

Ergebnisse ≥1 Jahr nach dem Wechsel der Behandlung von Ibrutinib (ibru) zu Zanubrutinib (zanu) in der ASPEN-Studie

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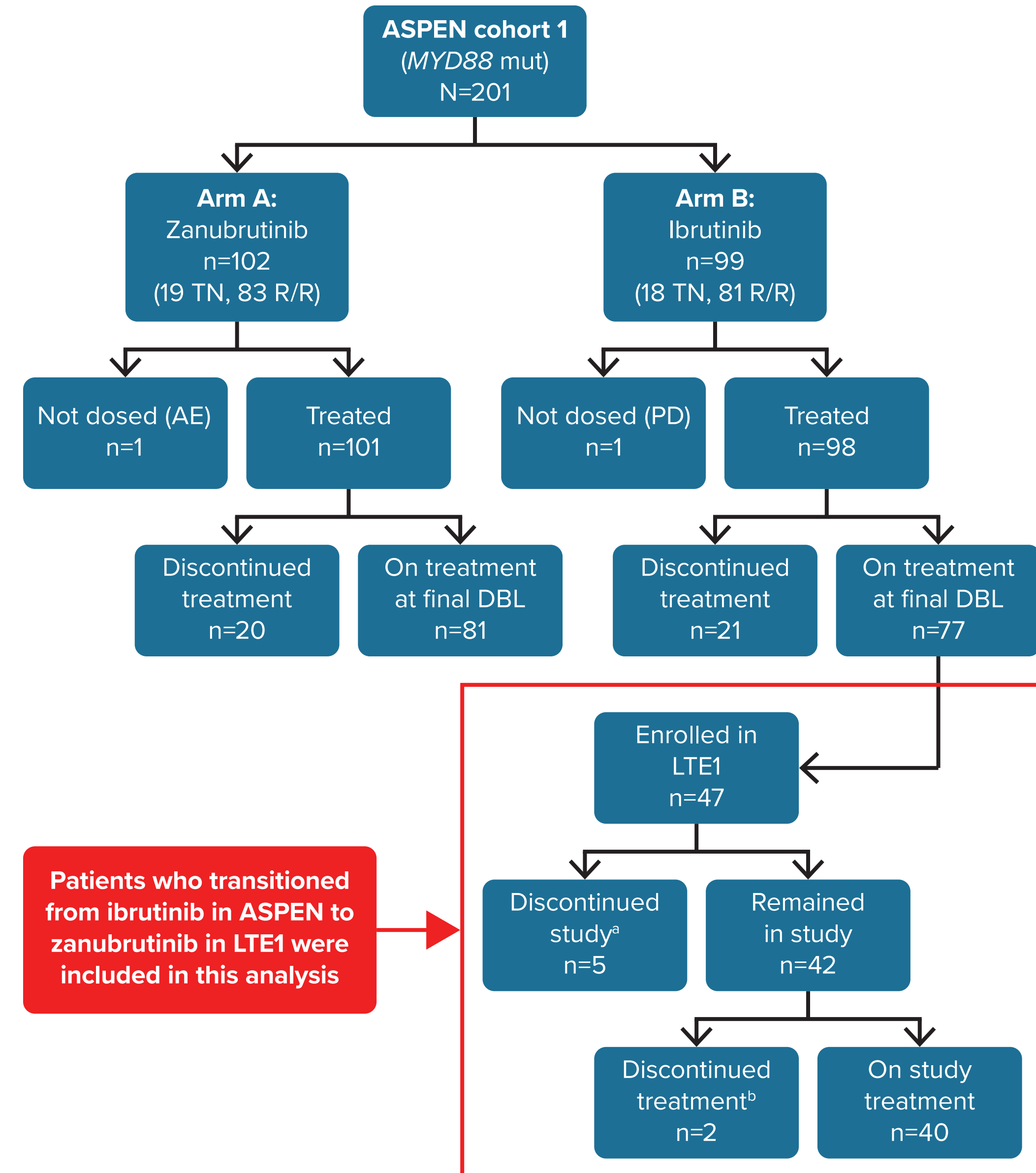
INTRODUCTION

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

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

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 AEs 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 Occurring in ASPEN and LTE1

Patients With ≥1 TEAE	ASPEN: Ibrutinib, N=47 n (%)	LTE1: Zanubrutinib, N=47 n (%)
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 Occurring in LTE1

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

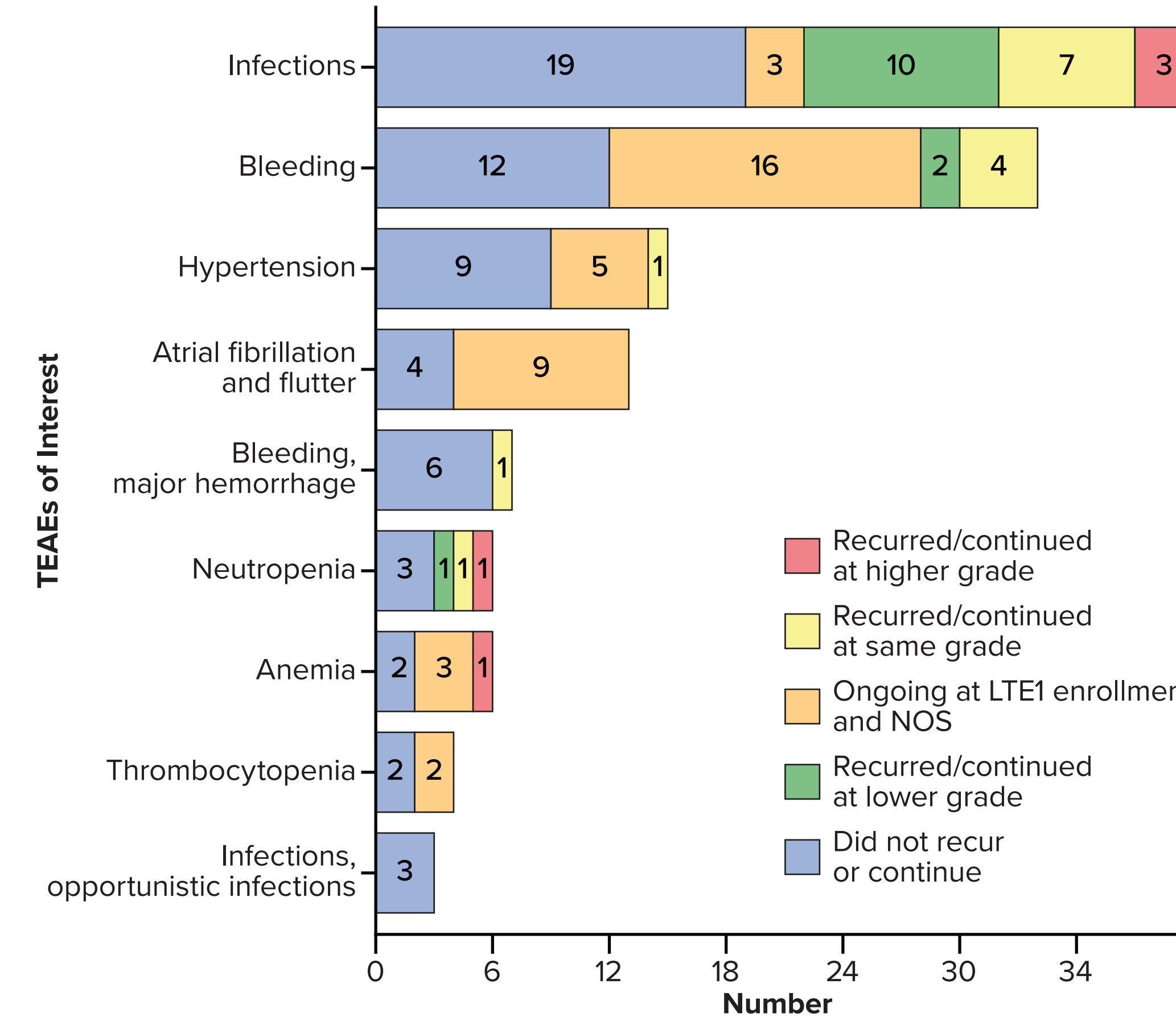
PT, preferred term; TEAE, treatment-emergent adverse event.

Table 4. TEAEs of Interest in Zanubrutinib-Treated Patients Occurring in LTE1

AEs of Interest for Zanubrutinib	Any Grade, N=47 n (%)	Grade ≥3, N=47 n (%)
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 AEs 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

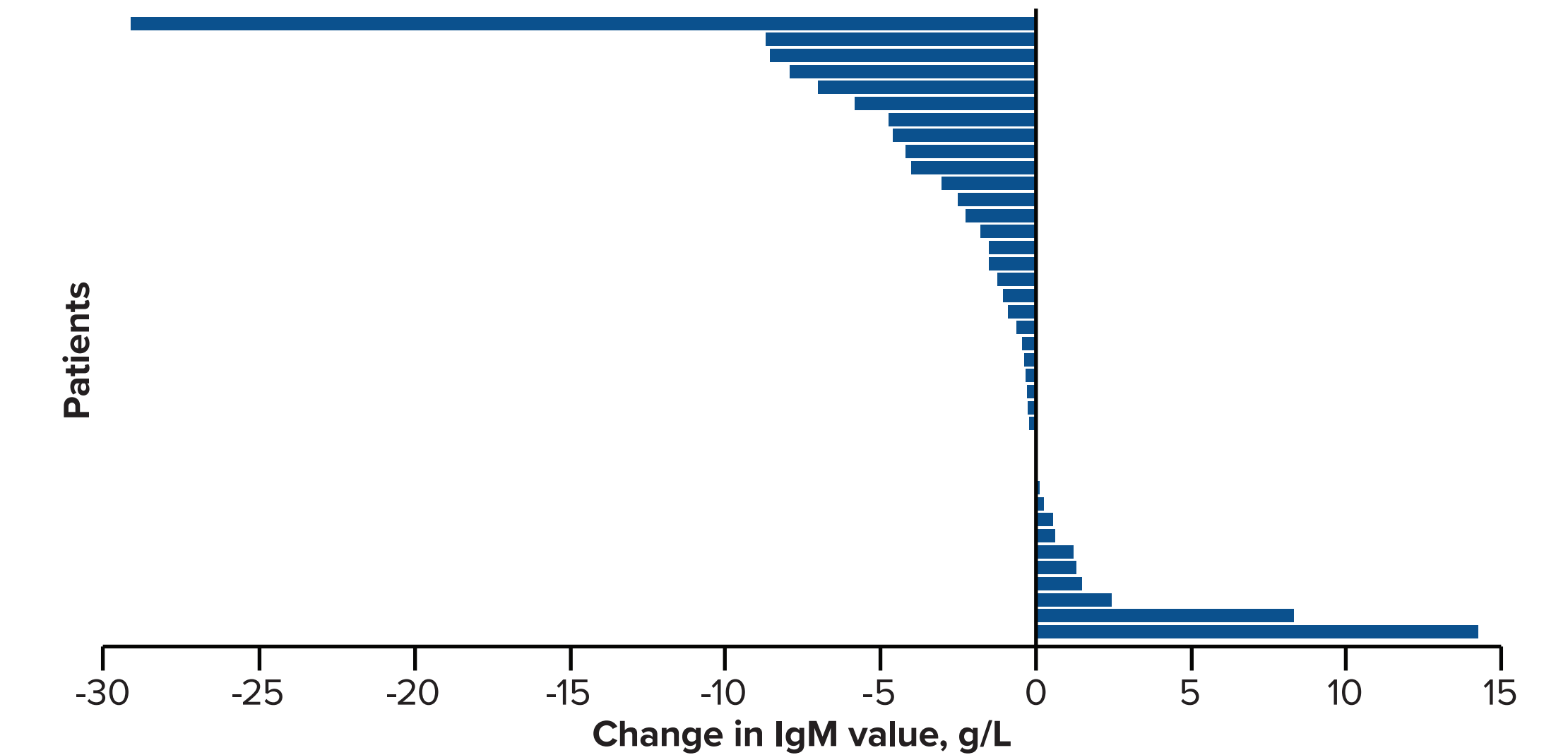
- Categorical best overall response in LTE1 was unchanged or improved from last response in ASPEN in 96% of evaluable patients (44/46; Table 5)
 - One patient in partial response (PR) and 1 patient in very good partial response at the end of ASPEN had a deepening response achieving a negative immunofixation 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, N=47	ASPEN BOR n (%)	ASPEN Last RA n (%)	LTE1 BOR n (%)
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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DISCLOSURES

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