Zanubrutinib Is Well Tolerated and Effective in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

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Disclosures

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manuscript fee	x	
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contributions or endowed chair	x	
fees of testimony, judgment, comment, etc.	x	
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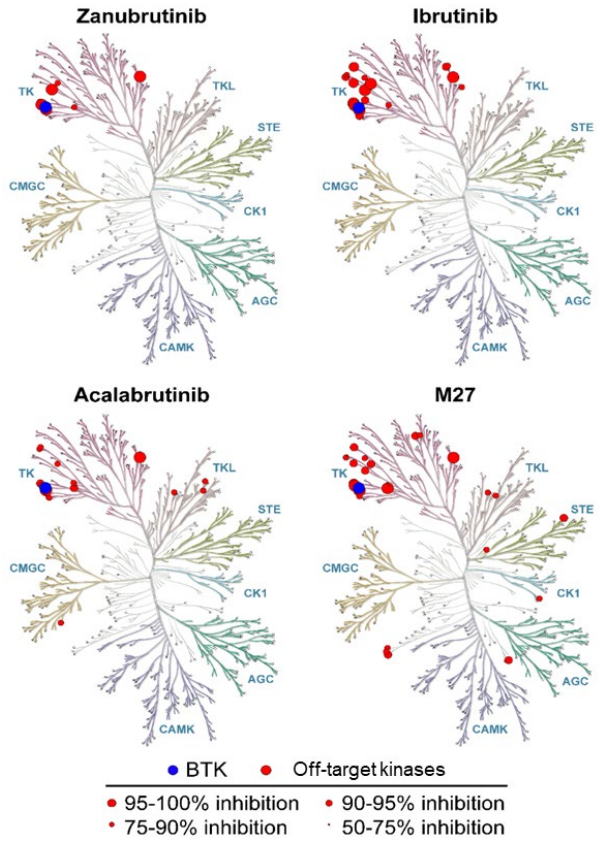
Introduction

- BTK inhibitors are a mainstay of treatment for B-cell malignancies; however, their use can be limited by AEs, many of which are potentially caused by off-target inhibition of other tyrosine kinases[1-3]
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and potency as well as increased selectivity to increase efficacy and to minimize off-target kinase binding and associated AEs[4]
- Previous results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib was well tolerated in patients who were intolerant of ibrutinib and/or acalabrutinib[5]
- Here, we report updated results on the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (cohort 2)

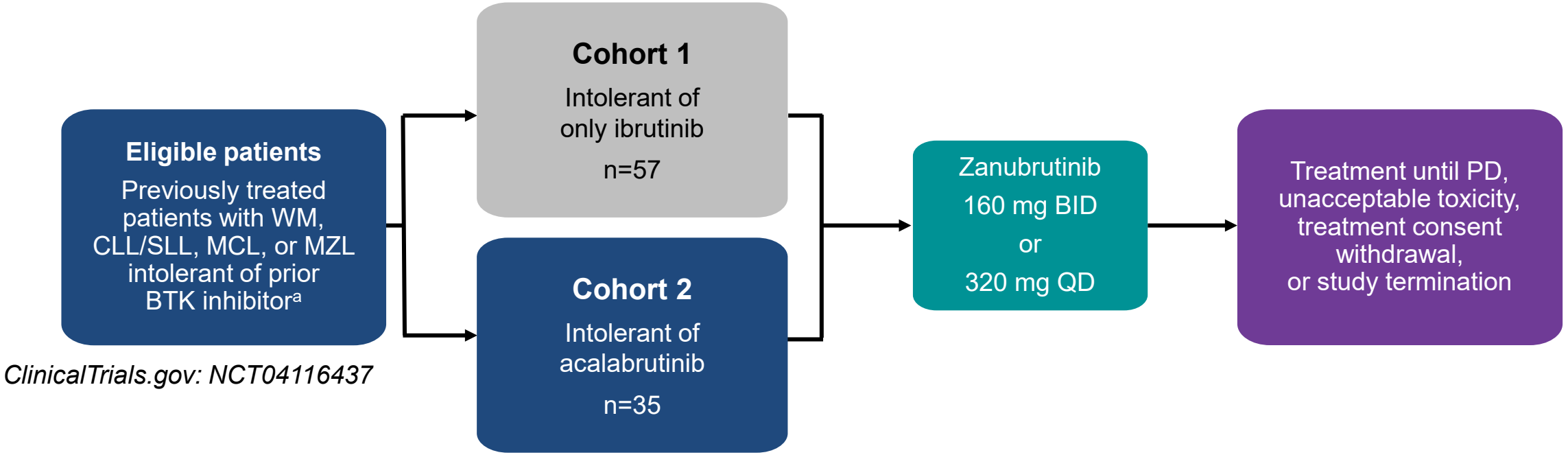
Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and Acalabrutinib Metabolite M27



AE, adverse event; BTK, Bruton tyrosine kinase.

1. Stephens DM, Byrd JC. *Blood.* 2019;133(12):1298-1307; 2. Furman RR, et al. *Leukemia*. 2021;35(11):3201-321; 3. Mato AR, et al. *Haematologica*. 2018;103(5):874-879; 4. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 5. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45; 6. Shadman M, et al. *Blood.* 2021;138(suppl 1). Abstract 1410.

BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437

Primary objective: evaluate safety of zanubrutinib in acalabrutinib-intolerant patients, as assessed by recurrence and change in severity of acalabrutinib-intolerance AEs

Secondary objective: evaluate efficacy of zanubrutinib by investigator-assessed ORR, DCR, PFS, and patient-reported outcomes

AE, adverse event; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DCR, disease control rate; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Methods

- Acalabrutinib intolerance is defined as an unacceptable toxicity were, in the opinion of the investigator, treatment should be discontinued despite optimal supportive care as a result of one of the following:
  - Grade ≥1 nonhematologic toxicities with ≥3 recurrent episodes or episodes lasting >7 days, or grade ≥3 toxicities of any duration
  - Grade 3 neutropenia with infection or fever of any duration
  - Grade 4 heme toxicity persisting to the point that the investigator chose to stop therapy due to toxicity, not progression
  - Inability to use acid-reducing agents or anticoagulants (eg, proton pump inhibitors, warfarin) due to concurrent acalabrutinib use
- Data is reported for both the SAS and the EES
  - The EES is defined as patients in the SAS who had a baseline disease assessment and ≥1 post-baseline disease assessment; patients who discontinued the study due to AEs or death prior to their first scheduled disease assessment are included in the EES
- Patients with Richter transformation or PD while receiving prior BTK inhibitor treatment were excluded

BTK, Bruton tyrosine kinase; EES, efficacy evaluable set; PD, progressive disease; SAS, safety analysis set.

Patient Disposition

- As of May 1, 2024, of 35 acalabrutinib-intolerant patients, 23 (65.7%) received zanubrutinib 160 mg twice daily, and 12 (34.3%) received 320 mg once daily
- 11 patients (31.4%) discontinued zanubrutinib treatment

Patients, n (%)	Acalabrutinib-intolerant (n=35)
Remaining on study	31 (88.6)[a]
Remaining on treatment	24 (68.6)
Discontinued from treatment	11 (31.4)
AE	5 (14.3)[b]
Physician decision	3 (8.6)
PD	2 (5.7)
Withdrawal by patient	1 (2.9)
Death, n (%)	1 (2.9)[c]
Zanubrutinib treatment duration, median (range), months	14.8 (0.1-43.8)
Survival follow-up, median (range), months	18.9 (0.1-43.8)

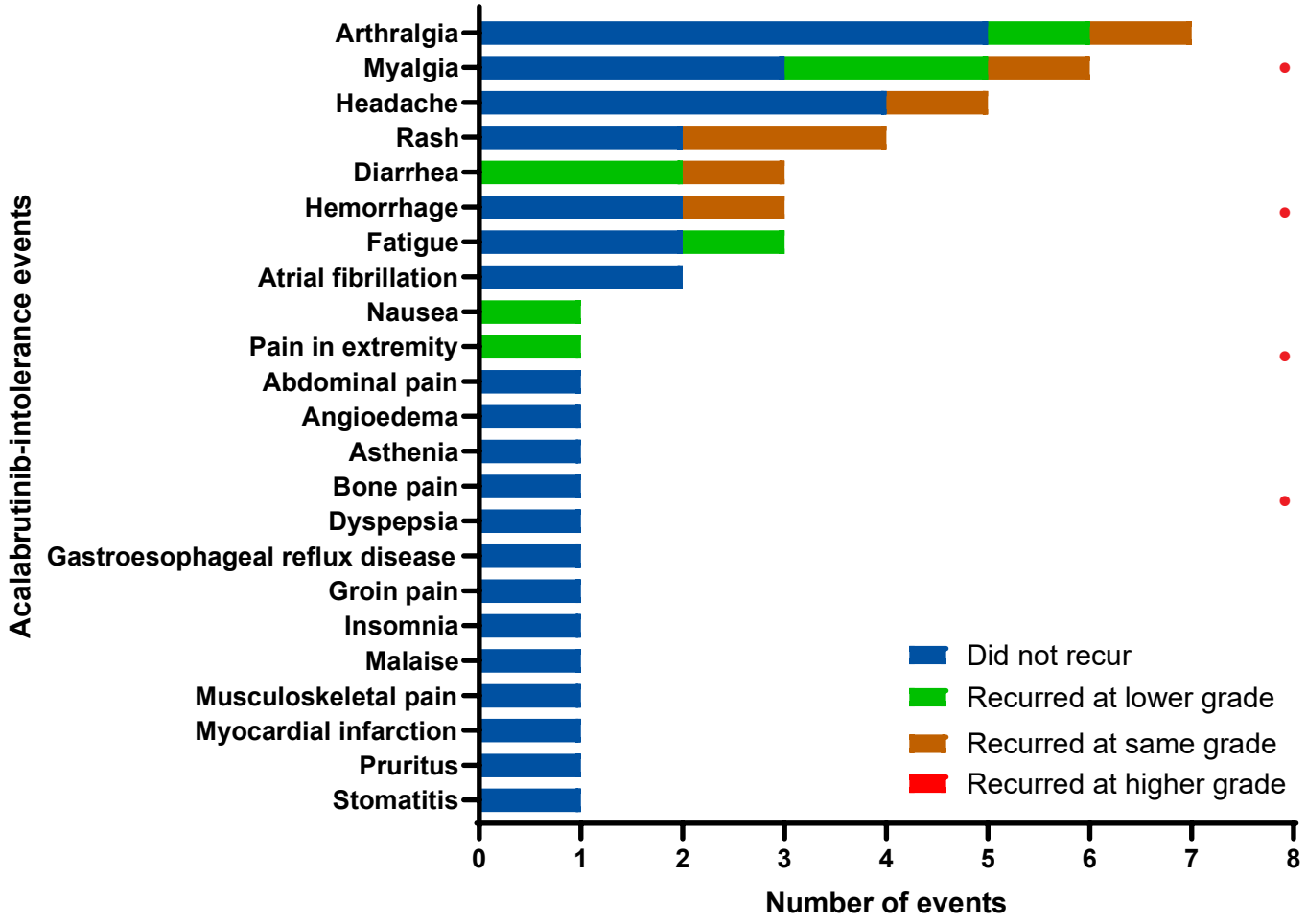
[a] Study discontinuations were due to patient withdrawal (n=2), lost to follow-up (n=1), and death (n=1). [b] Diarrhea (n=2), skin toxicity, myalgia, and rash (n=1 for each). [c] PD.
AE, adverse event; PD, progressive disease.

Patient Demographics and Baseline Characteristics

Characteristic	Acalabrutinib-intolerant (n=35)
Indication, n (%)	
CLL	25 (71.4)
WM	4 (11.4)
SLL	2 (5.7)
MCL	2 (5.7)
MZL	2 (5.7)
Age, median (range), years	71 (51-87)
Sex, n (%)	
Male	19 (54.3)
Female	16 (45.7)
ECOG PS, n (%)	
0	23 (65.7)
1	10 (28.6)
2	2 (5.7)
No. of prior anticancer therapy regimens, median (range)	2 (1-6)
Prior BTK inhibitor, n (%)	
Acalabrutinib monotherapy	32 (91.4)
Acalabrutinib combination therapy	3 (8.6)
Ibrutinib monotherapy	13 (37.1)
Ibrutinib combination therapy	1 (2.9)
Cumulative acalabrutinib exposure, median (range), months	5.7 (0.2-68.6)

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Recurrence of Acalabrutinib-Intolerance Events on Zanubrutinib



- 23 of 35 patients (66%) did not experience any recurrence of the prior acalabrutinib-intolerance events
- Most acalabrutinib-intolerance events (33 of 48 [69%]) did not recur at any grade with zanubrutinib
- Of the 15 that did recur, none recurred at a higher severity (8 at a lower grade; 7 at the same grade)
- 3 patients discontinued zanubrutinib due to recurrence of a prior acalabrutinib-intolerance event (myalgia, rash, and diarrhea; all recurred at the same grade)

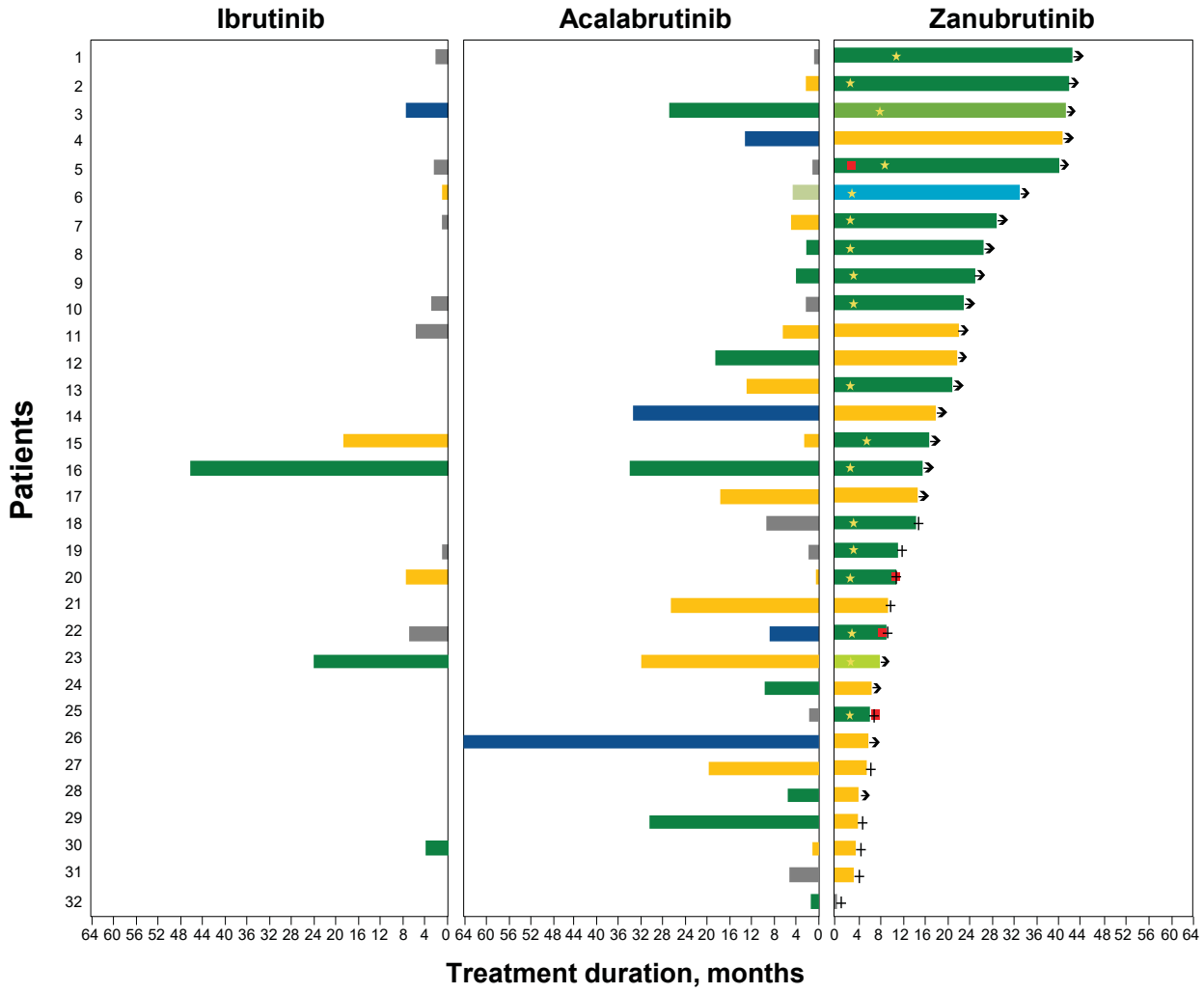
Overall Summary of TEAEs for Patients on Zanubrutinib

Patients, n (%)	Any grade (n=35)
Serious TEAE	9 (25.7)
Grade ≥3 TEAE	17 (48.6)[a]
Leading to treatment discontinuation	5 (14.3)
Leading to dose interruption	23 (65.7)
Leading to dose reduction	8 (22.9)
Grade 5 TEAE	0

- No AEs led to death
- The most common TEAEs (any grade occurring in ≥15% of patients) were diarrhea, fatigue, COVID-19, arthralgia, cough, hypertension, and contusion
  - The most common grade ≥3 AE was neutrophil count decreased, which occurred in 3 patients (8.6%)
  - Anemia and thrombocytopenia did not occur at any grade

[a] The most common grade ≥3 AEs (≥2 patients) included cellulitis, COVID-19 pneumonia, hypertension, neutrophil count decreased, and neutropenia.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Treatment Duration With Best Overall Response by Investigator Assessment



- In the 32 efficacy-evaluable patients, the disease control rate was 93.8% (95% CI, 79.2%-99.2%)
- Best overall response:
  - SD: 13 patients (40.6%)
  - Better than SD: 17 patients (53.1%)
  - PD: 1 patient (3.1%)

CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response.

Conclusions

- Zanubrutinib was well-tolerated in patients with prior acalabrutinib intolerance
- Among the minority of recurrent events, none recurred at a higher grade, and few (3/15) led to discontinuation of zanubrutinib
- Zanubrutinib provided a clinically meaningful efficacy benefit in patients who were previously intolerant of acalabrutinib, as measured by a disease control rate of 94%, maintaining response after treatment, and deepening of response on treatment with zanubrutinib
- The results from this study demonstrated that switching to zanubrutinib may be an excellent treatment option for patients who are intolerant of other covalent BTK inhibitors, ibrutinib[1] and acalabrutinib

1. Stephens DM, Byrd JC. *Blood.* 2019;133(12):1298-1307.

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