Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma: Initial Results of the MAGNOLIA (BGB-3111-214) Trial

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Abstract 339

Introduction: MZL

- 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 HCV infection
  - Nodal (10%)[3,7]
    - Disseminated peripheral lymphadenopathy
    - Long-term outcome less favorable than extranodal MZL

BTK, Bruton's tyrosine kinase; ORR, overall response rate; R/R MZL, relapsed/refractory marginal zone lymphoma.

1. Denlinger et al *Cancer Manag Res*. 2018;10:615-624. 2. Kahl B and Yang D. *Hematology Am Soc Hematol Educ Program.* 2008:359–364. 3. Nathwani BN, et al. *J Clin Oncol.* 1999;17:2486-92. 4.Thieblemont C, et al. J Clin Oncol. 1997;15: 1624-1630 5. Zucca E, et al. *Blood*. 2003;101:2489-95. 6. Arcaini L, et al. *Cancer*. 2004;100:107-15. 7. Berger F, et al. *Blood*. 2000;95:1950-6. 8.Thieblemont C. *Hematology Am Soc Hematol Educ Program.* 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 the 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 R/R MZL, demonstrating a 48% ORR[5]

BTK, Bruton's tyrosine kinase; ORR, overall response rate; R/R MZL, relapsed/refractory marginal zone lymphoma.

1. Seiler and Dreyling, 2017; 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 PK/PD properties[1]
  - Can be co-administered with strong/moderate CYP3A inhibitors at a reduced dose, proton-pump inhibitors, acid-reducing agents, and anti-thrombotic 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]

BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; ORR, overall response rate; PK/PD, pharmacokinetic/pharmacodynamic; R/R MZL, relapsed/refractory marginal zone lymphoma.

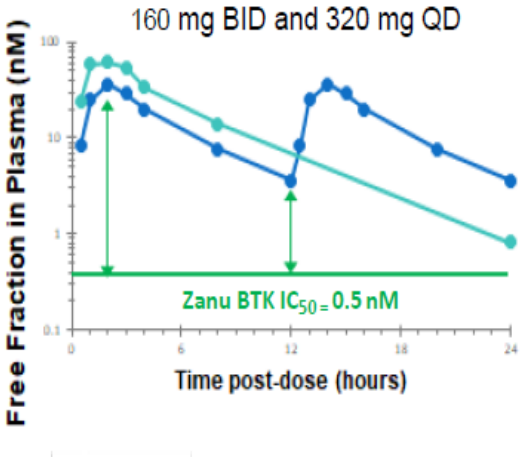
1. Tam CS, et al. ASH 2016. 2. Mu S, et al. *Cancer Chemother Pharmacol*. 2020;85:391-399. 3. Data on file. 4. Tedeschi A, et al. EHA 2020.

Zanubrutinib Is a Potent and Selective BTK Inhibitor

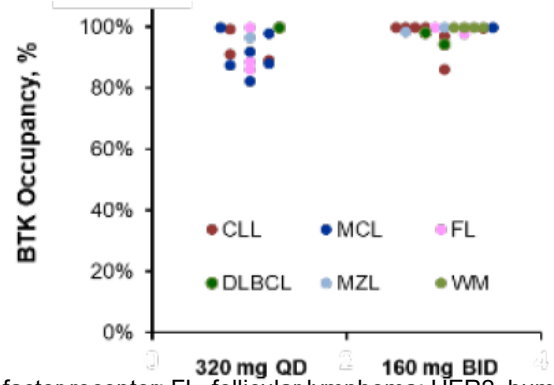
Preclinical Potency and Selectivity of Zanubrutinib and Ibrutinib[1]

Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
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	1.0
	BTK Biochemical Assay	0.22	0.2	1.1
EGFR	p-EGFR HTRF Cellular Assay	606	101	6
	A431 Proliferation	3210	323	9.9
ITK	ITK Occupancy Cellular Assay	606	189	17
	p-$PLC_{\gamma1}$ 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]



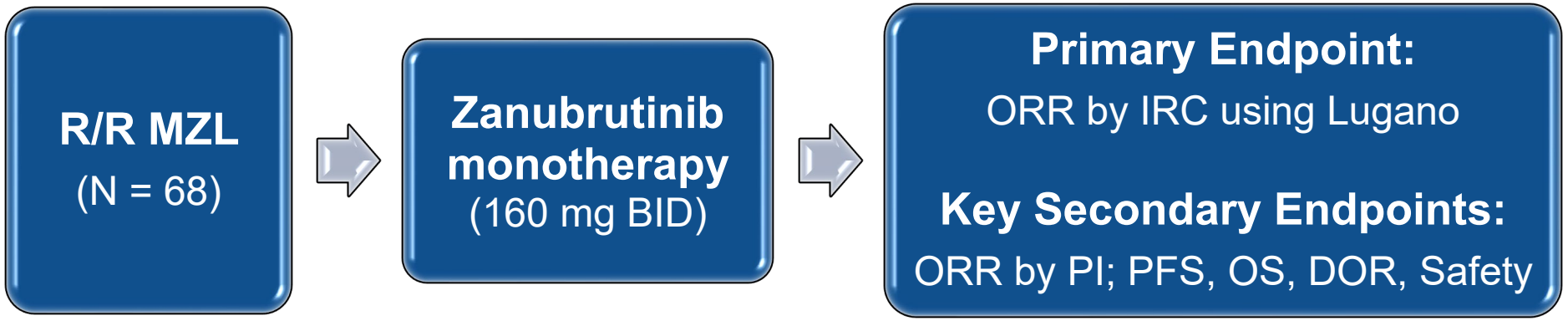
Complete, Sustained BTK Occupancy[3]



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, IL2-inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; QD: once daily; WM, Waldenström's macroglobulinemia; Zanu, zanubrutinib.

1.Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 2.Tam CS, et al. *Blood*. 2019;134:851-859. 3. Tam CS, et al. *Blood* 2015; 126(23), 832–832

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

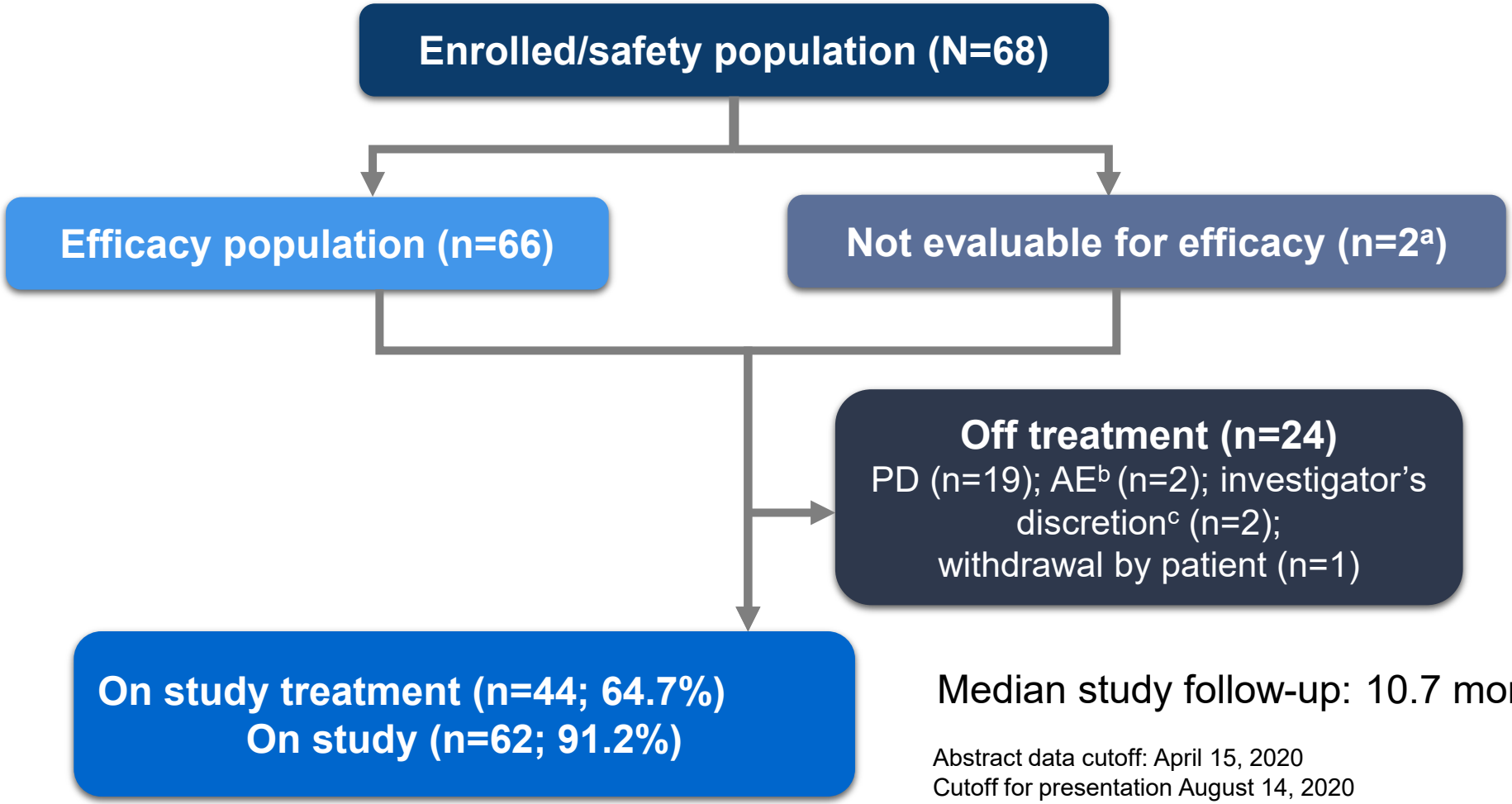


- Enrolled a total of 68 patients with R/R MZL who received at least one prior line of CD20-directed regimen
- Tumor response by investigator assessment will be presented herein
  - Response is based on the Lugano classification for non-Hodgkin lymphoma[1]
  - Blinded response assessment by independent review committee is ongoing

1. Cheson et al, 2014

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: 10.7 months

Abstract data cutoff: April 15, 2020
Cutoff for presentation August 14, 2020

[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Two patients discontinued due to AE (pyrexia later attributed to disease progression; fatal myocardial infarction in a patient with pre-existing cardiovascular disease).
[c]Two patients discontinued per the investigator's discretion (requiring prohibited medications).
AE, adverse event; 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)
Sex, n (%)	
Male	36 (52.9)
Female	32 (47.1)
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	4 (5.9)
Lymphoma involvement in bone marrow, n (%)	29 (42.6)
Prior lines of systemic therapy, median (range)	2 (1-6)

Data cutoff: August 14, 2020

ECOG, Eastern Cooperative Oncology Group; MZL: marginal zone lymphoma.

Best Overall Response by Investigator Assessment

Best response	N=66[a]
ORR (CR or PR), n (%) 95% CI[b]	49 (74.2) (61.99, 84.22)
Complete response	16 (24.2)
Partial response	33 (50.0)
Stable disease	10 (15.2)
Progressive disease	5 (7.6)
Discontinued prior to 1st assessment/missing[c]	2 (2.9)
Time to response (months), median (range)	2.8 (1.7-11.1)
Study follow-up (months), median (range)	10.7 (1.6-16.7)

Data cutoff: August 14, 2020

[a]Two patients were excluded from the efficacy population due to lack of central confirmation of MZL.
[b]2-sided Clopper-Pearson 95% CI
[c]One patient withdrew consent prior to the first disease assessment; One patient had imaging performed but overall assessment is still pending.
CI, confidence interval; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response.

Best Overall Response by Investigator Assessment and MZL Subtypes (N=66)

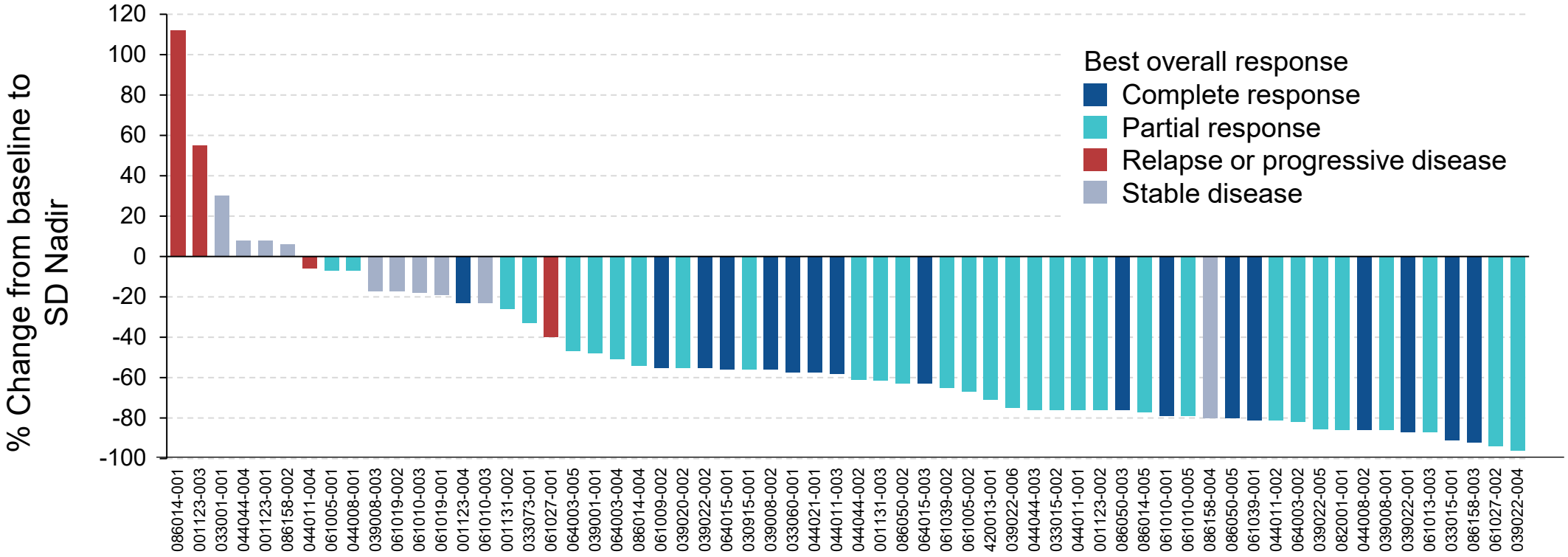
Best response, n (%)	Extranodal (N=25)	Nodal (N=25)	Splenic (N=12)	Unknown (N=4)	Total (N=66[b])
ORR (CR or PR), n (%) 95% CI[a]	17 (68.0) (46.50-85.05)	21 (84.0) (63.92-95.46)	9 (75.0) (42.81-94.51)	2 (50.0) (6.76-93.24)	49 (74.2) (61.99-84.22)
Complete response	10 (40.0)	4 (16.0)	1 (8.3)	1 (25.0)	16 (24.2)
Partial response	7 (28.0)	17 (68.0)	8 (66.7)	1 (25.0)	33 (50.0)
Stable disease	5 (20.0)	2 (8.0)	1 (8.3)	2 (50.0)	10 (15.2)
Progressive disease	2 (8.0)	2 (8.0)	1 (8.3)	0	5 (7.6)

Data cutoff: August 14, 2020

[a]2-sided Clopper-Pearson 95% CI
[b]One patient (extranodal MZL) withdrew consent prior to the first disease assessment; One patient (splenic MZL) had imaging performed but overall assessment is still pending.
CI, confidence interval; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response.

Majority of Patients had Reduction in Tumor Burden

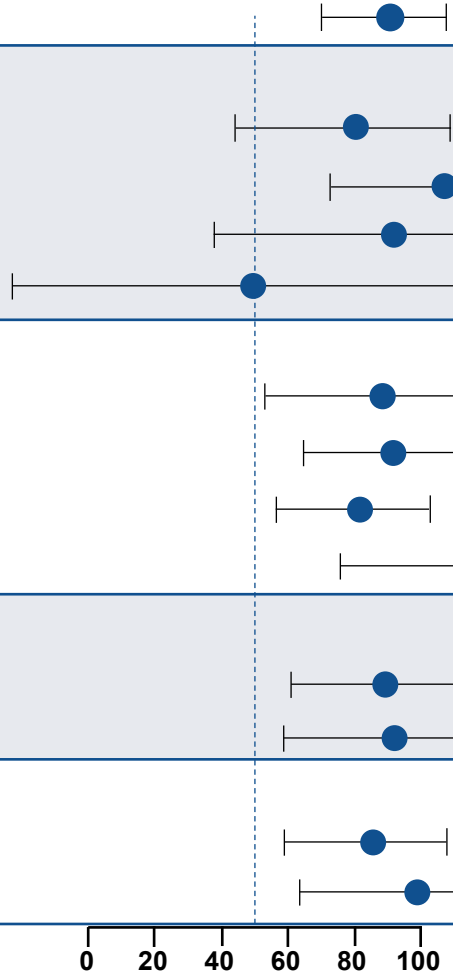
Best Percent Change from Baseline in Target Lesion Sum of Perpendicular Diameters by Best Overall Response (Investigator Assessment)



Note: Only patients with non-missing BOR and SPD% changes were included (n=62)

Responses were Generally Consistent Across Subgroups

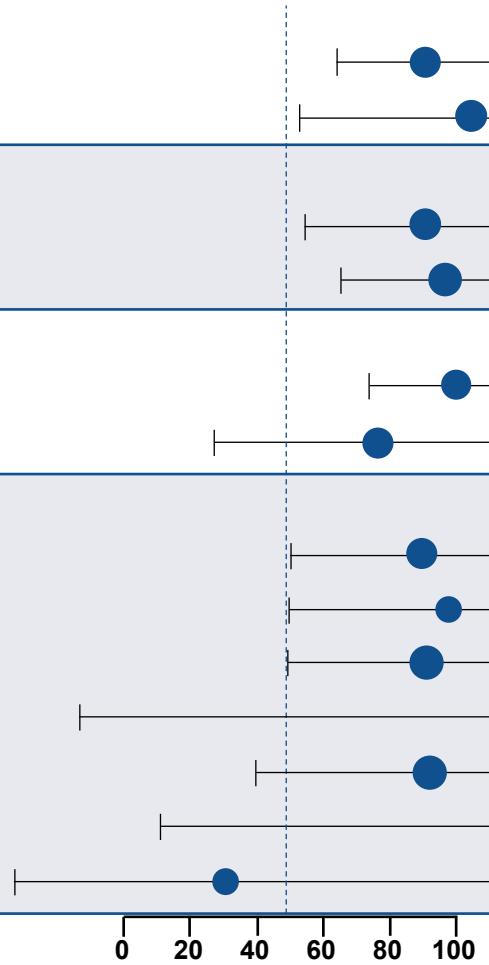
	No. of Patients	Overall response rate (95% CI)*	
All patients	66	74.2	(61.99 – 84.22)
MZL subtype			
EMZL	25	68.0	(46.50 – 85.05)
NMZL	25	84.0	(63.92 – 95.46)
SMZL	12	75.0	(42.81 – 94.51)
Unknown	4	50.0	(6.76 – 93.24)
Age Group			
< 65 years	26	73.1	(52.21 – 88.43)
≥ 65 years	40	75.0	(58.80 – 87.31)
< 75 years	48	68.8	(53.75 – 81.34)
≥ 75 years	18	88.9	(65.29 – 98.62)
ECOG Performance status			
0	38	73.7	(56.90 – 86.60)
≥ 1	28	75.0	(55.13 – 89.31)
Bulky disease			
LDi ≤ 5 cm	42	71.4	(55.42 – 84.28)
LDi > 5 cm	24	79.2	(57.85 – 92.87)



[a]2-sided Clopper-Pearson 95% confidence intervals for Overall Response Rate.
ECOG, Eastern Cooperative Oncology Group; EMZL, Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue; NMZL, Nodal Marginal Zone Lymphoma; longest diameter, LDi; SMZL, Splenic Marginal Zone Lymphoma; BM, Bone Marrow.

Responses were Generally Consistent Across Subgroups (cont'd)

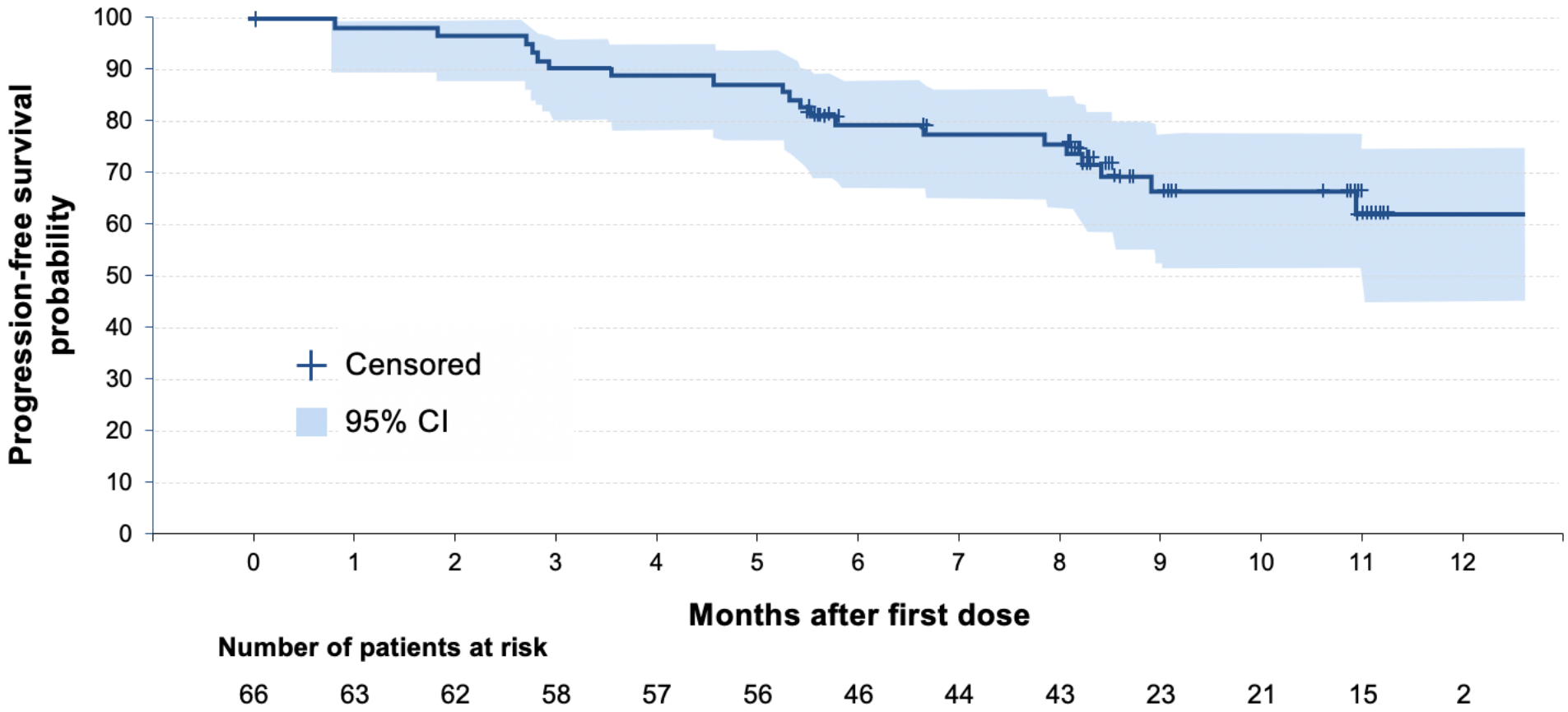
	No. of Patients	Overall response rate (95% CI)*	
Baseline Extra-nodal disease			
Yes	51	72.5	(58.26 – 84.11)
No	15	80.0	(51.91 – 95.67)
Bone marrow involvement			
Yes	29	72.4	(52.76 – 87.27)
No	15	75.7	(58.80 – 88.23)
Prior line of systemic therapy			
< 3	49	77.6	(63.38 – 88.23)
≥ 3	17	64.7	(38.33 – 85.79)
Prior treatment			
RCVP	25	72.0	(50.61 – 87.93)
RCHOP	17	76.5	(50.10 – 93.19)
BR	22	72.7	(49.78 – 89.27)
R-lenalidomide	2	100.0	(15.81 – 100.00)
Rituximab monotherapy	15	73.2	(44.90 – 92.21)
CHOP	3	100.0	(29.24 – 100.00)
R-chlorambucil	5	40.0	(5.27 – 85.34)



[a]2-sided Clopper-Pearson 95% confidence intervals for Overall Response Rate.
BR, bendamustine/rituximab; CHOP, cyclophosphamide/doxorubicin/Oncovin/prednisone; R, rituximab; RCVP, rituximab, , cyclophosphamide, vincristine, prednisone; RCHOP, rituximab, cyclophosphamide/doxorubicin/Oncovin/prednisone;

Progression-Free Survival by Investigator Assessment

- PFS median follow-up of 9.13 months (range 0.03, 16.46)
- Progression-free rate: 80% (6 months), 67% (9 months)



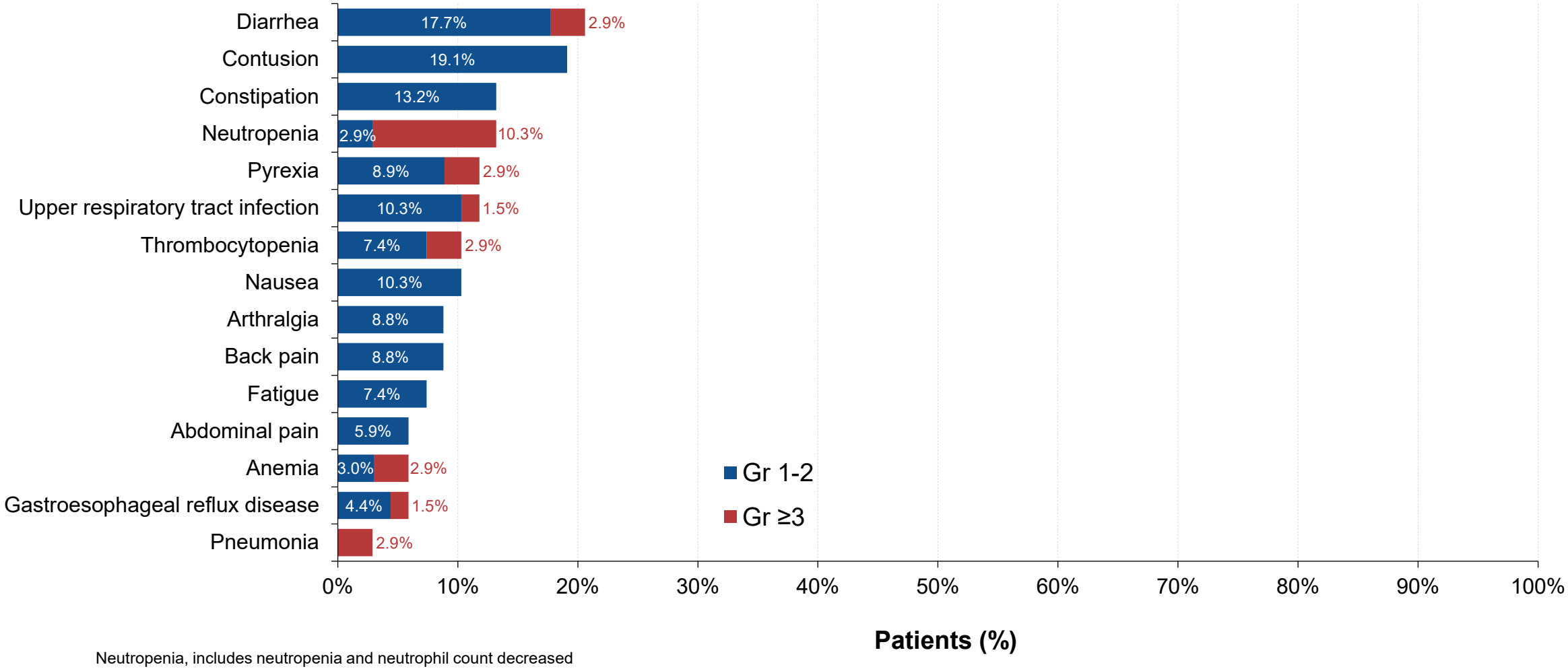
Summary of TEAEs

	N=68 n (%)
Patients with at least 1 TEAE	65 (95.6)
Grade 3 or higher TEAE	26 (38.2)
Serious TEAE	22 (32.4)
TEAE leading to dose interruption	16 (23.5)
TEAE leading to study drug discontinuation	2 (2.9)[a]
TEAE leading to death	1 (1.5)[b]
TEAE leading to dose reduction	0

Data cutoff: August 14, 2020

[a] One patient discontinued due to pyrexia (later attributed to disease progression); 1 patient died from myocardial infarction.
[b] One patient with pre-existing cardiovascular disease died from myocardial infection.
TEAE, treatment-emergent adverse event.

TEAEs in ≥5% of Patients or Grade ≥3 TEAEs in ≥2 Patients Regardless of Causality



Neutropenia, includes neutropenia and neutrophil count decreased
Thrombocytopenia, includes thrombocytopenia and platelet count decreased
TEAE, treatment-emergent adverse event.

Summary of TEAE of Interest

	N=68	
TEAE of Interest	All Grade	≥Grade 3
Infection	27 (39.7)	9 (13.2)
Hemorrhage	22 (32.4)	0
Diarrhea	14 (20.6)	2 (2.9)
Neutropenia[a]	9 (13.2)	7 (10.3)
Thrombocytopenia[b]	7 (10.3)	2 (2.9)
Second primary malignancy	4 (5.9)[c]	2 (2.9)
Atrial fibrillation/flutter	2 (2.9)[d]	1 (1.5)
Hypertension	0	0
Major hemorrhage	0	0

[a]Includes neutropenia and neutrophil count decreased
[b]Includes thrombocytopenia and platelet count decreased
[c]Includes basal cell and squamous cell carcinoma (in 1 patient with history of skin cancer); basal cell carcinoma (in 1 patient 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).
[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

MAGNOLIA enrolled patients with high-risk features

- Elderly patients
  - Median age 70 years
  - 19 (28%) patients were ≥75 years old
- Heavily pre-treated
  - Median of 2 prior lines of therapy
  - 23 (34%) patients had ≥3 prior treatments
  - 67 (98.5%) patients received prior chemotherapies
- Refractory disease
  - 22 (32.4%) patients
- Nodal MZL
  - 26 (38.2%) patients

Summary (cont'd)

Zanubrutinib was shown to be highly active in patients with R/R MZL

- Investigator-assessed ORR of 74.2%
  - CR rate 24.2%
- Responses observed in all MZL subtypes
- PFS rate at 6, 9 months: 80%, 67%
- DOR rate at 6 months: 79%
- OS rate at 12 months: 94%

- Clinical benefit (SD/PR/CR) observed in 89% of patients
- Responses consistent across subgroups including high-risk patients
  - Age ≥75: ORR 89%
  - ≥3 prior lines: ORR 65%
  - Refractory disease: ORR 71%
  - Nodal MZL: ORR 84%

CR, complete response, DOR, duration of response, PFS, progression-free survival, ORR, overall response rate; OS, overall survival; PR, partial response; R/R MZL, relapsed/refractory marginal zone lymphoma; SD, stable disease.

Summary (cont'd)

Zanubrutinib was generally well tolerated

- No AE led to dose reduction
- Two patients discontinued treatment due to AE
  - Both unrelated to zanubrutinib
- One patient died from myocardial infarction
- Atrial fibrillation and atrial flutter occurred in 1 patient each
  - Appears similar to the background rate[1] given the age of study population

- Low-grade bleeding events occurred in 22 (32%) patients
  - No major hemorrhage
  - Antiplatelets and anticoagulants allowed in the study
- No hypertension
- Good tolerability resulted in high treatment adherence
  - 99.6% median relative dose intensity[a]

[a]Relative dose intensity is defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity equals to (160*2) mg/day.
AE, adverse event.
1. Camm AJ, et al. *Eur Heart J* 2012;21:2719-2747.

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