Extended Follow-Up of a Phase 2 Trial of the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Chinese Patients With Relapsed/Refractory Waldenström Macroglobulinemia

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Disclosures

- **Lugui Qiu** has nothing to disclose.

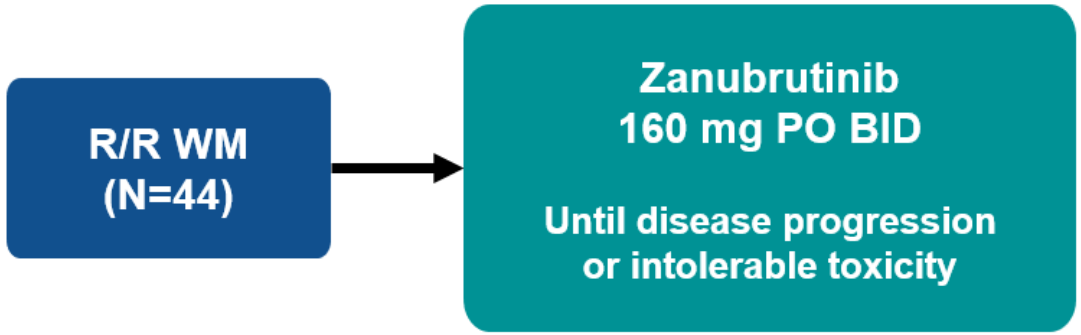
Introduction

- BTK plays a critical role in B-cell receptor signaling, and this pathway is constitutively activated in WM (>90% with *MYD88* mutations), contributing to malignant cell survival[1,2]
  - BTK inhibition is an established standard of care for treating WM[3]
- Zanubrutinib is a potent, highly selective, irreversible, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Equipotent against BTK compared to ibrutinib; higher selectivity vs EGFR, ITK, JAK3, HER2, and TEC[4]
  - Advantageous PK/PD properties, demonstrating median 24-hour BTK occupancy of 100% with twice daily dosing in PBMCs 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]
- Here, we present long-term follow-up results of zanubrutinib in adult Chinese patients with R/R WM, a group with limited data

CY3PA, cytochrome P450, family 3, subfamily A; Bruton tyrosine kinase, BTK; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, IL2-inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; MYD88, myeloid differentiation primary response 88; PBMC, peripheral blood mononuclear cell; PK/PD, pharmacokinetics/pharmacodynamics; R/R, relapsed/refractory.

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.

BGB-3111-210: A Phase 2 Study of Zanubrutinib in Chinese Patients With R/R WM



ClinicalTrials.gov: NCT03332173

Primary Endpoint: MRR (CR+VGPR+PR rate) by independent review committee according to an adaptation of the response criteria updated at the 6th IWWM[1,2]

Secondary Endpoints: PFS, ORR, DOMR, and safety

Key Eligibility Criteria

- Adult (≥18 years) patients with R/R WM
- WM pathology confirmation by central lab
- Met ≥1 criterion for treatment according to consensus panel criteria from the 7th IWWM[3]
- ≥1 prior line of standard chemotherapy-containing regimen (with completion of ≥2 continuous treatment cycles)
- Documented failure to achieve at least MR or documented disease progression after response to the most recent treatment regimen

BID, twice daily; CR, complete response; DOMR, duration of major response; MR, minor response; MRR, major response rate; PO, oral; PR, partial response; PFS, progression-free survival; ORR, overall response rate; R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

1. Owen RG, et al. *Br J of Haematol* 2013;160:171-176. 2. NCCN Guidance Insights. *JNCCN* 2012;10:1211-1218. 3. Dimopoulos MA, et al. *Blood* 2014; 124:1404-1411.

Baseline Patient Characteristics

Characteristic	Zanubrutinib (N = 44)
Age, median (range), years	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 no. of prior systemic therapy regimens (range)	2 (1-6)
Baseline IgM median (range), g/L	30.9 (3.2-96.5)
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 x 10^9/L)	9 (20.5)
Neutropenia (ANC ≤ 1.5 x 10^9/L)	11 (25.0)

ANC, absolute neutrophil count; CXCR4, CXC-chemokine receptor 4; ECOG, Eastern Cooperative Oncology Group; MYD88, myeloid differentiation primary response gene 88; CXCR4, CXC-chemokine receptor 4; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome; WT, wildtype.

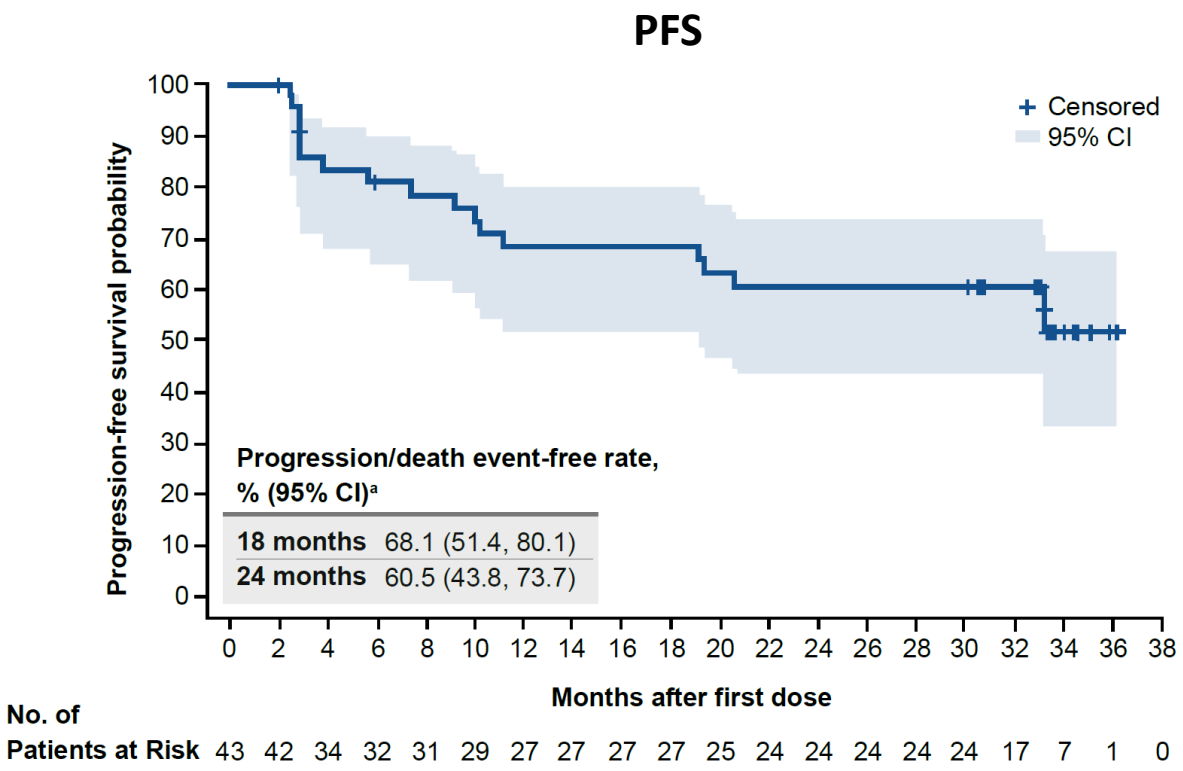
Efficacy: BOR per Investigator

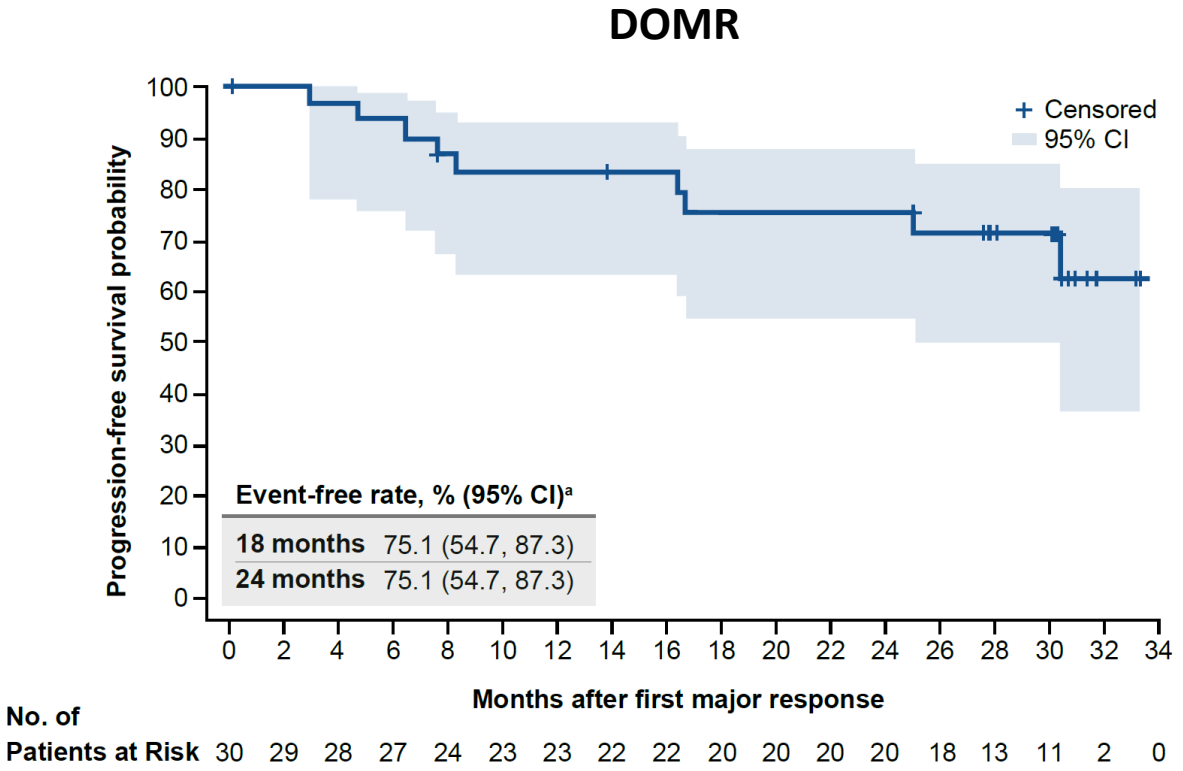
Efficacy per investigator	Zanubrutinib (N=43[a])
BOR, n (%)	
CR	0
VGPR	14 (32.6)
PR	16 (37.2)
MR	3 (7.0)
SD	2 (4.7)
PD	7 (16.3)
Discontinued study prior to first tumor assessment	1 (2.3)
CR+VGPR rate, n (%); (95% CI)[b]	14 (**32.6**); (19.1, 48.5)
MRR (PR or better), n (%); (95% CI)[b]	30 (**69.8**); (53.9, 82.8)
ORR (MR or better), n (%); (95% CI)[b]	33 (**76.7**); (61.4, 88.2)

Data cutoff: January 11, 2021
Median study follow-up: 33.0 months (range, 3.2-36.5)

[a]One patient was excluded from the efficacy analysis owing to baseline immunoglobulin M level <5g/L.
[b]Calculated using the Clopper-Pearson method.
BOR, best overall response; CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Efficacy: PFS and DOMR per Investigator





- The median PFS and DOMR were not reached

[a]Estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.
DOMR, duration of major response; PFS, progression-free survival.

Efficacy: Time to Response per Investigator[a]

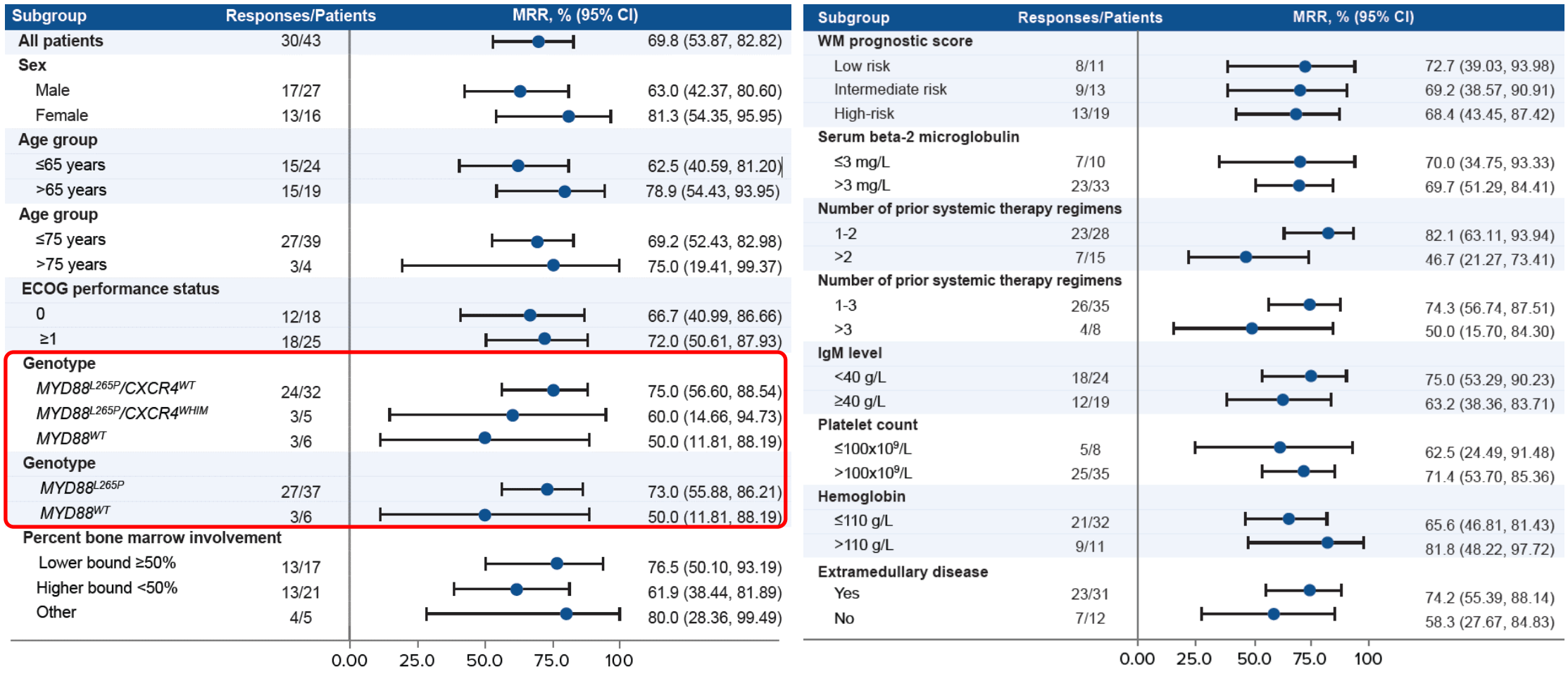
Time to response per investigator, months	Zanubrutinib (N=43)
Time to VGPR or CR	
n	14
Median	4.2
Min, max	2.7, 33.6
Time to major response	
n	30
Median	2.8
Min, max	2.7, 27.6
Time to overall response	
n	33
Median	2.8
Min, max	2.7, 5.5

[a]Ad hoc analysis.
CR, complete response; VGPR, very good partial response.

Efficacy: MRR by Subgroup per Investigator

Subgroup	Responses/Patients	MRR, % (95% CI)
All patients	30/43	69.8 (53.87, 82.82)
Sex		
Male	17/27	63.0 (42.37, 80.60)
Female	13/16	81.3 (54.35, 95.95)
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	12/18	66.7 (40.99, 86.66)
≥1	18/25	72.0 (50.61, 87.93)
Genotype		
MYD88^{L265P}/*CXCR4*^{WT}	24/32	75.0 (56.60, 88.54)
MYD88^{L265P}/*CXCR4*^{WHIM}	3/5	60.0 (14.66, 94.73)
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%	13/17	76.5 (50.10, 93.19)
Higher bound <50%	13/21	61.9 (38.44, 81.89)
Other	4/5	80.0 (28.36, 99.49)

Subgroup	Responses/Patients	MRR, % (95% CI)
WM prognostic score		
Low risk	8/11	72.7 (39.03, 93.98)
Intermediate risk	9/13	69.2 (38.57, 90.91)
High-risk	13/19	68.4 (43.45, 87.42)
Serum beta-2 microglobulin		
≤3 mg/L	7/10	70.0 (34.75, 93.33)
>3 mg/L	23/33	69.7 (51.29, 84.41)
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		
≤100x10^9/L	5/8	62.5 (24.49, 91.48)
>100x10^9/L	25/35	71.4 (53.70, 85.36)
Hemoglobin		
≤110 g/L	21/32	65.6 (46.81, 81.43)
>110 g/L	9/11	81.8 (48.22, 97.72)
Extramedullary disease		
Yes	23/31	74.2 (55.39, 88.14)
No	7/12	58.3 (27.67, 84.83)



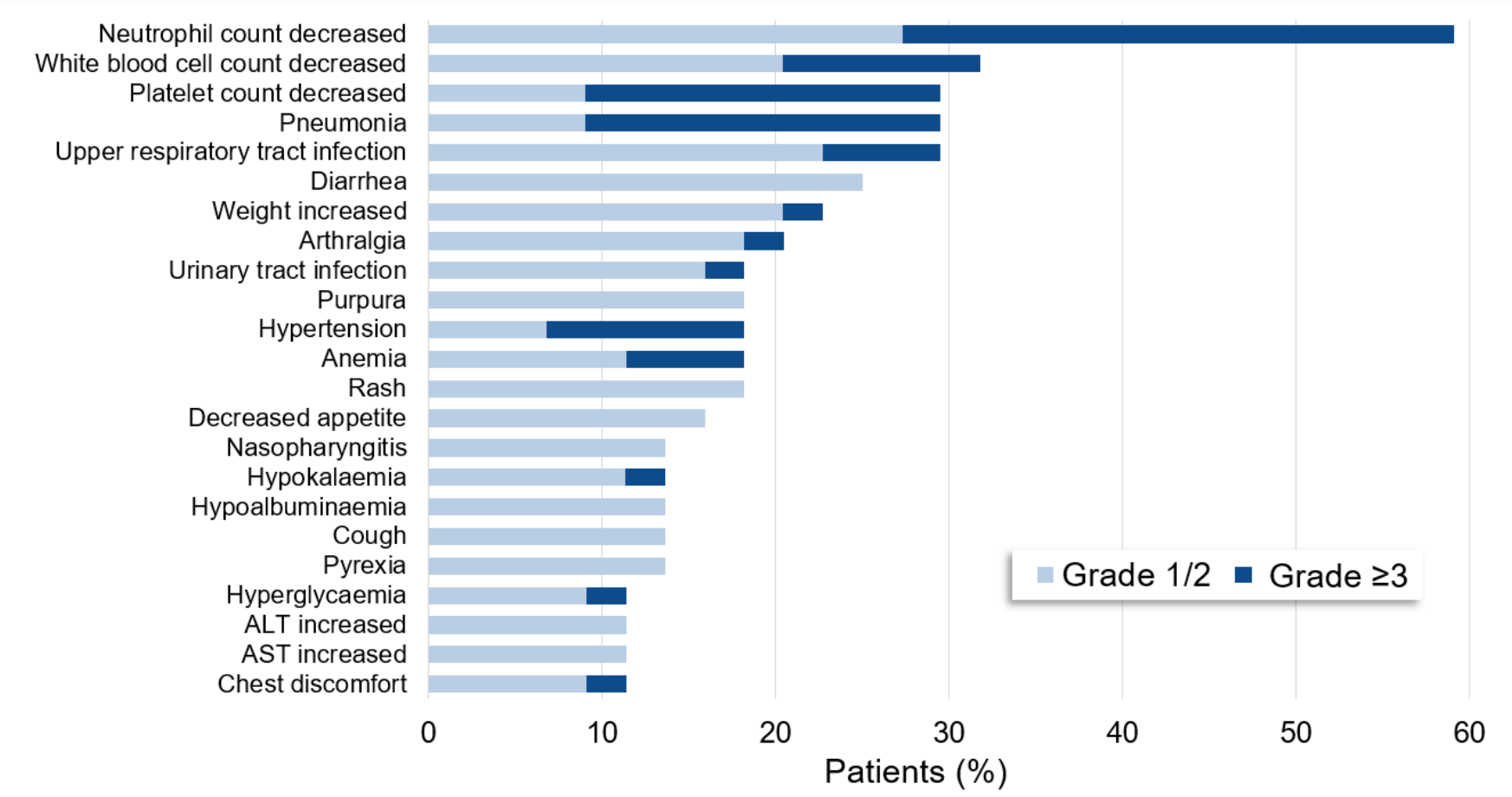
CXCR4, CXC-chemokine receptor 4; ECOG, Eastern Cooperative Oncology Group; MRR, major response rate; *MYD88*, myeloid differentiation primary response gene 88; *CXCR4*, CXC-chemokine receptor 4; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome; WT, wildtype.

Summary of TEAEs

Event, n (%)	Zanubrutinib (N=44)
Grade ≥3 TEAEs	34 (77.3)
Serious TEAEs	25 (56.8)
TEAEs leading to study drug discontinuation[a]	5 (11.4)
TEAEs leading to death[b]	2 (4.5)
Death with unknown reason	1 (2.3)
Multiple organ failure	1 (2.3)
Acute hepatitis B	1 (2.3)
TEAEs of special interest	
Hypertension	9 (20.5)
Major hemorrhage[c]	2 (4.5)
Atrial fibrillation/flutter	0
Secondary primary malignancy	3 (6.8)
Tumor lysis syndrome	0
Infection	35 (79.5)
Cytopenia	
Anemia	8 (18.2)
Neutropenia	26 (59.1)
Thrombocytopenia	13 (29.5)

[a]TEAEs leading to discontinuation of zanubrutinib included pneumonia (1 patient), laryngeal cancer (1 patient), WM (investigator reported and suspected transformation; 1 patient), intracranial mass (1 patient), acute hepatitis B, and multiple organ dysfunction syndrome (1 patient). [b]Death within 30 days of last dose of zanubrutinib. [c]Upper gastrointestinal hemorrhage (1 patient), ecchymosis and retinal hemorrhage (1 patient).
TEAE, treatment-emergent adverse event.

TEAEs in ≥10% of Patients



ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Conclusions

- After median follow-up of 33.0 months, zanubrutinib demonstrated a high rate of deep, rapid, and durable response in Chinese patients with R/R WM
  - MRR was 69.8% and CR+VGPR rate was 32.6% as assessed by the investigator
  - The median PFS and DOMR have not been reached
  - The median time to overall response was 2.8 months
- Subgroup analysis revealed a treatment benefit for zanubrutinib across all subgroups examined
- The safety and tolerability profile of zanubrutinib was consistent with that of previous reports in WM[1]
- These findings support the use of zanubrutinib as an effective and tolerable treatment for Chinese patients with R/R WM

CR, complete response; DOMR, duration of major response; MRR, major response rate; PFS, progression-free survival; R/R, relapsed/refractory; VGPR, very good partial response.

1. Tam CS, et al. *Blood* 2020;136(18):2038-2050.

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