Final Independent Review Data Supports Sustained Benefit of Zanubrutinib over Ibrutinib in Patients with R/R CLL/SLL in ALPINE

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Background:

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).

Aims:

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.

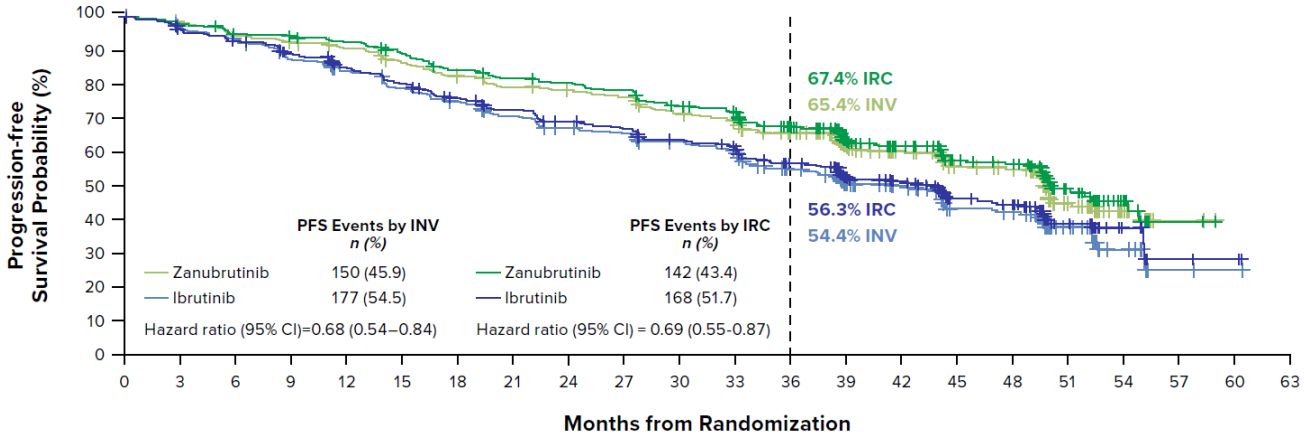
Results:

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).

Summary/Conclusion:

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. 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.