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Impact of initial dosing and subsequent dose reduction of zanubrutinib in patients with Waldenström macroglobulinemia

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Abstract:
Zanubrutinib is the preferred Bruton tyrosine kinase inhibitor for Waldenström macroglobulinemia (WM), yet data on dosing strategies remain limited. We evaluated 236 WM patients who received zanubrutinib monotherapy between 2018 and 2025. We assessed the impact of initial dosing and subsequent dose reductions on very good partial response (VGPR) and progression-free survival (PFS). Multivariate logistic and Cox models identified independent predictors of VGPR and PFS. Among 236 patients, 193 (82%) initiated 160 mg twice-daily, 22 (9%) initiated 320 mg daily, and 21 (9%) initiated sub-standard-dosing (<320 mg daily). With a median follow-up of 33 months (95% CI, 30.4-35.2), standard-dose regimens produced comparable outcomes: VGPR 39% (71/184) with 160 mg twice-daily vs. 40% (8/20) with 320 mg daily (p=0.90), and 30-month PFS rate 89% vs. 89% (p=0.86). Sub-standard initiation yielded inferior efficacy, with VGPR of 14% (3/21; p=0.03) and a 30-month PFS rate of 54% (p<0.001). In multivariable analysis, sub-standard-dose initiation independently predicted lower VGPR attainment (OR 0.10; p=0.04) and worse PFS (HR 11.09; p=0.001). In contrast, subsequent, toxicity-driven, dose reductions after standard-dose initiation that occurred in 51/215 (24%), patients did not worsen outcomes (VGPR 49% vs. 36%, p=0.09; 30-month PFS rate 95% vs. 88%, p=0.13) and improved symptoms in 34/51 (67%), particularly for rheumatologic and gastrointestinal toxicities. In conclusion, findings from this largest off-trial WM cohort support standard-dose zanubrutinib initiation with either 320 mg daily or 160 mg twice daily, while suggesting that dose reductions may be better reserved for toxicity management after standard-dose initiation rather than used preemptively.

Conflict of interest: COI declared - see note

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Key Points:

- Standard-dose zanubrutinib (160 mg twice-daily or 320 mg daily) yields equivalent efficacy in WM; sub-standard initiation worsens outcomes
- 2anubrutinibToxicity-driven dose reductions after standard-dose initiation preserve efficacy and improve symptoms

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Abstract

Zanubrutinib is the preferred Bruton tyrosine kinase inhibitor for Waldenström macroglobulinemia (WM), yet data on dosing strategies remain limited. We evaluated 236 WM patients who received 3anubrutinib monotherapy between 2018 and 2025. We assessed the impact of initial dosing and subsequent dose reductions on very good partial response (VGPR) and progression-free survival (PFS). Multivariate logistic and Cox models identified independent predictors of VGPR and PFS. Among 236 patients, 193 (82%) initiated 160 mg twice-daily, 22 (9%) initiated 320 mg daily, and 21 (9%) initiated sub-standard-dosing (<320 mg daily). With a median follow-up of 33 months (95% CI, 30.4-35.2), standard-dose regimens produced comparable outcomes: VGPR 39% (71/184) with 160 mg twice-daily vs. 40% (8/20) with 320 mg daily (p=0.90), and 30-month PFS rate 89% vs. 89% (p=0.86). Sub-standard initiation yielded inferior efficacy, with VGPR of 14% (3/21; p=0.03) and a 30-month PFS rate of 54% (p<0.001). In multivariable analysis, sub-standard-dose initiation independently predicted lower VGPR attainment (OR 0.10; p=0.04) and worse PFS (HR 11.09; p=0.001). In contrast, subsequent, toxicity-driven, dose reductions after standard-dose initiation that occurred in 51/215 (24%), patients did not worsen outcomes (VGPR 49% vs. 36%, p=0.09; 30-month PFS rate 95% vs. 88%, p=0.13) and improved symptoms in 34/51 (67%), particularly for rheumatologic and gastrointestinal toxicities. In conclusion, findings from this largest off-trial WM cohort support standard-dose 3anubrutinib initiation with either 320 mg daily or 160 mg twice daily, while suggesting that dose reductions may be better reserved for toxicity management after standard-dose initiation rather than used preemptively.

Introduction

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Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of Waldenström macroglobulinemia (WM). Ibrutinib was the first BTKi to gain regulatory approval, establishing proof of concept for this therapeutic class [1-4]. Subsequently, the Phase III ASPEN trial established 4anubrutinib as the preferred alternative, with a superior safety profile, including a significantly lower incidence of atrial fibrillation (~4% vs. ~17%) [5,6]. Accordingly, both the National Comprehensive Cancer Network (NCCN) and the 12th International Workshop on Waldenström's macroglobulinemia (IWWM-12) guidelines support the preferential use of 4anubrutinib in WM due to its safety profile [7,8], making it the currently preferred novel therapy frontline regimen overall for the treatment of WM.

Despite its increasing global use, off-trial experience with 4anubrutinib remains limited, particularly regarding dosing strategies employed in real-world practice, which were outside the scope of the landmark clinical trial [5,6]. ASPEN employed 4anubrutinib 160 mg twice daily (BID), and experience in other lymphomas and in WM has supported a potential role for the alternative 320 mg once-daily (QD) schedule [9-12] , given its comparable clinical efficacy and the early-phase trial demonstrating near-identical BTK occupancy [9,10].

Moreover, initiating BTKi at lower doses is not uncommon in clinical practice [13,14]. However, this approach lacks any supportive clinical evidence. In contrast, post-response dose reductions of ibrutinib have demonstrated sustained long-term efficacy,[15] but have not been studied with 4anubrutinib.

To inform recommendations for these commonly used dosing patterns, we evaluated initial dosing schedules and dose intensities, as well as subsequent dose reductions, in 236 consecutive WM patients treated with 4anubrutinib monotherapy.

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Methods

We conducted a retrospective cohort study of 236 consecutive WM patients who were treated at our Institution and received 5anubrutinib monotherapy between 2018 and 2025. Patients were identified through the institutional pharmacy informatics database and the Electronic Medical Record Search Engine (EMERSE) [16], and a manual review of the electronic medical records confirmed eligibility. Eligible patients had a confirmed diagnosis of WM according to IWWM-2 criteria [17] and received 5anubrutinib monotherapy. Patients who transitioned from ibrutinib to 5anubrutinib were excluded. Responses were assessed per IWWM-11 criteria [18].

Genetic testing for *MYD88*, *CXCR4*, and *TP53* was performed on bone marrow samples using clinically validated assays. *MYD88* and *CXCR4* mutations were assessed by a combination of allele-specific PCR, Sanger sequencing, or next-generation sequencing, applied to either CD19-selected [19-21] or unselected bone marrow samples, according to the availability of CD19-selected material. *TP53* alterations (mutations and 17p deletions) were evaluated using next generation sequencing or fluorescence in situ hybridization on unselected bone marrow mononuclear cells. Clinical and laboratory data were extracted from institutional electronic medical records.

The Modified Staging System for Waldenström Macroglobulinemia (MSS-WM) score was calculated for all patients with available baseline data at the time of 5anubrutinib initiation [22].

The primary exposures of interest were (1) initial 5anubrutinib dosing (standard dosing: 160 mg twice daily or 320 mg daily vs. low dosing: <320 mg daily) and (2) subsequent dose reductions. The primary outcomes were very good partial response (VGPR) and progression-free survival (PFS). VGPR was defined as a ≥90% reduction in serum IgM from baseline or normalization of

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serum IgM levels with a detectable monoclonal spike. PFS was defined as the time from treatment initiation to disease progression, last follow-up, or death from any cause. We additionally evaluated time to next treatment (TTNT), defined as the time from treatment initiation to next treatment initiation, last follow-up, or death from any cause. Secondarily, we evaluated the toxicities leading to dose reduction or treatment discontinuation, as well as the clinical benefit of dose reductions on symptom improvement. The data cutoff for follow-up was May 1, 2026.

Statistical Analysis

Descriptive statistics summarized baseline characteristics. Categorical variables were reported as counts and percentages and compared using *Chi*-squared tests. Continuous variables were expressed as medians with ranges and compared using the Wilcoxon rank-sum test. PFS was estimated with the Kaplan-Meier method and compared between groups using the log-rank test. Predictors of VGPR were evaluated using logistic regression, and predictors of PFS were assessed using Cox proportional-hazard regression models. Both univariate and multivariate analyses were performed. The outcome measure for the logistic regression models was the odds ratio (OR) with 95% confidence interval (CI), and for the Cox regression models was the hazard ratio (HR) with 95% CI. The median follow-up was calculated using the reverse Kaplan-Meier method. Statistical analyses were conducted with Stata 18.0 (College Station, TX, USA).

Ethics Statement

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This study was approved by the Dana-Farber Cancer Institute's Institutional Review Board (IRB) and was conducted in accordance with the Declaration of Helsinki. A waiver of informed consent was granted owing to the retrospective design of the study.

Results

We identified 236 consecutive patients with WM treated with 7anubrutinib (**Table 1**). Patients on ibrutinib who switched over to 7anubrutinib were excluded from this analysis. The median age was 72 (range 23-96) years, and 103 (44%) had received treatment prior to 7anubrutinib. Nearly all patients (221/226; 98%) carried mutated *MYD88,* while mutated *CXCR4* and altered *TP53* occurred in 65/188 (35%) and 19/159 (12%) patients, respectively. The median study follow-up was 33 months (95% CI, 30.4-35.2; crude interquartile range, 21.3-43.5). Among 225 evaluable patients (11 non-evaluable: 3 with missing data and 8 with normal baseline IgM), objective responses were achieved in 94% of patients, while 84% attained a major response (partial response or better) and 36% attained a VGPR. The 30-month PFS rate was 86% (95% CI 80.5-90.4).

Initial Zanubrutinib Treatment and Outcomes

The majority (215/236; 91%) of patients received 7anubrutinib at standard dosing, i.e. 160 mg twice daily (n=193) and 320 mg once daily (n=22). For some patients (21/236; 9%), 7anubrutinib was initiated at sub-standard dosing: 80 mg twice daily (n=13), 160 mg daily (n=6), 240 mg daily (n=1), and 80 mg daily (n=1). No dose increases were observed, except in one patient who

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escalated from 80 mg daily to 160 mg daily. Reasons for sub-standard dose initiation were non-standardized and included age and/or performance status (n=8), baseline thrombocytopenia (n=3), patient preference (n=2), low body weight (n=2), history of atrial fibrillation (n=2), and drug interaction (n=1). The reason for initial reduced dosing was not reported for three patients. As shown in **Table 2**, patients starting at lower than standard dosing were older (median 81 vs. 71 years; p<0.001), had lower baseline hemoglobin levels (9.9 vs. 10.3 g/dL; p=0.02), and constituted more treatment-naïve patients (86% vs. 54%; p=0.004). Low-dose patients also had a higher MSS-WM score, with a greater proportion classified as high risk (61% vs. 19%; p=0.001) (**Table 2**).

Among patients treated 8anubrutinibtinib at 160 mg twice daily, VGPR was achieved at best response in 71/184 (39%), and the 30-month PFS rate was 89% (95% CI 83-93). For patients star8anubrutinibtinib at 320 mg once daily, VGPR was attained at best response in 8/20 (40%) of cases, and the 30-month PFS rate was 89% (95% CI 63-97). The outcomes between the two standard dosing cohorts did not differ for attainment of VGPR (p=0.90) or PFS (p=0.86). In contrast, patients who received sub-standard dosing (<320 mg daily) showed lower VGPR rates at best response (3/21; 14%) compared to those receiving standard-8anubrutinibtinib (p=0.03) (**Figure 1A**). Moreover, the 30-month PFS rate was 54% (95% CI, 28-74) in this subgroup, which was significantly shorter than that observed in patients receiving standard-8anubrutinibtinib (p<0.001) (**Figure 1B**).

In multivariable logistic regression analysis adjusting for age, sex, *MYD88*, *CXCR4*, and *TP53* mutation status, ECOG performance status (≥2 vs <2), prior therapy, and MSS-WM risk category

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(high-risk vs other categories), initiatio9anubrutinibtinib at a sub-standard dose (<320 mg/day) was independently associated with lower odds of achieving a VGPR (OR 0.10; 95% CI 0.01-0.86; p=0.04). In a Cox regression model adjusting for the same covariates, sub-standard dose initiation was independently associated with worse PFS (HR 11.09; 95% CI 2.62-46.99; p=0.001). Additional variables independently associated with worse PFS included prior therapy (HR 2.74; 95% CI 1.10-6.86; p=0.03), high-risk MSS-WM (HR 2.82; 95% CI 1.02-7.73; p=0.045), and ECOG ≥2 (HR 3.77; 95% CI 1.40-10.14; p=0.008).

To confirm that the observed PFS effect was not driven by non-WM-related deaths, we performed an additional Cox regression analysis using the same covariates, in which only clinical/biochemical progression events were considered, while deaths without documented WM progression were censored. In this model, sub-standard dose initiation remained independently associated with worse PFS (HR 9.88; 95% CI 1.90-51.35; p=0.006), together with prior therapy (HR 3.94; 95% CI 1.29-12.04; p=0.016). Similarly, when assessing time to next treatment as an additional endpoint to mitigate potential bias related to retrospective assessment of progression, 30-month TTNT was 81% (95% CI 75-86%) among patients initiated at standard dose versus 49% (95% CI 25-69%) among those initiated at a sub-standard dose (p<0.001). In multivariable analysis using the same covariates, sub-standard dose initiation remained independently associated with shorter TTNT (HR 7.64; 95% CI 2.49-23.41; p<0.001), along with worse performance status (HR 2.78; 95% CI 1.21-6.40; p=0.016).

Subsequent Zanubrutinib Dose Reductions and Outcomes

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Among patients who started at the standard dose, 51 (24%) required dose reduction. Dose reduction occurred in 49/193 (25%) patients receiving 160 mg twice daily and in 2/22 (9%) patients who received 320 mg once daily as their initial dose (p=0.09). Patients requiring dose reduction after initiation of standard 10anubrutinibtinib were older (median age 75 vs. 70 years; p=0.003), had a lower baseline serum IgM level (2482 vs. 3464 mg/dL; p=0.04), and were less commonly *CXCR4* mutated (18% vs. 39%; p=0.02) (**Table 3**). Among patients with measurable serum IgM at the time of dose reduction, 34/38 (89%) had already achieved a response, most commonly a partial response or better (31/38, 82%). The median d10anubrutinibtinib dose was 160 (range 80-240) mg/day following dose reduction.

Among patients who underwent dose reduction, the median time from standard-dose initiation (320 mg once daily or 160 mg twice daily) to dose reduction was 5.02 (range 0.26-48.3) months. In time-to-event analysis across the overall cohort, the cumulative incidence of dose reduction was 13% (95% CI 9-19) at 6 months, 19% (95% CI 14-25) at 1 year, and 23% (95% CI 17-31) at 2 years, and was more common among patients receiving 160 mg twice daily versus 320 mg once daily (p = 0.06; **Figures 2A and B**).

With a median follow-up from dose reduction of 32.7 (95% CI 20.7-37.2) months, among the 38 patients with measurable serum IgM at the time of dose reduction, 20 (53%) maintained the same categorical response, 17 (45%) experienced a deepened response over time (3 no response to minor response, 2 minor response to partial response, 1 minor response to VGPR, and 11

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partial response to VGPR), and 1 (3%) remained without a response both before and after dose reduction. No IgM rebound was observed following dose reduction.

Subsequent dose reductions following standard-dose initiation did not impact outcomes. VGPR rates at best response were 49% in the subsequent dose-reduction group vs. 36% in the non-dose-reduction group (p=0.09) (**Figure 2C**). The 30-month PFS rate was 95% (95% CI 80-99) in the subsequent dose-reduction group vs. 88% (95% CI 81-92) in the non-dose-reduction group; p=0.13 (**Figure 2D**).

Multivariate analysis adjusting for age, sex, *MYD88*, *CXCR4*, and *TP53* status, ECOG performance status (≥2 vs <2), prior therapy, MSS-WM risk category (high-risk vs other categories), and dosing schedule confirmed that subsequent dose reductions did not affect VGPR attainment (OR 2.33; 95% CI 0.71-7.65; p=0.16) or PFS (HR 0.40; 95% CI 0.07-2.16; p=0.29).

Toxicity Leading to Dose Reduction and Discontinuation

Overall, 60/215 patients (28%) who started at the standard dose developed toxicity requiring dose modification: 41/60 (68%) had dose reduction only, 10/60 (17%) had dose reduction followed by discontinuation, and 9/60 (15%) had discontinuation only. The most common toxicities leading to dose modification were rheumatologic (myalgias, arthralgias, muscle cramping), occurring in 15/215 (7%) patients, followed by cardiac (arrhythmia, hypertension, palpitations, chest pain) in 13/215 (6%) (**Figure 3A**). Among cardiac toxicities, 9/13 were rhythm-

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related, including electrocardiographically confirmed atrial fibrillation (n=5) and palpitations without electrocardiographic confirmation (n=4).

Of the 51 patients who had their dose reduced due to adverse effects (40 requiring single dose reduction; 11 requiring two dose reductions), 34 (67%) reported at least an improvement of the symptom(s) that prompted the dose reduction. The lowest daily dose reached was not associated with symptom improvement, whether analyzed as a continuous variable (OR 1.00 per mg/day; p=0.74) or categorically, with 160 mg daily vs 240 mg daily (p=0.23) and 80 mg daily vs 240 mg daily (p=0.53). Instead, symptom improvement after dose reduction appeared toxicity type dependent, with higher rates of improvement for gastrointestinal (9/10, 90%), rheumatologic (11/14, 79%), and cardiac (7/11, 64%) adverse events, and limited improvement for bleeding and/or bruising (2/6, 33%) and edema (1/5, 20%) (**Figure 3B**).

Overall, 19 patients (9%) discontinued therapy due to toxicity; of these, 10/19 (53%) had a prior dose reduction (only 1 at the minimum dose of 80 mg daily), while 9/19 (47%) discontinued without prior dose reduction (**Figure 4**). Treatment discontinuation most commonly occurred in the context of those with bleeding (6/8; 75%), edema (5/6; 83%) and fatigue (5/9; 56%).

Outcomes and Toxicity Among Patients Initiated at Sub-Standard Zanubrutinib Dosing

Among patients who sta12anubrutinibtinib at a sub-standard dose (n=21), subsequent dose modification patterns appeared overall similar to those observed among patients who started at full dose. Overall, 7/21 (33%) developed toxicity requiring dose modification, including 6/21

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(29%) requiring further dose reduction and 3/21 (14%) discontinuing therapy due to toxicity. All subsequent dose reductions consisted of reduction from 160 mg daily to 80 mg daily. The most common toxicity associated with dose modification was gastrointestinal toxicity (2/21; 10%), while rheumatologic, renal, bleeding, cardiac, edema, central nervous system, and cytopenia-related toxicities each occurred in 1/21 (5%) patients. Within this subcohort, subsequent dose reductions were not associated with PFS in either univariate (HR 1.31; 95% CI 0.31–5.54; p=0.72) or multivariable analysis adjusted for age, sex, and prior therapy (HR 1.46; 95% CI 0.34-6.34; p=0.61).

Importantly, the proportion of patients requiring subsequent dose reduction or discontinuation due to toxicity was similar among those initiated at standard (60/215; 28%) versus sub-standard doses (7/21; 33%; p=0.60).

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Discussion

In the first-in-h14anubrutinibtinib study for B-cell malignancies, 160 mg twice daily was selected as the preferred dose over 320 mg once daily because a greater proportion of patients maintained >95% lymph node BTK occupancy at trough (89% vs 50%). However, the median levels were nearly identical (100% vs 94%), and both regimens consistently achieved similarly high peripheral blood B-cell BTK occupancy [9]. The two schedules have shown comparable efficacy and safety across different lymphomas [10,23,24].

Available data suggest a potential signal for slightly increased toxicity with twice-daily compared with once-daily dosing. Grade ≥3 events were more frequent with twice-daily dosing in both the expanded-access WM study (17% vs. 11%) [11] and the phase 1a WM cohort (66% vs. 39%) [12]. Similarly, in the pooled safety populatio14anubrutinibtinib's p½e 1/2 studies across B-cell malignancies, grade ≥3 treatment-emergent events occurred more frequently with twice-daily than once-daily dosing (66% [n=278] vs. 52% [n=95]), with more hematologic events, particularly neutropenia, in the twice-daily group. Although 320 mg once daily produces higher peak concentrations, these have not been associated with toxicity in pharmacokinetic studies [10]. One possibility is that more sustained BTK occupancy in healthy cells with twice-daily dosing may contribute to adverse events, particularly for on-target (BTK-driven) toxicities such as neutropenia [25]. Additional factors may favor choice of once-daily schedule, with some authors suggesting that it may improve adherence [26,27]. Herein, our findings show that administration of either 160 mg twice daily or 320 mg once daily produces similar response depth and PFS

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279 outcomes. In the absence of definitive evidence favoring either regimen, schedule selection
280 should be individualized based on patient-specific considerations
281
282 In contrast, among the small subgroup of patients initiated on sub-stan15anubrutinibtinib dosing
283 (n=21), we observed a signal for inferior outcomes, including lower VGPR rates shorter PFS and
284 TTNT after multivariable adjustment. This observation differs from dose reductions after
285 standard-dose initiation, which did not affect outcomes in a large ibrutinib study [15] and were
286 likewise not associated with worse outcomes in15anubrutinibtinib cohort. While lymph node BTK
287 occupancy was not assessed at doses below 320 mg daily in the phase 1 tr15anubrutinibtinib
288 exposure (AUC) decreased approximately proportionally with dose, with AUC at 80 and 160 mg
289 daily representing approximately 21% and 67%, respectively, of that observed with 320 mg daily
290 [9]. Such lower exposure may be inadequate to achieve sufficient BTK inhibition at treatment
291 initiation but be sufficient to maintain disease control once microenvironmental changes have
292 been made and/or the tumor burden has been reduced after achieving a response to standard
293 doses. This may be particularly relevant given the recently described role of BTK inhibition in
294 modulating inflammatory pathways within the microenvironment, including BTK expression in
295 myeloid cells such as myeloid-derived suppressor cells [28-30] and clinical data showing improved
296 outcomes in WM patients with high inflammatory markers treated with BTKi compared to
297 chemoimmunotherapy [31,32]. Nonetheless, the possibility exists that longer follow-up may reveal
298 reduced efficacy with subsequent dose reduction that is not yet apparent, particularly as an
299 imbalance in high-risk features, with fewer *CXCR4* and *TP53* alterations among subsequently
300 dose-reduced patients, may have obscured such an effect.

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Likewise, starting at a low dose in our study was not random, as it most commonly occurred in older patients with higher-risk disease [22]. Although multivariable analyses adjusted for the major measured imbalances, residual confounding remains possible given the small sample size and unmeasured factors, such as comorbidities that could not be reliably captured retrospectively. Nonetheless, these higher-risk patients may be precisely those for whom complete BTK inhibition is most important to achieve disease control, given their expected poorer outcomes [22,33].

Taken together, these findings raise concern about preemptive sub-standard dosing and support standard-16anubrutinibtinib initiation followed by individualized dose reductions when toxicity occurs. This approach may be particularly relevant given the difficulty of predicting treatment-emergent toxicity [34], arguing against a priori low-dose initiation solely to improve tolerability. Nonetheless, clinical scenarios may arise in which full-dose initiation is not feasible, including relevant drug interactions or relative contraindications to BTKi therapy [34,35]. Although these situations were not evaluated in our cohort, when reduced-dose initiation is clinically necessary, strategies such as prompt dose escalation could be explored. Additional strategies, that were not evaluated in this study, could also be explored, including the impact of temporary dose interruptions on tolerability and long-term efficacy, which are generally minimized because of concerns for IgM rebound [36].

The safety profile observed in our cohort was overall consistent with the ASPEN trial and supports the tolerabilit16anubrutinibtinib, including its relatively low incidence of atrial fibrillation [5,6,37]. Still, it should be noted that toxicity data were limited to adverse events that led to a dose

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reduction or treatment discontinuation to reduce bias from inconsistently documented adverse events in the electronic medical record, which inherently selected for clinically relevant toxicities, potentially excluding lower-grade toxicities [38,39].

While adverse events leading to dose reduction were somewhat more frequently documented in our cohort (24% *vs*. 16% in ASPEN), rates of toxicity-related discontinuation were comparable between studies (9.0% *vs*. 8.9%, respectively) [6]. Importantly, our findings underscore the clinical benefit of dose reductions as an effective strategy for symptom improvement, particularly for rheumatologic and gastrointestinal toxicities, patterns consistent with prior reports showing high symptom resolution with ibrutinib dose de-escalation [15]. In contrast, some adverse events, such as peripheral edema and bleeding associated with BTK inhibitor therapy, may be less responsive to dose reduction [40]. In these situations, alternative management approaches, including treatment discontinuation, have been reported as more effective for symptom resolution [41].

It is essential to recognize that cardiac and bleeding toxicities, although infrequent in our cohort and occurring at lower rates than those historically reported with ibrutinib in cross-study comparisons, remained among the most common reasons17anubrutinibtinib discontinuation. These events therefore continue to pose clinically meaningful risks, particularly for patients with baseline arrhythmias or those receiving anticoagulation, respectively [42,43]. Taken together, these observations indicate that although zanubrutinib demonstrates an improved safety profile compared to ibrutinib, patients with a higher baseline risk warrant close monitoring for cardiac and bleeding complications.

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The limitations of our study should be considered when interpreting the results. These include its retrospective design, which inherently involves missing data (including inconsistent or variably timed measurements and adverse effect reporting), and its conduct within a specialized referral setting, which may not fully reflect global practice patterns. Of particular relevance is the small number of patients who initiated treatment at a low dose, which, despite the strong observed signal, limits the statistical precision of our estimates and the ability to robustly adjust for potential confounding variables. Additionally, patients seen at referral centers are more likely to be younger, have higher income and educational level, and have better performance status than the general population [44,45]. Lastly, long-term effects may not yet be apparent within the current follow-up period, potentially limiting assessment of variables that take longer to influence outcomes.

Despite these limitations, this study features a large, well-characterized cohort with a particularly high proportion of genotyped patients, all of whom were systematically followed by a specialized laboratory and clinical team. As a referral center, the cohort comprises patients primarily managed at our institution, as well as those mainly followed at external practices and only peripherally seen here, including individuals who initiated zanubrutinib both within and outside our institution. Collectively, these features provide a framework for examining the effectiveness of commonly employed dosing strategies and for generating recommendations that may directly inform clinical practice.

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Conclusion

Standard-dose zanubrutinib (160 mg twice daily or 320 mg once daily) produced equivalent VGPR rates and PFS, whereas initiating therapy at lower doses showed a signal for inferior efficacy. Subsequent dose reductions after full-dose initiation did not appear to compromise disease control and frequently improved tolerability. These findingssupport standard-dose initiation with selective dose de-escalation for adverse events, rather than pre-emptive sub-standard dosing, although the longer-term effects of these strategies will require continued evaluation.

Conflict of interest

SRS received research funding or consulting fees from ADC Therapeutics, AstraZeneca, BeOne, Cellectar, and Sobi. JJC received research funds or consulting fees from AbbVie, AstraZeneca, BeOne, Cellectar, Johnson & Johnson, Loxo, Nurix, Pharmacyclics, and Schrodinger. SPT received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc., Johnson and Johnson, BeOne Inc., and Eli Lilly Pharmaceuticals.

Authors contributions

AG, SRS and JJC designed the study. AG, ND, NT, MK and AK collected the data. SRS, JJC, THM, CVE and AB evaluated the patients. NT, AK, MLG, ZH and SPT performed the laboratory studies. AG, SRS and JJC performed the statistical analyses. SRS, JJC, SPT and ZH provided overall supervision. AG, SRS and JJC drafted the initial version of the manuscript. All authors critically reviewed and approved the final manuscript.

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Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1. Baseline clinical and molecular characteristics of the study cohort. Continuous variables are presented as median (range). Categorical variables are shown as counts with percentages.

Factor	Level	Value
N		236
Age (years), median (Range)		72 (23-96)
Sex	Female	98 (42%)
	Male	138 (59%)
Ethnicity	Asian	9 (4%)
	Black	2 (1%)
	White (Non-Hispanic)	220 (93%)
	White (Hispanic)	5 (2%)
Hemoglobin (g/dL), median (Range)		10.1 (4.8-16.8)
Platelets (x10^9/L), median (Range)		223 (14-1427)
Albumin (g/dL), median (Range) (n=233)		3.7 (2.0-5.3)
IgM (mg/dL), median (Range) (n=234)		3323 (120-10952)
LDH (U/L), median (Range) (n=185)		160 (81-685)
Beta-2-microglobulin (mg/L), median (Range) (n=139)		3.7 (1.3-13)
Bone marrow involvement (%), median (Range) (n=160)		60 (3-95)

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Treatment status	Untreated	133 (56%)
	Treated	103 (44%)
Performance status (n=197)	ECOG PS < 2	159 (81%)
	ECOG PS ≥ 2	38 (19%)
MYD88 (n=226)	WT	5 (2%)
	Mutated	221 (98%)
CXCR4 (n=188)	WT	123 (65%)
	Mutated	65 (35%)
TP53 (n=159)	Unaltered	140 (88%)
	Altered	19 (12%)
Initial zanubrutinib dose	160 mg BID	193 (82%)
	320 mg QD	22 (9%)
	<320 mg daily	21 (9%)
Dose reduction*	No	164 (76%)
	Yes	51 (24%)
Discontinuation*	No	196 (91%)
	Yes	19 (9%)
MSS-WM (n=184)	Low risk	32 (17%)
	Low intermediate risk	49 (27%)
	Intermediate risk	60 (33%)
	High risk	43 (23%)

IgM: immunoglobulin M; LDH: lactate dehydrogenase; WT: wild-type; QD: once daily; BID: twice daily; MSS-WM: Modified Staging System for WM; *: Due to side effects within standard dose cohort (n=215).

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Table 2. Baseline clinical and molecular characteristics of patients receiving initial standard-dose zanubrutinib (160 mg twice-daily [BID]) or 320 mg daily [QD]) and low-dose zanubrutinib (<320 daily). Continuous variables are summarized as the median (range), and categorical variables are summarized as the number (percentage). P-values were calculated using the Wilcoxon rank-sum test for continuous variables and the *Chi*-square test for categorical variables.

Factor	**Level**	**Standard dose (160 mg BID or 320 QD)**	**Sub-standard dose (<320 mg daily)**	***p*-value**
N		215	21	
Age (years), median (Range)		70.6 (23-93)	81.3 (64-96)	**<0.001**
Sex	Female	87 (40.5%)	11 (52.4%)	0.29
	Male	128 (59.5%)	10 (47.6%)	
Hemoglobin (g/dL), median (Range)		10.3 (4.8-16.8)	9.9 (5.5-11.6)	**0.023**
Platelets (x10^9/L), median (Range)		226.0 (14.0-774.0)	216.0 (15.0-1427.0)	0.41
Albumin (g/dL), median (Range) (n=233)		3.7 (2.0-5.3)	3.5 (2.2-4.5)	0.061
IgM (mg/dL), median (Range) (n=234)		3280 (120 -10952)	3950 (954-8218)	0.22
LDH (U/L), median (Range) (n=185)		157.0 (81.0-685.0)	198.5 (91.0-523.0)	**0.025**
Beta-2-microglobulin (mg/L), median (Range) (n=139)		3.3 (1.3-13.0)	5.3 (1.8-11.2)	0.094
Bone Marrow Involvement (%), median (Range) (n=160)		60 (3-95)	65 (5-90)	0.99
Treatment Status	Untreated	115 (54%)	18 (86%)	**0.004**
	Treated	100 (47%)	3 (14%)	
Performance Status (n=197)	ECOG PS < 2	144 (81%)	15 (75%)	0.50
	ECOG PS ≥ 2	33 (19%)	5 (25%)	
MYD88 (n=226)	WT	4 (2%)	1 (5%)	0.40
	Mutated	201 (98%)	20 (95%)	
CXCR4 (n=188)	WT	113 (66%)	10 (59%)	0.55
	Mutated	58 (34%)	7 (41%)	
TP53 (n=159)	Unaltered	126 (88%)	14 (88%)	0.94
	Altered	17 (12%)	2 (12%)	
MSS-WM (n=184)	Low risk	31 (19%)	1 (6%)	**0.001**
	Low intermediate risk	47 (28%)	2 (11%)	
	Intermediate risk	56 (34%)	4 (22%)	
	High risk	32 (19%)	11 (61%)	

IgM: immunoglobulin M; LDH: lactate dehydrogenase; WT: wild-type; QD: once daily; BID: twice daily; ECOG: Eastern Cooperative Oncology Group; MSS-WM: Modified Staging System for WM.

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Table 3. Baseline clinical and molecular characteristics of patients who underwent a subsequent dose reduction compared with those who remained on standard-dose zanubrutinib (160 mg twice-daily [BID]) or 320 mg daily [QD]). Continuous variables are summarized as the median (range), and categorical variables are summarized as the number (percentage). P-values were calculated using the Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables.

Factor	Level	No dose reduction	Subsequent dose reduction	*p*-value
N		164	51	
Age (years), median (Range)		70 (23-84)	75 (52-93)	**0.003**
Sex	Female	62 (38%)	25 (49%)	0.15
	Male	102 (62%)	26 (51%)	
Hemoglobin (g/dL), median (Range)		10.2 (6.4-15.7)	10.4 (4.8-16.8)	0.79
Platelets (x10^9/L), median (Range)		224 (14-774)	228 (75-715)	0.91
Albumin (g/dL), median (Range) (n=212)		3.8 (2-5)	3.8 (2.7-5.3)	0.75
IgM (mg/dL), median (Range) (n=213)		3464 (120-10952)	2482 (214-9636)	**0.04**
LDH (U/L), median (Range) (n=167)		157 (81-685)	158 (104-309)	0.83
Beta-2-microglobulin (mg/L), median (Range) (n=127)		3.3 (1.3-13)	3.9 (1.7-12.4)	0.23
Bone Marrow Involvement (%), median (Range) (n=145)		60 (3-95)	60 (13-95)	0.97
Treatment Status	Untreated	91 (56%)	24 (47%)	0.29
	Treated	73 (45%)	27 (53%)	
Performance Status (n=177)	ECOG PS < 2	116 (84%)	28 (72%)	0.083
	ECOG PS ≥ 2	22 (16%)	11 (28%)	
MYD88 (n=205)	WT	3 (2%)	1 (2%)	0.88
	Mutated	157 (98%)	44 (98%)	
CXCR4 (n=171)	WT	81 (61%)	32 (82%)	**0.02**
	Mutated	51 (39%)	7 (18%)	
TP53 (n=143)	Unaltered	96 (86%)	30 (97%)	0.092
	Altered	16 (14%)	1 (3%)	
Schedule	160 mg BID	144 (88%)	49 (96%)	0.09
	320 mg QD	20 (12%)	2 (4%)	
MSS-WM (n=166)	Low risk	26 (20%)	5 (13%)	0.31
	Low intermediate risk	39 (31%)	8 (21%)	
	Intermediate risk	39 (31%)	17 (45%)	
	High risk	24 (19%)	8 (21%)	

IgM: immunoglobulin M; LDH: lactate dehydrogenase; WT: wild-type; QD: once daily; BID: twice daily; ECOG: Eastern Cooperative Oncology Group; MSS-WM: Modified Staging System for WM.

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Figure 1. Treatment outcomes according to initial zanubrutinib dosing. (A) Best response distribution in patients treated with initial low dosing (<320 mg daily), standard dosing (160 mg BID), or alternative standard dosing (320 mg QD). (B) Progression-free survival by dosing group.

Figure 2. Clinical outcomes associated with subsequent dose reduction. (A) Time to dose reduction among patients who initiated zanubrutinib at standard dose. (B) Time to dose reduction by dosing schedule. (C) Best response distribution in patients maintained on standard dosing (160 mg BID or 320 mg QD) versus those who initiated standard dose and later underwent dose reduction. (D) Progression-free survival by subsequent dose-de-escalation group.

Figure 3. Adverse events leading to dose modification in patients initiated at standard dose. (A) Distribution of adverse events resulting in dose reduction or discontinuation. (B) Outcomes of dose modification, including improvement with dose reduction, no improvement, or direct discontinuation.

Figure 4. Swimmer plot of zanubrutinib toxicity-driven dose reductions and discontinuations. Swimmer plot of the 60 patients who underwent dose modifications (reductions or discontinuations) due to toxicity among those who started at the full dose (n=215). The plot shows treatment duration and the timing of dose reductions, discontinuation due to toxicity, and progression, illustrating patterns of dose modification over time. Dosage represents the total daily dose administered, regardless of schedule.

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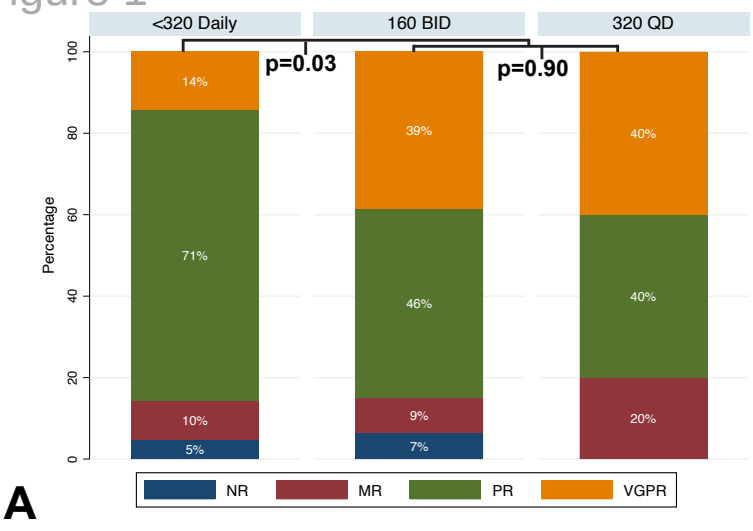
Figure 1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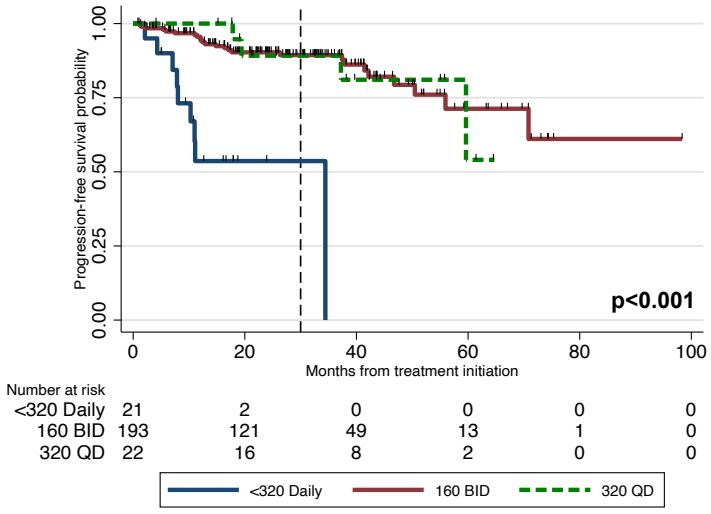
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Months from treatment initiation
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Number at risk
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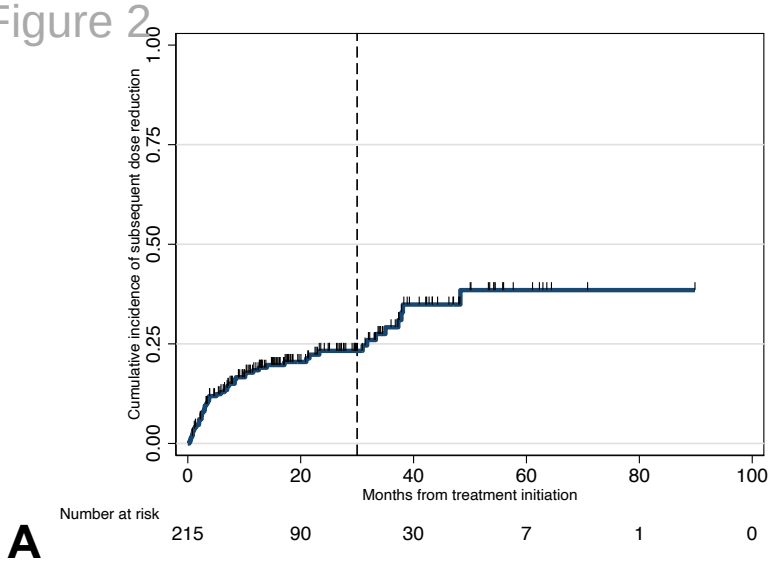
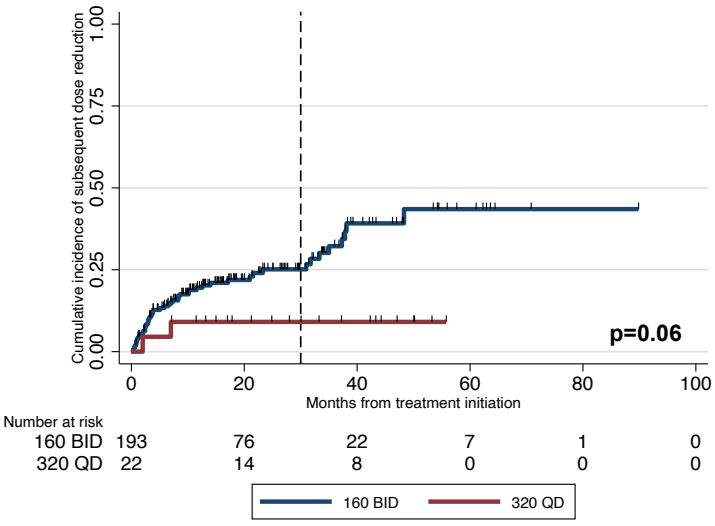
B

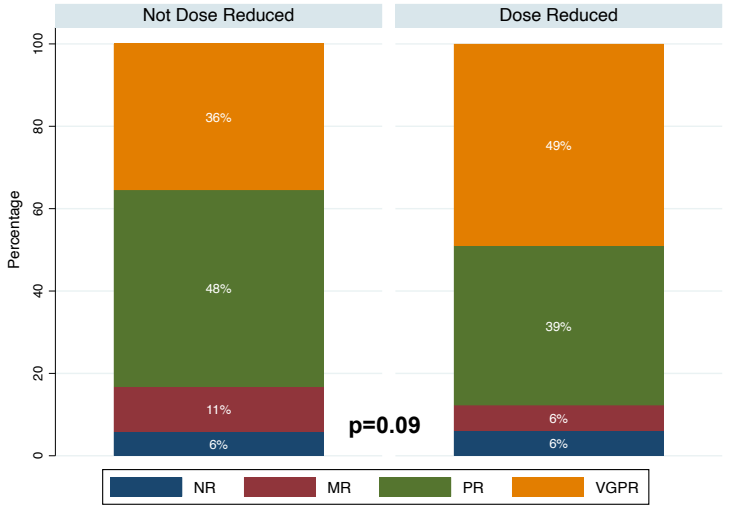
Figure 2



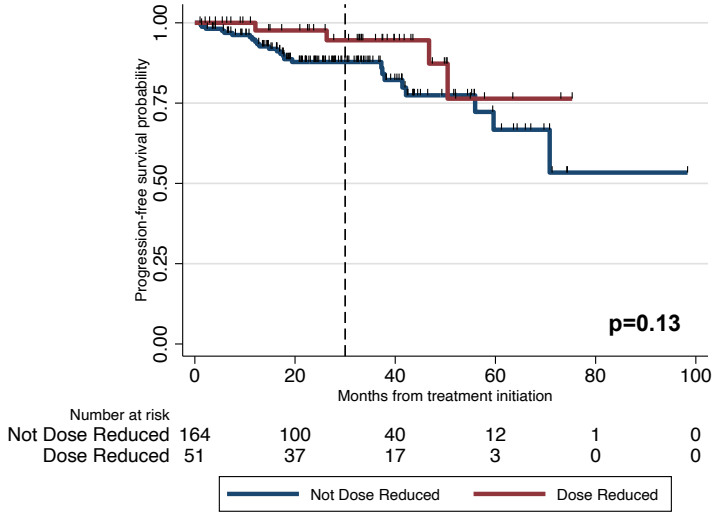
A



B



C



D

Figure 3

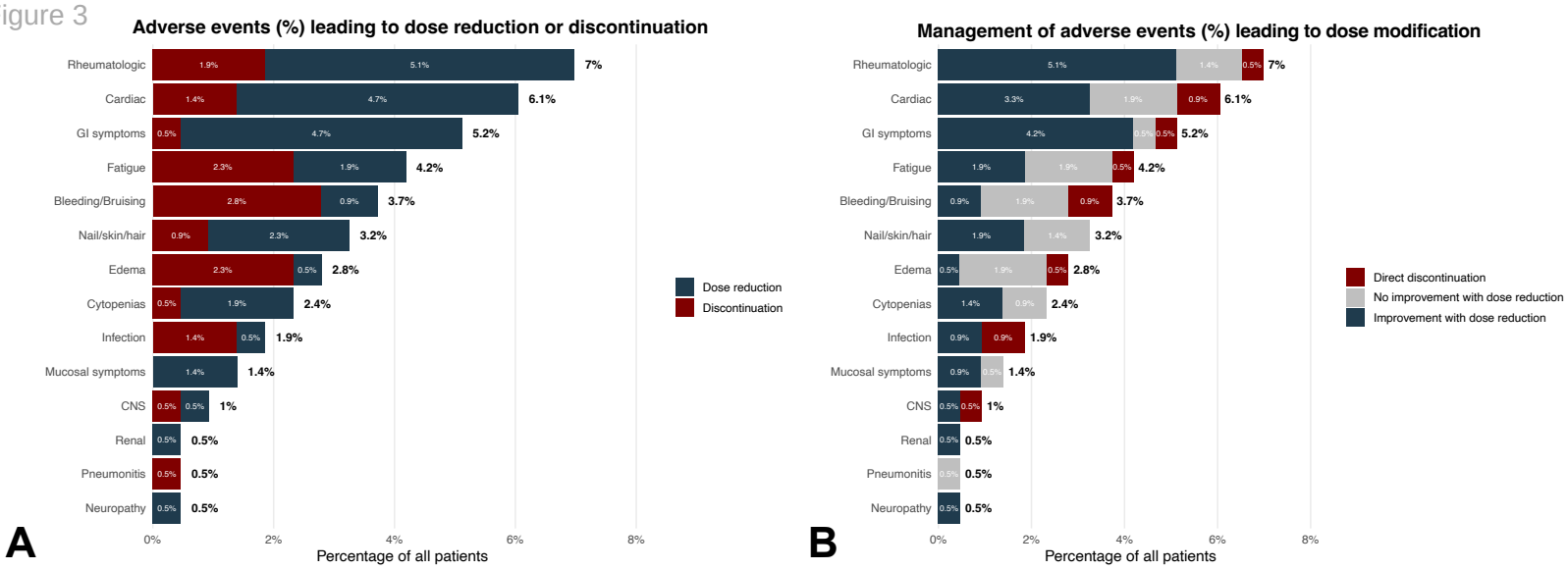
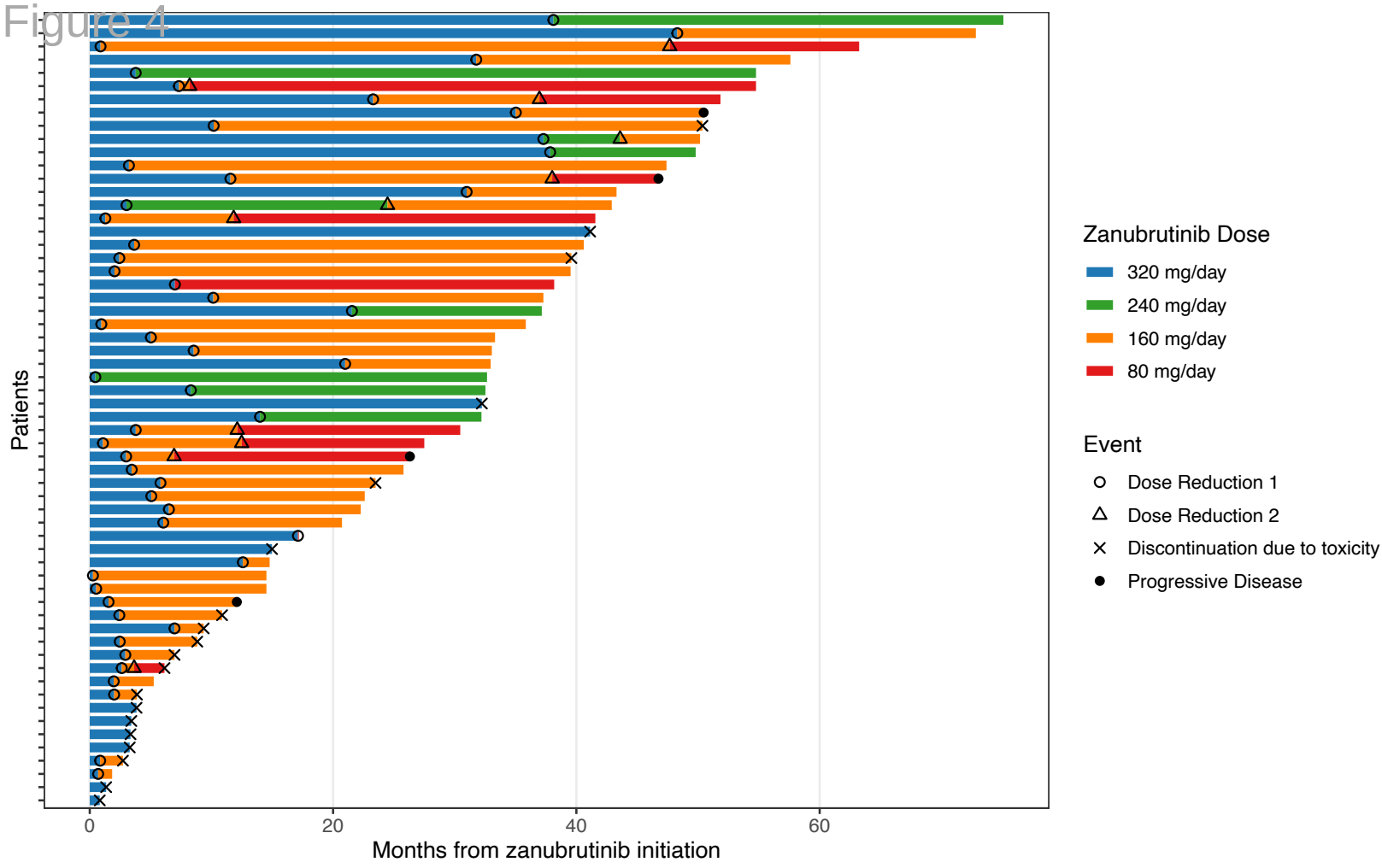

Adverse events (%) leading to dose reduction or discontinuation
Rheumatologic
Cardiac
GI symptoms
Fatigue
Bleeding/Bruising
Nail/skin/hair
Edema
Cytopenias
Infection
Mucosal symptoms
CNS
Renal
Pneumonitis
Neuropathy
1.9%
5.1%
7%
1.4%
4.7%
6.1%
0.5%
4.7%
5.2%
2.3%
1.9%
4.2%
2.8%
0.9%
3.7%
0.9%
2.3%
3.2%
2.3%
0.5%
2.8%
0.5%
1.9%
2.4%
1.4%
0.5%
1.9%
1.4%
1.4%
0.5%
0.5%
1%
0.5%
0.5%
0.5%
0.5%
0.5%
0.5%
0%
2%
4%
6%
8%
Percentage of all patients
Dose reduction
Discontinuation
A
Management of adverse events (%) leading to dose modification
Rheumatologic
Cardiac
GI symptoms
Fatigue
Bleeding/Bruising
Nail/skin/hair
Edema
Cytopenias
Infection
Mucosal symptoms
CNS
Renal
Pneumonitis
Neuropathy
5.1%
1.4%
0.5%
7%
3.3%
1.9%
0.9%
6.1%
4.2%
0.5%
0.5%
5.2%
1.9%
1.9%
0.5%
4.2%
0.9%
1.9%
0.9%
3.7%
1.9%
1.4%
3.2%
0.5%
1.9%
0.5%
2.8%
1.4%
0.9%
2.4%
0.9%
0.9%
1.9%
0.9%
0.5%
1.4%
0.5%
0.5%
1%
0.5%
0.5%
0.5%
0.5%
0%
2%
4%
6%
8%
Percentage of all patients
Direct discontinuation
No improvement with dose reduction
Improvement with dose reduction
B

Figure 4


Patients
0
20
40
60
Months from zanubrutinib initiation
Zanubrutinib Dose
320 mg/day
240 mg/day
160 mg/day
80 mg/day
Event
Dose Reduction 1
Dose Reduction 2
Discontinuation due to toxicity
Progressive Disease