The Btk Inhibitor PCI-32765 is highly active and tolerable in patients with poor-risk CLL: Interim results from a Phase Ib/II study.

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Disclosures

Susan O'Brien, MD

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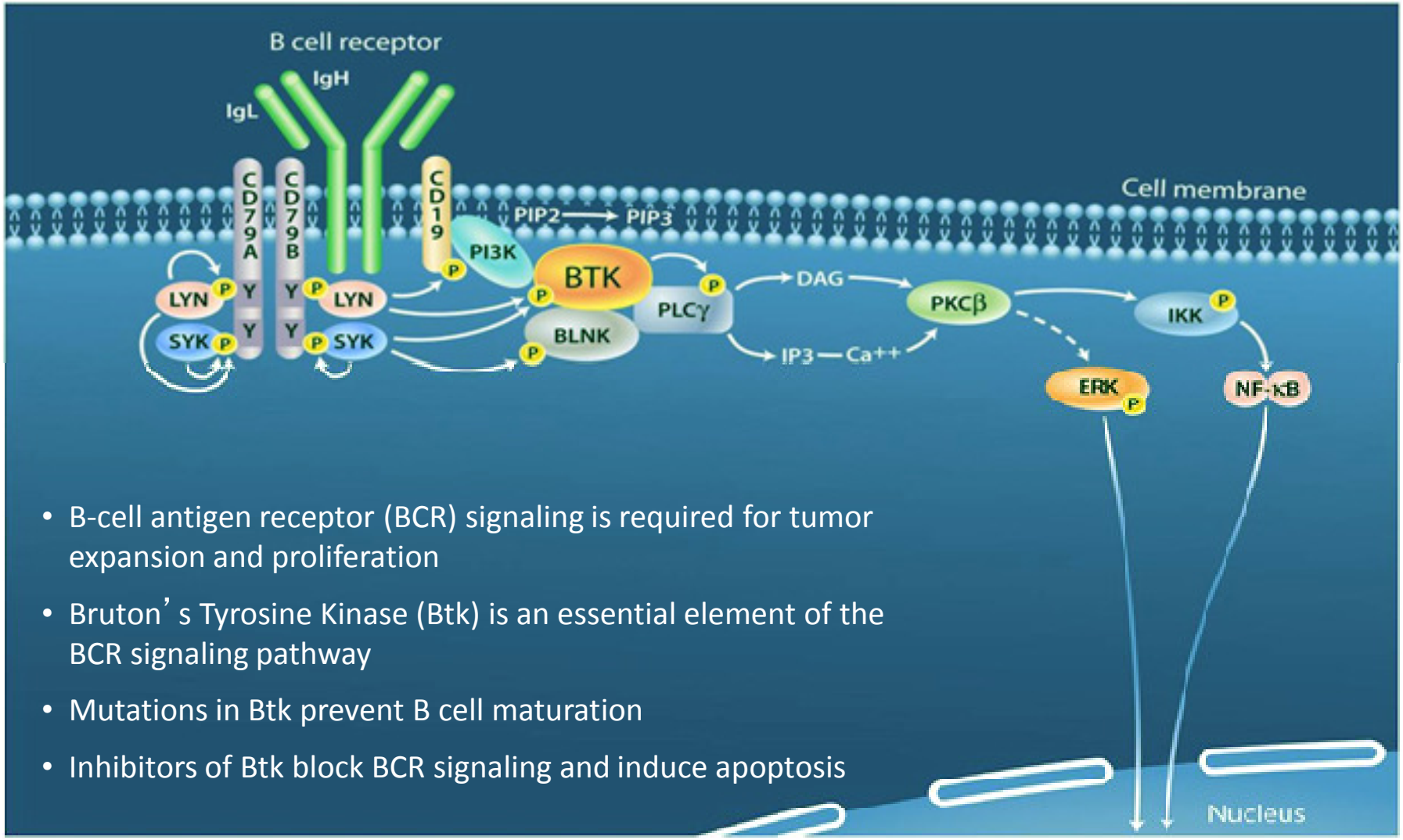
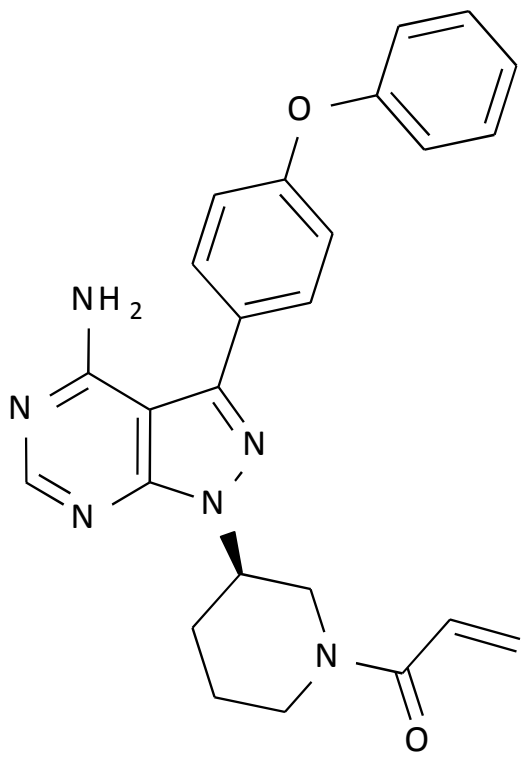
Bruton's Tyrosine Kinase (Btk)

A Critical B-Cell Signaling Kinase



- 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
- Mutations in Btk prevent B cell maturation
- Inhibitors of Btk block BCR signaling and induce apoptosis

PCI-32765: Novel Small Molecule Inhibitor of BTK



PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition at IC_{50} = 0.5 nM
- Orally bioavailable with daily dosing resulting in 24-hr target inhibition
- Inhibits BCR signaling and active 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

Study Design: PCYC 1102

- Single-agent, multi-cohort study of PCI-32765 in two subject populations with symptomatic CLL/SLL
  - Treatment-Naïve, aged ≥ 65 years
    - Dose (May 2010 – March 2011) : 420 mg/day until progression
  - Relapsed/Refractory (RR)
    - Dose #1 (May – September 2010): 420 mg/day until progression
    - Dose #2 (October 2010 – March 2011): 840 mg/day until progression

- Objectives:
  - To determine the response rate , duration of response, PFS, PK/PD, and toxicity in 3 separate cohorts of CLL/SLL subjects
  - To examine influence of genomic features on clinical response to PCI-32765

Interim Analysis of an Ongoing Trial

- Based on data entered into the Pharmacyclics study database by investigators as of May 9, 2011
- Safety population:
  - Subjects initiating treatment prior to March 7: n=83
    - Due to differential follow-up time[1], subjects treated in the 840 mg/d cohort are evaluable only for overall and significant adverse events
- Efficacy (response rate) population:
  - Subjects in safety population AND at least one post-baseline tumor assessment in database as of May 9, 2011 (unless withdrawal prior to first post-baseline assessment): n= 81
    - Due to differential follow-up time[1], subjects treated in the 840 mg/d cohort are evaluable only for the initial (cycle 2) efficacy assessment

[1]Differential follow-up as measured by subject- year: 10.5 for 420 mg/d Treatment Naïve, 16.4 vs 11.3 for 420 mg/d vs 840 mg/d Relapsed Refractory.

Subject Eligibility

- Diagnosis of CLL or SLL and requirement for treatment per NCI or IWG guidelines
- For relapsed/refractory cohorts: ≥2 prior therapies including a purine analog
- Adequate end-organ function
  - ANC ≥ 0.75 x 10^9/L * Platelets ≥ 50 x 10^9/L *
  - ALT ≤ 2.5 x ULN Creatinine ≤ 1.5 x ULN
- No active/uncontrolled infection
- No secondary malignancy limiting survival to < 2 years

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

Subject Characteristics

	Treatment-Naïve 420 mg/d (N=23)	Relapsed/Refractory 420 mg/d (N=27)	Relapsed/Refractory 840 mg/d (N=33)
Age, y			
Median:	71	64	65
Range:	66 – 84	40 – 81	44 – 80
Dx, # pts			
CLL:	22 (96%)	26 (96%)	32 (97%)
SLL:	1 (4%)	1 (4%)	1 (3%)
Prior Rx, #			
Median:	0	3	5
Range:		2 – 10	2 – 12
Prior therapy, %			
Nucleoside analog	0 (0%)	27 (100%)	33 (100%)
Rituximab	0 (0%)	25 (93%)	32 (97%)
Alkylator	0 (0%)	24 (89%)	27 (82%)
Alemtuzumab	0 (0%)	5 (19%)	3 (9%)
Bendamustine	0 (0%)	8 (30%)	13 (39%)
Ofatumumab	0 (0%)	8 (30%)	10 (30%)

Subject Characteristics (cont.)

	Treatment-Naïve 420 mg/d (N=23)	Relapsed/ Refractory 420 mg/d (N=27)	Relapsed/ Refractory 840 mg/d (N=33)
Cytopenia at baseline, %			
ANC < 1500/UL	1 (4%)	6 (22%)	17 (52%)
HGB < 11g/dL	7 (30%)	4 (15%)	19 (58%)
Platelets < 100,000/uL	9 (39%)	8 (30%)	22 (67%)
Prognostic Markers, %*			
IgVH unmutated:	8/16 (50%)	17/24 (71%)	18/24 (75%)
Del(17p):	2/17 (12%)	9/24 (38%)	10/25 (40%)
Del(11q):	0/17 (0%)	8/24 (33%)	12/25 (48%)
β Microglobin < 3mg/L	10/16 (62%)	14/23 (61%)	8/25 (32%)
β Microglobin ≥ 3mg/L	6/16 (38%)	9/23 (39%)	17/25 (68%)

* Includes only subjects for whom interphase cytogenetics and IgVH mutational status were available

Subject Disposition

		Treatment-Naïve 420 mg/d (N=23)	Relapsed/ Refractory 420 mg/d (N=27)	Relapsed/ Refractory 840 mg/d (N=33)
Number of subjects		23	27	33
Follow-up	Median (months)	6.3	7.8	4.6
	Range	1.4 - 9.2	0.7 - 9.5	0.3 - 6.5
Subjects still on study		21 (91%)	22 (81%)	28 (85%)
Subject Discontinued		2 (9%)	5 (19%)	5 (15%)
Primary Reasons for Discontinuation				
Disease Progression		0 (0%)	2 (7%)	1 (3%)
Death		0 (0%)	0 (0%)	2 (6%)
Adverse Event		1 (4%)	1 (4%)	1 (3%)
Other		1 (4%)	2 (7%)	1 (3%)

Overview of Safety

	Treatment-Naïve 420 mg/d (n=23)	Relapsed/ Refractory 420 mg/d (n=27)	Relapsed/ Refractory 840 mg/d (n=33)
Death on study, # (%)[1]	0 (0%)	0 (0%)	2 (6%)
Subject with AE leading to discontinuation, # (%)	1 (4%)	1 (4%)	1 (3%)
Subjects with SAE, # (%) --Related SAE, # (%) --All infectious SAEs	4 (17%) 0 (0%) 1 (4%)	11 (41%) 5 (19%) 6 (22%)	15 (46%) 2 (6%) 9(27%)
Subjects with any AE --Grade 3/4 (%, %)	21 (91%) 6/1 (26%, 4%)	27 (100%) 11/3 (41%, 11%)	29 (88%) 16/7 (49%, 21%)
Subjects with Related AE --Related Grade 3/4 (%, %)	17 (74%) 3/0 (13%, 0%)	27 (100%) 5/2 (19%, 7%)	21 (64%) 4/3 (12%, 9%)

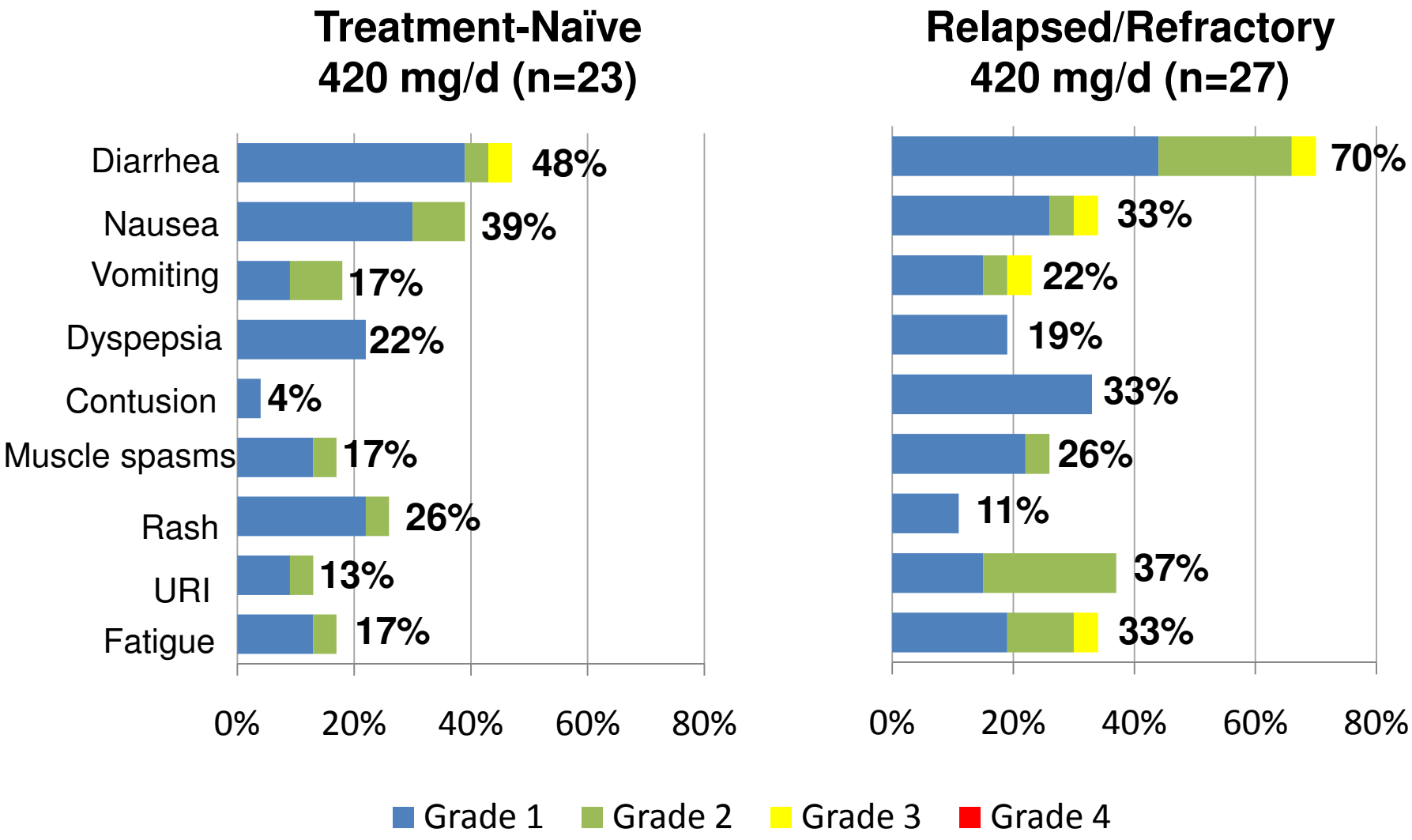
[1] Cause of death: 1 pneumonia, 1 ARDS/cryptooccal pneumonia

Grade 3/4 Hematology Toxicity

Grade 3/4 Hematology toxicity[1]	Treatment-Naïve 420 mg/d (n=23)		Relapsed/ Refractory 420 mg/d (n=27)		Relapsed/ Refractory 840 mg/d (n=33)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Neutropenia	0%	0%	4%	0%	9%	9%
Anemia	4%	0%	7%	0%	9%	3%
Thrombocytopenia	0%	4%	0%	4%	9%	0%

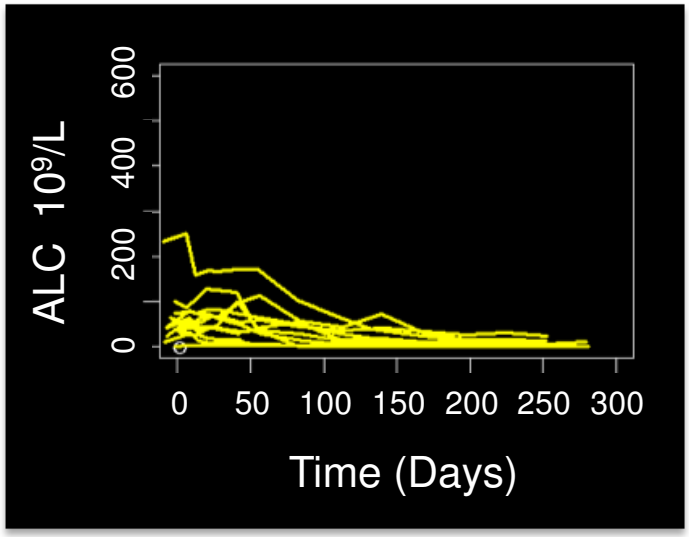
[1] Reported as AEs

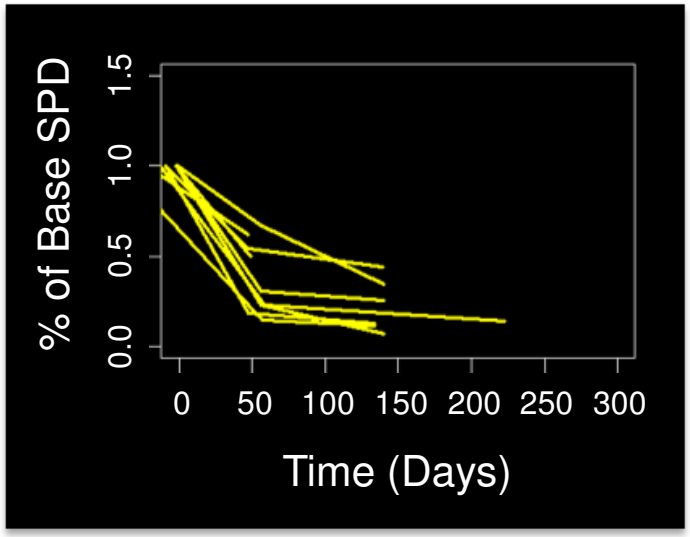
Common AEs (All Grades)



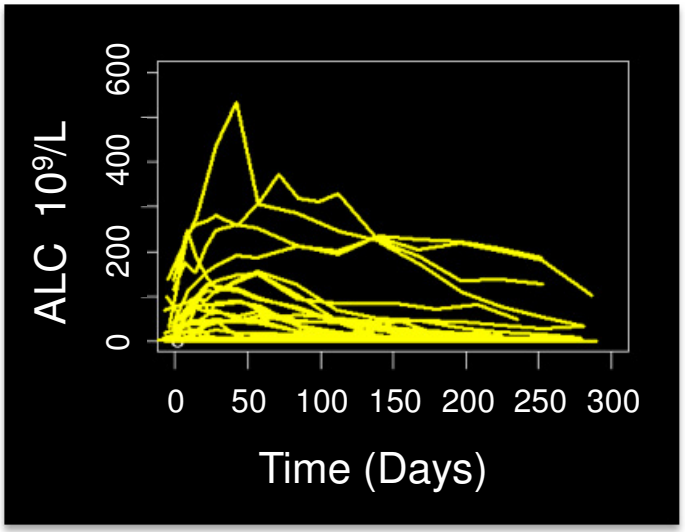
Pattern of Response: Blood Lymphocytes vs Lymph Nodes

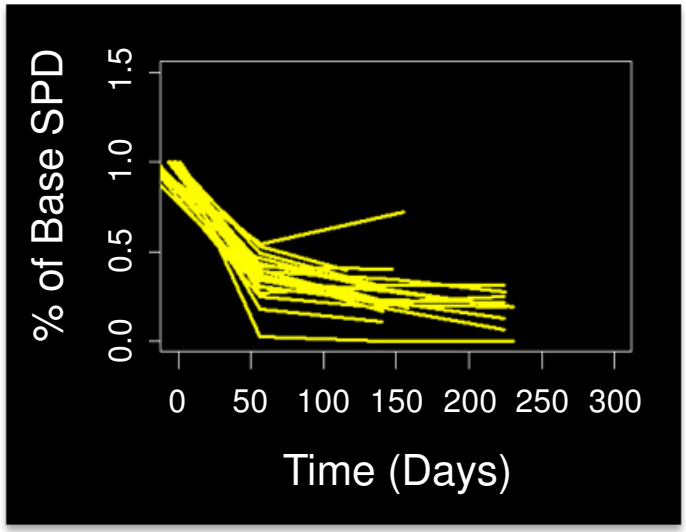
Treatment-Naïve Patients





Relapsed/Refractory Patients





Response Criteria

- NHL IWG criteria[1] were applied to SLL cases without modification.
- The 2008 CLL IWG criteria[2] were applied to CLL cases with the following modifications:
  - An isolated lymphocytosis, in the absence of other parameters meeting the criteria for PD, was not considered PD.
  - Subjects experiencing a lymphocytosis, but obtaining a PR by other measurable parameters, were classified as "nodal" response until there was a 50% reduction in ALC from baseline.
  - Subjects with a normal ALC (<5K) at baseline with treatment-related lymphocytosis required normalization to <5K to be categorized as PR.
  - All investigators applied these rules in adjudication.

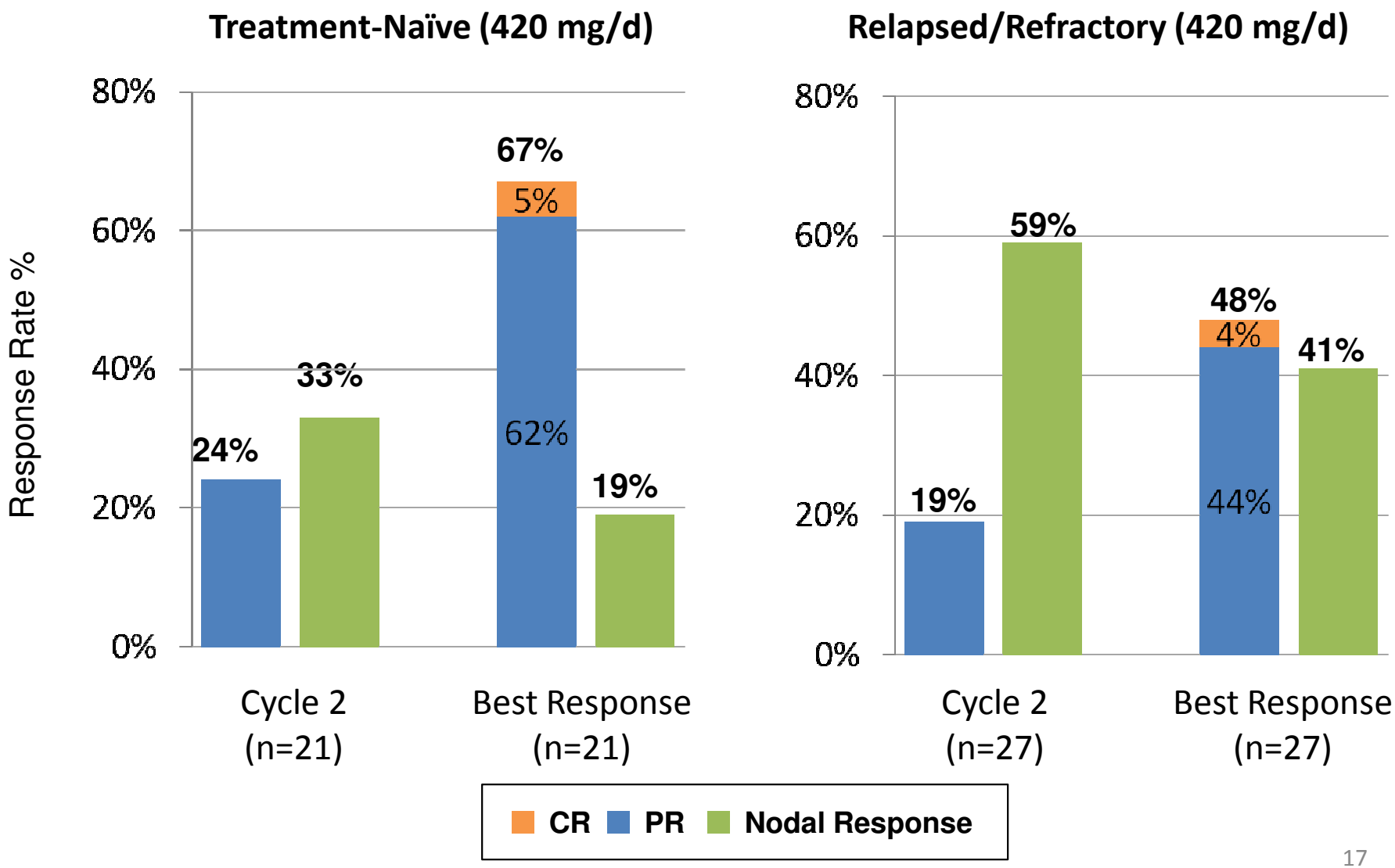
[1] Cheson, et al, J Clin Oncol, 2007

[2] Hallek, et al, Blood, 2008

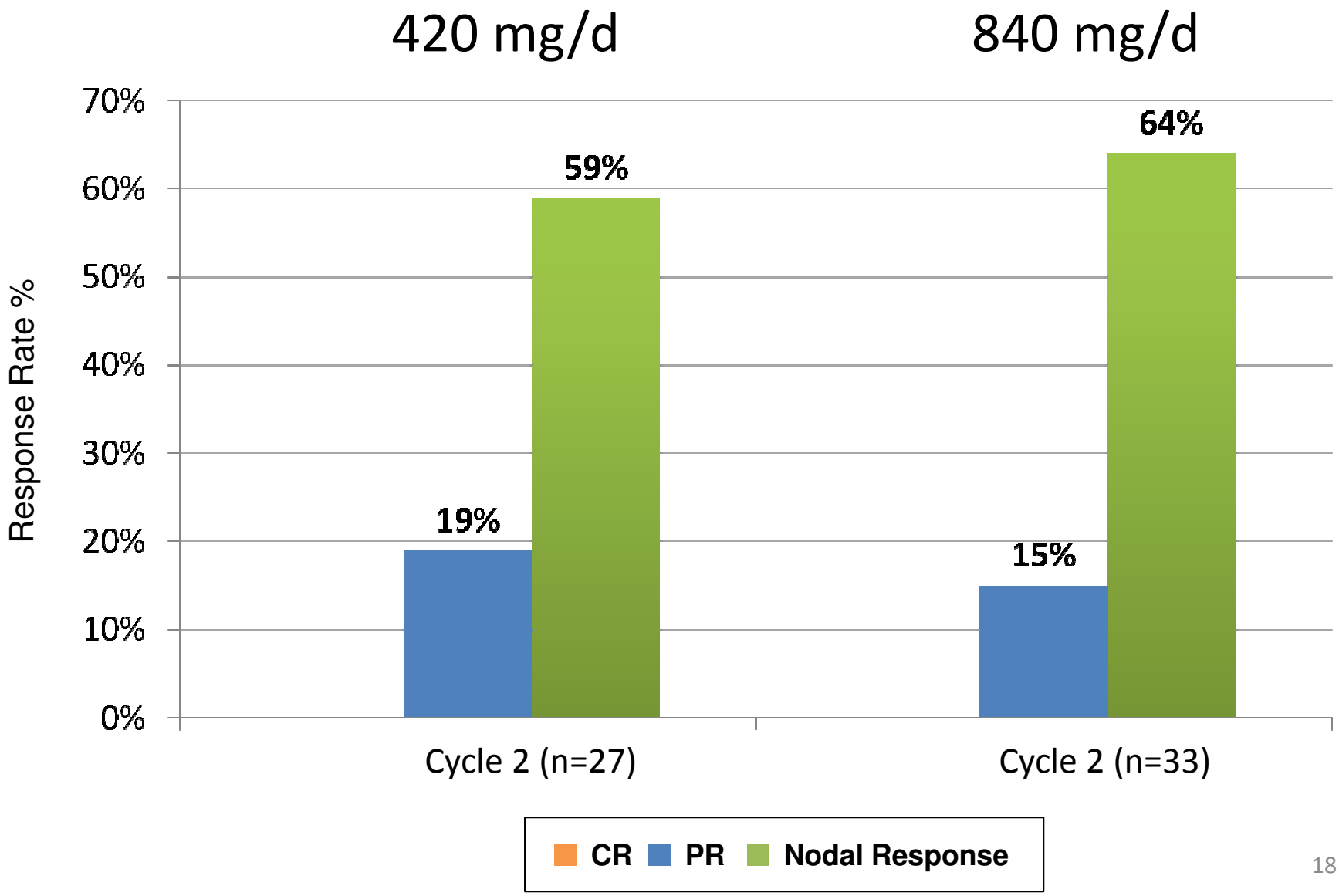
Best Response

	Treatment-Naïve 420 mg/d	Relapsed/ Refractory 420 mg/d
N	21	27
CR	1 (5%)	1 (4%)
PR	13 (62%)	12 (44%)
ORR%	**67%**	**48%**
Nodal	4 (19%)	11 (41%)
SD	2 (10%)	1 (4%)
PD	0	1 (4%)
NE	1 (5%)	1 (4%)

Initial (Cycle 2) Response Assessment and Best Response (420 mg/d Cohorts)



Initial (Cycle 2) Response Assessment by Dose: Relapsed/Refractory



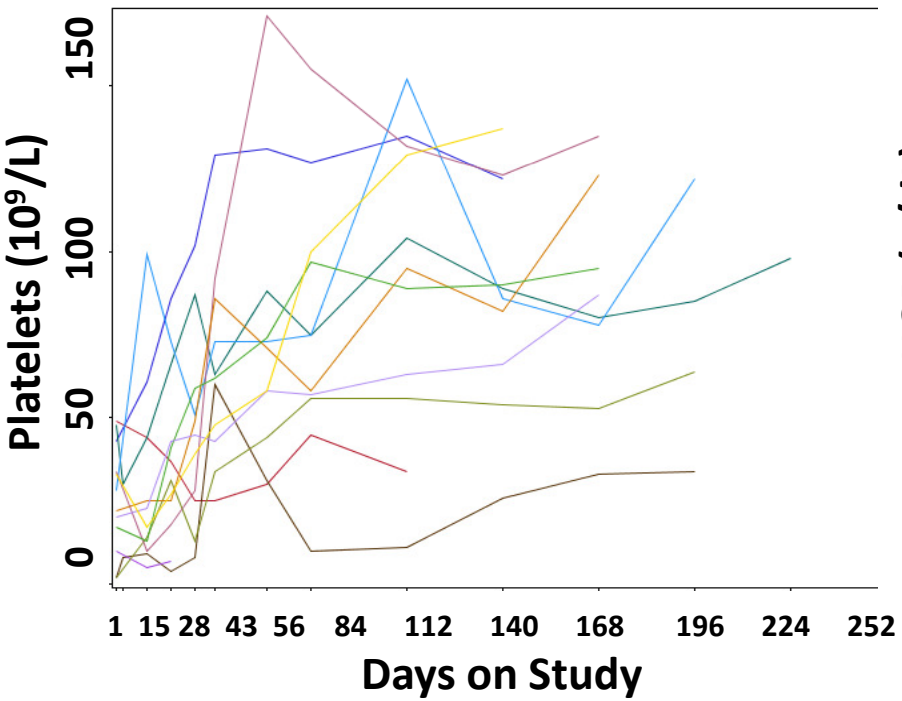
Best Response by Risk Features

Relapsed/Refractory Patients: 420 mg/d Cohort

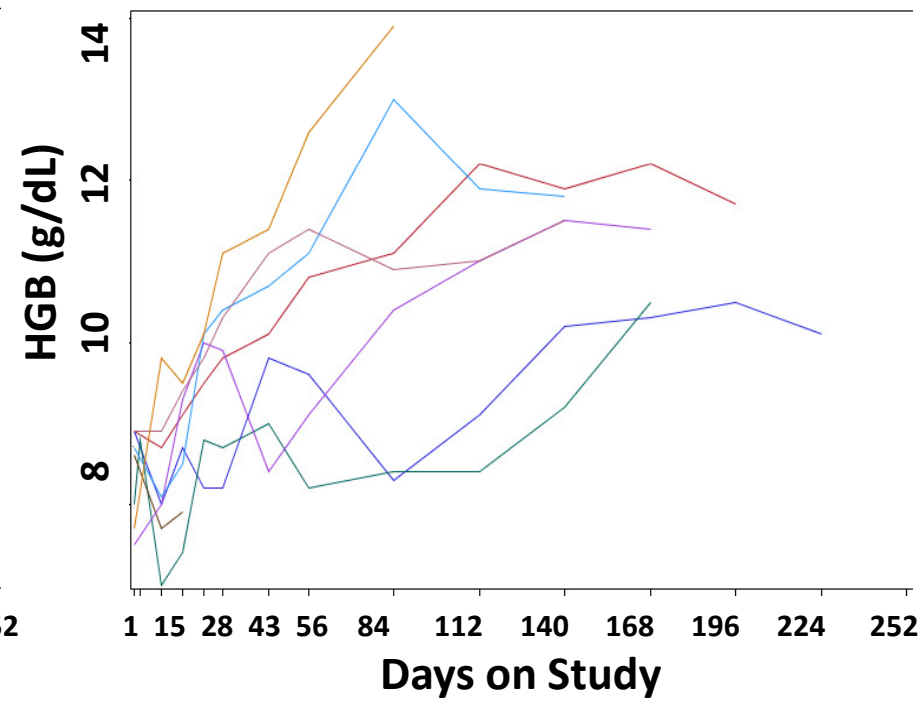
		Best Response	
Molecular Risk Feature	**N**	**IWG Response**	**Nodal Response**
Overall	**27**	**48%**	**41%**
Del17p	9	4/9 (44%)	3/9 (33%)
Del11q	8	5/8 (63%)	3/8 (38%)
IgVH unmutated	17	9/17 (53%)	5/17 (29%)

Improvement in Hematologic Parameters

Platelets over time
in subjects with plt <50x109/L
at study entry
(n=12)

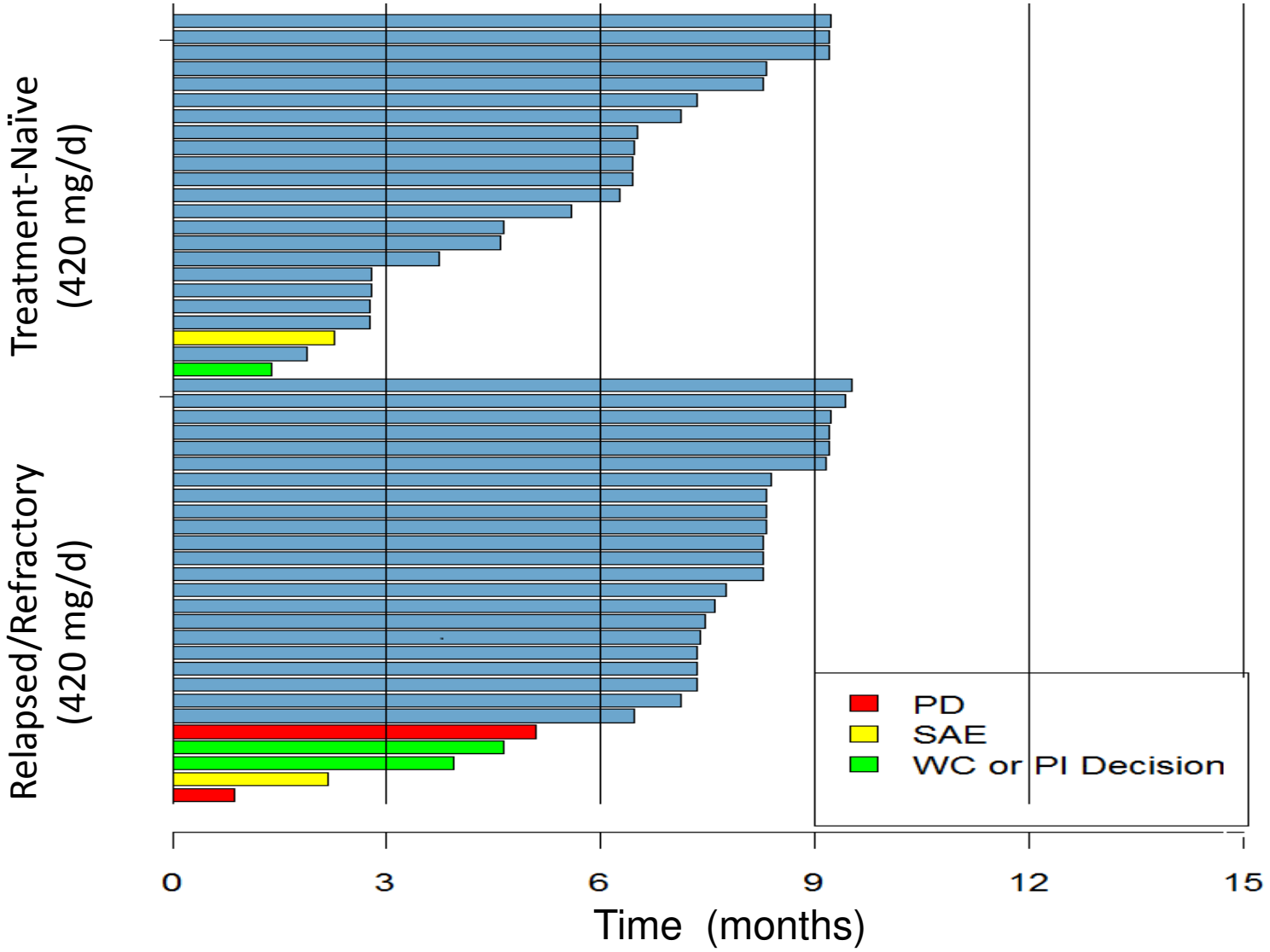


Hemoglobin over time
in subjects with Hgb <9g/dL
at study entry
(n=8)



Subjects from all treatment groups with low baseline measurements are included

Time on Study



Conclusions

- Toxicity of PCI-32765 is modest, generally allowing extended continuous dosing in CLL
  - The majority of adverse events are grade 1 or 2 in severity
  - Cytopenias were relatively uncommon in patients treated at 420 mg/day
    - Grade 3/4 neutropenia was more common in the 840 mg group
- The interim Phase II data confirm that PCI-32765 is highly active in both treatment-naïve and relapsed/ refractory CLL/ SLL patients
  - 2008 CLL IWG objective responses (PR + CR) and nodal responses appear to be durable and independent of high risk genomic features
  - A high proportion (81%) of relapsed or refractory patients are free-of-progression beyond 6 months (420 mg/d cohort)