

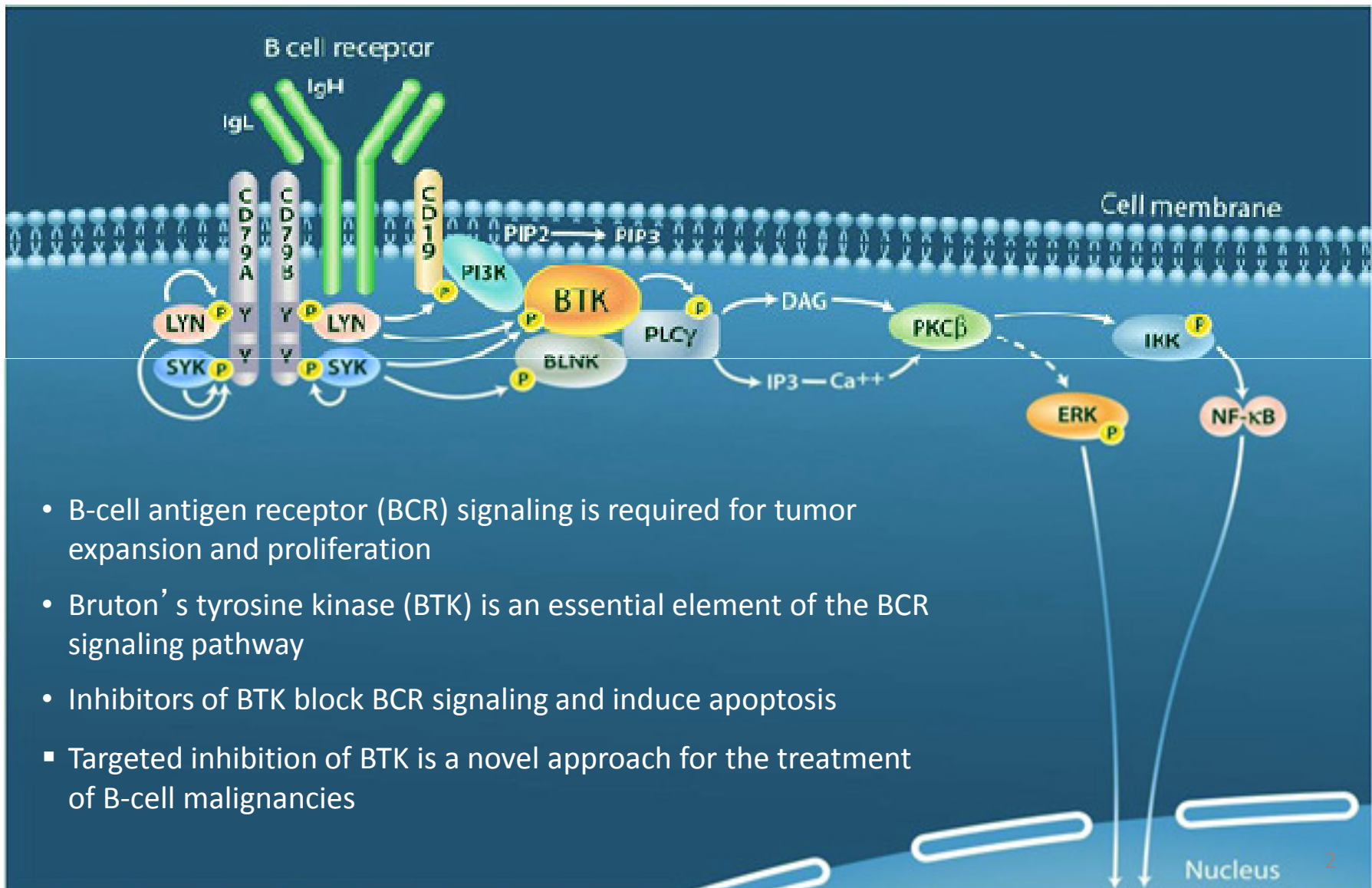
# The Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 Induces Durable Responses in Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Follow-up of a Phase Ib/II Study

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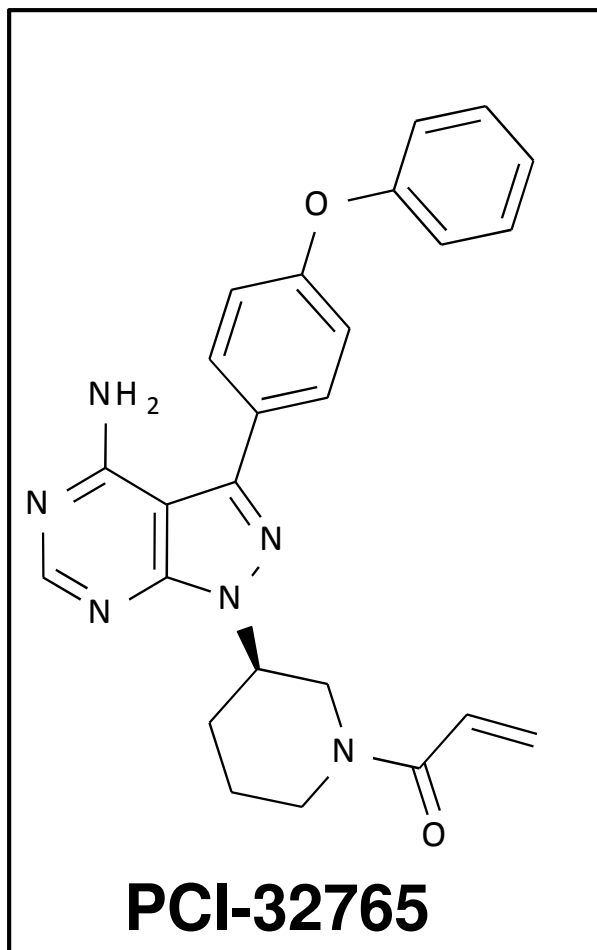
# Bruton's Tyrosine Kinase (BTK)

A critical kinase for lymphoma cell survival and proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies

# PCI-32765: First-in Class Inhibitor of BTK

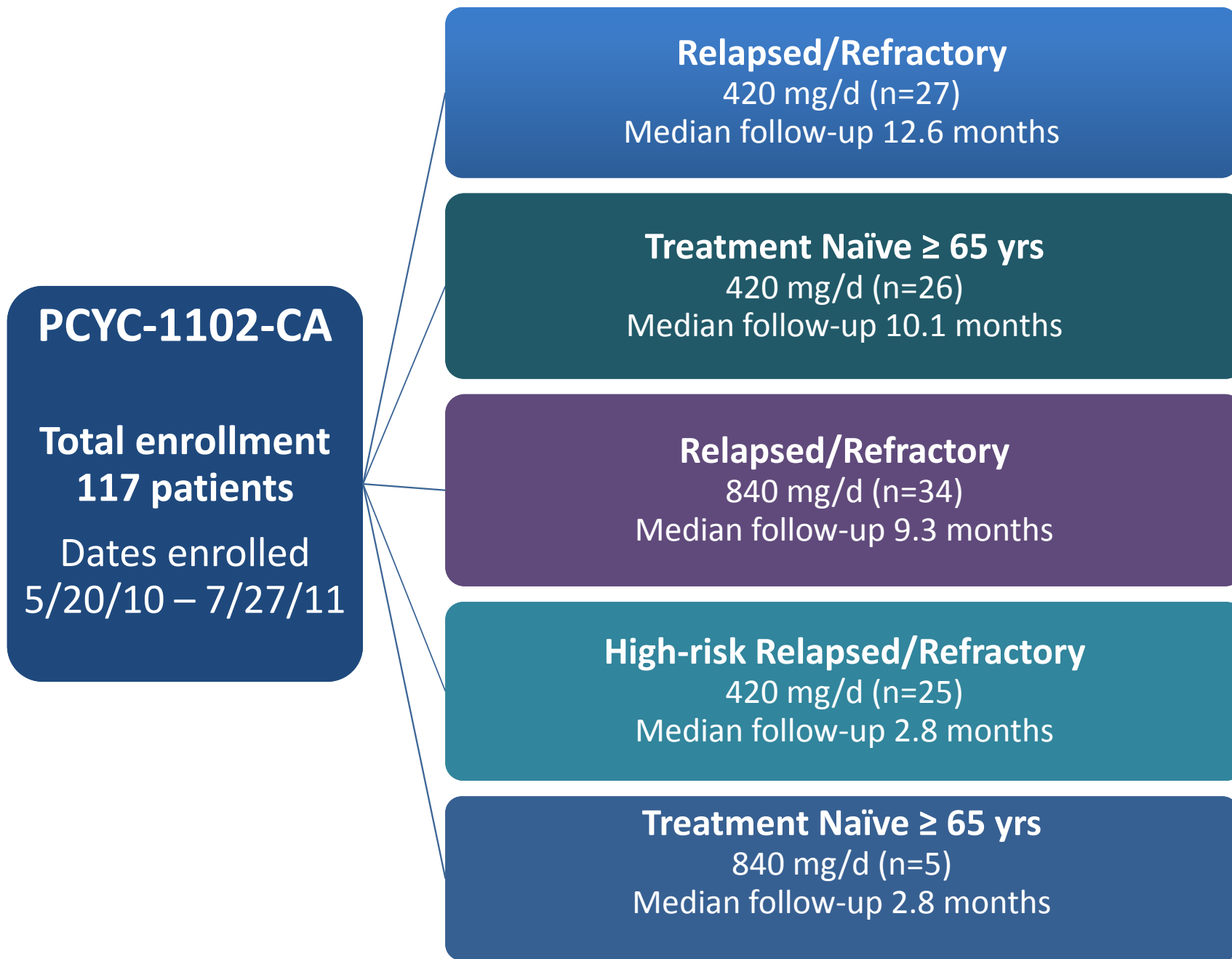


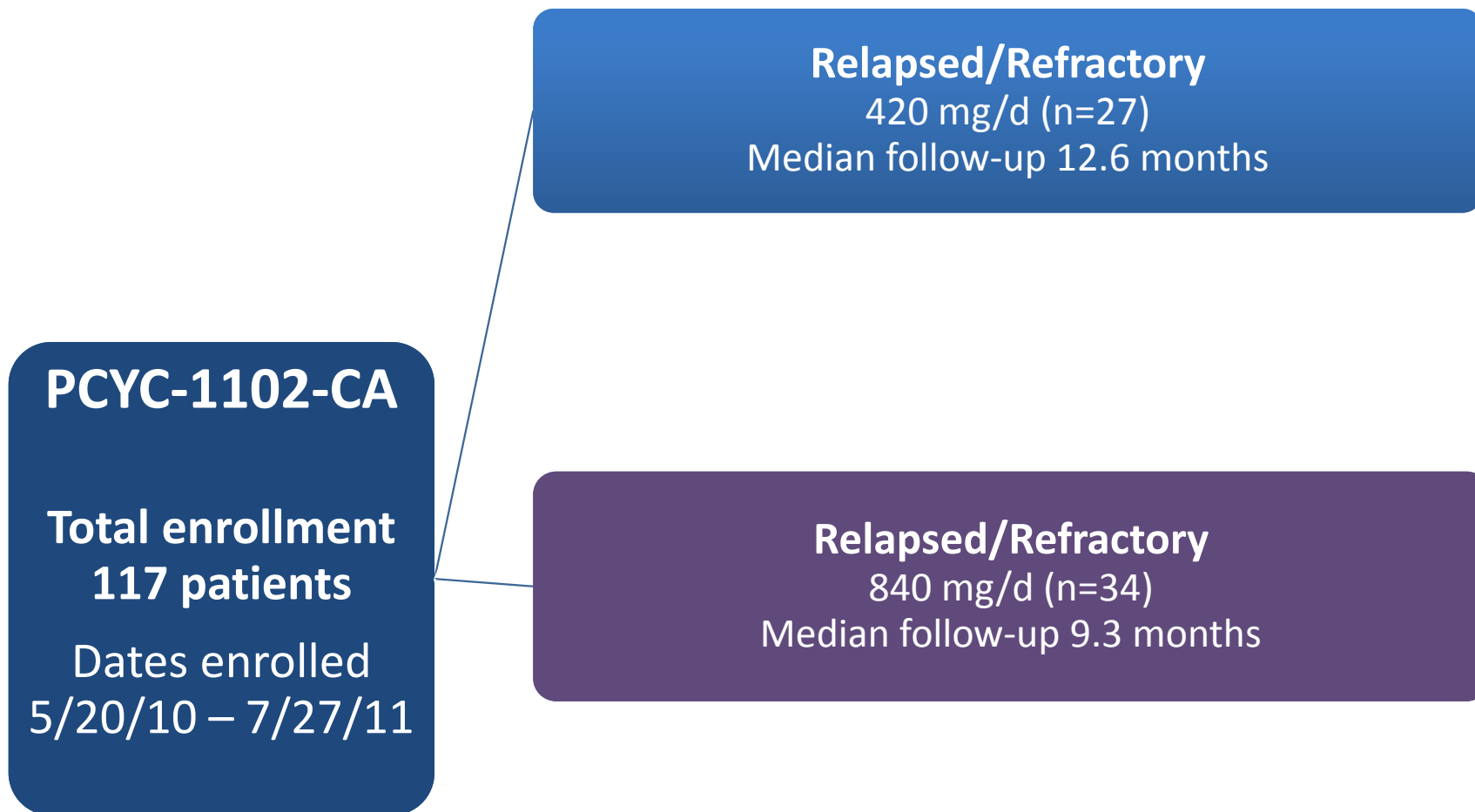
- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at  $IC_{50} = 0.5 \text{ nM}$
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- In CLL cells promotes apoptosis, inhibits ERK1/AKT phosphorylation, NF- $\kappa$ B DNA binding, CpG mediated proliferation
- Inhibits CLL cell migration and adhesion
- No cytotoxic effect on T-cells or NK-cells

Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075, 2010  
Herman SEM et al: Blood 117: 6287-6296, 2011  
Ponader, et al., ASH Meeting Abstracts 116:45, 2010

# Study Design: PCYC-1102-CA

- Multi-cohort study PCI-32765 as a single agent for symptomatic and/or progressive CLL/SLL
- Two fixed continuous doses 420 mg/day or 840 mg/day until disease progression
- Objectives:
  - Response rate, response duration, and PFS
  - Evaluate safety
  - Examine pharmacokinetics, pharmacodynamics, and influence of genomic features on clinical activity





*October 25, 2011 data-cut for presentation* ◦

# Patient Eligibility

- Diagnosis of CLL or SLL and requirement for treatment per NCI or IWCLL guidelines
- $\geq 2$  prior therapies including a purine analog
- Adequate end-organ function
  - ANC  $\geq 0.75 \times 10^9/L$  \*      Platelets  $\geq 50 \times 10^9/L$  \*
  - ALT  $\leq 2.5 \times \text{ULN}$       Creatinine  $\leq 1.5 \times \text{ULN}$
- No active/uncontrolled infection
- No malignancy limiting survival to  $< 2$  years
- No malabsorption syndrome, or disease significantly affecting GI function

*\*Restriction was removed in Protocol Amendment dated August 18, 2010*

# Patient Characteristics

	420 mg/d (N=27)	840 mg/d (N=34)	Total (N=61)
<b>Age, years</b> Median:	64	64	64
Range:	40 – 81	44 – 80	40 – 81
≥70 years, # (%)	9 (33)	10 (29)	19 (31)
<b>Diagnosis, # (%)</b> CLL:	26 (96)	33 (97)	59 (97)
SLL :	1 (4)	1 (3)	2 (3)
<b>ECOG Performance Status, # (%)</b> 0	11 (41)	13 (38)	24 (39)
1/2	16 (59)	21 (62)	37 (61)
<b>Prior Rx, #</b> Median:	3	5	4
Range:	2 – 10	1 – 12	1 – 12
<b>Prior therapy, # (%)</b>			
Nucleoside analog	27 (100)	34 (100)	61 (100)
Rituximab	25 (93)	33 (97)	58 (95)
Alkylator	24 (89)	28 (82)	52 (85)
Alemtuzumab	5 (19)	3 (9)	8 (13)
Bendamustine	8 (30)	13 (38)	21 (34)
Ofatumumab	8 (30)	10 (29)	18 (30)

# Patient Characteristics (cont.)

	420 mg/d (N=27)	840 mg/d (N=34)	Total (N=61)
<b>Bulky Disease, # (%)</b>			
≥ 5 cm	13 (48)	20 (59)	33 (54)
≥ 10 cm	1 (4)	9 (26)	10 (16)
<b>Cytopenia at baseline, # (%)</b>			
ANC < 1500/μL	7 (26)	17 (50)	24 (39)
HGB < 11g/dL	4 (15)	18 (53)	22 (36)
Platelets < 100,000/μL	8 (30)	24 (71)	32 (52)
HGB < 11g/dL or PLT < 100,000 μL	9 (33)	27 (79)	36 (59)
<b>Purine Analog Refractory, # (%)</b> (< 12 month treatment free interval following purine analog regimen)	10 (37)	18 (53)	28 (46)
<b>Prognostic Markers, # (%)</b>			
IgVH unmutated:	19/25 (76)	23/28 (82)	42/53 (79)
Del(17p):	9/24 (38)	11/32 (34)	20/56 (36)
Del(11q):	8/24 (33)	14/32 (44)	22/56 (39)
β2 Microglobulin > 3mg/L	9/25 (36)	20/32 (63)	29/57 (51)

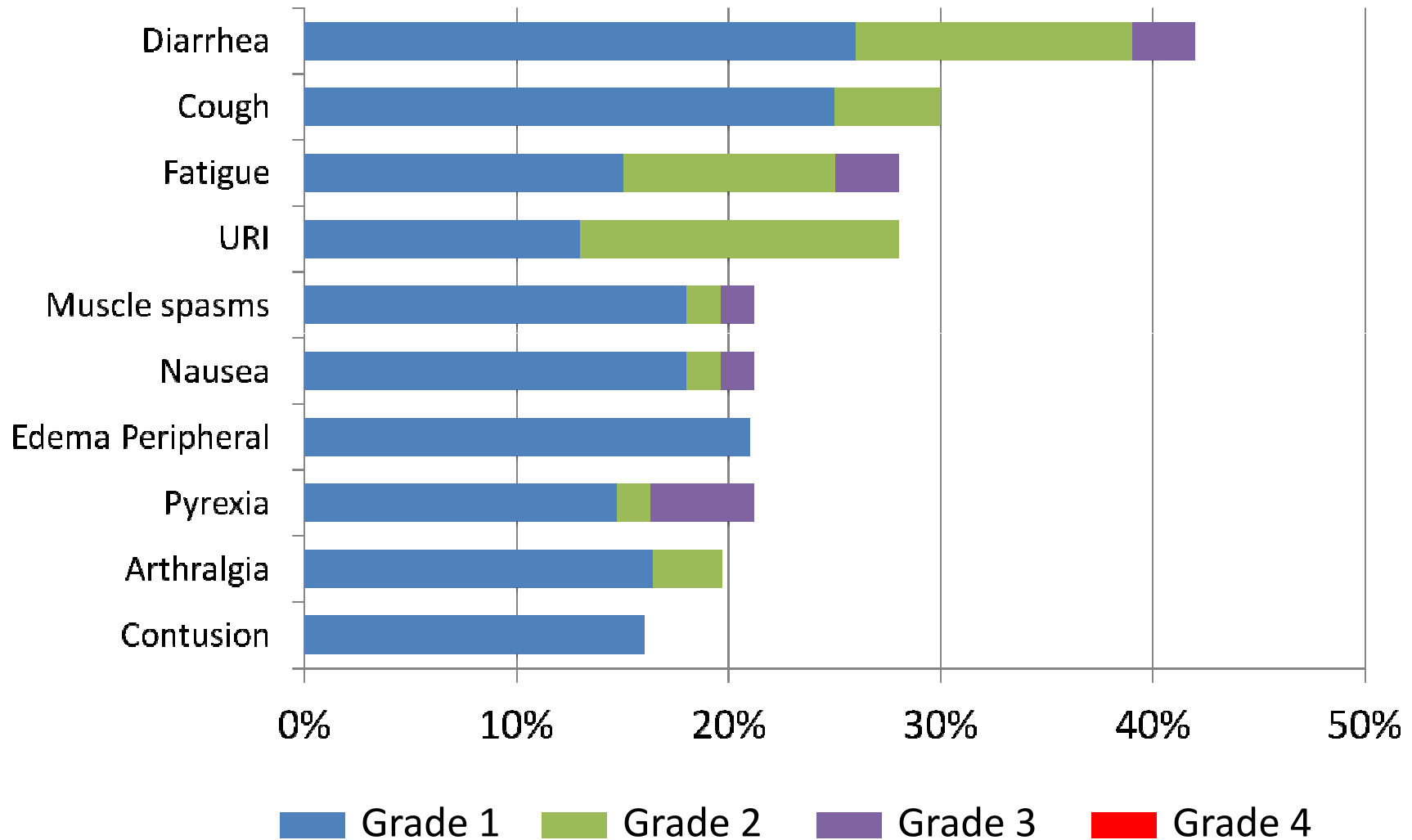
# Patient Disposition

	420 mg/d (N=27)	840 mg/d (N=34)
<b>Number of Patients</b>	27	34
<b>Follow-up</b> Median (months)	12.6	9.3
Range	0.9 – 15.0	0.3 – 11.1
<b>Patients Still on Study, # (%)</b>	20 (74)	26 (76)
<b>Patients Discontinued, # (%)</b>	7 (26)	8 (24)
<b>Primary Reasons for Discontinuation, # (%)</b>		
Disease Progression	2 (7)	1 (3)
Death <sup>1</sup>	1 (4)	2 (6)
Adverse Event	1 (4)	1 (3)
Other <sup>2</sup>	3 (11)	4 (12)

<sup>1</sup> Cause of death: 1 pneumonia, 1 ARDS/cryptococcal pneumonia, 1 histiocytic sarcoma

<sup>2</sup> Other: 5 transplant, 1 NSCLC diagnosed day 5, 1 off study drug > 2 weeks

# Common AEs (All Grades)—Events occurring in > 15% of Patients (regardless of attribution) (n=61)



# Grade 3/4 Infectious and Hematologic Toxicity (regardless of attribution)

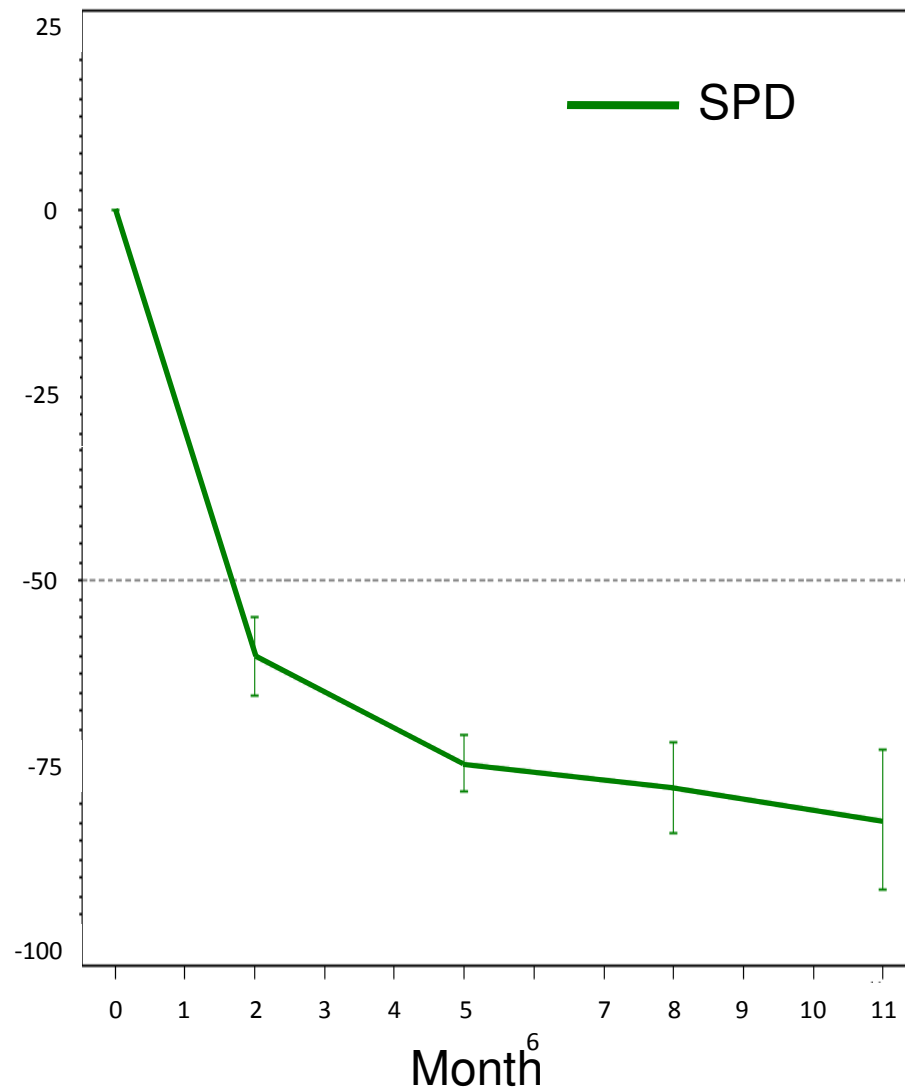
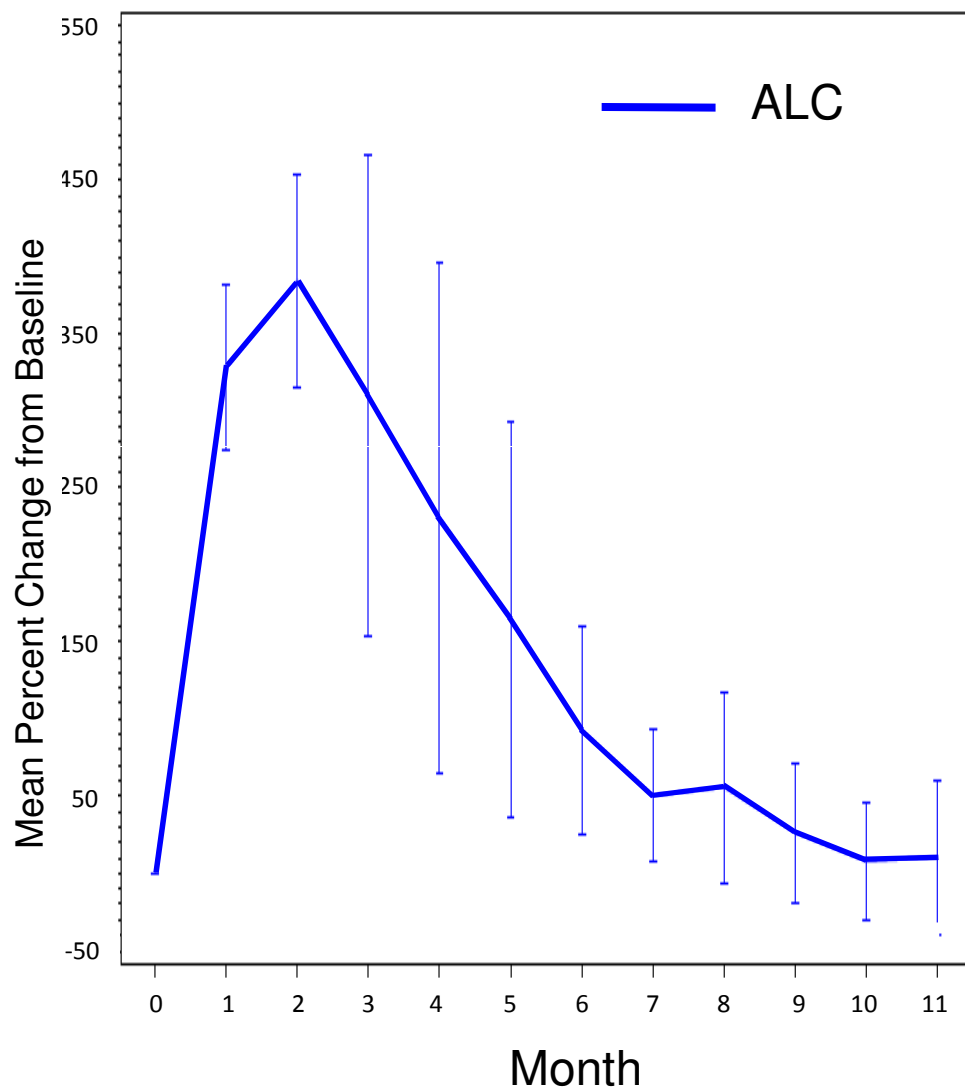
Grade 3/4 Hematology toxicity <sup>1</sup>	420 mg/d (n=27)		840 mg/d (n=34)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	4%	4%	12%	9%
Anemia	7%	0%	9%	3%
Thrombocytopenia	0%	7%	9%	0%

Grade 3/4 Infectious toxicity	420 mg/d (n=27)		840 mg/d (n=34)	
	Grade 3	Grade 4	Grade 3	Grade 4
Patients with any Grade 3/4	19%	7%	26%	3%

<sup>1</sup> Reported as AEs



# Pattern of Response: Blood Lymphocytes vs Lymph Nodes



$SPD = \text{sum of products of lymph node dimension}$

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# Response Criteria

- NHL IWG criteria<sup>1</sup> were applied to SLL cases
- The 2008 IWCLL criteria<sup>2</sup> were applied to CLL cases with the following modifications:
  - Treatment-related lymphocytosis, in the absence of other parameters meeting the criteria for PD, was not considered PD.
  - “Nodal” response describes patients who achieved a PR by other parameters until a 50% reduction in ALC from baseline was achieved or ALC (<5K).
  - Patients with a normal ALC at baseline with treatment-related lymphocytosis required normalization for a PR.
  - Best response refers to any time during therapy or follow-up.
- All investigators applied these rules in adjudication.

<sup>1</sup>Cheson, et al, J Clin Oncol, 2007

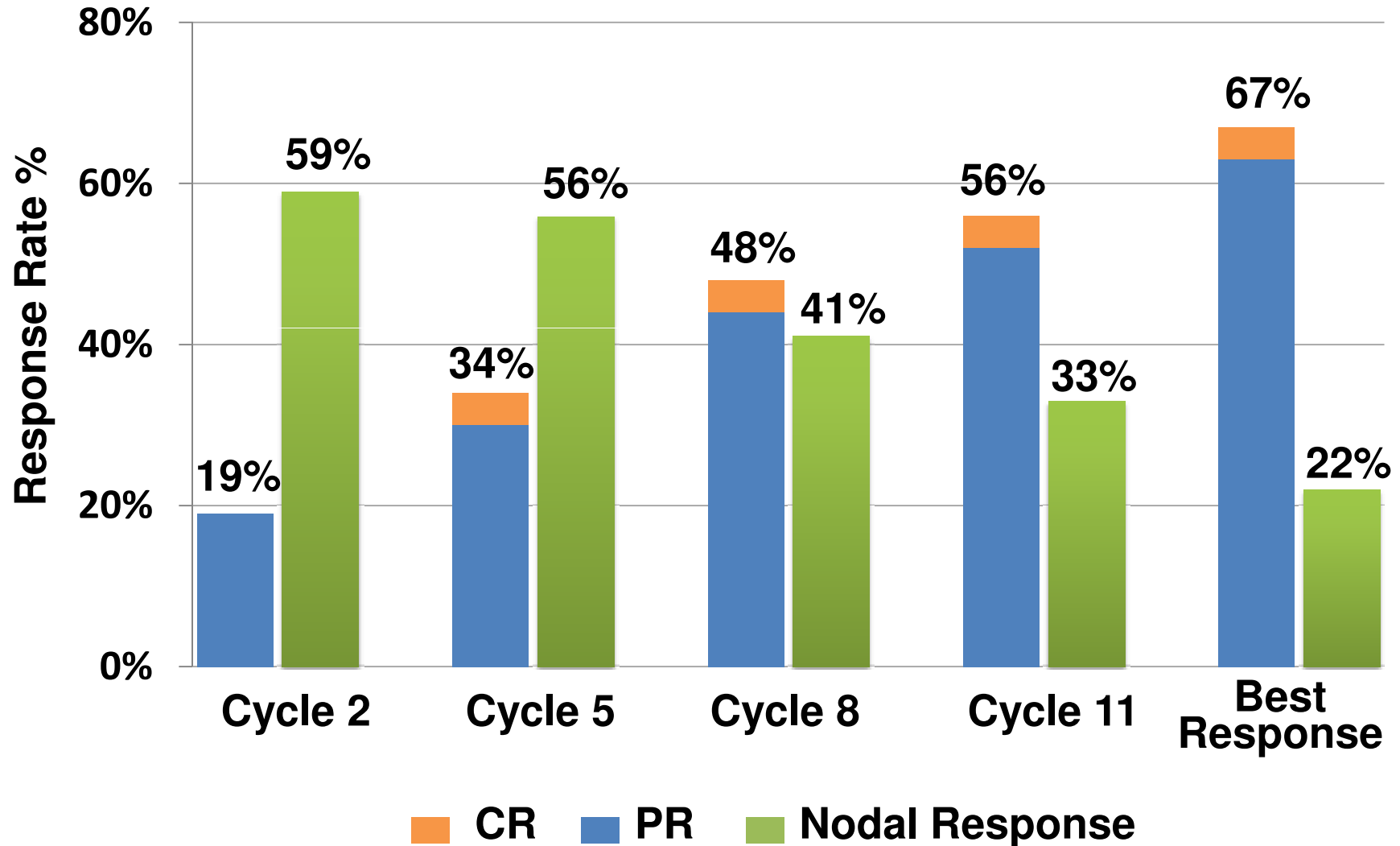
<sup>2</sup>Hallek, et al, Blood, 2008

# Best Response

	420 mg/d (N=27)	840 mg/d (N=34)	Total (N=61)
	# (%)	# (%)	# (%)
<b>CR</b>	1 (4)	0 (0)	1 (2)
<b>PR</b>	17 (63)	23 (68)	40 (66)
<b>ORR*</b>	<b>67%</b>	<b>68%</b>	<b>67%</b>
<b>Nodal</b>	6 (22)	8 (24)	14 (23)
<b>SD</b>	1 (4)	1 (3)	2 (3)
<b>PD</b>	1 (4)	0 (0)	1 (2)
<b>NE</b>	1 (4)	2 (6)	3 (5)

\*Per IWCLL 2008 criteria

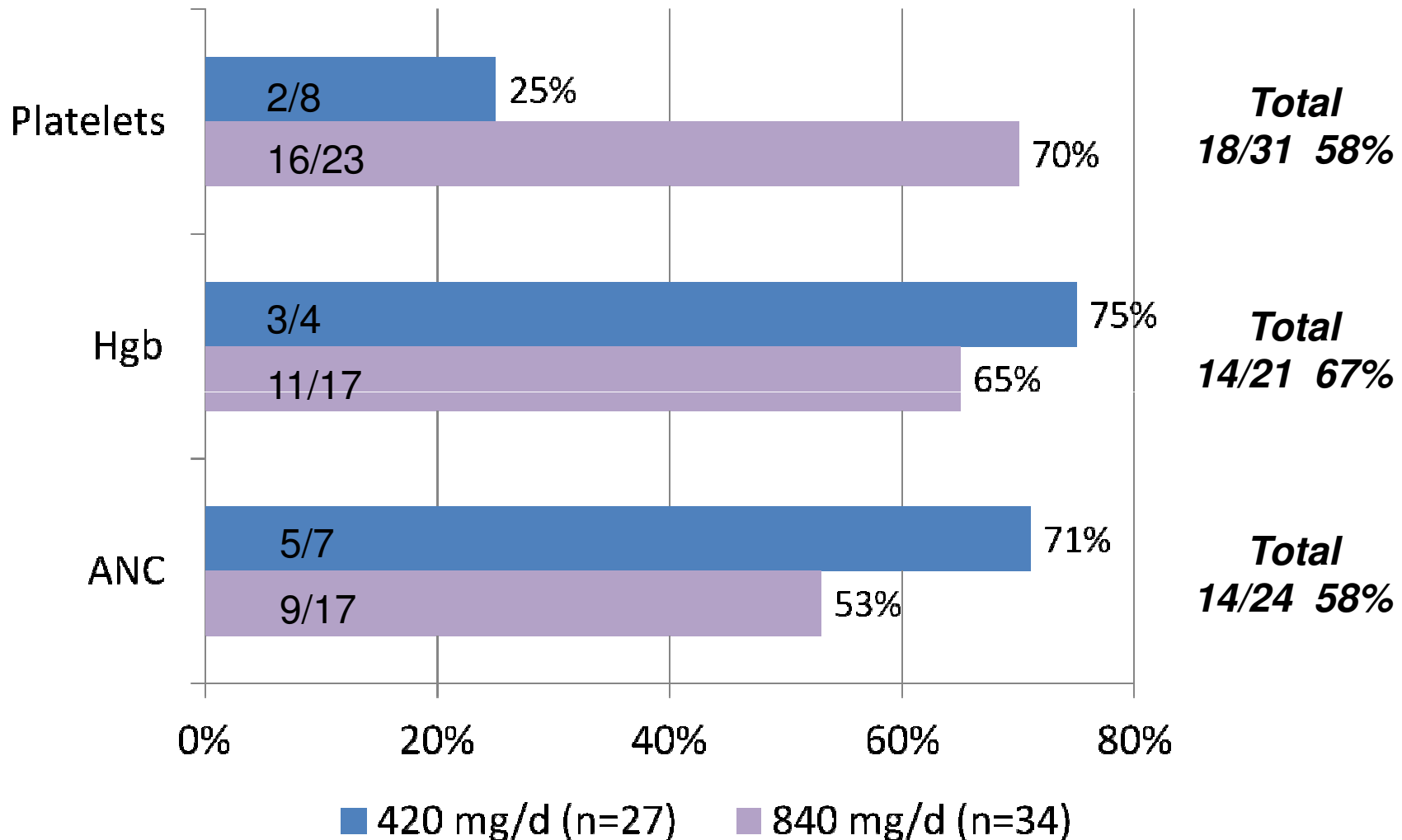
# Cumulative Best Response 420 mg/d cohort (n=27)



# Best Response by Risk Features

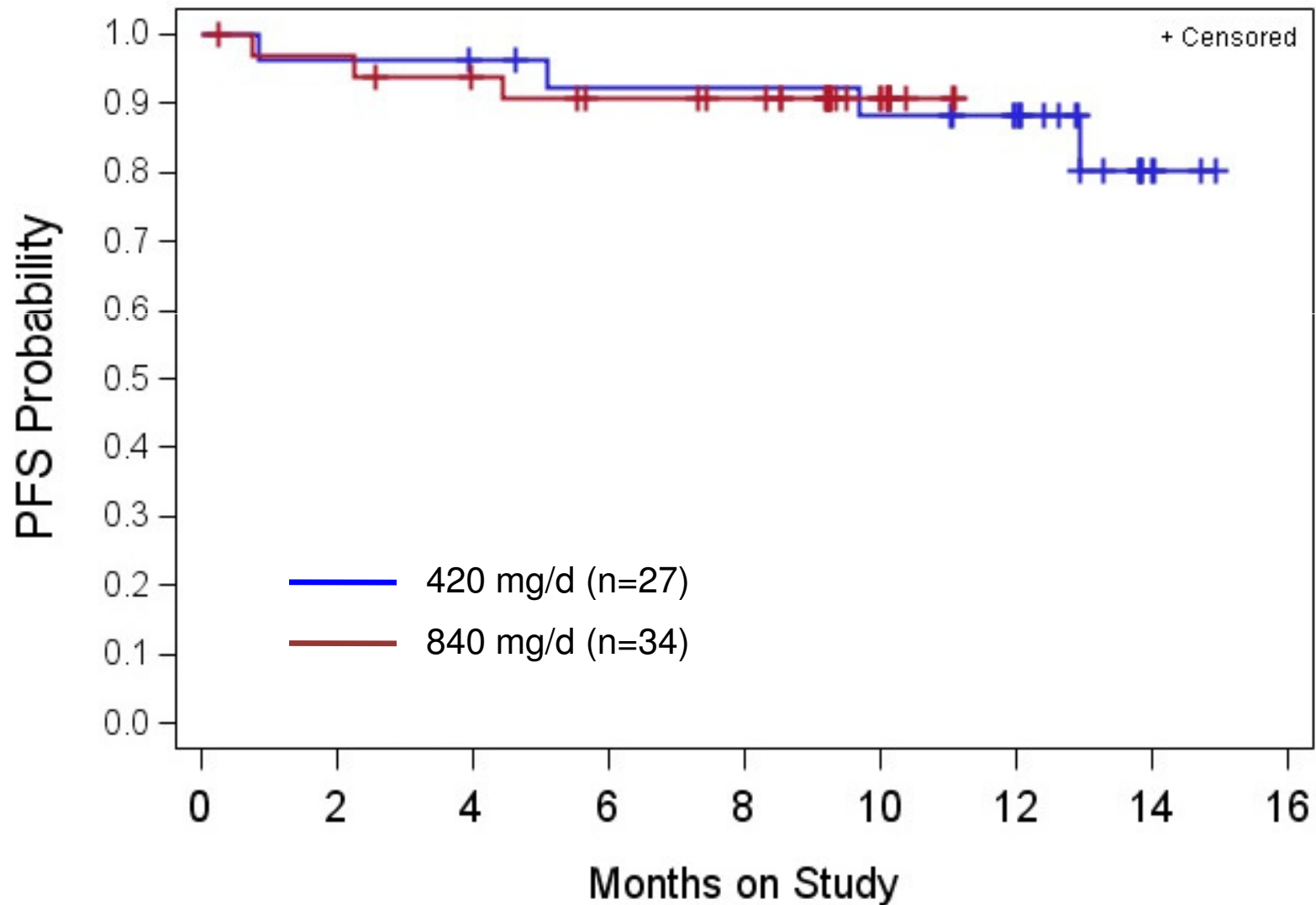
	n/N	ORR %
<b>All Patients</b>	<b>41/61</b>	<b>67</b>
<b>≥ 70 years age</b>	13/19	68
<b>Bulky disease ≥ 5 cm</b>	24/33	73
<b>Bulky disease ≥ 10 cm</b>	7/10	70
<b>Hgb &lt; 11 g/dL or PLT &lt; 100K/μL at screening</b>	22/36	61
<b>IgVH unmutated</b>	31/42	74
<b>Del 17p</b>	13/20	65
<b>Del 11q</b>	16/22	73
<b>β2 Microglobulin &gt; 3mg/L</b>	19/29	66
<b>Purine Analog Refractory</b> (< 12 mos from any purine analog to next therapy)	17/28	61

# Sustained Improvement\* in Blood Counts in Patients with Pre-treatment Cytopenias



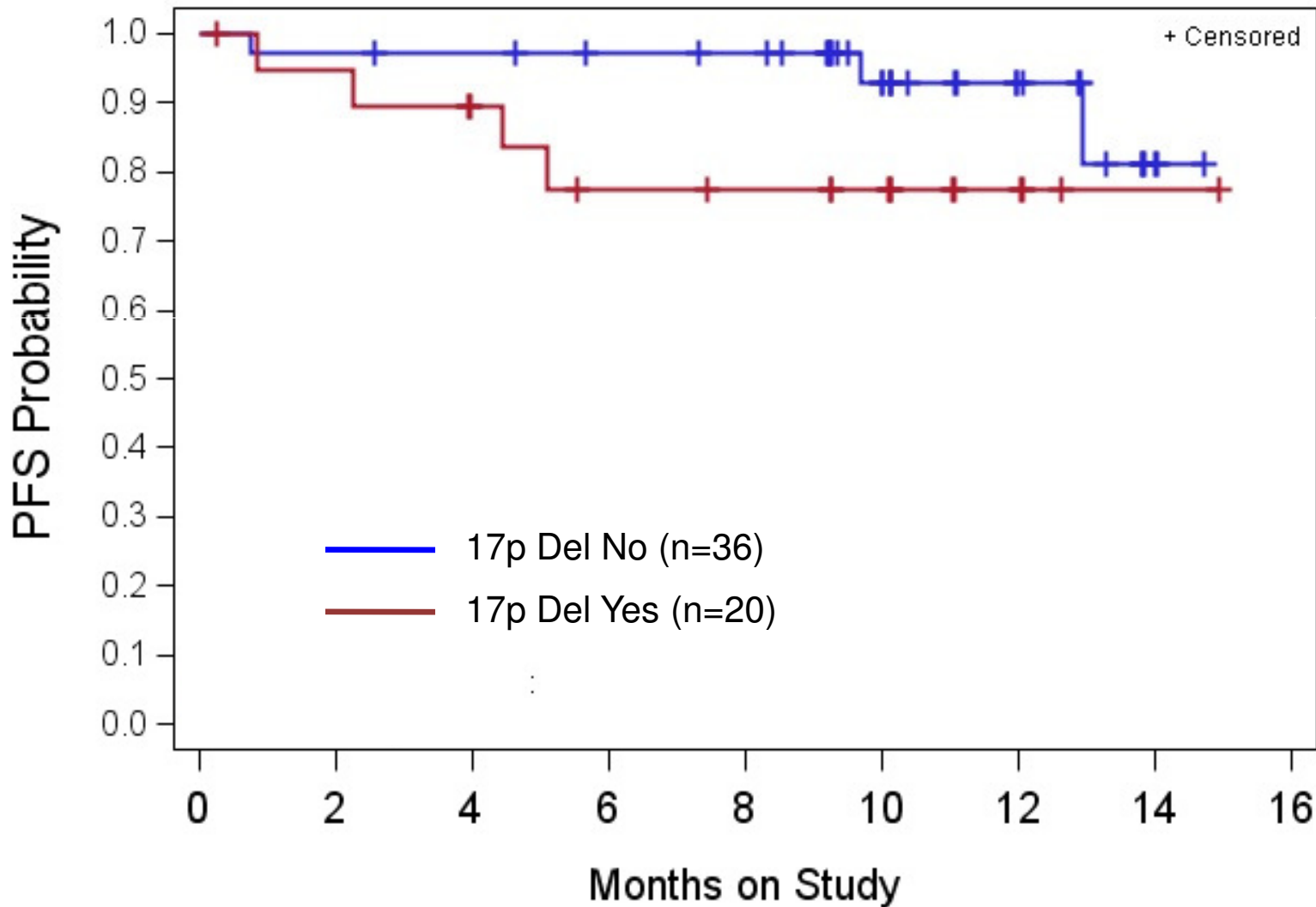
\*Sustained improvement is defined as improvement in cytopenia by >50%, or Hgb >11 g/dL, ANC > 1500 cells/ $\mu$ L, plts >100,000 with the duration of improvement lasting for  $\geq$  60 days without blood transfusion or G-CSF

# Progression-free Survival



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# Progression-free Survival by 17p Del Status



# Conclusions

- PCI-32765 a first-in-class, selective, covalent irreversible inhibitor of BTK administered as a single-agent to patients with relapsed or refractory CLL:
  - Resulted in a high ORR (67%) with 12-month PFS of 86%
  - Clinical activity is independent of poor-risk clinical or genetic features
  - Continuous daily dosing is well tolerated allowing for extended treatment
- Two dose levels demonstrate similar clinical activity and safety

# Acknowledgement

Thank you to all the patients who participated in the study, their families, all the clinical institutes and research staff, and Pharmacocyclics.