

# **Btk Inhibitor PCI-32765 Monotherapy Induces Objective Responses in Patients with Relapsed Aggressive NHL: Evidence of Antitumor Activity from a Phase I Study**

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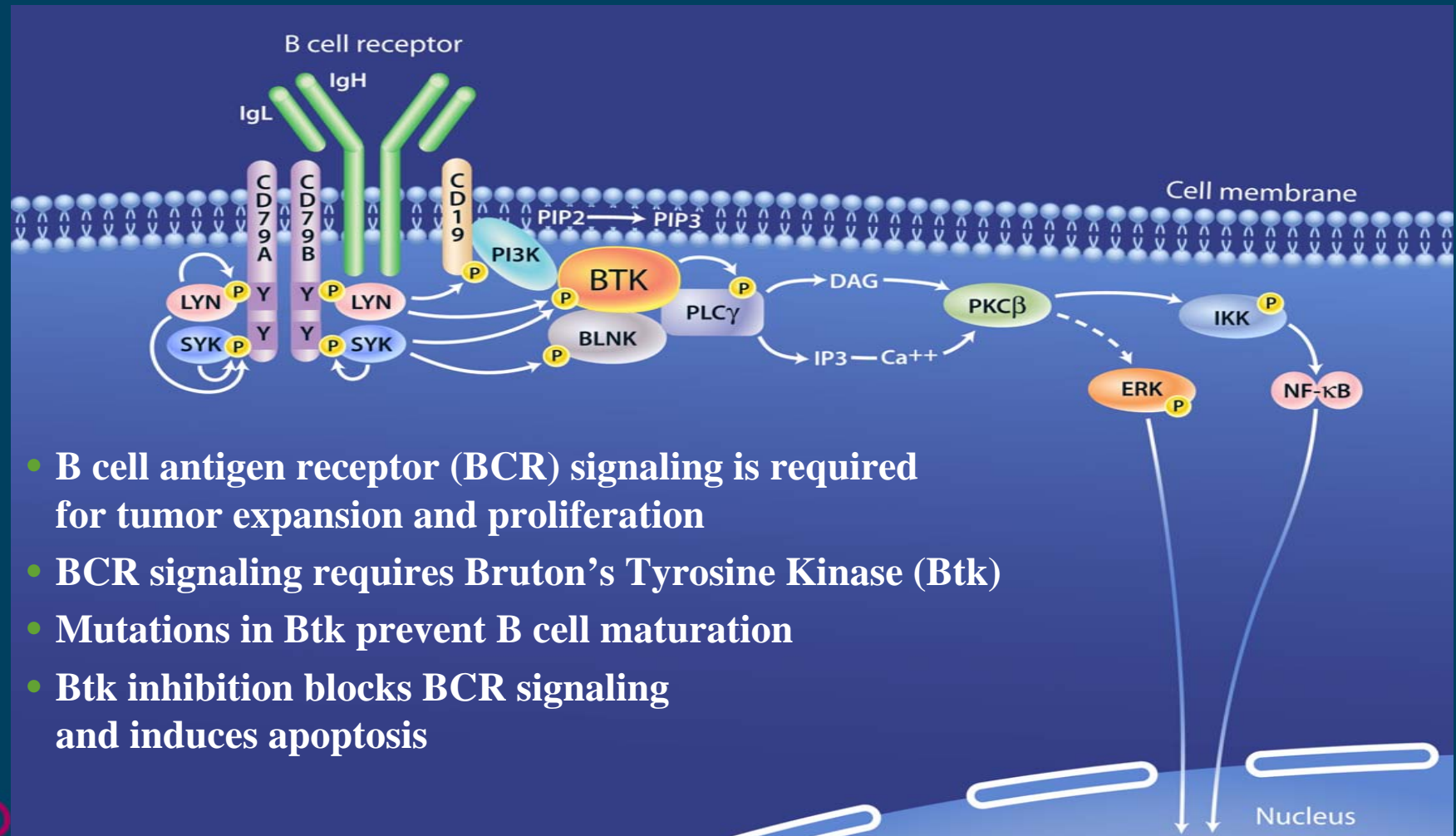
## Disclosure: Nathan Fowler, MD

- **Research funding/PI: Pharmacyclics**
- **Employee:N/A**
- **Stockholder:N/A**
- **Consultant: Pharmacyclics**
- **Scientific advisory board: Pharmacyclics**

## Disclosure: Ranjana Advani, MD

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# B Cell Receptor Signaling Pathway

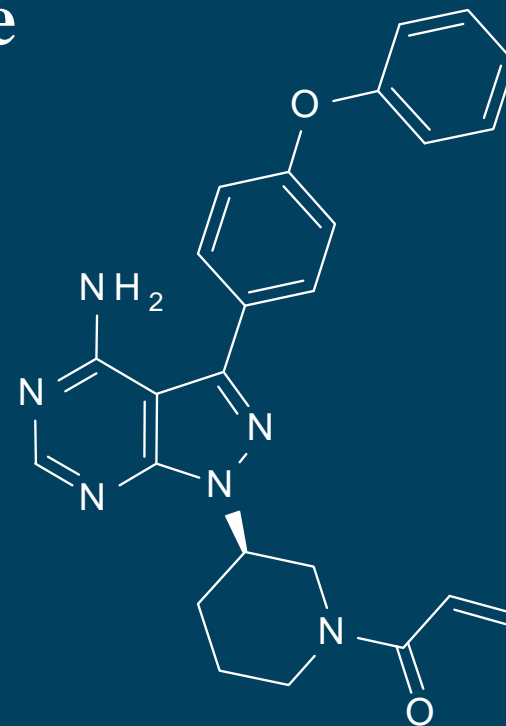


- B cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- BCR signaling requires Bruton's Tyrosine Kinase (Btk)
- Mutations in Btk prevent B cell maturation
- Btk inhibition blocks BCR signaling and induces apoptosis

# PCI-32765

## Novel Small Molecule Btk Inhibitor

- **Forms a specific and irreversible bond with cysteine-481 in Btk**
- **Potent Btk inhibition**
  - $IC_{50} = 0.5 \text{ nM}$
- **Orally available**



PCI-32765

# PCI-32765 Preclinical Findings

- *In vitro* data
  - Blocks BCR-stimulated activation of NF- $\kappa$ B and ERK
  - Inhibits growth and induces apoptosis B cell lymphoma cell lines
  - Does not affect T cell
- Active in multiple *in vivo* models
  - Transgenic murine model of BCR-driven lymphoma
  - Spontaneous B cell lymphoma in canines
  - Mouse models of autoimmune disease

# Study Design

- **Ongoing, dose-escalation, multicenter, open-label, study of PCI-32765 in recurrent B cell lymphoma**
- **Design**
  - Cohorts  $n \geq 6$  patients
  - If  $\geq 2$  DLTs are observed during Cycle 1, MTD will be established as the previous cohort
  - Tumor assessment performed every 2 cycles
- **Dosing**
  - 1.25, 2.5, 5.0, 8.3, 12.5, 17.5 mg/kg/d (QD 28 days + 7-days rest)
  - Continuous dosing at 8.3 mg/kg/day (QD 35 days + 0-days rest)
  - Current dose level = 12.5 mg/kg/day

# Objectives

- **Primary Objectives:**
  - Establish the safety and the MTD
  - Determine the pharmacokinetics of study drug
  - Measure the pharmacodynamic parameters, including drug occupancy of Btk
- **Secondary Objective:**
  - Evaluate tumor response

## Eligibility: Key Inclusion / Exclusion Criteria

- **Recurrent CD 20<sup>+</sup> B cell NHL including CLL/SLL and WM**
- **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
- **Prior treatment:  $\geq 1$  and  $\leq 4$**
- **No known CNS involvement or uncontrolled infection**
- **ECOG  $\leq 1$**
- **Laboratory:**
  - Platelets count  $\geq 75,000/\mu\text{L}$  and ANC  $\geq 1500/\mu\text{L}$  (unless CLL with BM involvement)
  - Adequate renal /hepatic function

# Results: Baseline Patient Characteristics (n=47)

**Median age, years (range)** **65 (41-82)**

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**Histology at diagnosis, n (%)**

<b>FL</b>	<b>16 (34)</b>
<b>CLL/SLL</b>	<b>15 (32)</b>
<b>DLBCL</b>	<b>7 (15)</b>
<b>MCL</b>	<b>4 (9)</b>
<b>MZL</b>	<b>4 (9)</b>
<b>WM</b>	<b>1 (2)</b>

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**Median prior therapies, (range)** **3 (1-4)**

**Therapy, n (%)**

<b>Rituximab</b>	<b>43 (91)</b>
<b>Alkylators</b>	<b>40 (85)</b>
<b>Nucleoside analogs</b>	<b>27 (57)</b>
<b>Anthracyclines</b>	<b>19 (40)</b>

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# Results: Enrollment (n=47)

Cohorts (mg/kg/day)	n
I: 1.25	7
II: 2.5	9
III: 5.0	6
IV: 8.3	8
CD: 8.3 (Continuous dosing)	10
V: 12.5	7

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Disposition	n
On study	25
Discontinuation of drug	22
Disease progression	13
Patient decision	2
PI decision	1
SAE	4
DLT	2

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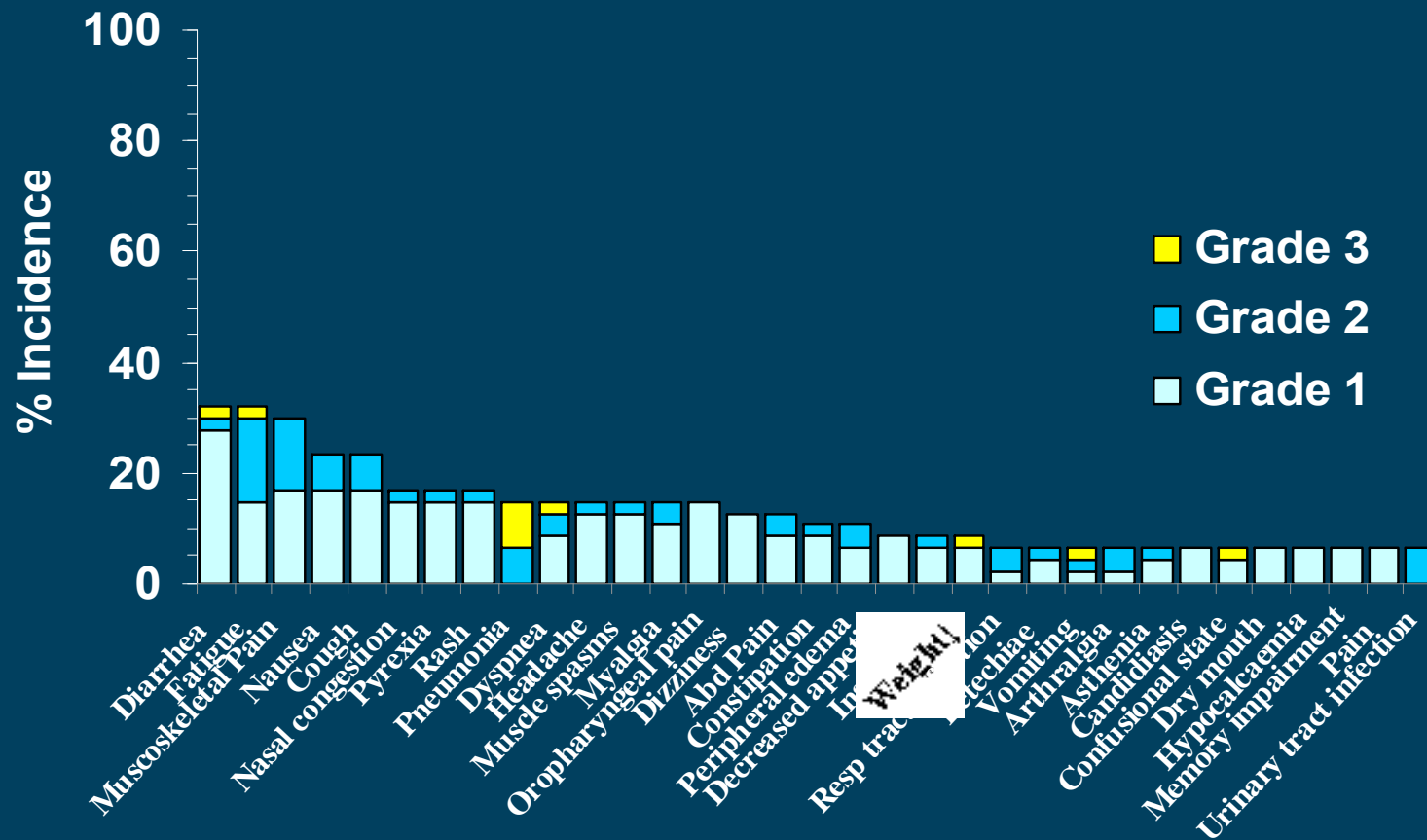
## Results: Frequency of Adverse Events (n=47)

	n (%)
Any AE	47 (100)
Grade $\geq$ 3 AE	18 (38)
Any Related AE	38 (81)
Related Grade $\geq$ 3 AE	6 (13)
Any SAEs	13 (28)
Related SAEs	2 (4)
Deaths*	4 (9)

Note: Counts in the table represent numbers of patients

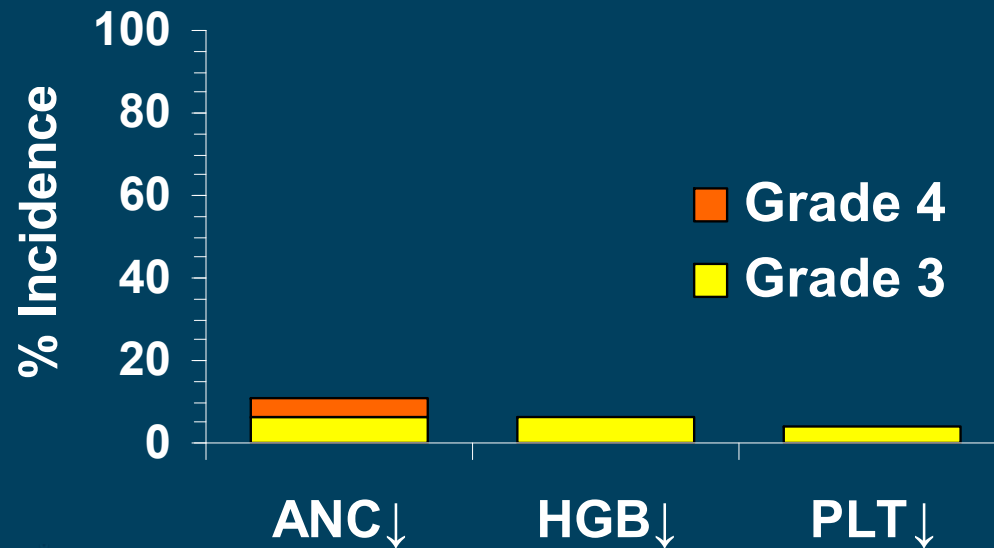
\*All deaths due to documented disease progression

# Results: All Non Hematologic AE ( $\geq 5\%$ Incidence) n = 47



## Results: laboratory (n=47)

- No change in circulating normal B, T, or NK cells in peripheral blood
- No consistent changes in hepatic and renal functions
- Hematologic findings:



# Results: All Patients with Related AEs by Dose Level (n=47)

Grade	I 1.25 mg/kg n=7	II 2.5 mg/kg n=9	III 5 mg/kg n=6	IV 8.3 mg/kg n=8	CD 8.3 mg/kg n=10	V 12.5 mg/kg n=7
Grade 1	7	7	5	5	7	4
Grade 2	5	4	3	3	1	3
Grade 3	0	3	0	3	0	0
Grade 4	0	2	0	0	0	0

•No consistent relationship between dose level and reported adverse events

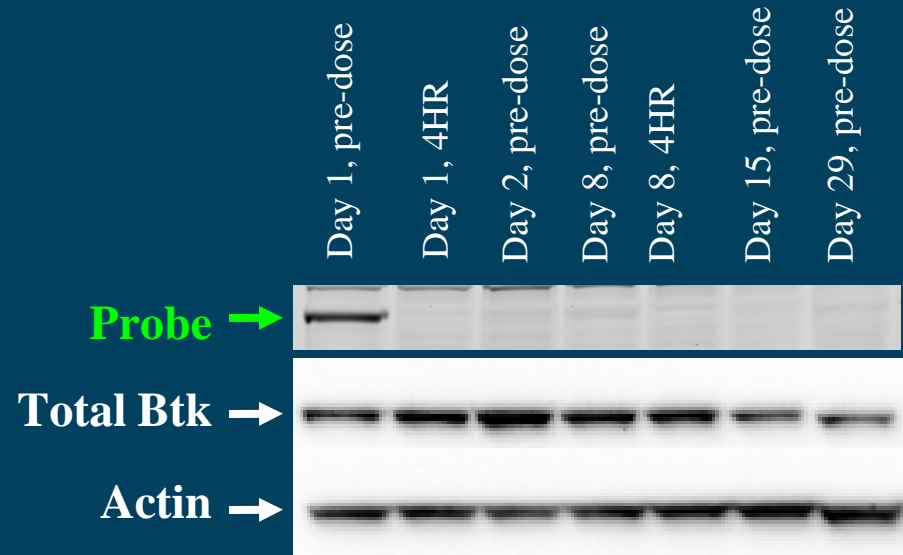
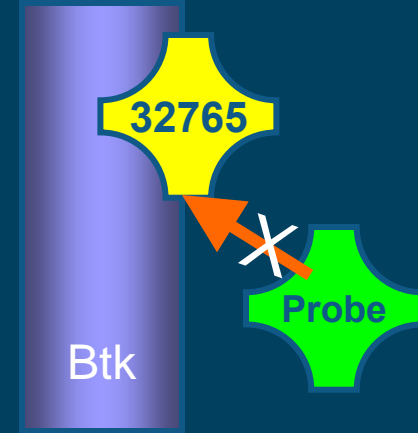
# Results: Pharmacodynamic Assay Fluorescent Probe Used to Detect Btk Occupancy

Cohort 1 patient dosed with 1.25 mg/kg/day

Absence of drug:

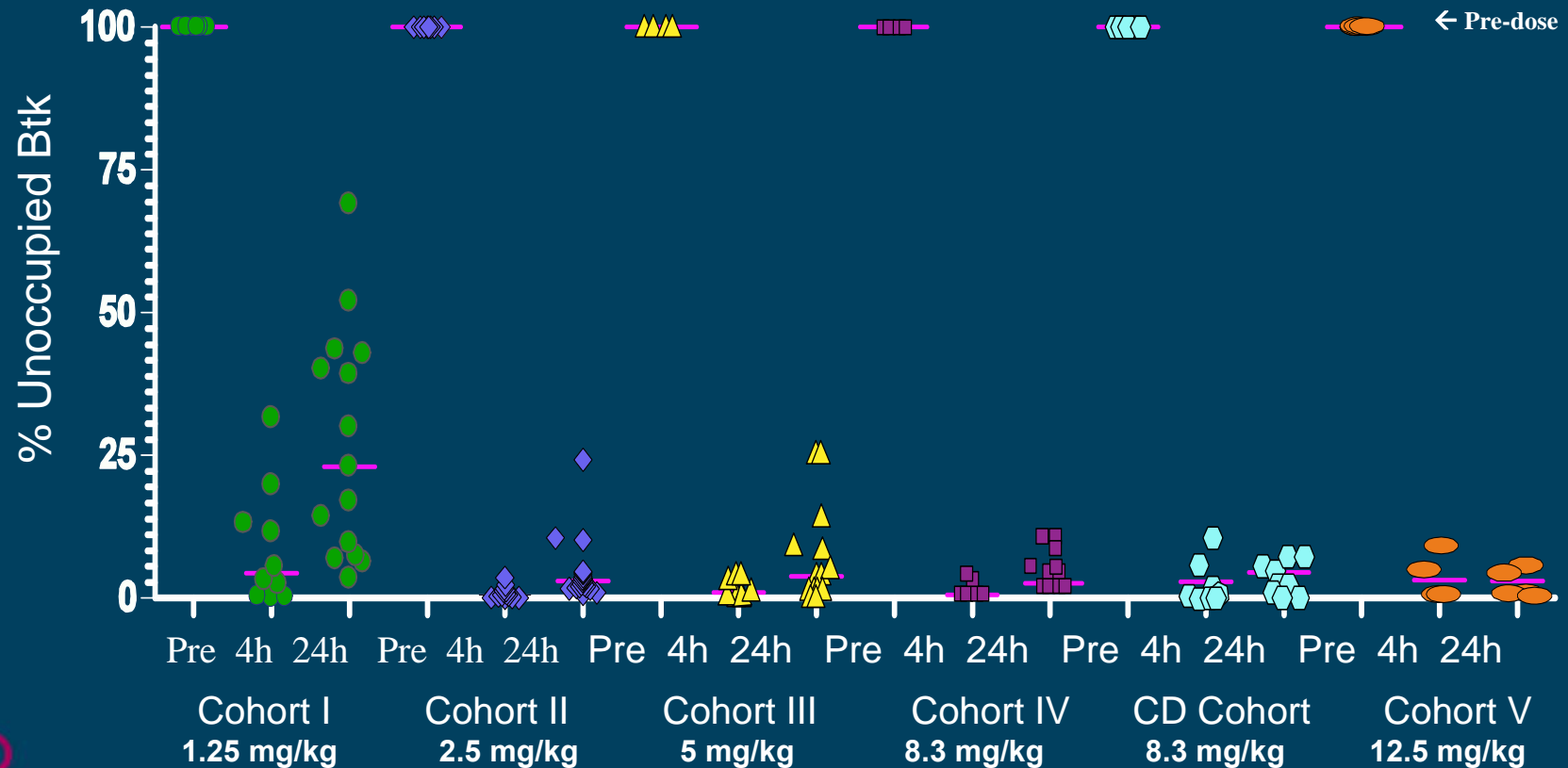


Presence of drug:



# Results: Durable and Dose-Dependent Pharmacodynamic Effects

Btk Occupancy (Probe Assay)



# Results: Pharmacokinetics

- Mean T<sub>max</sub> not dose dependent - 1.0 to 2.3 h after oral delivery
- Mean t<sub>1/2</sub> increased with increasing dose - 6.3 to 10.8 h
- Day-8 steady state AUC increased by 75% to 250% over Day 1 AUC
- Btk full occupancy occurred at AUC<sub>0-inf</sub> values ≥ 455 nM•h

# Results: Response According To Histology (N=40)<sup>1</sup>

	N	CR	PR	SD	PD	NE*	ORR %
CLL/SLL	13	1	8	2		2	69%
MCL	4	1	2	1			75%
DLBCL	6		1	1	4		17%
FL	13		3	4	4	2	23%
MZL	4		1	1	1	1	25%
Total	40	2	15	9	9	5	

**Evaluable<sup>3</sup> response rate = 49% (17/35)**

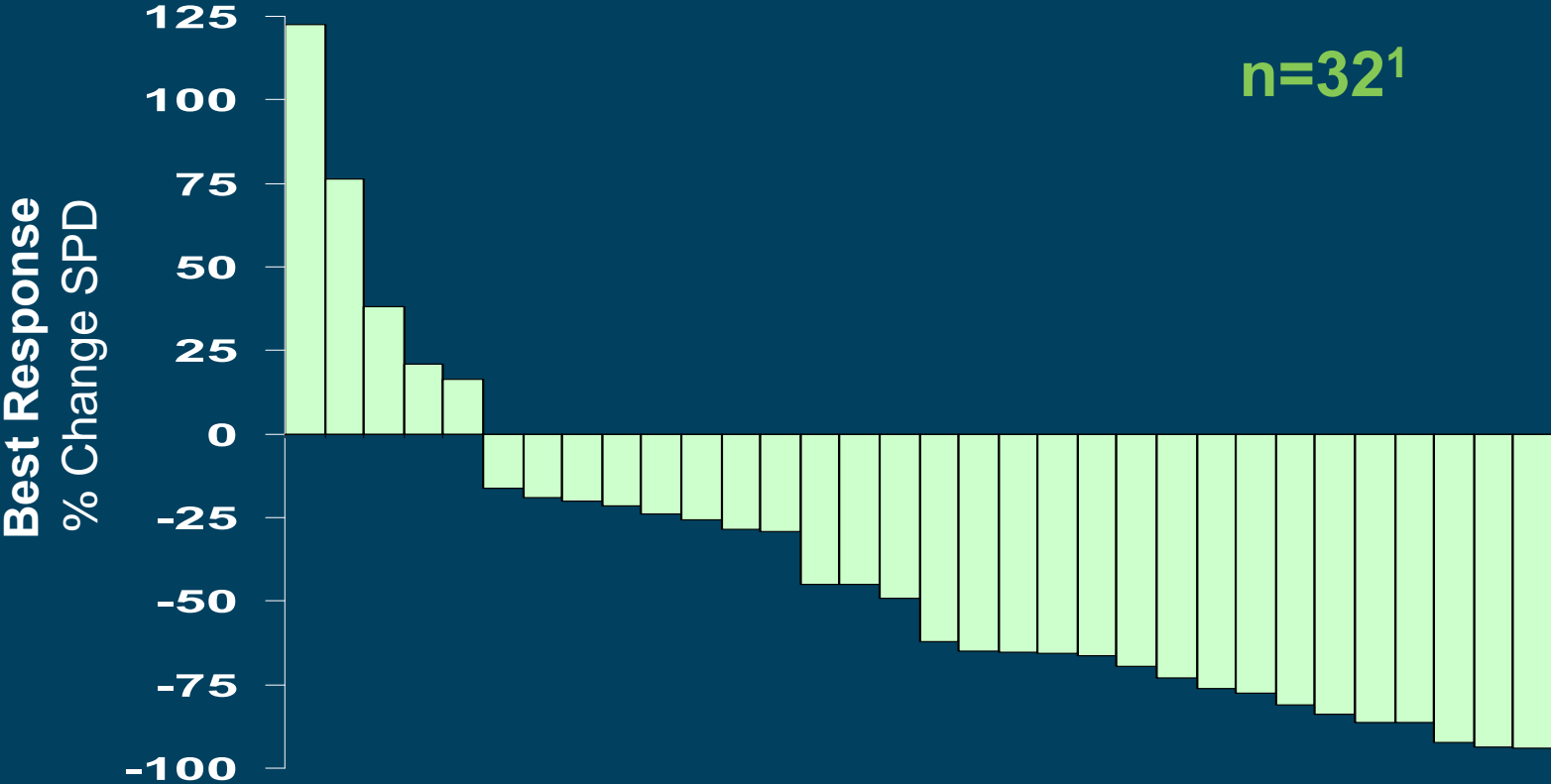
**ITT response rate = 43% (17/40)**

# Response by Ascending-Dose Cohort

Cohort <sup>1</sup>	Dose (mg/kg)	# of Pts	Clinical Finding				
			CR	PR	SD	PD	NE
I	1.25	7		2	1	4	
II	2.5	9		4	1	2	2
III	5.0	6	1	2	1	1	1
IV	8.3	8	1	2	3	1	1
Continuous	8.3	10		5	3	1	1
	<b>Total</b>	<b>40</b>	<b>2</b> 5%	<b>15</b> 37.5%	<b>9</b> 22.5%	<b>9</b> 22.5%	<b>5</b> 12.5%

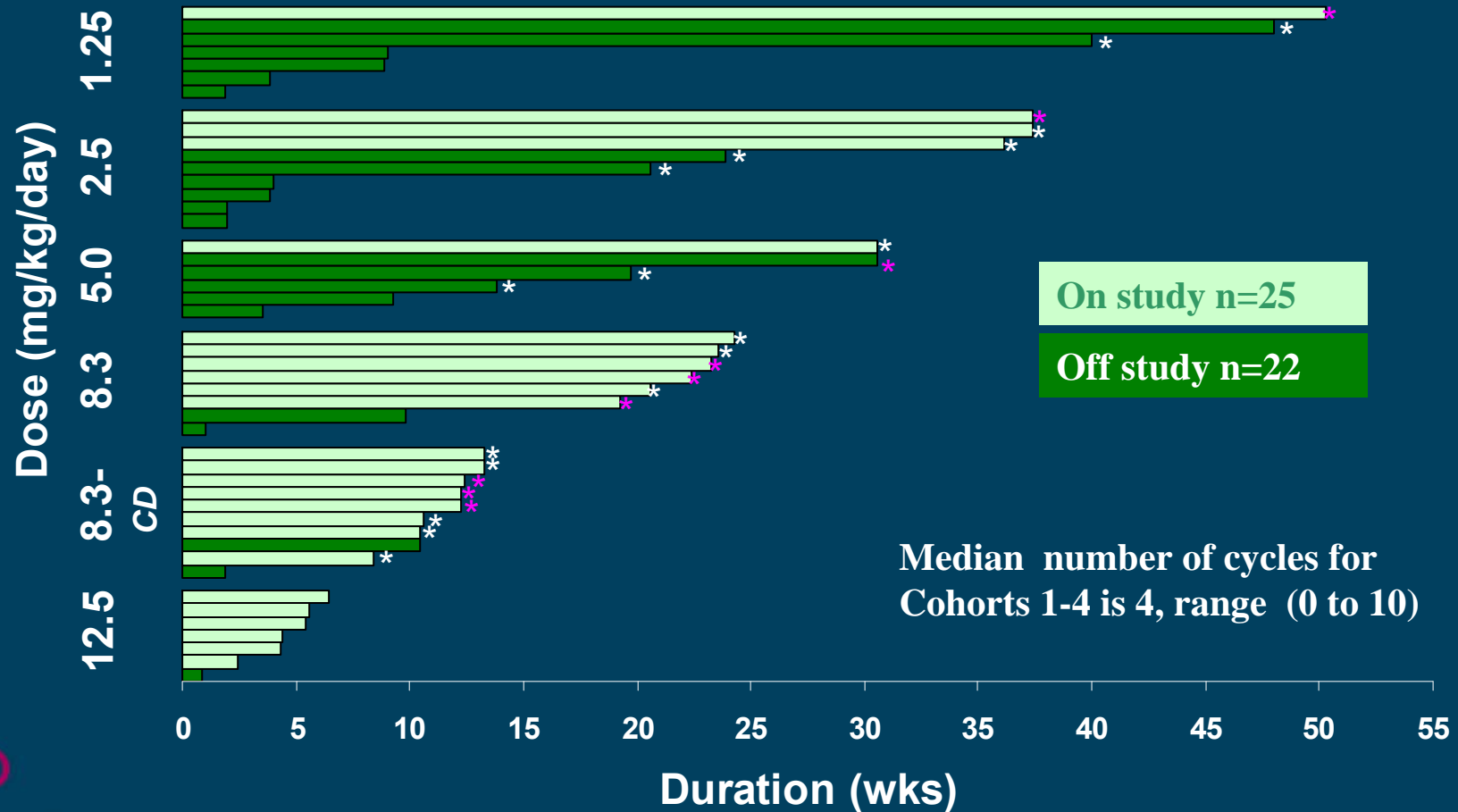
<sup>1</sup> Responses in 5<sup>th</sup> dose-level cohort (12.5 mg/kg) have yet to be determined

# Results: Change in Tumor Burden in Cohorts 1-4 and Continuous Dose Cohort



<sup>1</sup> 8 patients were not included due to lack of tumor evaluation (2 PD, 2 SAE, 2 DLT, 1 Pt decision, 1 TBD)

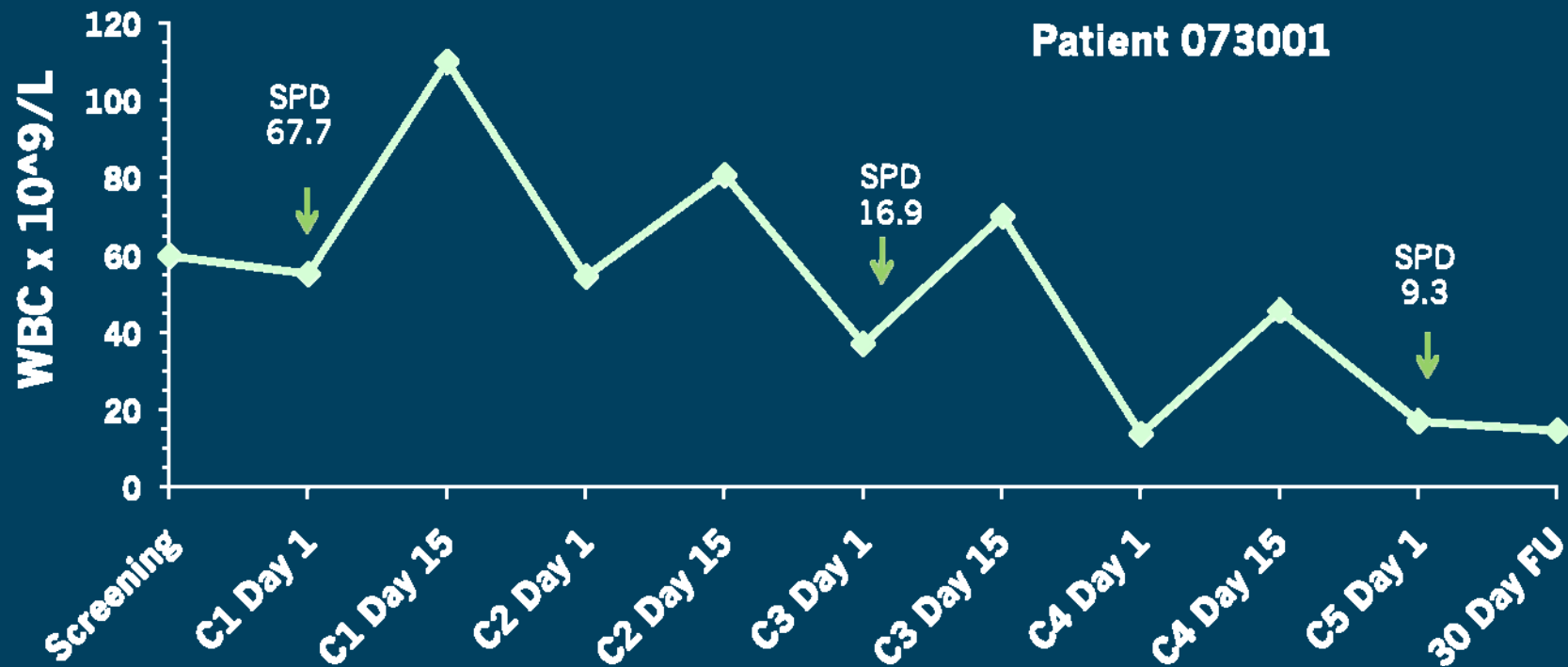
# Results: Time on Treatment



\* Partial or complete response  
 \* Stable disease

# Results: CLL Response in Circulating Cells Over Time

- Transient increases in circulating CLL cells associated with observed decrease in lymph node size



# Conclusions

- Btk inhibition in B-cell malignancies is a novel and promising treatment approach
- PCI-32765 is first-in-class potent inhibitor of Btk that demonstrated clinical benefit with single agent oral dosing.
- Well tolerated with minimal toxicities at doses up to 12.5 mg/kg/day, MTD not reached
- Responses observed in patients with CLL/SLL, MCL, FL, and DLBCL
- Safety and response assessment is ongoing