

Clinical Outcomes in Patients With Waldenström Macroglobulinemia Receiving Ibrutinib on the Phase 3 ASPEN Study ≥1 Year After Transitioning to Zanubrutinib

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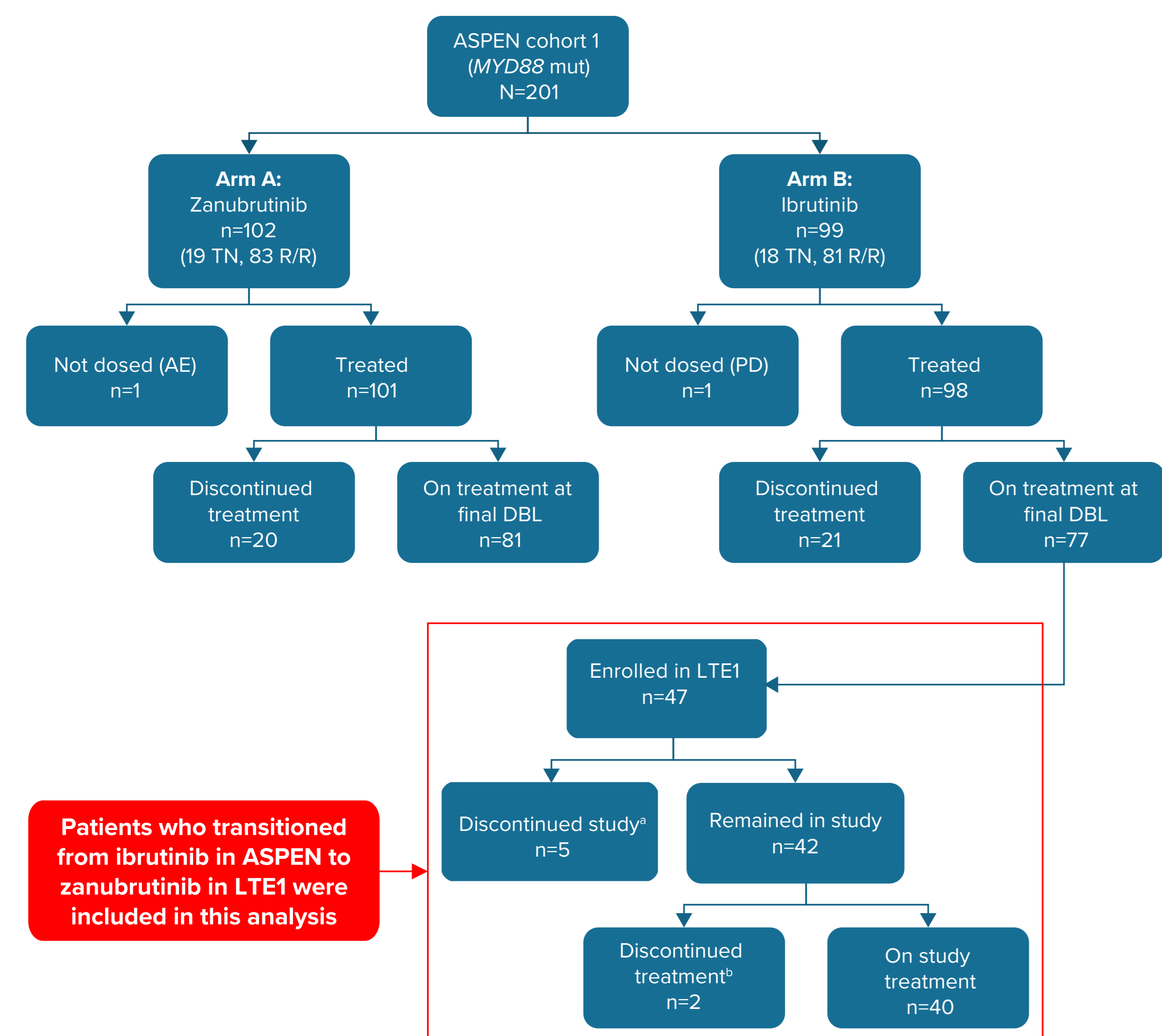
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become a standard of care in treating patients with Waldenström macroglobulinemia (WM)¹
- Zanubrutinib, a next-generation BTK inhibitor, was developed to ensure greater BTK specificity and potency than ibrutinib to avoid toxicities associated with off-target binding and improve efficacy²
- The ASPEN study (BGB-3111-302; NCT03053440) directly compared outcomes of zanubrutinib and ibrutinib treatment in patients with myeloid differentiation primary response 88 (MYD88)-mutated WM³
- The BGB-3111-LTE1 study (LTE1, NCT04170283) is a long-term extension study in which eligible patients can enroll following participation in parent studies of zanubrutinib for treatment of B-cell malignancies, including patients from comparator treatment arms
- Here, we report safety and efficacy outcomes in patients with WM receiving ibrutinib in ASPEN at ≥1 year after transitioning to zanubrutinib in the LTE1 study

METHODS

- All patients (N=47) who enrolled in LTE1 from the ibrutinib arm of ASPEN (arm B) were included in this *ad hoc* analysis (Figure 1)
- Patients began treatment with zanubrutinib at 320-mg total daily dose upon enrollment
- Safety and efficacy outcomes were evaluated, including the recurrence of ibrutinib treatment-emergent adverse events (TEAEs)
- Investigators assessed disease response every 6 months, or more frequently as indicated, based on the modified Owen criteria and using parameters at ASPEN study entry (BTK inhibitor pretreatment); alternatively, investigators could assess “no evidence of progressive disease” using their clinical judgment

Figure 1. CONSORT Diagram of the ASPEN and LTE1 Studies



* Reasons for study discontinuation (5 patients): death (n=3), lost to follow-up (n=1), and withdrawal (n=1).
 † Reasons for treatment discontinuation (5 patients who left the study plus 2 who remained in the study): “other” reasons (n=3), AEs (n=2), PD (n=1), and withdrawal (n=1).
 AE, adverse event; DBL, database lock; MYD88, myeloid differentiation primary response 88; PD, progressive disease; R/R, relapsed/refractory.

RESULTS

Disposition

- Between June 26, 2020, and June 23, 2022, 47 patients treated with ibrutinib in ASPEN enrolled in LTE1
 - Patient and disease characteristics are shown in Table 1
 - At enrollment in LTE1, the median time since ibrutinib treatment initiation was 50.4 months (range, 26-59.3)
- As of June 23, 2023, 40 patients (85%) remained on study treatment; the median zanubrutinib treatment duration was 15.3 months (range, 5.1-22.1), and the overall median treatment duration with BTK inhibitors was 65.5 months (range, 48.1-76.7)
- The median time from ASPEN study discontinuation to zanubrutinib initiation in LTE1 was 0.07 months (range, 0-4)

Table 1. Baseline Demographics and Clinical Characteristics of Enrolled Patients as They Proceeded From ASPEN to LTE1 (N=47)

At Enrollment in Parent Study (ASPEN)	After Enrollment in Long-Term Extension (LTE1)		
Age, median (range), years	68 (38-84)	Age, median (range), years	73 (44-89)
Age group, n (%)		Age group, n (%)	
<65 years	16 (34)	<65 years	8 (17)
≥65 and <75 years	22 (46.8)	≥65 and <75 years	21 (44.7)
≥75 years	9 (19.1)	≥75 years	18 (38.3)
Male, n (%)	34 (72.3)	ECOG performance status, n (%)	
Treatment status, n (%)		0	27 (57.4)
TN	10 (21.3)	1	17 (36.2)
R/R	37 (78.7)	2	1 (2.1)
Prior lines, median (range), n	1 (1-6)	Missing	2 (4.3)

ECOG, Eastern Cooperative Oncology Group; R/R, relapsed/refractory; TN, treatment naïve.

Safety Results

- Grade ≥3 and serious TEAEs occurred in 23% and 13% of patients, as presented in Table 2
 - Two deaths occurred in LTE1; both were due to COVID-19
- Infections (6.4%; all COVID-19) were the only grade ≥3 TEAEs that occurred in more than 2 patients, and no serious TEAEs occurred in more than 2 patients (Table 3)
- TEAEs of interest for zanubrutinib are presented in Table 4
- The majority of ibrutinib-emergent adverse events did not recur or worsen with zanubrutinib (Figure 2)
- Worsening of ibrutinib TEAEs of interest for BTK inhibitor treatment following the transition to zanubrutinib included infections (n=3), all of which were due to COVID-19 (Figure 2), anemia (n=1), and neutropenia (n=1)
- No ongoing hypertension worsened in severity and no new or recurrent episodes of hypertension occurred after patients switched from ibrutinib to zanubrutinib
- Of the 7 patients who experienced cardiovascular AEs (8 events) in LTE1, all but 1 (grade 2 tachycardia) experienced at least 1 cardiovascular AE during ibrutinib treatment in ASPEN; no cardiovascular TEAE led to death in LTE1
 - No resolved ibrutinib treatment-emergent atrial fibrillation/flutter recurred; no ongoing atrial fibrillation/flutter worsened following the transition to zanubrutinib
 - One new case of atrial fibrillation occurred on LTE1 day 12 in a patient with an extensive cardiovascular history who also experienced grade 2 pericarditis 2 days prior (LTE1 day 10)
 - Three patients, all with prior cardiovascular AEs on ibrutinib in the ASPEN study, developed pericarditis during the LTE1 study: on day 11, at 4 months, and at 9 months of zanubrutinib treatment, respectively; all cases resolved and were deemed unrelated to zanubrutinib by investigator

Table 2. TEAEs in Patients Participating in ASPEN and LTE1

Patients With ≥1 TEAE	ASPEN: Ibrutinib, n (%); N=47	LTE1: Zanubrutinib, n (%); N=47
TEAE	47 (100)	38 (80.9)
Treatment related	42 (89.4)	17 (36.2)
Serious	22 (46.8)	6 (12.8)
Treatment related	15 (31.9)	–
Leading to treatment discontinuation	3 (6.4)	2 (4.3) ^a
Leading to dose reduction	11 (23.4)	–
Leading to dose interruption	30 (63.8)	11 (23.4)
Fatal TEAE	–	2 (4.3) ^b

^aHematuria, COVID-19 pneumonia. ^bRespiratory failure, COVID-19 pneumonia. TEAE, treatment-emergent adverse event.

Table 3. Serious/Grade ≥3 TEAEs in Patients Participating in LTE1

Grade ≥3 TEAEs	n (%); N=47
Hypertension	1 (2.1)
Anemia	2 (4.3)
COVID-19	3 (6.4)
Neutropenia	2 (4.3)
Serious TEAEs	n (%); N=47
Pneumonia	2 (4.3)

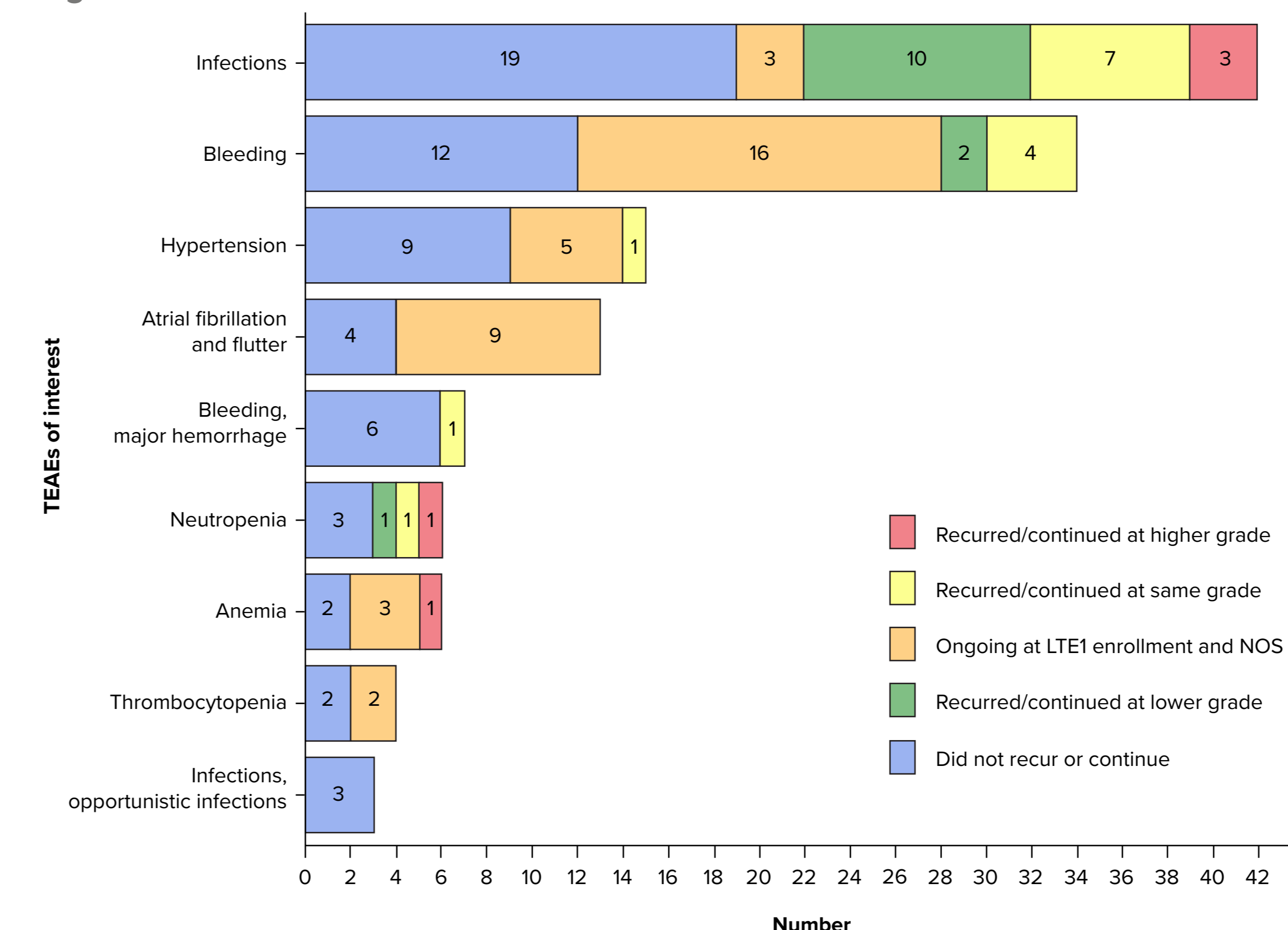
PT, preferred term; TEAE, treatment-emergent adverse event.

Table 4. TEAEs of Interest in Patients Treated With Zanubrutinib in LTE1

AEs of Interest for Zanubrutinib	Any Grade, n (%); N=47	Grade ≥3, n (%); N=47
Infections	22 (46.8)	3 (6.4)
Hemorrhage	6 (12.8)	1 (2.1)
Second primary malignancies – skin cancer	4 (8.5)	–
Second primary malignancies – non-skin cancer ^a	1 (2.1)	–
Hypertension	1 (2.1)	1 (2.1)
Atrial fibrillation/flutter	1 (2.1)	–
Neutropenia ^b	5 (10.6)	2 (4.3)
Thrombocytopenia ^b	1 (2.1)	–
Anemia ^b	4 (8.5)	2 (4.3)

^aProstate cancer. ^bGrouped terms. AE, adverse event; TEAE, treatment-emergent adverse event.

Figure 2. Recurrence or Continuation of Ibrutinib TEAEs on Zanubrutinib



NOS, not otherwise specified; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- The majority of ibrutinib-emergent adverse events did not recur or worsen with zanubrutinib treatment, despite advanced and increasing age
- WM disease response was maintained or improved in 96% of efficacy-evaluable patients (44/46)
- While limited by sample size and nonrandomized/ad hoc analysis, data suggest that patients who are tolerating ibrutinib may switch to zanubrutinib without compromising, and may improve upon, safety or efficacy; long-term follow-up is ongoing

Efficacy Results

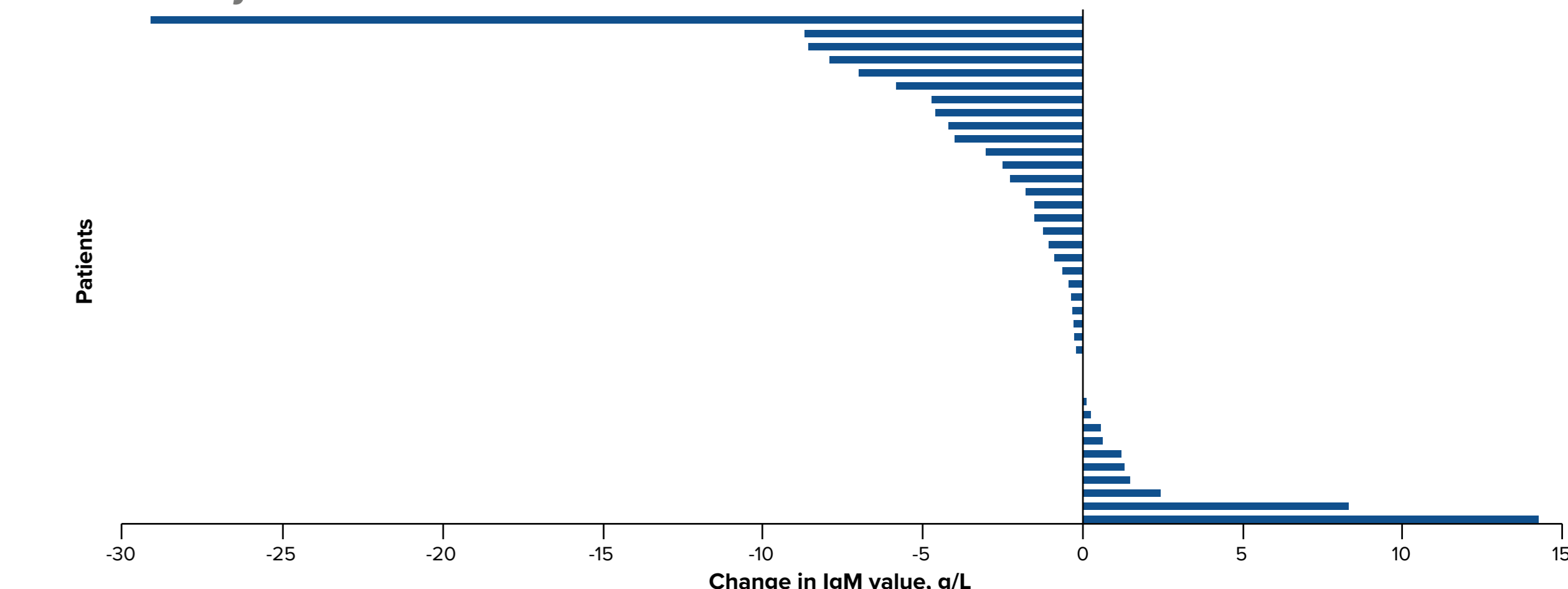
- Categorical best overall response in LTE1 was unchanged from the last response in ASPEN in 34 patients (72%) and improved in 10 patients (21%; Table 5)
 - One patient in partial response (PR) and 1 patient in very good partial response at the end of ASPEN had a deepening response achieving a negative immunofixation in LTE1
 - One patient with last response assessment of PR in ASPEN after over 4 years on ibrutinib (local [IgM] at end of treatment already met criteria for minor response: decreased 45% from baseline) was assessed to be in minor response after 6 months ([IgM] 44% decreased from baseline) and 12 months ([IgM] 48% decreased from baseline) on zanubrutinib
 - One patient had “no evidence of progressive disease” and 1 patient discontinued before response assessment
- [IgM] was stable or decreased in the majority of evaluable patients (Figure 3)

Table 5. Overall Response Assessments in Patients Enrolled in ASPEN and LTE1

Overall Response Assessment by PI	ASPEN BOR	ASPEN Last RA	LTE1 BOR
	n (%); N=47		
CR	0	0	2 (4.3)
VGPR	15 (31.9)	13 (27.7)	17 (36.2)
PR	31 (66)	27 (57.4)	23 (48.9)
MR	1 (2.1)	3 (6.4)	3 (6.4)
IgM flare	N/A	1 (2.1)	N/A
PD	N/A	2 (4.3)	N/A
Not evaluable	N/A	1 (2.1)	N/A
No evidence of PD	N/A	N/A	1 (2.1)
Discontinued prior to assessment	N/A	N/A	1 (2.1)

* Grouped terms. BOR, best overall response; CR, complete response (negative immunofixation, not confirmed by bone marrow biopsy); IgM, immunoglobulin M; MR, minor response; N/A, not applicable; PD, progressive disease; PI, principal investigator; PR, partial response; RA, response assessment; VGPR, very good partial response.

Figure 3. Change in [IgM] From Last Response Assessment in ASPEN Study to BOR in LTE1 Study



BOR, best overall response; IgM, immunoglobulin M.

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