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Atrial fibrillation risk by age in patients with chronic lymphocytic leukemia treated with covalent Bruton tyrosine kinase inhibitors

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Background: Atrial fibrillation (AFib) is a clinically important cardiovascular complication event in patients with chronic lymphocytic leukemia (CLL), especially in those being considered or being treated with covalent Bruton tyrosine kinase inhibitors (cBTKi). The risk of AFib may increase with age. However, real-world evidence remains limited regarding the association between age and AFib risk and whether the rate of AFib varies according to first-line (1L) cBTKi treatment in CLL patients. This study evaluated AFib rates by age among patients with CLL and assessed the risk of AFib across 2-year age groups among patients who received 1L cBTKi treatments.

Methods: This retrospective analysis of the US Symphony database identified adult CLL patients aged between 55 and 79 years. The exact age of patients aged ≥80 years could not be determined due to privacy protection. Rates of AFib within 1 year of treatment initiation were assessed by age among overall CLL patients. A further exploration study was conducted among patients who received 1L cBTKi; in these patients, 1-year AFib rates were summarized across 2-year age groups. A second descriptive analysis excluded patients with pre-existing AFib at baseline, defined as AFib diagnosis occurring 1 year on or before the index date.

Results: Among overall CLL patients, 213,473 patients aged 55-79 years at CLL diagnosis were identified. The mean Charlson Comorbidity Index (CCI) score was 3.1; 43.2% had hypertensive disease, 21.1% heart disease, 19.3% diabetes mellitus, 13.9% kidney disease, 13.5% cancers other than B-cell malignancies, 8.0% COPD, 6.0% cerebrovascular disease, 4.6% liver disease, and 3.9% peripheral vascular disease. The 1-year rate of AFib increased linearly with age, from 3.5% at age 55, to 13.6% at age 70, and to 24.7% at age 79. Similarly, in the sensitivity analysis excluding patients with pre-existing AFib, the 1-year rate of new-onset AFib increased progressively from 1.9% at age 59, to 5.5% at age 70, and 8.6% at age 79.

Among the patients who initiated 1L cBTKi, 14,243 patients received ibrutinib, 5105 received acalabrutinib, and 1777 received zanubrutinib. Mean CCI scores were 3.3 with zanubrutinib, 3.3 with acalabrutinib, and 2.8 with ibrutinib; rates of heart disease, hypertensive disease, diabetes, and kidney disease were numerically higher in the zanubrutinib and acalabrutinib cohorts than in the ibrutinib cohort. Among patients who received 1L ibrutinib, AFib rates were 5.1% at age 55-56, 16.6% at age 69-70, and 22.8% at age 79. Corresponding rates for patients treated in 1L with acalabrutinib were 4.4% at age 55-56, 12.3% at age 69-70, and 18.6% at age 79, respectively, and for 1L zanubrutinib were 0% at age 55-56, 9.5% at age 69-70, and 16% at age

79, respectively. Overall, rates of AFib by 2-year age group with 1L zanubrutinib were consistently lower than those observed with 1L ibrutinib and 1L acalabrutinib. Among patients without baseline AFib (n=13,050, n=4535, and n=1579 for 1L ibrutinib, acalabrutinib, and zanubrutinib, respectively), rates of new-onset AFib followed similar patterns, but were uniformly lower, ranging from 3.8%-15.5%, 0.8%-10.3%, and 0%-7.0%, respectively.

Conclusions: In this real-world analysis of patients with CLL receiving 1L cBTKi therapy, rates of AFib increased progressively with age, including among those without baseline AFib. Despite a higher burden of baseline cardiovascular and metabolic comorbidities, patients treated with zanubrutinib consistently experienced lower AFib rates across age strata than those treated with ibrutinib or acalabrutinib. These findings address an important evidence gap by providing age-specific estimates of AFib risk associated with cBTKi therapy in routine clinical practice. Incorporating patient age and cardiovascular risk factors into treatment selection, alongside proactive cardiovascular monitoring, may help optimize outcomes and improve the benefit-risk profile of cBTKi therapy, particularly for older adults. These results also extend prior real-world evidence linking AFib development in patients with CLL to increased healthcare resource utilization (Ermann et al., *JONT*, 2026).