Rate of Cardiac Disorders in Patients (Pts) With B-Cell Malignancies Who Undergo Treatment With Zanubrutinib (Zanu)

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Background: Bruton tyrosine kinase inhibitors (BTKi) improved treatment of B-cell malignancies, but the first-generation BTKi, ibrutinib (ibr), is associated with an increased risk for cardiovascular toxicities such as atrial fibrillation (Afib) and ventricular arrhythmia (VA) (O'Brien *Clin Lymphoma Myeloma Leuk* 2018). Zanu, an irreversible, next-generation BTKi designed to maximize BTK occupancy and minimize off-target inhibition (Guo *J Med Chem* 2019), is generally well tolerated in clinical trials. Here we report the occurrence of Afib/flutter and idiopathic VA (IVA: VA without history of myocardial infarction/left ventricular ejection fraction <50%/active infections) in ALPINE (NCT03734016), ASPEN (NCT03053440), and a pooled analysis of 10 zanu trials.

Methods: ALPINE and ASPEN cohort 1 compared zanu with ibr in relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or Waldenström macroglobulinemia, respectively. Pts were evaluated for exposure-adjusted incidence rate (EAIR) of Afib and symptomatic (grade ≥2) IVA. EAIR differences based on asymptotic normal distribution were calculated.

Results: In the pooled analyses, 1550 pts received zanu monotherapy, 938 had CLL/SLL (525 R/R CLL/SLL), and the median age was 67 y (61% ≥65 y). Most pts were men (66%) and White (67%), with ECOG PS of 0-1 (93.9%). In ALPINE, 5.9% (19/324; zanu) vs 5.6% (18/324; ibr) had a history of Afib/flutter, whereas 1.9% vs 8.0% experienced a new Afib/flutter event (median exposure 13.5 and 12.8 months), respectively. In ASPEN cohort 1, 9.9% (10/101; zanu) vs 8.2% (8/98; ibr) had a history of Afib/flutter and 5.9% vs 22.4% experienced a new Afib/flutter event (median exposure 35.0 and 34.6 months), respectively. The EAIR of Afib/flutter per 100 person-months was significantly lower with zanu vs ibr in the pooled analyses (0.13 vs 0.82; $P<0.0001$), ALPINE (0.16 vs 0.79; $P=0.0003$) and ASPEN (0.19 vs 0.86; $P=0.0010$). Among pts in ALPINE, 0.6% (2/324; zanu) vs 0.3% (1/324; ibr) had a history of VA, whereas 0.6% vs 1.5% experienced a new symptomatic IVA event, respectively. In ASPEN, no symptomatic IVA events were reported with zanu vs 1 (1/98 pts) event with ibr. The EAIR of symptomatic IVA was significantly lower with zanu vs ibr in the pooled analysis (0.14 vs 0.87; $P=0.0028$) and numerically lower in ALPINE (0.43 vs 1.19; $P=0.2270$).

Conclusions: The low rates of cardiac arrhythmias support zanu use as a treatment option for B-cell malignancies.