PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (MAGNOLIA STUDY)

Abstract EP783

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INTRODUCTION

- B-cell receptor-mediated signaling has been identified as a critical step in marginal zone lymphoma (MZL) pathogenesis[1]
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[2-4]
  - First-generation BTK inhibitor ibrutinib has shown activity in relapsed/refractory (R/R) MZL, demonstrating a 48% overall response rate (ORR)[5]
- Zanubrutinib (BGB-3111) is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Zanubrutinib has been shown to be an irreversible, highly potent, selective, and bioavailable BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[6]
- The safety and efficacy of zanubrutinib in patients with R/R MZL were evaluated in the MAGNOLIA study
  - Study enrollment is complete; a total of 68 patients received at least 1 dose of zanubrutinib

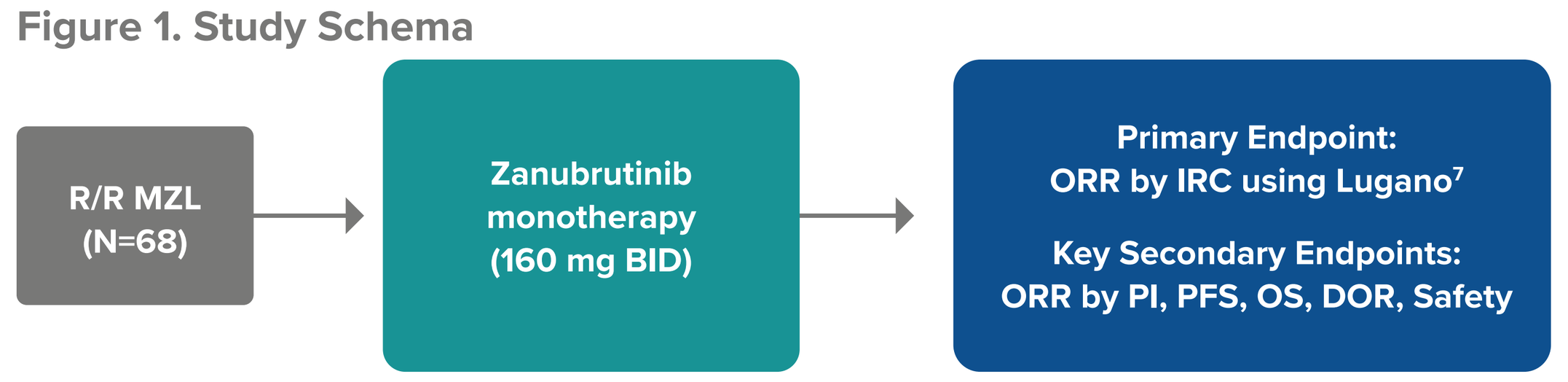
STUDY OBJECTIVES

- The primary endpoint was ORR as determined by an independent review committee based on the Lugano 2014 classification[7]

METHODS

- The MAGNOLIA (BGB-3111-214) is a phase 2, single-arm, multicenter study of zanubrutinib in patients with R/R MZL who had received ≥1 CD20-based regimen (**Figure 1**)

Figure 1. Study Schema



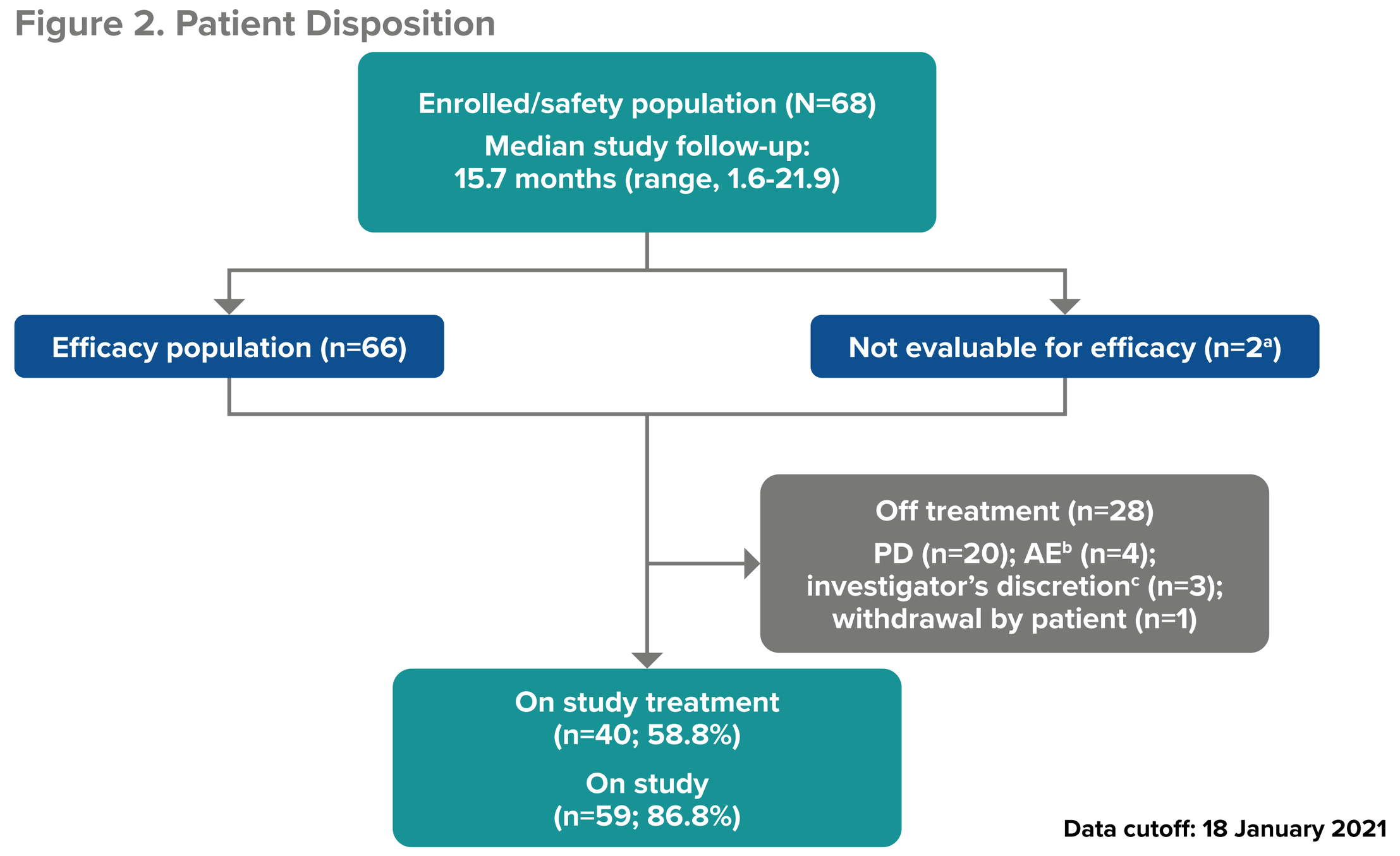
BID, twice a day; DOR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; R/R, relapsed/refractory.

KEY ELIGIBILITY CRITERIA

- Age ≥18 years
- Histologically confirmed MZL including splenic, nodal, and extranodal subtypes
- Previously received ≥1 CD20-directed regimen, with documented failure to achieve at least partial response or documented progressive disease after the most recent systemic treatment
- Measurable disease by computerized tomography or magnetic resonance imaging
- Adequate organ function
- No prior BTK inhibitor exposure

RESULTS

Figure 2. Patient Disposition



Data cutoff: 18 January 2021

[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Four patients discontinued due to AE (pyrexia later attributed to disease progression, n=1; fatal myocardial infarction in a patient with pre-existing cardiovascular disease, n=1; COVID-19 pneumonia leading to death, n=2).
[c]Three patients discontinued per the investigator's discretion (requiring prohibited medications).
AE, adverse event; MZL, marginal zone lymphoma; PD, progressive disease.

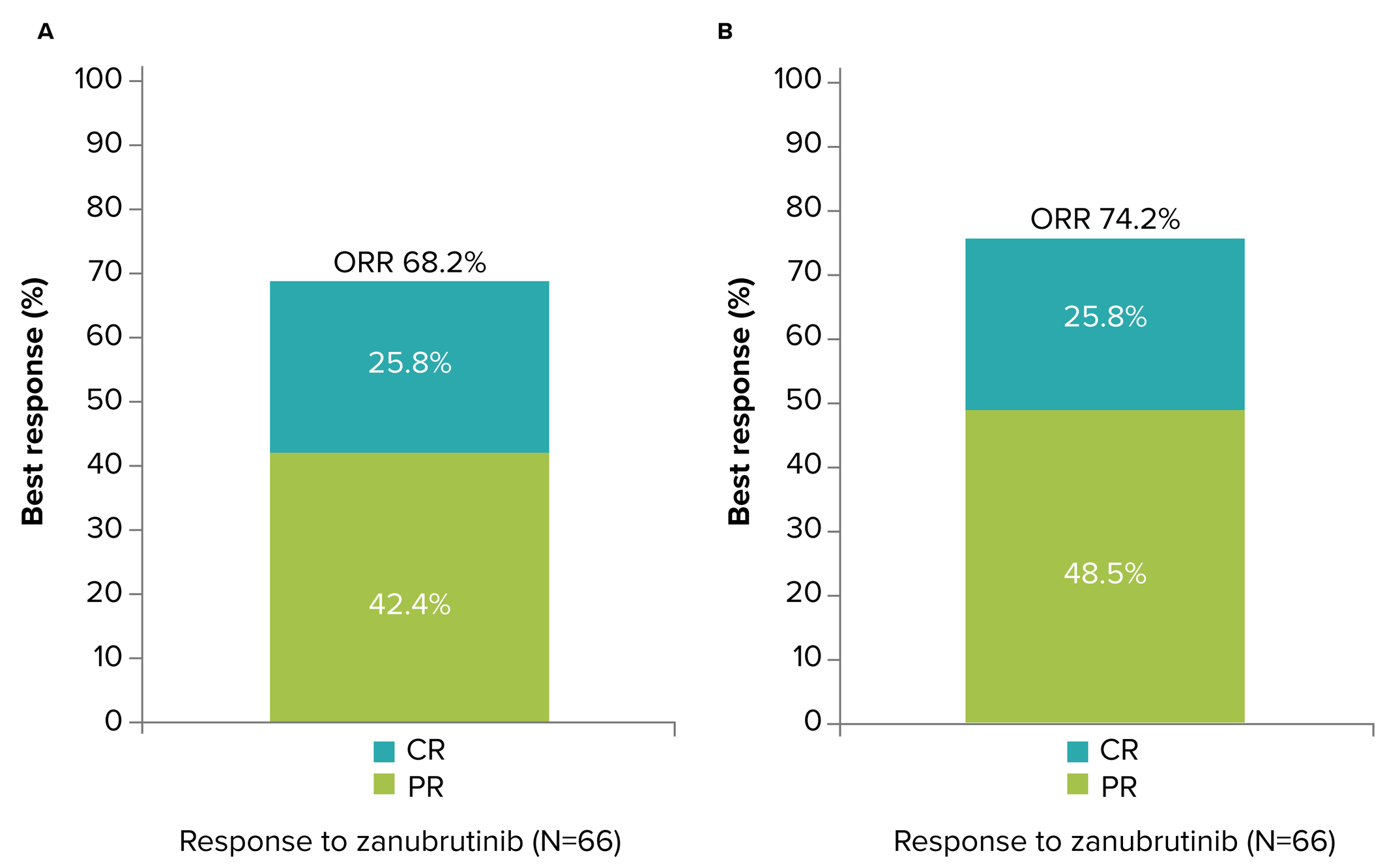
RESULTS *(CONTINUED)*

Table 1. Patient and Disease Characteristics

Characteristic	Total (N=68)
Age, median (range), years	70 (37-95)
Age category, n (%)	
≥65 years	41 (60.3)
≥75 years	19 (27.9)
Male, n (%)	36 (52.9)
ECOG performance status, n (%)	
0-1	63 (92.6)
Disease status, n (%)	
Relapsed	44 (64.7)
Refractory	22 (32.4)
MZL subtypes, n (%)	
Extranodal	26 (38.2)
Nodal	26 (38.2)
Splenic	12 (17.6)
Unknown[a]	4 (5.9)
Lymphoma involvement in bone marrow, n (%)	29 (42.6)
Prior lines of systemic therapy, median (range)	2 (1-6)

[a]Four patients presented with both nodal and extranodal lesions; investigators were unable to classify the MZL subtype.
ECOG, Eastern Cooperative Oncology Group; MZL, marginal zone lymphoma.

Figure 3. ORR by (A) Independent Review and (B) Investigator Assessment



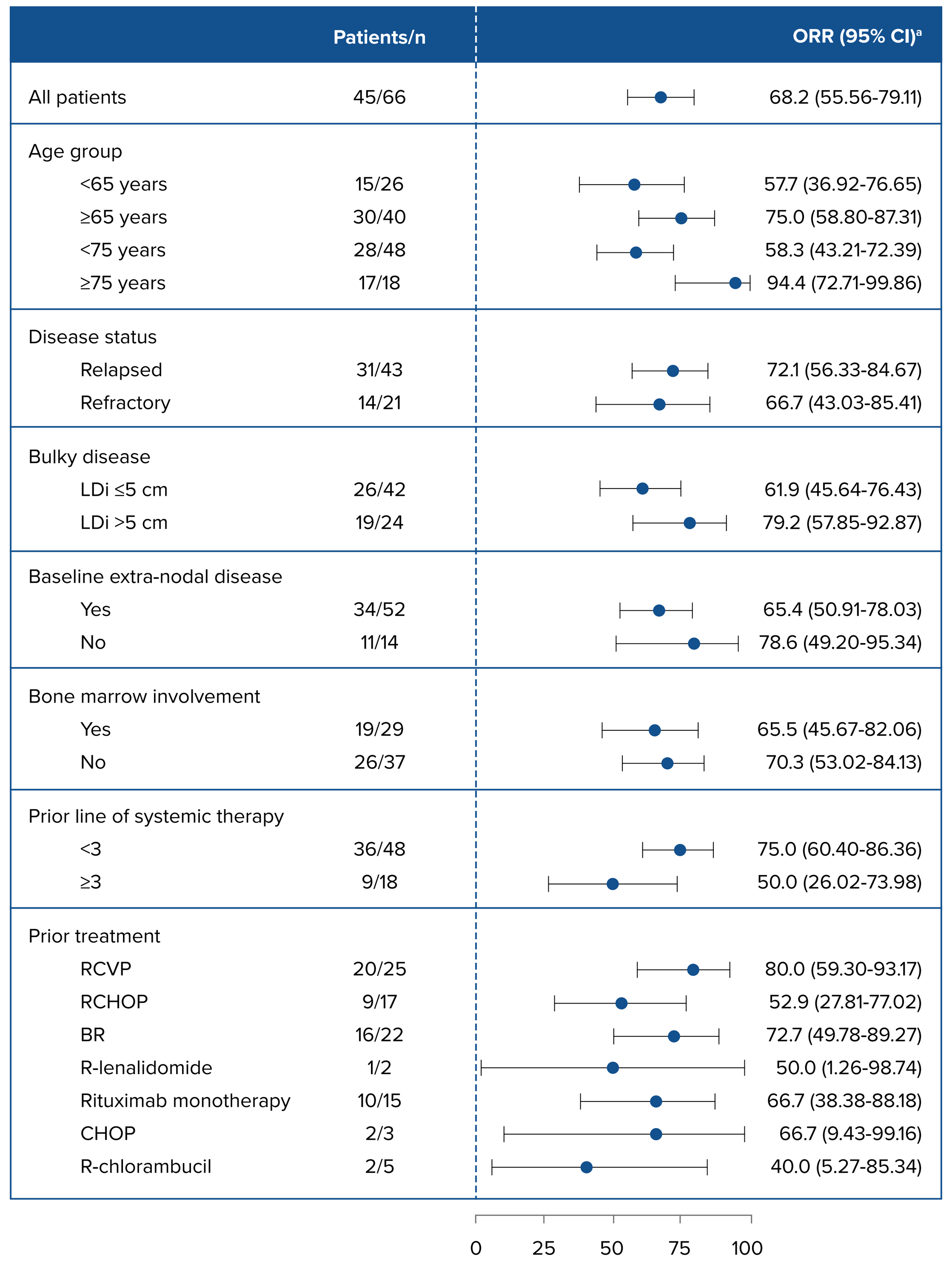
CR, complete response; ORR, overall response rate; PR, partial response.

Table 2. Best Overall Response by Independent Review and MZL Subtypes

Best response	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (N=4)	Total (N=66[a])
ORR (CR or PR), n (%) **95% CI[b]**	16 (64.0) (42.52-82.03)	19 (76.0) (54.87-90.64)	8 (66.7) (34.89-90.08)	2 (50.0) (6.76-93.24)	45 (68.2) (55.56-79.11)
Complete response	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
Partial response	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	28 (42.4)
Stable disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	13 (19.7)
Nonprogressive disease	1 (4.0)[c]	0	0	0	1 (1.5)
Progressive disease	(12.0)	1 (4.0)	1 (8.3)	1 (25.0)	6 (9.1)
Discontinued prior to first assessment	1 (4.0)[d]	0	0	0	1 (1.5)

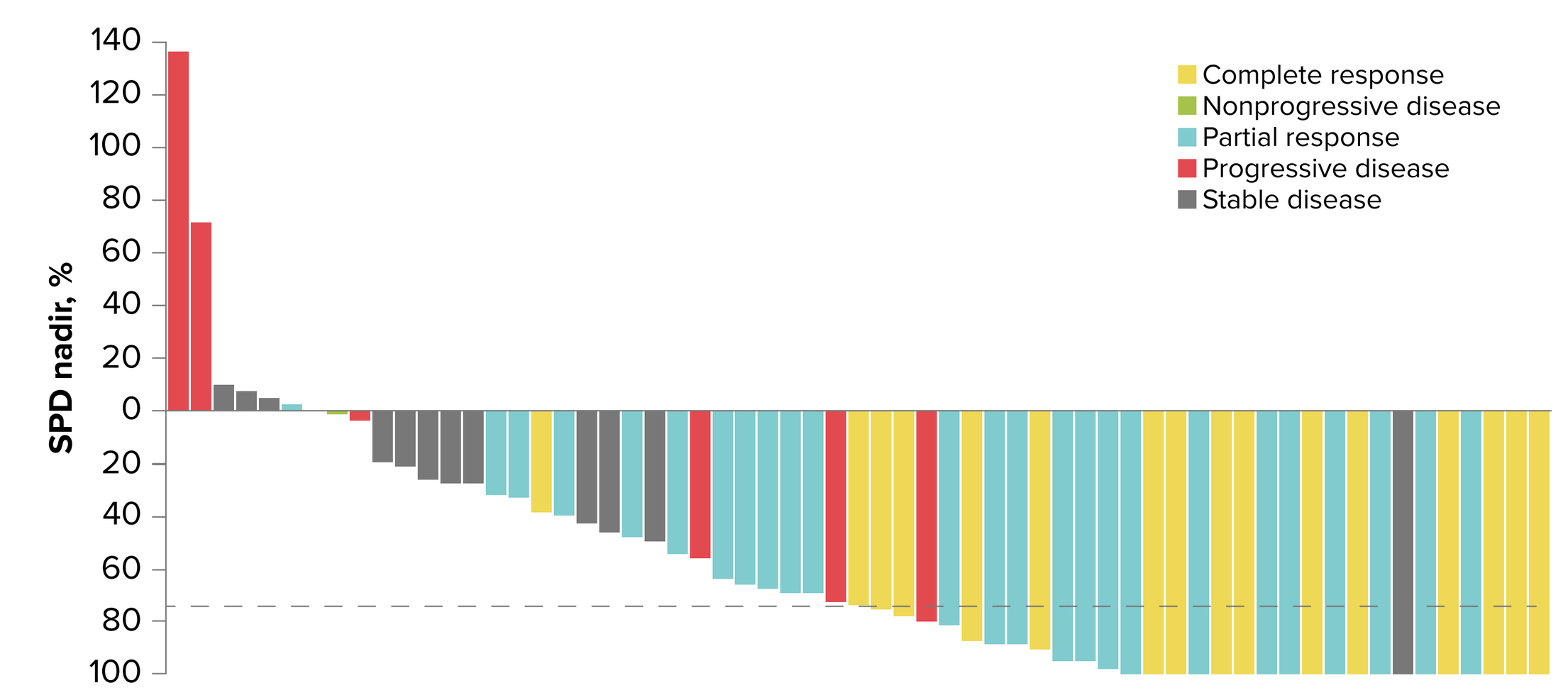
Data cutoff: January 18, 2021.
[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Two-sided Clopper-Pearson 95% CI.
[c]One patient with FDG-avid disease missed the PET scan at Cycle 3 and was assessed as having nonprogressive disease by independent review due to missing PET scan. CT scan results showed stable disease at Cycle 3.
[d]One patient (extranodal MZL) withdrew consent prior to the first disease assessment.
CR, complete response; CT, computed tomography; FDG, fludeoxyglucose; MZL, marginal zone lymphoma; ORR, overall response rate; PET, positron emission tomography; PR, partial response.

Figure 4. Subgroup Analysis of ORR by Independent Review



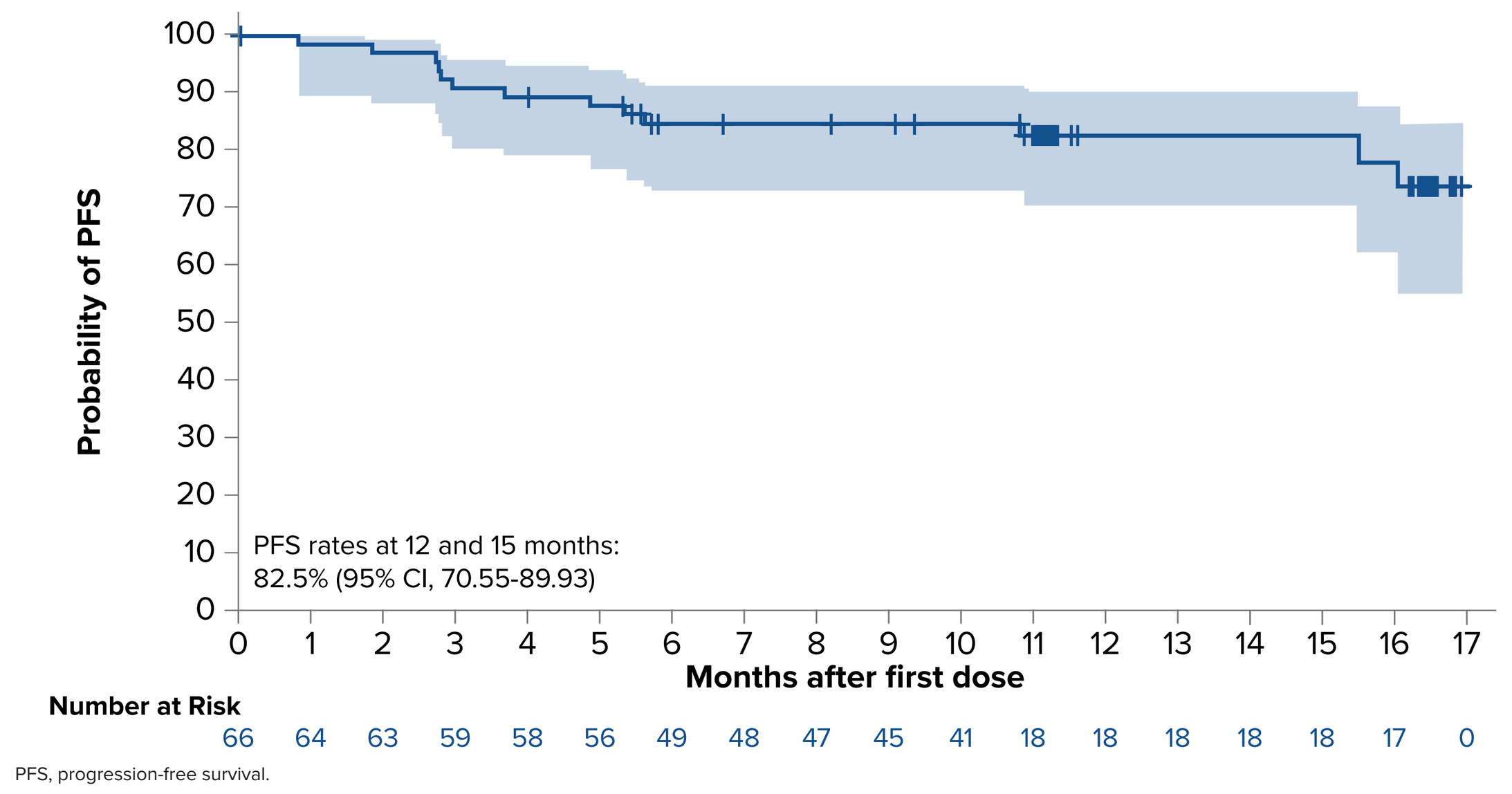
[a]Two-sided Clopper-Pearson 95% CIs for ORR.
BR, bendamustine/rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; LDi, longest diameter; ORR, overall response rate; R, rituximab; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine/prednisone.

Figure 5. Change in Target Lesion SPD From Baseline by Independent Review



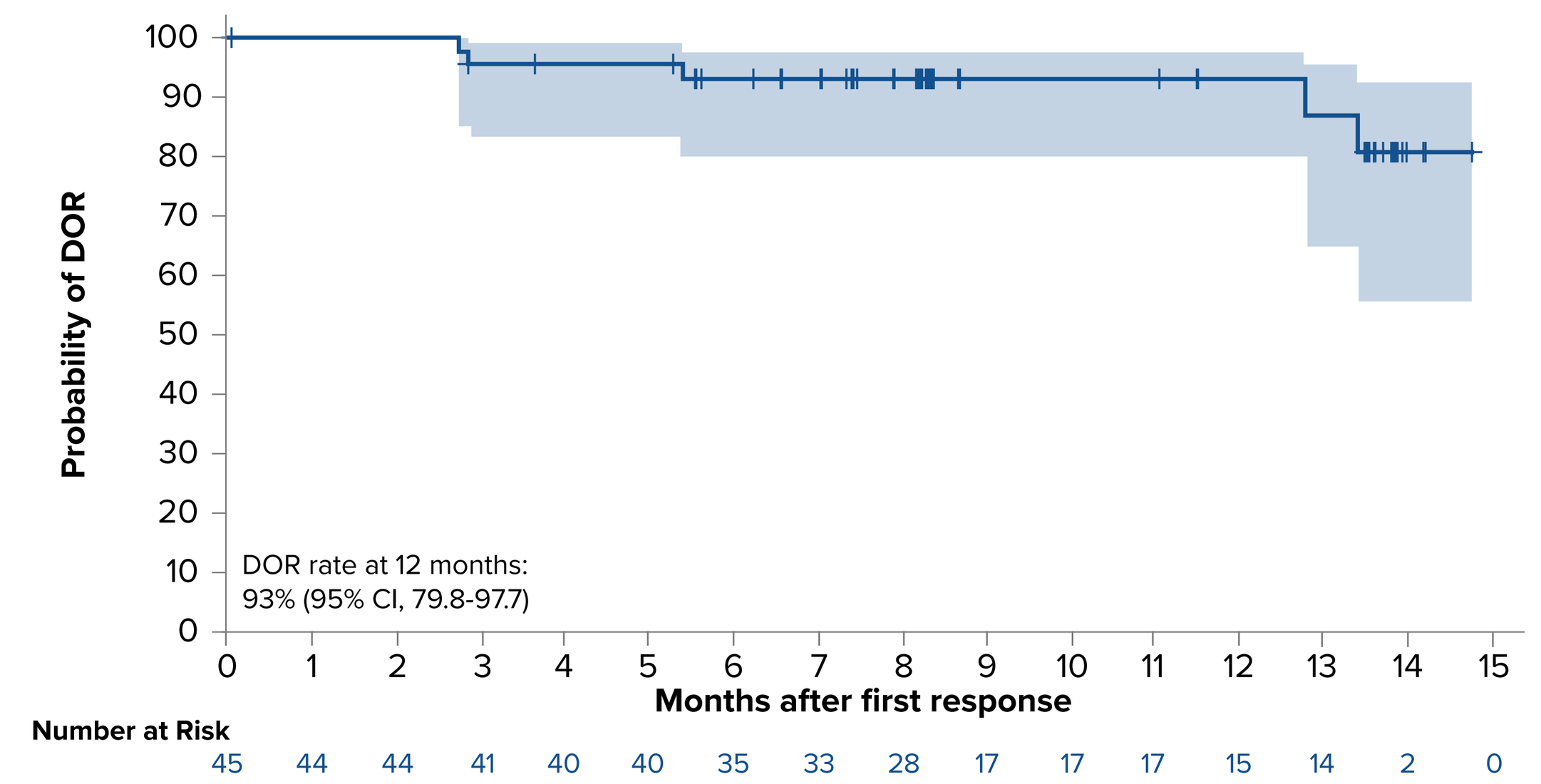
Only patients with nonmissing best overall response and SPD percent changes were included (n=61).
Dashed lines = median reduction in SPD (-74%).
SPD, sum of products of perpendicular diameters.

Figure 6. PFS by Independent Review



PFS, progression-free survival.

Figure 7. DOR by Independent Review



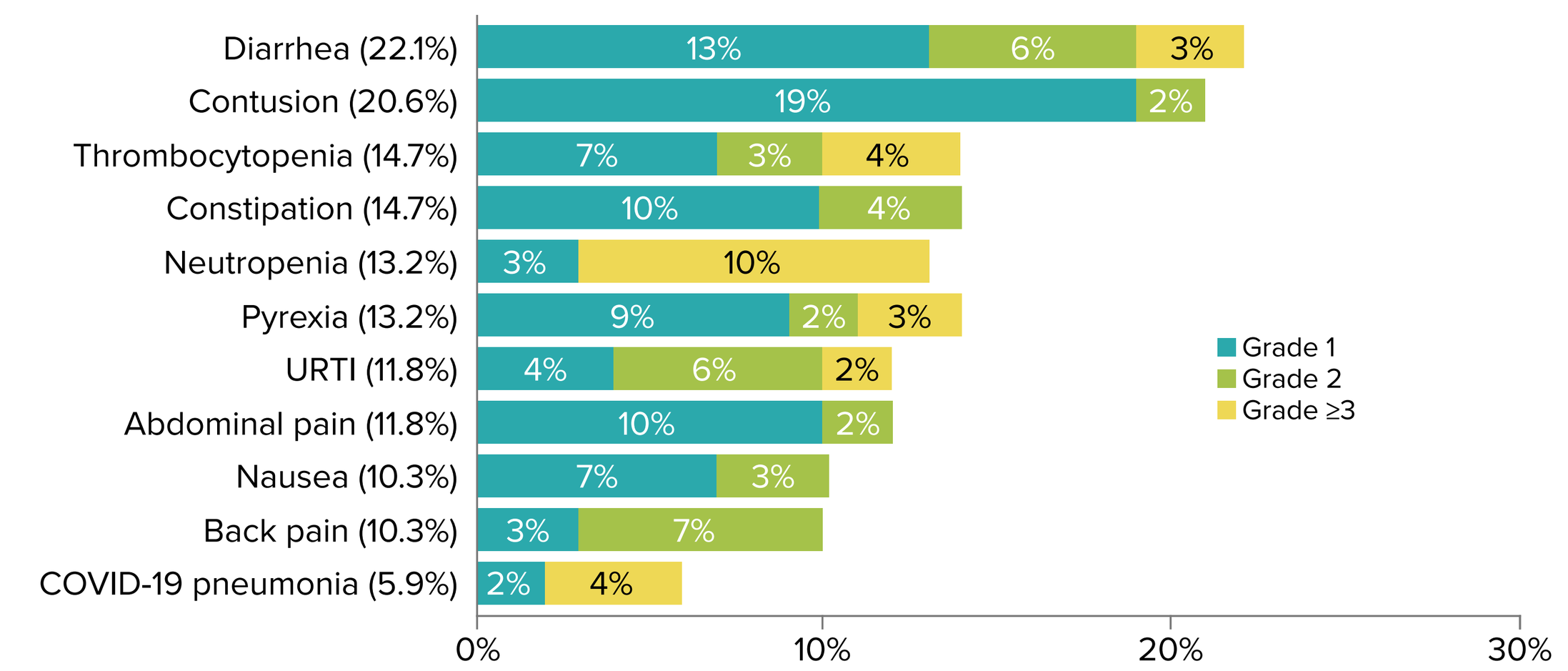
DOR, duration of response.

Table 3. Safety Summary

	N=68 n (%)
Patients with at least 1 TEAE	65 (95.6)
Grade 3 or higher TEAE	27 (39.7)
Serious TEAE	26 (38.2)
TEAE leading to dose interruption	20 (29.4)
TEAE leading to study drug discontinuation	4 (5.9)[a]
TEAE leading to death	3 (4.4)[a]
TEAE leading to dose reduction	0

[a]One patient discontinued due to pyrexia (later attributed to disease progression); 1 patient died from myocardial infarction; 2 patients died from COVID-19 pneumonia.
TEAE, treatment-emergent adverse event.

Figure 8. TEAEs Occurring in ≥10% of Patients Regardless of Causality



TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Table 4. TEAEs of Interest

TEAE of interest	All grade (N=68)	Grade ≥3 (N=68)
Infection	31 (45.6)	11 (16.2)
Hemorrhage	25 (36.8)	0
Diarrhea	15 (22.1)	2 (2.9)
Thrombocytopenia[a]	10 (14.7)	3 (4.4)
Neutropenia[b]	9 (13.2)	7 (10.3)
Second primary malignancy[c]	5 (7.4)	3 (4.4)
Atrial fibrillation/flutter[d]	2 (2.9)	1 (1.5)
Hypertension	2 (2.9)	1 (1.5)
Major hemorrhage	0	0

[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes basal cell and squamous cell carcinoma (in 2 patients with history of skin cancer); papillary thyroid carcinoma (in 1 patient with pre-existing thyroid nodule); recurrent bladder cancer (in 1 patient with history of bladder cancer), and acute myeloid leukemia (in 1 patient with prior chemotherapy with alkylating agents).
[d]Atrial fibrillation occurred in a patient with pre-existing atrial fibrillation (21 days after end of treatment due to disease progression).
TEAE, treatment-emergent adverse event.

SUMMARY

- The MAGNOLIA study met its primary endpoint
- Zanubrutinib was highly active with a favorable safety profile in patients with R/R MZL
- After a median study follow-up of 15.7 months:
  - High ORR of 68.2% and CR rate of 25.8% by independent review
    - ORR higher than prespecified null ORR of 30% ($P<0.0001$)
    - Responses were observed in all MZL subtypes
  - Median PFS and median DOR not reached
    - 93% of responders were progression/death-free at 12 months after initial response
    - PFS rate was 82.5% at 15 months
  - Treatment discontinuation due to AEs occurred in 4 patients; none were considered related to zanubrutinib
  - Grade 5 AEs occurred in 3 patients (including 2 patients who died from COVID-19 pneumonia)
  - Atrial fibrillation/flutter occurred in 2 patients
  - No major hemorrhage was reported

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DISCLOSURES

SO served as a consultant for AbbVie, AstraZeneca, Celgene, CSL, Gilead, Janssen, Merck, Mundipharma, Roche, and Takeda; received honoraria from AbbVie, AstraZeneca, Celgene, Gilead, Janssen, Merck, Roche, and Takeda; received research funding from AbbVie, AstraZeneca, BeiGene, Epizyme, Gilead, Janssen, Merck, Roche, and Takeda; and received travel expenses from Roche.
AT served as a consultant for AbbVie, AstraZeneca, BeiGene, and Janssen and as speakers' bureau for AbbVie, AstraZeneca, BeiGene, and Janssen.
KL served as a consultant for BeiGene, Celgene, Gilead, Karyopharm, Roche, and Takeda; received research funding for BeiGene, Genmab, Pharmacyclics, and Roche; received honoraria from Roche; and received travel expenses from Bristol Myers Squibb, Celgene, Janssen, and Roche.
PM served as a consultant for BeiGene, Celgene, Janssen, and Kite and received honoraria from Recordati and Roche.
BH served as a consultant for Cellectar Biosciences and Kite and received research funding from BeiGene, Celgene, and Roche/Genentech.
HC served as a consultant for AbbVie, EUSA Pharma, and Janssen and received honoraria from Janssen and travel expenses from Celgene, Janssen.
PLZ served as a consultant for ADC Therapeutics, Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, Merck Sharp and Dohme Corp, MSD, Roche, Sanofi, Servier, Sandoz, TG Therapeutics, Takeda, and Verastem and as speakers' bureau for Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, Merck Sharp and Dohme Corp, Roche, Servier, Takeda, TG Therapeutics, and Verastem.
MC received research funding from AbbVie, AstraZeneca, Bristol Meyers Squibb, Celgene, and Pharmacyclics.
PB served as a consultant for Janssen-Cilag and Merck Sharp and Dohme Corp and received research funding from Roche and Shire.
RM served as a consultant for MEI Pharma.
CP served as a consultant for BeiGene, Genentech, Jansen, Kite/Gilead, Morphosys, and Pharmacyclics and received research funding from AbbVie, Acerta, AstraZeneca, Genentech, Infinity, Kite, SeaGen, TG Therapeutics, VelosBio, and Xencor.
CT Served as a consultant for Celgene/Bristol Myers Squib, Gilead, Janssen, Novartis, and Roche and received honoraria from Celgene/Bristol Myers Squibb, Gilead, Janssen, Novartis, and Roche and travel expenses from Bristol Myers Squibb, Celgene, Gilead, Novartis and Roche.
FB served as a consultant for AbbVie and Bristol Meyers Squibb.
PW served as a consultant for Acerta and BeiGene.
EH served as a consultant for Antigene, Bristol Myers Squibb, Gilead, Janssen, Merck Sharpe & Dohme, and Roche and as speakers' bureau for Roche and received travel expenses from Janssen and Roche and research funding from AstraZeneca, Bristol Myers Squibb, Merck KgA, and Roche.
MC, XL, WZ have current employment and equity ownership from BeiGene.
JH has current employment, leadership, equity ownership, patents/equity ownership, and travel expenses from BeiGene.
JT received research funding from BeiGene, Celgene, Janssen, Pharmacyclics LLC, Roche, and Takeda.
JJ, MS-T, XK, MS, SM, S-JH have nothing to disclose.

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