The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) is Highly Active and Tolerable in Treatment Naïve (TN) Chronic Lymphocytic Leukemia (CLL) Patients: Interim Results of a Phase Ib/II Study

JOHN C. BYRD, MD[1], RICHARD FURMAN, MD[2], STEVEN COUTRE, MD[3], JAN BURGER, MD, PHD[4], KRISTIE BLUM, MD[1], JEFF SHARMAN, MD[5], IAN FLINN, MD, PHD[6], BARBARA GRANT, MD[7], NYLA HEEREMA, PHD[1], AMY JOHNSON, PHD[1], TASHEDA NAVARRO[8], DANELLE JAMES, MD, MAS[8], ERIC HEDRICK, MD[8], SUSAN O'BRIEN, MD[4]

[1]Division of Hematology and The Department of Pathology, The Ohio State University, Columbus, OH
[2]Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medical College, New York, NY
[3]Divisions of Hematology and Oncology and Stanford Cancer Center, Stanford University School of Medicine, Stanford, CA
[4]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[5]US Oncology, Springfield, OR
[6]Sarah Cannon Research Institute, Nashville, TN
[7]Department of Medicine, Vermont Cancer Center, University of Vermont, Burlington, VT
[8]Pharmacyclics, Inc, Sunnyvale, CA

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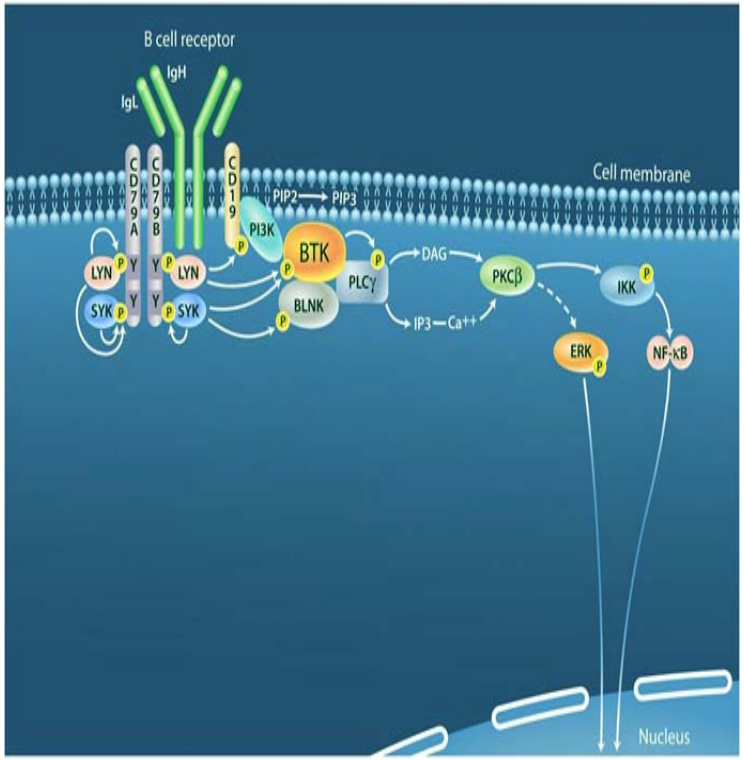
Bruton's Tyrosine Kinase (BTK)

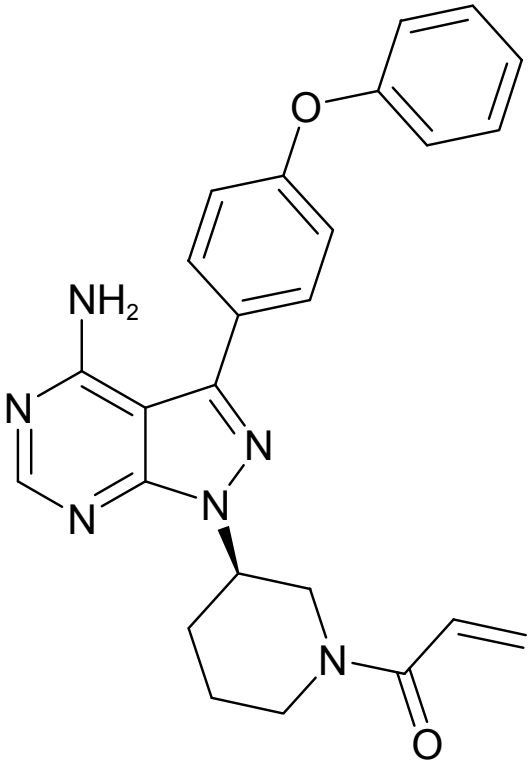
A critical kinase for lymphoma cell survival and proliferation

- BTK is expressed and functional across non-T-cell hematopoietic lineages
- BTK functions downstream in a variety of receptors
  - Essential element of B-cell receptor signaling
  - Chemokine mediated migration & adhesion
  - TLR signaling

- B-cell tumors may be dependent upon BTK for proliferation and survival



Ibrutinib (PCI-32765), a selective inhibitor of BTK



- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or NK-cells
- In CLL cells promotes apoptosis and inhibits CLL cell migration and adhesion
- Phase I/II data of single agent ibrutinib in relapsed/refractory CLL patients demonstrated a high frequency of durable response (O'Brien ASH 2011)

PCYC-1102-CA: Phase IB/II in CLL/SLL

PCYC-1102-CA

Total enrollment 117 patients

Dates enrolled 20th May 10 – 27th Jul 11

Relapsed/Refractory
420 mg/d (n=27)
Median follow-up 17.5 months

Treatment Naïve ≥ 65 yrs
420 mg/d (n=26)
Median follow-up 14.4 months

Relapsed/Refractory
840 mg/d (n=34)
Median follow-up 13.8 months

High-risk Relapsed/Refractory
420 mg/d (n=25)
Median follow-up 7.4 months

Treatment Naïve ≥ 65 yrs
840 mg/d (n=5)
Median follow-up 7.4 months

PCYC-1102-CA: Phase IB/II in CLL/SLL
(Treatment Naïve ≥ 65 yrs population)

PCYC-1102-CA

117 patients

Dates enrolled
20th May 10
– 27th Jul 11

Treatment Naïve ≥ 65 yrs
420 mg/d (n=26)
Median follow-up 14.4 months

Treatment Naïve ≥ 65 yrs
840 mg/d (n=5)*
Median follow-up 7.4 months

**The 840mg TN cohort was terminated after comparable activity and safety between doses was shown in R/R patients. One patient in this cohort received only 420 mg daily.*

Study Design:

- Ibrutinib as a single agent for treatment naïve CLL/SLL patients aged 65 and older
- Two fixed continuous doses 420 mg/day or 840 mg/day until disease progression
- Objectives to evaluate:
  - Safety
  - Response rate
  - PFS

Patient Characteristics

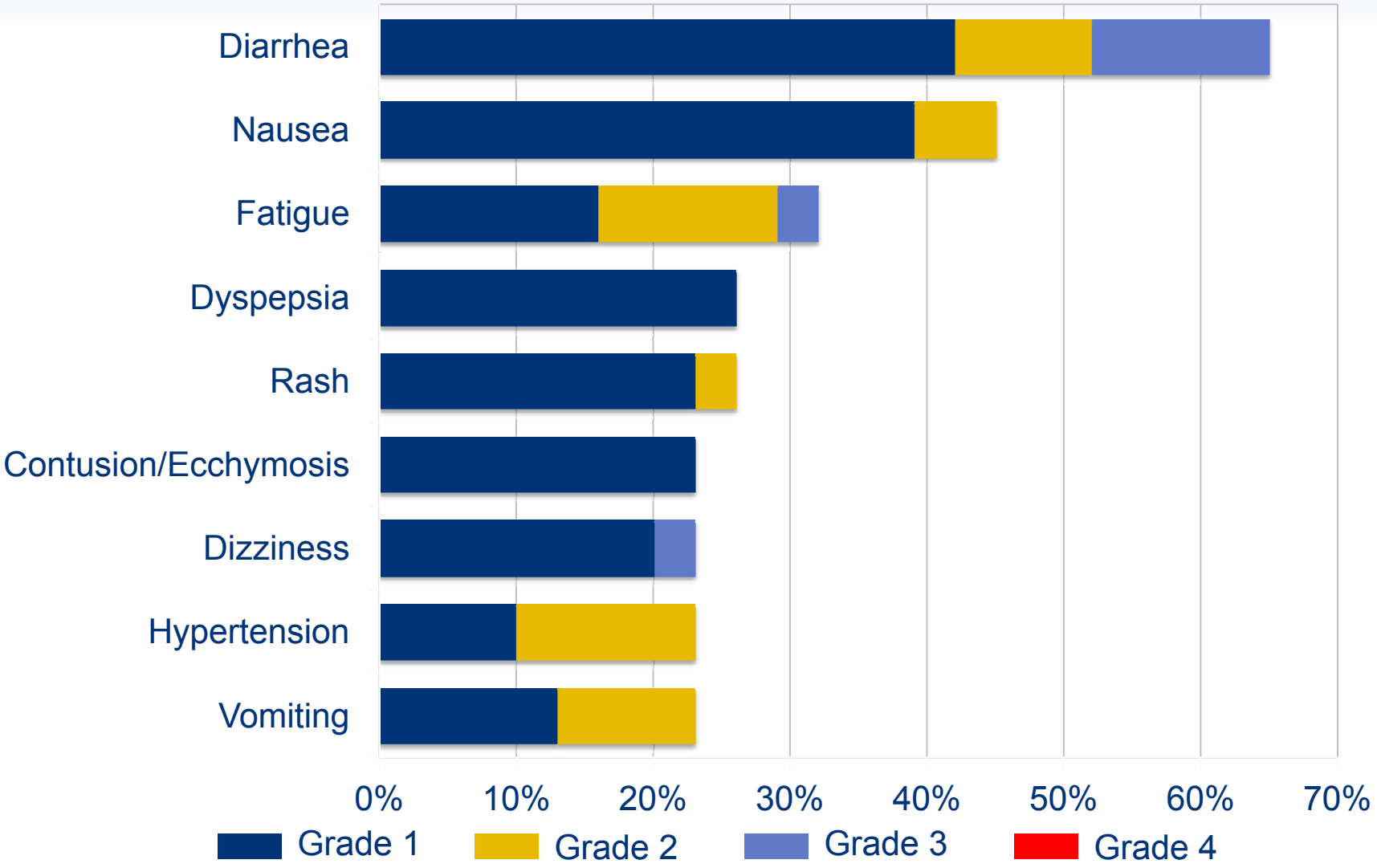
	420 mg/d (N=26)	840 mg/d (N=5)	Total (N=31)
Age, years			
Median (Range):	71 (66 – 84)	71 (65 – 77)	71 (65 – 84)
≥70 years, # (%)	20 (77)	3 (60)	23 (74)
ECOG Performance Status, # (%)			
0	18/25 (72)	2 (40)	20/30 (67)
1	7/25 (28)	3 (60)	10/30 (33)
β2 Microglobulin > 3mg/L	7 (27)	0	7 (23)
Cytopenia at baseline, # (%)			
HGB < 11g/dL	8 (31)	2 (40)	10 (32)
Platelets < 100,000/µL	11 (42)	1 (20)	12 (39)
HGB < 11g/dL or PLT < 100,000 µL	16 (62)	3 (60)	19 (61)
Prognostic Markers, # (%)			
IgVH unmutated:	11 (42)	2/4 (50)	13/30 (43)
Del(17p):	2 (8)	0	2 (6)

PCYC-1102-CA: Patient Disposition (Treatment Naïve ≥ 65 yrs)

	420 mg/d (N=26)	840 mg/d (N=5)
Subjects Discontinued, # (%)	4 (15)	1 (20)
Primary Reasons for Discontinuation, # (%)		
Disease Progression	1 (4)[a]	0 (0)
Adverse event Unrelated: viral syndrome Unrelated: Worsening GI hemorrhage Possibly related: fatigue	2 (8)[b,c]	1 (20)[e]
Subject withdrew consent "desired faster response"	1 (4)[d]	
Death on study, # (%)	0	0

days on ibrutinib: a) 280 days; b) 41 days; c) 115 days; d) 41 days; e) 9 days

Common AEs (> 20 %) regardless of relationship
(Treatment Naïve ≥ 65 yrs)



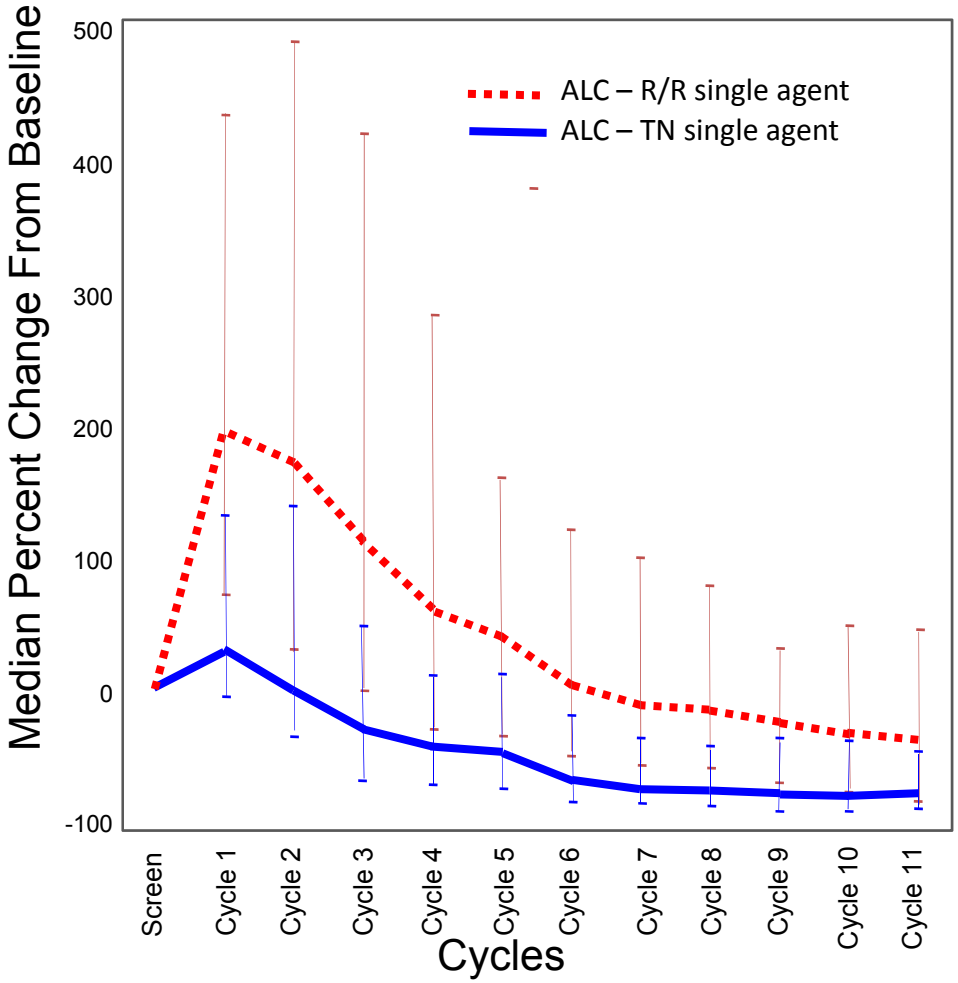
Safety (Treatment Naïve ≥ 65 yrs)

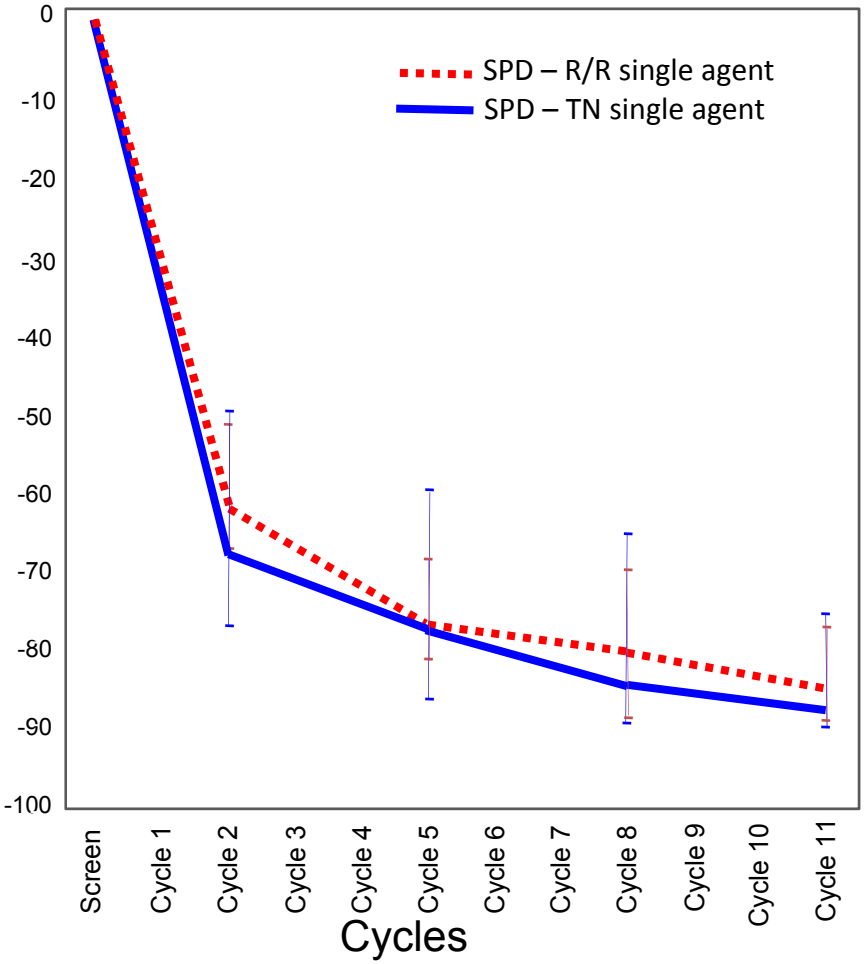
	Total (N=31)	
	Grade 3	Grade 4
Grade 3/4 hematology toxicity, # (%)	**2 (6)**	**2 (6)**
Neutropenia	0	0
Anemia	1 (3)	1 (3)
Thrombocytopenia	1 (3)	1 (3)
Grade 3/4 non-hematology toxicity regardless of relatedness	**6 (19)**	0
Diarrhea	4 (13)	0
Hyponatremia	2 (6)	0
Enterocolitis hemorrhagic	1 (3)	0
Grade 3/4 infections	**3 (10)**	**0**

[1] Reported as AEs

Treatment related lymphocytosis – ibrutinib affects microenvironment

Transient surge in lymphocytes, less pronounced in TN ≥ 65 yrs occurring with rapid resolution of lymph nodes





Response Criteria

- NHL IWG criteria[1] were applied to SLL cases
- The 2008 IWCLL criteria[2] 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 in line with modified IWCLL (2012) and NCCN (2011)
  - "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.
- Responses reviewed and agreed upon by all investigators and Co-PI's (John C. Byrd, MD and Susan O'Brien, MD)

[1]Cheson, et al, J Clin Oncol, 2007
[2]Hallek, et al, Blood, 2008

Best Response

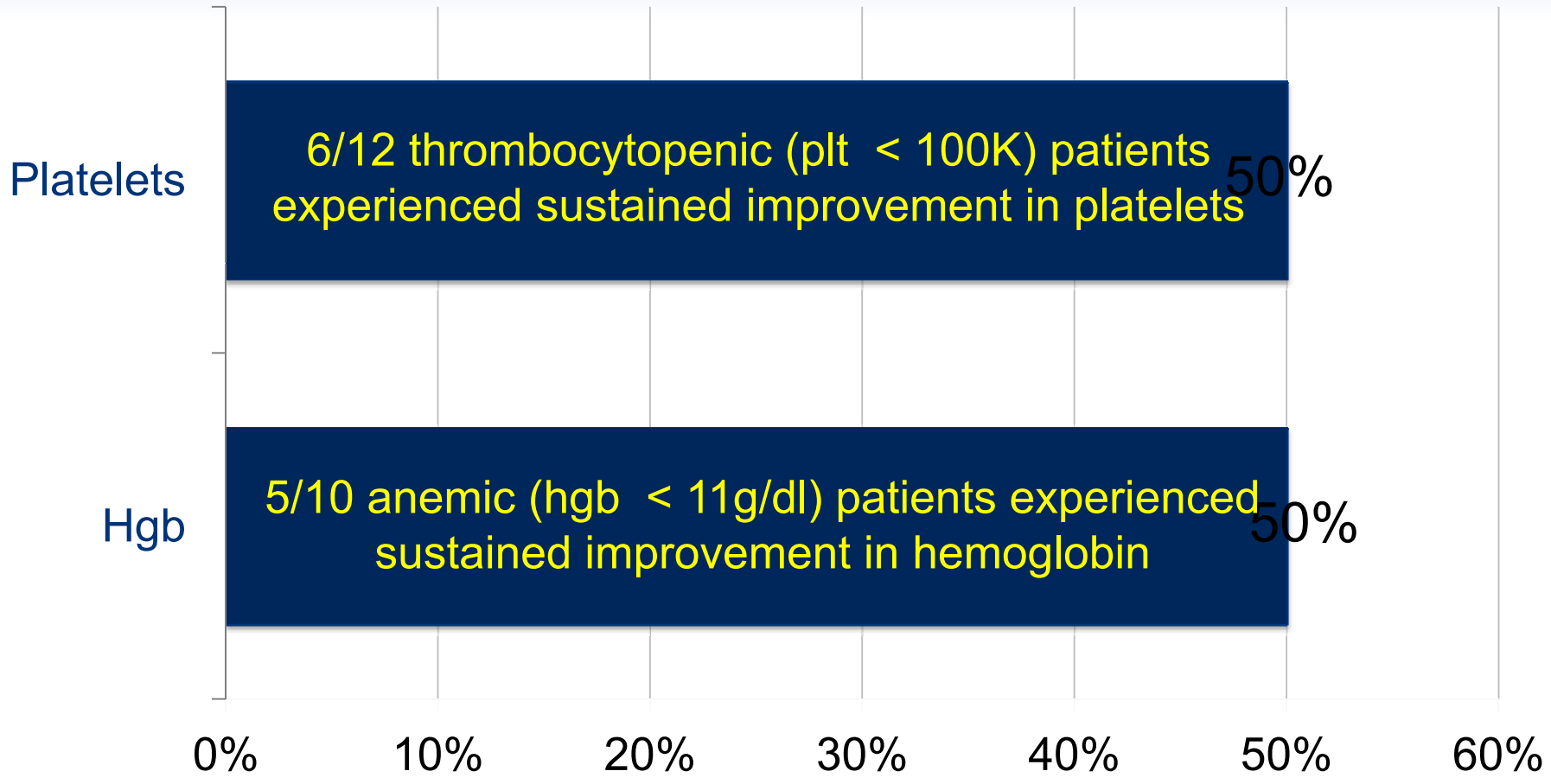
	420 mg/d (N=26) Median f/u = 14.4 mos	840 mg/d (N=5) Median f/u = 7.4 mos	Total (N=31) Median f/u = 12.8 mos
	# (%)	# (%)	# (%)
CR	3 (12)	0	3 (10)
PR	18 (69)	2 (40)	20 (65)
ORR*	**81%**	**40%**	**74%**
Nodal	3 (12)	1 (20)	4 (13)
SD	1 (4)	1 (20)	2 (6)
PD	0	0	0
NE	1 (4)	1 (20)	2 (6)

*Per IWCLL 2008 criteria

PCYC-1102-CA: Best Response by Risk Features (Treatment Naïve ≥ 65 yrs)

	N	ORR % (n)	CR % (n)
All Patients	31	**74** (23)	**10** (3)
≥ 70 years age	23	**70** (16)	**13** (3)
Hgb < 11 g/dL or PLT < 100K/µL at screening	19	**79** (15)	**11** (2)
IgVH unmutated	13	**92** (12)	**15** (2)
Del17p present	2	**100** (2)	**0** (0)
β2 Microglobulin > 3mg/L	7	**86** (6)	**29** (2)

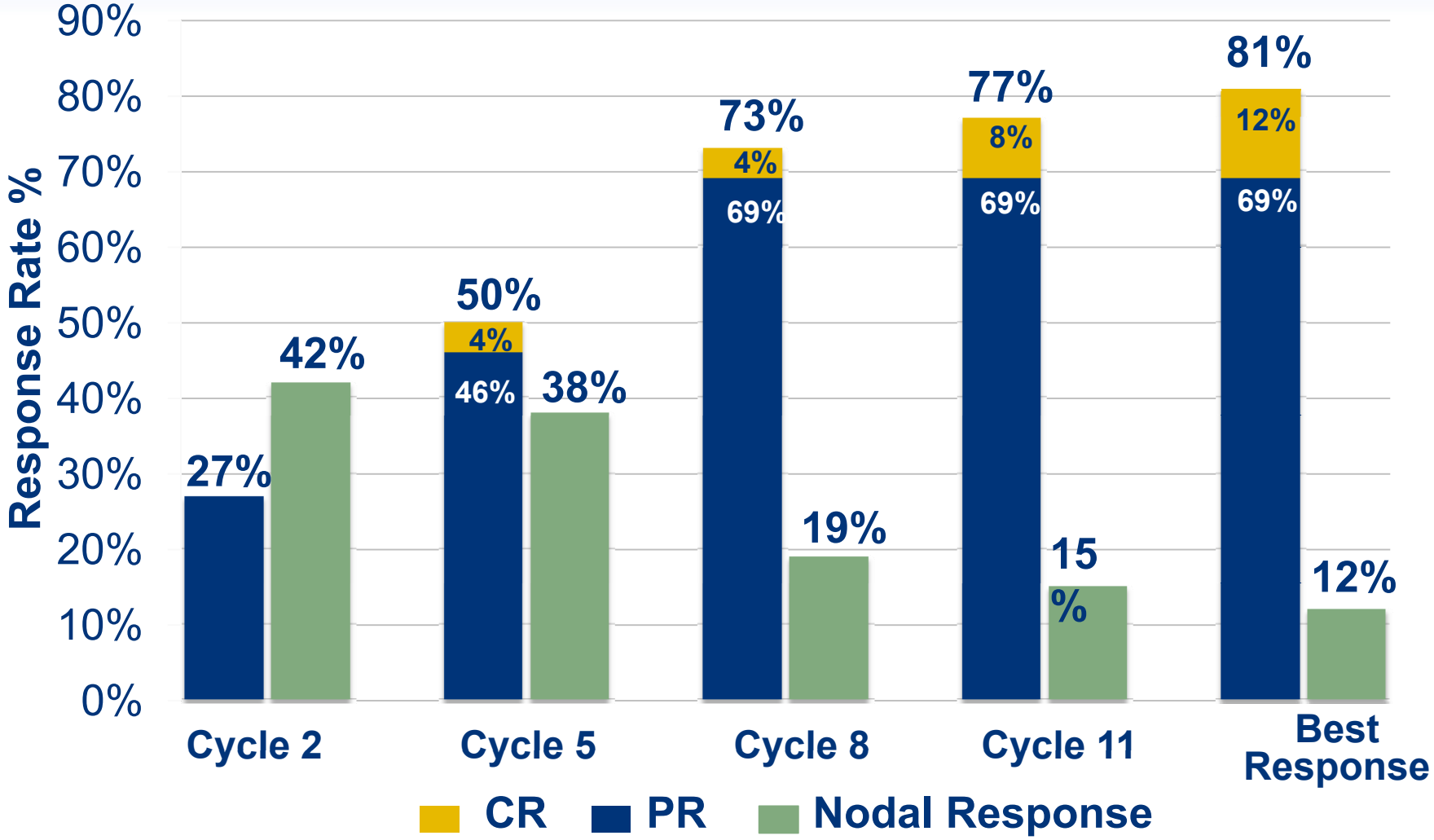
Sustained Improvement* in Hemoglobin and platelet counts in patients with Pre-treatment Cytopenias



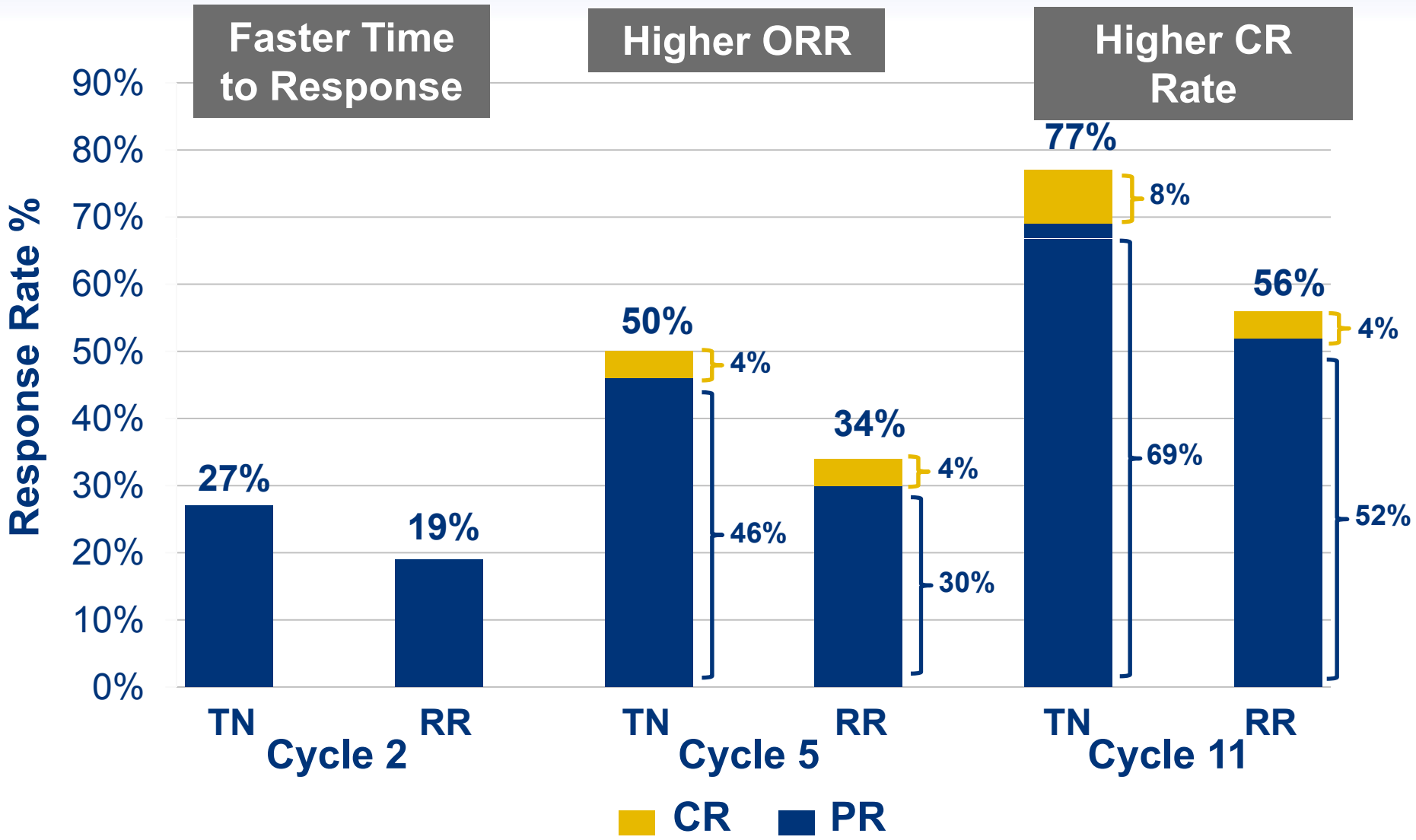
*Sustained improvement is defined as improvement in pretreatment cytopenia by >50%, or achieving a Hgb >11 g/dL OR plts >100,000 sustained for ≥ 60 days without blood transfusion

Cumulative Best Response—Treatment Naïve ≥ 65 yrs

420 mg/d cohort (n=26)—Median f/u 14.4 months

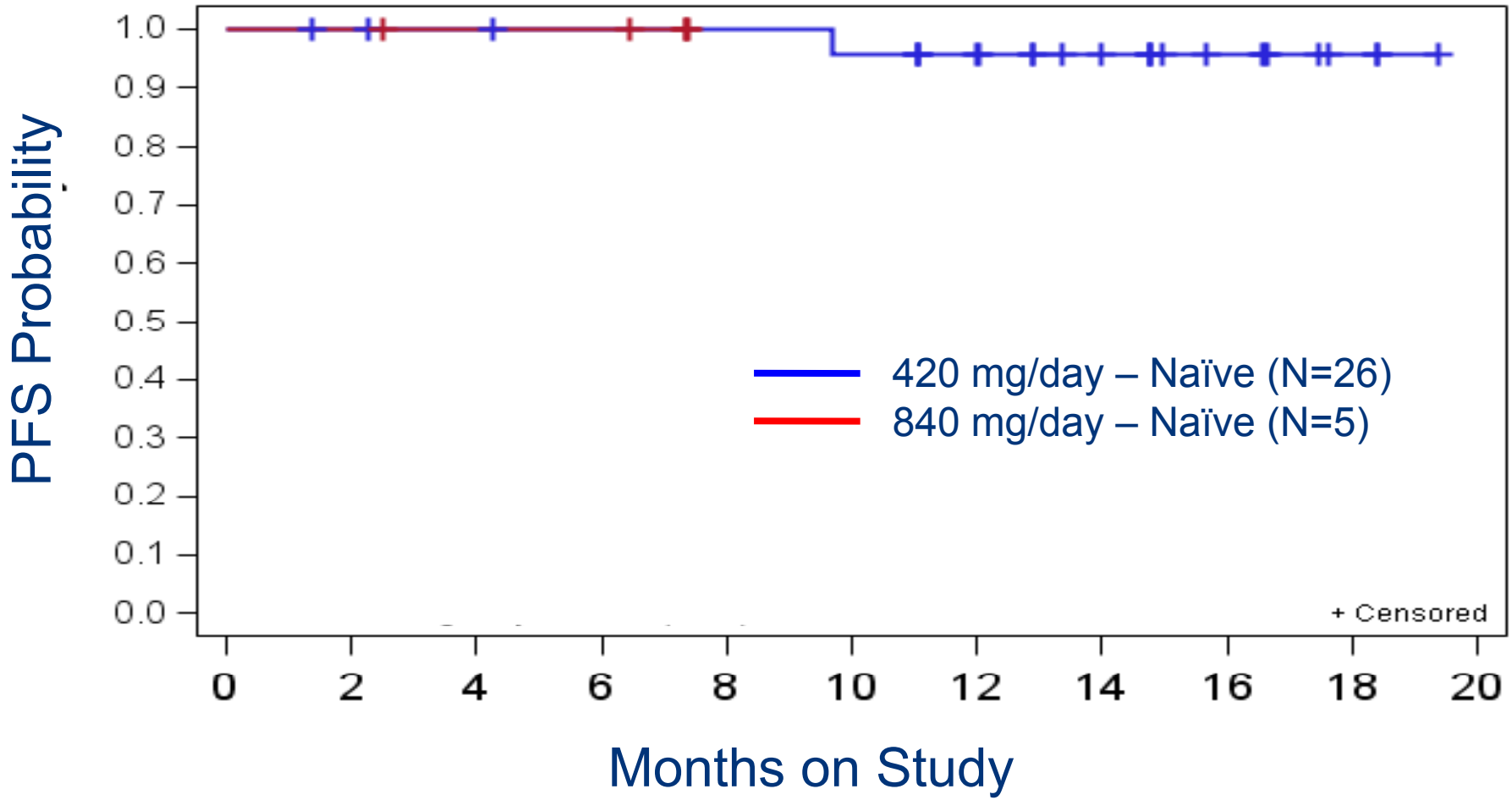


Cumulative Best Response: Comparison of Relapsed/Refractory (n=27) and Treatment Naïve ≥ 65 yrs (n=26) populations at 420 mg



PCYC-1102-CA: Progression-free Survival (Treatment Naïve ≥ 65 yrs)

Estimated 15 mo PFS at 420mg/d = 96%



Data cut-off of 13MAR2012

Summary

Ibrutinib administered as a single-agent to patients ≥ 65 years with treatment naïve CLL:

- Resulted in 81% of patients achieving an IWCLL response with estimated 15-month PFS of 96% with 420mg/d suggesting early durability of treatment benefit
- Responses to the single agent include complete remissions with no morphologic evidence of CLL
- Continuous daily dosing is well tolerated allowing for extended treatment

Acknowledgement

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