Characterization of Bruton Tyrosine Kinase Inhibitor (BTKi)-Related Adverse Events in a Head-to-Head Trial of Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia (CLL)

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Background:
The phase 3 head-to-head trial of acalabrutinib (acala) vs ibrutinib (ibr) (NCT02477696) demonstrated noninferior efficacy and improved tolerability with acala in previously treated CLL (Byrd *J Clin Oncol* 2021). We now report additional data to further characterize BTKi-related adverse events (AEs) and the safety profile of acala and ibr, including measures of AE burden that account for frequency, duration, and drug exposure, which are not captured by incidence alone.

Methods:
Patients (pts) received oral acala 100 mg BID or ibr 420 mg QD until disease progression or unacceptable toxicity. Overall incidence, exposure-adjusted (exp-adj) incidence, and exp-adj time with event (sum of event durations [all grades]*100/sum of treatment-emergent period [for all pts in each arm]) were assessed for the most common BTKi-related AEs. Atrial fibrillation (afib)/flutter, hypertension (htn), and bleeding events were further characterized by time to onset, cumulative incidence by Kaplan-Meier method, pt subgroup, and AE management.

Results: A total of 533 pts (acala, n=268; ibr, n=265) were randomized; median treatment exposures were 38.3 and 35.5 mo, respectively. Incidence and exp-adj incidence and time with event are reported for the most common AEs and events of clinical interest (ECIs) (Table). Among cardiovascular (CV) ECIs, incidences of any-grade afib/flutter, htn, and bleeding were statistically higher with ibr, with higher exp-adj incidence (2.0-, 2.8-, and 1.6-fold, respectively) and exp-adj time with event (2.8-, 3.7-, and 1.8-fold). Ventricular arrhythmias were reported in 3 ibr-treated pts vs 0 pts in the acala arm. Among other BTKi-related AEs, incidences of any-grade diarrhea, arthralgia, contusion, urinary tract infection (UTI), back pain, muscle spasms and dyspepsia were statistically higher with ibr, with a 1.5- to 4.1-fold higher exp-adj incidence, and a 1.4- to 13.1-fold higher exp-adj time with event (except for UTI, which had a 1.4-fold lower exp-adj time with event for ibr). Incidences of headache and cough were statistically higher with acala, with a 1.6- and 1.2-fold higher exp-adj incidence, respectively, and a 1.4- and 1.1-fold higher exp-adj time with event. The total exp-adj time with event for all any-grade AEs was 37% higher with ibr (234 [acala] vs 320 [ibr] mo/100 person-mo).

For any-grade afib/flutter, median time to onset was longer for acala vs ibr (28.8 vs 16.0 mo), and cumulative incidence was lower for acala at 6 mo (2% vs 6%), 12 mo (3% vs 8%), 18 mo (4% vs 10%), and 24 mo (5% vs 12%). Afib/flutter also occurred less frequently with acala vs ibr in subgroups of age (<65 y: 3% vs 7%; ≥65 y: 15% vs 23%), prior line of therapy (1-3: 10% vs 16%; ≥4: 7% vs 19%), and among pts without prior history (6% vs 15%). Cox

proportional-hazards (PH) analysis of new-onset afib/flutter showed a 63% rate reduction favoring acala (Figure 1). Among all pts, concomitant medication use for afib/flutter was less common for acala (8%) vs ibr (14%), with antithrombotic use reported in 5% vs 9% of pts, respectively.

For any-grade htn, median time to onset was similar for acala and ibr (8.1 vs 7.0 mo), but cumulative incidence was lower for acala at 6 mo (5% vs 12%), 12 mo (6% vs 16%), 18 mo (8% vs 20%), and 24 mo (8% vs 23%). Htn also occurred less frequently with acala vs ibr in subgroups of age (<65 y: 9% vs 23%; ≥65 y: 10% vs 23%), prior line of therapy (1-3: 10% vs 25%; ≥4: 4% vs 11%), and among pts without prior history (7% vs 23%). Cox PH analysis of new-onset htn showed a 77% rate reduction favoring acala (Figure 2). No dose reductions or treatment discontinuations due to htn occurred in either arm. Concomitant medication use for htn was less common for acala (5%) vs ibr (19%).

For any-grade bleeding events, the median time to onset was similar for acala vs ibr (1.2 vs 1.2 mo), and cumulative incidence was lower for acala at 6 mo (29% vs 42%), 12 mo (32% vs 45%), 18 mo (34% vs 49%), and 24 mo (38% vs 51%). Bleeding events also occurred less frequently with acala vs ibr in most subgroups of age (<65 y: 26% vs 47%; ≥65 y: 49% vs 55%) and prior line of therapy (1-3: 39% vs 54%; ≥4: 32% vs 30%). Bleeding events were associated with dose reduction in 3 vs 2 pts in the acala vs ibr arms, respectively, and led to treatment discontinuation in 2 vs 4 pts.

Conclusions*:*
In this head-to-head trial of BTKis in CLL, event-based analyses demonstrated a higher BTKi-related toxicity burden with ibr, with a lower impact of CV-related toxicity with acala across subgroups.