Final independent review data supports sustained benefit of zanubrutinib over ibrutinib in patients with R/R CLL/SLL in ALPINE

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ABSTRACT

Introduction: ALPINE, a randomized, global, phase 3 study (NCT03734016) in patients with R/R CLL/SLL, established the superiority of zanubrutinib over ibrutinib for progression-free survival (PFS) and overall response rate (ORR), and confirmed the favorable safety/tolerability profile of zanubrutinib (Brown et al. *NEJM*; 2022). Final efficacy results (data cutoff date: 28 Feb 2024) using investigator-assessed (INV) responses and safety data have been published (Brown et al, *Blood*; 2024). Here, we report final efficacy results (data cutoff date: 28 Feb 2024) using independent review committee-assessed (IRC) responses.

Methods: As previously published, patients with R/R CLL/SLL who had received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive zanubrutinib or ibrutinib. Efficacy assessments, including PFS and ORR, were evaluated by the IRC based on 2008 iwCLL criteria; sensitivity analyses to confirm PFS results were also conducted. IRC and INV concordance rates were assessed.

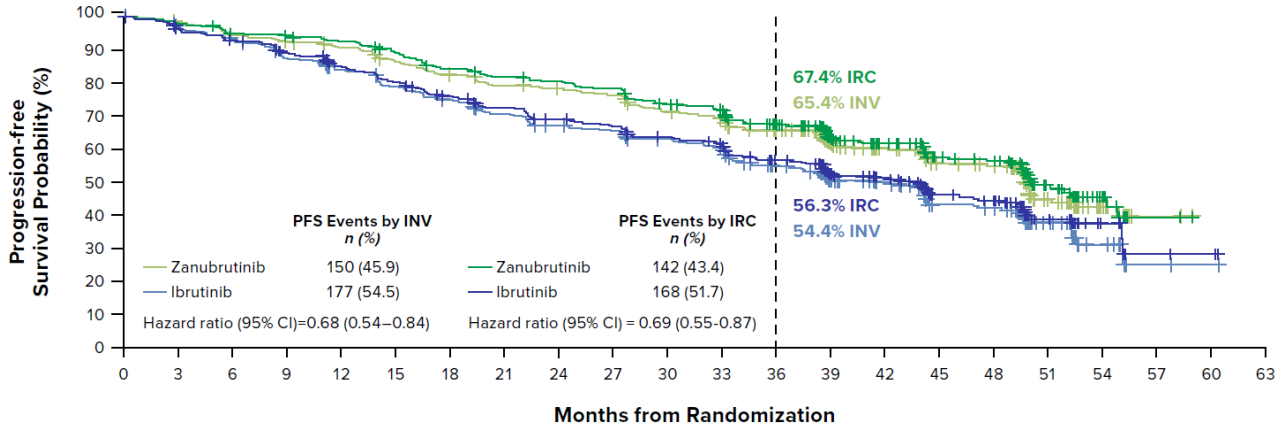
Results: Overall, 652 patients were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325). As of study closure date (28 Feb 2024), 56.0% (n=183/327) and 41.5% (n=135/325) of patients were receiving zanubrutinib and ibrutinib, respectively. At a median study follow-up of 42.5 months, IRC-assessed data showed the PFS benefit of zanubrutinib over ibrutinib was sustained (HR, 0.69 [95% CI,

0.55-0.87]; Figure). At 36 months, the PFS rates were 67.4% with zanubrutinib and 56.3% with ibrutinib. Benefits in PFS with zanubrutinib were also observed across major subgroups, including in patients with del(17p)/*TP53* mutation (HR, 0.56 [95% CI, 0.36-0.88]), when assessing progression and death events that occurred only in patients who remained on active treatment (HR, 0.71 [95% CI, 0.52-0.96]), and when censoring for COVID-19 related deaths (HR, 0.67 [95% CI, 0.53-0.86]). ORR (defined as PR or better) remained higher with zanubrutinib vs ibrutinib (88.4% vs 76.6%), with the response ratio of 1.15 (95% CI, 1.07-1.23); the rates of PR-L or better were 91.4% vs 83.1%. CR/CRi rates of 13.5% for zanubrutinib and 8.6% for ibrutinib were observed. INV- vs IRC-assessed overall responses had high concordance rates (95.4% for zanubrutinib and 93.8% for ibrutinib).

Conclusions: ALPINE is the first study to demonstrate PFS superiority in a global head-to-head comparison of BTK inhibitors. At a median follow-up of 3.5 years of IRC-assessed data, the study showed consistently improved PFS benefits of zanubrutinib over ibrutinib. IRC efficacy results have a high concordance rate with previously published INV results, consolidating the superiority of zanubrutinib over ibrutinib in patients with R/R CLL/SLL by INV assessment.

Figure:

Figure. PFS by IRC and INV Assessment



No. at Risk

IRC	Zanubrutinib	327	315	304	301	294	281	265	256	251	244	227	219	195	149	127	106	101	45	18	2	0	0
	Ibrutinib	325	305	293	277	260	246	229	215	203	195	182	173	151	116	104	81	76	31	10	3	2	0
INV	Zanubrutinib	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0	0
	Ibrutinib	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1	0

CI, confidence interval; INV, investigator assessment; IRC, independent review committee assessment; PFS, progression-free survival.