

# The Btk inhibitor PCI-32765 is highly active and well tolerated in patients with relapsed/refractory B cell malignancies: Final results from a phase I study

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# Disclosures

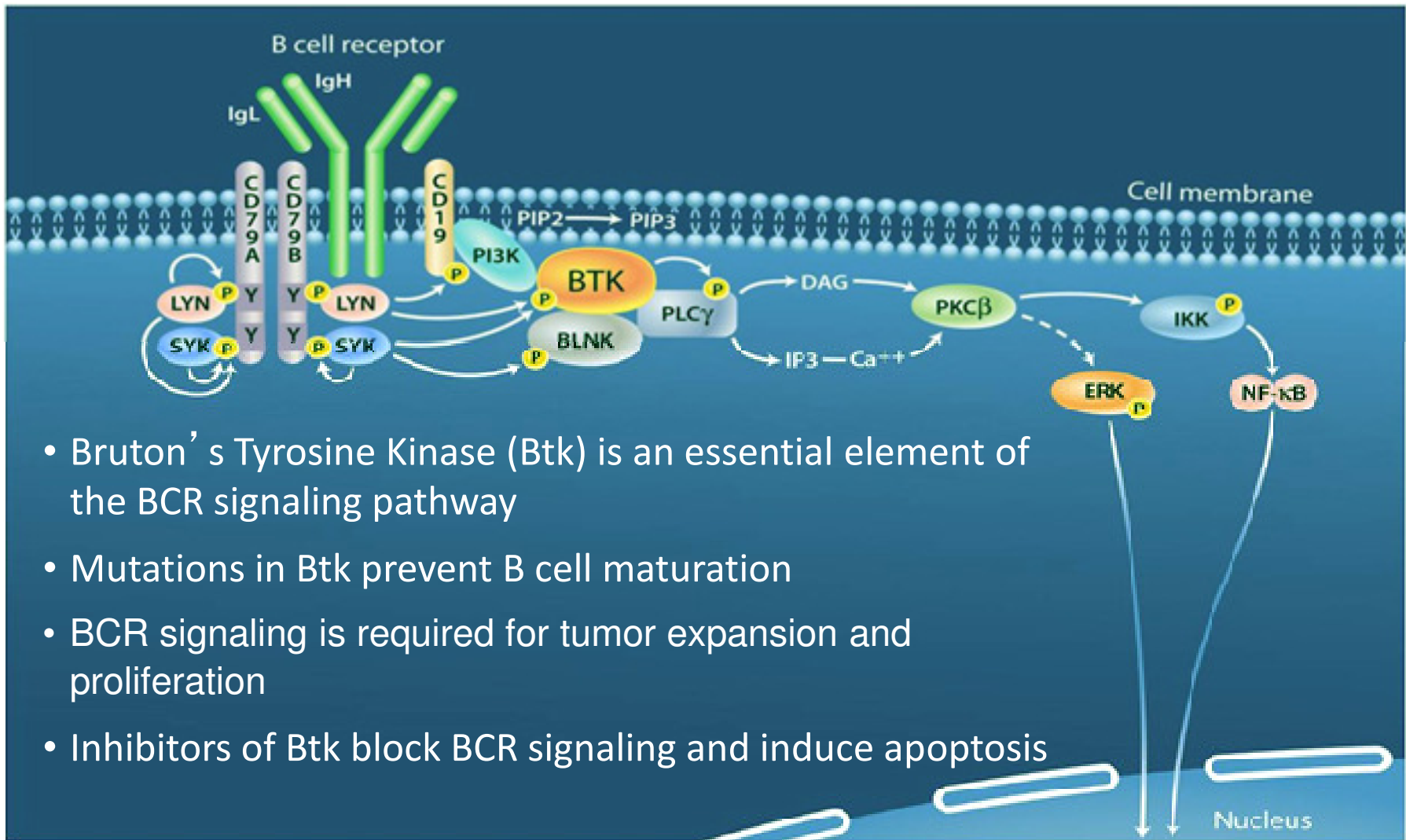
## Ranjana Advani, MD

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- RESEARCH FUNDING/PI: Pharmacyclics
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- SCIENTIFIC ADVISORY BOARD: Pharmacyclics

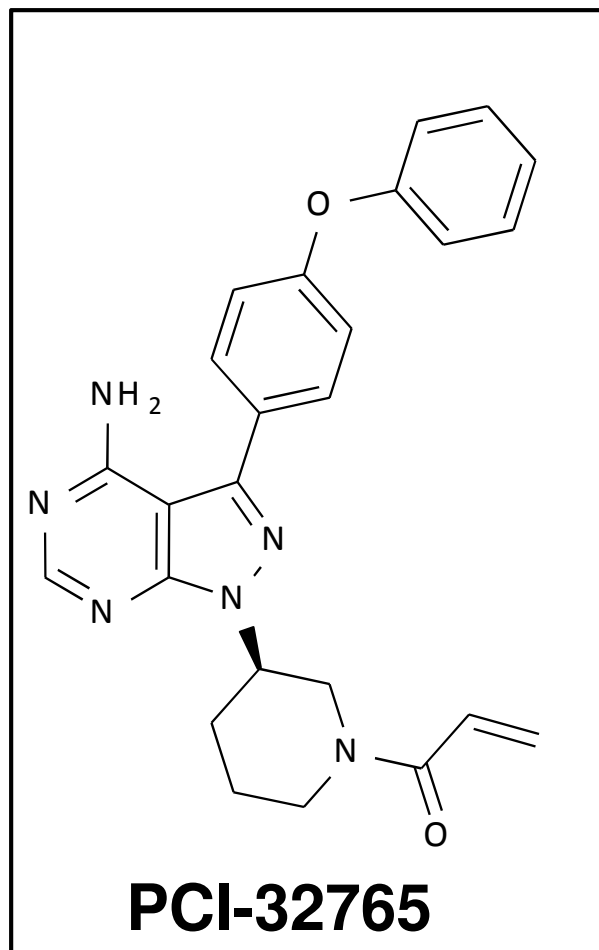
# Bruton's Tyrosine Kinase (Btk)

## A Critical B-Cell Signaling Kinase



- Bruton's Tyrosine Kinase (Btk) is an essential element of the BCR signaling pathway
- Mutations in Btk prevent B cell maturation
- BCR signaling is required for tumor expansion and proliferation
- Inhibitors of Btk block BCR signaling and induce apoptosis

# PCI-32765: Novel Small Molecule Inhibitor of BTK



- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition at IC<sub>50</sub> = 0.5 nM
- Orally bioavailable with daily dosing resulting in 24-hr target inhibition
- Inhibits BCR signaling and has activity in spontaneous canine B-cell lymphoma
- In CLL cells promotes apoptosis, inhibits ERK1/AKT phosphorylation, NF-κB DNA binding, CpG mediated proliferation
- Inhibits CLL cell migration and adhesion

Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075, 2010  
Herman SEM et al: Blood. 2011 Mar 21. [Epub]  
Ponader, et al., Proc ASH, 2010

# Objectives

- **Primary Objectives**
  - Establish the safety and the maximum tolerated dose (MTD)
  - Determine the pharmacokinetics of study drug
  - Measure PBMC Btk receptor occupancy as assessed by a fluorescent probe assay
- **Secondary Objective**
  - Evaluate tumor response

# Study Design

- Dose-Escalation Study
  - Cohorts  $n \geq 6$  patients
  - Escalate to MTD or 3 dose levels above complete Btk active site occupancy
  - Tumor assessment performed every 2 cycles\*

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- Dosing
  - 1.25, 2.5, 5.0, 8.3, 12.5 mg/kg/d PO (Cycle=28 days + 7-days rest)
  - 2 continuous dosing cohorts (Cycle=35 days)
    - 8.3 mg/kg/day PO
    - 560 mg/day (fixed dose) PO
  - Pts with SD or > roll-over to extension trial after six months of therapy

\* Cheson, et al, J Clin Oncol, 2007; 2 Hallek, et al, Blood, 2008

# Key Inclusion / Exclusion Criteria

- Relapsed or refractory B-cell malignancies
- ECOG  $\leq 1$
- Prior treatment:  $\geq 1$  and  $\leq 4$  (except for CLL)
- Measurable disease
  - $\geq 2$  cm diameter for NHL or  $\geq 5000$  leukemia cells/mm<sup>3</sup> for CLL or IgM level  $\geq 1000$  mg/dL + BM infiltration for WM
- No known CNS involvement or uncontrolled infection
- Laboratory:
  - Platelets count  $\geq 75,000/\mu\text{L}$  and ANC  $\geq 1500/\mu\text{L}$  (unless CLL with cytopenias secondary to BM involvement)
  - Adequate renal /hepatic function

# Baseline Characteristics (N=56)

<b>Median age, years (range)</b>	65 (41-82)
<b>M/ F, n (%)</b>	38 (68) / 18 (32)
<b>Histology, n (%)</b>	
FL	16 (29)
CLL/SLL	16 (29)
MCL	9 (16)
DLBCL	7 (16)
MZL / MALT	4 (7)
WM	4 (7)
<b>Median prior therapies, number (range)</b>	3 (1-10)

# Results: Enrollment

## Phase IA Cohorts

I: 1.25 mg/kg/day  
n=7

II: 2.5 mg/kg/day  
n=9

III: 5.0 mg/kg/day  
n=6

IV: 8.3 mg/kg/day  
n=8

CD: 8.3 mg/kg/day  
(Continuous Dosing)  
n=10

V: 12.5 mg/kg/day  
n=7

CD2: 560 mg/day  
(Fixed Continuous Dosing)  
n=9

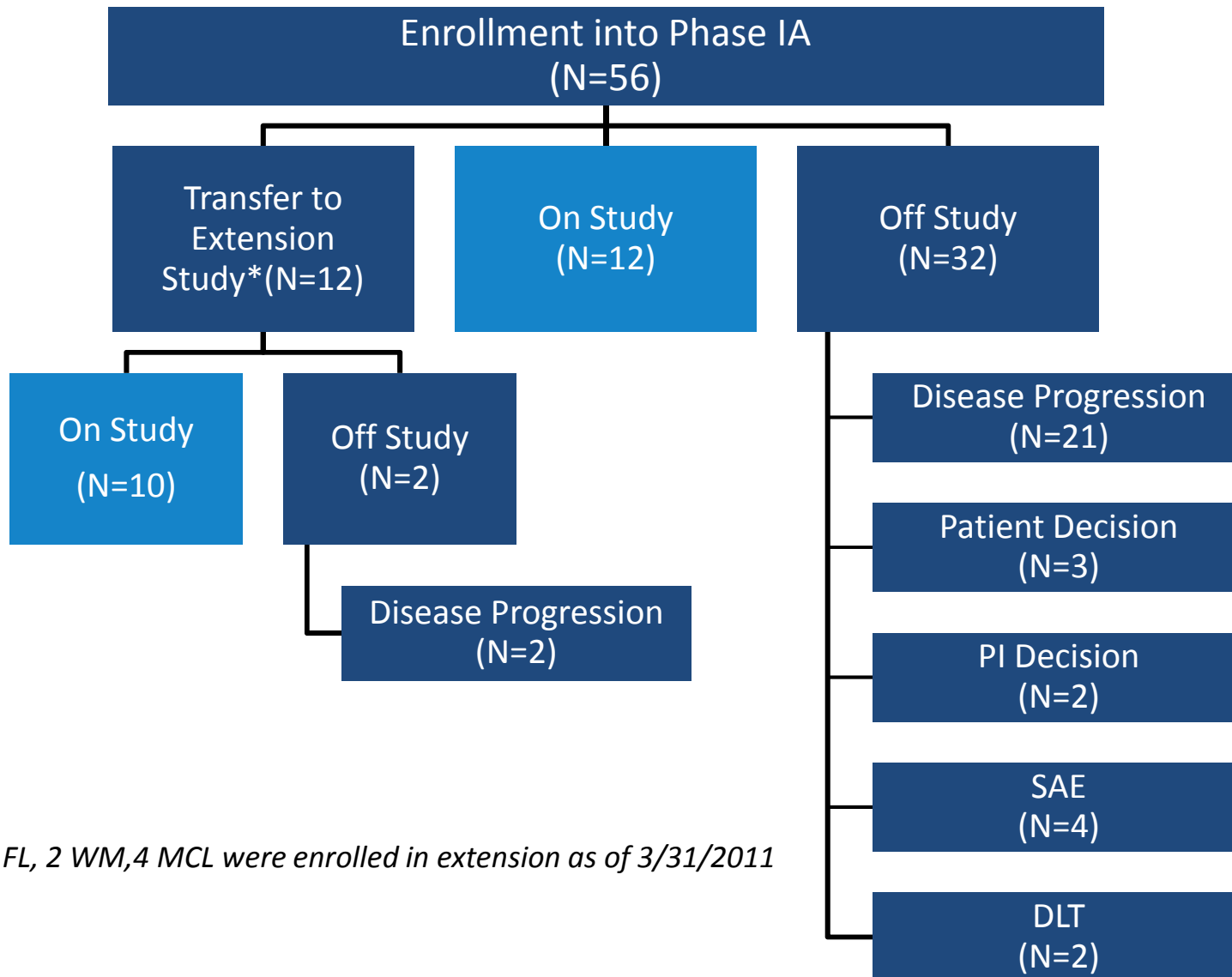
## Extension Cohorts\*

420: 420 mg/day  
(Fixed Continuous Dosing)  
n=2

560: 560 mg/day  
(Fixed Continuous Dosing)  
n=9

*\*1 additional subject dosed at 120 mg/day  
(Fixed Continuous Dosing)*

# Disposition



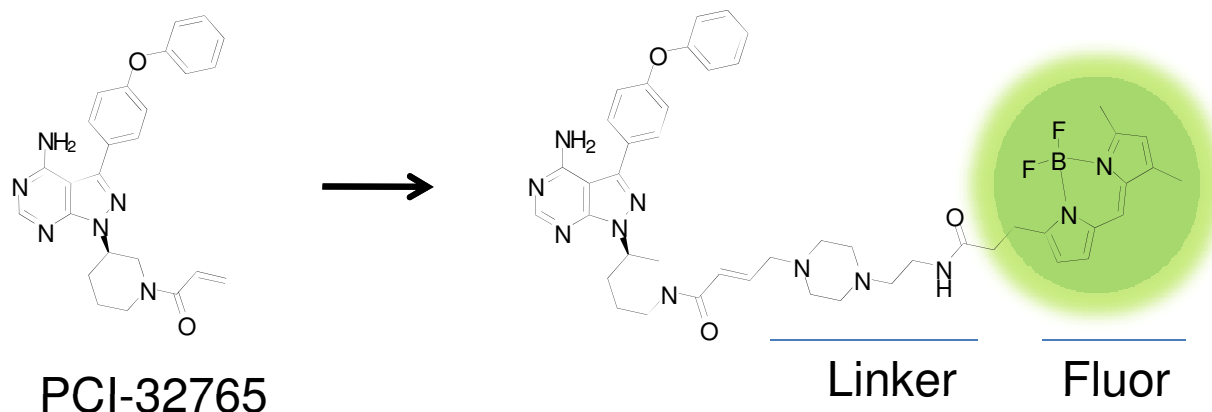
*\*5CLL, 1 FL, 2 WM, 4 MCL were enrolled in extension as of 3/31/2011*

# PCI-32765 : PK Summary

- Rapidly absorbed and eliminated after oral administration with mean  $T_{max}$  ranging from 1 to 2 hours and mean  $T_{1/2}$  ranging from 4-8 hours
- Exposure ( $C_{max}$  and AUC) generally increases in a dose-proportional manner
- No accumulation of PCI-32765 after repeated daily oral dosing

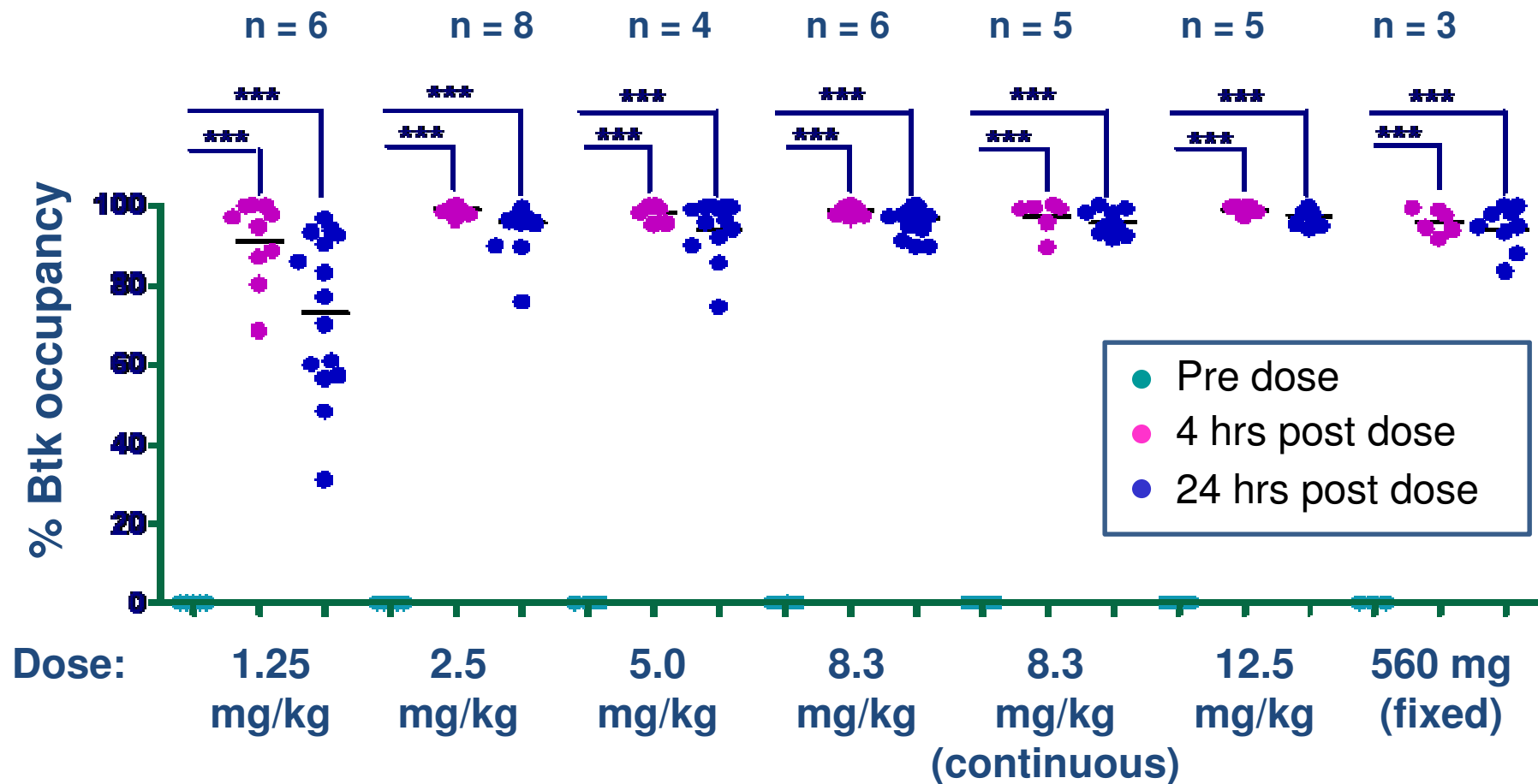
Dose (mg/kg)	N	Mean [%CV] $AUC_{\infty}$ (ng*h/mL)
1.25	7	134 [82%]
2.5	9	495 [83%]
5	6	419 [95%]
8.3	15	956 [78%]
12.5	7	1550 [57%]

# Fluorescent probe assay to detect Btk occupancy by drug



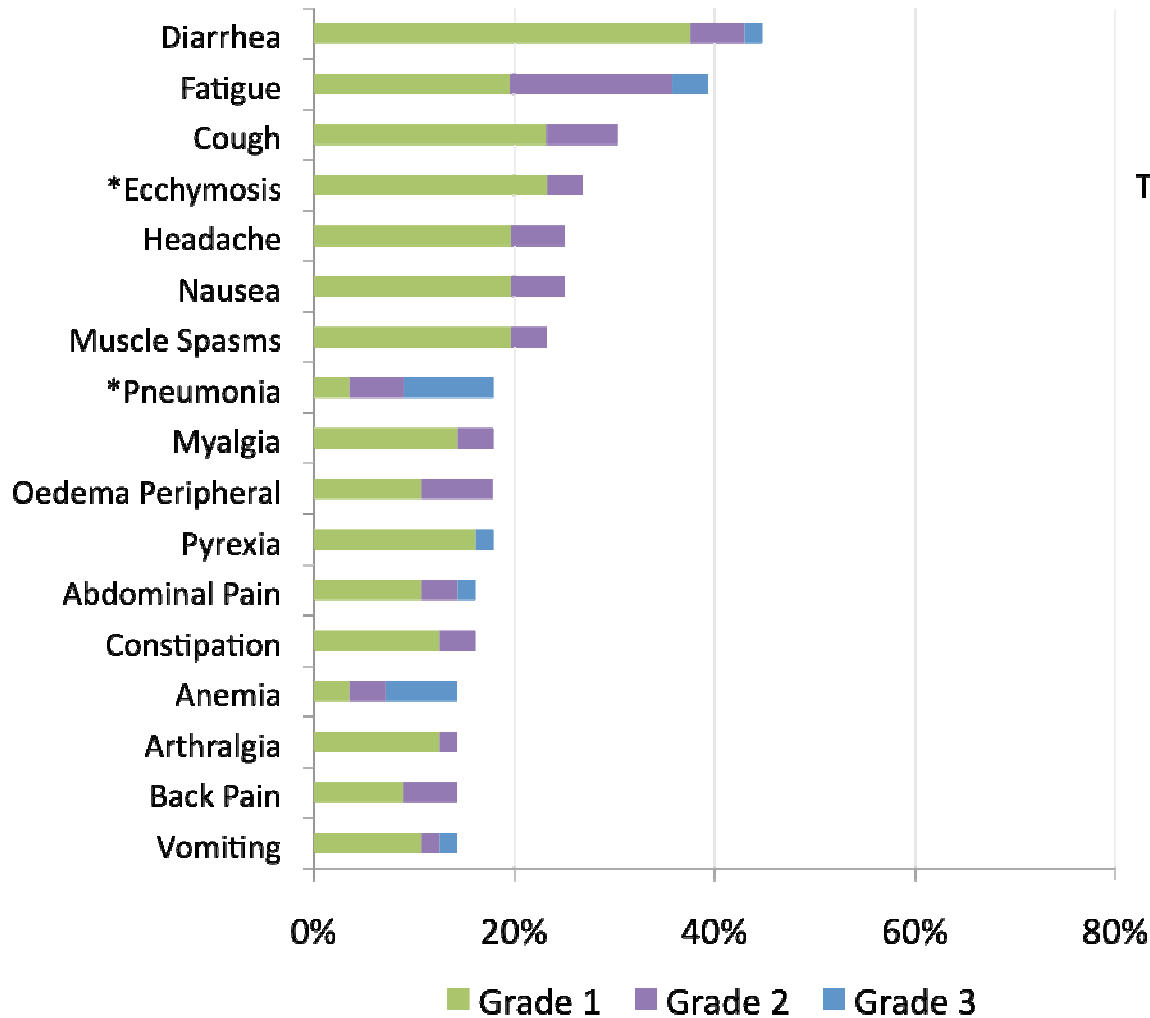
- Fluorescent probe used to determine % PCI-32765 bound to Btk in PBMCs
  - Samples collected in cohort I at baseline, 4h and 24 h on d 1 & 8
- Probe binds to Btk active site to create a fluorescent complex
- Probe cannot bind if PCI-32765 is already there (reduced fluorescent signal)

# Complete occupancy of Btk at doses $\geq 2.5$ mg/kg/day

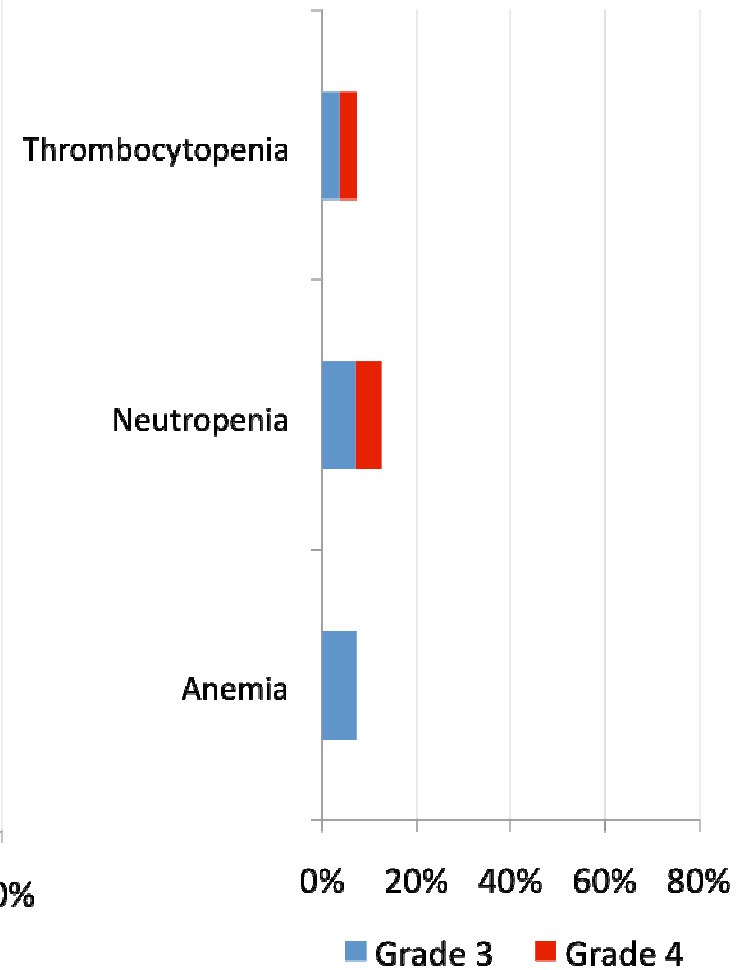


# Adverse Events

## Most Common Adverse Events<sup>1</sup>



## Grade 3/4 Hematology<sup>2</sup>



<sup>1</sup> AEs >14%

\* Ecchymosis and pneumonia are combination of several preferred terms

<sup>2</sup> Based on clinical review of AE and Lab data

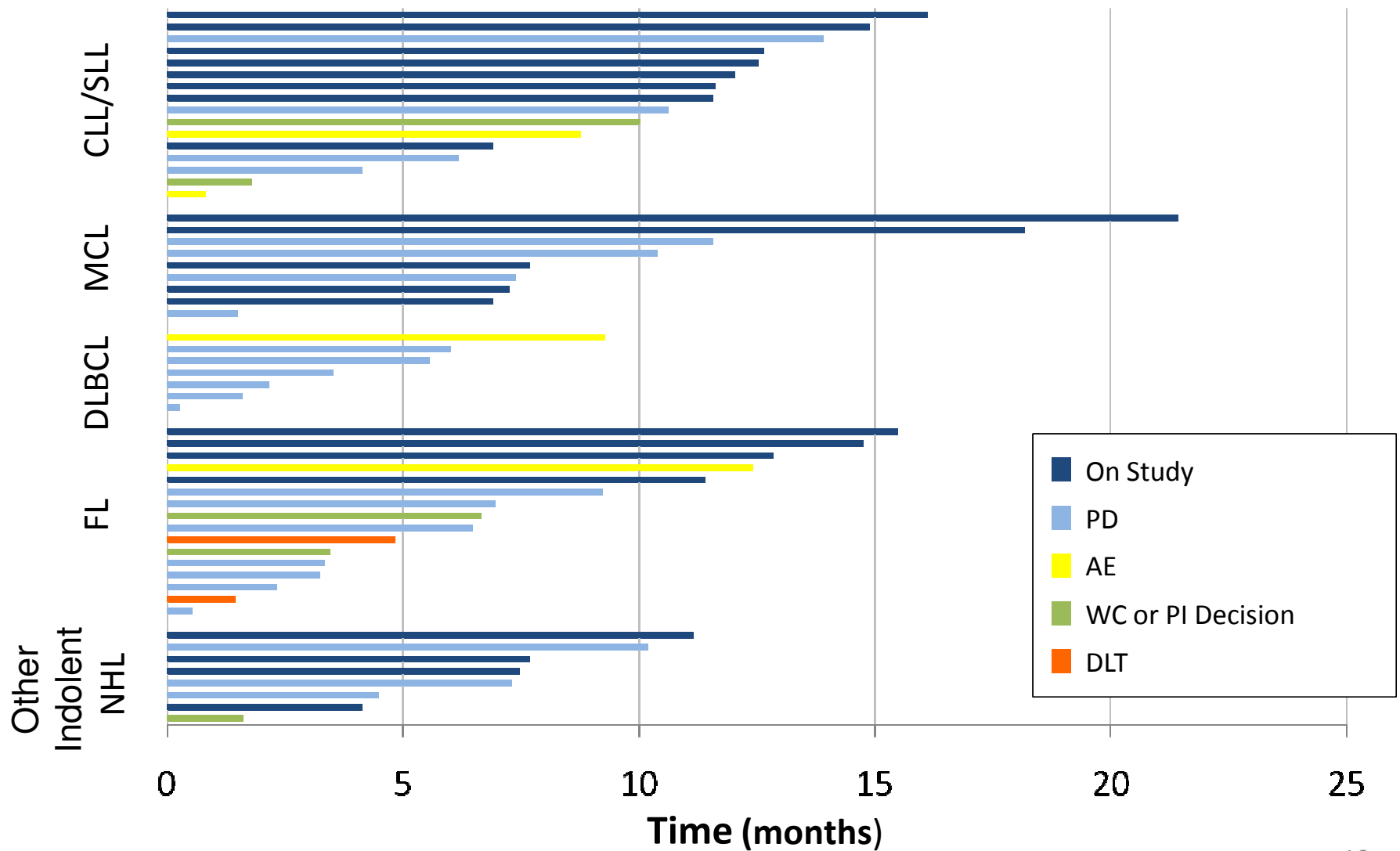
# Best Response According To Histology

	N	CR	PR	SD	PD	NE	ORR% ITT (n=56)	ORR% Eval (n=50)
CLL/SLL	16	1	10	3*		2	69%	79%
MCL	9	3	4	1	1		78%	78%
WM	4		3**	1			75%	75%
FL	16	3	3	3	4	3	38%	46%
MZL/MALT	4		1	1	1	1	25%	33%
DLBCL	7		2	1	4		29%	29%
<b>TOTAL</b>	<b>56</b>	<b>7</b>	<b>24</b>	<b>9</b>	<b>10</b>	<b>6</b>	<b>55%</b>	<b>62%</b>

\* 1 CLL pt had nodal response with lymphocytosis;

\*\* Based on IgM

# Time on Treatment





# Conclusions

## Oral BTK inhibitor PCI-32765

- Well tolerated with a modest toxicity profile
- Majority of adverse events were Grade 1 or 2 in severity and easily managed/reversible
- No cumulative toxicity with treatment duration > 6 months
- Continuous occupancy of Btk at doses  $\geq 2.5$  mg/kg
- Significant activity with durable responses observed in multiple histologic subtypes
- Data strongly support continued clinical evaluation in various B-cell malignancies
- Phase II trials ongoing in MCL, DLBCL and CLL