Safety and Efficacy of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MAGNOLIA Phase 2 Study)

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Introduction: MZL

- Marginal zone lymphoma (MZL) is uncommon and heterogenous[1,2]
- Arising from memory B cells in the marginal zone of secondary lymphoid follicles[2]
- Three subtypes:
  - Extranodal (MALT) (70%)[1,3-5]
    - Chronic inflammation (infection, autoimmune causes)
    - Stomach (most common site), intestine, thyroid, lung, skin
  - Splenic (20%)[6-8]
    - Linked to hepatitis C infection
  - Nodal (10%)[3,7]
    - Disseminated peripheral lymphadenopathy
    - Long-term outcome less favorable than extranodal MZL

1. Denlinger NM, et al. *Cancer Manag Res*. 2018;10:615-624. 2. Kahl B, Yang D. *Hematology Am Soc Hematol Educ Program.* 2008;2008:359-364. 3. Nathwani BN, et al. *J Clin Oncol.* 1999;17:2486-2492. 4.Thieblemont C, et al. *J Clin Oncol*. 1997;15:1624-1630. 5. Zucca E, et al. *Blood*. 2003;101:2489-2495. 6. Arcaini L, et al. *Cancer*. 2004;100:107-115. 7. Berger F, et al. *Blood*. 2000;95:1950-1956. 8.Thieblemont C. *Hematology Am Soc Hematol Educ Program.* 2017;2017:371-378.

Introduction: MZL (cont'd)

- Optimal therapeutic strategies have been difficult to define due to its rarity
- Chemoimmunotherapy approach is often based on studies of follicular lymphoma
- Advanced disease is incurable; continuing pattern of relapse and remission
- B-cell receptor-mediated signaling has been identified as a critical step in MZL pathogenesis[1]
- Bruton's 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]

1. Seiler T, Dreyling M, *Expert Opin Investig Drugs.* 2017; 26(8): 909-915. 2. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 3. Choe H, Ruan J. *Oncology (Williston Park)*. 2016;30:847-858. 4. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443. 5. Noy A, et al. *Blood*. 2017;129:2224-2232.

Introduction: Zanubrutinib

- 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
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[1]
  - Can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton-pump inhibitors, acid-reducing agents, and antithrombotic agents[2,3]
  - An early-phase study in 20 patients with R/R MZL treated with zanubrutinib monotherapy showed an ORR of 80% after a median follow-up of 27.1 months[4]

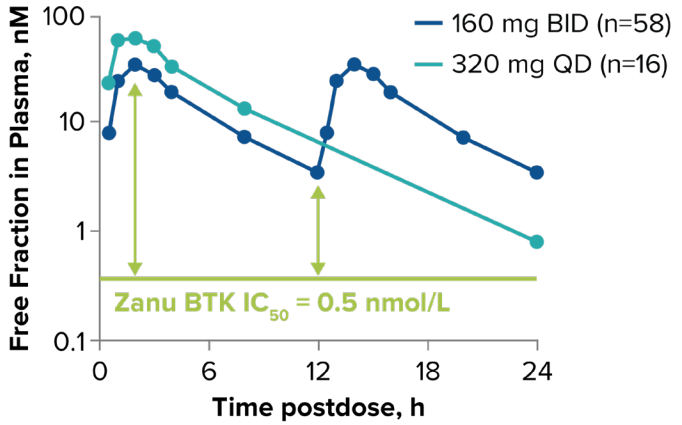
1. Tam CS, et al. ASH 2016, abstract 642. 2. Mu S, et al. *Cancer Chemother Pharmacol*. 2020;85:391-399. 3. Data on file. 4. Tedeschi A, et al. EHA 2020, 06/12/20; 293654; EP1165.

Zanubrutinib Is a Potent and Selective BTK Inhibitor

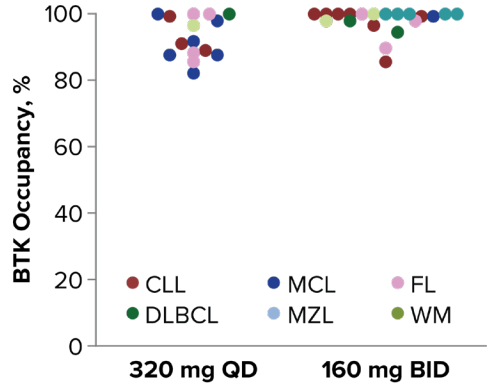
Preclinical Potency and Selectivity of Zanubrutinib and Ibrutinib[1]

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-PLCγ1 Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4

C_{max} and C_{trough} > BTK IC_{50} Over 24 Hours[2]



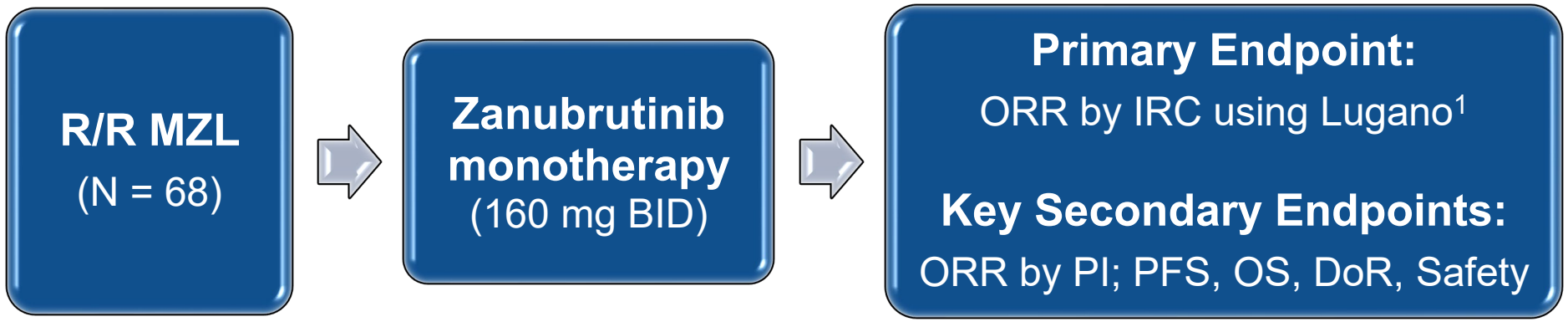
Complete, Sustained BTK Occupancy[3]



1. Tam CS, et al. ICML Session 7, June 16, 2017 [abstr]. 2. Tam CS, et al. *Blood*. 2019;134:851-859. 3. Tam CS, et al. *Blood* 2015;126:832-.

Abbreviations: BID, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; IC_{50}, half maximal inhibitory concentration; ITK, IL-2–inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; QD, once daily; TEC, Tyrosine-protein kinase Tec; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

BGB-3111-214: A Phase 2, Multicenter, Open-Label, Single-Arm Trial (NCT03846427)

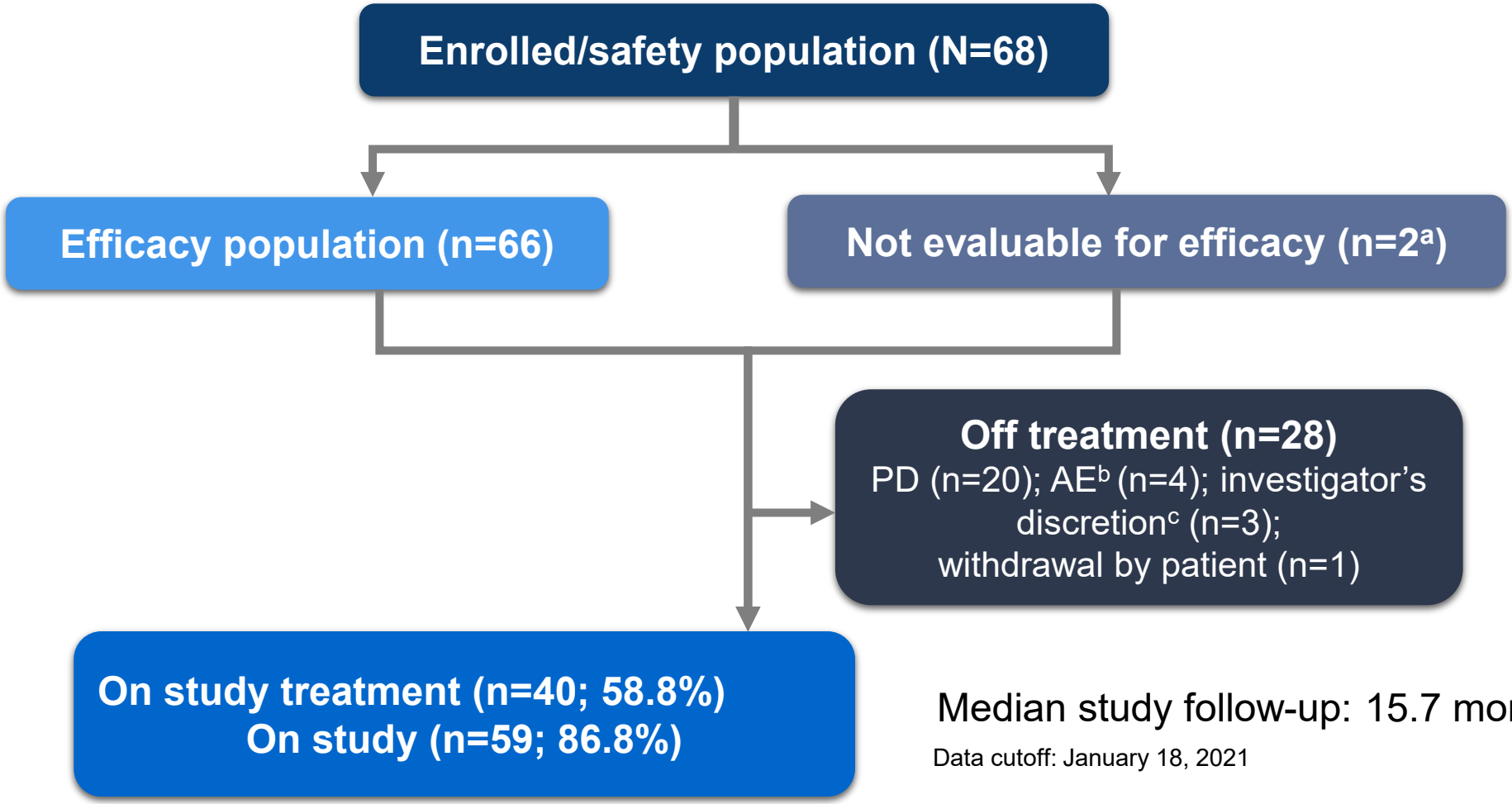


- Enrolled a total of 68 patients with R/R MZL who received at least one prior line of CD20-directed regimen
- Response is based on the Lugano classification for non-Hodgkin lymphoma[1]

1. Cheson BD et al. *J Clin Oncol*. 2014; 32:3059-3068.

Abbreviations: 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.

Patient Disposition



Median study follow-up: 15.7 months

Data cutoff: January 18, 2021

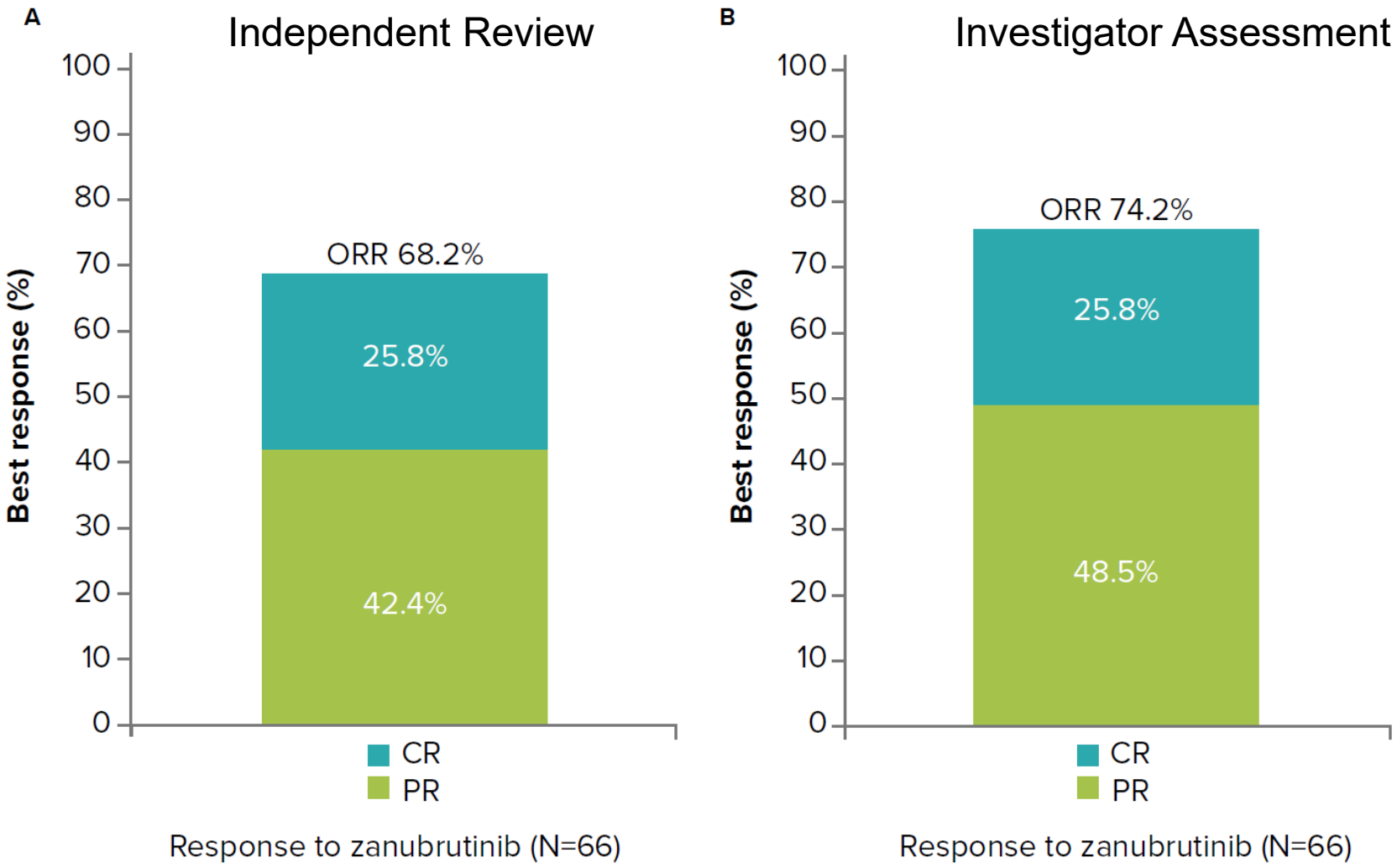
[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Four patients discontinued due to AE (pyrexia later attributed to disease progression, n=1; fatal myocardial infarction in a patient with preexisting cardiovascular disease, n=1; COVID-19 pneumonia leading to death, n=2).
[c]Three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

Patient and Disease Characteristics

Characteristic	Total (N=68)
Age, years, median (range)	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.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; MZL, marginal zone lymphoma.

ORR by (A) Independent Review and (B) Investigator Assessment



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

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	3 (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.

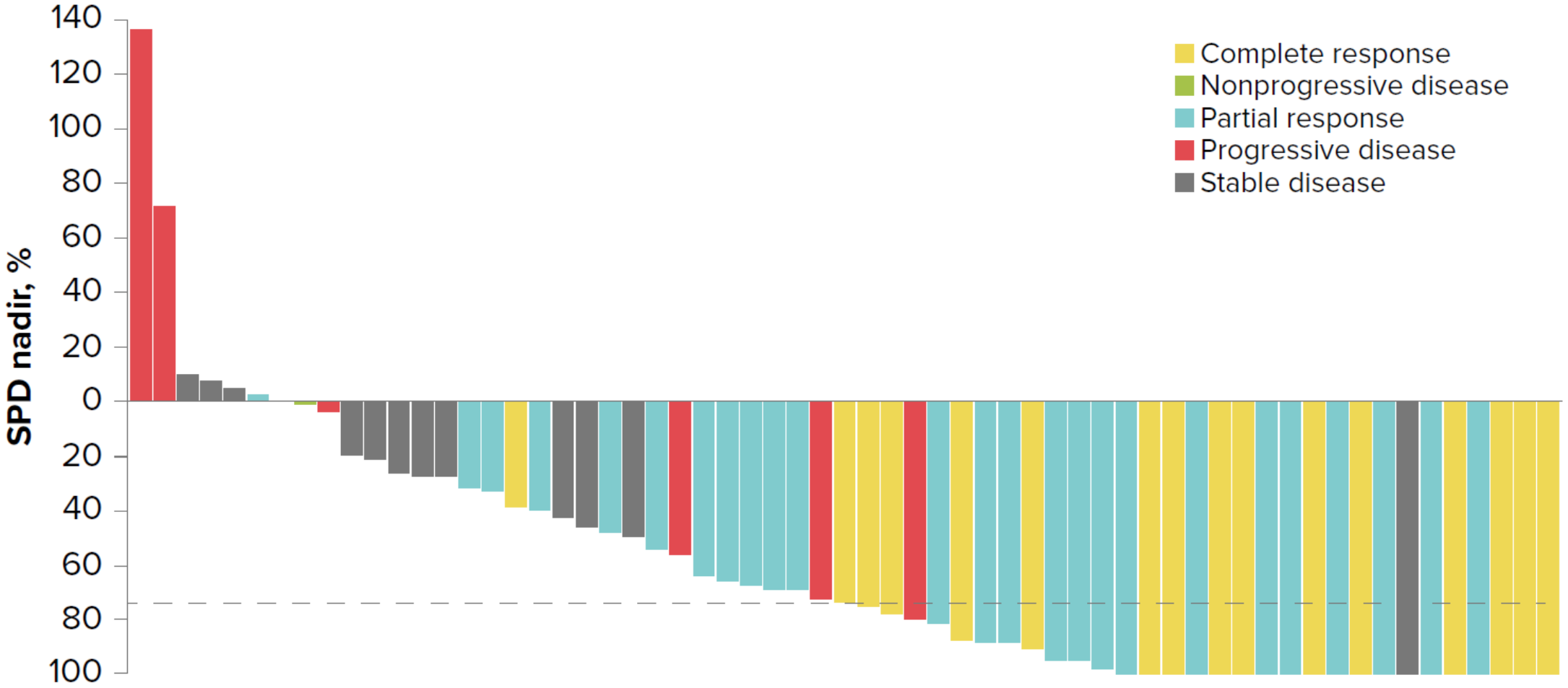
[b]Two-sided Clopper-Pearson 95% CI.

[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.

Abbreviations: CI, confidence interval; CR, complete response; CT, computed tomography; FDG, fluorodeoxyglucose; MZL, marginal zone lymphoma; ORR, overall response rate; PET, positron emission tomography; PR, partial response.

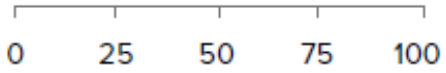
Majority of Patients Had Reduction in Tumor Burden



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

Responses Were Generally Consistent Across Subgroups

	Patients/n	ORR (95% CI)[a]
All patients	45/66	68.2 (55.56-79.11)
Age group		
<65 years	15/26	57.7 (36.92-76.65)
≥65 years	30/40	75.0 (58.80-87.31)
<75 years	28/48	58.3 (43.21-72.39)
≥75 years	17/18	94.4 (72.71-99.86)
Disease status		
Relapsed	31/43	72.1 (56.33-84.67)
Refractory	14/21	66.7 (43.03-85.41)
Bulky disease		
LDi ≤5 cm	26/42	61.9 (45.64-76.43)
LDi >5 cm	19/24	79.2 (57.85-92.87)
Baseline extra-nodal disease		
Yes	34/52	65.4 (50.91-78.03)
No	11/14	78.6 (49.20-95.34)

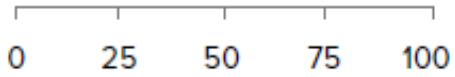


[a]Two-sided Clopper-Pearson 95% CIs for ORR.

Abbreviations: BR, bendamustine/rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, confidence interval; LDi, longest diameter; ORR, overall response rate; R, rituximab; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine/prednisone.

Responses Were Generally Consistent Across Subgroups (cont'd)

	Patients/n	ORR (95% CI)[a]
Bone marrow involvement		
Yes	19/29	65.5 (45.67-82.06)
No	26/37	70.3 (53.02-84.13)
Prior line of systemic therapy		
<3	36/48	75.0 (60.40-86.36)
≥3	9/18	50.0 (26.02-73.98)
Prior treatment		
RCVP	20/25	80.0 (59.30-93.17)
RCHOP	9/17	52.9 (27.81-77.02)
BR	16/22	72.7 (49.78-89.27)
R-lenalidomide	1/2	50.0 (1.26-98.74)
Rituximab monotherapy	10/15	66.7 (38.38-88.18)
CHOP	2/3	66.7 (9.43-99.16)
R-chlorambucil	2/5	40.0 (5.27-85.34)



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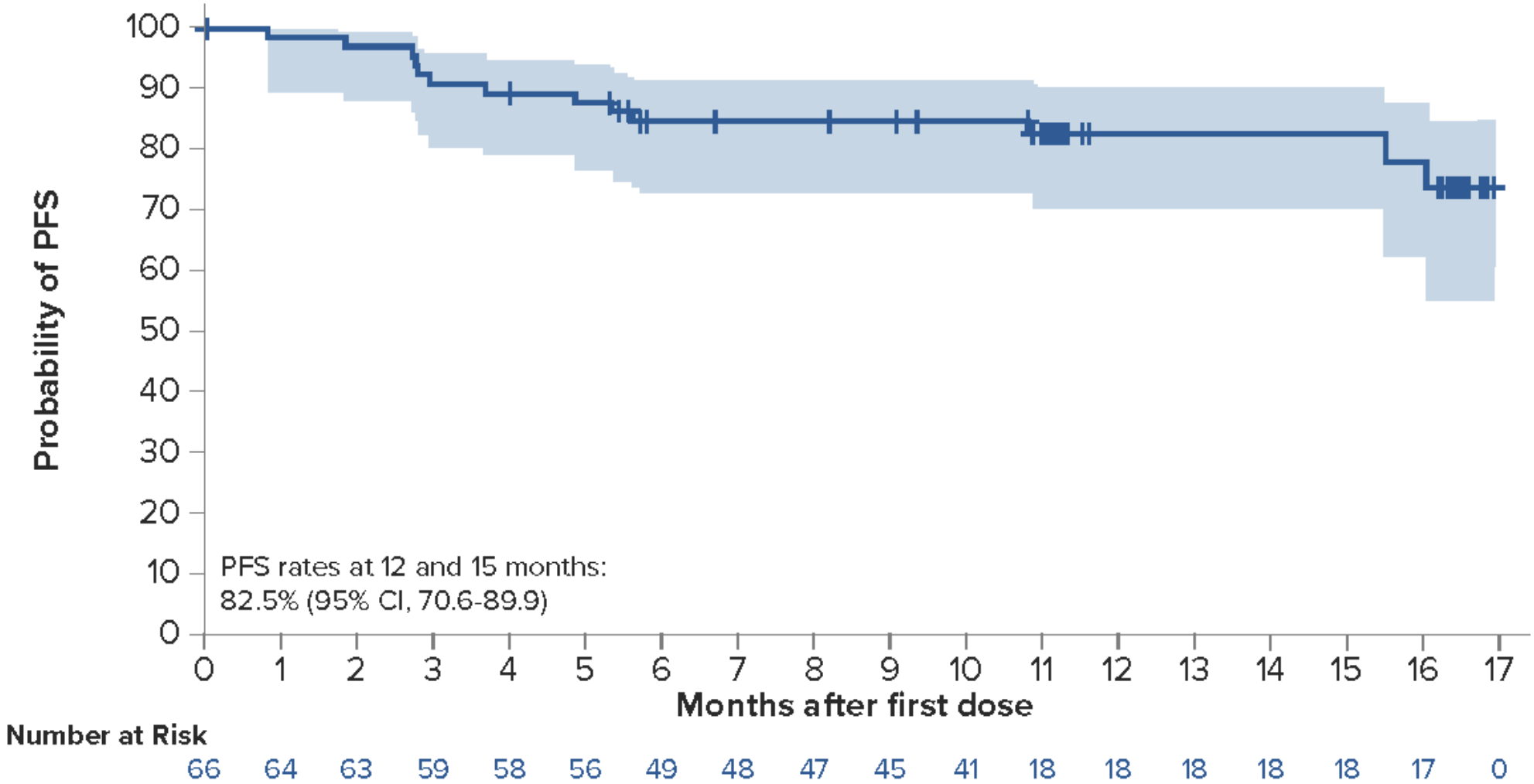
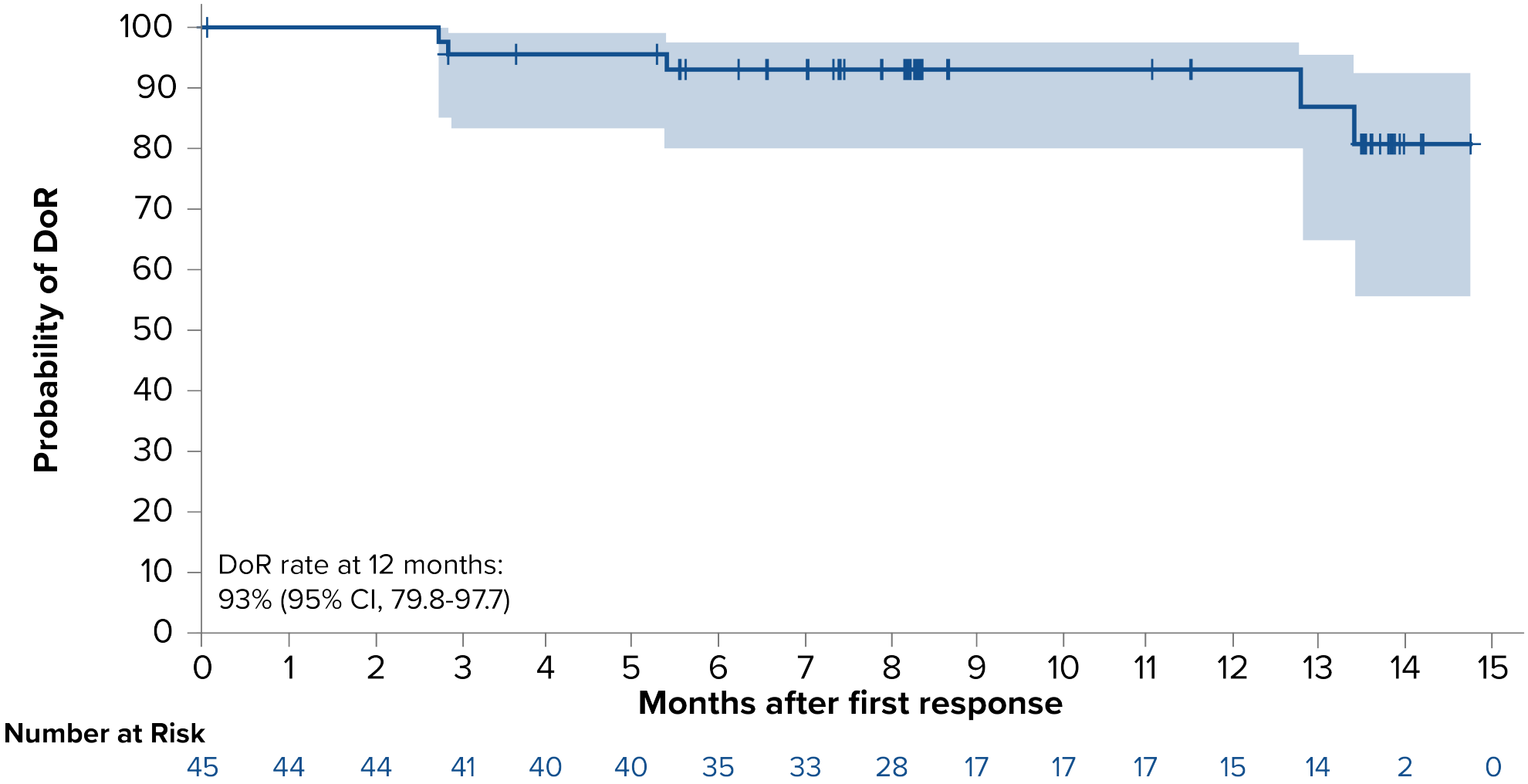
Progression-Free Survival by Independent Review



Abbreviations: CI, confidence interval; PFS, progression-free survival.

Duration of Response by Independent Review



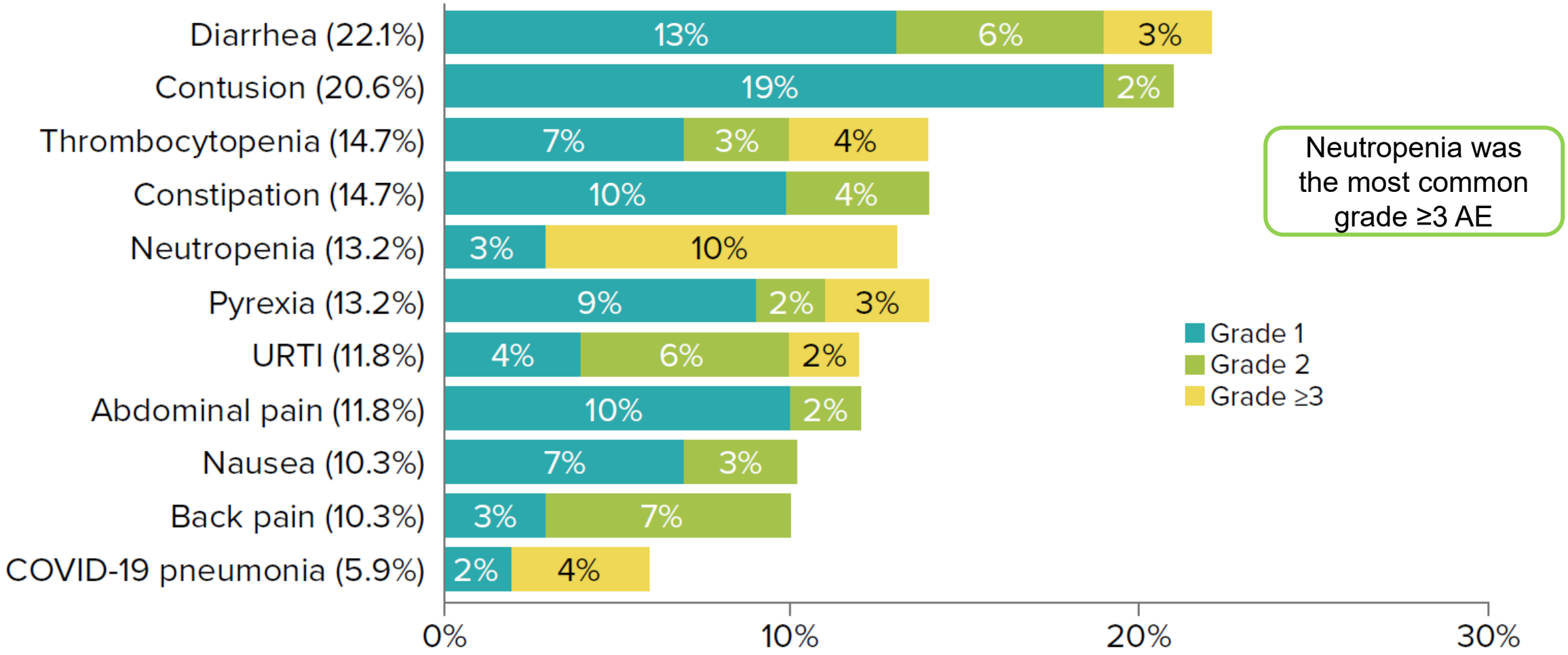
Abbreviations: CI, confidence interval; DoR, duration of response.

Summary of TEAEs

	N=68 n (%)
Patients with at least one 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); One patient died from myocardial infarction; two patients died from COVID-19 pneumonia.
Abbreviation: TEAE, treatment-emergent adverse event.

TEAEs Occurring in ≥10% of Patients Regardless of Causality



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

TEAEs of Interest

TEAEs 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 two patients with history of skin cancer); papillary thyroid carcinoma (in one patient with preexisting thyroid nodule); recurrent bladder cancer (in one patient with history of bladder cancer), and acute myeloid leukemia (in one patient with prior chemotherapy with alkylating agents).
[d]Atrial fibrillation occurred in a patient with preexisting atrial fibrillation (21 days after end of treatment due to disease progression).
Abbreviation: 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 progression-free survival (PFS) and median duration of response were not reached
  - 93% of responders were progression-free/alive at 12 months after initial response
  - PFS rate was 82.5% at 15 months

Summary (cont'd)

- Treatment discontinuation due to adverse events (AEs) occurred in four patients; none were considered related to zanubrutinib
- Grade 5 AEs occurred in three patients (including two patients who died from COVID-19 pneumonia)
- Atrial fibrillation/flutter occurred in two patients
- No major hemorrhage was reported

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