Outcomes ≥1 year after transitioning from treatment with ibrutinib in the ASPEN study to zanubrutinib

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ABSTRACT

Introduction: ASPEN (NCT03053440) compared Bruton tyrosine kinase inhibitors (BTKi), zanubrutinib and ibrutinib in patients with *MYD88*-mutated Waldenström macroglobulinemia (WM). LTE1 (NCT04170283) is a zanubrutinib long-term extension study. We report clinical outcomes ≥1 year after transition from ibrutinib in ASPEN to zanubrutinib in LTE1.

Methods: Upon LTE1 enrollment, ibrutinib-treated patients from ASPEN began zanubrutinib at 320 mg/day. Disease response was assessed every 6 months using modified Owen criteria or "no evidence of progressive disease" at investigator discretion. Safety and efficacy outcomes were analyzed *ad hoc*.

Results: Between 06/26/2020–06/23/2022, 47 ibrutinib-treated patients from ASPEN enrolled in LTE1; most (79%) had relapsed/refractory WM prior to ASPEN participation. At LTE1 enrollment, median age was 73 years; median time from ASPEN discontinuation to zanubrutinib initiation was 0.07 months. As of 06/23/2023, 40 patients (85%) remained on study treatment. Median treatment duration was 50.4 months for ibrutinib prior to transition, and 15.3 for zanubrutinib. During LTE1, grade ≥3/serious treatment-emergent adverse events (TEAEs) occurred in 23%/13% of patients; infections (6.4%; all COVID-19) were the only grade ≥3 TEAEs affecting >2 patients; no serious TEAEs affected >2 patients. Most ibrutinib TEAEs of interest for BTKi treatment did not continue or worsen following transition to zanubrutinib (exceptions: infections [n=3, all due to COVID-19], anemia [n=1], and neutropenia [n=1]. Six of 7 patients who experienced cardiovascular AEs (8 events) in LTE1 had experienced at least 1 ibrutinib-emergent cardiovascular AE during ASPEN. No worsening or new hypertension occurred following transition to zanubrutinib. There was no recurrence or worsening of atrial fibrillation/flutter; 1 new case of atrial fibrillation occurred (LTE1 day 12) in a patient with extensive cardiovascular history and concurrent pericarditis (LTE1 day 10). No cardiovascular TEAE led to death in LTE1. Two deaths occurred,

both due to COVID-19. Best overall response (BOR) in LTE1 was unchanged in 34 (72%) and improved in 10 patients (21%) from last response assessment in ASPEN. Median [IgM] change was -36 mg/dL, and [IgM] was stable/decreased in 29 patients (73%) from last response assessment in ASPEN to BOR in LTE1.

Conclusion: Following transition to zanubrutinib, at median ibrutinib treatment duration of 50.4 months, most ibrutinib-emergent TEAEs of interest for BTKis did not recur or worsen at 15 months median zanubrutinib treatment duration. Response was maintained or improved in 96% (n=44/46) of efficacy-evaluable patients. Although limited, these data suggest that transitioning ibrutinib-tolerant WM patients to zanubrutinib does not compromise safety or efficacy; long-term follow-up is ongoing.