***Title (Italian)*: ZANUBRUTINIB VS IBRUTINIB NELLA LEUCEMIA LINFATICA CRONICA RECIDIVA/REFRATTARIA E NEL LINFOMA A PICCOLI LINFOCITI: IMPATTO SULLA QUALITÀ DELLA VITA CORRELATA ALLA SALUTE**

***Title (English)*: ZANUBRUTINIB VS IBRUTINIB IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA (R/R CLL/SLL): IMPACT ON HEALTH-RELATED QUALITY OF LIFE (HRQOL)**

Authors:
L. Laurenti[1], B. Eichhorst[2], N. Lamanna[3], S.M. O'Brien[4], C.S. Tam[5], L. Qiu[6], K. Yang[7], K. Wu[7,8], T. Salmi[9], G. Barnes[7], J.R. Brown[10]

Author Affiliations:
[1]Fondazione Universitaria Policlinico A. Gemelli di Roma; [2]Department of Internal Medicine, University of Cologne, Center for Integrated Oncology; [3]Herbert Irving Comprehensive Cancer Center, Columbia University; [4]Chao Family Comprehensive Cancer Center, University of California; [5]The Alfred Hospital and Monash University; [6]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences; [7]BeiGene USA, Inc.; [8]BeiGene (Beijing) Co., Ltd; [9]BeiGene International, GmbH; [10]Department of Medical Oncology, Dana-Farber Cancer Institute

Cities:
1. Roma (IT), 2. Aachen, Bonn, Cologne, Duesseldorf (DE), 3. New York (USA), 4. Irvine (USA), 5. Melbourne (AU), 6. Poznan (PL), 7. San Mateo (USA), 8. Beijing (CN), 9. Basel (CH), 10. Boston (USA)

Background: Zanubrutinib is a potent, highly selective, next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target effects. In the ALPINE study (NCT03734016), zanubrutinib demonstrated superior progression-free survival and overall response rate compared with ibrutinib as treatment for R/R CLL/SLL and had a more favorable safety profile.

Methods: EORTC QLQ-C30 and EQ-5D-5L were used to measure patient-reported outcome (PRO) endpoints (global health status [GHS], physical and role functions, fatigue, pain, diarrhea, and nausea/vomiting) at baseline, cycle (C) 1, and every third 28-day cycle until end of treatment. Descriptive analysis, using a mixed, repeated-measures model of key PRO endpoints at C7 (6 months) and C13 (12 months), was performed.

Results: Patients (pts) randomized to receive zanubrutinib (n=327) or ibrutinib (n=325) had similar baseline characteristics and similar GHS, functional, and symptom scale scores at baseline. Adjusted PRO completion rates (the number of pts who completed the questionnaires at each cycle divided by those still on treatment) were high at C7 and C13 in both arms—89.6% and 94.3% (zanubrutinib) and 87.7% and 92.3% (ibrutinib), respectively—despite more pts discontinuing treatment due to adverse events with ibrutinib vs zanubrutinib (22.2% vs 15.4%). Zanubrutinib improved GHS scores compared with ibrutinib at C7 (LS mean change difference, 3.0; 95% CI, 0.23-5.77; nominal *P*=0.0338) but not C13 (1.34; 95% CI, −1.37 to 4.06; nominal *P*=0.3304) (**Table**). Clinically meaningful improvements (mean change difference from baseline of ≥5%) in physical and role functioning, pain, and fatigue at C7 and C13 were observed in the zanubrutinib arm, as well as lower diarrhea scores, but the difference between arms was not significant. Nausea/vomiting scores were maintained in both arms, with no measurable difference. Visual analog scale scores showed greater improvement from baseline at C7 (7.92 vs 3.44) and C13 (7.75 vs 3.92) with zanubrutinib vs ibrutinib, respectively.

Conclusions: In ALPINE, zanubrutinib demonstrated improvement in GHS compared with ibrutinib at C7 (6 months) in pts with R/R CLL/SLL. Improvement in other endpoints over time suggests that treatment with zanubrutinib positively affected HRQOL; however, given the generally good HRQOL at baseline in both arms, the differences between the arms were small and not significant.

Table. LS Mean Differences (95% CI) From Baseline Within and Between Treatment Arms

	Cycle 7 (6 months)			Cycle 13 (12 months)		
	Zanubrutinib (n=327)	**Ibrutinib (n=325)**	**Difference between the arms**	**Zanubrutinib (n=327)**	**Ibrutinib (n=325)**	**Difference between the arms**
	Difference within the arm	Difference within the arm		Difference within the arm	Difference within the arm	
GHS	8.18 (6.25 to 10.12)	5.18 (3.20 to 7.17)	3.00 (0.23 to 5.77)[a]	7.28 (5.41 to 9.15)	5.93 (3.97 to 7.89)	1.34 (−1.37 to 4.06)
Physical functioning	6.55 (4.96 to 8.15)	4.73 (3.08 to 6.38)	1.82 (−0.47 to 4.12)	5.46 (3.87 to 7.04)	4.31 (2.65 to 5.97)	1.15 (−1.15 to 3.44)
Role functioning	6.95 (4.85 to 9.06)	6.32 (4.14 to 8.50)	0.63 (−2.40 to 3.66)	6.81 (4.61 to 9.02)	5.01 (2.69 to 7.33)	1.80 (−1.40 to 5.00)
Fatigue[b]	−12.54 (−14.47 to −10.60)	−10.63 (−12.63 to −8.62)	−1.91 (−4.70 to 0.87)	−11.13 (−13.19 to −9.08)	−10.78 (−12.93 to −8.63)	−0.35 (−3.32 to 2.62)
Nausea/vomiting[b]	−1.21 (−2.03 to −0.38)	−0.92 (−1.77 to −0.07)	−0.29 (−1.48 to 0.89)	−0.92 (−1.94 to 0.10)	−0.40 (−1.47 to 0.66)	−0.51 (−1.99 to 0.96)
Pain[b]	−5.06 (−7.21 to −2.91)	−3.63 (−5.85 to −1.42)	−1.43 (−4.51 to 1.66)	−5.18 (−7.38 to −2.97)	−2.75 (−5.06 to −0.44)	−2.43 (−5.62 to 0.77)
Diarrhea[b]	−2.11 (−3.80 to −0.42)	−0.52 (−2.27 to 1.22)	−1.59 (−4.01 to 0.84)	−3.23 (−4.79 to −1.66)	−1.38 (−3.03 to 0.27)	−1.85 (−4.12 to 0.43)

Data cutoff: August 8, 2022.

GHS, global health status.

[a] Nominal $P<0.05$.

[b] Negative values indicate improvement.