean (%CV)

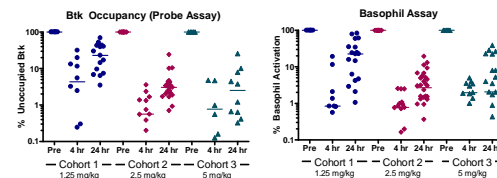
Pharmacokinetic data from cohort 1 (1.25 mg/kg). Bioanalytical data were evaluated using WinNonlin (version 5.01). Terminal half-life (t<sub>1/2</sub>) values derived from data obtained 4 to 24 hour post dose



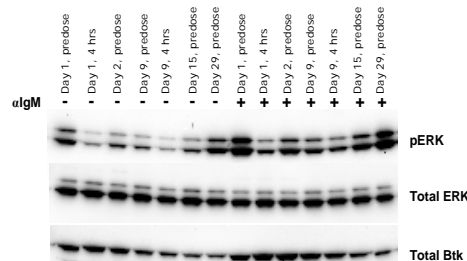
Relationship between systemic drug exposure and occupancy of the active site of Btk in PBMCs (6 patients in cohort 1)

## RESULTS

### Pharmacodynamics



$\geq 99\%$  occupancy of the active site of Btk (left) and inhibition of basophil degranulation (right) by PCI-32765. Each point represents a single time point and patient; the line represents the median



Inhibition of basal and stimulated pERK in PBMCs from a patient with chronic lymphocytic leukemia (CLL) treated at 2.5 mg/kg PCI-32765 daily

### Adverse Events > Grade 1 (Cohorts 1 and 2)

- DLT (neutropenia) (N=1, cohort 2)
- Grade 4 hypokalemia (N=1, cohort 2)\*
- Grade 3 hypophosphatemia (N=1, cohort 2)\*
- Grade 2 fatigue (N=2), thrombocytopenia (N=2), nausea (N=2), neuropathy (N=1), cough (N=1), edema (N=1), lymph node pain (N=1), myalgia (N=1), glaucoma (N=1), cramps (N=1), vomiting (N=1)

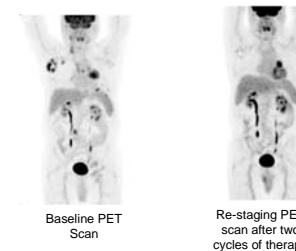
\*Same patient experienced both toxicities

### Responses

Cohort 1 (1.25 mg/kg) N = 7
Partial Response = 2 (FL and MCL)
Stable Disease = 1 (MCL)
Cohort 2 (2.5 mg/kg) N = 9
Partial Response = 3 (1MCL, 2 CLL/SLL)
Stable Disease=2 (FL and MCL)
Overall Response Rate (ORR)= 5/16 (31%)
Median Duration of Response not reached

All PR and SD patients in Cohorts 1 & 2 are ongoing, with patients continuing on study

### Response in a patient with MCL (cohort 1)



## CONCLUSIONS

- PCI-32765 is a novel, well-tolerated and active oral agent
- Evidence of drug activity in the first two cohorts evaluated
  - Overall response rate = 5/16 (31%)
- MTD not reached (Cohort 1 had no DLT; cohort 2 had 1/7 DLT)
- Good correlation (R<sup>2</sup> = 0.93) found between Btk active-site occupancy in PBMCs (mean of Days 1 and 8) and PCI-32765 plasma AUC<sub>0-∞</sub> (Day 1) at the 1.25 mg/kg dose
- PD assays suggest that at 2.5 mg/kg daily, PCI-32765 fully binds its target Btk, fully inhibits basophil degranulation, and blocks basal and stimulated pERK in CLL cells
- Accrual is ongoing with planned dose escalation to three dose levels above maximum occupancy dose, as occupancy in the tumor may be less than measured occupancy in the blood

Conflict of interest statement: AMS, MS, LAH, JJB, and AH are employees of Pharmacyclics, Inc.