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FIRST RESULTS OF A HEAD-TO-HEAD TRIAL OF ACALABRUTINIB VERSUS IBRUTINIB IN PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA

Topic: 06. Chronic lymphocytic leukemia and related disorders - Clinical

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Background: The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib is more selective than ibrutinib, which may improve tolerability.

Aims: We conducted an open-label, randomized, noninferiority, phase 3 trial to compare acalabrutinib and ibrutinib in patients with previously treated chronic lymphocytic leukemia (CLL).

Methods: Patients with previously treated CLL who had del(17p) or del(11q) by central lab were randomized to receive acalabrutinib 100 mg orally twice daily or ibrutinib 420 mg orally once daily until progression or unacceptable toxicity. Randomization was stratified by del(17p) status, Eastern Cooperative Oncology Group performance status (2 vs ≤1), and number of prior therapies (1–3 vs ≥4). The primary endpoint was progression-free survival as assessed by independent review committee; secondary endpoints of all grade atrial fibrillation, grade ≥3 infection, Richter transformation, and overall survival were assessed in hierarchical order. Informed consent was obtained from all patients prior to trial enrollment.

Results: A total of 533 patients (acalabrutinib, n=268; ibrutinib, n=265) were randomized. Patients had a median age of 66 years and had received a median of 2 prior therapies; 45.2% of patients had del(17p), and 64.2% had del(11q). At a median follow-up of 40.9 months (range, 0.0–59.1), acalabrutinib demonstrated noninferiority to ibrutinib, with a median progression-free survival of 38.4 months in both arms (hazard ratio [HR], 1.00; 95% CI, 0.79–1.27). Acalabrutinib was statistically superior to ibrutinib in the incidence of all-grade atrial fibrillation (9.4% vs 16.0%; *P*=0.023). Among the other secondary endpoints, incidences of grade ≥3 infection (acalabrutinib: 30.8%, ibrutinib: 30.0%) and Richter transformation (acalabrutinib: 3.8%, ibrutinib: 4.9%) were comparable between the

treatment arms. Median overall survival was not reached in either arm (HR, 0.82; 95% CI, 0.59–1.15), with 63 (23.5%) deaths in the acalabrutinib arm and 73 (27.5%) in the ibrutinib arm. Among any-grade adverse events occurring in ≥20% of patients in either arm, acalabrutinib was associated with a lower incidence of hypertension (9.4%, 23.2%), arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). Adverse events led to treatment discontinuation in 14.7% of acalabrutinib-treated patients compared with 21.3% of ibrutinib-treated patients. Among any-grade events of clinical interest, cardiac events, hypertension, and bleeding events were less frequent with acalabrutinib (Table).

Image:

Table. Selected events of clinical interest

	Acalabrutinib (n=266)		Ibrutinib (n=263)	
Events, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Atrial fibrillation[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events[c]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Second primary malignancies excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes preferred terms of atrial fibrillation and atrial flutter
[b]Includes preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased
[c]Any hemorrhagic event that was serious, grade ≥3, or a central nervous system hemorrhage (any grade)

Summary/Conclusion: In this first head-to-head trial of BTK inhibitors in patients with previously treated CLL, acalabrutinib demonstrated non-inferior progression-free survival with less cardiotoxicity and fewer discontinuations due to adverse events compared with ibrutinib.

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