Phase 2 Study of Zanubrutinib in BTK Inhibitor-Intolerant Patients (Pts) With Relapsed/Refractory B-cell Malignancies

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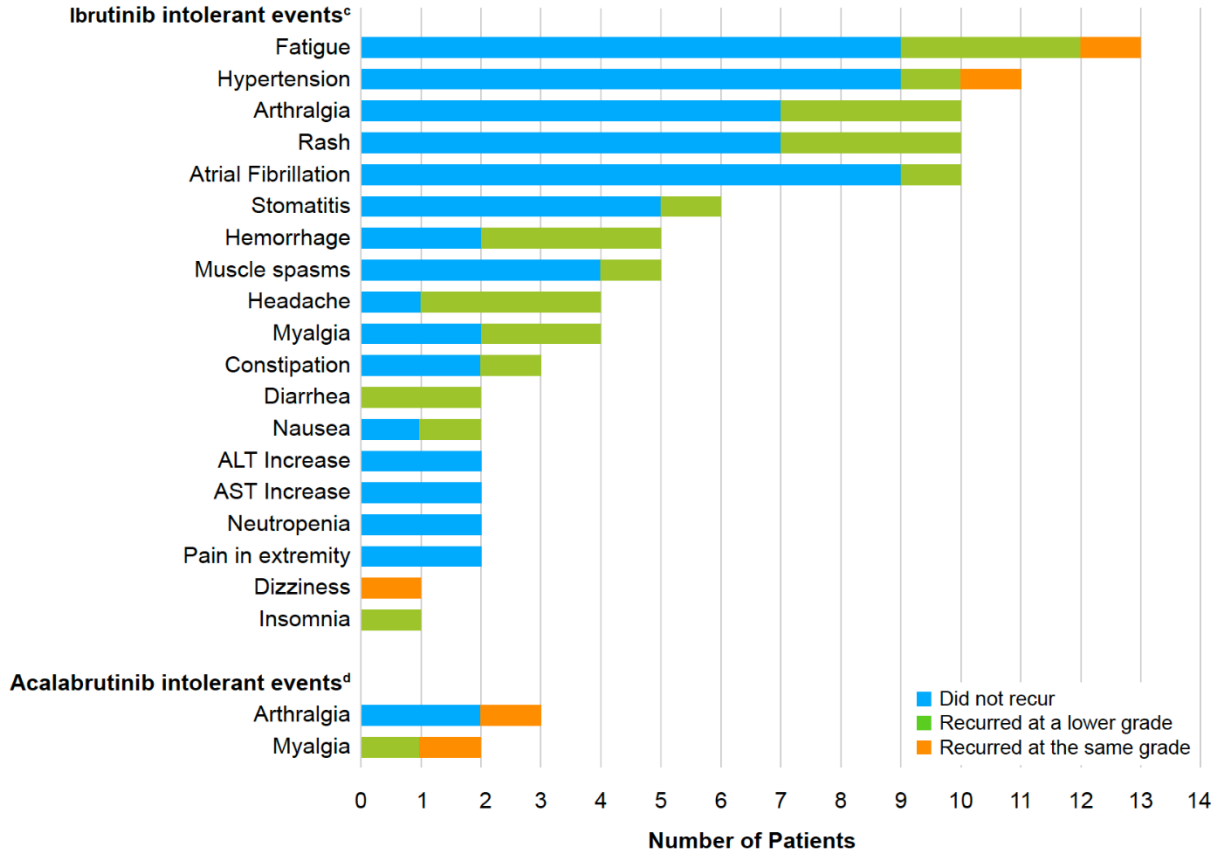
Background: Bruton tyrosine kinase inhibitors (BTKis) are important tools to treat B-cell malignancies. However, duration of treatment may be limited by adverse events (AEs). Zanubrutinib (zanu) is a BTKi approved for mantle cell lymphoma (MCL) and is in development for other hematologic malignancies. Data from phase 3 head-to-head trials of zanu vs ibrutinib (ibr) in pts with Waldenström macroglobulinemia (WM) or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) demonstrated that pts treated with zanu showed lower rates of AEs leading to discontinuation (*Blood* 2020;136(18):2038-50; EHA 2021 LB1900). Preliminary results from BGB-3111-215 (NCT04116437) show that zanu was well-tolerated in pts who discontinued ibr and/or acalabrutinib (acala) treatment due to AEs (EHA 2021 EP642). Here, we report updated results from the BGB-3111-215 study with a median follow-up of 9 months.

Methods: This study is an ongoing US, phase 2, multicenter, single-arm, open-label study. The safety and efficacy of zanu monotherapy (160 mg twice daily or 320 mg once daily) were evaluated in pts with B-cell malignancies who met criteria for continued treatment after having become intolerant to prior BTKi therapy. Pts were divided into cohort 1 (pts who were intolerant to ibr only) and cohort 2 (pts who were intolerant to acala alone/and ibr). Pts with documented progressive disease (PD) on prior BTKi therapy were excluded. Efficacy and safety, including recurrence of intolerant AEs to the prior BTKi, were evaluated. AEs were assessed for severity, seriousness, and relation to zanu; as well as dose reductions, holds, or discontinuations. Response was assessed by investigators based on response criteria for their respective indications (*Blood* 2008;131:2745; *J Clin Oncol* 2012;30:2820; *J Clin Oncol* 2014;32:3059; *Br J Haemtol* 2013;160:171). Disease parameters from study entry were the baseline for response assessment. Mutational analysis was performed on pts who discontinued treatment, and data will be shared once available. To support clinical findings, kinase selectivity was assessed using Kinome profiling at 100X IC50 (against BTK) for zanu, ibr, acala and its major metabolite, M27 (Reaction Biology Corp).

Results: As of 7 June 2021 (data cutoff), 57 pts (n=44 CLL/SLL; n=9 WM; n=2 MCL; n=2 marginal zone lymphoma [MZL]) were enrolled in cohort 1, and 7 pts were enrolled in cohort 2 (n=4 CLL; n=1 WM; n=1 MCL; n=1 MZL). All received ≥1 dose of zanu and were analyzed for safety. The median age was 71 years (range, 49–91) in cohort 1 and 71 years (range, 65–76) in cohort 2; median duration of treatment was 8.7 months (range, 0.6–17.9) in cohort 1 and 8.2 months (range, 6.4–11.4) in cohort 2; median number of prior regimens was 1 (range, 1–12) in cohort 1 and 3 (range, 2–5) in cohort 2. Within cohort 2, 5 pts were intolerant to both ibr and acala. Median number of intolerant events per pt for both cohorts 1 and 2 was 2 (range, 1–5). Overall, 73% of pts did not experience recurrence of their ibr or acala intolerant events and 79% of recurrent events recurred at a lower severity (**Figure 1**). At cutoff, 54 pts remained on treatment. Reasons for treatment discontinuation were AEs (n=4), PD (n=4), physician's decision (n=1), and consent withdrawal (n=1). Grade ≥3 AEs were reported in 18 pts (28%), and serious AEs occurred in 7 pts (11%). AEs requiring dose interruptions occurred in 17 pts (27%), and AEs leading to dose reduction occurred in 3 pts (5%). One death, due to COVID-19, was reported. Pts demonstrated maintained (41%) and improved (53%) response with zanu treatment from their reported best overall response on prior BTKis for a total disease control rate of 94% (including a 42% partial response rate in pts with CLL/SLL, 30% in pts with WM, and a 20% very good partial response rate in pts with WM). Zanu also demonstrated good selectivity by kinase profiling. It showed >50% inhibition on 7/370 kinases, while ibr, acala, and M27 had more off-target binding (17, 15 and 23 kinases, respectively) at their respective 100X IC50 (BTK) concentrations (**Figure 2**).

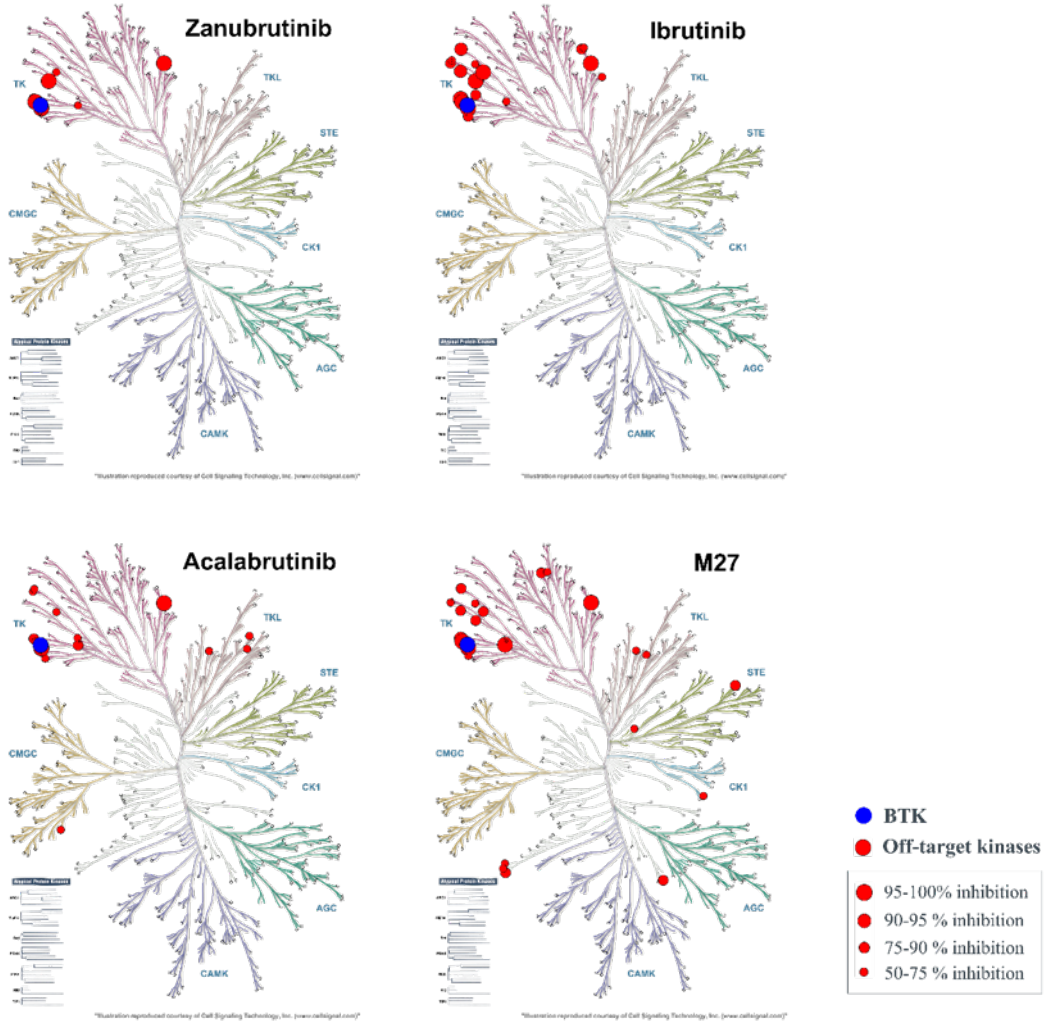
Conclusion: In pts with B-cell malignancies intolerant to ibr and/or acala, zanu treatment resulted in continued disease control or improved response. Zanu was well-tolerated, and most AEs that led to discontinuation of previous BTKi therapy did not recur or recurred at a lower grade. In support of clinical findings, differentiation between BTKi selectivity profiles favor zanu over ibr and acala.

Figure 1: Recurrence of Ibrutinib and Acalabrutinib Intolerant Events on Zanubrutinib[a, b]



ALT, alanine transaminase; AST, aspartate aminotransferase.
[a]Intolerant events occurring in ≥2 patients or recurring in ≥1 patient.
[b]No intolerant event recurred at a higher severity.
[c]Ibrutinib intolerant events that occurred in 1 patient and did not recur were arthritis, bone pain, bronchitis, embolism, irregular heart rate lymphedema, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, thrombocytopenia, transaminases increased, ventricular extrasystoles, vertigo, and vomiting.
[d]Acalabrutinib intolerant events that occurred in 1 patient and did not recur were atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, and pain in extremity.

Figure 2. Kinome profiling of BTK inhibitors[a,b]



AUC, area under the curve; BTK, Bruton tyrosine kinase.

[a]M27 is a major metabolite of acalabrutinib with exposure 2- to 3-fold higher than parent AUC (*CPT Pharmacometrics Syst Pharmacol*. 2019;8(7):489-99).

[b]Assayed by Reaction Biology Corp. at 100X of IC50 (against BTK) concentrationwith IC50 (BTK) of 0.71±0.09, 0.32±0.09, 24±9.2 and 63±28 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib and M27, respectively.