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A RANDOMIZED PHASE 3 TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB IN SYMPTOMATIC WALDENSTRÖM MACROGLOBULINEMIA:THE ASPEN STUDY

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Abstract:
Bruton tyrosine kinase (BTK) inhibition is an effective treatment approach for patients with Waldenström macroglobulinemia (WM). The phase 3 ASPEN study compared the efficacy and safety of ibrutinib, a first-generation BTK inhibitor, with zanubrutinib, a novel, highly selective BTK inhibitor, in patients with WM. Patients with *MYD88*^{L265P} disease were randomly assigned 1:1 to treatment with either ibrutinib or zanubrutinib. The primary endpoint was the proportion of patients achieving a complete or very good partial response (CR or VGPR) by independent review. Key secondary endpoints included major response rate (MRR), progression-free survival (PFS), duration of response (DOR), disease burden, and safety. A total of 201 patients were randomized, and 199 received {greater than or equal to}1 dose of study treatment. No patient achieved a CR. Twenty-nine (28%) zanubrutinib and 19 (19%) ibrutinib patients achieved a VGPR, a non-statistically significant difference (P = .09). MRRs were 77% and 78% , respectively. Median DOR and PFS were not reached; 84% and 85% of ibrutinib and zanubrutinib patients were progression-free at 18 months. Incidence of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were all lower among zanubrutinib recipients. Incidence of neutropenia was higher with zanubrutinib, although grade {greater than or equal to}3 infection rates were similar in both arms (1.2 and 1.1 events/100 person-months). These results demonstrate that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality and less toxicity, particularly cardiovascular toxicity.

Conflict of interest: COI declared - see note

COI notes: C.S.T. receives research funding from Janssen and AbbVie and receives honoraria from Janssen, AbbVie, BeiGene, Novartis, 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. S.D. participates in a speakers bureau for Amgen; receives research funding from Janssen, BeiGene and travel expenses from Janssen. W.J. consults for Astra Zeneca, Debiopharm, Janssen, Gilead, and Roche; receives research funding from Acerta, Astra Zeneca, Janssen, BeiGene, Bayer, Celrtion, Debiopharm, Epizyme, Merck, Morphosys, MEI Pharma, Servier, Roche, and TG Therapeutics. H-P.L. has equity ownership in CSL; receives honoraria from Roche and receives travel expenses from AbbVie. G.C. receives research funding from BeiGene, Acerta, Glycomimetics. R.G.O. receives honoraria from Janssen and Celgene; consults for and receives travel expenses from Janssen. P.M. has nothing to

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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: constantine.tam@petermac.org.

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Key Points (140 char limit each incl spaces):

- While not statistically significant, a higher rate of CR/VGPR was observed for zanubrutinib versus ibrutinib (28% and 19%, respectively).
- The incidence and severity of most BTK-associated toxicities (including atrial fibrillation) were lower with zanubrutinib than ibrutinib.

Abstract (248/250 words):

Bruton tyrosine kinase (BTK) inhibition is an effective treatment approach for patients with Waldenström macroglobulinemia (WM). The phase 3 ASPEN study compared the efficacy and safety of ibrutinib, a first-generation BTK inhibitor, with zanubrutinib, a novel, highly selective BTK inhibitor, in patients with WM. Patients with *MYD88*^{L265P} disease were randomly assigned 1:1 to treatment with either ibrutinib or zanubrutinib. The primary endpoint was the proportion of patients achieving a complete or very good partial response (CR or VGPR) by independent review. Key secondary endpoints included major response rate (MRR), progression-free survival (PFS), duration of response (DOR), disease burden, and safety. A total of 201 patients were randomized, and 199 received ≥1 dose of study treatment. No patient achieved a CR. Twenty-nine (28%) zanubrutinib and 19 (19%) ibrutinib patients achieved a VGPR, a non-statistically significant difference (P = .09). MRRs were 77% and 78% , respectively. Median DOR and PFS were not reached; 84% and 85% of ibrutinib and zanubrutinib patients were progression-free at 18 months. Incidence of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were all lower among zanubrutinib recipients. Incidence of neutropenia was higher with zanubrutinib, although grade ≥3 infection rates were similar in both arms (1.2 and 1.1 events/100 person-months). These results demonstrate that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality and less toxicity, particularly cardiovascular toxicity.

Introduction

Waldenström macroglobulinemia (WM) is a B-cell malignancy, characterized by bone marrow infiltration with monoclonal, immunoglobulin M (IgM) secreting, lymphoplasmacytic cells that exhibit constitutive activation of the B-cell receptor signaling complex, of which Bruton tyrosine kinase (BTK) is a critical component.[1,2] In addition, the pathogenetic role of somatic mutations in myeloid differentiation factor 88 (MYD88) and chemokine receptor 4 (*CXCR4*) has been extensively characterized.[3-7] MYD88, a component of interleukin-1 and toll-like receptor signaling complexes, is mutated in >90% of patients with WM.[8] Studies have shown that hematopoietic cell kinase is activated in *MYD88*^{L265P} cells and can transactivate BTK, contributing additional prosurvival signals.[9] Mutations in CXCR4 lead to constitutive CXCR4 signaling and are seen in 30%-35% of patients with WM.[10]

Ibrutinib, a first-generation BTK inhibitor, has emerged as a standard of care for patients with WM. In a Phase 2 study of 63 patients with relapsed/refractory (R/R) WM, 73% of patients achieved a major response (≥partial response [PR]) and estimated 2-year progression-free survival (PFS) was 69%.[10] With longer treatment (median 47 months), the major response rate (MRR) increased to 78%, including 27% of patients with very good PR (VGPR); median progression-free survival (PFS) was >5 years.[11] In a companion study of 30 treatment-naive (TN) patients, MRR was 83%, including 20% with VGPR, after a median treatment duration of 13.4 months.[8] Although effective, ibrutinib treatment is associated with frequent toxicities.[12] In a retrospective review of 112 ibrutinib-treated patients with WM (treatment durations ≤43 months), 11% experienced atrial fibrillation.[13] Grade ≥3 atrial fibrillation and hypertension were reported by 12% and 13% of patients treated with ibrutinib + rituximab, respectively, with median ibrutinib treatment duration of 26 months.[14] Inhibition of off-target kinases may explain

many ibrutinib-associated toxicities, including diarrhea, hypertension, muscle spasms, bleeding, and atrial fibrillation.[12,15-20]

Zanubrutinib is a novel, potent BTK inhibitor that exhibits less off-target inhibition than ibrutinib. In a Phase 1/2 study of patients with B-cell malignancies, 45% of 73 patients with WM achieved a VGPR or complete response (CR) and 82% achieved a major response after a median follow-up of 32.7 months. Treatment was generally well-tolerated with atrial fibrillation, major hemorrhage, and grade ≥3 diarrhea reported in 5%, 4%, and 3% of patients, respectively.[21]

Based on promising activity and the potential for less off-target toxicity than first-generation BTK inhibitors, this Phase 3 trial was designed to directly compare safety and efficacy of ibrutinib versus zanubrutinib in patients with WM (NCT03053440).

Methods

Study design and treatments

BGB-3111-302 (ASPEN) is a randomized, open-label, Phase 3 study comparing ibrutinib and zanubrutinib in patients with WM who required treatment based on consensus criteria.[22] Patients with *MYD88*^{L265P} disease were assigned 1:1 to receive ibrutinib at the approved dose of 420 mg once daily or zanubrutinib 160 mg twice daily in 28-day cycles until progression or intolerance (Cohort 1). Randomization was stratified by *CXCR4*^{WHIM} mutation status and number of prior lines of therapy. Patients with *MYD88*^{WT} disease or with undetermined *MYD88* mutation status were enrolled in Cohort 2 and received zanubrutinib on a third non-randomized arm. Treatment modifications are outlined in **Supplemental Table 1** for zanubrutinib and followed local prescribing information for ibrutinib. Treatment interruption for ≤2 consecutive cycles and ≤2 dose reductions were permitted for management of recurring, grade 3/4, treatment-related

toxicities. Crossover at progression or due to intolerance in Cohort 1 was not permitted. Results from Cohort 2 will be reported separately.

Trial oversight and conduct

The trial was approved by the institutional review board or independent ethics committee at each study site and conducted in accordance with applicable regulatory requirements, the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent.

Patients

Eligible patients had R/R WM after ≥1 prior line of therapy or TN WM unsuitable for standard immunochemotherapy based on the presence of documented comorbidities or risk factors (**Supplemental Table 2**). Patients were required to have measurable disease, adequate end-organ function, and absolute neutrophil and platelet counts of 0.75 and 50 x 10^9/L, respectively. Patients with prior BTK-inhibitor exposure, disease transformation, active central nervous system (CNS) lymphoma, clinically significant cardiovascular disease, or who required warfarin or another vitamin K antagonist were excluded.

Assessments

Bone marrow aspiration and biopsy were collected at baseline, Week 48, and as clinically indicated thereafter (including for confirmation of CR). Baseline bone marrow samples were assayed for *MYD88* and *CXCR4* mutations prior to cohort assignment (**Supplemental methods)**. Quantitative serum immunoglobulins (IgM, IgG, IgA), M-paraprotein, and β_2-microglobulin levels were measured at baseline, the beginning of each cycle until cycle 12, and every 3 cycles thereafter. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging scans

were performed at baseline; patients with extramedullary disease underwent follow-up scans every 3 cycles until Cycle 12 and every 6 cycles thereafter until progression. Electrocardiograms (ECGs) were performed on Day 1 of Cycles 1 and 2, every 4 cycles thereafter, and at end of treatment. Quality-of-life (QoL) assessments (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the European Quality of Life Five Dimensions Questionnaire [EQ-5D]) were collected at baseline, every 3 cycles until Cycle 12, and every 6 cycles thereafter.

Outcomes

The primary endpoint was the proportion of patients in Cohort 1 who achieved a VGPR or CR as assessed by independent review (IRC; PAREXEL Informatics, Waltham, MA) based on the 6th International Workshop on Waldenström Macroglobulinemia (IWWM) consensus criteria.[23] Criteria that define each response category (assessed every 28 days and every 84 days after Cycle 12) are listed in **Supplemental Table 3**. Secondary endpoints included IRC-assessed MRR, duration of response (DOR; time from initial qualifying response until progression or death), and PFS (time from randomization until progression or death), investigator-assessed efficacy outcomes, reductions in bone marrow and extramedullary tumor burden, and safety. Overall survival (OS) and changes in QoL were exploratory endpoints. Adverse event (AE) assessments (including adverse events of interest, **Supplemental Table 4**) included type, incidence, outcomes, and severity of AEs with severity graded according to the National Cancer Institute Common Toxicity Criteria version 4.03.

Statistical analysis

The primary efficacy analysis was planned to occur ~12 months after the last R/R patient was randomized. Comparisons between ibrutinib and zanubrutinib for the primary endpoint in Cohort

1 followed a hierarchical fixed-sequence procedure to adjust for multiplicity. Testing for the CR/VGPR superiority rate of zanubrutinib versus ibrutinib in patients with R/R WM was performed first. If the aforementioned comparison was statistically significant, further testing was to be performed including all randomized Cohort 1 patients (including ~38 TN patients with *MYD88*^{L265P} disease). A Cochran-Mantel-Haenszel (CMH) test for difference in CR/VGPR rates was performed for both comparisons with the magnitude of difference estimated as the weighted average across the randomization stratification factors, age groups (≤65 versus >65 years), and the corresponding 2-sided, 95% confidence intervals (CIs).[24,25] Superiority was to be declared if the 2-sided *P* value from the CMH test was <0.05 and the estimated difference was positive. Statistical significance for the first or both response comparisons was to trigger a test of non-inferiority in MRRs between zanubrutinib and ibrutinib, using the estimated difference and its 95% CIs. Non-inferiority would be declared if the lower limit of the 95% CI for the estimated difference in MRRs between zanubrutinib and ibrutinib excluded the pre-specified margin for non-inferiority, -8%. If the lower limit of the 95% CI excluded 0%, superiority of zanubrutinib in MRR would be declared. A total of 150 R/R patients randomized 1:1 in Cohort 1 would provide 81.4% power to demonstrate superiority under an assumed CR/VGPR rate of 35% for zanubrutinib versus 15% for ibrutinib, using a normal approximation of a binomial test and a 2-sided alpha of 0.05. Non-inferiority was powered to 85.5% under assumed MRRs of 90% and 80% for zanubrutinib and ibrutinib, respectively, and a non-inferiority margin of 0.08.

Reductions of IgM levels from baseline were assessed with both parametric and non-parametric methods. A likelihood-based, repeated-measures mixed model was used to estimate the slopes of IgM reduction from baseline and to compare the estimated slopes between arms. IgM reduction was also summarized as area under the [IgM] x time curve (AUC) with the

treatment arm difference tested using the Mantel-Haenszel test. Log-transformed IgM levels were used in both analyses.

PFS by treatment arm was estimated at the time of primary efficacy analysis by Kaplan-Meier (K-M) methodology with censoring.[26] Two-sided, 95% CIs for median PFS were estimated with the Brookmeyer and Crowley method.[27] K-M methodology was used to estimate PFS at selected time points, with corresponding 95% CIs estimated using Greenwood's Formula.[28] Analysis methods for DOR were similar to those for PFS. Follow-up for PFS and DOR was estimated using the reverse K-M method. Rates of CR/VGPR for selected subgroups defined by pre-specified characteristics were summarized for each treatment arm in a forest plot. Crude incidence rates for all AEs and exposure-adjusted incidence rates for AEs of interest (AEI) included all Cohort 1 patients who received any dose of ibrutinib or zanubrutinib and were summarized using descriptive statistics. The distribution of times to first occurrence of AEIs was summarized using K-M methodology.

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: constantine.tam@petermac.org.

Results

Patient characteristics and disposition

Between January 2017 and July 2018, 164 R/R and 37 TN patients with WM from 58 study sites were enrolled in Cohort 1. Two R/R patients were randomized but never dosed (1

ibrutinib patient had CNS lymphoma identified prior to dosing, and 1 zanubrutinib patient had acute kidney injury; **Figure 1**). Most common (>20%) indications for therapy initiation were fatigue, anemia, B-symptoms, hyperviscosity, and peripheral neuropathy (**Supplemental Table 5**). Treatment arms were generally balanced for key baseline characteristics however, more patients randomized to zanubrutinib than ibrutinib were >75 years old (33% versus 22%, respectively) and more were anemic (hemoglobin ≤110 g/L in 66% versus 54% of patients, respectively; **Table 1**). Overall, 8% and 11% of ibrutinib and zanubrutinib patients had a *CXCR4*^{WHIM} mutation. Approximately 85% were in the intermediate or high-risk prognostic category[29] and 77% had CT evidence of extramedullary disease. Most R/R patients (>90%) received 1–3 prior lines of therapy with a median of 1 in each arm; over 90% and 85% had at least 1 prior exposure to anti-CD20 and alkylator therapy, respectively (**Supplemental Table 6**). Eight (8%) and 11 (10%) ibrutinib and zanubrutinib patients had a history of atrial fibrillation or flutter; 43% and 38% reported a history of hypertension, respectively. At a median follow-up of 19.4 months, 79% of patients remained on study treatment and 89% remained on study.

Responses

No patient achieved a CR. Frequency of IRC-assessed VGPRs was higher among zanubrutinib than ibrutinib patients (28% and 19%, respectively, 2-sided $P = .09$), a trend observed among both R/R (29% versus 20%; $P = .12$) and TN (26% versus 17%; $P = .54$) patients (**Table 2**). Investigator-assessed rates of VGPR were 28% and 17% in the zanubutinib and ibrutinib arms, respectively ($P = .04$). Concordance rates between IRC- and investigator-assessed best responses were 94% and 95% for zanubrutinib and ibrutinib arms. IRC-assessed best responses based on reductions in serum IgM alone and those based on the 6th IWWM consensus guidelines were concordant in 92% and 95%, respectively. The rates of VGPR were

mostly comparable between the arms for prognostically important subgroups (eg, intermediate- or high-risk, based on the International Prognostic Scoring System [IPSS]; age >65 years; hemoglobin ≤110g/L; platelet count ≤100 x 10^9/L; and β2-microglobulin >3 mg/dL) (**Figure 2**). MRR among zanubrutinib and ibrutinib patients were 77% and 78% overall, 78% and 80% among R/R and 74% and 67% among TN patients, respectively. The non-inferiority hypothesis for MRR difference was not tested due to the lack of statistically-significant superiority of CR/VGPR rates for zanubrutinib.

One patient in each arm with a *CXCR4*^{WHIM} mutation achieved a VGPR; 18 (20%) ibrutinib- and 28 (31%) zanubrutinib-treated patients with *CXCR*^{WT} disease achieved a VGPR. MRRs for *CXCR*^{WHIM} and *CXCR4*^{WT} patient subsets were comparable across treatment arms (63% versus 64% and 80% versus 79%, respectively). Median times to achieve a VGPR were skewed in favor of zanubrutinib, owing to the large difference observed for TN patients (5.6 and 22.1 months with zanubrutinib and ibrutinib; P = .35). However, among R/R patients, these were comparable at 4.7 and 5.1 months (P = .17), respectively. Median time to major response for both arms was 2.8 months, with little difference in either R/R or TN subsets or among patients with *CXCR4*^{WT} disease; the median times to major response for ibrutinib and zanubrutinib patients with *CXCR4*^{WHIM} mutations were 6.6 and 3.1 months, respectively. Median DOR has not been reached in either treatment arm (**Table 2, Figure 3B, Figure 3C**). One zanubrutinib and 4 ibrutinib patients who achieved a VGPR progressed as of August 31, 2019. The 18-month event-free rates for major responders were similar in the zanubrutinib and ibrutinib arms (85% and 88% overall, and 87% and 86% for R/R patients, respectively) (**Table 2**).

Progression-free and overall survival

After median follow-up for PFS of 18.0 and 18.5 months, 15 (15%) zanubrutinib and 16 (16%) ibrutinib patients progressed or died. Median PFS was not reached for either arm. Event-free rates at 18 months were comparable at 85% and 84% overall (86% and 82% for R/R patients) (**Table 2, Figure 3A**). Six (3 R/R; 3 TN) zanubrutinib and 8 (8 R/R; 0 TN) ibrutinib patients died; estimated OS rates at 18 months were 97% and 93%, respectively.

IgM and hemoglobin levels

Median IgM levels were reduced by 79% (Q1–Q3: 88–63) and 72% (Q1–Q3: 86–58) for zanubrutinib and ibrutinib patients, respectively (**Supplemental Figure 1A**). Zanubrutinib demonstrated significantly greater and more sustained reductions of IgM by both the repeated-measures mixed-effect model (P = .03) and AUC (P = .04) comparisons (**Supplemental Table 7**). Most patients in both arms were anemic at baseline (**Table 1**). Median baseline hemoglobin concentrations were 103 (Q1–Q3: 91–116) and 109 (Q1–Q3: 94–122) g/L for zanubrutinib and ibrutinib patients, respectively. Rapid increases in hemoglobin concentrations were noted in both arms through Cycle 6, with a plateau observed thereafter (**Supplemental Figure 1B**). Median maximal hemoglobin concentrations increased by 27 (Q1–Q3: 15–46) and 28 (Q1–Q3: 15–43) g/L among zanubrutinib and ibrutinib patients, respectively.

Bone marrow and extramedullary disease

Overall, 69% and 73% of zanubrutinib and ibrutinib patients exhibited reductions in bone marrow infiltration. Median maximal reductions from baseline were 10% (Q1–Q3: 30–0) and 15% (Q1–Q3: 35–0) for zanubrutinib and ibrutinib patients. Reductions in lymph node and/or spleen dimensions were noted in 81% and 80% respectively. Median maximal reductions in the

sum of target lymph node perpendicular diameters were 58% (Q1–Q3: 40–85) and 50% (Q1–Q3: 31–63) for zanubrutinib and ibrutinib patients; median maximal reductions in vertical spleen length among patients with splenomegaly were 27% (Q1–Q3: 24–39) and 24% (Q1–Q3: 5–36), respectively.

Safety and patient reported outcomes

Median treatment durations were comparable in the zanubrutinib (18.7 months) and ibrutinib (18.6 months) treatment arms; 89% and 84% of patients had minimal exposures of 12 months. Median relative dose intensities were 98% in both arms. Median treatment duration for TN patients was 21 months in both arms.

Most common (reported in >20% of patients) AEs among zanubrutinib patients were neutropenia, upper repiratory infection (URI), and diarrhea (**Table 3**). Most common AEs among ibrutinib patients were diarrhea, URI, contusion, and muscle spasms. Atrial fibrillation, diarrhea, contusion, muscle spasms, peripheral edema, and pneumonia were reported at a ≥10% higher incidence among ibrutinib versus zanubrutinib patients; neutropenia was ≥10% higher among zanubrutinib patients. Grade ≥3 AEs were reported in 63% and 58% of ibrutinib and zanubrutinib patients, respectively. Grade ≥3 hypertension and pneumonia were reported at a ≥5% higher incidence among ibrutinib than zanubrutinib patients; grade ≥3 neutropenia was reported at a ≥5% higher incidence among zanubrutinib patients. Overall, 41% and 40% of ibrutinib and zanubrutinib patients, respectively, experienced ≥1 serious AE (**Supplemental Table 8**). Most common serious AEs (ibrutinib versus zanubrutinib) were pneumonia (9 patients versus 1), neutropenia and febrile neutropenia (each 0 versus 3), influenza (1 versus 3), and pyrexia and sepsis (each 3 versus 2). Three deaths (all R/R patients) were attributed to AEs. Two

deaths in ibrutinib patients resulted from complications of sepsis, and 1 zanubrutinib patient died from complications of cardiac arrest post-plasmapheresis.

Infections were common in both arms (**Table 3**). Grade ≥3 infections were similar between arms, although the incidence of pneumonia was higher among ibrutinib patients. One zanubrutinib-treated patient developed cryptococcal sepsis, while 2 ibrutinib-treated patients developed esophageal candidiasis. Two R/R zanubrutinib patients exhibited findings consistent with hepatitis B virus reactivation (1 while taking lamivudine); both were managed with treatment interruption and anti-viral therapy. More ibrutinib- than zanubrutinib-treated patients received anti-infective therapies (83% and 63%, respectively). Exposure-adjusted grade 1/2 bleeding incidence was higher among ibrutinib patients; major hemorrhage was reported in 6 zanubrutinib and 9 ibrutinib patients. Ibrutinib patients experienced ~10-fold higher incidence of atrial fibrillation/flutter and ~2-fold increased frequency of hypertension on an exposure-adjusted basis (**Table 3**). Atrial fibrillation occurred within 6 months of treatment onset in 7 ibrutinib- and 1 zanubrutinib-treated patients; 4 ibrutinib- and no zanubrutinib-treated patients had onset of atrial fibrillation >12 months after treatment onset. Onset of hypertension beyond 12 months also occurred more frequently in the ibrutinib versus zanubrutinib (6 patients versus 1) treatment arm. Zanubrutinib patients experienced >2 times the incidence of any grade (25% versus 12%) and grade ≥3 (20% versus 8%) neutropenia versus ibrutinib patients. More neutropenic patients in the zanubrutinib arm received granulocyte colony-stimulating factor than in the ibrutinib arm (47% versus 31%). Time to event plots for the first occurrence of AEIs by treatment arm are provided in **Figure 4**.

More ibrutinib than zanubrutinib patients required dose reductions for AEs (23% versus 14%, respectively). Nine (9%) ibrutinib patients discontinued study treatment for AEs

(myocardial infarction, bacterial sepsis, sepsis, death, cause unspecified, drug-induced liver injury, hepatitis, interstitial lung disease, pneumonia, and pneumonitis). Four (4%) zanubrutinib patients discontinued study treatment due to AEs (subdural hemorrhage, cardiac arrest, neutropenia, and IgA multiple myeloma).

In most QoL assessments, zanubrutinib trended toward greater improvement, particularly among patients who achieved a VGPR (**Supplemental Figure 2**). This was most notable in EQ-5D and QLQ–C30 subscales of appetite, dyspnea, fatigue, physical functioning, and role functioning. The functional scale for diarrhea trended worse for ibrutinib than zanubrutinib patients, consistent with the frequency of diarrhea reported for each treatment arm.

Discussion

Most studies of BTK-inhibitor therapy in WM have been single-arm trials that have reported variable safety and tolerability owing to differences in study populations, prior treatment history, and the toxicity profiles of individual BTK inhibitors.[8,11,30,31] Here, we report results from the largest randomized, controlled trial of BTK-inhibitor monotherapy in WM to date, and the only study comparing outcomes for two different BTK inhibitors.

This study demonstrated greater frequency of VGPRs among zanubrutinib- than ibrutinib-treated patients after a median follow-up duration of 19.4 months. Phase 2 studies of both ibrutinib and zanubrutinib have demonstrated improved response quality with longer treatment.[10,11,32] A 27% VGPR rate was reported in the Phase 2 ibrutinib study of R/R WM patients after a median treatment duration of almost 4 years.[11] In the Phase 2 zanubrutinib study, 51% of 49 R/R patients achieved a VGPR or CR after a median follow-up of 36 months.[32] Thus, the full potential for zanubrutinib patients to achieve CR/VGPR may not have been fully realized

at the time of this analysis. Longer follow-up will allow an assessment of whether deeper responses correlate with more durable disease control, as has been observed with conventional therapies.[33,34]

One unanticipated outcome of this study was the low proportion of patients with a *CXCR4*^{WHIM} mutation (9% overall) compared with historical series.[10,35] Reasons for this include the use of Sanger sequencing for CXCR4 mutation detection. Since CXCR4 mutation status was a stratification variable, this was deemed the most expedient approach to identifying patients with common *CXCR4*^{WHIM} mutations. A 10%–15% lower limit of mutant allele detection (LLD), the subclonal nature of *CXCR4*^{WHIM} mutations, and the lack of B-cell enrichment likely contributed to an underrepresentation of patients with documented *CXCR4*^{WHIM} mutations at randomization.[36] A post-hoc analysis of baseline bone marrow from 190 (95%) patients using next generation sequencing (NGS) for CXCR4 mutation detection (LLD, 0.25%; see **Supplemental methods**) revealed the presence of *CXCR4*^{WHIM} mutations in 53 (28%) patients. VGPR rates based on NGS data were comparable to those reported in the primary efficacy analysis based on Sanger sequencing, with zanubrutinib demonstrating a higher rate overall (29% and 21% among zanubrutinib and ibrutinib patients, respectively) as well as among *CXCR4*^{WT} (34% and 24% respectively) and *CXCR4*^{WHIM} patients (18% and 10%, respectively), despite an imbalance in the number of patients with *CXCR*^{WHIM} mutations favoring ibrutinib (34% and 22%, respectively) (**Supplemental Table 9**).

Given that IgM overproduction is the hallmark of WM, the ability to reduce IgM provides an additional efficacy metric with which to evaluate BTK inhibitors. In this regard,

results of 2 separate analyses demonstrated significantly deeper and more sustained IgM reductions with zanubrutinib versus ibrutinib.

We observed several clinically significant differences in the safety and tolerability profiles of the 2 BTK inhibitors, likely consistent with the higher degree of selectivity of zanubrutinib for BTK versus off-target kinases. Both atrial fibrillation and hypertension were reported at greater frequency with ibrutinib, compared with zanubrutinib treatment. Atrial fibrillation is a well-recognized complication of ibrutinib therapy, and relative to an age-matched controlled population, patients appear to be at continuously increased risk for development of atrial fibrillation over the course of therapy.[37] Age ≥65 years and history of atrial fibrillation were identified as independent risk factors for atrial fibrillation in a pooled analysis of 4, randomized, controlled studies of ibrutinib.[37] An analysis of this study suggests that the risk for development of atrial fibrillation later in the course of therapy was disproportionately higher with ibrutinib, compared with zanubrutinib. Likewise, ibrutinib treatment has been associated with a significant cumulative risk for the development of hypertension.[38] In this study, the cumulative incidence of hypertension was higher in the ibrutinib treatment arm, with more ibrutinib-treated patients presenting with hypertension later in their treatment course.

In our study, zanubrutinib treatment was associated with less minor bleeding or bruising, as well as fewer major hemorrhages than ibrutinib. The combined effects of tyrosine kinase expressed in hepatocellular carcinoma (TEC) and BTK inhibition in platelets of ibrutinib-treated patients may explain the higher frequency of bleeding noted among ibrutinib patients.[17] Consistent with prior experience, the frequency of diarrhea among zanubrutinib patients in our study was half that reported among ibrutinib patients, on an exposure-adjusted basis (1.3 and 2.6

events/100 person-months, respectively), likely due to less potent inhibition of epidermal growth factor receptor (EGFR) by zanubrutinib.[20]

Grade 3 neutropenia (including febrile neutropenia) was more common among zanubrutinib patients. Since both agents inhibit BTK in neutrophil precursors by similar mechanisms, higher rates of severe neutropenia among zanubrutinib patients may be a function of its greater bioavailability.[20] Importantly, the higher incidence of severe neutropenia did not result in a higher infection incidence when compared with that for ibrutinib. Paradoxically, the incidence of some respiratory tract infections (notably pneumonias) was higher among ibrutinib recipients.

The pharmacokinetic, pharmacodynamic, and selectivity profile of zanubrutinib predicts that it has the potential to be more efficacious with a superior safety profile versus ibrutinib. This study established that zanubrutinib is highly effective in the treatment of WM; zanubrutinib is associated with important safety advantages, especially with respect to cardiovascular toxicity. While the study did not meet its primary endpoint, there was a trend toward better disease control for zanubrutinib versus ibrutinib, including higher rates of VGPR, greater and more sustained IgM reduction, and greater improvement in most QoL measures. Longer follow-up will allow for a more comprehensive assessment of the relative efficacy and safety profiles of zanubrutinib and ibrutinib.

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Author contributions

All author investigators (C.S.T., S.O., S.D'S., W.J., H-P.L., G.C., R.G.O., P.M., B.E.W., R.G.S., H.M., S.M., A.T., J.J.C., J.C., C.F.deL., D.B., E.L., J.M., M.M., T.S., M.T., M.T., M.C.M., C.B., V.L., M.D.) collected data (full list of ASPEN investigators appears in the Supplemental materials). The sponsor confirmed the accuracy of the data and compiled the data for analysis. All the authors contributed to data interpretation, reviewed the manuscript, and made the decision to submit it for publication and vouch for the accuracy and completeness of the data and analyses and adherence to the trial protocol. Together with BeiGene authors (W.Y.C., J.S., S.R., A.C., J.H.), ASPEN study steering committee members (C.S.T., R.G.O., A.T., C.B. and V.L.) were responsible for study design, and with authors M.D., S.D'S., R.G.S, J.C., further contributed to data interpretation and analysis.

Conflict-of-interest disclosure:

C.S.T. receives research funding from Janssen and AbbVie and receives honoraria from Janssen, AbbVie, BeiGene, Novartis, 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. S.D. participates in a speakers bureau for Amgen; receives research funding from Janssen, BeiGene and travel expenses from Janssen.

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Data sharing: 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: constantine.tam@petermac.org.

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Table 1. Baseline demographic and disease characteristics.*

Characteristic	Relapsed/Refractory		Treatment-naive		Overall	
	Ibrutinib (n=81)	Zanubrutinib (n=83)	Ibrutinib (n=18)	Zanubrutinib (n=19)	Ibrutinib (n=99)	Zanubrutinib (n=102)
Median age, years (min, max)	69 (52, 90)	69 (45, 87)	72 (38, 89)	74 (50, 81)	70 (38, 90)	70 (45, 87)
>75 years, n (%)	16 (20)	27 (33)	6 (33)	7 (37)	22 (22)	34 (33)
Male, n (%)	53 (65)	58 (70)	12 (67)	11 (58)	65 (66)	69 (68)
ECOG PS, n (%)						
0/1	76 (94)	78 (94)	16 (89)	18 (95)	92 (93)	96 (94)
2	5 (6)	5 (6)	2 (11)	1 (5)	7 (7)	6 (6)
Prognostic category at study entry[a], n (%)						
Low	12 (15)	16 (19)	1 (6)	1 (5)	13 (13)	17 (17)
Intermediate	34 (42)	30 (36)	8 (44)	8 (42)	42 (42)	38 (37)
High	35 (43)	37 (45)	9 (50)	10 (53)	44 (44)	47 (46)
Median time from initial diagnosis, years (min, max)	5.9 (0.1, 25)	5.3 (0.1, 23)	1.7 (0.1, 17)	0.5 (0.1, 9)	4.9 (0.1, 25)	4.4 (0.1, 23)
Median prior lines of therapy, n (min, max)	1 (1, 6)	1 (1, 8)	0 (0, 0)	0 (0, 0)	1 (0, 6)	1 (0,8)
0, n (%)	0	0	18 (100)	19 (100)	18 (18)	19 (19)
1-3, n (%)	74 (91)	76 (92)	0	0	74 (75)	76 (75)
>3, n (%)	7 (9)	7 (8)	0	0	7 (7)	7 (7)
Prior stem cell transplant, n (%)	1 (1)	3 (4)	0	0	1 (1.0)	3 (2.9)
Median IgM[b], g/L (min, max)	33.4 (2.4, 108)	30.4 (5.8, 73)	36.8 (9.9, 100)	35.7 (8.1, 87)	34.2 (2.4, 108)	31.8(5.8, 87)
≥40 g/L, n (%)	30 (37)	288 (34)	8 (44)	8 (42)	38 (38)	36 (35)
<40 g/L, n (%)	50 (62)	55 (66)	10 (56)	11 (58)	60 (61)	66 (65)
Missing, n (%)	1 (1)	0	0	0	1 (1.0)	0
Median β-2 microglobulin, mg/L (min, max)	4.2 (1.7, 13.6)	4.1 (1.6, 21.7)	4.1 (1.8, 10.3)	4.7 (2.1, 12.1)	4.2 (1.7, 13.6)	4.3 (1.6, 21.7)
>3 mg/L, n (%)	60 (74)	62 (75)	14 (78)	13 (68)	74 (75)	75 (74)
MYD88[c]/CXCR4 genotype, n (%)						
MYD88^{L265P} */ CXCR4*^{WT}	73 (90)	73 (88)	17 (94)	18 (95)	90 (91)	91 (89)
MYD88^{L265P} */ CXCR4*^{WHIM}	8 (10)	10 (12)	0 (0)	1 (5)	8 (8)	11 (11)
MYD88^{L265P} */ CXCR4*$^{UNK\ d}$	0	0	1 (6)	0	1 (1.0)	0
Bone marrow involvement, n (%)	72 (89)	77 (93)	17 (94)	19 (100)	89 (90)	96 (94)
Median percent tumor cells, % (min, max)	60 (0, 90)	60 (0, 90)	70 (8, 90)	70 (10, 90)	60 (0, 90)	60 (0, 90)
Extramedullary disease[e], n (%)	58 (72)	64 (77)	15 (83)	17 (90)	73 (74)	81 (79)
Lymphadenopathy	53 (65)	63 (76)	14 (78)	16 (84)	67 (68)	79 (78)
Splenomegaly	10 (12)	14 (17)	3 (17)	3 (16)	13 (13)	17 (17)

Other[f]	3 (4)	0	0	1 (5)	1 (1)	4 (2)
Peripheral blood cytopenias						
Hemoglobin ≤110 g/L, n (%)	43 (53)	51 (61)	10 (56)	16 (84)	53 (54)	67 (66)
Platelet count ≤100 x 10^9/L, n (%)	12 (15)	10 (12)	0	2 (11)	12 (12)	12 (12)
Absolute neutrophil count ≤1.5 x 10^9/L, n (%)	7 (9)	8 (10)	0	3 (16)	7 (7)	11 (11)

* Percentages may not total 100 due to rounding.

[a] Patients were assigned 1 point for each of the following baseline characteristics: age >65 years; hemoglobin ≤11.5 g/dL; platelet count ≤100 x 10^9/L; β-2 microglobulin level >3 mg/L; and M paraprotein levels >7.0 g/dL. Patients with a score of 0 or 1 (excepting age) were assigned to the low risk category, those >65 years old or a score of 2, were assigned to the intermediate risk category and those with a score of ≥3 were assigned to the high risk category (Morel P et al. *Blood* 2009;113:4163-4170). M-paraprotein levels were quantitated by serum protein electrophoresis.

[b] Central laboratory nephelometric assessments.

[c] Three patients (all zanubrutinib-treated and all treatment-naive [TN]) had 2nd missense mutations detected within the toll/IL-1 receptor (TIR) binding domain of MYD88: M232T, V217F, and P182L. Additional mutations were identified in non-TIR binding domains in 4 patients: D165del (relapsed/refractory [R/R] zanubrutinib patient); W91ter, G93ter (R/R ibrutinib patient); L72M (RR zanubrutinib patient); and T107S, fs24ter (TN, zanubrutinib patient). See **Supplemental methods** for the specific *CXCR4*^{WHIM} mutations detected.

[d] Mutation testing using a next-generation sequencing method performed in a local laboratory revealed the presence of *MYD88* ^{L265P} in baseline bone marrow aspirate.

[e] Based on imaging studies, as assessed by independent review. Lymphadenopathy was defined as the presence of one or more lymph nodes with a long axis of more than 1.5 cm or a short axis of more than 1.0 cm. Splenomegaly was defined as a spleen length (cranial to caudal) of more than 13 cm.

[f] 3 patients had discrete extranodal splenic lesions; 1 patient had 2 breast lesions.

Abbreviations: CXCR4, chemokine receptor 4; ECOG PS, Eastern Cooperative Oncology Group performance status; MYD88, myeloid differentiation primary response protein 88; WHIM, warts, hypogammaglobulinemia, infections, myelokathexsis.

Table 2. IRC-assessed efficacy outcomes.

	Relapsed/Refractory		Treatment-naive		Overall	
	Ibrutinib (n=81)	**Zanubrutinib (n=83)**	**Ibrutinib (n=18)**	**Zanubrutinib (n=19)**	**Ibrutinib (n=99)**	**Zanubrutinib (n=102)**
Best overall response, n (%)						
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VGPR	16 (20)	24 (29)	3 (17)	5 (26)	19 (19)	29 (28)
PR	49 (61)	41 (49)	9 (50)	9 (47)	58 (59)	50 (49)
MR	11 (14)	13 (16)	4 (22)	4 (21)	15 (15)	17 (17)
SD	2 (3)	3 (4)	1 (6)	0 (0)	3 (3)	3 (3)
PD	2 (3)	1 (1)	0 (0)	1 (5)	2 (2)	2 (2)
Not evaluable[a]	1 (1)	1 (6)	1 (1)	0 (0)	2 (2)	1 (1)
Response rates, % (95% CI[b])						
VGPR or CR	20 (12–30)	29 (20–40)	17 (4–41)	26 (9–51)	19[c] (12–28)	28 (20–38)
P	.12		--		.09	
MRR	80 (70–88)	78 (68–87)	67 (41–87)	74 (49–91)	78 (68–86)	77 (68–85)
ORR	94 (86–98)	94 (87–98)	89 (65–99)	95 (74–100)	93 (86–97)	94 (88–98)
Duration of CR/VGPR, months						
Median (range)	NE (1, 21+)	NE (0+, 19+)	NE (0+, 3+)	NE (0+, 22+)	NE (0+, 21+)	NE (0+, 22+)
18-mo event-free rate, % (95% CI)[d]	64 (29–85)	90 (47–99)	NE (NE, NE)	100 (NE, NE)	64 (29–85)	93 (59–99)
Duration of major response, months						
Median (range)	NE (0+, 26+)	NE (0+, 25+)	NE (3+, 28+)	NE (0+, 25+)	NE (0+, 28+)	NE (0+, 25+)
18-mo event-free rate, % (95% CI)[d]	86 (73–93)	87 (73–94)	100 (NE, NE)	80 (39–95)	88 (77–94)	85 (72–93)
Progression-free survival, months						
Median (range)	NE (0, 28+)	NE (0+, 28+)	NE (0+, 31+)	NE (1, 31+)	NE (0+, 31+)	NE (0+, 31+)
18-mo event-free rate, % (95% CI)[d]	82 (71–89)	86 (74–93)	94 (63–99)	78 (52–91)	84 (75–90)	85 (75–91)

Percentages are based on N, the number of randomized patients.

[a]Not evaluable includes patients with unknown response, disease flare, and study discontinuation prior to first disease assessment.

[b]95% CIs estimated using the Clopper-Pearson method.

[c] Two R/R, ibrutinib-treated patients assessed as having VGPRs by independent review were assigned a best response of PR and MR by their investigators.

[d]Event-free rates were estimated by Kaplan-Meier methodology with 95% CIs estimated using Greenwood's formula.

Abbreviations: CI, confidence interval; CR, complete response; mo, month; IRC, independent review committee; MR, minimal response; MRR, major response rate; NE, not estimable; ORR, overall response rate; PD progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response. "+" indicates censored observations.

Table 3. Treatment-emergent adverse events[a]

	Ibrutinib (n=98)		Zanubrutinib (n=101)	
Event term, n (%)	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Non-hematologic AEs				
Diarrhea	31 (32)	1 (1)	21 (21)	3 (3)
Upper respiratory tract infection	28 (29)	1 (1)	24 (24)	0
Contusion	23 (24)	0	13 (13)	0
Muscle spasms	23 (24)	1 (1)	10 (10)	0
Epistaxis	19 (19)	0	13 (13)	0
Peripheral edema	19 (19)	0	9 (9)	0
Cough	17 (17)	0	13 (13)	0
Rash	16 (16)	0	13 (13)	0
Hypertension	16 (16)	11 (11)	11 (11)	6 (6)
Arthralgia	16 (16)	0	13 (13)	3 (3)
Fatigue	15 (15)	1 (1)	19 (19)	1 (1)
Atrial fibrillation/flutter	15 (15)	4 (4)	2 (2)	0
Nausea	13 (13)	1 (1)	15 (15)	0
Vomiting	13 (13)	1 (1)	9 (9)	0
Pyrexia	12 (12)	2 (2)	13 (13)	2 (2)
Pneumonia	12 (12)	7 (7)	2 (2)	1 (1)
Headache	11 (11)	1 (1)	15 (15)	1 (1)
Urinary tract infection	10 (10)	2 (2)	10 (10)	0
Hematuria	10 (10)	2 (2)	7 (7)	0
Dizziness	9 (9)	0	13 (13)	0
Constipation	7 (7)	0	16 (16)	0
Nasopharyngitis	7 (7)	0	11 (11)	0
Extremity pain	7 (7)	0	11 (11)	1 (1)
Back pain	6 (6)	0	14 (14)	4 (4)
Dyspnea	6 (6)	0	14 (14)	0
Hematologic AEs				
Neutropenia	13 (13)	8 (8)[b]	29 (29)	19 (20)[b]
Febrile neutropenia	0	0	4 (4)	4 (4)
Thrombocytopenia	10 (10)	3 (3)	10 (10)	6 (6)
Anemia	10 (10)	5 (5)	12 (12)	5 (5)
Adverse events of interest, events/100 person-month[c]	**Ibrutinib**		**Zanubrutinib**	
	All grade	**Grade ≥3**	**All grade**	**Grade ≥3**
Infections	8.3	1.2	7.9	1.1
Opportunistic infections	0.1	0	0.1	0.1
Bleeding	7.0	0.5	4.4	0.3
Major hemorrhage	0.6	0.5	0.3	0.3
Hypertension	1.2	0.8	0.7	0.3
Atrial fibrillation/flutter	1.0	0.2	0.1	0
Neutropenia	0.9	0.5	2.1	1.3
Thrombocytopenia	0.8	0.2	0.6	0.3
Second primary malignancies	0.7	0.1	0.7	0.1
Skin cancers	0.6	0	0.5	0
Anemia	0.6	0.3	0.7	0.3
Tumor lysis syndrome	0	0	0	0

[a]Data are for treatment-emergent adverse events in all Cohort 1 patients. Listed events were reported in ≥10% of

patients (all grade) or for grade ≥3, in ≥ 5% in either arm. Events are listed in descending order or frequency by all-grade incidence in the ibrutinib arm. **Bolded** events are those for which the difference in all-grade incidence between arms is ≥10%. *P* = .05, 0.005 and .02 for comparisons of all-grade diarrhea, muscle spasms, and peripheral edema, respectively. *P* = .0004 and .02 for the comparisons of all-grade and grade ≥3 atrial fibrillation, and .002 and .02 for all-grade and grade ≥3 pneumonia, respectively. All *P*-statistics (1-sided, testing ibrutinib > zanubrutinib event rates) are calculated using Barnard's exact test without adjustment for multiplicity.

[b]Includes the Medical Dictionary for Regulatory Activities (MedDRA)-preferred term "neutrophil count decreased" in 1 and 4 patients in the ibrutinib and zanubrutinib arms, respectively.

[c] *P* = .08, .001, and .009 for the comparisons of all-grade bleeding, atrial fibrillation, and neutropenia, respectively. *P* = .05 and .03 for the comparisons of grade ≥3 atrial fibrillation and neutropenia, respectively. All *P*-statistics are two-sided without adjustment for multiplicity [39]

Figure Legends:

Figure 1. BGB-3111-302 (ASPEN) patient disposition.

Figure 2. Forest plot of subgroup differences in the rate of CR/VGPR.

Figure 3. Kaplan-Meier curves for (A) progression-free survival (HR, 0.85 [95% CI, 0.43–1.76]; *P* = .69), (B) major response, and (C) duration of VGPR. All Kaplan-Meier distributions are based on IRC-assessed responses for both relapsed/refractory and treatment-naive patients in each respective arm.

Figure 4. Time-to-event analyses for adverse events of interest.

Figure 1

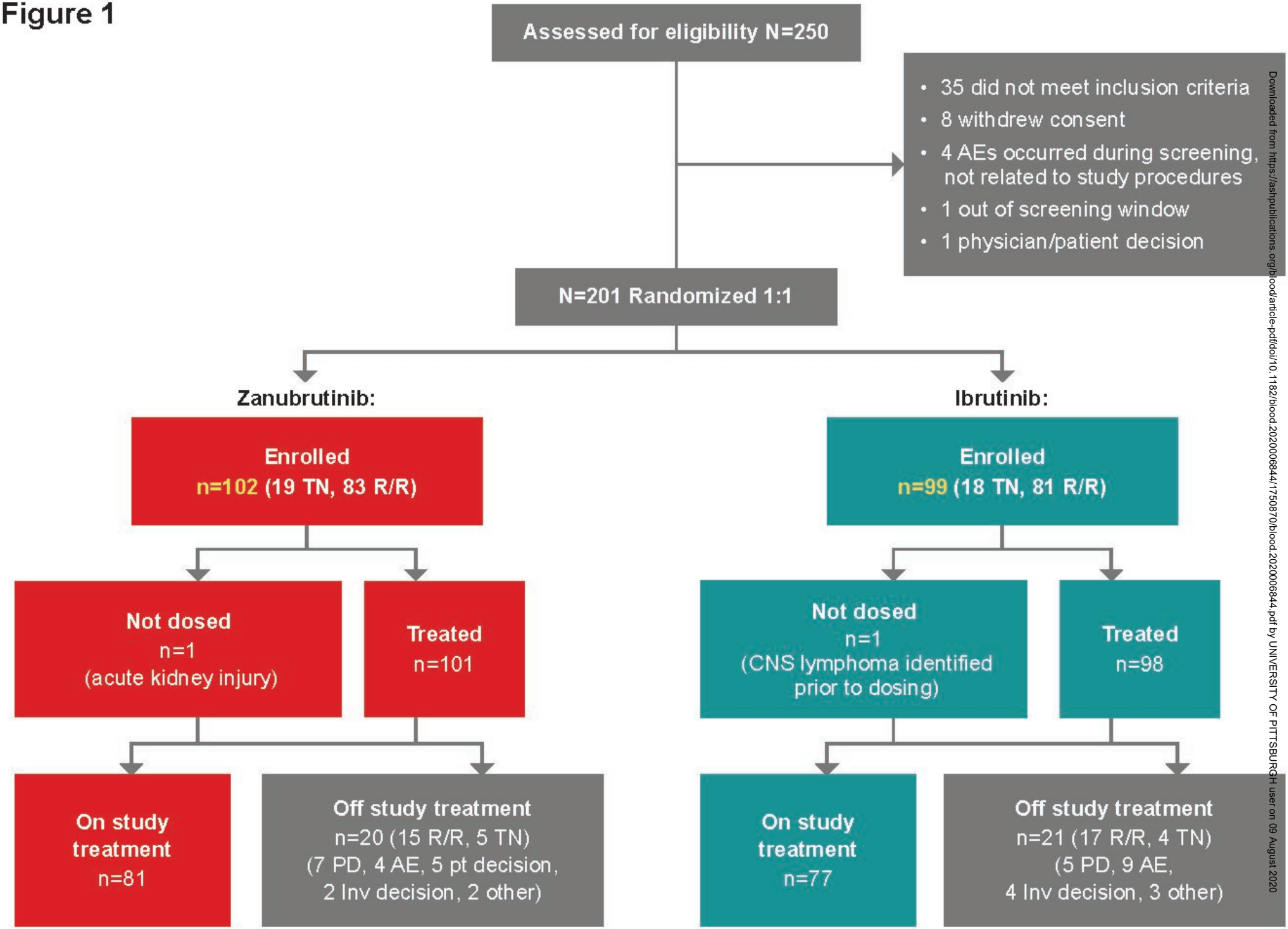

Figure 2

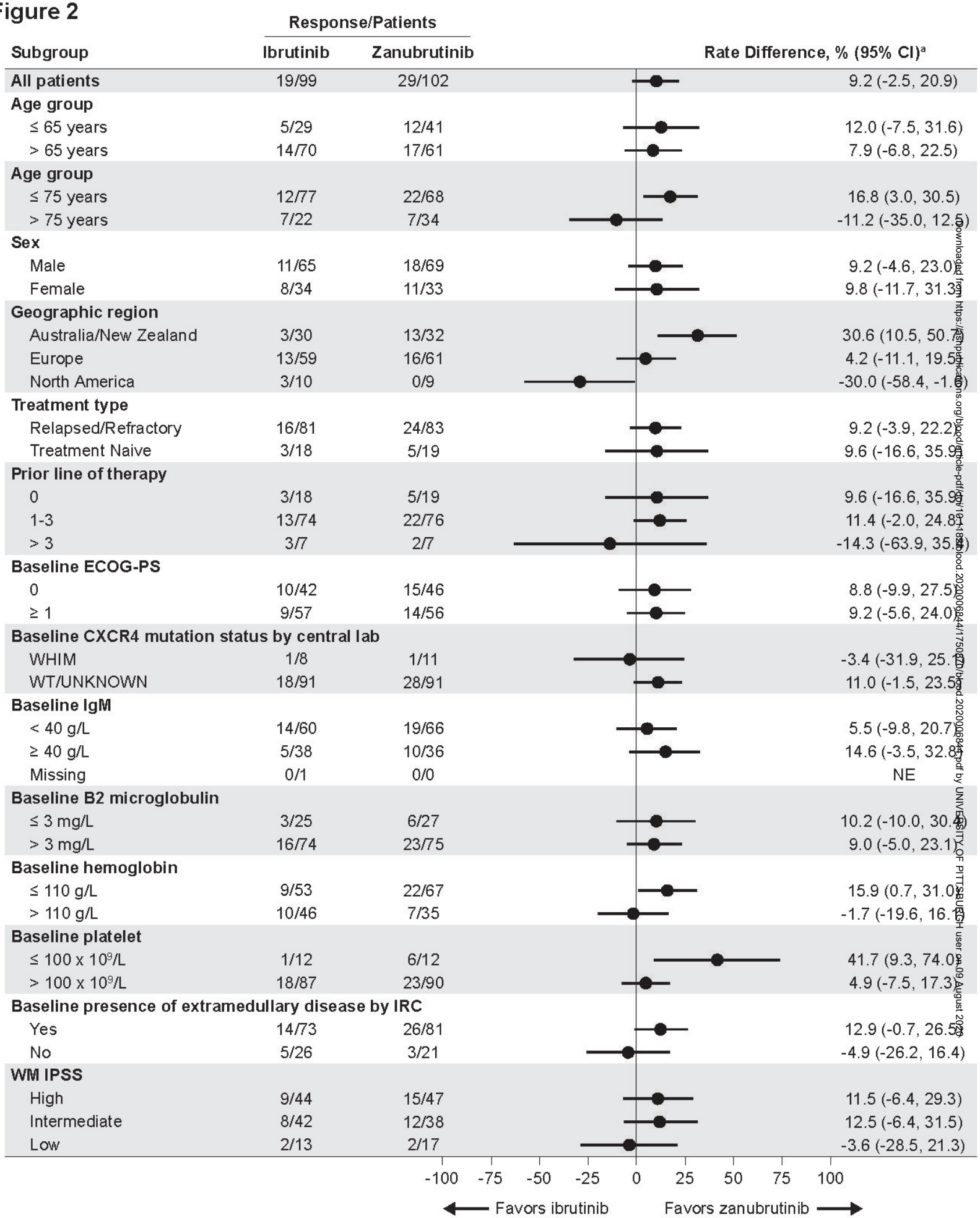

Figure 3

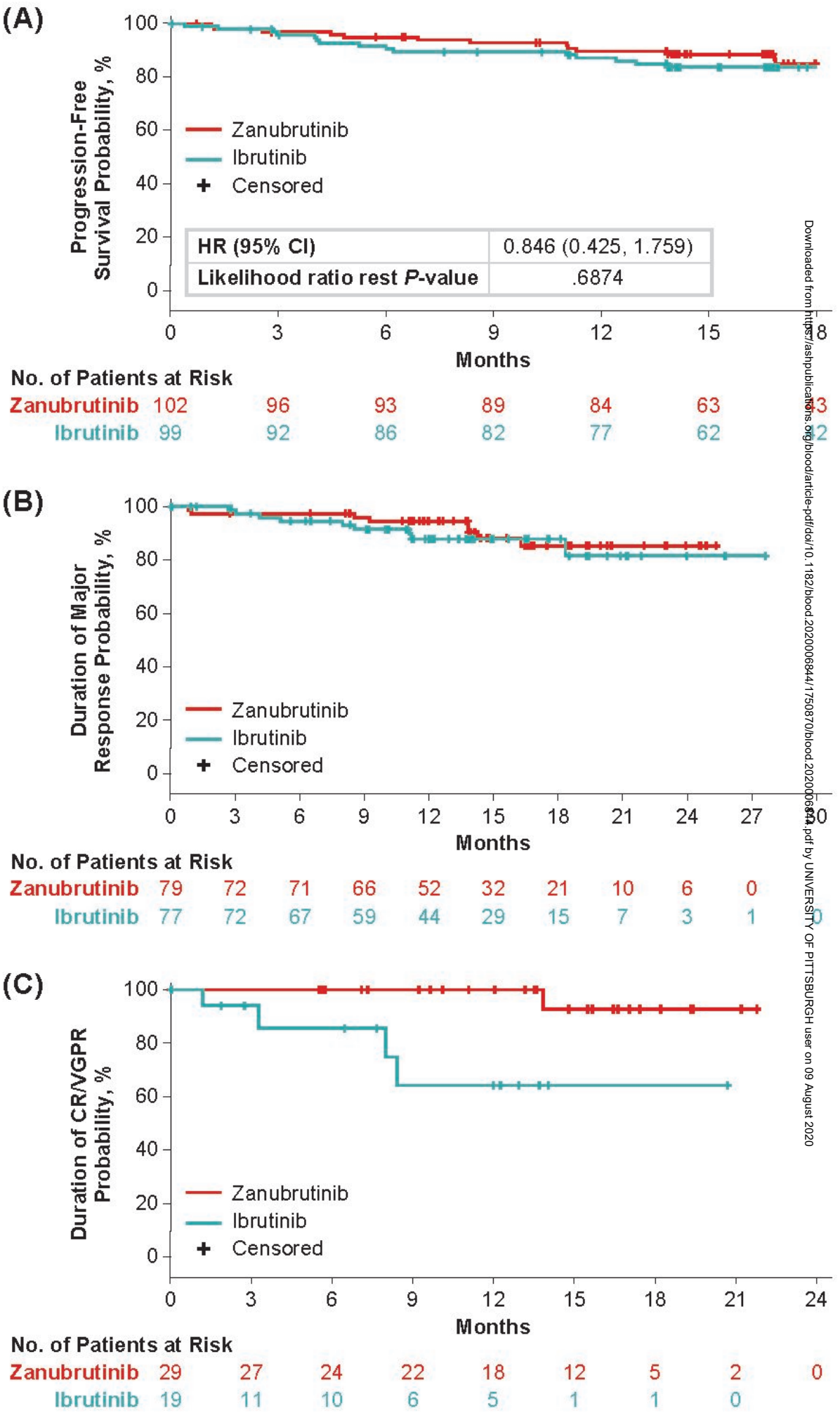

Figure 4