Treatment With the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) Demonstrates High Overall Response Rate and Durable Responses in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Updated Results From a Phase 1/2 Trial

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Introduction

- Zanubrutinib (BGB-3111) is an investigational next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
- AU-003 is a first-in-human phase 1/2 study designed to evaluate the safety, pharmacokinetics, and antitumor activity of zanubrutinib in patients with B-cell malignancies
  - This study includes disease-specific cohorts, including treatment naïve and relapsed/refractory CLL/SLL
  - Enrollment is complete, and a total of 384 patients have been dosed in this study, including 123 CLL/SLL patients
- With a median follow-up of 13.7 months, preliminary data from this study show encouraging clinical activity for zanubrutinib in patients with CLL/SLL[2]

➢ **Here we present updated zanubrutinib safety and activity findings from AU-003 with additional follow-up (median, 29.5 months)**

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; SLL, small lymphocytic lymphoma.

1. Tam S, et al. ASH 2019. Abstract #499. 2. Tam CS, et al, *Blood.* 2019;134:851-859.

AU-003 Study Schema

Indication-Specific Expansion Cohorts

DOSE ESCALATION

Dose		All Dosed (CLL/SLL)
40 mg	qd	3 (0)
80 mg	qd	4 (0)
160 mg	qd	5 (2)
320 mg	qd	1 (0)
160 mg	bid	4 (2)

RP2D[a]

320 mg qd

or

160 mg bid

DOSE EXPANSION

Pop	RP2D Dose	Disease	All Dosed (CLL/SLL)
R/R	qd	All B-cell	18 (2)
R/R	bid	All B-cell	21 (4)
R/R	bid	Non-GCB DLBCL	37
R/R	bid	CLL/SLL	71 (71)
R/R	bid	WM	20
R/R	qd	CLL/SLL	20 (20)
Any	Any	WM	50
R/R	Any	MCL	20
TN	Any	CLL/SLL	21 (21)
TN	Any	MCL	20
R/R	Any	HCL	11
R/R	bid	iNHL	40
R/R	bid	Richter Transformation	15
R/R	bid	All B-cell (prior BTKi)	3 (1)

Eligibility:

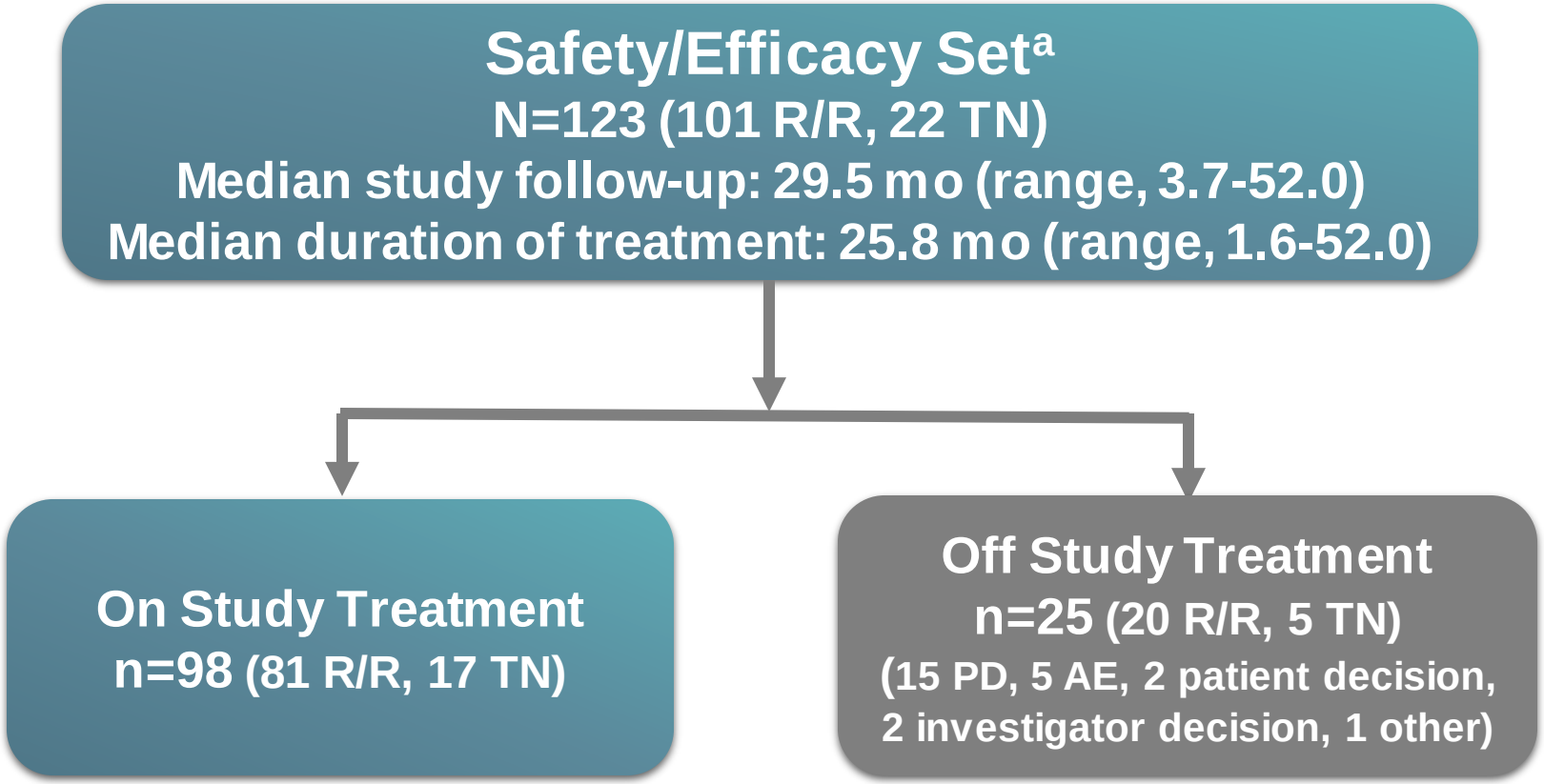
- WHO-defined B-cell malignancy
- >1 Prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG PS 0-2
- ANC >1000/µL, platelets >100000/µL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

ANC, absolute neutrophil count; bid, twice daily; BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB-DLBCL, germinal center B-cell–like diffuse large B-cell lymphoma; HCL, hairy cell leukemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; qd, every day; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TN, treatment naïve; WM, Waldenström macroglobulinemia.

[a]Both doses RP2D but as of protocol v.6, all patients were encouraged to switch to 160 mg bid. [b]Growth factor/transfusion allowed. [c]Anticoagulation allowed.

Disposition for Patients With CLL/SLL

As of May 8, 2019



AE, adverse event; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naïve.

[a]Safety/efficacy set excludes patients who had prior BTK inhibitor therapy (n=1) or prior Richter transformation (n=1).

Patient and Disease Characteristics

Characteristic	CLL/SLL (n=123)
Age, median (range), y	67 (24-87)
≥75, n (%)	21 (17.1)
Male sex, n (%)	92 (74.8)
Prior treatment status	
TN, n (%)	22 (17.9)
R/R, n (%)	101 (82.1)
Prior therapies, median (range)	2 (1-10)
SLL, n (%)	5 (4.1)
Molecular risk factors, n (%)	
Del(17p)	**16/99 (16.2)**
p53 mutation	13/42 (31.0)
Del(11q)	23/98 (23.5)
Unmutated IGHV	28/41 (68.3)
Bulky disease, n (%)	
>5 cm	47 (38.2)
>10 cm	4 (3.3)

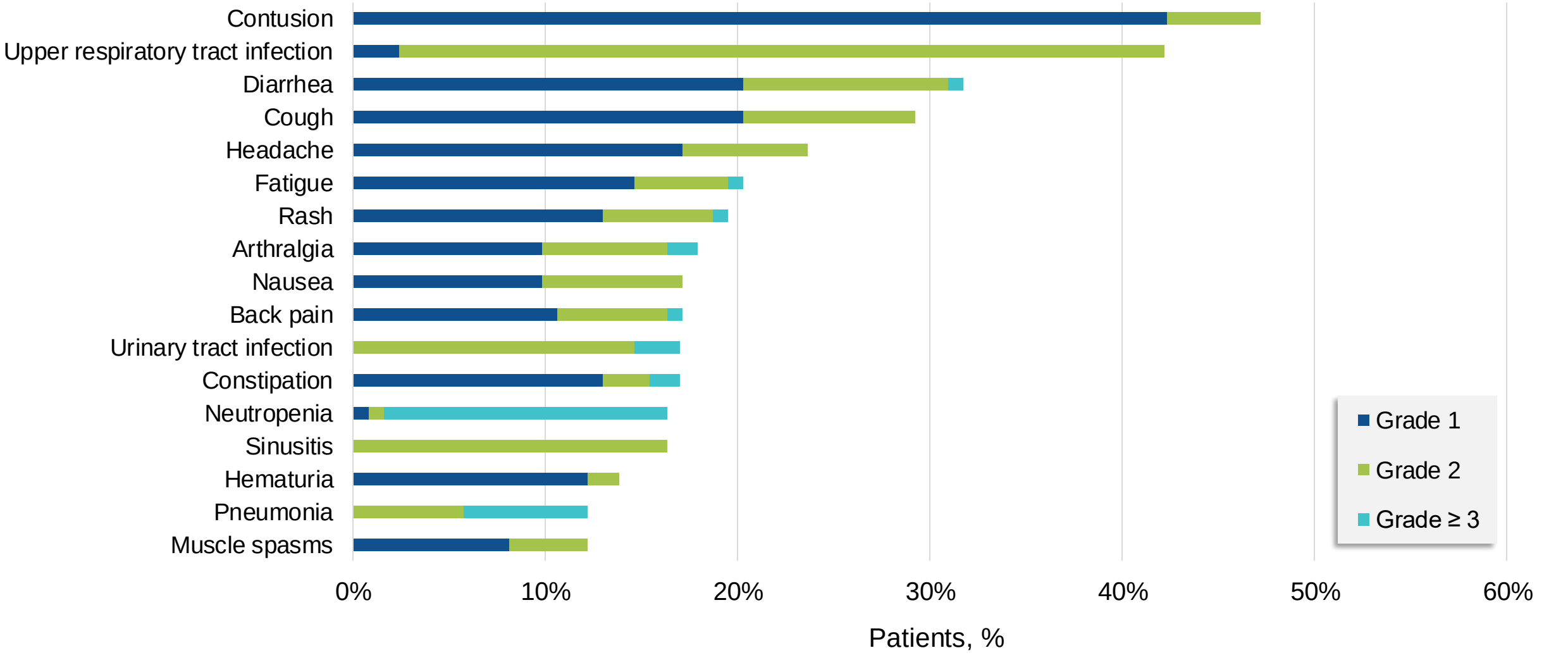
Data cutoff: May 8, 2019.
IGHV, immunoglobulin heavy-chain variable region gene; R/R, relapsed/refractory; TN, treatment-naïve.

Safety Summary

Event, n (%)	CLL/SLL (n=123)
Any AE	123 (100.0)
Grade ≥3 AE	76 (61.8)
Serious AE	58 (47.2)
AEs leading to treatment discontinuation	5 (4.1)[a]
AEs leading to death	1 (0.8)[b]

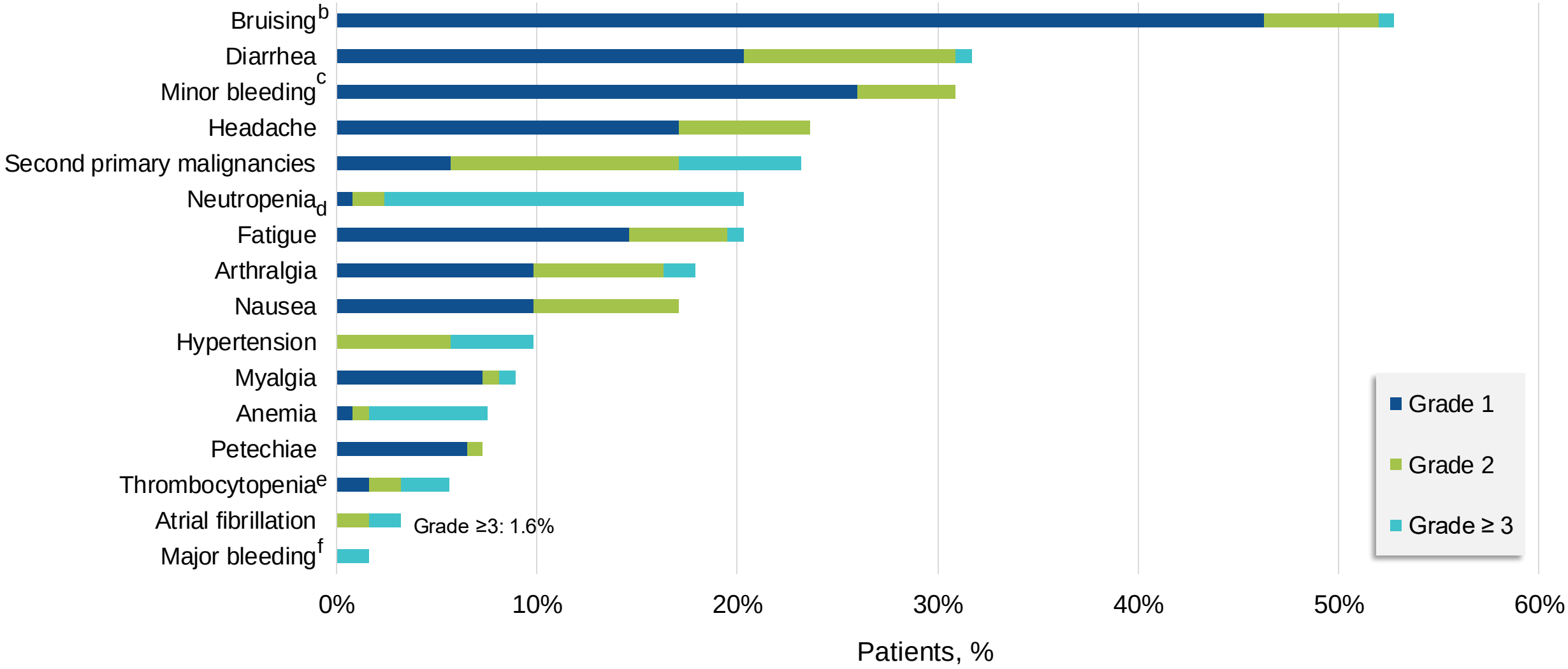
Data cutoff: May 8, 2019.
Note: Richter transformation reported as AE and PD (unrelated).
AE, adverse event.
[a]Muscle weakness grade 3 (unrelated), neoplasm-malignant recurrent squamous cell carcinoma (right periauricular area) grade 5 (fatal; unrelated), wide complex tachycardia grade 3 (related), cryptogenic pneumonia grade 3 (unrelated), pleural effusion grade 2 (related). [b]Neoplasm-malignant recurrent squamous cell carcinoma (right periauricular area); unrelated.

Common Adverse Events Regardless of Causality (All Grade ≥10% of Patients)



Data cutoff: May 8, 2019. AE by Preferred Term.

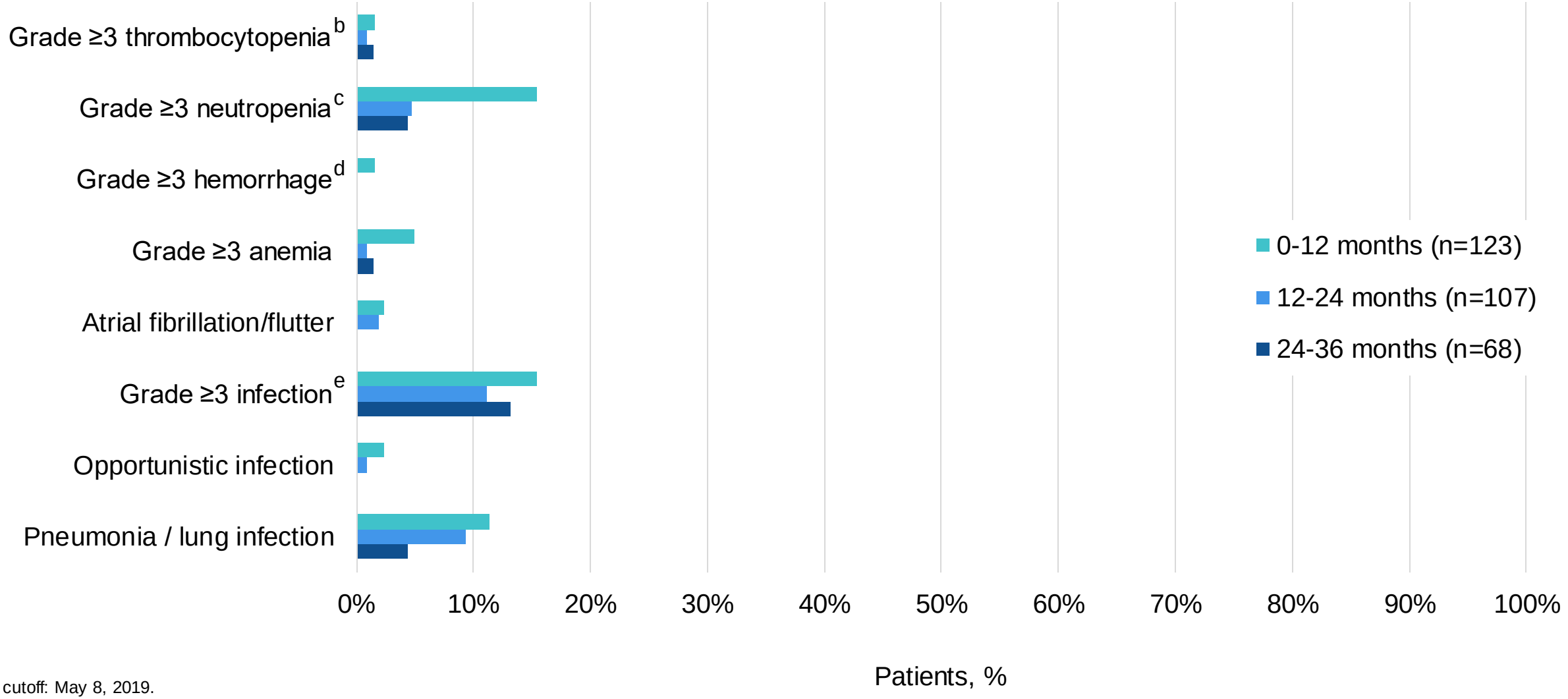
Adverse Events of Interest[a]



Data cutoff: May 8, 2019. [a]*(Pooled Terms Where Appropriate)*

[b]Purpura, contusion, ecchymosis, or increased tendency to bruise. [c]Pooled term of bleeding, not included in bruising petechiae, or major bleeding. [d]Neutropenia, neutrophil count decreased, or febrile neutropenia. [e]Thrombocytopenia or platelet count decreased. [f]Purpura, hemathrosis, or major hemorrhage.

Prevalence of Adverse Events of Interest Over Time[a]



Data cutoff: May 8, 2019.

[a]Pooled terms where appropriate. [b]Thrombocytopenia or platelet count decreased. [c]Neutropenia, neutrophil count decreased, or febrile neutropenia. [d]Purpura, hemathrosis, or major hemorrhage. [e]All infection terms pooled. Only grade ≥3 infections reported here. Opportunistic infections and pneumonia/lung infections are a subgroup of all pooled infections.

Disease Response by Investigator Assessment

	TN (n=22)	R/R (n=101)	Overall (N=123)
Follow-up, median (range), mo	31.7 (11.1-47.6)	24.3 (3.7-52.0)	29.5 (3.7-52.0)
Best response, n (%)			
ORR	22 (100.0)	96 (95.0)	118 (95.9)
CR	5 (22.7)	14 (13.9)	19 (15.4)
CRi	0	1 (1.0)	1 (0.8)
PR	17 (77.3)	73 (72.3)	90 (73.2)[a]
PR-L	0	8 (7.9)	8 (6.5)
SD	0	4 (4.0)	4 (3.3)
Discontinued before first assessment, n (%)	0	1 (1.0)	1 (0.8)
Event rate remaining in response at 12 mo, % (95% CI)[b]	95.2 (70.7-99.3)	97.6 (90.8-99.4)	97.2 (91.5-99.1)

Data cutoff: May 8, 2019.

CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

[a]As of data cutoff (May 8, 2019), 4 patients met criteria for CR except required bone marrow to confirm; of these, 2 submitted bone marrow after data cutoff and confirmed CR. [B] Duration of response is summarized only for responders. Estimated using Kaplan-Meier method.

Disease Response by Investigator Assessment
Patients With Del(17p)

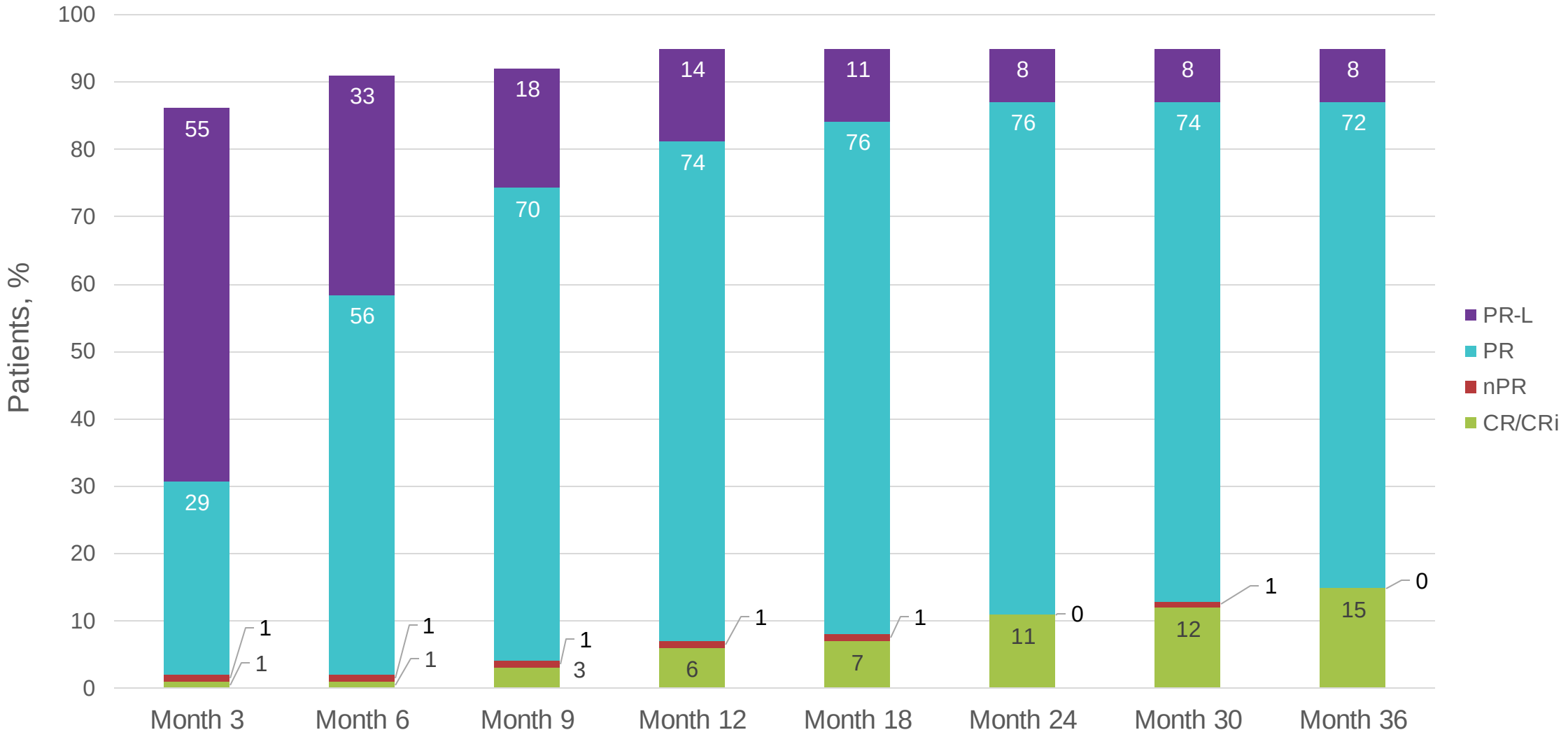
	TN (n=3)	R/R (n=13)	Overall (n=16)
Follow-up, median (range), mo	34.8 (31.8-35.3)	24.5 (9.4-43.5)	31.2 (9.4-43.5)
Best response, n (%)			
ORR	3 (100.0)	12 (92.3)	15 (93.8)
CR	0	1 (7.7)	1 (6.3)
PR	3 (100.0)	9 (69.2)	12 (75.0)
PR-L	0	2 (15.4)	2 (12.5)
SD	0	1 (7.7)	1 (6.3)
Event rate remaining in response at 12 mo, % (95% CI)[a]	100 (NE-NE)	100 (NE-NE)	100 (NE-NE)

Data cutoff: May 8, 2019.

CR, complete response; CRi, complete response with incomplete bone marrow recovery; NE, not evaluable; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

[a] Duration of response is summarized only for responders. Estimated using Kaplan-Meier method.

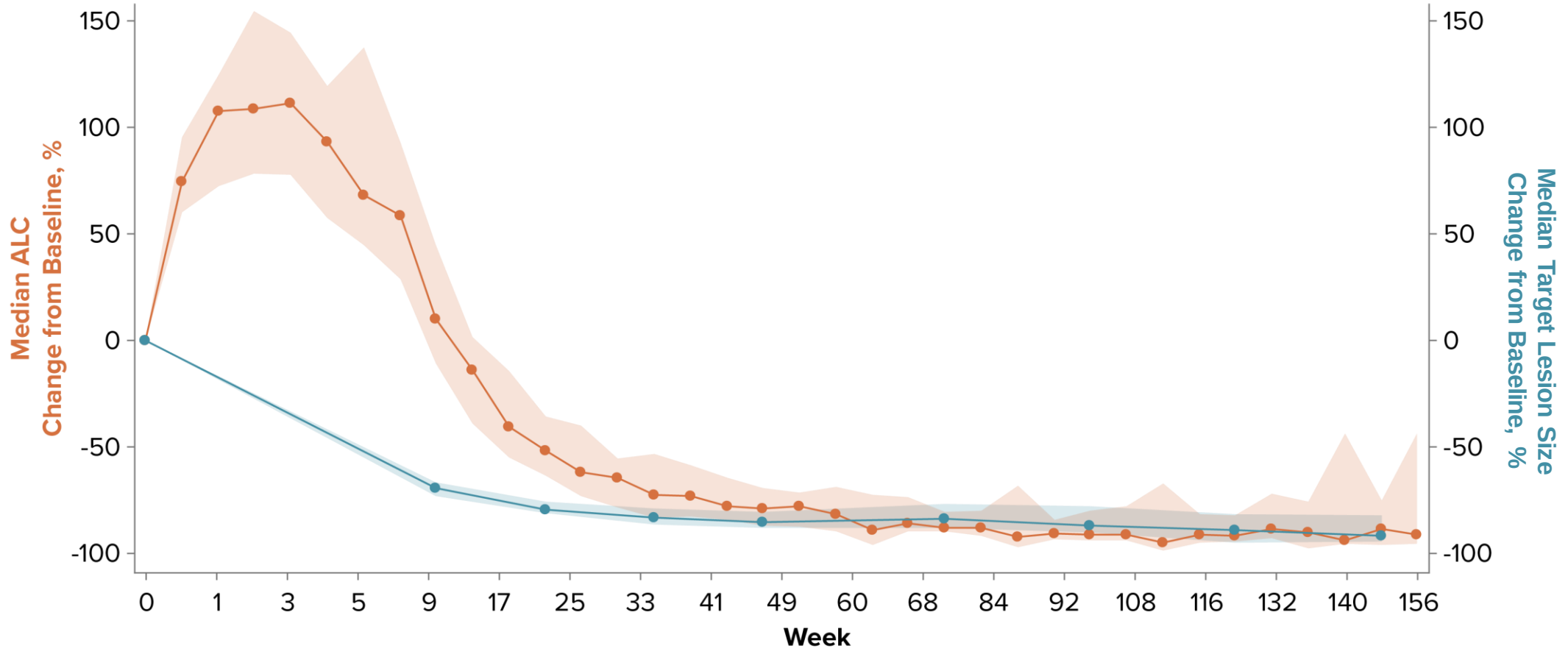
Best Response Over Time (Relapsed/Refractory)



Data cutoff: May 8, 2019.

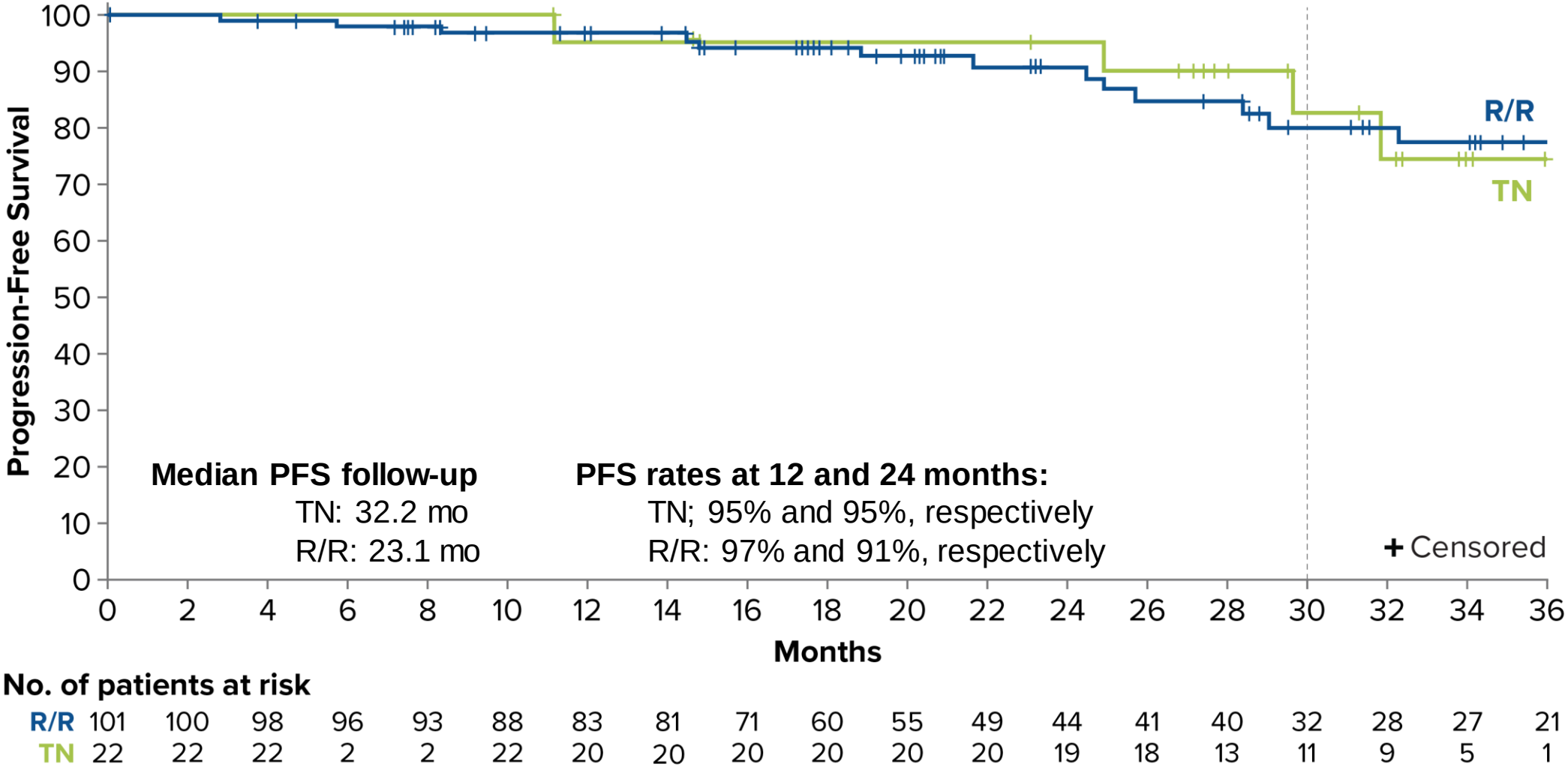
CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, near partial response; PR, partial response; PR-L, partial response with lymphocytosis.

Change in Lymphocyte Count and Target Lesion Size



Data cutoff: May 8, 2019.
Note: contains data for any time point with data for at least 10 patients. Week 1 data (ALC) was taken on day 3. Shaded areas show the 95% CIs.
ALC, absolute lymphocyte count; SPD, sum of the product of the greatest diameters.

Progression-Free Survival



Data cutoff: May 8, 2019.
PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naïve.

Summary

- Zanubrutinib monotherapy was generally well tolerated and active in patients with CLL/SLL, irrespective of del(17p) status
- With a median 29.5 months of follow-up
  - ORR was 96%, and CR/CRi rate of 16% appears favorable with response improving over time
  - The most common cause for treatment discontinuation was PD (12%; 15/123)
  - Discontinuation due to AEs occurred in 4%
  - The rate of Grade ≥3 atrial fibrillation was 1.6%
- A global randomized registration trial of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL is ongoing (NCT03734016)[2]

AE, adverse event; CR, complete response; CRi, complete response with incomplete bone marrow recovery; PD, progressive disease; R/R, relapsed/refractory.

1. Mato AR, et al. *Haematologica*. 2018;103:874-879. 2. Hillmen P, et al. ASH 2019. Abstract #4307.

Acknowledgments

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