P1161 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)

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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Background: ZANU is a potent and selective next-generation Bruton tyrosine kinase inhibitor (BTKi) designed to have greater affinity to BTK while minimizing off-target inhibition of TEC- and EGFR-family kinases. ASPEN (NCT03053440) is a randomized, open-label, phase 3 study comparing ZANU with the first-generation BTKi IBR in pts with WM. We present data with a median follow-up of 43 months.

Aims: To compare the efficacy and safety of ZANU vs IBR in pts with MYD88 mutant (MYD88mut) WM and ZANU in pts with wild-type MYD88 (MYD88wt) WM.

Methods: Pts with MYD88mut WM were assigned to cohort 1 and randomized 1:1 to receive ZANU 160 mg twice daily or IBR 420 mg once daily. Pts with MYD88wt were assigned to cohort 2 and received ZANU 160 mg twice daily until disease progression. Randomization was stratified by CXCR4 mutational status by Sanger sequencing and lines of prior therapy (0, 1-3, or >3). All pts gave informed consent. The primary endpoint was proportion of pts achieving very good partial response or better (VGPR + complete response [CR]). Primary analysis occurred at 19 months median follow-up, and final analysis is planned to occur ~4 years after the first pt enrolled.

Results: A total of 201 pts (102 ZANU; 99 IBR) were enrolled in cohort 1 and 28 pts in cohort 2. Baseline characteristics in cohort 1 differed between pts treated with ZANU vs IBR in CXCR4 mutations by next-generation sequencing (32% vs 20%, or 33 of 98 vs 20 of 92 available samples, respectively) and pts aged >75 years (33% vs 22%, respectively). Median duration of treatment was 42 months (ZANU) and 41 months (IBR), with 67% and 58% remaining on treatment, respectively. The VGPR+CR rate by investigator was 36% with ZANU vs 22% with IBR.
(descriptive \( p = 0.02 \)) in cohort 1, and 31% in cohort 2. One pt in cohort 2 obtained a CR. In pts with wild-type (65 ZANU; 72 IBR) or mutant \( CXCR4 \) (33 ZANU; 20 IBR) from cohort 1, VGPR+CR rates with ZANU vs IBR were 45% vs 28% \(( p = 0.04)\) and 21% vs 5% \(( p = 0.15)\), respectively. Median progression-free survival and overall survival were not reached.

Consistent with less off-target inhibition, rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events (AEs) leading to discontinuation or death were lower with ZANU vs IBR (Table); neutropenia (including grade ≥3) was the only AE of interest that was higher with ZANU (33.7%) vs IBR (19.4%). Rate of grade ≥3 infection was lower with ZANU (20.8%) vs IBR (27.6%). AE incidence with ZANU was similar across cohorts 1 and 2.

Annual prevalence analysis of cohort 1 AEs showed reduced prevalence of hemorrhage over time and lower prevalence with ZANU vs IBR at all intervals. In pts treated with ZANU, neutropenia and infection prevalence decreased over time. Prevalence of infection was lower in pts treated with ZANU vs IBR, and neutropenia was similar between arms (8.8% vs 9.7%, respectively) at ≥24–36 months of treatment. Prevalence of atrial fibrillation remained ≤5% and hypertension remained stable with ZANU, each with a lower prevalence at all intervals vs an increasing trend seen with IBR.

Consistently, exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with ZANU vs IBR (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months, respectively; \( p < 0.05 \)).

### Table

| AE (All Grade), % of Treated Patients | Cohort 1 ZANU (n=101) | Cohort 1 IBR (n=98) | Cohort 2 ZANU (n=20) |
|-------------------------------------|-----------------------|---------------------|----------------------|
| AE, grade ≥3                        | 74.3                  | 72.4                | 71.4                 |
| AE leading to discontinuation       | 8.9                   | 19.4                | 14.3                 |
| Atrial fibrillation/flutter*         | 7.9                   | 23.5                | 7.1                  |
| Diarrhea                            | 21.3                  | 34.7                | 32.1                 |
| Hemorrhage*                         | 55.4                  | 62.2                | 39.9                 |
| Major bleeding*                     | 7.9                   | 12.2                | 7.1                  |
| Hypertension*                       | 14.9                  | 25.5                | 10.7                 |
| Muscle spasm                        | 10.9                  | 28.6                | 14.3                 |
| Localized infection                 | 1.0                   | 11.2                | 7.1                  |
| Neutropenia*                        | 33.7                  | 19.4                | 21.4                 |
| Pneumonia                           | 5.0                   | 18.4                | 14.3                 |
| Infection, all grade (grade ≥3)     | 78.2 [20.8]           | 79.6 [27.6]         | 82.1 [32.1]          |

*Grouped term.

*Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.

### Summary/Conclusion:

ASPERN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 months, ZANU was associated with a higher VGPR+CR rate and demonstrated clinically meaningful advantages in long-term safety and tolerability vs IBR.

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