ZANUBRUTINIB IN ACALABRUTINIB-INTOLERANT PATIENTS WITH B-CELL MALIGNANCIES

Authors: *Pier Luigi Zinzani*,[1] Mazyar Shadman,[2] Ian W. Flinn,[3] Edwin C. Kingsley,[4] Benjamin Freeman,[5] Moshe Y. Levy,[6] Jennifer Cultrera,[7] Charles M. Farber,[8] Arvind Chaudhry,[9] Ryan Porter,[10] Rocco Crescenzo,[11] Adam Idoine,[11] Xiaoping Zhang,[11] Aileen Cohen,[11] Kunthel By,[11] Jeff P. Sharman[12]

[1]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy; [2]Fred Hutchinson Cancer Research Center, University of Washinton, Seattle, WA; [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN USA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]Summit Medical Group, Florham Park, NJ, USA; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [7]Florida Cancer Specialists & Research Institute, Leesburg, FL, USA; [8]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ USA; [9]Summit Cancer Centers, Spokane, WA, USA; [10]SSM Health Dean Medical Group, Madison, WI, USA; [11]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [12]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA

ABSTRACT

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 kinase inhibition. The next-generation BTKi zanubrutinib (zanu) was designed to minimize off-target effects to prolong treatment duration and limit AEs. In phase 3 trials in WM and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), zanu has consistently shown higher tolerability vs ibrutinib (ibr). Previous results from the ongoing, multicenter, single-arm, phase 2 study, BGB-3111-215 (NCT04116437), show that zanu was well tolerated in patients (pts) who discontinued (d/c) ibr and/or acalabrutinib (acala) due to AEs. Here, we report updated results from acala-intolerant pts in BGB-3111-215. Eligible acala-intolerant pts with CLL/SLL, WM, MCL, or MZL were enrolled in cohort 2; progression on prior BTKi was not allowed. Pts received zanu 160 mg twice daily or 320 mg once daily and were evaluated for efficacy and safety, including recurrence of intolerant AEs from prior BTKi. Investigator-assessed responses were recorded every 3 cycles per standard response criteria. As of 6Jan2022, 13 pts received zanu (9 CLL/SLL; 2 WM; 1 MCL; 1 MZL); 10 pts remain on treatment. Median age was 73 y (range 51-83); median treatment duration was 9.2 mo (range 0.5-16.0) and median follow-up was 12.9 mo (range 0.8-16.0). Median number of prior therapies was 2; 62% of pts received ibr before acala, which was the most recent therapy for all. Three pts d/c treatment (myalgia, progressive disease, and withdrawal; 1 each) and withdrew from the study thereafter. 22 acala-intolerant AEs occurred in 13 pts, most commonly, arthralgia (4), myalgia (3), headache (2), and hemorrhage (2). 73% of acala-intolerant AEs did not recur on zanu; 62% of pts had no AE recurrence. 6 AEs recurred: 1 at lower grade, 5 at same grade, and 0 at higher grade (**figure**). One pt d/c due to recurrence (myalgia, same grade). 3 pts who experienced the same intolerant AEs (pain in extremity, diarrhea, and atrial fibrillation) on ibr and acala did not have recurrence on zanu. Among 10 pts on zanu with ≥90 d of follow-up, 80% had at least stable disease and 70% had a deepening of response. These data suggest that zanu may be a viable therapeutic option for pts who are acala-intolerant–80% of pts received clinical benefit,

and most did not experience recurrence of prior intolerant AEs. Enrollment and follow-up are ongoing.

Figure: Recurrence and Severity of Acala-Intolerant AEs While on Zanu Treatment