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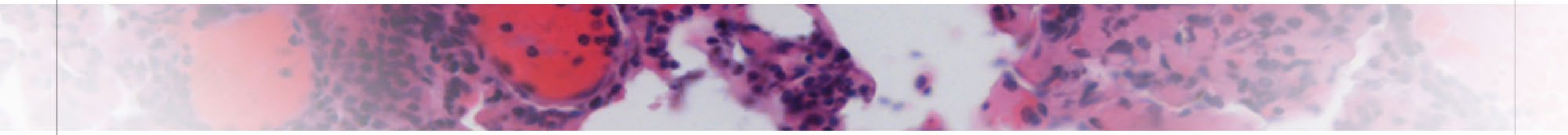

Safety and Efficacy of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Waldenström Macroglobulinemia from a Phase 2 Trial

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Abstract 2940

Introduction

- BTK plays a critical role in B-cell receptor signaling; this pathway is constitutively activated in WM (>90% with *MYD88* mutations), leading to malignant cell survival[1,2]
- BTK inhibition is an emerging standard of care for WM[3]
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Potent, selective, irreversible
  - Equipotent to ibrutinib against BTK; higher selectivity vs EGFR, ITK, JAK3, HER2, and TEC[4]
  - Advantageous PK and PD properties: complete and sustained BTK occupancy in PBMC and lymph nodes[5]
  - Favorable drug–drug interaction properties: can be co-administered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]
  - **Approved for patients with R/R MCL in the United States, November 2019**
  - **Approved for patients with R/R MCL and R/R CLL/SLL in China, June 2020**

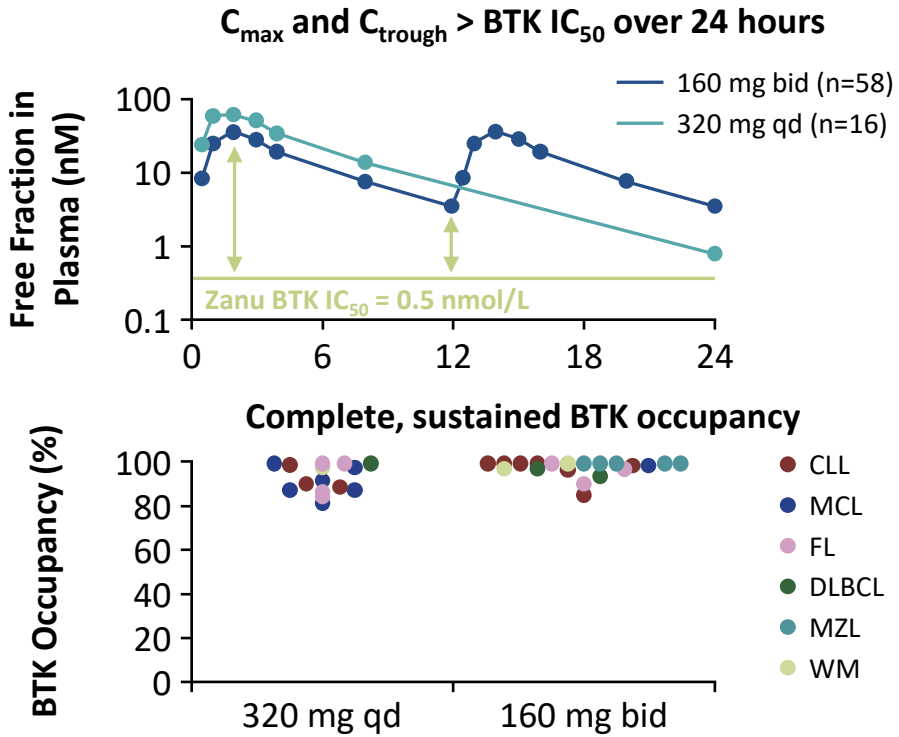
BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; MCL, mantle cell lymphoma; *MYD88*, myeloid differentiation primary response gene 88; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamic; PK, pharmacokinetic; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

1. Rickert RC. Nat Rev Immunol. 2013;13:578-591. 2. Argyropoulos KV, et al. Leukemia. 2016;30:1116-1125. 3. Treon SP et al, J Clin Oncol. 2020;38:1198-1208. 4. Guo Y, et al. J Med Chem. 2019;62:7923-7940. 5. Tam CS, et al. Blood. 2019;134:851-859.
6. Mu S, et al. Cancer Chemother Pharmacol. 2020;85:391-399. 7. Data on file.

Zanubrutinib: A Potent and Selective BTK Inhibitor[1,2]

- Potent, selective, irreversible; minimize off-target inhibition

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-$PLC_{\gamma 1}$ 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

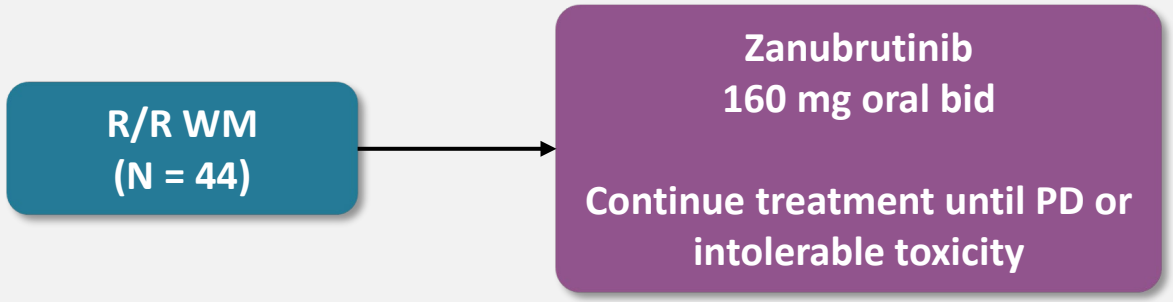


bid, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{max}, maximum concentration; C_{trough}, trough concentration; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HTRF, homogeneous time-resolved fluorescence; IC_{50}, half maximal inhibitory concentration; ITK, interleukin-2-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 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.

Study Design

- BGB-3111-210 (ClinicalTrials.gov: NCT03332173) is a pivotal, single-arm, open-label, multicenter, phase 2 study conducted in R/R WM patients in China



Primary endpoint:

- MRR (CR + VGPR + PR rate) assessed by IRC according to an adaptation of the response criteria updated at the 6th IWWM[1,2]

Secondary endpoints:

- PFS, ORR, DOMR, safety

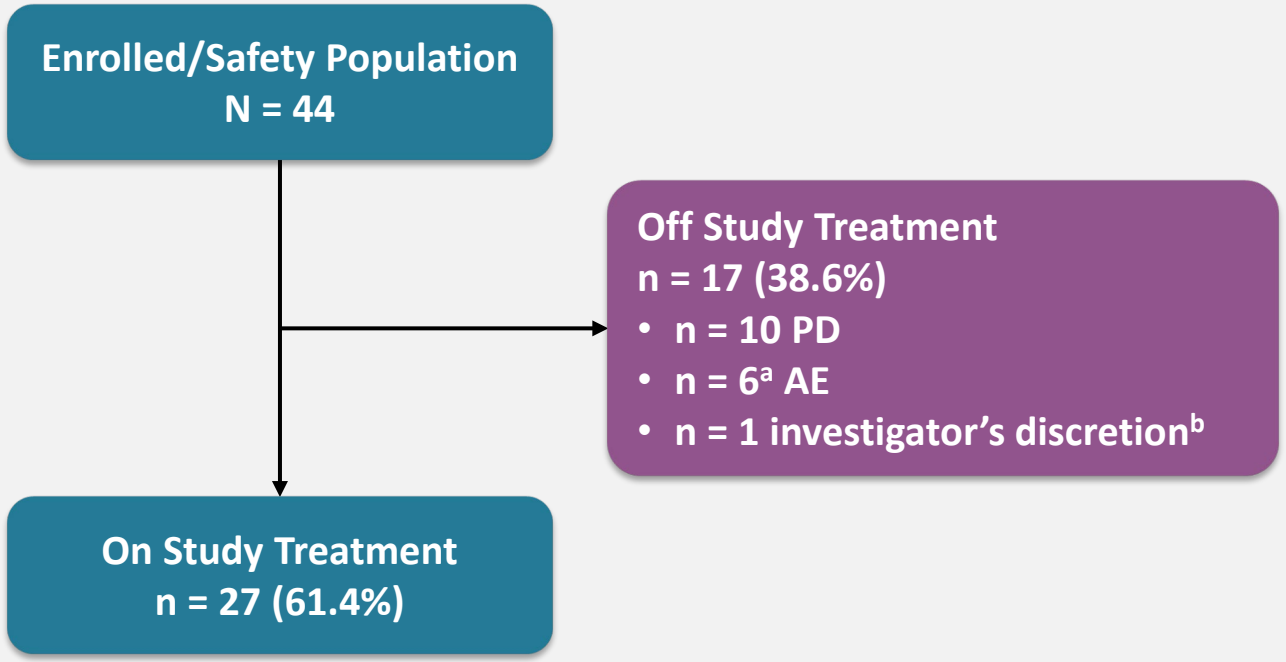
Eligible patients:

- Meet at least one criterion for treatment according to consensus panel criteria from the 7th IWWM[3]
- WM pathology confirmation by central lab
- Previously treated with a minimum of one prior line of standard chemotherapy-containing regimen (with completion of ≥2 continuous treatment cycles)
- Documented failure to achieve at least minor response or documented disease progression after response to the most recent treatment regimen

bid, twice daily; CR, complete response; DOMR, duration of major response; IRC, independent review committee; IWWM, International Workshop on Waldenström's Macroglobulinemia; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

1. Owen RG, et al. Br J Haematol. 2013;160:171-176. 2. Anderson KC, et al. J Natl Compr Canc Netw. 2012;10:1211-1219. 3. Dimopoulos MA, et al. Blood. 2014;124:1404-1411.

Patient Disposition (Median Follow-up:18.58 months)



[a]One patient discontinued study treatment and subsequently died due to 'progression of Waldenström macroglobulinemia' that was reported as an adverse event.
[b]The patient achieved MR and was discontinued per the investigator's discretion.
AE, adverse event; MR, minor response; PD, progressive disease.

Patient Demographics and Disease Characteristics

Characteristic	Total (N = 44)
Median age, years (range)	65 (41–83)
Sex, n (%)	
Male	27 (61.4)
Female	17 (38.6)
ECOG performance status, n (%)	
0/1	41 (93.2)
2	3 (6.8)
WM prognostic score, n (%)	
Low risk	11 (25.0)
Intermediate risk	13 (29.5)
High risk	20 (45.5)
Median number of prior systemic therapy, regimens (range)	2 (1–6)
Median baseline IgM, g/L (range)	30.85 (3.16–96.50)
Genotype, n (%)	
MYD88^{L265P}/*CXCR4*^{WT}	32 (72.7)
MYD88^{L265P}/*CXCR4*^{WHIM}	5 (11.4)
MYD88^{WT}	7 (15.9)
Peripheral blood cytopenias, n (%)	
Anemia (hemoglobin ≤110 g/L)	33 (75.0)
Thrombocytopenia (platelet count ≤100 × 10^9/L)	9 (20.5)
Neutropenia (ANC ≤1.5 × 10^9/L)	11 (25.0)

ANC, absolute neutrophil count; *CXCR4*, CXC-chemokine receptor 4; ECOG, Eastern Cooperative Oncology Group; IgM, immunoglobulin M; *MYD88*, myeloid differentiation primary response gene 88; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and Myelokathexis syndrome; WM, Waldenström macroglobulinemia; WT, wild type.

Efficacy: Best Overall Response as Assessed by IRC

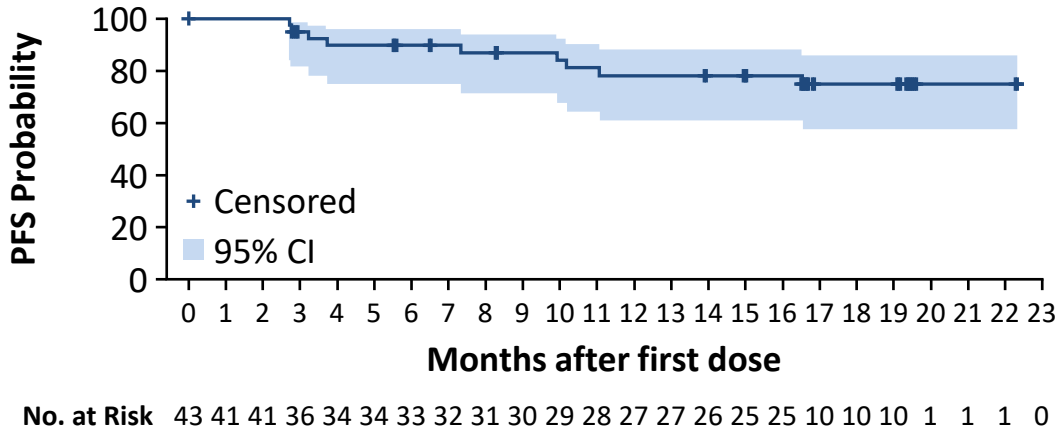
Efficacy per IRC	N = 43[a]
BOR, n (%)	
CR	0
VGPR	14 (32.6)
PR	16 (37.2)
MR	4 (9.3)
SD	4 (9.3)
PD	2 (4.7)
Unknown	3 (7.0)
CR + VGPR rate, n (%); (95% CI)[b]	14 (32.6); (19.08, 48.54)
Major response rate (PR or better), n (%); (95% CI)[b]	30 (69.8); (53.87, 82.82)
Overall response rate (MR or better), n (%); (95% CI)[b]	34 (79.1); (63.96, 89.96)

[a]One patient was excluded from the efficacy analysis due to baseline immunoglobulin M <5g/L.
[b]Calculated using the Clopper-Pearson method.
BOR, best overall response; CI, confidence interval; CR, complete response; IRC, independent review committee; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Efficacy: PFS and DOMR as Assessed by IRC

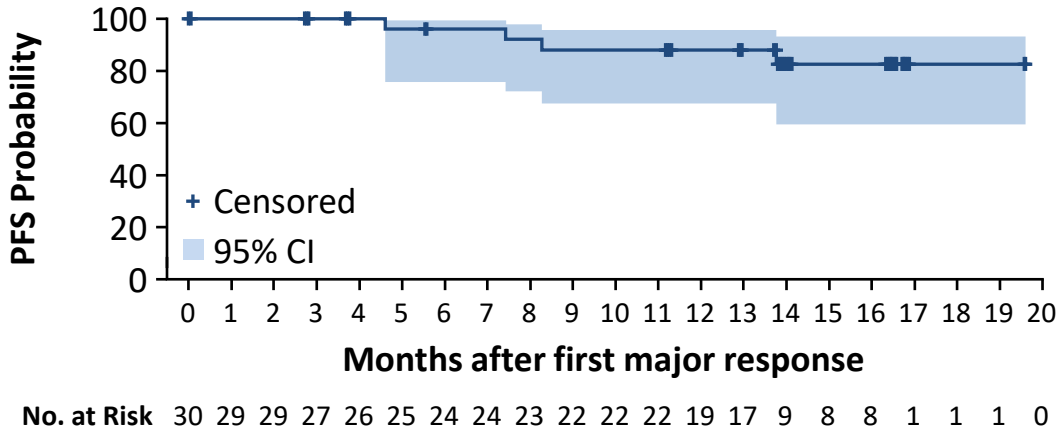
- The median PFS and DOMR were not reached

Kaplan–Meier Plot of Progression-Free Survival by IRC



Event-free Rate at, % (95% CI)[a]	
6 months, % (95% CI)	89.8 (75.1, 96.1)
9 months, % (95% CI)	87.0 (71.5, 94.4)
12 months, % (95% CI)	78.3 (61.2, 88.6)

Kaplan–Meier Plot of Duration of Major Response by IRC



Event-free Rate at, % (95% CI)[a]	
6 months, % (95% CI)	96.2 (75.7, 99.4)
9 months, % (95% CI)	88.1 (67.6, 96.0)
12 months, % (95% CI)	88.1 (67.6, 96.0)

[a]Estimated by Kaplan–Meier method with 95% CIs estimated using the Greenwood formula.
CI, confidence interval; DOMR, duration of major response; IRC, independent review committee; PFS, progression-free survival.

Efficacy: Time to Response as Assessed by IRC

- The response was achieved quickly. The median time to overall response was 2.76 months

Time to Response per IRC	Zanubrutinib (N = 43)
Time to VGPR or CR, months	
n	14
Median	2.87
Min, max	2.7, 11.1
Time to major response, months	
n	30
Median	2.79
Min, max	2.7, 13.8
Time to overall response, months	
n	34
Median	2.76
Min, max	0.8, 5.5

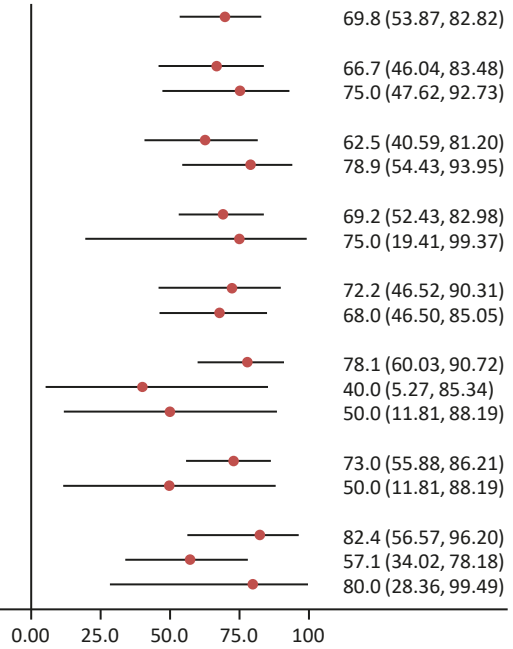
CR, complete response; IRC, independent review committee; VGPR, very good partial response.

Efficacy: IRC assessed MRR by subgroup

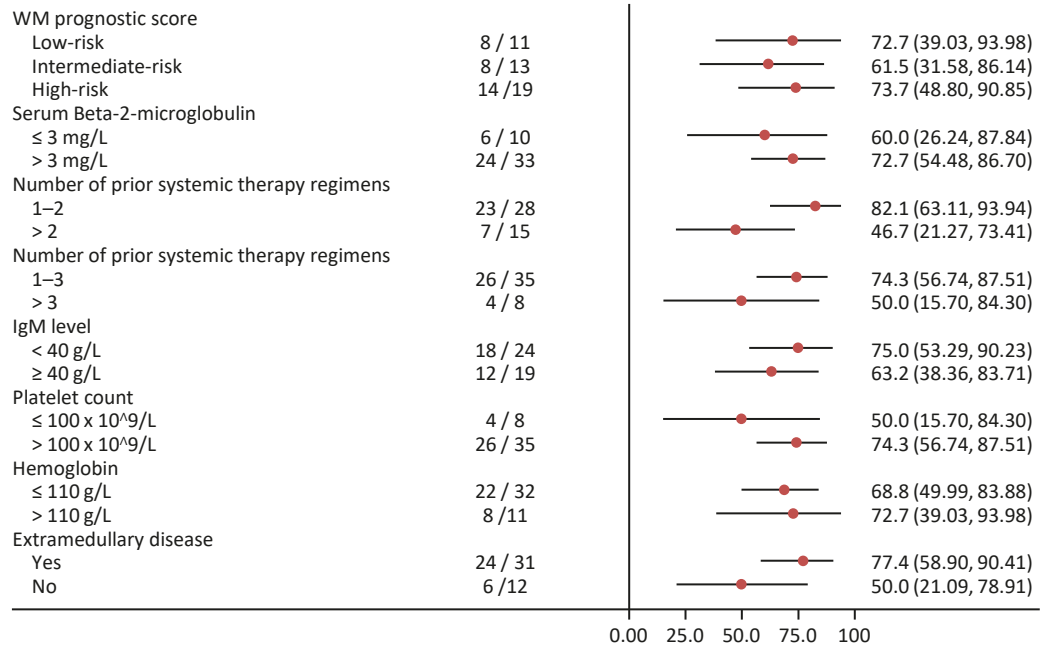
- Subgroup analysis revealed that the treatment benefit of zanubrutinib was generally consistent across the subgroups with adequate sample size.

Forest Plot of Major Response Rate by IRC

Subgroup	Responses / Patients	Major response rate (%) (95% CI)
All patients	30 / 43	69.8 (53.87, 82.82)
Sex		
Male	18 / 27	66.7 (46.04, 83.48)
Female	12 / 16	75.0 (47.62, 92.73)
Age group		
≤ 65 years	15 / 24	62.5 (40.59, 81.20)
> 65 years	15 / 19	78.9 (54.43, 93.95)
Age group		
≤ 75 years	27 / 39	69.2 (52.43, 82.98)
> 75 years	3 / 4	75.0 (19.41, 99.37)
ECOG-performance status		
0	13 / 18	72.2 (46.52, 90.31)
≥ 1	17 / 25	68.0 (46.50, 85.05)
Genotype		
MYD88^{L265P}/*CXCR4*^{WT}	25 / 32	78.1 (60.03, 90.72)
MYD88^{L265P}/*CXCR4*^{WHIM}	2 / 5	40.0 (5.27, 85.34)
MYD88^{WT}	3 / 6	50.0 (11.81, 88.19)
Genotype		
MYD88^{L265P}	27 / 37	73.0 (55.88, 86.21)
MYD88^{WT}	3 / 6	50.0 (11.81, 88.19)
Percent bone marrow involvement		
Lower bound ≥ 50%	14 / 17	82.4 (56.57, 96.20)
Higher bound < 50%	12 / 21	57.1 (34.02, 78.18)
Other	4 / 5	80.0 (28.36, 99.49)



Subgroup	Responses / Patients	Major response rate (%) (95% CI)
WM prognostic score		
Low-risk	8 / 11	72.7 (39.03, 93.98)
Intermediate-risk	8 / 13	61.5 (31.58, 86.14)
High-risk	14 /19	73.7 (48.80, 90.85)
Serum Beta-2-microglobulin		
≤ 3 mg/L	6 / 10	60.0 (26.24, 87.84)
> 3 mg/L	24 / 33	72.7 (54.48, 86.70)
Number of prior systemic therapy regimens		
1–2	23 / 28	82.1 (63.11, 93.94)
> 2	7 / 15	46.7 (21.27, 73.41)
Number of prior systemic therapy regimens		
1–3	26 / 35	74.3 (56.74, 87.51)
> 3	4 / 8	50.0 (15.70, 84.30)
IgM level		
< 40 g/L	18 / 24	75.0 (53.29, 90.23)
≥ 40 g/L	12 / 19	63.2 (38.36, 83.71)
Platelet count		
≤ 100 x 10^9/L	4 / 8	50.0 (15.70, 84.30)
> 100 x 10^9/L	26 / 35	74.3 (56.74, 87.51)
Hemoglobin		
≤ 110 g/L	22 / 32	68.8 (49.99, 83.88)
> 110 g/L	8 /11	72.7 (39.03, 93.98)
Extramedullary disease		
Yes	24 / 31	77.4 (58.90, 90.41)
No	6 /12	50.0 (21.09, 78.91)



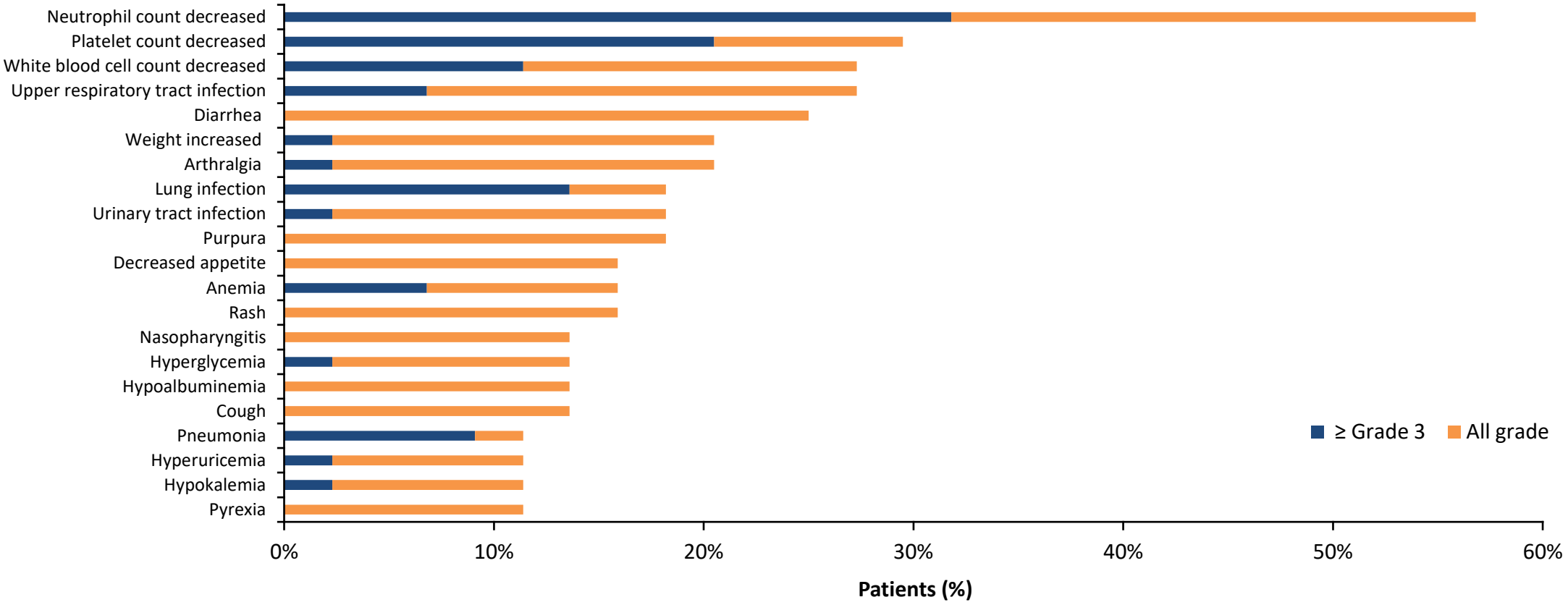
MRR, major response rate; *MYD88*, myeloid differentiation primary response gene 88; CXCR4, CXC-chemokine receptor 4; WHIM, Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis syndrome; WM, Waldenström's macroglobulinemia; WT, wildtype; IRC, independent review committee.

Summary of TEAEs Regardless of Causality

Event, n (%)	N = 44
Grade ≥3 TEAEs	32 (72.7)
Serious TEAEs	22 (50.0)
TEAEs leading to study drug discontinuation	5 (11.4)
TEAEs leading to death (preferred term)[a]	2 (4.5)
Death	1 (2.3)
Multiple organ dysfunction syndrome	1 (2.3)
Acute hepatitis B	1 (2.3)
TEAEs of special interest (pooled terms)	
Hypertension	5 (11.4)
Major hemorrhage[b]	2 (4.5)
Atrial fibrillation/flutter	0
Secondary primary malignancy	3 (6.8)
Tumor lysis syndrome	0
Infection	35 (79.5)
Cytopenia	
Anemia	7 (15.9)
Neutropenia	25 (56.8)
Thrombocytopenia	13 (29.5)

[a]Death within 30 days of last dose of zanubrutinib.
[b]Upper gastrointestinal hemorrhage (one subject), ecchymosis, and retinal hemorrhage (one subject).
TEAEs, treatment-emergent adverse events. A treatment-emergent AE was defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurred first.

TEAEs in ≥10% of Patients



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Note: AEs were coded using MedDRA Version 22.0. Preferred terms are listed.

Conclusions

- After a median follow-up of 18.58 months, zanubrutinib demonstrated a high, deep, quick, and durable efficacy in R/R WM patients
  - MRR was 69.8% and CR + VGPR rate was 32.6% per IRC
  - The median PFS and DOMR were not reached
  - The median time to overall response was 2.76 months
- The safety and tolerability profiles of zanubrutinib shown in this study were consistent with previous reports in WM patients
- Data from study BGB-3111-210 has been submitted to the NMPA seeking approval for zanubrutinib in WM

CR, complete response; DOMR, duration of major response; IRC, independent review committee; MRR, major response rate; NMPA, National Medical Products Administration; PFS, progression-free survival; R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Conflict of interest disclosures

There are no relationships to disclose.

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