ASPEN: LONG-TERM FOLLOW-UP RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB (ZANU) VS IBRUTINIB (IBR) IN PATIENTS (PTS) WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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Objectives: To compare the efficacy and safety of ZANU vs IBR in pts with *MYD88* mutant (*MYD88*^{mut}) WM and describe ZANU treatment outcomes in pts with wild-type *MYD88* (*MYD88*^{wt}) WM in the ASPEN study (NCT03053440). **Methods**: Pts with *MYD88*^{mut} WM (cohort 1) were randomized 1:1 to receive ZANU 160 mg twice daily (bid) or IBR 420 mg once daily. Pts with *MYD88*^{wt} (cohort 2) received ZANU 160 mg bid until disease progression. Randomization was stratified by *CXCR4* mutational status (Sanger sequencing) and lines of prior therapy (0, 1-3, or >3). The primary endpoint was proportion of pts achieving very good partial response or better (VGPR + complete response [CR]). **Results**: A total of 201 pts (102 ZANU; 99 IBR) enrolled in cohort 1 and 28 pts in cohort 2. ZANU and IBR arms in cohort 1 differed in proportions of pts with *CXCR4* mutations (next-generation sequencing; 32% vs 20%, or 33/98 vs 20/92 available samples) and age >75 y (33% vs 22%). Median treatment duration was 42 mo (ZANU) and 41 mo (IBR), with 67% and 58% remaining on treatment. The VGPR+CR rate by investigator was 36% (ZANU) vs 22% (IBR; descriptive p=0.02) in cohort 1, and 31% in cohort 2. One pt in cohort 2 achieved CR. In pts with wild-type (65 ZANU; 72 IBR) or mutant *CXCR4* (33 ZANU; 20 IBR) in cohort 1, VGPR+CR rates with ZANU vs IBR were 45% vs 28% (p=0.04) and 21% vs 5% (p=0.15). Median progression-free survival and overall survival were not reached. Rates of atrial fibrillation (AF; 7.9% vs 23.5%), diarrhea (21.8% vs 34.7%), hypertension (HTN; 14.9% vs 25.5%), localized infection (1.0% vs 11.2%), hemorrhage (55.4% vs 62.2%), muscle spasms (10.9% vs 28.6%), pneumonia (5.0% vs 18.4%), and adverse events (AEs) leading to discontinuation (8.9% vs 19.4%) or leading to death (2.0% vs 5.1%) were lower with ZANU vs IBR; neutropenia was the only AE of interest that was higher with ZANU (33.7%) vs IBR (19.4%). Grade ≥3 infection rate was lower with ZANU (20.8%) vs IBR (27.6%). AE incidence with ZANU was similar in cohorts 1 and 2. Annual prevalence analysis of cohort 1 AEs showed reduced hemorrhage prevalence over time and lower prevalence with ZANU vs IBR at all intervals. Neutropenia and infection prevalence decreased over time with ZANU. Infection prevalence was lower with ZANU vs IBR, and neutropenia was similar between arms (8.8% vs 9.7%) at >24-36 mo of treatment. AF prevalence was ≤5% and HTN was stable with ZANU, with lower prevalence at all intervals vs a trend of increasing prevalence with IBR. Exposure-adjusted incidence rates of AF/flutter and HTN were lower with ZANU vs IBR (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months; p<0.05). **Conclusions**: ASPEN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 mo, ZANU was associated with a higher VGPR+CR rate and clinically meaningful advantages in long-term safety and tolerability vs IBR.