***Title (Italian)*:** RISULTATI AGGIORNATI DI SICUREZZA ED EFFICACIA DI ZANUBRUTINIB (ZANU) IN PAZIENTI (PTS) CON NEOPLASIE A CELLULE B CHE SONO INTOLLERANTI A IBRUTINIB (IBR) E/O ACALABRUTINIB (ACA)

***Title (English)*:** UPDATED SAFETY AND EFFICACY RESULTS OF ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH B-CELL MALIGNANCIES WHO ARE INTOLERANT OF IBRUTINIB (IBR) AND/OR ACALABRUTINIB (ACA)

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Background: Pts with B-cell malignancies treated with Bruton tyrosine kinase inhibitors (BTKis) require continuous treatment, but many treated with IBR or ACA discontinue due to treatment-related intolerance. The phase 2 BGB-3111-215 (NCT04116437) study showed that ZANU, a BTKi designed to maximize tolerability by minimizing off-target effects, is well tolerated in these pts. We report updated safety and efficacy results from this study.

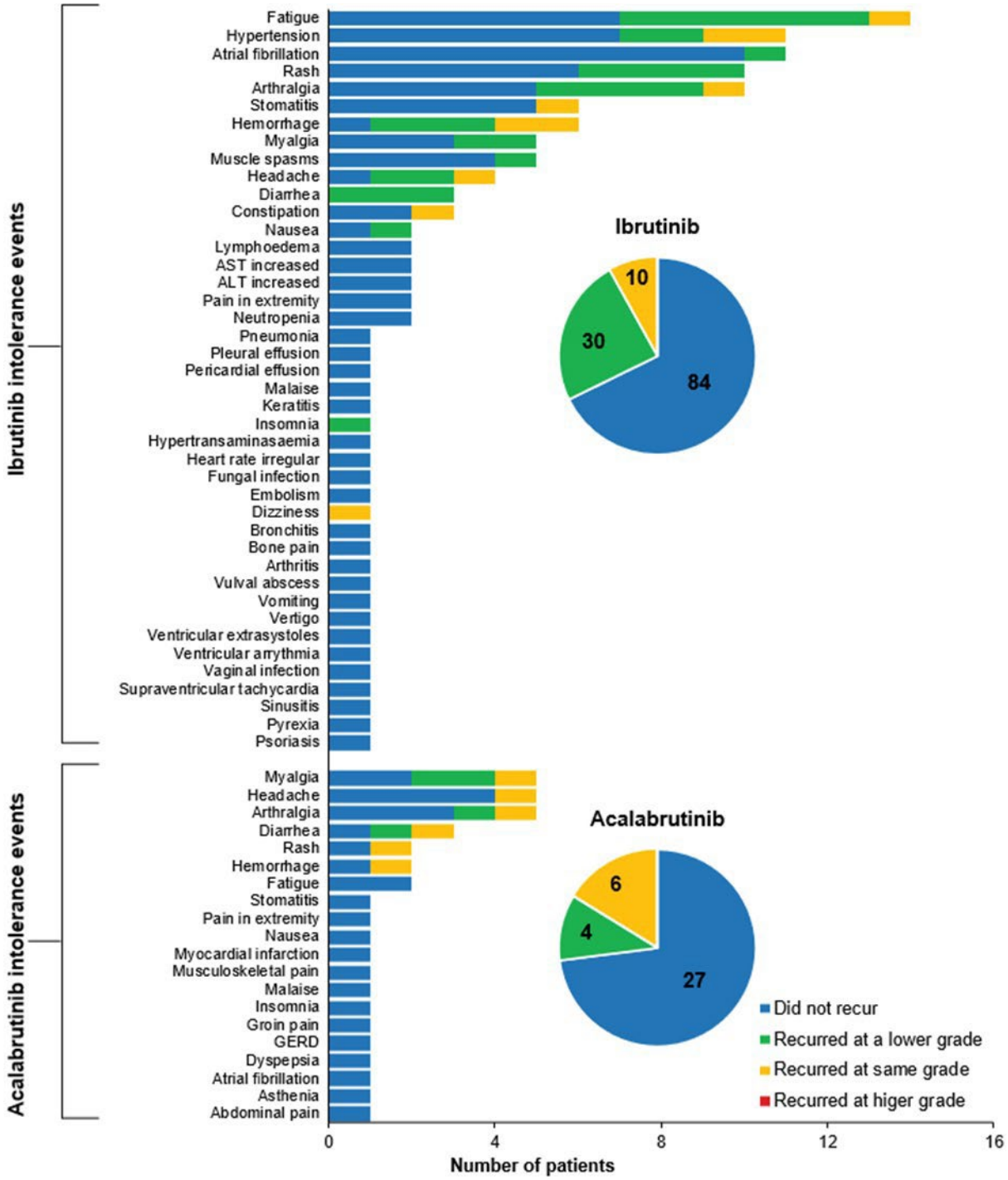
Methods: Pts intolerant of IBR or ACA who had no documented progressive disease (PD) during prior BTKi treatment were given ZANU monotherapy (160 mg twice daily or 320 mg once daily). Recurrence of the adverse events (AEs) that led to intolerance of prior BTKis and other treatment-emergent AEs were assessed per Common Terminology Criteria for Adverse Events v5.0. Every third 28-day cycle, the investigator assessed responses (vs disease at baseline [study entry]) using standard criteria.

Results: As of 3 Jan 2023 (median follow-up, 25.2 mo), 82 pts with intolerance of IBR only (n=57 [69.5%]), ACA only (n=14 [17.1%]), or both (n=11 [13.4%]) were enrolled. The median number of prior therapies was 2 (range, 1-12). Median prior exposure was 9.2 mo for IBR and 5.1 mo for ACA. Most pts had >1 intolerance event (IBR, 124 events in 68 pts; ACA, 37 events in 25 pts); in pts who received ZANU, 84 (67.7%) IBR and 27 (73%) ACA intolerance events did not recur. Of intolerances that did recur, 30/40 (75.0%) with IBR and 4/10 (40.0%) with ACA were at a lower grade **(Figure)**. No events recurred at a higher grade. Median ZANU exposure was 23.7 mo, markedly longer than prior BTKi exposure. Of the 82 pts, 48 (58.5%) did not

experience recurrence of prior intolerance events, and 58 (70.7%) remain on treatment; 24 (29.3%) discontinued treatment (AEs [myalgia, stomatitis, penile hemorrhage, COVID-19 pneumonia, alanine and aspartate aminotransferases increased, autoimmune hemolytic anemia, diarrhea], n=7; PD, n=7; other, n=10). Safety on study was generally consistent with the known ZANU safety profile, with grade ≥3 AEs in 37 pts (45.1%), serious grade ≥3 AEs in 19 (23.2%), and 6 (7.3%) deaths (1 due to AE). In efficacy-evaluable pts, disease was controlled in 54/56 (96.4%) previously intolerant of only IBR and 19/20 (95.0%) previously intolerant of ACA.

Conclusion: Updated safety and efficacy results suggest that switching to ZANU may provide clinical benefit for pts previously intolerant of other BTKis. Enrollment and follow-up are ongoing.

Figure: Recurrence of ibrutinib and acalabrutinib intolerance events in patients receiving zanubrutinib



ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; GERD, gastroesophageal reflux disease.