Safety and Activity of the Highly Specific BTK Inhibitor, BGB-3111 Plus Obinutuzumab in Patients with Follicular Lymphoma and Chronic Lymphocytic Leukemia

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Disclosures

- C Tam, H Quach, A Nicol, H Rose, M Leahy, R Eek, N Wickham, S Patil, and I Flinn have no relevant financial relationships to disclose.
- X Badoux: Roche
- H Prince: Janssen and Celgene
- J Huang, X Zhang, L Wang, E Hedrick, and W Novotny are employed by BeiGene

Background

- Bruton's Tyrosine Kinase (BTK) plays a critical role in B cell receptor signaling, which mediates B cell proliferation, migration, and adhesion[1-3]
  - B cell receptor signaling pathway members are frequently mutated in FL[4]
- Ibrutinib, the first generation BTK inhibitor, has shown activity in FL and CLL in combination with rituximab[5,6]
- BGB-3111 is a potent and specific BTK inhibitor, designed to minimize off target inhibition of TEC- and EGFR-family kinases
  - BGB-3111 has minimal inhibitory effects against ITK and does not inhibit ITK-mediated rituximab-induced ADCC[7]
- Presented here are interim results of an ongoing study of BGB-3111 in combination with obinutuzumab in patients with CLL/SLL and follicular lymphoma

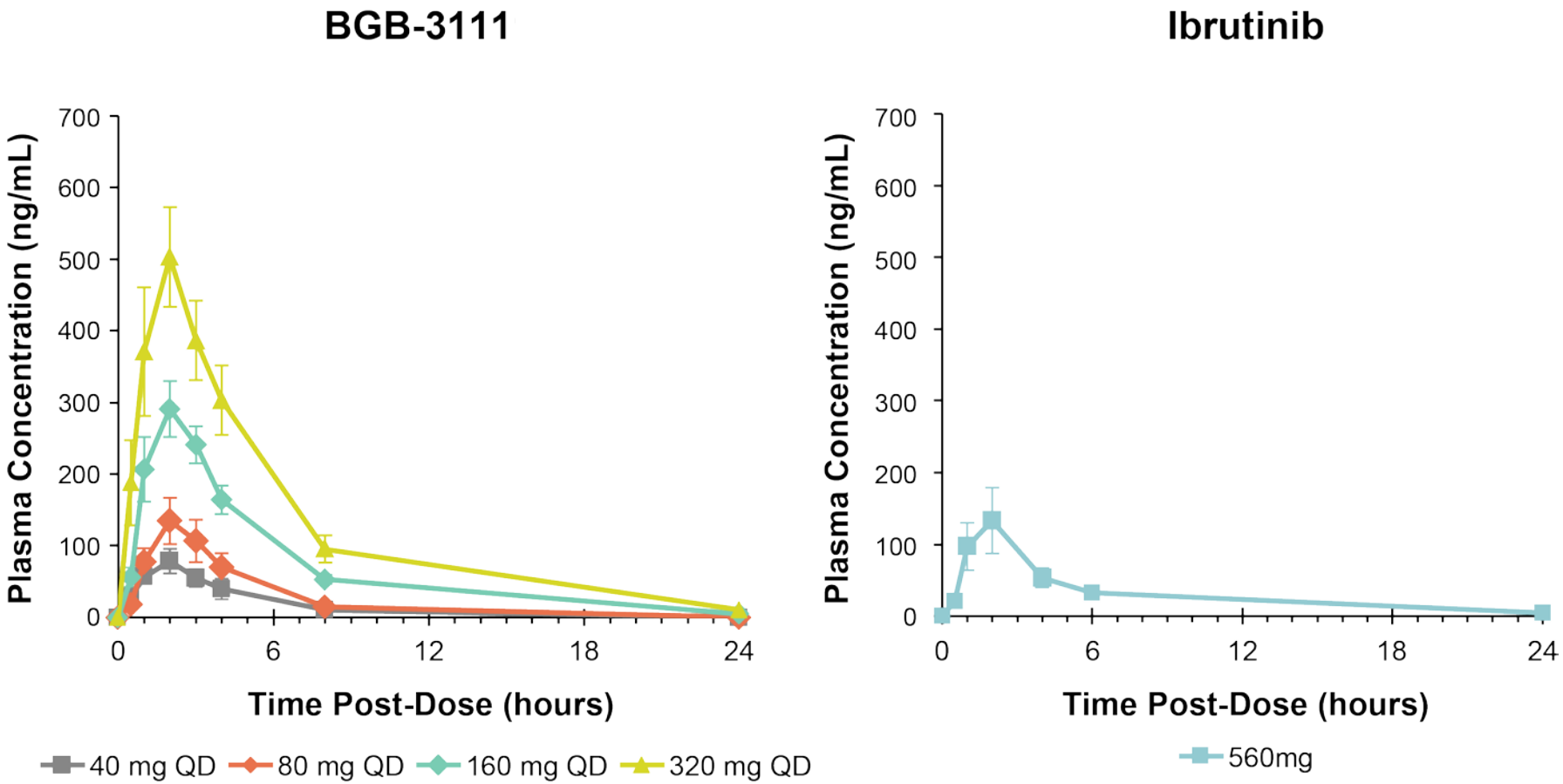
[1] Rickert RC. *Nat Rev Immunol.* 2013. [2] Choe H, Ruan J. *Oncology (Williston Park)*. 2016. [3] Aalipour A, Advani RH. *Br J Haematol.* 2013. [4] Krysiak K, et al. *Blood*. 2017. [5] Fowler N, et al. *Blood.* 2016 [abstract]. [6] Burger JA, et al. *Lancet Oncol.* 2014. [7] Li N, et al. *Cancer Res.* 2015 [abstract].

BGB-3111: Kinase Selectivity Relative to Ibrutinib

Equipotent against BTK compared to ibrutinib
Higher selectivity vs EGFR, ITK, JAK3, HER2 and TEC

Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3,210	9.9
ITK	ITK Occupancy Cellular Assay	189	3,265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3,433	45
	IL-2 Production Cellular Assay	260	2,536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

Plasma Exposure Comparison for BGB-3111 and Ibrutinib

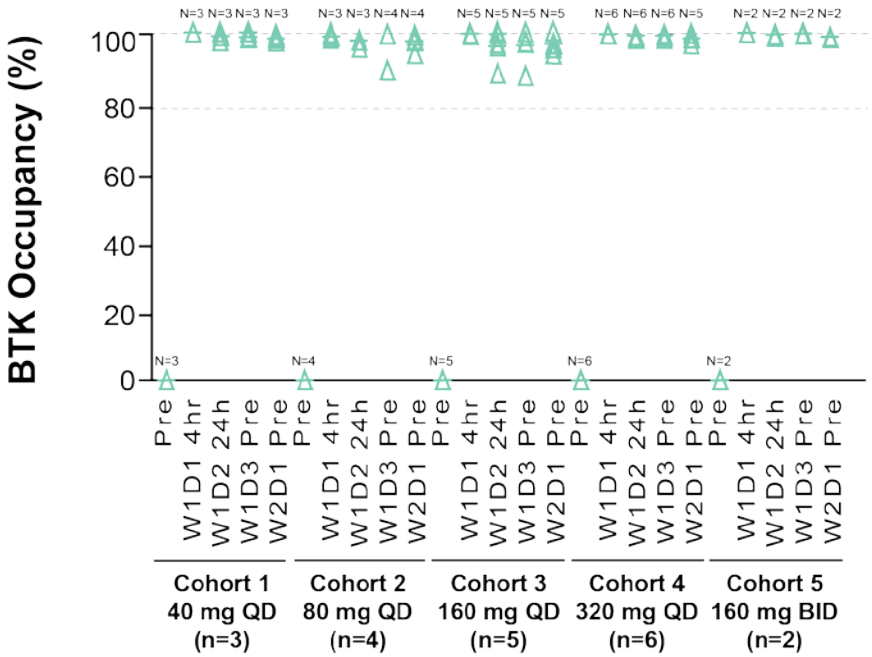


Adapted from Advani, et al, *J Clin Oncol*, 2013[2]

[1] Tam CS, et al. *Blood*. 2015 [abstract]. [2] Advani RH, et al. *J Clin Oncol*. 2013.

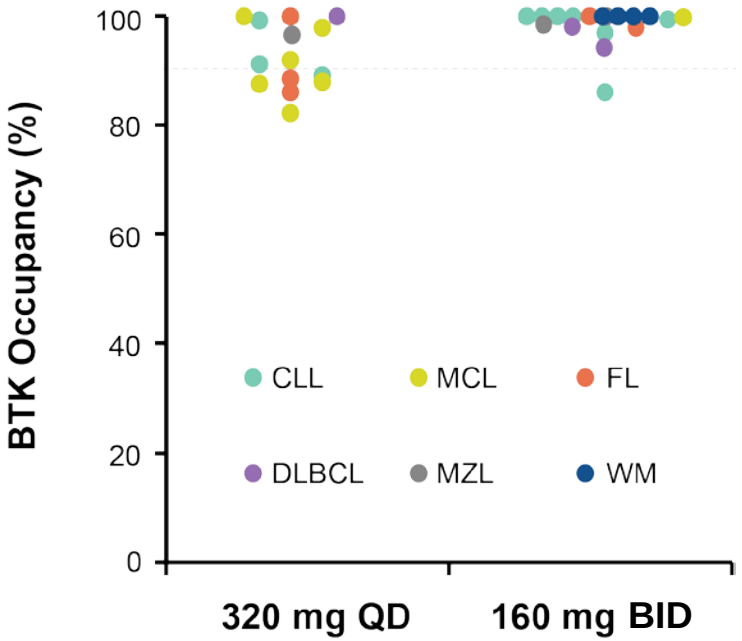
Complete and Sustained BTK Occupancy in PBMC and Lymph Node

PBMC



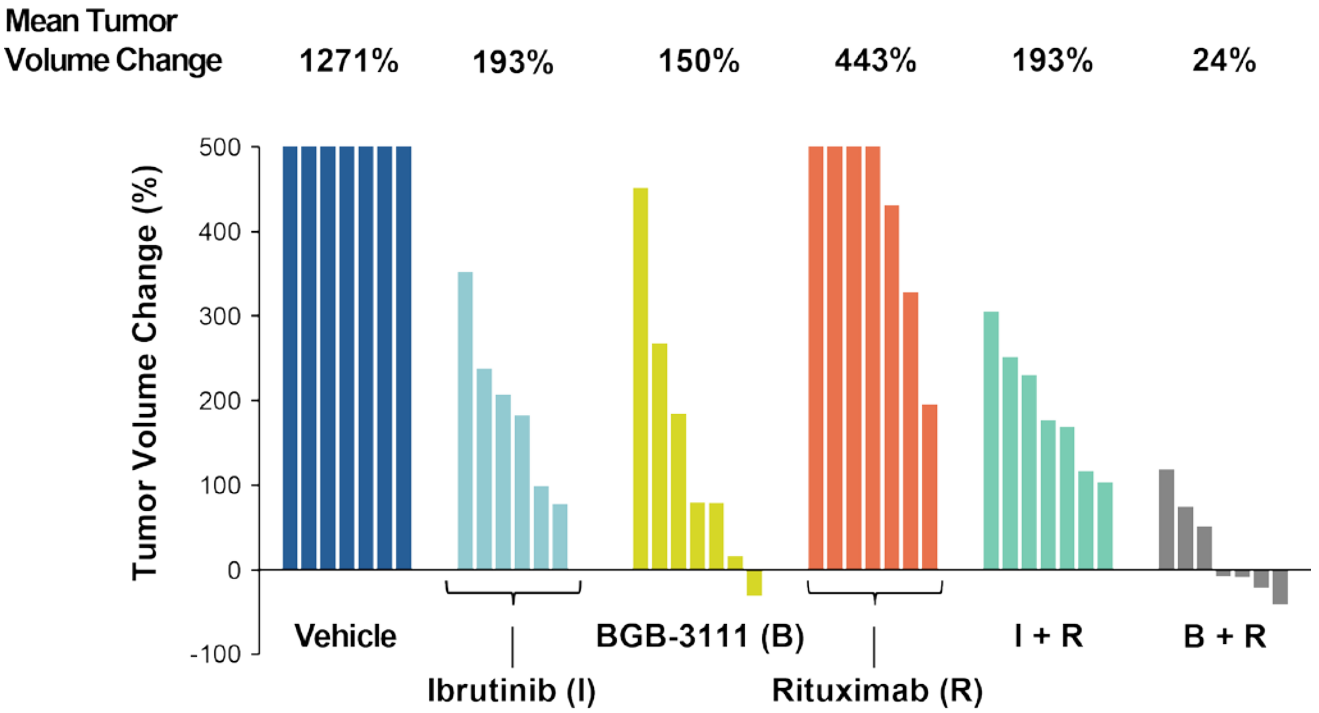
- Complete BTK occupancy in PBMCs at the starting dose (40 mg)

Lymph Node



- Paired lymph node biopsies were collected during screening and pre-dose on day 3
- Median trough occupancy: 100% (160mg BID) vs 94% (320mg QD), p=0.002
- Proportion >90% trough occupancy: 94% (160mg BID) vs 58% (320mg QD), p=0.027

BGB-3111 Does Not Impair Rituximab-Induced ADCC



- Published preclinical data suggest that off-target effects of ibrutinib may be detrimental to CD20 mAb-induced ADCC and the activity of the combination
- In a human MCL xenograft model, the combination of BGB-3111 and CD20 antibody demonstrated improved anti-tumor activity as compared to monotherapies and combination of ibrutinib and CD20 antibody

[1] Li N, et al. *Cancer Res.* 2015;75:2597 [abstract].

Study Design: BGB-3111 in Combination with Obinutuzumab

DOSE ESCALATION

Cohort	BGB-3111* (D1-28/28-day cycles)	Obinutuzumab	Patients Dosed
1a	320 mg QD	Cycle 1 D2: 100 mg Cycle 1 D3: 900 mg Cycle 1 D9 and D16: 1000 mg Cycles 2-6 D1: 1000 mg	4
1b	160 mg BID		5

* BGB-3111 treatment continued until progression, death, or unacceptable toxicity.
† Cohort -1a and -1b will be opened if 2 or more DLTs are observed in Cohorts 1a and 1b.

Eligibility:

- WHO defined B cell lymphoid malignancy
- ≥1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG 0-2
- ANC >1,000/µl, platelets >40,000/µl‡
- Adequate renal and hepatic function
- No significant cardiac disease§

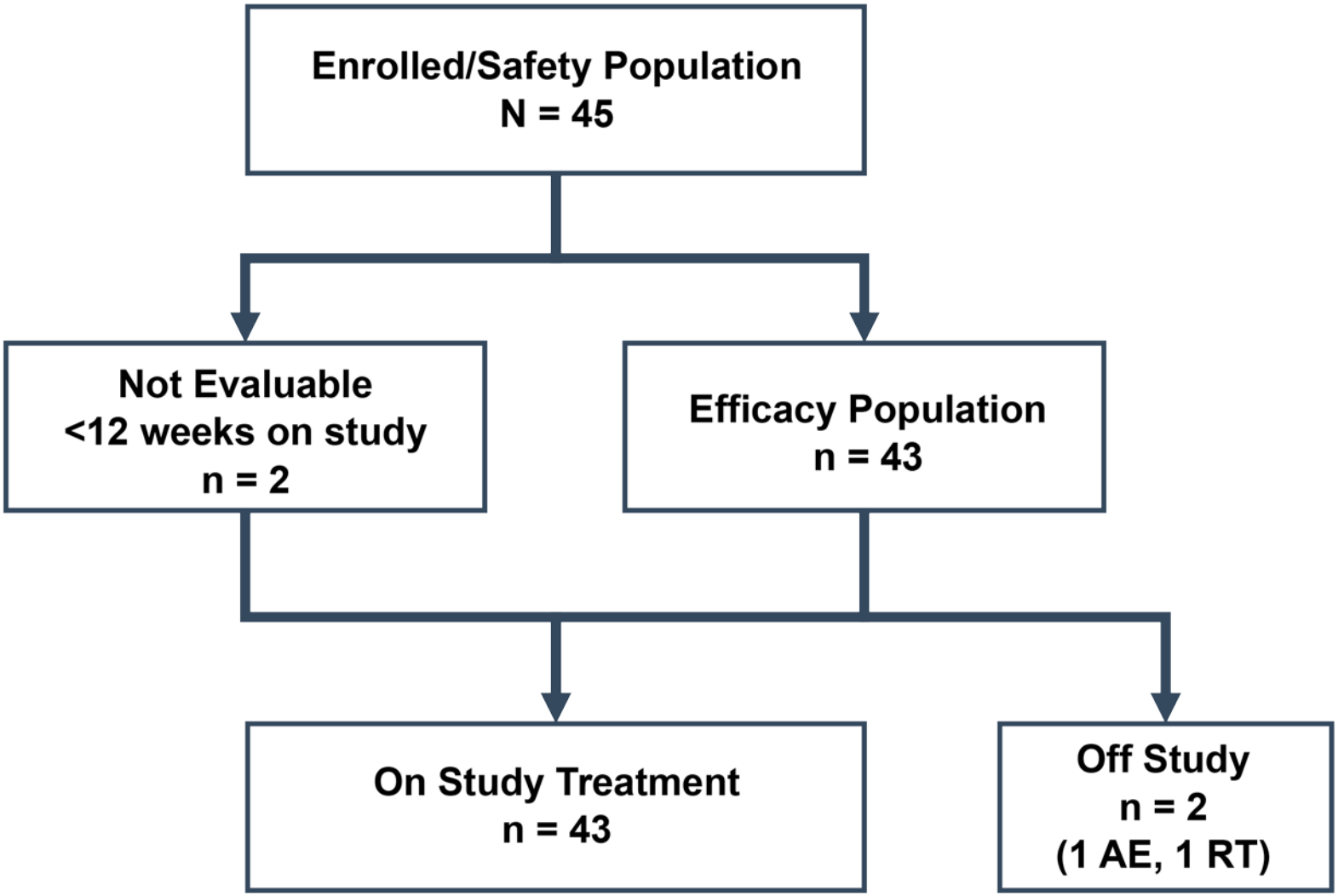
‡ Growth factor/transfusion allowed.
§Anti-coagulation allowed.

DOSE EXPANSION

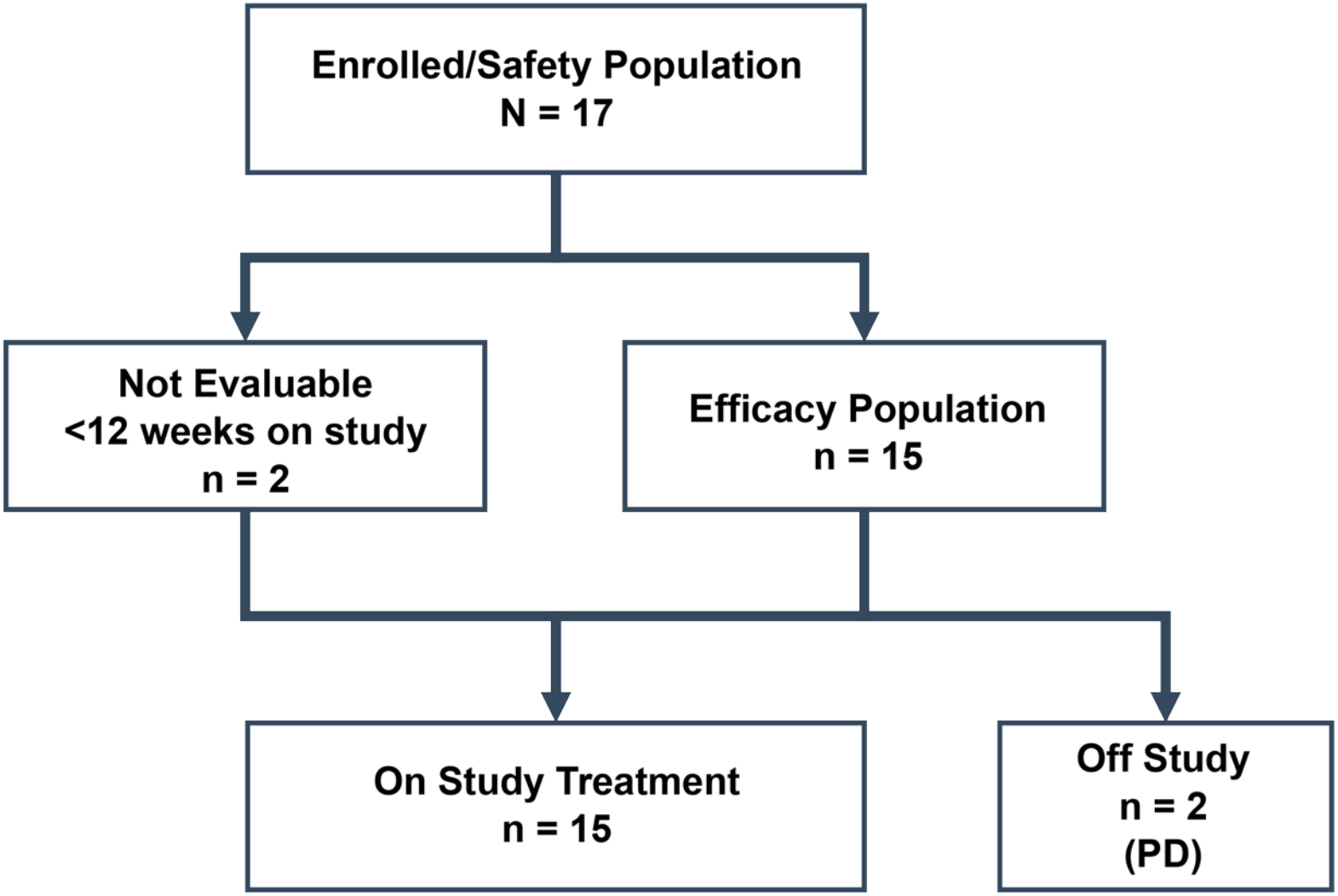
Pop	Disease	Planned
TN	CLL/SLL	20
R/R	CLL/SLL	20
R/R	non-GCB DLBCL	20
R/R	FL, MCL, MZL, and WM	20
R/R	FL	40

NCT02569476

CLL/SLL Patient Disposition (as of 31 March 2017)



FL Patient Disposition (as of 31 March 2017)

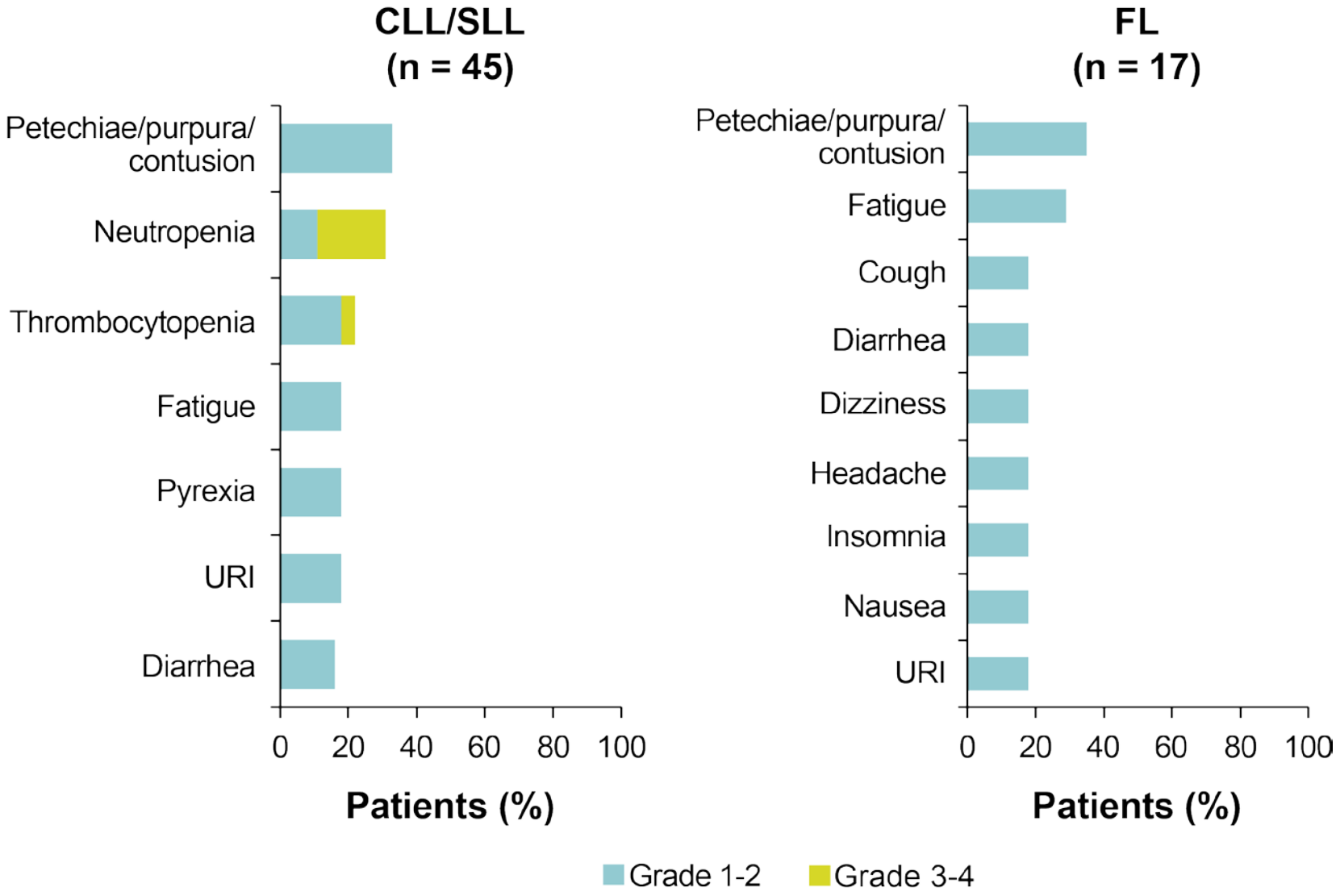


Patient and Disease Characteristics

Characteristic	CLL/SLL (n = 45)	FL (n = 17)
Age, years, median (range)	68 (38-82)	56 (41-86)
ECOG Performance Status, (%) 0 1 2	 19 (42.2) 25 (55.6) 1 (2.2)	 14 (82.4) 2 (11.8) 1 (5.9)
Follow-up, months, median (range)	6.5 (0.5-14.0)	7.9 (0.1-14.2)
Prior Treatment Status Treatment-naïve, n (%) Relapsed/refractory, n (%) Number of prior therapies, median (range)	 20 (44.4) 25 (55.6) 1 (1-4)	 0 17 (100) 3 (1-7)
Bulky Disease*,n (%)	0	2 (11.8)
Molecular Risk Factors, n (%) del17p/p53mut (n = 37) 11q- (n = 37) IGHV unmutated (n = 37) Complex karyotype (n = 37)	 6 (16.2) 6 (16.2) 19 (51.4) 7 (18.9)	 N/A N/A N/A N/A

* Any lymph node >10 cm in maximum diameter.

Most Common Adverse Events
(Regardless of Causality)



Selected Adverse Events

Event, n (%)	CLL/ SLL (n = 45)	FL (n = 17)
Patients with at least one AE Grade ≥3	19 (42.2)	4 (23.5)
Patients with at least one SAE	11 (24.4)	4 (23.5)
Events leading to treatment discontinuation	1 (2.2)*	0

* Patient with a history of squamous cell carcinoma discontinued due to squamous cell carcinoma

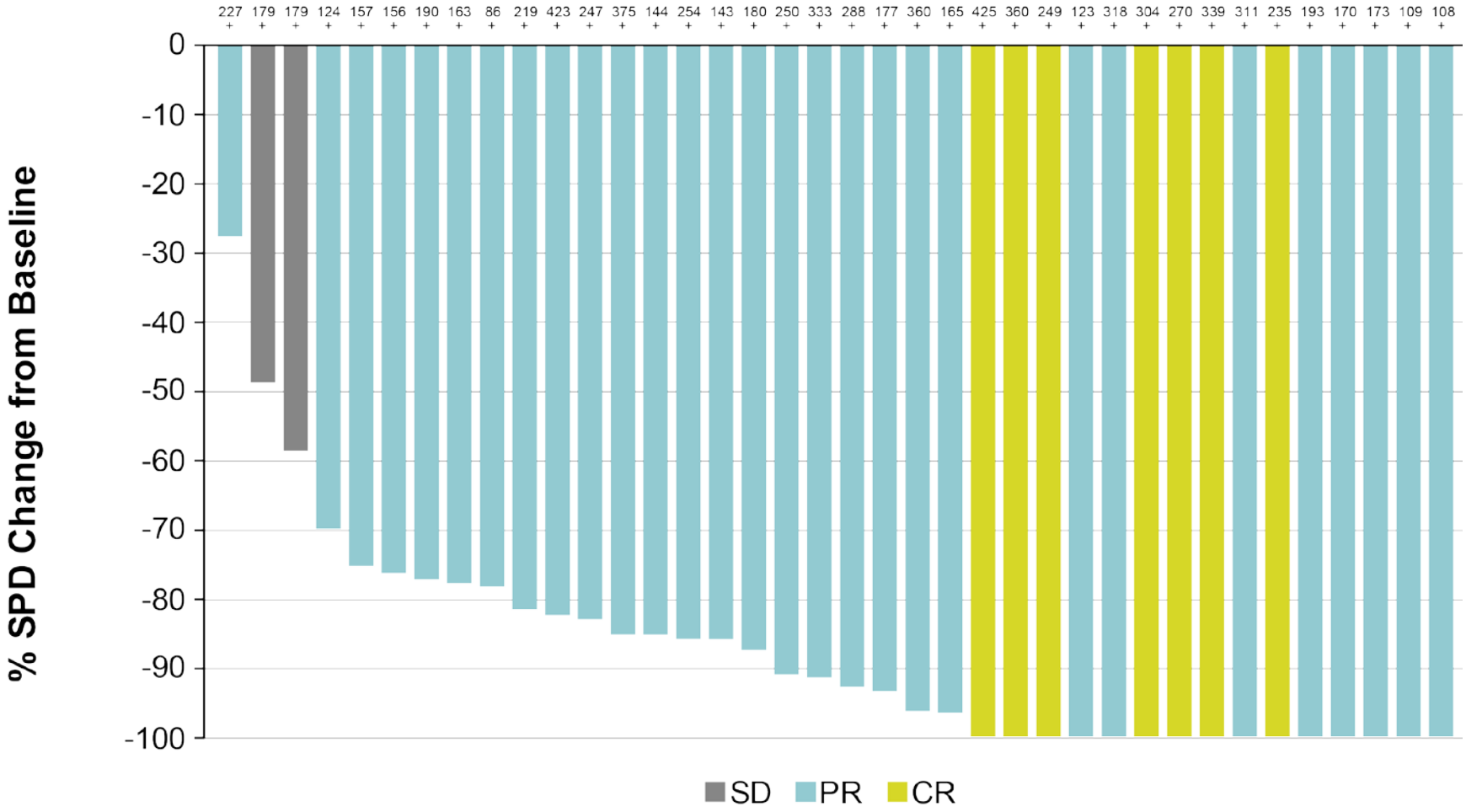
AE of Special Interest, n (%)	CLL/SLL (n = 45)		FL (n = 17)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Diarrhea	7 (15.6)	0	3 (17.6)	0
Serious hemorrhage*	0	0	0	0
Atrial fibrillation	0	0	0	0
Infusion-related reactions	11 (24.4)	1 (2.2)	1 (5.9)	0

* ≥Grade 3 hemorrhage, or central nervous system hemorrhage of any grade.

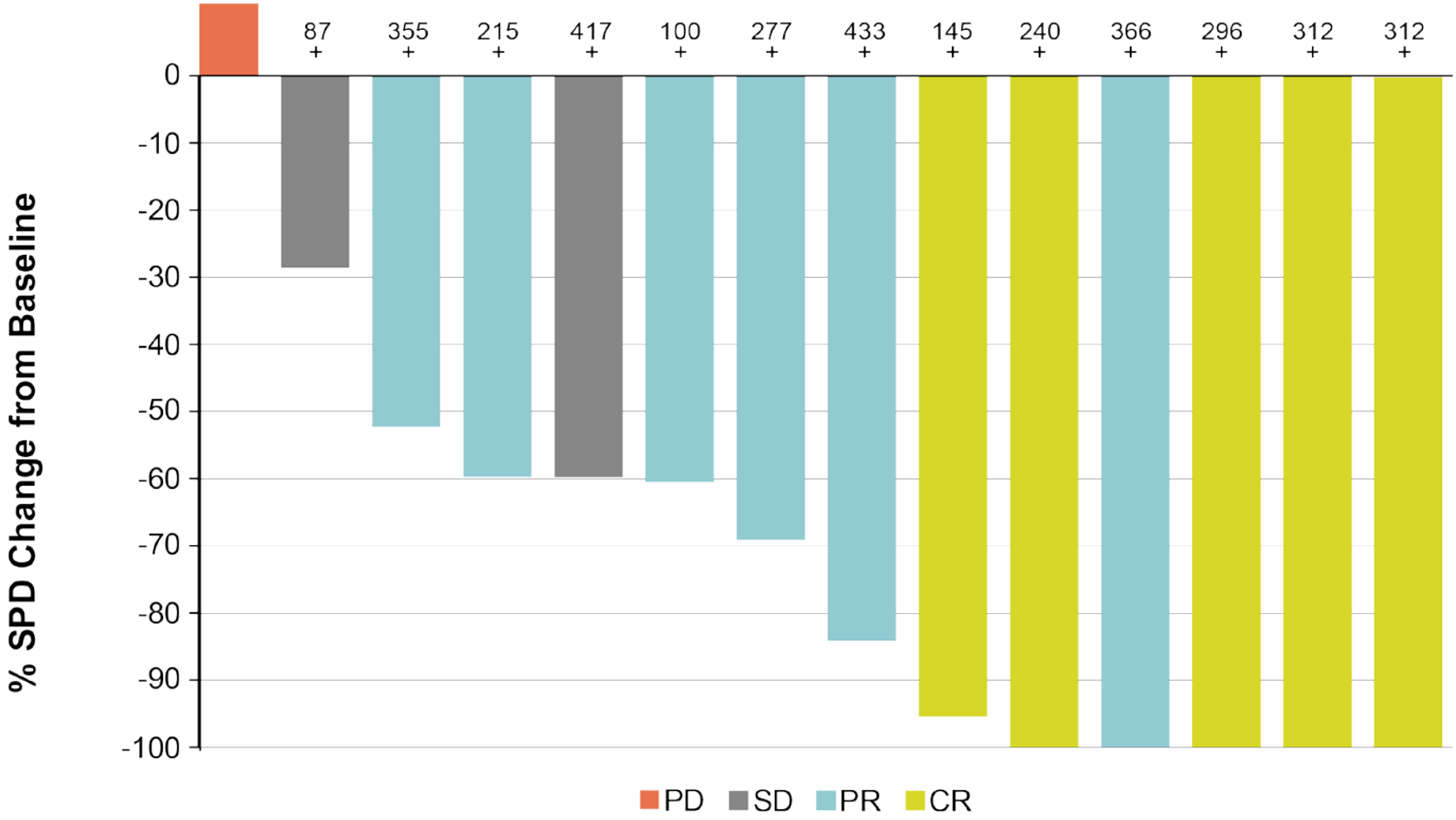
Disease Response

Follow-up and Response	TN CLL/SLL (n = 18)	R/R CLL/SLL (n = 25)	FL (n = 15)
Median follow-up, mo (range)	7.0 (2.8-11.8)	8.0 (3.8-14.0)	6.2 (1.2-10.7)
Best Response			
ORR	**16 (88.9)**	**23 (92.0)**	**11 (73.3)**
CR	4 (22.2)	4 (16.0)	5 (33.3)
PR	12 (66.7)	19 (76.0)	6 (40.0)
PR-L	0	0	N/A
SD	2 (11.1)	1 (4.0)	2 (13.3)
PD	0	1 (4.0)	2 (13.3)

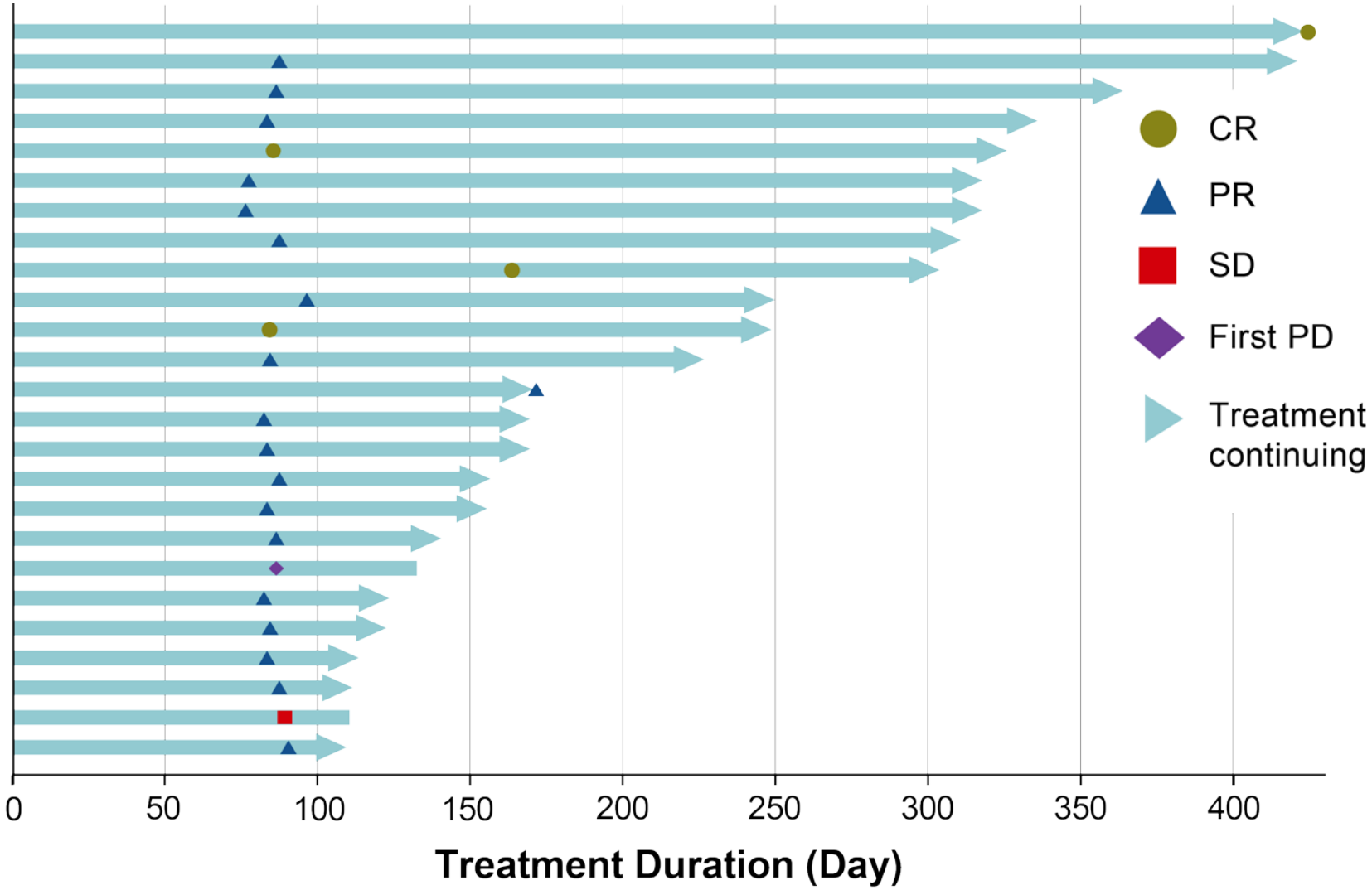
CLL/SLL: Maximum Improvement in SPD



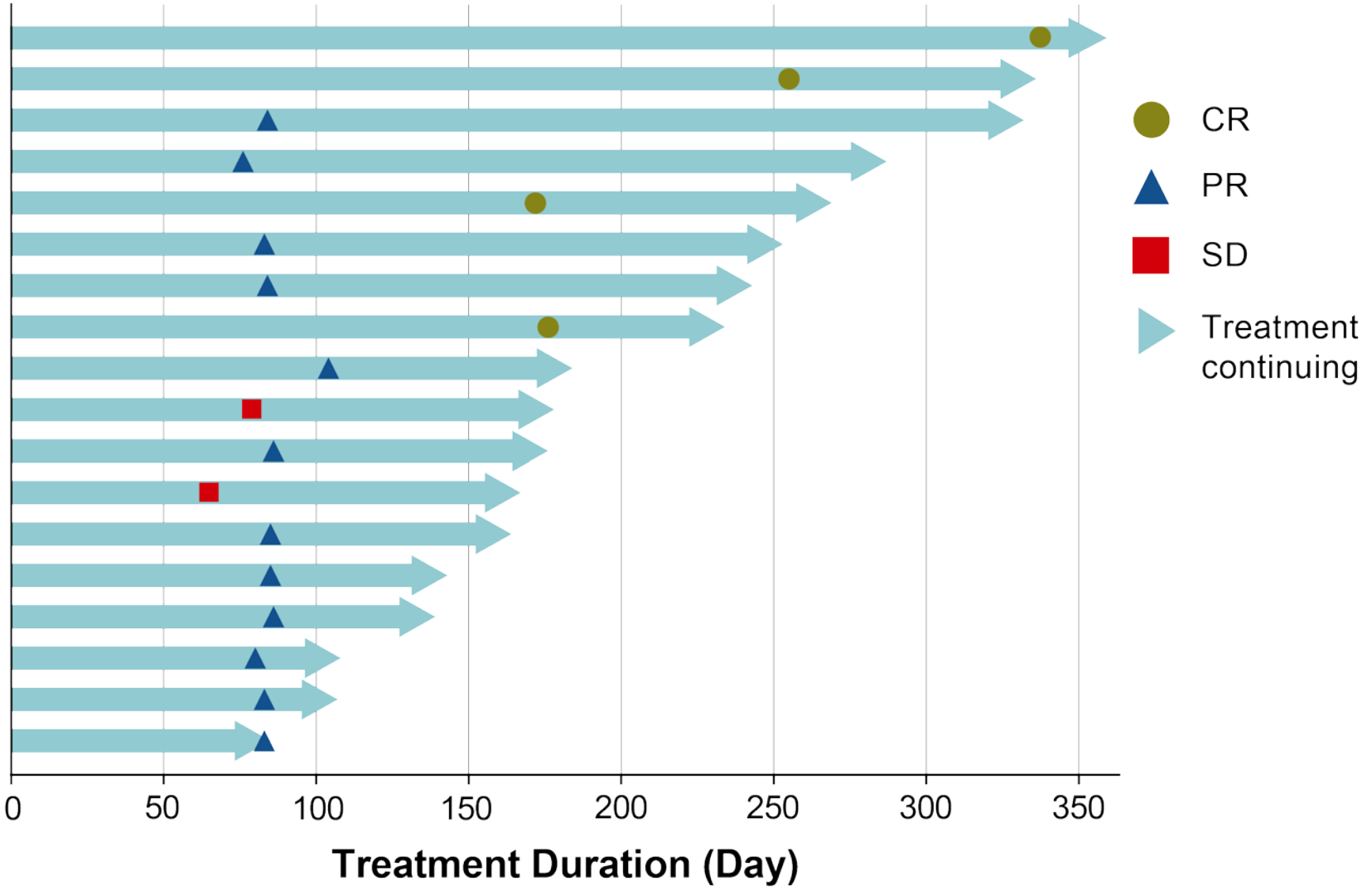
FL: Maximum Improvement in SPD



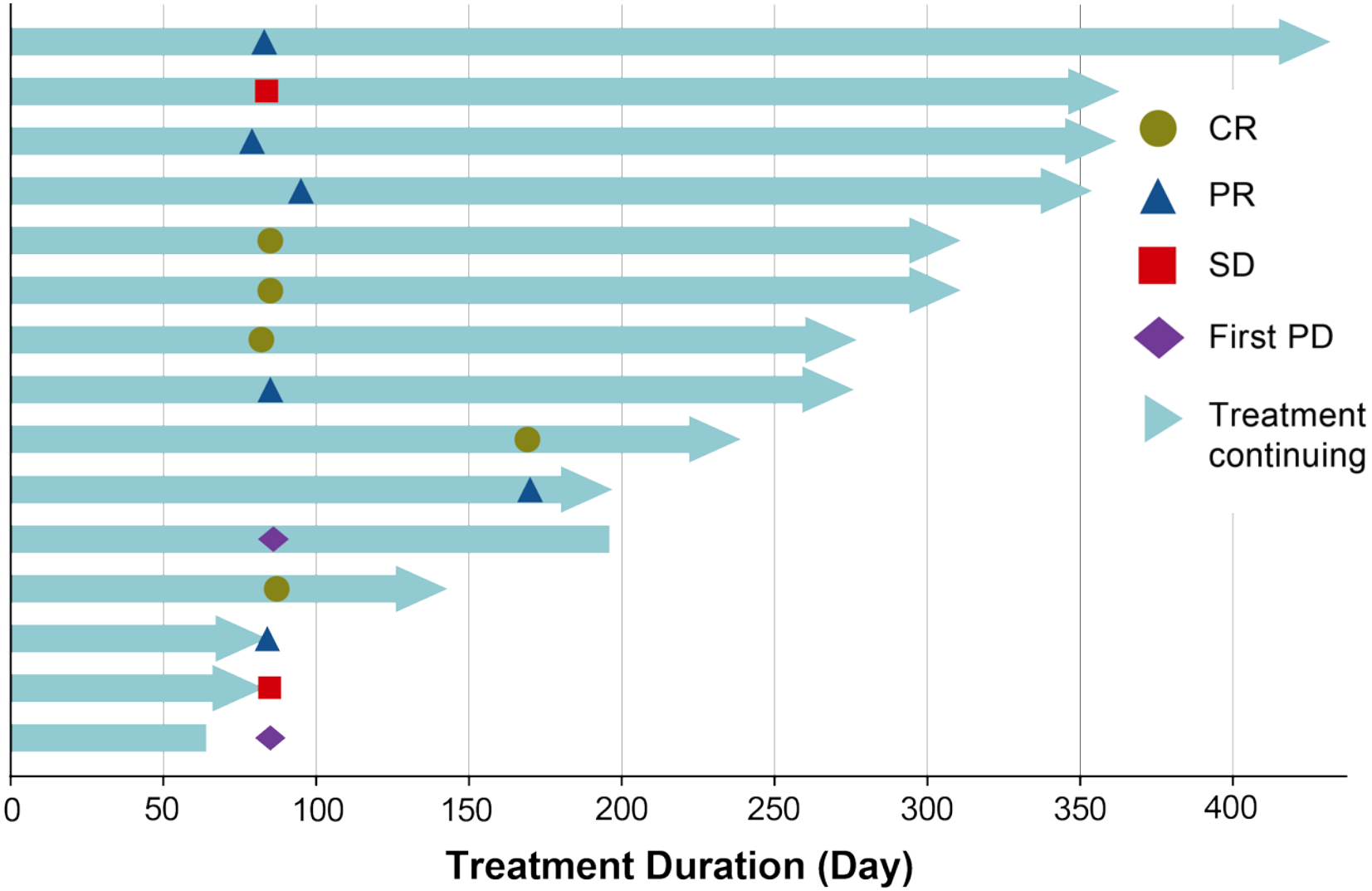
R/R CLL/SLL: Duration of Treatment



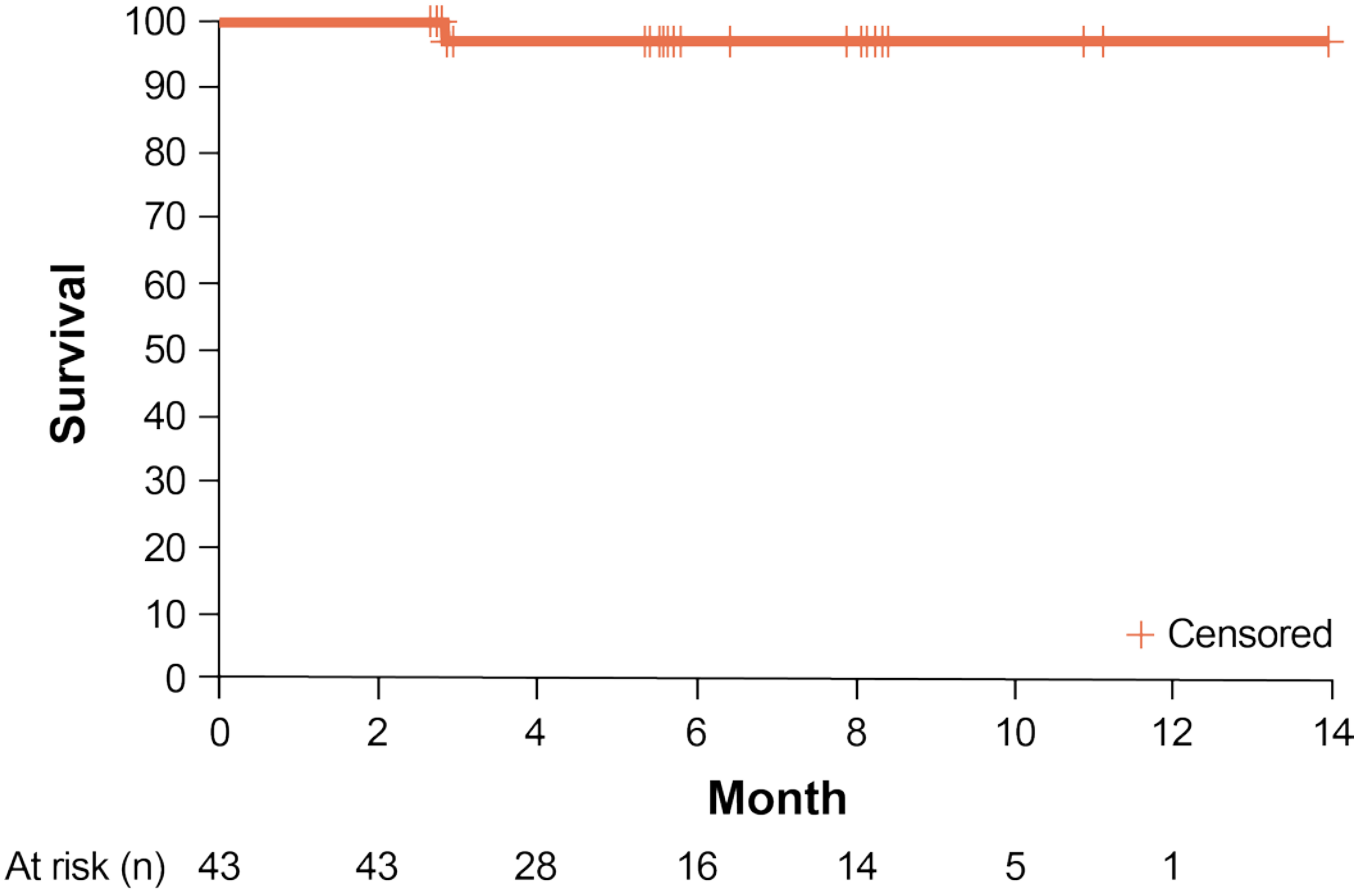
TN CLL/SLL: Duration of Treatment



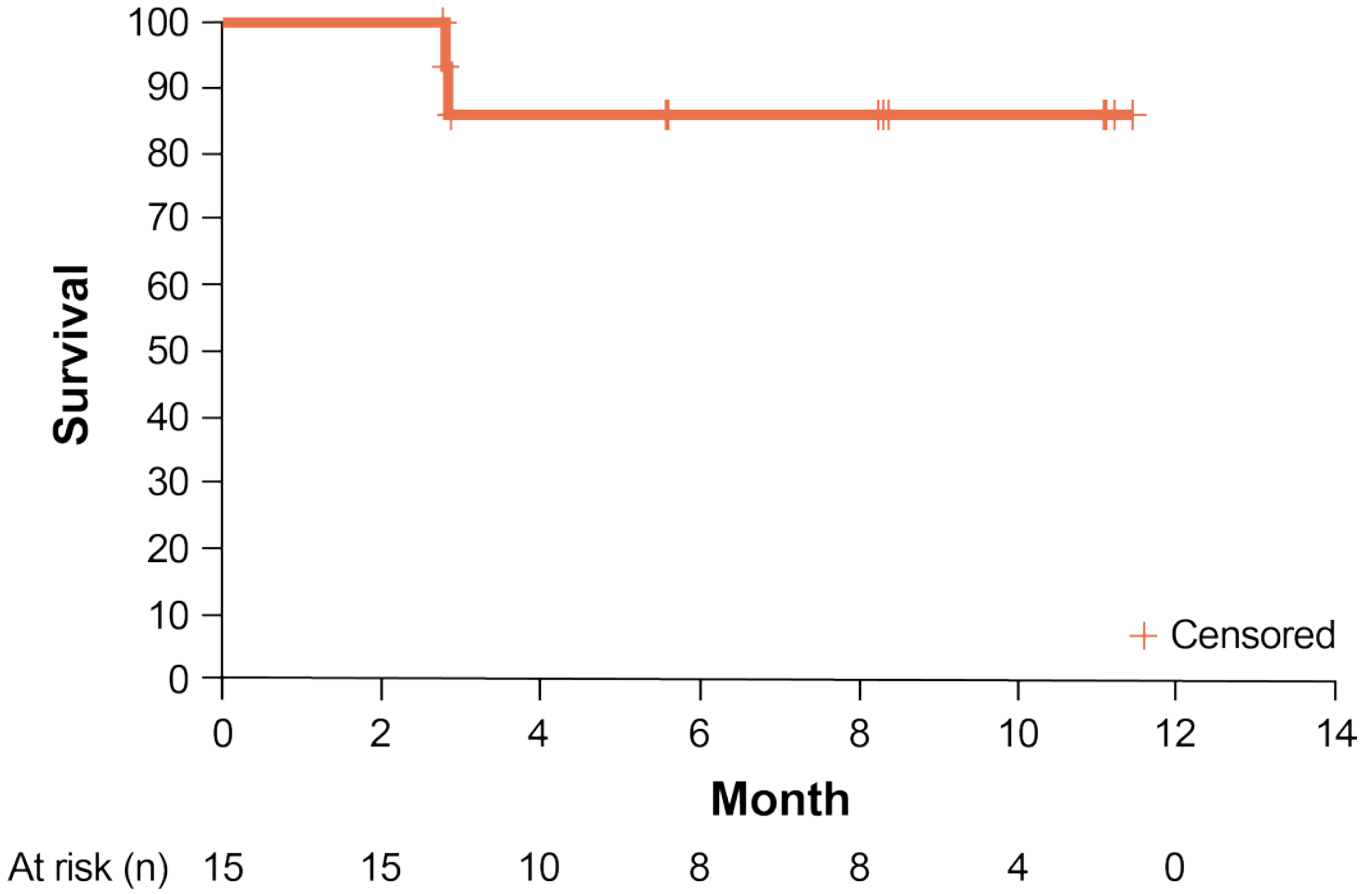
FL: Duration of Treatment



CLL/SLL: Progression-Free Survival



FL: Progression-Free Survival



Conclusions

- The potent and selective BTK inhibitor BGB-3111 and the anti-CD20 antibody obinutuzumab are safe and well-tolerated when given in combination in patients with CLL/SLL and FL
- The combination of BGB-3111 and obinutuzumab is highly active in CLL/SLL and FL
- Early CR rate in CLL/SLL is favorable compared to the expected rate with BTK-inhibitors or anti-CD20 antibodies alone
- Both the frequency and depth of response in FL (overall and complete response rates) are favorable compared to reported data with BTK-inhibitors or anti-CD20 antibodies alone
- BeiGene is planning late-stage trials of this combination in FL

Acknowledgments

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