ZANUBRUTINIB IN ACALABRUTINIB-INTOLERANT PATIENTS (PTS) WITH B-CELL MALIGNANCIES

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Background

Bruton tyrosine kinase inhibitors (BTKi) are highly effective against several B-cell malignancies; however, their use is limited by adverse events (AEs), potentially due to off-target inhibition of other kinases. The next-generation BTKi zanubrutinib was designed to minimize off-target inhibition thereby prolonging duration of treatment with limited AEs. Zanubrutinib is approved in the US for Waldenström's macroglobulinemia (WM), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL) and in Europe for WM. In phase 3 trials of zanubrutinib versus ibrutinib in WM and chronic lymphocytic lymphoma/small lymphocytic lymphoma (CLL/SLL), zanubrutinib has consistently shown higher tolerability than ibrutinib (*Blood* 2020;136(18):2038-50; EHA 2021 LB1900). Previous results from this ongoing phase 2 study, BGB-3111-215 (NCT04116437), show that zanubrutinib was well tolerated in pts who discontinued ibrutinib and/or acalabrutinib due to AEs (*Blood* 2021;138[suppl 1]:1410). Here, we report updated results from acalabrutinib-intolerant pts (cohort 2) in BGB-3111-215.

Aims

To assess the safety of zanubrutinib in pts intolerant to acalabrutinib by the recurrence and change in severity of AEs that led to acalabrutinib intolerance.

Methods

In this ongoing, multicenter, single-arm, phase 2 study in the US, eligible acalabrutinib-intolerant pts with CLL/SLL, WM, MCL, or MZL who met protocol-defined acalabrutinib-intolerance criteria and gave informed consent were enrolled in cohort 2. Pts who progressed on prior BTKi therapy were excluded. Pts received zanubrutinib 160 mg twice daily or 320 mg once daily and were evaluated for safety and efficacy, including recurrence of any intolerance events from prior BTKi. Responses were assessed by investigators every 3 cycles based on

standard response criteria for each indication using parameters at study entry as baseline (*Blood* 2008;131:2745; *J Clin Oncol* 2012;30:2820; *J Clin Oncol* 2014;32:3059; *Br J Haemtol* 2013;160:171).

Results

As of 6 January 2022, 13 pts received zanubrutinib in cohort 2 (9 CLL/SLL; 2 WM; 1 MCL; 1 MZL). Median age was 73 years (range 51-83) and median duration of treatment was 9.2 months (range 0.5-16.0), with a median follow-up of 12.9 months (range 0.8-16.0). Median number of prior therapies was 2; 62% of pts received ibrutinib before acalabrutinib. Acalabrutinib was the most recent therapy for all pts. Ten pts remain on treatment. Three pts discontinued treatment (myalgia, progressive disease and withdrawal; 1 pt each) and withdrew from the study thereafter.

Twenty-two acalabrutinib-intolerance events were reported in 13 pts, most commonly arthralgia (4), myalgia (3), headache (2), and hemorrhage (2). A total of 73% of the acalabrutinib-intolerance events did not recur on zanubrutinib, corresponding to 62% of pts not experiencing a recurrence of any event. Six events recurred: 1 at lower grade, 5 at same grade, and none at higher grade (**Figure**). One pt discontinued due to recurrence of their acalabrutinib-intolerance event (myalgia; same grade). Three pts who experienced the same intolerance events (pain in extremity, diarrhea, and atrial fibrillation) on ibrutinib and acalabrutinib did not have a recurrence of those on zanubrutinib. Among the 10 pts on zanubrutinib with ≥90 days of follow-up, 80% achieved at least stable disease and 70% achieved a deepening of response.

Conclusion/Summary

Zanubrutinib may be a viable therapeutic option for pts who are intolerant to acalabrutinib—80% of pts received clinical benefit, and most did not experience recurrence of their prior intolerance events. Enrollment and follow-up are ongoing.

Figure: Recurrence and Severity of Acalabrutinib-Intolerance Events While on Treatment With Zanubrutinib