blood

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: three years of follow-up

Tracking no: BLD-2020-006449R2

Judith Trotman (Concord Repatriation General Hospital and University of Sydney, Australia) Stephen Opat (Monash Medical Centre, Australia) David Gottlieb (University of Sydney, Australia) David Simpson (North Shore Hospital, New Zealand) Paula Marlton (University of Queensland Faculty of Medicine, Australia) Gavin Cull (Sir Charles Gairdiner Hospital, Australia) Javier Munoz (Banner MD Anderson Cancer Center, United States) Alessandra Tedeschi (ASST Grande Ospedale Metropolitano Niguarda Hospital, Italy) Andrew Roberts (The Walter and Eliza Hall Institute of Medical research, Australia) John Seymour (Peter MacCallum Cancer Institute, Australia) Siminder Atwal (BeiGene USA, Inc., United States) Yiling Yu (BeiGene (Shanghai), LTD, China) William Novotny (BeiGene USA, Inc, United States) Eric Holmgren (BeiGene USA, Inc., United States) Ziwen Tan (BeiGene (Shanghai) Co, Ltd., China) James Hilger (BeiGene, United States) Jane Huang (BeiGene USA, Inc, United States) Constantine Tam (Peter MacCallum Cancer Centre, Australia)

Abstract:
Inhibitors of Bruton's tyrosine kinase (BTK) have established therapeutic activity in patients with Waldenström macroglobulinemia (WM). Zanubrutinib, a potent and selective BTK inhibitor, was evaluated in a phase 1/2 study in patients with WM who were either treatment-naïve (TN) or had relapsed/refractory (R/R) disease. Patients had disease requiring treatment per International Workshop on Waldenström Macroglobulinemia (IWWM) criteria. Treatment was oral zanubrutinib 160 mg twice daily (n=50) or 320 mg once daily (n=23). Efficacy endpoints included overall response rate (ORR) and very good partial response/complete response (VGPR/CR) rates per IWWM-6 criteria (with modification of VGPR definition based on Treon 2015). Between September 2014 and March 2018, 77 patients (24 TN and 53 R/R) began treatment. At a median follow-up of 36.0 months for patients with R/R disease and 23.5 months for TN, 72.7% remained on treatment. Reasons for treatment discontinuation included any adverse events in 13.0% of patients (1 treatment related), disease progression (10.4%), and other (3.9%). The ORR was 95.9%, and the VGPR/CR rate was 45.2%, which increased over time: 20.5% at 6 months, 32.9% at 12 months, and 43.8% at 24 months. Estimated 3-year progression-free survival rate was 80.5%, and overall survival rate was 84.8%. Adverse events of interest included contusion (32.5%, all grade 1), neutropenia (18.2%), major hemorrhage (3.9%), atrial fibrillation/flutter (5.2%), and grade 3 diarrhea (2.6%). Long-term treatment with single-agent zanubrutinib resulted in deep and durable responses in some patients with WM. The safety profile of long-term zanubrutinib therapy in these patients was acceptable.

Conflict of interest: COI declared - see note

COI notes: J.T. receives research funding from BeiGene, Janssen, Celgene, Pharmacyclics, and Roche. S.O. consults for AbbVie, Janssen, Gilead, Roche, Mundipharma, Merck, BMS, and Celgene; receives research funding from Abbvie, BeiGene, Janssen, Gilead, Roche, Celgene, and Epizyme; and receives honoraria from Abbvie, Janssen, Gilead, Roche, Mundipharma, Merck, BMS, and Celgene. D.G. is an employee of the University of Sydney; consults for Novartis, Gilead, AbbVie, and Merck; and receives research funding from and serves on advisory committees for Haemalogix P/L. D.S. receives research funding from Amgen, BeiGene, AbbVie, Roche, Celgene, MSD, Acerta, Pharmacyclics, Sanofi, and Glaxo-Smith-Kline; and receives honoraria from Janssen, Roche, and AbbVie. P.M. receives honoraria from Celgene, Roche, and AbbVie; serves on advisory committee for Abbvie, Roche, Novartis, Janssen, Astellas, and Celgene. G.C. receives travel, accommodations, and expenses from Amgen, Glycomimetics, and AbbVie. J.M. consults for Pharmacyclics, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, BMS, Kyowa, Alexion, BeiGene, and Seattle Genetics; receives research funding from Kite Pharma, Celgene, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, and Janssen; receives honoraria from Kyowa and Seattle Genetics; and participates in a speakers bureau for BeiGene, Kite Pharma, Gilead, Fosunkite, Kyowa, Bayer, Pharmacyclics, and AstraZeneca. A.T. receives honoraria from BeiGene; participates in a speakers bureau for Janssen Cilag SpA; and serves on advisory committees for Janssen Cilag SpA, Sunesis, and Astra Zeneca. A.W.R. receives research funding from AbbVie and Janssen; and receives royalties from Walter and Eliza Hall Institute. J.F.S. consults for Roche; receives research funding from AbbVie, Celgene, Janssen, and Roche; receives honoraria from AbbVie, Acerta, Celgene, Gilead, Janssen, Roche, and Takeda; participates in a speakers bureau for AbbVie and Roche; and serves on advisory committees for AbbVie, Acerta, Celgene, Gilead, Janssen, Roche, and Takeda. S.K., YY, W.N., J.D.H., and J.H. are employees of and have equity ownership in BeiGene. S.R. is an employee of BeiGene, has equity ownership in BeiGene and Amgen, and reports patents and royalties from Roche Molecular Diagnostics. C.S.T. receives research funding from Janssen and AbbVie and receives honoraria from Janssen, AbbVie, BeiGene, Novartis, and Roche.

Preprint server: No;

Author contributions and disclosures: Together with BeiGene authors (W.N., S.R., J.D.H., J.H., S.K.A., and Y.Y.), C.S.T., J.T., J.F.S., S.O., and A.W.R. were responsible for study design, and J.T., S.O., D.G., D.S., P.M., J.M., A.W.R., J.F.S., and C.S.T. contributed to data interpretation and analysis. All investigators (J.T., S.O., D.G., D.S., P.M., G.C., J.M., A.T., A.W.R., J.F.S., and C.S.T.) and their respective research teams reviewed patient records and contributed to data collection. BeiGene authors (J.D.H., S.R.) confirmed data accuracy and compiled data for summation and analysis. J.D.H., S.R., S.K.A., and Y.Y. performed data analysis and interpretation. All authors contributed to manuscript preparation. BeiGene was involved in study design, compilation of data, and statistical analysis. The corresponding author, J.T., had final responsibility to submit for publication. All authors had full access to all of the data. All authors carefully reviewed the manuscript and approved the final version.

Non-author contributions and disclosures: Yes; Medical writing and editorial assistance were funded by BeiGene and provided by Gordon Bray, MD from BeiGene, and Stacey Rose, PhD from Bio Connections (Chicago, IL, USA).

Agreement to Share Publication-Related Data and Data Sharing Statement: Additional data are provided in the data supplement available online. Individual participant data will not be shared prior to regulatory approval of zanubrutinib for the treatment of WM. Requests for copies of the protocol and statistical analysis plan will be considered: Judith.Trotman@health.nsw.gov.au

Clinical trial registration information (if any): NCT02343120; ClinicalTrials.gov

Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: three years of follow-up

Judith Trotman,[1] Stephen Opat,[2] David Gottlieb,[3] David Simpson,[4] Paula Marlton,[5,6] Gavin Cull,[7] Javier Munoz,[8] Alessandra Tedeschi,[9] Andrew W. Roberts,[10] John F. Seymour,[10,11] Siminder Kaur Atwal,[12] Yiling Yu,[13] William Novotny,[12] Eric Holmgren,[12] Ziwen Tan,[13] James D. Hilger,[12] Jane Huang,[12] and Constantine S. Tam[10,11,14]

[1]Concord Repatriation General Hospital and University of Sydney, Concord, New South Wales, Australia; [2]Monash Health and Monash University, Clayton, Victoria, Australia; [3]Faculty of Medicine and Health, University of Sydney, Westmead Hospital Sydney, Australia; [4]North Shore Hospital, Auckland, New Zealand; [5]Department of Haematology, Princess Alexandra Hospital, Woolloongabba, Brisbane, Australia; [6]University of Queensland Faculty of Medicine, Brisbane, Australia; [7]Haematology Department, Sir Charles Gairdner Hospital, Nedlands, and University of Western Australia, Perth, Western Australia, Australia; [8]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [10]Haematology Department, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia; [11]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia [12]BeiGene USA, Inc, San Mateo, CA, USA; [13]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [14]St Vincent's Hospital, Fitzroy, Victoria, Australia.

Corresponding author: Judith Trotman, MBChB
Concord Repatriation General Hospital
University of Sydney
Concord, Australia
Tel: +61 2 9767 7243
Fax: +61 2 9767 7650
judith.trotman@health.nsw.gov.au

Running header: Zanubrutinib for Waldenström macroglobulinemia

Key Points

- Long-term zanubrutinib treatment of patients with WM resulted in an overall response rate of 96% and VGPR/CR rate of 45%
- Long-term treatment with single-agent zanubrutinib was well tolerated in both treatment-naïve and relapsed/refractory patients.

Abstract

Inhibitors of Bruton's tyrosine kinase (BTK) have established therapeutic activity in patients with Waldenström macroglobulinemia (WM). Zanubrutinib, a potent and selective BTK inhibitor, was evaluated in a phase 1/2 study in patients with WM who were either treatment-naïve (TN) or had relapsed/refractory (R/R) disease. Patients had disease requiring treatment per International Workshop on Waldenström Macroglobulinemia (IWWM) criteria. Treatment was oral zanubrutinib 160 mg twice daily (n=50) or 320 mg once daily (n=23). Efficacy endpoints included overall response rate (ORR) and very good partial response/complete response (VGPR/CR) rates per IWWM-6 criteria (with modification of VGPR definition based on Treon 2015). Between September 2014 and March 2018, 77 patients (24 TN and 53 R/R) began treatment. At a median follow-up of 36.0 months for patients with R/R disease and 23.5 months for TN, 72.7% remained on treatment. Reasons for treatment discontinuation included any adverse events in 13.0% of patients (1 treatment related), disease progression (10.4%), and other (3.9%). The ORR was 95.9%, and the VGPR/CR rate was 45.2%, which increased over time: 20.5% at 6 months, 32.9% at 12 months, and 43.8% at 24 months. Estimated 3-year progression-free survival rate was 80.5%, and overall survival rate was 84.8%. Adverse events of interest included contusion (32.5%, all grade 1), neutropenia (18.2%), major hemorrhage (3.9%), atrial fibrillation/flutter (5.2%), and grade 3 diarrhea (2.6%). Long-term treatment with single-agent zanubrutinib resulted in deep and durable responses in some patients with WM. The safety profile of long-term zanubrutinib therapy in these patients was acceptable.

Clinical trial NCT02343120.

Introduction

Waldenström macroglobulinemia (WM) is a mature B-cell neoplasm characterized by the growth and accumulation of lymphoplasmacytic lymphoma cells and secretion of monoclonal immunoglobulin M (IgM) by malignant cells.[1] Most cases involve the bone marrow, and some involve lymph nodes and extranodal sites. Most patients experience weakness and fatigue from anemia. The monoclonal IgM protein can result in hyperviscosity syndrome, peripheral neuropathy, cryoglobulinemia, and immune complex vasculitis.[2] Although clinically indolent, WM is incurable and the disease course frequently includes episodes of symptomatic recurrence requiring treatment.

Molecularly, the disease is characterized by a specific point mutation in the *MYD88* gene (*MYD88*^{L265P}), present in over 90% of cases, which results in constitutive NFκB activation.[3] In approximately 30% of patients the malignant cells also have an additional mutation in the *CXCR4* gene (*CXCR4*^{WHIM}), encoding a chemokine receptor involved in cell-cell adhesion.[4] Patients whose WM is wild type (WT) for *MYD88* demonstrate significantly higher mortality than patients with WM harboring *MYD88*^{L265P}.[5] Data suggest that progression-free survival (PFS) and very good partial response (VGPR) rates are lower when patients with both *MYD88*^{L265P} and *CXCR4*^{WHIM} WM (compared to *MYD88*^{L265P} alone) are treated with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib.[6]

Inhibitors of BTK have established therapeutic activity in patients with WM. Ibrutinib, the first-in-class BTK inhibitor, was evaluated in 63 patients with relapsed or refractory (R/R) WM in a phase 2 study.[7] With a median 47 months follow-up, the major response rate (MRR) was 78% and median PFS was greater than 5 years.[8] In a companion study in 30 treatment-naïve (TN) patients with *MYD88*^{MUT} disease, after a median of 13.4-months, the MRR was 83% and

the VGPR rate was 20%.[9] In both studies, MRRs were higher among patients with *MYD88*^{MUT}/*CXCR4*^{WT} disease than among patients who had *MYD88*^{MUT}/*CXCR4*^{MUT} disease. Patients with *MYD88*^{WT} disease had the least favorable outcomes, with no major responses observed and a median PFS of 21 months.[8]

Toxicities experienced by patients with R/R WM treated with ibrutinib, have included infections (68%), diarrhea (42%), grade 1 or 2 bleeding (39%), increased tendency to bruise (23%), hypertension (23%), neutropenia (20%), thrombocytopenia (16%), fatigue (13%), and pneumonia (6%).[10] Among patients with R/R WM, 11% developed atrial fibrillation, 6% discontinued ibrutinib for toxicity, and 3% had disease transformation.[11] It is believed that inhibition of structurally related tyrosine kinases such as epidermal growth factor receptor (EGFR), tyrosine kinase expressed in hepatocellular carcinoma (TEC), interleukin-2-inducible T-cell kinase (ITK), and others[12] may explain many of the toxicities, including diarrhea, bleeding,[13,14] and atrial fibrillation.[15]

Zanubrutinib is a novel, potent, and selective BTK inhibitor. In kinase inhibition and cell-based assays, it was more selective than ibrutinib for BTK inhibition, exhibiting less off-target activity against EGFR, TEC, ITK and other tyrosine kinases.[16] Zanubrutinib is maximally absorbed in 2 to 3 hours, with a 2- to 4-hour terminal half-life.[12] At the recommended phase 2 dose (RP2D) of 160 mg twice daily, zanubrutinib steady-state plasma levels were approximately 8-fold higher than those observed for ibrutinib at 560 mg daily, resulting in complete and sustained BTK inhibition in blood and lymph node compartments.[12,17,18]

In early clinical studies, zanubrutinib was well tolerated, demonstrating promising anti-tumor activity in a variety of mature B-cell neoplasms, including WM, mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).[12,19]

Sustained complete (>95%) BTK occupancy in patient lymph node biopsy specimens was more frequent with 160 mg twice daily than 320 once daily (89% vs 50%; *P*=0.034).[12] Consequently, 160 mg twice daily was selected for further investigation. In a cohort of 78 patients with CLL/SLL treated with zanubrutinib monotherapy, the overall response rate (ORR) was 96.2% (95% CI, 89.2-99.2 and estimated PFS at 12 months was 100%.[12] In 86 patients with relapsed/refractory MCL after a median follow-up of 18.4 months, 84% achieved an objective response, with 68.6% achieving a complete response (CR). Median duration of response (DOR) and PFS were 19.5 and 22.1 months respectively.[20] Here we report the safety and efficacy of long-term zanubrutinib therapy in patients with TN and R/R WM, a subset of patients in an ongoing phase 1/2 study of B-cell malignancies.[12]

Methods

Study Design and Treatment

BGB-3111 AU-003 (NCT02343120) is a first-in-human, multicenter, phase 1/2 study of zanubrutinib in patients with B-cell malignancies at 24 sites in 6 countries. The study has 2 parts: part 1 is the dose escalation portion focused on identifying the RP2D; part 2 is the expansion portion that includes several disease-specific patient cohorts. No maximally tolerated dose was identified in part 1, and both 160 mg twice daily or 320 mg daily were identified as the RP2Ds.[12] Part 2 included mostly disease-specific patient cohorts with R/R B-cell malignancies and a smaller number of patients with TN MCL, CLL/SLL and WM who either refused or were deemed unsuitable for standard front-line therapy were also enrolled. As data accumulated, 160 mg twice daily was eventually chosen as the preferred RP2D, based primarily on pharmacodynamic results demonstrating near complete BTK occupancy in disease affected

lymph nodes.[12] The sample size determination for the WM cohort in Part 2 was based on the assumption of a response rate of 80%. With a total of 50 patients enrolled, the lower bound of the 95% CI was 66% if the observed response rate was 80%. Data presented herein report outcomes for patients with TN or R/R WM enrolled in either part of the study.

All patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation guidelines. Institutional review boards and independent ethics committees approved the protocol. Data were collected by the investigators and their research teams. All authors had full access to and were responsible for analyzing and interpreting the data.

Patients

Eligible patients were required to be ≥18 years old, have Eastern Cooperative Oncology Group performance status 0 to 2, adequate baseline hematologic (neutrophil and platelet counts $>1.0\times10^9$/L and $\geq50\times10^9$/L, respectively), renal (measured or estimated creatinine clearance ≥30 mL/min), and liver (transaminase levels ≤3 times the upper limit of normal [ULN], total bilirubin ≤1.5 times ULN) function, and without previous exposure to a BTK inhibitor. Patients with current central nervous system involvement, significant cardiac disease, histologic transformation to aggressive lymphoma, and those requiring concurrent, strong CYP3A inhibitors/inducers or QT prolonging medications were excluded. Patients with a history of atrial fibrillation and those requiring concurrent antithrombotic medications (eg. aspirin, anticoagulants) were not excluded. Full inclusion/exclusion criteria are shown in the **Supplemental methods**.

Assessments

Blood samples for nephelometric IgM and paraprotein quantitation by serum protein electrophoresis (SPEP) were collected at screening, every 4 weeks through week 52, every 12 weeks thereafter, and at treatment discontinuation. Responses were investigator-assessed in accordance with the 6th International Workshop on WM with modification for VGPR definition per Treon et al (see **Supplemental methods**).[21,22] If baseline quantitative IgM levels were unavailable, responses were assessed by changes in paraprotein levels measured by SPEP. All patients had bone marrow aspiration and biopsy at screening, within 7 days of the end of week 12, and thereafter, as clinically indicated for confirmation of CR or disease progression. All patients had computed tomography (CT) scans at baseline; those with extramedullary disease (lymphadenopathy or splenomegaly by imaging or physican exam, as described in **Supplemental methods**) had CT scans every 12 weeks until week 48 and every 24 weeks thereafter.

Safety assessments included monitoring of type, frequency, severity, and outcomes of AEs. All AEs that occurred from the first treatment day until 30 days after study treatment discontinuation were summarized. AEs of interest were a predefined subgroup of AEs known to be associated with ibrutinib. They were identified in accordance with predefined Medical Dictionary for Regulatory Activities, version 22.0, search criteria and included: bleeding (including major hemorrhage), atrial fibrillation/flutter, hypertension, second primary malignancies (including skin cancers), tumor lysis syndrome, infections (including opportunistic infections), neutropenia, thrombocytopenia and anemia. AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

MYD88 mutational status was analyzed on bone marrow aspirates using a proprietary, polymerase chain reaction (PCR)-based assay that employs locked oligonucleotides to block amplification of *MYD88*^{WT} DNA during PCR followed by bidirectional Sanger sequencing of the amplicon.[23] This approach captures all mutations from amino acids 260 to 278 in the Toll/IL-1R domain of *MYD88* with limit of detection ~0.5%. Mutations in *CXCR4* were detected using a validated next-generation sequencing assay (**Supplemental methods**). Samples were collected at baseline where possible but if unavailable, postbaseline samples were assessed for *MYD88/CXCR4* genotype. B-cell selection was not used for *MYD88* or *CXCR4* determination.

Statistical Analyses

Safety analyses included all patients with WM receiving at least 1 zanubrutinib dose and no prior BTK inhibitor exposure (a later cohort enrolled 1 patient with WM intolerant to prior BTK inhibitor therapy; this patient was excluded from the analysis). Standard descriptive statistics were used to summarize AE data in the safety population. The efficacy-evaluable population consisted of all patients in the safety population with a baseline IgM level ≥5 g/L. The primary efficacy endpoint was the proportion of patients achieving VGPR or CR. This endpoint was based on the observation that patients achieving a VGPR after treatment with rituximab-based chemoimmunotherapy had a PFS outcome similar to patients achieving a CR.[24] Other efficacy endpoints included MRR (≥PR), ORR (≥minimal response), PFS, DOR, overall survival (OS), and changes from baseline in serum IgM levels, hemoglobin concentrations, and extramedullary disease burden. Rates and depths of response as a function of *MYD88/CXCR4* genotype were also examined.

Response rates were summarized as the percentage of responders for each category (CR and VGPR, MRR, and ORR) with 95% CIs.[25] DOR was assessed as time from first qualifying

response until disease progression or death from any cause. The proportion of patients with VGPR/CR over time was estimated with simple proportions (number of patients in VGPR/CR up to each time point divided by total number of patients). PFS was measured from time of first study drug dose to disease progression or death from any cause. Patients not experiencing progressive disease (PD) or death were censored on the day of last tumor assessment before subsequent anticancer therapy initiation for DOR and PFS analyses. Median DOR, PFS and event-free rates at landmark timepoints were estimated using Kaplan-Meier methodology with corresponding 95% CIs.[26] Median follow-up times for PFS and DOR were estimated by the reverse Kaplan-Meier method. OS was defined as time from first study drug dose until death from any cause.

Results

Treatment and Patient Disposition

Between September 2014 and March 2018, 77 patients with WM (24 TN and 53 R/R) and without prior BTK inhibitor exposure were enrolled then treated with zanubrutinib. Seventy-three of these patients received an initial total daily dose of 320 mg. Of patients with R/R disease, 36 received 160 mg twice daily and 13 received 320 mg daily. Of patients with TN disease, 14 received 160 mg twice daily and 10 received 320 mg daily. Four patients with R/R disease received a starting dose of zanubrutinib <320 mg/day in the dose-escalation part of the study; of these, 3 patients escalated to a dose of 160 mg twice daily. Upon protocol amendment, 12 patients (4 R/R, 8 TN) who were initially assigned to 320 mg once daily were switched to 160 twice daily.

In the safety population, the median study follow-up was 36.0 months for patients with R/R disease and 23.5 months for TN patients, the difference in follow-up time between patients with R/R disease and TN patients was due to exclusive enrollment of those with R/R disease at the beginning of the study. Fifty-six patients were continuing study treatment at the data cutoff date of August 31, 2019 (19/24 TN, 37/53 R/R). Twenty-one patients discontinued study drug: 10 for AEs (3 TN, 7 R/R); 8 for PD (1 TN, 7 R/R); 2 for other reasons (both R/R); and 1 for investigator's decision (1 TN) (**Supplemental Figure S1**).

Patient Demographics and Baseline Disease Characteristics

Baseline characteristics are presented in **Table 1**. Median age was 67 years (range, 40-87), with approximately one-fifth of patients >75 years old. The majority were male. The median times from initial diagnosis to enrollment on study were 0.7 and 5.3 years for TN and R/R cohorts, respectively. Among the patients with R/R disease, the median number of prior regimens was 2 (range, 1-8). The most common prior treatments included rituximab-based therapy, alkylating agents, and corticosteroids (**Supplemental Table S1**). Across both cohorts, approximately one-third of patients had serum IgM levels ≥40 g/L. Mutation testing was performed in 90% of patients (n = 69). Fifty-eight patients (20 TN, 38 R/R) had disease with a *MYD88*^{L265P} mutation (84% of those tested); 11 (3 TN; 8 R/R) were *MYD88*^{WT}. Among cases with *MYD88*^{L265P} mutated disease, WM in 11 also harbored *CXCR4*^{WHIM} mutations (19%; 4 TN, 7 R/R). Among patients with *MYD88*^{WT} disease, all 11 had *CXCR4*^{WT} disease.

Response Rates

Seventy-three patients were evaluable for efficacy (another 4 had baseline IgM concentrations <5 g/L). Across both cohorts, 45.2% (95% CI 33.5-57.3) of patients achieved a best response of VGPR or CR (33.3% [95% CI 15.6-55.3] and 51.0% [95% CI 36.3-65.6] in the

TN and R/R cohorts respectively; **Table 2**). Major responses were seen in 82.2% of patients (87.5% TN, 79.6% R/R). Median time to major response was 2.8 months for TN and R/R cohorts. The proportion of patients achieving a best response of VGPR/CR increased with treatment duration: 20.5% at 6 months, 32.9% at 12 months, and 43.8% at 24 months. In patients with R/R disease, the rate of VGPR/CR was 24.5% at 6 months, 38.8% at 12 months, and 49.0% at 24 months; evidence of a plateau beginning at approximately 20 months (**Supplemental Figure S2**). ORR, MRR, and VGPR/CR rate in the 160 mg twice daily arm were 97.9%, 80.9%, and 48.9% as compared with the 320 mg daily arm at 90.9%, 81.8%, and 31.8%.

Among efficacy-evaluable patients with available genotype data (n=65), the proportion with *MYD88*^{L265P} mutated disease achieving VGPR/CR was 49.1% (28/57) and 25% (2/8) for those with *MYD88*^{WT} WM (including 1 CR and 1 VGPR). The VGPR/CR rate in the subset of patients who had *MYD88*^{L265P}/*CXCR4*^{WT} WM was 59.0% (23/39), and 27.3% (3/11) in patients with *MYD88*^{L265P}/*CXCR4*^{WHIM} WM **Figure 1**). However, MRRs were similar between patients with *MYD88* ^{L265P}/*CXCR4*^{WT} and *MYD88*^{L265P}/*CXCR4*^{WHIM} genotypes overall, (34/39 [87.2%] and 10/11 [90.9%], respectively). Median DORs were not reached for any response category (**Table 2**).

IgM, Hemoglobin, and Extramedullary Disease

Serum IgM levels decreased with increasing treatment duration (**Figure 2; Supplemental Figure S3**). Overall, 36 patients had dose holds of ≥8 days; 18 of whom experienced a IgM rebound of ≥50%. Of those 18, 13 experienced subsequent IgM declines comparable to nadir levels, 3 had IgM declines but not to nadir levels, and 2 progressed.

Hemoglobin concentrations increased with time on treatment, exhibiting a median maximal improvement of 35 g/L, a 32.7% improvement over baseline (25th-75th percentile:

17.8%, 56.6%). Among patients with a baseline hemoglobin concentration ≤110 g/L, the median maximal increase was more pronounced at 44.5 g/L.

Among the 31 patients with baseline lymphadenopathy by CT scan, 16 (51.6%) exhibited a >50% reduction in the sum of the products of perpendicular diameters (SPD) of target lesions while on study. The median maximal reduction from baseline in target lymph node SPD was 53.4%. Similarly, all 18 patients with both baseline splenomegaly and post-baseline spleen assessment exhibited reductions in craniocaudal spleen length measured by CT scan while on study; median maximal reduction was 19.2%. Follow-up bone marrow examinations were required only for patients with bone marrow involvement at baseline, and only at end of week 12. Among patients with serial bone marrow biopsies (20 TN, 41 R/R), there was no change in the median percentage involvement by lymphoma at week 13 compared with baseline.

Survival

The median PFS in patients with R/R disease was not reached after a median follow-up of 36.8 months (**Figure 3B**). The estimated event-free rates at 18, 24, and 36 months were 83.7%, 76.2%, and 76.2%, respectively. There were 13 PFS events in R/R patients: 9 patients experienced PD and 4 died without PD (and were counted as a PFS event). The median PFS in TN patients was not reached after a median follow-up of 23 months (**Figure 3A**). The estimated event-free rates at 18 and 24 months were both 91.5%. Two TN patients experienced PD, and neither died.

Safety

All patients reported at least one AE of any grade; 58.4% reported at least one grade 3 or higher AE (**Table 3**). The most commonly reported AEs were upper respiratory tract infection (51.9%), contusion (32.5%), and cough (22.1%). Grade 3 or higher AEs reported in more than

one patient were neutropenia (15.6%), anemia (9.1%), basal cell carcinoma and cellulitis (each 5.2%), hypertension and pneumonia (each 3.9%), diarrhea, headache, fall, and actinic keratosis (each 2.6%). In total, 9 patients died while on study (all R/R); 2 due to PD, 2 from unknown causes, and 5 had AEs leading to death: abdominal sepsis (day 1242), bacterial arthritis (day 887), *Scedosporium* infection (day 62), gastric adenocarcinoma, (day 526) and worsening bronchiectasis (day 121) (**Supplemental Table S3**). Four of the 5 events were assessed as not related to study drug. Relatedness was not assessed for the patient with bacterial arthritis.

The most commonly reported AEs of special interest were infections: 90.9% of patients reported at least one infection of any grade (treatment-related in 15 of 70 patients with event) and; 27.3% of patients reported at least one grade 3 infection. The most common grade ≥3 infections were cellulitis and pneumonia (n=4 and 3, respectively, all R/R). The exposure-adjusted incidence rate (EAIR) for grade 3 or higher infections was 1.12 events per 100 person-months. Fungal infections occurred in 4 patients with R/R disease; the events were bronchopulmonary aspergillosis (grade 2), cryptococcal meningitis (grade 3), esophageal candidiasis (grade 2), and disseminated *Scedosporium* infection (grade 5). All of these infections, except the disseminated *Scedosporium* infection resolved with treatment, and the patients were able to continue zanubrutinib therapy. The patient with *Scedosporium* infection had a prior history of neck *Scedosporium* abscess that had been treated, but while on this study the infection recurred, worsened, and was ultimately fatal. One patient, an 80-year-old Asian male with R/R WM, not receiving prophylactic antiviral therapy, developed hepatitis B reactivation without elevation in aspartate aminotransferase or alanine aminotransferase. This was successfully treated with lamivudine, and the patient continued zanubrutinib without interruption or further complication.

Thirteen (54.2%) TN and 35 (66.0%) patients with R/R disease reported at least one bruising or bleeding event, 45/48 (93.8%) of which were grade 1 or 2: most commonly contusion (32.5%), petechiae (13.0%), epistaxis (13.0%), hematuria (7.8%), purpura and rectal hemorrhage (3.9% each). Three patients experienced grade 3 hemorrhages: purpura in a TN patient; hemothorax and melena occurred in a TN patient – the hemothorax occurred following thoracentesis; and hemorrhagic cystitis in a patient with R/R disease who had locally recurrent bladder cancer. The hemorrhagic cystitis event was managed with treatment interruption for 11 days. One patient required zanubrutinib discontinuation for bleeding (grade 3 purpura). The EAIR for any hemorrhage and major hemorrhage were 4.49 events/100 person-months and 0.13 events/100 person-months, respectively.

Atrial fibrillation was reported in 4 (5.2%) patients (1 TN, 3 R/R) for an EAIR of 0.19 events/100 person-months; 1 patient had a prior history of atrial fibrillation. One atrial fibrillation event in a TN patient was grade 3, and no patients required dose reductions or treatment discontinuation. Second primary malignancies (EAIR, 0.98 events/100 person-months) consisted primarily of non-melanoma skin cancers (i.e, basal cell carcinoma, squamous cell carcinoma, intraepidermal squamous cell carcinoma; EAIR, 0.66 events/100 patient-months), all but 1 in patients with R/R disease, and most from Australia and New Zealand, a region with particularly high background prevalence. Grade 3 or higher neutropenia was reported in 15.6% of patients. Ten patients received 1-8 courses of granulocyte colony stimulating factor. No patients required dose reduction or treatment discontinuation for neutropenia. No patient developed tumor lysis syndrome.

Discussion

The first-in-class BTK inhibitor, Ibrutinib has demonstrated substantial activity in patients with WM. However, challenges remain with respect to the benefit/risk ratio of ibrutinib, especially for patients with disease of *MYD88*^{L265P}*/CXCR4*^{WHIM} and *MYD88*^{WT} where reponse rates are lower, and for those experiencing toxicity. For this reason, we investigated zanubrutinib, a potent and selective BTK inhibitor, in patients with WM. Results from this ongoing study demonstrate that long-term treatment with zanubrutinib was tolerable and resulted in deep and durable responses in the majority of patients with WM.

After an overall median follow-up of 36.0 months in patients with R/R disease and 23.5 months in TN patients, the observed safety profile of single-agent zanubrutinib was consistent with both the natural history of WM and the known toxicity profile of BTK inhibitor therapy.[27] Although minor bleeding was common, only 3 patients (3.9%) experienced major hemorrhagic events (hemothorax/melena, purpura, and hemorrhagic cystitis), with other contributing factors implicated in two. This low frequency is consistent with the favorable platelet inhibition profile of zanubrutinib as compared with ibrutinib *in vitro*.[28] Of the 4 patients with atrial fibrillation, 1 had a prior history and none required treatment discontinuation.

Infections were the most common and worrisome AE, with both zanubrutinib (treatment-related for 15 of 70 patients with events) and immunocompromise from underlying WM and prior immunochemotherapy (including fludarabine and bendamustine) contributing. These were mainly respiratory tract infections, and in most patients (67/70, 95.7%) they were managed without the need for treatment discontinuation. There were 4 proven fungal infections (all in patients with R/R disease); 2 were grade ≥3. Although rates were low in clinical trials, since its initial approval, there have been multiple reports of opportunistic infections caused by *P. jirovecii*, *C. neoformans,* and ubiquitous airborne filamentous fungi (eg, aspergillus species) in

association with ibrutinib therapy.[3,24] Physicians currently consider prophylaxis in patients who are at increased risk for infections and who receive BTK inhibitor therapy.

While commonly reported AEs observed in this study are comparable to those reported for ibrutinib, there are potential differences. Most notably, the incidence of diarrhea in patients treated with zanubrutinib (19.5%) was less than half that reported for patients with R/R WM treated with ibrutinib (42%).[10] This may be related to the diminished inhibition of EGFR with zanubrutinib observed in vitro.[12]

Responses were observed in both patients with R/R disease and TN patients and across all *MYD88/CXCR4* genotypes. For both cohorts, the rate of deep responses appears to improve with increasing treatment duration, and the longer exposure of patients with R/R disease may explain their apparently higher rate of VGPR/CR. Longer follow-up will determine whether a comparably high rate of deep responses can be achieved in TN patients. Improved VGPR rates upon longer treatment duration have previously been noted for ibrutinib in R/R WM.[8]

Recognizing the limitations of cross-study comparisons and small sample sizes, the proportion of patients with R/R disease who achieved a deep response in the current study (51%) compares favorably with that reported for patients in the ibrutinib pivotal trial (27%) despite the significantly longer treatment duration in the latter study (median, 46.6 months).[8] TN patients in this study (including 3 with *MYD88*^{WT} disease and 1 with unknown genotype) also demonstrated a high rate of early deep responses (33.3%).[9] The rate of CXCR4 mutations in this study was also somewhat lower than that reported in ibrutinib trials, however the lack of B-cell selection in bone marrow aspirates may have contributed to an under-recognition herein.

Across both cohorts, MRRs were comparably high in patients with disease harboring the *MYD88*^{L265P} mutation with (90.9%) or without (87.2%) an accompanying *CXCR4*^{WHIM} mutation.

MRRs reported from the ibrutinib pivotal study were comparable to those in the current study for patients with *MYD88*^{L265P}/*CXCR4*^{WT} genotype WM (97%) but possibly lower for those with *MYD88*^{L265P}/*CXCR4*^{WHIM} disease (67% and 71% in R/R and TN cohorts, respectively).[8,29] While the MRRs did not differ between the aforementioned genotypes in the current study, there was a clear difference in the rate of deep responses, favoring patients with *MYD88*^{L265P}/*CXCR4*^{WT} genotype disease (**Figure 1**). Among patients with *MYD88*^{WT} disease, 2/8 (25.0%) achieved a deep response (including the only patient across both cohorts achieving a CR) and 5 (62.5%) achieved a major response. While these data indicate meaningful clinical benefit for patients across all *MYD88/CXCR4* genotypes (including *MYD88*^{WT}), small sample sizes warrant caution in their interpretation.

In summary, these results showed that long-term treatment with zanubrutinib resulted in deep and durable responses in the majority of patients with WM, and was well-tolerated. Deep responses were seen in patients with both TN and R/R disease and in all molecular subtypes, including *MYD88*^{WT}. As a potent and selective BTK inhibitor, zanubrutinib offers the potential for improved efficacy, safety and tolerability over existing treatment options. To address this question, a randomized phase 3 study comparing the safety and efficacy of zanubrutinib with ibrutinib in patients with WM is underway (NCT03053440).

Acknowledgments

We thank the patients who participated in the study, their supporters, and the investigators and clinical research staff from the study centers. This study was supported by research funding from BeiGene (Beijing) Co., Ltd., Beijing, China. Medical writing and

editorial assistance were funded by BeiGene and provided by Gordon Bray, MD, and Bio Connections (Chicago, IL, USA).

Authorship

Contributions: Together with BeiGene authors (W.N., S.R., J.D.H., J.H., S.K.A., and Y.Y.), C.S.T., J.T., J.F.S., S.O., and A.W.R. were responsible for study design, and J.T., S.O., D.G., D.S., P.M., J.M., A.W.R., J.F.S., and C.S.T. contributed to data interpretation and analysis. All investigators (J.T., S.O., D.G., D.S., P.M., G.C., J.M., A.T., A.W.R., J.F.S., and C.S.T.) and their respective research teams reviewed patient records and contributed to data collection. BeiGene authors (J.D.H., S.R.) confirmed data accuracy and compiled data for summation and analysis. J.D.H., S.R., S.K.A., and Y.Y. performed data analysis and interpretation. All authors contributed to manuscript preparation. BeiGene was involved in study design, compilation of data, and statistical analysis. The corresponding author, J.T., had final responsibility to submit for publication. All authors had full access to all of the data. All authors carefully reviewed the manuscript and approved the final version.

Conflict-of-interest disclosure:

J.T. receives research funding from BeiGene, Janssen, Celgene, Pharmacyclics, and Roche. S.O. consults for AbbVie, Janssen, Gilead, Roche, Mundipharma, Merck, BMS, and Celgene; receives research funding from AbbVie, BeiGene, Janssen, Gilead, Roche, Celgene, and Epizyme; and receives honoraria from AbbVie, Janssen, Gilead, Roche, Mundipharma, Merck, BMS, and Celgene. D.G. is an employee of the University of Sydney; consults for Novartis, Gilead, AbbVie, and Merck; and receives research funding from and serves on advisory

committees for Haemalogix P/L. D.S. receives research funding from Amgen, BeiGene, AbbVie, Roche, Celgene, MSD, Acerta, Pharmacyclics, Sanofi, and Glaxo-Smith-Kline; and receives honoraria from Janssen, Roche, and AbbVie. P.M. receives honoraria from Celgene, Roche, and AbbVie; serves on advisory committee for AbbVie, Roche, Novartis, Janssen, Astellas, and Celgene. G.C. receives travel, accommodations, and expenses from Amgen, Glycomimetics, and AbbVie. J.M. consults for Pharmacyclics, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, BMS, Kyowa, Alexion, BeiGene, and Seattle Genetics; receives research funding from Kite Pharma, Celgene, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, and Janssen; receives honoraria from Kyowa and Seattle Genetics; and participates in a speakers bureau for BeiGene, Kite Pharma, Gilead, Fosunkite, Kyowa, Bayer, Pharmacyclics, and AstraZeneca. A.T. receives honoraria from BeiGene; participates in a speakers bureau for Janssen Cilag SpA; and serves on advisory committees for Janssen Cilag SpA, Sunesis, and Astra Zeneca. A.W.R. receives research funding from AbbVie and Janssen; and receives royalties from Walter and Eliza Hall Institute. J.F.S. consults for Roche; receives research funding from AbbVie, Celgene, Janssen, and Roche; receives honoraria from AbbVie, Acerta, Celgene, Gilead, Janssen, Roche, and Takeda; participates in a speakers bureau for AbbVie and Roche; and serves on advisory committees for AbbVie, Acerta, Celgene, Gilead, Janssen, Roche, and Takeda. S.K., YY, W.N., J.D.H., and J.H. are employees of and have equity ownership in BeiGene. S.R. is an employee of BeiGene, has equity ownership in BeiGene and Amgen, and reports patents and royalties from Roche Molecular Diagnostics. C.S.T. receives research funding from Janssen and AbbVie and receives honoraria from Janssen, AbbVie, BeiGene, Novartis, and Roche.

Correspondence: Judith Trotman, Concord Repatriation General Hospital, University of Sydney, Concord, Australia, judith.trotman@health.nsw.gov.au

Data Sharing Statement

Additional data are provided in the data supplement available online. Individual participant data will not be shared prior to regulatory approval of zanubrutinib for the treatment of WM. Requests for copies of the protocol and statistical analysis plan will be considered: Judith.Trotman@health.nsw.gov.au

References

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30(2):110-115.
2. Gertz MA. Waldenstrom macroglobulinemia: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2019;94(2):266-276.
3. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2012;367(9):826-833.
4. Cao Y, Hunter ZR, Liu X, et al. CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P)-directed survival signalling in Waldenstrom macroglobulinaemia cells. *Br J Haematol*. 2015;168(5):701-707.
5. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. *Blood*. 2014;123(18):2791-2796.
6. Castillo JJ, Xu L, Gustine JN, et al. CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. *Br J Haematol*. 2019;187(3):356-363.
7. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440.
8. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of previously treated patients who received ibrutinib for symptomatic waldenstrom's macroglobulinemia: update of pivotal clinical trial. *Blood*. 2017;130(Suppl 1):2766.
9. Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naive patients With Waldenstrom macroglobulinemia. *J Clin Oncol*. 2018;36(27):2755-2761.
10. Dimopoulos MA, Trotman, J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refreatory Waldenstrom's macroglobulinemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol*. 2017;18(2):241-250.
11. Treon SP, Meid K, Bantilan K, et al. Ibrutinib shows prolonged progression-free survival in symptomatic, previously treated patients with MYD88 mutated Waldenstrom's Macroglobulinemia: Long-term follow-up of pivotal trial (NCT01614821). Poster presented at 2018 Annual Euriopean Hematology Association meeting. Abstract PS1185.
12. Tam CSL, Trotman J, Opat S, et al. Phase 1 study of selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859.
13. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia*. 2015;29(4):783-787.
14. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood*. 2014;124(26):3991-3995.
15. Tang CPS, McMullen J, Tam C. Cardiac side effects of Bruton tyrosine kinase (BTK) inhibitors. *Leuk Lymphoma*. 2018;59(7):1554-1564.
16. Li N, Sun Z, Liu Y, et al. Abstract 2597: BGB-3111 is a novel and highly selective Bruton's tyrosine kinase (BTK) inhibitor. *Cancer Research*. 2015;75(15 Supplement):2597-2597.
17. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31(1):88-94.
18. IMBRUVICA [Summary of Product Characteristics]. Janssen-Cilag International NV. Beerse, Belgium; 2018.

19. Song Y, Zhou K, Zou D, et al. Safety and activity of the investigational Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) in patients with mantle cell lymphoma from a phase 2 trial. *Blood*. 2018;132(Supplement 1):148-148.
21. Song Y, Zhou K, Zou D, et al. Treatment of relapsed or refractory mantle cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. *Clin Cancer Res*. 2020; in press.
21. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160(2):171-176.
22. Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood*. 2015;126(6):721-732.
23. Albitar A, Ma W, DeDios I, Estella J, Agersborg S, Albitar M. Positive selection and high sensitivity test for MYD88 mutations using locked nucleic acid. *Int J Lab Hematol*. 2016;38(2):133-140.
24. Treon SP, Yang G, Hanzis C, et al. Attainment of complete/very good partial response following rituximab-based therapy is an important determinant to progression-free survival, and is impacted by polymorphisms in FCGR3A in Waldenstrom macroglobulinaemia. *Br J Haematol*. 2011;154(2):223-228.
25. Clopper CJ PE. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404-413.
26. Brookmeyer R CJ. A confidence interval for the median survival time. *Biometrics*. 1982;38(1):29-41.
27. Tam CS OS, Zhu J, et al. Pooled analysis of safety data from monotherapy studies of the Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib (BGB-3111) in B-cell malignancies. 24th European Hematology Association Congress. Amsterdam, The Netherlands; 2019.
28. Dobie G, Kuriri FA, Omar MMA, et al. Ibrutinib, but not zanubrutinib, induces platelet receptor shedding of GPIb-IX-V complex and integrin alphaIIbbeta3 in mice and humans. *Blood Adv*. 2019;3(24):4298-4311.
29. Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. *Br J Haematol*. 2018;180(3):374-380.

Table 1. Demographic and clinical characteristics of patients at baseline

Characteristic	Treatment-naïve (n=24)	Relapsed/Refractory (n=53)	Total (N=77)
Age			
Years, median (range)	65 (40-87)	68 (45-87)	67 (40-87)
> 75 years, n (%)	3 (12.5)	13 (24.5)	16 (20.8)
Male, n (%)	16 (67)	45 (85)	61 (79)
ECOG performance status score, n (%)			
0/1	24 (100)	50 (94)	74 (96)
2	0 (0)	3 (6)	3 (4)
Serum IgM (g/L)[a]			
Median (range)	43.9 (5.3-91.9)	29.4 (1.2-88.5)	32.4 (1.2-91.9)
≥ 40 g/L, n (%)	13 (54)	11 (21)	24 (31)
Baseline hemoglobin (g/L)			
Median (range)	100.5 (68-132)	106.0 (63-155)	105.0 (63-155)
≤ 110 g/L, n (%)	14 (58)	32 (60)	46 (60)
Extramedullary disease			
Lymphadenopathy[b], n (%)	13 (54)	26 (49)	39 (51)
Splenomegaly, n (%)	9 (38)	17 (32)	26 (34)
Bone marrow infiltration			
Median cellularity (range)	42.5 (10-95)	27.5 (0-94)	35 (0-95)
No. of prior systemic therapies, median (range)	NA	2 (1-8)	2 (1-8)
Genotype, n (%)[c]			
MYD88^{L265P}/*CXCR4*^{WT}	14 (58.3)	26 (49.1)	40 (51.9)
MYD88^{L265P}/*CXCR4*^{WHIM}	4 (16.7)	7 (13.2)	11 (14.3)
MYD88^{L265P}/*CXCR4*^{FS}	2 (8.3)	4 (7.5)	6 (7.8)
MYD88^{L265P}/*CXCR4*^{NS}	2 (8.3)	3 (5.7)	5 (6.5)
MYD88^{L265P}/*CXCR4*^{UNK}	2 (8.3)	5 (9.4)	7 (9.1)
MYD88^{WT}/*CXCR4*^{WT}	3 (12.5)	8 (15.1)	11 (14.3)

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FS, frameshift mutation; IgM, immunoglobulin M; NA, not applicable; NS, nonsense mutation; UNK, unknown; WT, wild type.
[a]Based on nephelometric assessment (n=74) or in the absence of a quantitative IgM level, on serum protein electrophoresis
[b]Thirty-one patients had baseline lymphadenopathy based on CT imaging alone.
[c]Genotype data were obtained from baseline bone marrow aspirate samples, or if not available, postbaseline samples. Eight patients (1 TN and 7 R/R) did not provide bone marrow samples for MYD88/CXCR4 genomic profiling. Five of 8 had enrolled prior to protocol requirement for bone marrow analysis for MYD88/CXCR4 and 3 of 8 did not sign the optional informed consent for genetic testing of bone marrow.

Table 2. Efficacy outcomes

	Treatment-naïve (n=24)	Relapsed/Refractory (n=49)	Total (N=73)
Median duration of follow-up, mo	23.5	35.8	30.3
Best overall response, n (%)			
CR	0	1 (2.0)	1 (1.4)
VGPR	8 (33.3)	24 (49.0)	32 (43.8)
PR	13 (54.2)	14 (28.6)	27 (37.0)
MR	3 (12.5)	7 (14.3)	10 (13.7)
SD	0	3 (6.1)	3 (4.1)
PD	0	0	0
VGPR/CR rate, % (95% CI)	33.3 (15.6-55.3)	51.0 (36.3-65.6)	45.2 (33.5-57.3)
VGPR/CR rate by genotype, % (95% CI)			
MYD88^{L265P}/*CXCR4*^{WT} (n=39)			59.0 (42.1-74.4)
MYD88^{L265P}/*CXCR4*^{WHIM} (n=11)			27.3 (6.0-61.0)
MYD88^{L265P}/*CXCR4*^{FS} (n=6)			33.3 (4.3-77.7)
MYD88^{L265P}/*CXCR4*^{NS} (n=5)			20.0 (0.5-71.6)
MYD88^{WT} (n=8)			25.0 (3.2-65.1)
ORR (MR or better), % (95% CI)	100.0 (85.8-100.0)	93.9 (83.1-98.7)	95.9 (88.5-99.1)
MRR (PR or better), % (95% CI)	87.5 (67.6-97.3)	79.6 (65.7-89.8)	82.2 (71.5-90.2)
PFS, % (95% CI)			
24 mo	91.5 (70.0-97.8)	76.2 (60.9-86.2)	80.5 (68.5-88.3)
36 mo	91.5 (70.0-97.8)	76.2 (60.9-86.2)	80.5 (68.5-88.3)
OS, % (95% CI)			
24 mo	100 (NE-NE)	91.5 (78.8-96.7)	94.1 (84.9-97.7)
36 mo	100 (NE-NE)	80.2 (63.8-89.7)	84.8 (71.3-92.3)

Percentages are based on N, the number of patients who received ≥ 1 dose of zanubrutinib and had baseline IgM or M-paraprotein ≥ 5 g/L.
CR, complete response; mo, months; MR, minimal response; MRR, major response rate; ORR, overall response rate; OS, overall survival; PD progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

Table 3. Treatment-emergent AEs

Event Term[a]	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	All Grade, n (%)
Patients with ≥1 AE	5 (6.5)	27 (35.1)	30 (39.0)	10 (13.0)	5 (6.5)	77 (100.0)
Non-hematologic AEs						
Upper respiratory tract infection	1 (1.3)	39 (50.6)	0	0	0	40 (51.9)
Contusion	25 (32.5)	0	0	0	0	25 (32.5)
Cough	16 (20.8)	1 (1.3)	0	0	0	17 (22.1)
Diarrhea	8 (10.4)	5 (6.5)	2 (2.6)	0	0	15 (19.5)
Urinary tract infection	1 (1.3)	13 (16.9)	1 (1.3)	0	0	15 (19.5)
Headache	8 (10.4)	4 (5.2)	2 (2.6)	0	0	14 (18.2)
Rash	11 (14.3)	2 (2.6)	0	0	0	13 (16.9)
Hypertension	1 (1.3)	8 (10.4)	3 (3.9)	0	0	12 (15.6)
Constipation	7 (9.1)	5 (6.5)	0	0	0	12 (15.6)
Back pain	10 (13.0)	2 (2.6)	0	0	0	12 (15.6)
Fatigue	11 (14.3)	1 (1.3)	0	0	0	12 (15.6)
Gastroesophageal reflux disease	7 (9.1)	4 (5.2)	0	0	0	11 (14.3)
Nausea	8 (10.4)	3 (3.9)	0	0	0	11 (14.3)
Cellulitis	1 (1.3)	5 (6.5)	4 (5.2)	0	0	10 (13.0)
Epistaxis	9 (11.7)	1 (1.3)	0	0	0	10 (13.0)
Oropharyngeal pain	8 (10.4)	2 (2.6)	0	0	0	10 (13.0)
Petechiae	10 (13.0)	0	0	0	0	10 (13.0)
Pruritus	9 (11.7)	1 (1.3)	0	0	0	10 (13.0)
Basal cell carcinoma	1 (1.3)	4 (5.2)	0	0	0	9 (11.7)
Arthralgia	4 (5.2)	4 (5.2)	1 (1.3)	0	0	9 (11.7)
Fall	2 (2.6)	4 (5.2)	2 (2.6)	0	0	8 (10.4)
Lower respiratory tract infection	0	8 (10.4)	0	0	0	8 (10.4)
Pneumonia	0	1 (1.3)	3 (3.9)	0	0	4 (5.2)
Actinic keratosis	1 (1.3)	0	2 (2.6)	0	0	3 (3.9)
Hematologic AEs						
Neutropenia[b]	0	2 (2.6)	6 (7.8)	6 (7.8)	0	14 (18.2)
Anemia	1 (1.3)	3 (3.9)	7 (9.1)	0	0	11 (14.3)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; WM, Waldenström macroglobulinemia.

[a]Data are for treatment-emergent adverse events in the 77 zanubrutinib-treated patients with WM included in the study. Listed events occurred in >10% of patients or for grade ≥3, in >2% of patients, on or before the data cutoff date of August 31, 2019.

[b]Includes the MedDRA preferred terms neutropenia, neutrophil count decreased, and febrile neutropenia.

Table 4. AEI

Category of event	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	All Grade, n (%)	EAIR (All Severity Grades), events/100 person-months
Patients with ≥1 AEI[a]	7 (9.1)	30 (39.0)	25 (32.5)	9 (11.7)	4 (5.2)	75 (97.4)	--
Bleeding	40 (51.9)	5 (6.5)	3 (3.9)	0	0	48 (62.3)	4.49
Major hemorrhage	0	0	3 (3.9)	0	0	3 (3.9)	0.13
Atrial fibrillation/ flutter	1 (1.3)	2 (2.6)	1 (1.3)	0	0	4 (5.2)	0.19
Hypertension	1 (1.3)	8 (10.4)	3 (3.9)	0	0	12 (15.6)	0.61
2nd primary malignancies	3 (3.9)	6 (7.8)	7 (9.1)	2 (2.6)	1 (1.3)	19 (24.7)	0.98
Skin cancers	2 (2.6)	7 (9.1)	4 (5.2)	0	0	13 (16.9)	0.66
Tumor lysis syndrome	0	0	0	0	0	0	0
Infections	4 (5.2)	45 (58.4)	17 (22.1)	1 (1.3)	3 (3.9)	70 (90.9)	11.48
Hepatitis B reactivation[a]	1 (1.3)	0	0	0	0	1 (1.3)	--
Anemia	1 (1.3)	3 (3.9)	7 (9.1)	0	0	11 (14.3)	0.54
Neutropenia	0	2 (2.6)	6 (7.8)	6 (7.8)	0	14 (18.2)	0.73
Thrombocytopenia	3 (3.9)	2 (2.6)	1 (1.3)	0	0	6 (7.8)	0.28

AEI, adverse events of interest; EAIR, exposure adjusted incience rate.
[a]EAIR– not calculated.

Legend to Figures

Figure 1. Best overall response by *MYD88/CXCR4* genotype. For efficacy-evaluable patients with tumors harboring the *MYD88*^{L265P} mutation, best response is reported separately for those with *CXCR4*^{WT} disease and those with an accompanying *CXCR4*^{WHIM} mutation. No genotype data were available for 8 patients, and for an additional 7 patients with *MYD88*^{L265P} disease, the *CXCR4* genotype is unknown (*CXCR4*^{UNK}).

Figure 2. Waterfall plot of maximal percentage of IgM reductions and corresponding best overall response. Patients included are those who received ≥ 1 dose of zanubrutinib, had no prior BTK inhibitor exposure, and had baseline IgM or M-paraprotein ≥5 g/L. Only patients with data at both baseline and any postbaseline visits are included. If the nephelometric IgM test result was missing at baseline, the M-paraprotein result by serum protein electrophoresis was used throughout and summarized together with nephelometric IgM test results for this endpoint.

Figure 3. **Kaplan-Meier plots of progression-free survival for treatment-naïve (A) and relapsed/refractory (B) patients**. Gray areas indicate 95% CIs.

Figure 1.

	MYD88^{L265P}/ *CXCR4*^{WT} (n=39)	MYD88^{L265P}/ *CXCR4*^{WHIM} (n=11)	MYD88^{L265P}/ *CXCR4*^{UNK} (n=7)	*MYD88*^{WT} (n=8)
ORR	38 (97%)	11 (100%)	6 (86%)	8 (100%)
MRR	34 (87%)	10 (91%)	5 (71%)	5 (63%)
VGPR/CR	23 (59%)	3 (27%)	2 (29%)	2 (25%)

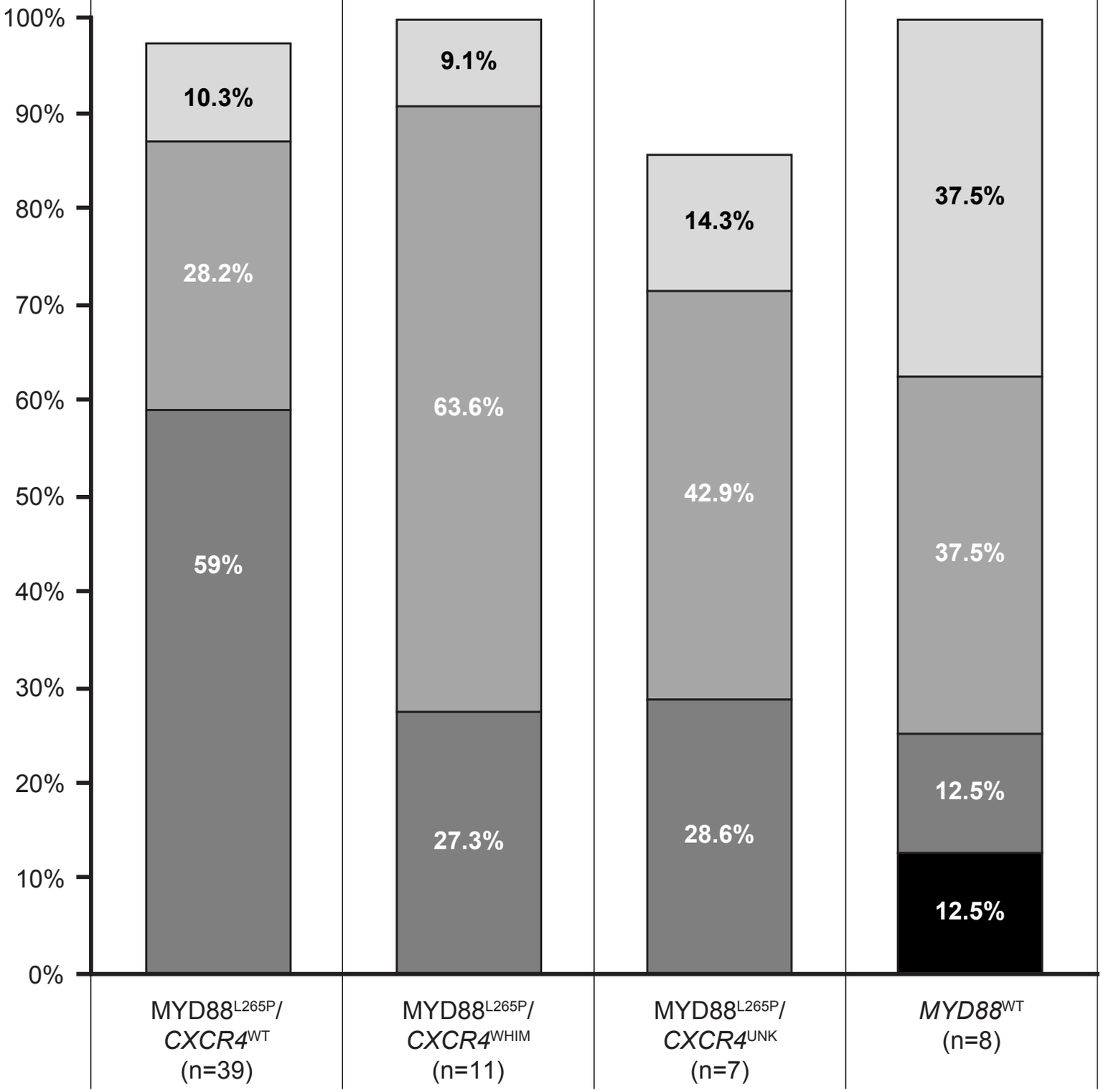

Figure 2.

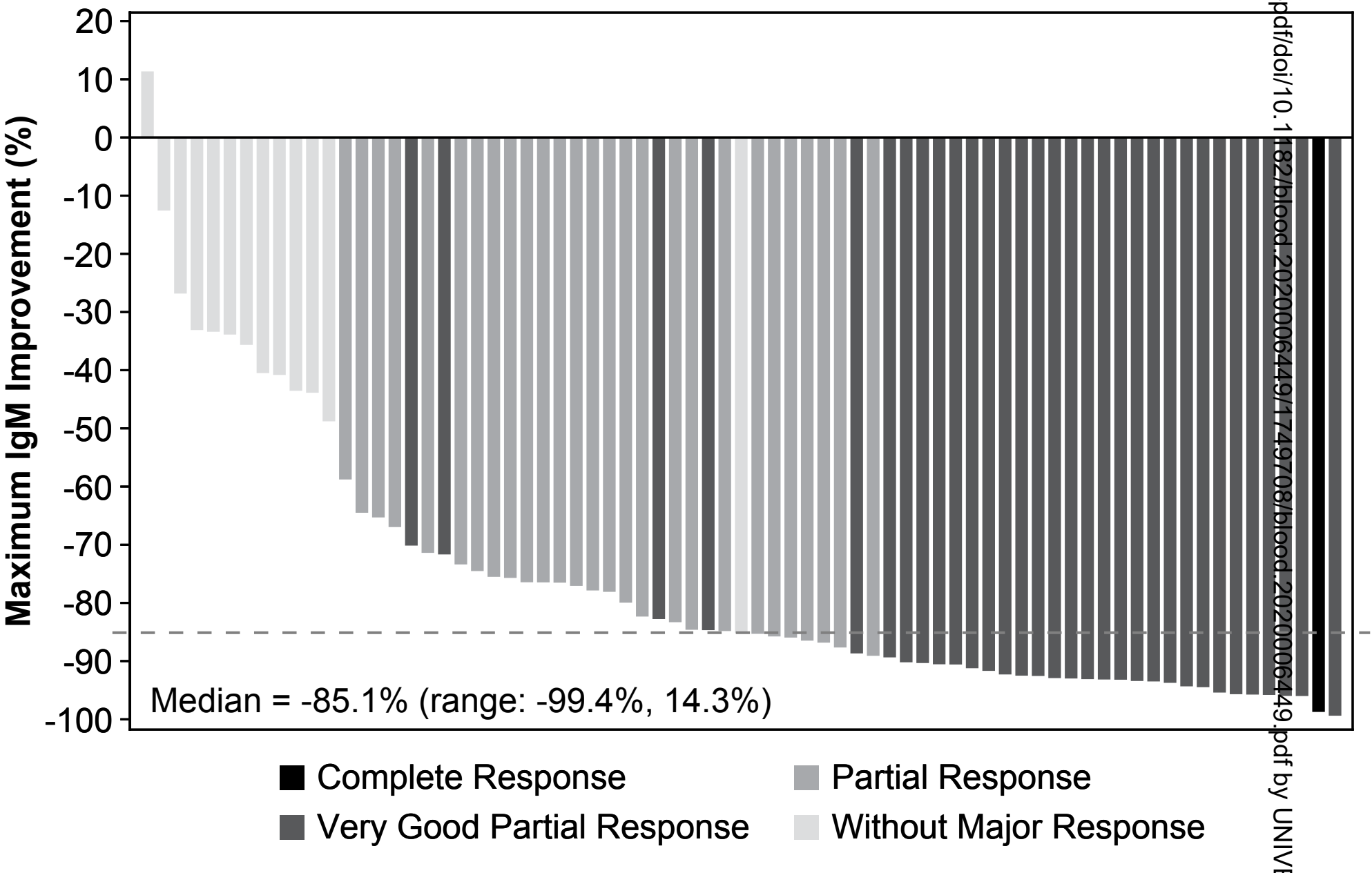

Figure 3.