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Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Elevate-TN four-year follow up.

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Background

Early results from ELEVATE-TN (NCT02475681) at a median follow-up of 28.3 mo demonstrated superior efficacy of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients (pts) with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) (Sharman et al. Lancet 2020;395:1278-91). Results from a 4-year update are reported here.

Methods

Pts received A±O or O+Clb. Crossover to A monotherapy was permitted in pts who progressed on O+Clb. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated.

Results

535 pts (A+O, n=179; A, n=179; O+Clb, n=177) were randomized with a median age of 70 y; 63% had unmutated IGHV and 9% del(17p). At a median follow-up of 46.9 mo (range, 0.0–59.4; data cutoff: Sept 11, 2020), the median PFS was not reached (NR) for A+O and A pts vs 27.8 mo for O+Clb pts (both P<0.0001). In pts with unmutated IGHV, the median PFS was NR (A+O and A) vs 22.2 mo among O+Clb pts (both P<0.0001). In pts with del(17p), the median PFS was NR (A+O and A) vs 17.7 mo for O+Clb (P<0.005). Estimated 48-mo PFS rates were 87% for A+O, 78% for A, and 25% for O+Clb. Median OS was NR in any treatment arm with a trend towards significance in the A+O group (A+O vs O+Clb, P=0.0604); estimated 48-mo OS rates were 93% (A+O), 88% (A), and 88% (O+Clb). ORR was significantly higher with A+O (96.1%; 95% CI 92.1–98.1) vs O+Clb (82.5%; 95% CI 76.2–87.4; P<0.0001); ORR with A was 89.9% (95% CI 84.7–93.5; P=0.035 vs O+Clb). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates were higher with A+O (26.8%/3.9%) vs O+Clb (12.4%/0.6%); 10.6%/0.6% had CR/CRi with A. Common adverse events (AEs) and AEs of interest are shown in the Table. Overall treatment discontinuation rates were 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb); the most common reasons were AEs (12.8%, 12.3%, 14.7%, respectively) and progressive disease (4.5%, 7.8%, 1.7%). Most pts (77.4%) completed O+Clb treatment.

Conclusions

With a median follow-up of 46.9 mo (~4y), the efficacy and safety of A+O and A monotherapy was maintained, with an increase in CR since the interim analysis (from 21% to 27% [A+O] and from 7% to 11% [A]) and low rates of discontinuation.

	A+O (n = 178)		A (n = 179)		O+Clb (n = 169)	
	Any grade	G ≥ 3	Any grade	G≥3	Any grade	G≥3
Common AEs (in ≥30% of pts [any grade] in any group), n (%)						
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	71 (39.9)	2 (1.1)	68 (38.0)	2 (1.1)	20 (11.8)	0
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	76 (45.0)	70 (41.4)
Nausea	41 (23.0)	0	41 (22.9)	0	53 (31.4)	0
Infusion-related reaction	25 (14.0)	5 (2.8)	0	0	68 (40.2)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0

Selected events of clinical interest.

Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	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 atrial fibrillation and atrial flutter [b]Includes hypertension, blood pressure increased, and blood pressure systolic increased [c]Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade).