Supplemental Methods

Full inclusion/exclusion criteria

Patients who met the following criteria were eligible to participate in the study:

1. Aged ≥ 18 years, voluntarily consented to the study.
2. Dose Escalation: Relapsed or refractory WHO-defined B-lymphoid malignancy following ≥ 1 line of therapy, with no therapy of higher priority available, with the exception of Burkitt lymphoma/leukemia, plasma cell myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, and plasmablastic lymphoma.
3. Safety, Schedule, and Efficacy Expansion:

- Cohort 2a: Relapsed or refractory WHO-defined mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma or germinal B-cell–like subtype of diffuse large B-cell lymphoma, with ≥ 1 lymph node that could be biopsied.
- Cohort 2b: Relapsed or refractory WHO-defined diffuse large B-cell lymphoma, non-germinal B-cell–like subtype, defined by the Hans algorithm; archival tumor tissues or agreement to have a tumor biopsy for confirmation of the diffuse large B-cell lymphoma subtype and for exploratory biomarker analysis.
- Cohort 2c: Relapsed or refractory WHO-defined CLL/SLL on the twice daily dosing schedule.
- Cohort 2d: Relapsed or refractory WHO-defined WM.
- Cohort 2e: Relapsed or refractory WHO-defined CLL/SLL on once daily or twice daily dosing schedule.

- Cohort 2f: Relapsed or refractory WHO-defined WM requiring treatment per the International Workshop on WM recommendations (Kyle RA et al. *Semin Oncol*. 2003;30:116-20), including treatment-naive patients who were unsuitable for standard chemotherapy.
- Cohort 2g: Relapsed or refractory WHO-defined mantle cell lymphoma.
- Cohort 2h: Previously untreated CLL/SLL requiring treatment per the International Workshop on Chronic Lymphocytic Leukemia guidelines (Hallek M, et al. *Blood*. 2008;111:5446-56) and who were unsuitable for standard chemotherapy.
- Cohort 2i: Previously untreated mantle cell lymphoma, age ≥ 65 years, and Cumulative Illness Rating Scale ≥ 6 points (Miller MD, et al. *Psychiatry Res*. 1992;41:237-48) and who were unsuitable for standard chemotherapy.
- Cohort 2j: Relapsed or refractory WHO-defined hairy cell leukemia.
- Cohort 2k: Relapsed or refractory WHO-defined indolent lymphoma (inclusive of follicular lymphoma, marginal zone lymphoma, and mucosa-associated lymphoid tissue lymphoma).
- Cohort 2l: Histologically-confirmed Richter's transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma; previous treatment with a BTK inhibitor other than zanubrutinib was allowed; must have had histologic confirmation of Richter's transformation before enrollment.
- Cohort 2m: B-cell malignancy (otherwise eligible for Cohort 2a to 2l) who failed to achieve a major response (PR or better) after ≥ 6 months, had disease progression on prior BTK-inhibitor therapy (ibrutinib, acalabrutinib, zanubrutinib, or other BTK-inhibitor therapy), or discontinued BTK-inhibitor therapy due to an adverse event. A minimal 7-day washout period is

required before initiation of zanubrutinib treatment. All prior BTK inhibitor related adverse events must have resolved to Grade 1 or less.

4. Requirement for treatment in the opinion of the investigator.
5. ECOG Performance Status of 0 to 2.
6. Adequate hematologic function, as defined by neutrophils $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L; patients with neutrophils $< 1.0 \times 10^9$/L due to marrow infiltration were allowed to receive growth factors to bring pre-treatment neutrophils to $\geq 1.0 \times 10^9$/L; patients with platelets $< 50 \times 10^9$/L due to marrow infiltration were allowed to receive platelet transfusion to bring pre-treatment platelets to $\geq 50 \times 10^9$/L.
7. Adequate renal function, as defined by creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation/Chronic Kidney Disease Epidemiology Collaboration equation or as measured by nuclear medicine scan or 24-hour urine collection).
8. Adequate liver function, as defined by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 times the upper limit of the normal reference range, and bilirubin ≤ 1.5 times the upper limit of the normal reference range (unless documented Gilbert's syndrome).
9. International normalized ratio ≤ 1.5 and activated partial thromboplastin time ≤ 1.5 times the upper limit of the normal reference range.

10. Female patients of childbearing potential and non-sterile males had to practice ≥ 1 of the following methods of birth control with their partner(s) throughout the study and for 90 days after discontinuing study drug: total abstinence from sexual intercourse, double-barrier contraception, intrauterine device, or hormonal contraceptive initiated ≥ 3 months before the first dose of study drug.
11. Male patients had to agree not to donate sperm from initial study drug administration, until 90 days after drug discontinuation.

Patients who met any of the following criteria were excluded from the study:

1. Current central nervous system involvement by lymphoma or leukemia.
2. Current histologically transformed disease, except patients in Cohort 2l.
3. Prior BTK inhibitor treatment, except patients in Cohort 2l and Cohort 2m.
4. Allogeneic stem cell transplantation within 6 months or had active graft-versus-host disease requiring ongoing immunosuppression.
5. Receipt of the following treatment before the first dose of zanubrutinib: corticosteroids given with anti-neoplastic intent within 7 days, chemotherapy or radiotherapy within 2 weeks, or monoclonal antibody within 4 weeks.
6. Not recovered from toxicity of any prior chemotherapy to Grade 1 or lower.
7. History of other active malignancies within 2 years of study entry, with the exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of the skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.

8. Uncontrolled systemic infection requiring parenteral anti-microbial therapy.
9. Major surgery in the past 4 weeks.
10. Known HIV, or active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction).
11. Cardiovascular disease resulting in New York Heart Association function status of ≥ 3.
12. QT interval corrected for heart rate using Fridericia's formula (QTcF) > 480 milliseconds (msec) or other significant ECG abnormalities including 2nd degree atrioventricular block type II, 3rd degree atrioventricular block, or bradycardia (ventricular rate < 50 beats/min).
13. Significant active renal, neurologic, psychiatric, hepatic, or endocrine disease that, in the investigator's opinion, would have adversely impacted participation in the study.
14. Inability to comply with study procedures.
15. Receiving medications that are strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers.
16. Pregnant or breastfeeding.

Extramedullary disease

Extramedullary disease was defined as either lymphadenopathy or splenomegaly by imaging or physical exam based on the following parameters:

- For lymphadenopathy by imaging, target lesions were selected on the basis of their size (large lesions will be given preference) and suitability for reproducible measurements. They must be clearly measurable in 2 dimensions: longest diameter and longest perpendicular diameter measurement. Lymph nodes/lesions were identified from different body regions representative of overall disease burden for the patient. Abnormal target lesions/lymph nodes were identified (>1.5cm) at baseline and bi-directional dimensions of lymph nodes were recorded. These lymph nodes/lesions were followed throughout the study.
- For patients with lymphadenopathy by physical exam, any lymph nodes with an assessment of abnormal was considered as extramedullary disease and followed throughout study.
- For splenomegaly by imaging, spleen craniocaudal length in cm was reported and spleen measurement >130mm in cranial caudal was considered as extramedullary disease.
- For splenomegaly by physical exam, enlarged spleen measurement was considered.

CXCR4 mutation detection

Mutations in *CXCR4* were detected using a validated, next-generation sequencing assay (analytical validation performed in the testing lab; unpublished) targeting a panel of 275 genes including CXCR4 (QIAseq Human Comprehensive Cancer Panel; Qiagen, Inc., Germantown, MD, USA). Samples containing 50 ng of DNA purified from bone marrow were used. Library preparation was performed according to optimized and validated proprietary protocols. In brief, enzymatically fragmented DNA were incorporated with IL-N7 adapters, molecular barcodes, and sample indexes via ligation. Library fragments were then enriched via single primer extension with a gene-specific and universal paired primer design. The purified libraries were pooled and sequenced with a NextSeq 500 instrument (Illumina, Inc., San Diego, CA, USA). Data were analyzed by a validated bioinformatics pipeline (NeoGenomics Laboratory, Inc., Alviso Viejo, CA, USA). The assay covered protein coding sequences of *CXCR4* (NM_001008540.1) and is sensitive to the detection of 3%-5% mutant alleles.

Response criteria

Response	**Criteria**
Complete response	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.
Very good partial response	A ≥90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Partial response	A ≥50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

Minor response	A ≥25% but <50% reduction of serum IgM. No new symptoms or signs of active disease.
Stable disease	A <25% reduction and <25% increase of serum IgM without progression of adenopathy/organopmegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive disease	A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidsis) attributable to WM.

Note: For very good partial response, IWWM-6 required complete resoluation of extramedullary disease, while the Treon modification (shown here) requires decrease in adenopathy/organomegaly (if present at baseline).

Supplemental Table S1. Prior systemic therapies for patients with relapsed/refractory WM*

	R/R WM (N=53) n (%)
Number of prior systemic anticancer regimens	
1	24 (45.3)
2	12 (22.6)
3	7 (13.2)
4	5 (9.4)
5	2 (3.8)
≥ 6	3 (5.7)
Any chemotherapy	53 (100.0)
Anti-CD20 (rituximab)	50 (94.3)
Alkylators (cyclophosphamide, chlorambucil, carmustine, busulfan, ifosfamide, dacarbazine, melphalan, and/or bendamustine)	48 (90.6)
Glucocorticoids (dexamethasone, prednisone, prednisolone, methylprednisolone)	39 (73.6)
Nucleoside analogues (fludarabine, cladribine, cytarabine)	19 (35.8)
Vinca alkaloids (vincristine, vinblastine)	14 (26.4)
Anthracyclines, anthracenediones (doxorubicin, mitoxantrone)	6 (11.3)
Proteasome inhibitor (bortezomib)	4 (7.5)
Immunomodulator (thalidomide)	1 (1.9)

Abbreviations: BTK, Bruton's tyrosine kinase; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.
*Categories of systemic therapies listed are not mutually exclusive (i.e., patients may have received multiple different categories).

Supplemental Table S2. Select characteristics at baseline by genotype

	MYD88^{WT} (n=11)	**MYD88$^{L265P/}$ CXCR4^{WT} (n=40)**	**MYD88$^{L265P/}$ CXCR4^{WHIM} (n=11)**	**MYD88$^{L265P/}$ CXCR4^{UNK} (n=7)**	**Unavailable (n=8)**	**Total (N=77)**
Baseline IgM (g/L), n	9	40	9	7	8	73
Median (range)	14.7 (1.2, 88.5)	32.6 (3.9, 68.4)	48.4 (5.3, 86.0)	16.1 (5.6, 91.9)	27.7 (15.0, 60.5)	32.4 (1.2, 91.9)
Extramedullary disease, n (%)						
Lymphadenopathy	3 (27.3)	24 (60.0)	3 (27.3)	4 (57.1)	5 (62.5)	39 (50.6)
Splenomegaly	3 (27.3)	14 (35.0)	2 (18.2)	3 (42.9)	4 (50.0)	26 (33.8)
Baseline hemoglobin (g/L), n	11	40	11	7	8	77
Median (range)	119.0 (105.0, 150.0)	97.5 (63.0, 155.0)	98.0 (83.0, 135.0)	113.0 (92.0, 131.0)	101.5 (71.0, 127.0)	105.0 (63.0, 155.0)
Bone marrow involvement, n (%)						
Yes	9 (81.8)	35 (87.5)	8 (72.7)	7 (100.0)	6 (75.0)	65 (84.4)
No	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Missing	1 (9.1)	5 (12.5)	3 (27.3)	0 (0.0)	2 (25.0)	11 (14.3)

Supplemental Table S3. Efficacy outcomes by dosing schedule

	Treatment-naïve (n=24)		Relapsed/Refractory (n=49)			Total (N=73)		
	160 mg bid (n=14)	320 mg qd (n=10)	<320 mg qd (n=4)	160 mg bid (n=33)	320 mg qd (n=12)	<320 mg qd (n=4)	160 mg bid (n=47)	320 mg qd (n=22)
Median duration of follow-up, mo	23.0	37.7	56.1	30.3	35.8	56.1	25.9	36.4
BOR, n (%)								
CR	0	0	0	0	1 (8.3)	0	0	1 (4.5)
VGPR	5 (35.7)	3 (30.0)	3 (75.0)	18 (54.5)	3 (25.0)	3 (75.0)	23 (48.9)	6 (27.3)
PR	6 (42.9)	7 (70.0)	1 (25.0)	9 (27.3)	4 (33.3)	1 (25.0)	15 (31.9)	11 (50.0)
MR	3 (21.4)	0	0	5 (15.2)	2 (16.7)	0	8 (17.0)	2 (9.1)
SD	0	0	0	1 (3.0)	2 (16.7)	0	1 (2.1)	2 (9.1)
PD	0	0	0	0	0	0	0	0
VGPR/CR rate, % (95% CI)	5 (35.7) (12.8-64.9)	3 (30.0) (6.7-65.2)	3 (75.0) (19.4-99.4)	18 (54.5) (36.4-71.9)	4 (33.3) (9.9-65.1)	3 (75.0) (19.4-99.4)	23 (48.9) (34.1-63.9)	7 (31.8) (13.9-63.9)
ORR (MR or better), % (95% CI)	14 (100.0) (76.8-100.0)	10 (100.0) (69.2-100.0)	4 (100.0) (39.8-100.0)	32 (97.0) (84.2-99.9)	10 (83.3) (51.6-97.9)	4 (100.0) (39.8-100.0)	46 (97.9) (88.7-99.9)	20 (90.9) (70.8-98.9)
MRR (PR or better), % (95% CI)	11 (78.6) (49.2-95.3)	10 (100.0) (69.2-100.0)	4 (100.0) (39.8-100.0)	27 (81.8) (64.5-93.0)	8 (66.7) (34.9-90.1)	4 (100.0) (39.8-100.0)	38 (80.9) (66.7-90.9)	18 (81.8) (59.7-94.8)

bid, twice daily; BOR, best overeall response; CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; qd, once daily; SD, stable disease; VGPR, very good partial response.

Supplemental Table S4. TEAEs leading to zanubrutinib discontinuation*

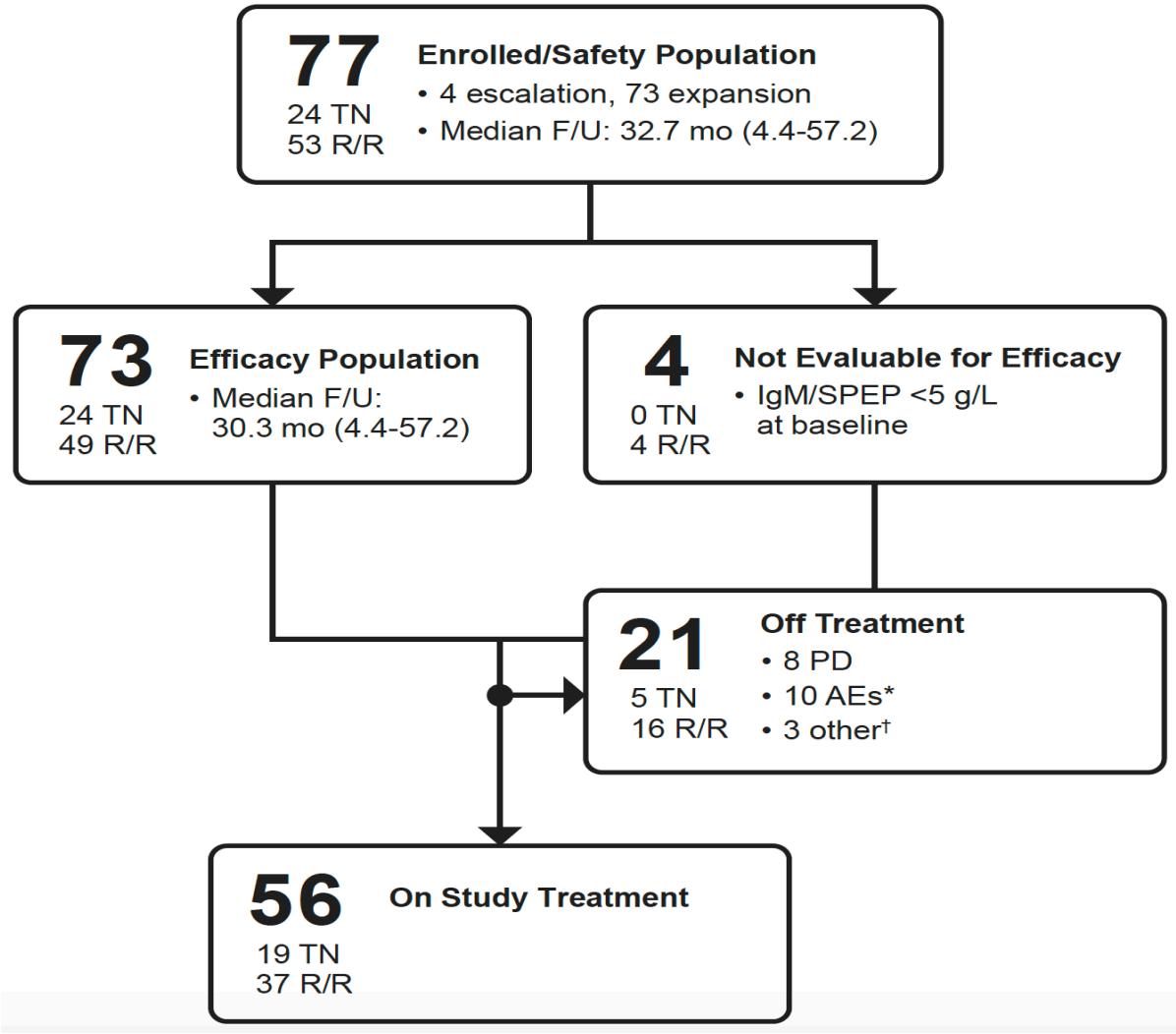
	n (%)
TEAEs leading to zanubrutinib discontinuation	
Patients with at least 1 TEAE leading to zanubrutinib discontinuation	10
Acute myeloid leukemia	1
Gastric adenocarcinoma	1†
Breast cancer	1 (treatment-naïve)
Metastatic neuroendocrine tumor	1 (treatment-naïve)
Prostate cancer	1
Abdominal sepsis	1†
Bacterial arthritis	1†
Scedosporium infection	1†
Bronchiectasis	1†
Purpura	1 (treatment-naïve)

*All reported in patients with R/R disease, unless otherwise specified. †Grade 5 events (see text).
R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

Supplemental Table S5. Summary of TEAEs by dosing schedule

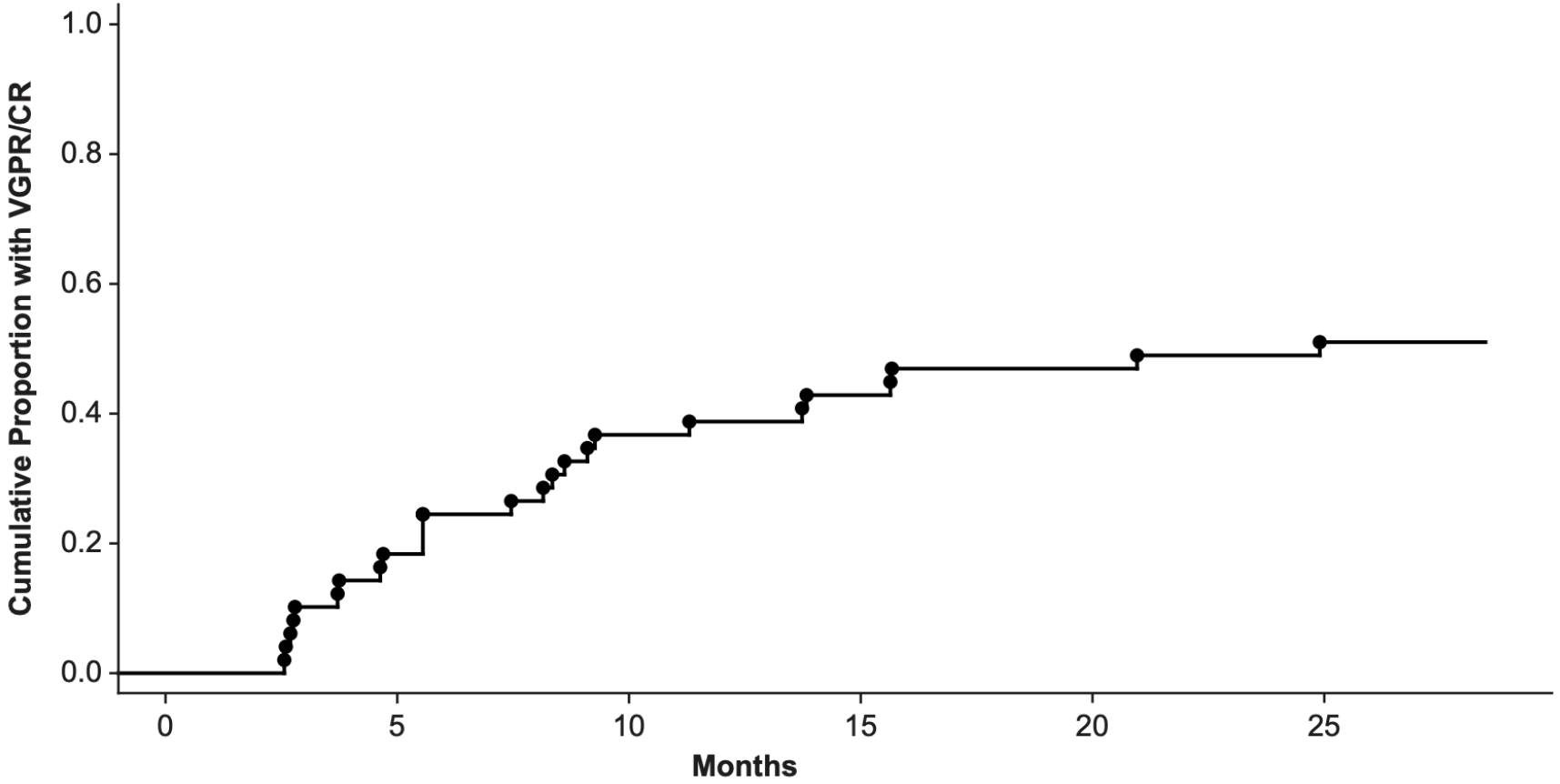
	160 mg bid (n=50)	320 mg qd (n=23)	<320 mg qd (n=4)	Total (N=77)
Patients with ≥1 TEAE	50 (100.0)	23 (100.0)	4 (100.0)	77 (100.0)
Grade ≥3 TEAEs	33 (66.0)	9 (39.1)	3 (75.0)	45 (58.4)
Serious TEAEs	28 (56.0)	7 (30.4)	3 (75.0)	38 (49.4)
Leading to death	4 (8.0)	0	1 (25.0)	5 (6.5)
Leading to treatment discontinuation	7 (14.0)	2 (8.7)	1 (25.0)	10 (13.0)
Leading to dose reduction	6 (12.0)	0	0	6 (7.8)
Patients with ≥1 treatment-related TEAE	38 (76.0)	17 (73.9)	3 (75.0)	58 (75.3)
Grade ≥3 TEAEs	17 (34.0)	1 (4.3)	1 (25.0)	19 (24.7)
Serious TEAEs	5 (10.0)	1 (4.3)	0	6 (7.8)
Leading to death	1 (2.0)	0	0	1 (1.3)
Leading to treatment discontinuation	2 (4.0)	0	0	2 (2.6)
Leading to dose reduction	4 (8.0)	0	0	4 (5.2)
Patients with ≥1 AESI	49 (98.0)	22 (95.7)	4 (100.0)	75 (97.4)
Grade ≥3 TEAEs	29 (58.0)	7 (30.4)	2 (50.0)	38 (49.4)
Serious TEAEs	19 (38.0)	6 (26.1)	2 (50.0)	27 (35.1)

Supplemental Figure S1. Patient disposition



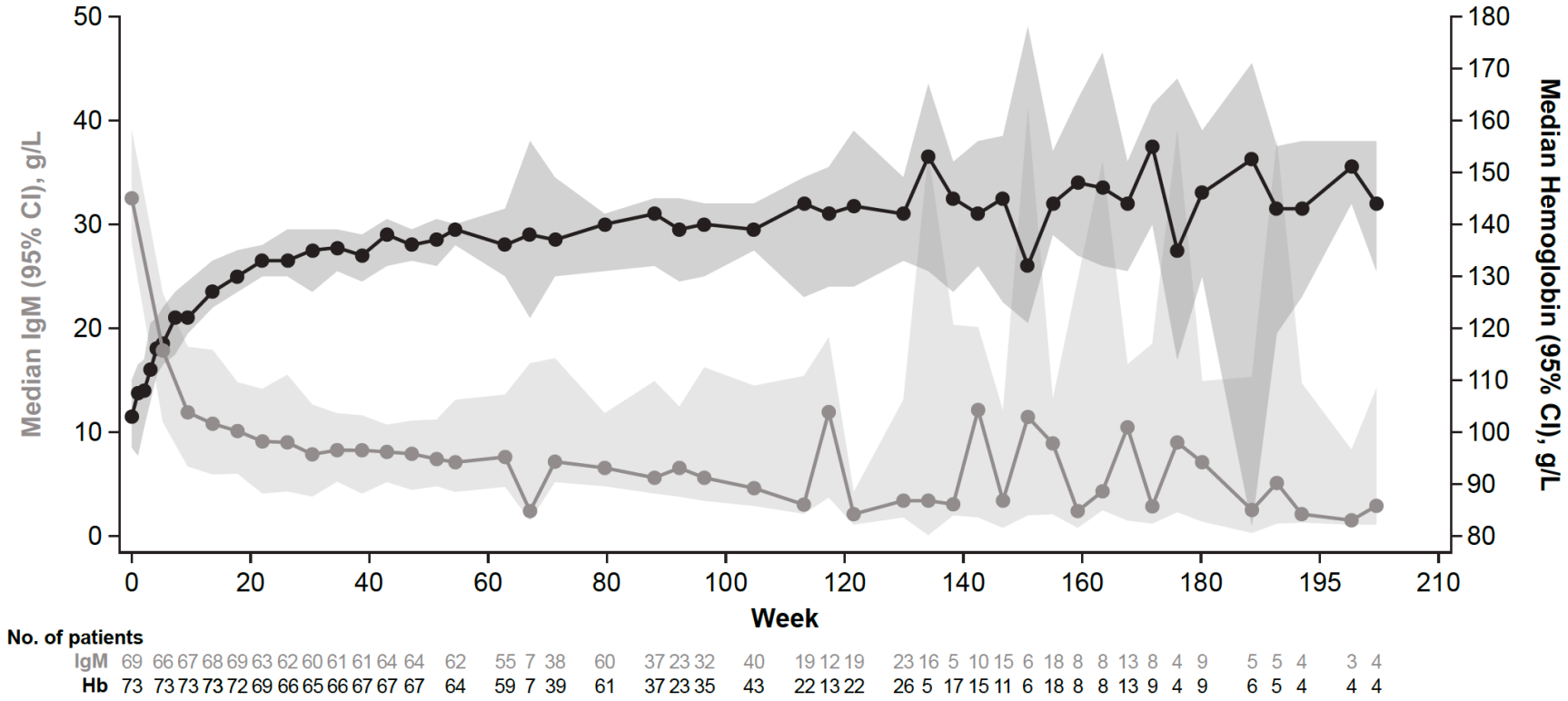
*AEs resulting in treatment discontinuation are listed in Supplemental Table S2.
†Investigator's decision (n=1) or other reasons (n=2).
AE, adverse event; F/U, follow-up; IgM, immunoglobulin M; PD, progressive disease; R/R, relapsed/refractory; SPEP, serum protein electrophoresis; TN, treatment-naïve.

Supplemental Figure S2. Proportion of patients with VGPR/CR over time for relapsed/refractory patients on study in ITT population.

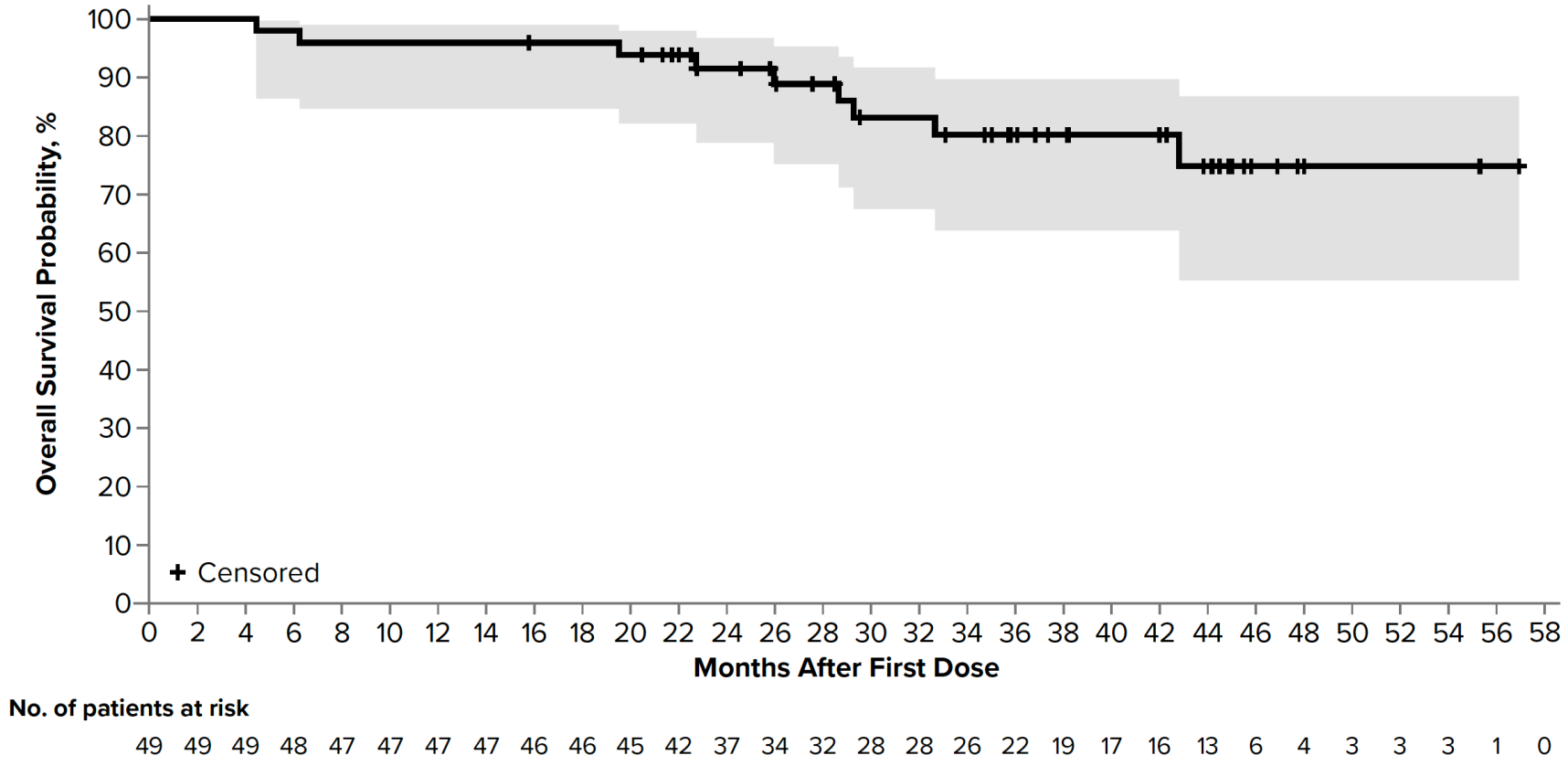


CR, complete response; VGPR, very good partial response

Supplemental Figure S3. Changes in IgM and hemoglobin concentrations over time. Changes from baseline in median IgM and hemoglobin levels for efficacy evaluable patients (n = 73) are shown. The number of patients included in the calculation of the median ±95% confidence intervals at each time point is indicated below the x-axis for IgM levels (light grey) and hemoglobin concentrations (dark grey). Week 0 is the baseline value, defined as the value most proximate to the start of treatment.

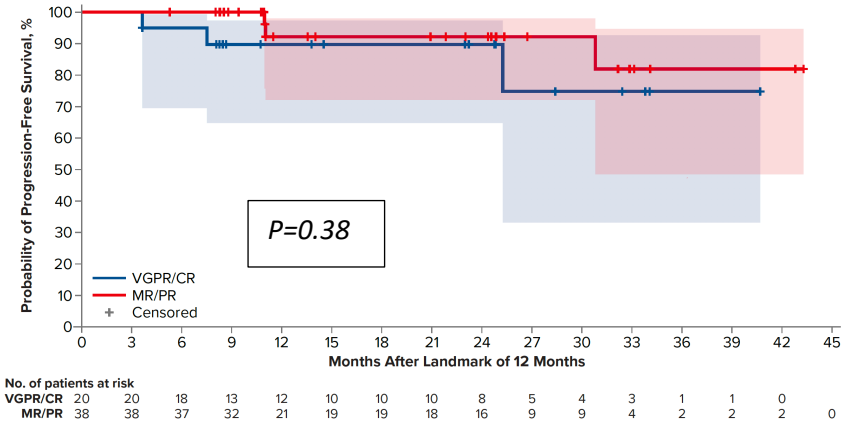


Supplemental Figure S4. **Kaplan-Meier plots of overall survival for relapsed/refractory patients**. Shaded area indicates 95% CI.

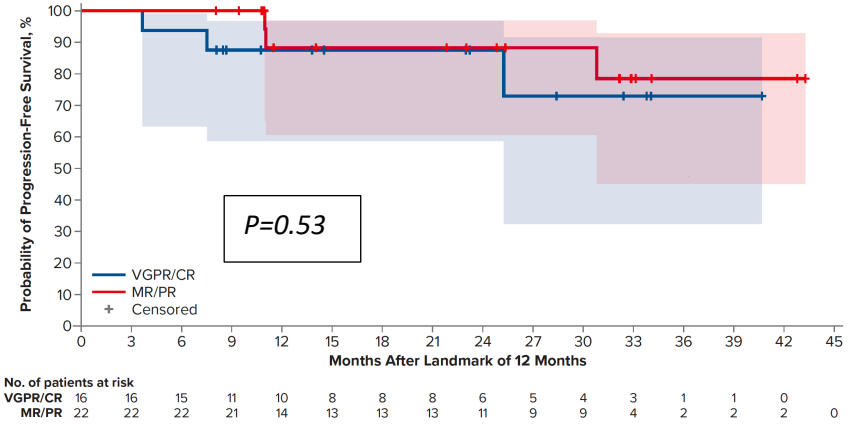


Supplemental Figure S5. Progression-free survival landmark analysis at 12 months by best overall response. Shaded areas indicate 95% CIs.

All patients



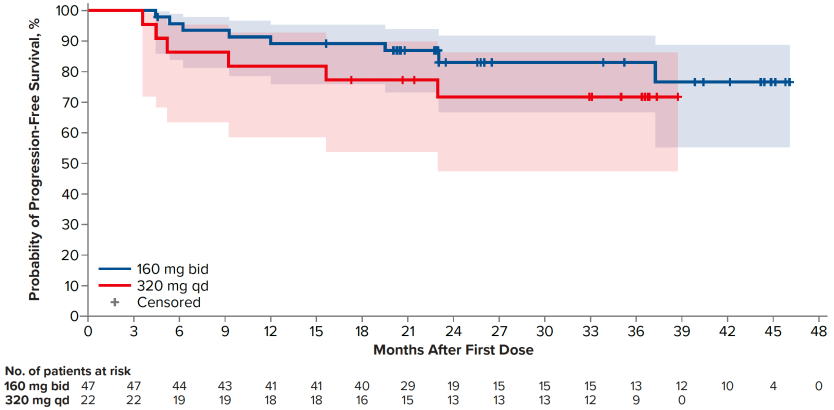
R/R patients



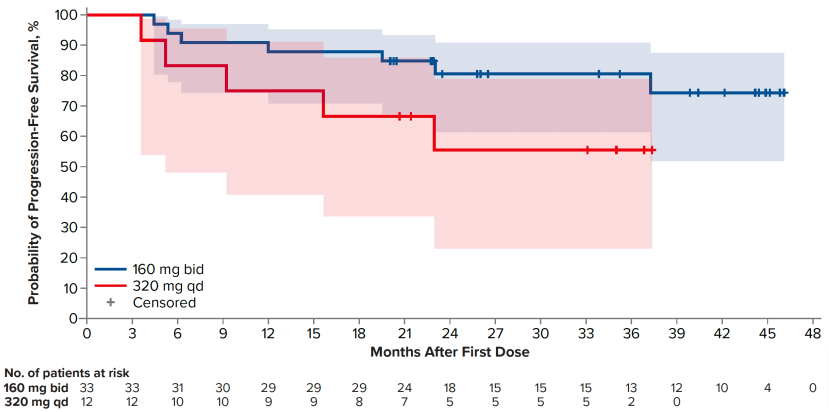
Supplemental Figure S6. Kaplan-Meier plots of progression-free survival by (A) dosing schedule or (B) genotype. Shaded areas indicate 95% CIs.

A.

All patients

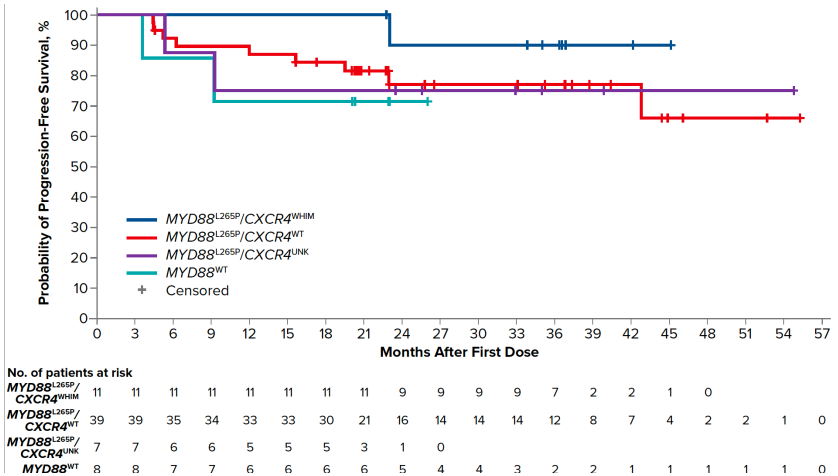


R/R patients



B.

All patients



R/R patients