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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Analysis of Ventricular Arrhythmias and Sudden Death with Acalabrutinib from 5 Prospective Clinical Trials

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Background: The approval of ibrutinib, the first covalent Bruton tyrosine kinase inhibitor (BTKi), provided an effective non-chemotherapy option for the treatment of B-cell malignancies, such as chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). While generally well tolerated, ibrutinib demonstrated significant toxicities in clinical studies, particularly cardiovascular adverse events such as hypertension, atrial fibrillation, and ventricular arrhythmias (VAs). Post hoc analysis of the phase 3 FLAIR trial in patients with previously untreated CLL reported an unexplained sudden or cardiac death rate of 0.5 patients per 100 patient-years with ibrutinib plus rituximab (Hillmen et al. *Lancet Oncol*. 2023). Acalabrutinib is a next-generation, more selective, irreversible BTKi approved to treat CLL/SLL and relapsed/refractory mantle cell lymphoma. Herein, the rates of nonfatal and fatal VAs and sudden deaths (SDs) from 5 acalabrutinib clinical trials of patients with CLL were analyzed.
Methods: Incidence and relative risk of nonfatal and fatal VAs and SDs were analyzed using pooled data from 5 prospective acalabrutinib clinical trials (nonrandomized trials: CL-001 [acalabrutinib monotherapy], CL-003 [acalabrutinib + obinutuzumab]; randomized trials: CL-006 [acalabrutinib vs ibrutinib], CL-007 [acalabrutinib ± obinutuzumab vs chlorambucil + obinutuzumab], CL-309 [acalabrutinib vs idelalisib + rituximab OR bendamustine + rituximab]). Acalabrutinib-containing arms were pooled as a single group; comparators, which were standard-of-care therapies, were pooled as a separate group. Events were identified by comprehensive data extraction of terms capturing nonfatal and fatal VAs and SDs (terms are defined in **Table 1** footnote). Nonfatal events were analyzed with and without the inclusion of premature ventricular contractions (PVCs). A subset of fatal events also was analyzed after adjudication through manual clinical review by the sponsor's medical, clinical, and safety leadership.
Results: In total, 1299 patients received acalabrutinib (cumulative exposure, 4568.4 patient-years) and 585 received standard-of-care therapies (comparator group) (941.3 patient-years). Considering only fatal VAs and SDs, 5 (0.4%) and 3 (0.5%) patients had an event in the acalabrutinib and comparator groups, respectively, via comprehensive data extraction (**Table 1**). Based on exposure-adjusted event rates per 100 patient-years, fatal VAs and SDs were numerically less frequent for acalabrutinib versus comparators; however, relative risks did not statistically favor either group. This trend persisted when events were adjudicated through manual clinical review. After adjudication, 2 of 5 patients in the acalabrutinib group and 2 of 3 patients in the comparator group were determined to have fatal VA or cardiac-related SD. Nonfatal VAs were reported in 11 (0.8%) patients in the acalabrutinib group and 3 (0.5%) patients in the comparator group. When PVCs were excluded, 2 patients in each group (acalabrutinib, 0.2%; comparator, 0.3%) had nonfatal VAs. These nonfatal VAs consisted of ventricular fibrillation (acalabrutinib, n=2 [grades 2 and 4]; comparator, n=1 [grade 4]) and unspecified VA (comparator, n=1 [grade 1]). Although the acalabrutinib group had a lower exposure-adjusted event rate per 100 patient-years than the comparator group, relative risk did not favor either group. With both fatal and nonfatal VAs (with or without PVCs), time to event was notably longer with acalabrutinib than with comparators (**Table 1**). A sensitivity analysis excluding the ibrutinib-treated patients from the comparator cohort yielded overall similar results (data not shown).
Conclusions: This pooled analysis of prospective acalabrutinib clinical trials demonstrates that the risk of VA and SD with acalabrutinib is low and similar to that of standard-of-care therapies when adjusted for exposure. The current analysis with

more than 1200 patients treated with acalabrutinib points to favorable safety outcomes and no specific trend with SDs and VAs. Additional analyses with larger cohorts from the clinical development program and all postmarketing sources will continue to further characterize the safety profile of acalabrutinib.

Disclosures Sharman: *AbbVie, AstraZeneca, BMS, Beigene, Lilly, Genentech, Inc., Genmab:* Consultancy; *Merck, Novartis:* Consultancy; *Seattle Genetics:* Research Funding; *AbbVie, AstraZeneca, BeiGene, BMS, Genentech, Inc., Lilly:* Consultancy. **Ghia:** *AstraZeneca:* Consultancy, Honoraria, Research Funding; *MSD:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *Lilly/Loxo Oncology:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria, Research Funding. **Palhares De Miranda:** *AstraZeneca:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Bajwa:** *AstraZeneca:* Current Employment. **Rule:** *AstraZeneca:* Current Employment. **Shaw:** *AstraZeneca:* Current Employment. **Seymour:** *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Hoffmann-La Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Genor Bio:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Beigene:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *TG Therapeutics:* Consultancy; *F. Hoffmann-La Roche Ltd:* Research Funding.

Table 1. Summary of nonfatal and fatal VA and SD events from pooled acalabrutinib clinical trials

	Events identified via comprehensive data extraction criteria[a,b]		Adjudicated fatal VA and SD events[c]	
	Pooled acalabrutinib-containing arms (including crossover)[d] n=1299	Pooled comparator arms[e] n=585	Pooled acalabrutinib-containing arms (including crossover)[d] n=1299	Pooled comparator arms[e] n=585
Fatal VA and SD events				
Patients with event, n (%)	5 (0.4)	3 (0.5)	2 (0.2)	2 (0.3)
Unadjusted relative risk vs comparator (95% CI)	—	0.751 (0.180, 3.130)	—	0.460 (0.064, 3.189)
P value[f]	—	0.7095	—	0.5925
Event rate per 100 patient-years (95% CI)[g]	0.109 (0.046, 0.263)	0.319 (0.103, 0.988)	0.044 (0.011, 0.175)	0.212 (0.053, 0.850)
Patient-years	4568.4	941.3	4568.4	941.3
Exposure-adjusted relative risk vs comparator (95% CI)	—	0.343 (0.082, 1.437)	—	0.206 (0.029, 1.463)
P value[h]	—	0.1433	—	0.1142
Time to event, months				
Median (range)	46.2 (30.5, 71.7)	8.3 (2.8, 43.7)	39.7 (31.3, 48.1)	5.6 (2.8, 8.3)
Nonfatal VA events, excluding PVCs				
Patients with event, n (%)	2 (0.2)	2 (0.3)		
Unadjusted relative risk vs comparator (95% CI)	—	0.460 (0.064, 3.189)		
P value[f]	—	0.5925		
Event rate per 100 patient-years (95% CI)[g]	0.044 (0.011, 0.175)	0.212 (0.053, 0.850)		
Patient-years	4568.4	941.3		
Exposure-adjusted relative risk vs comparator (95% CI)	—	0.206 (0.029, 1.463)		
P value[h]	—	0.1142		
Time to event, months				
Median (range)	22.4 (1.4, 43.4)	12.7 (5.6, 19.8)		
Nonfatal VA events, including PVCs				
Patients with event, n (%)	11 (0.8)	3 (0.5)		
Unadjusted relative risk vs comparator (95% CI)	—	1.651 (0.462, 5.897)		
P value[f]	—	0.5690		
Event rate per 100 patient-years (95% CI)[g]	0.241 (0.133, 0.435)	0.319 (0.103, 0.988)		
Patient-years	4568.4	941.3		
Exposure-adjusted relative risk vs comparator (95% CI)	—	0.755 (0.211, 2.708)		
P value[h]	—	0.6669		
Time to event, months				
Median (range)	11.8 (1.2, 55.4)	5.6 (0.9, 19.8)		

AEPTCD, adverse event preferred term code; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified; PT, preferred term; PVC, premature ventricular contraction; SD, sudden death; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event; VA, ventricular arrhythmia.
[a]Data extraction criteria for cardiac events: Fatal = TEAE with either PT of: cardiac death, death, death NOS, death from unknown, sudden cardiac death, sudden death, unwitnessed/unexplained death, and CTCAE grade 5 or high-level terms of ventricular arrhythmias and cardiac arrest with outcome of death.
[b]MedDRA narrow sub-SMQs for ventricular tachyarrhythmias were used to identify the following nonfatal AEPTCDs: parasystole, rhythm idioventricular, torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachycardia, accelerated idioventricular rhythm, ventricular pre-excitation, ventricular parasystole, cardiac fibrillation, ventricular tachyarrhythmia, arrhythmic storm, early repolarization syndrome.
[c]Subset of events from comprehensive data extraction identified by manual clinical review of data.
[d]Includes acalabrutinib monotherapy, acalabrutinib + obinutuzumab, and patients who crossed over from comparator to acalabrutinib monotherapy. Crossover patients also are included under the pooled comparator column; however, any reported events only appear for the treatment under which they occurred.
[e]Includes ibrutinib, chlorambucil plus obinutuzumab, idelalisib plus rituximab, and bendamustine plus rituximab.
[f]Based on Fisher's exact test.
[g]Only the first event is counted.
[h]Based on Poisson regression model with log duration of exposure as offset.

Figure 1

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