Number of deaths avoided with use of zanubrutinib versus ibrutinib for the treatment of chronic lymphocytic leukemia (CLL) in Europe

Authors

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Background

Bruton tyrosine kinase inhibitors (BTKis), including first-generation ibrutinib (ibru) and next-generation zanubrutinib (zanu), are approved for CLL in Europe. Both have demonstrated efficacy as monotherapy for first-line (1L) treatment versus other agents (zanu in SEQUOIA [NCT03336333]; ibru in RESONATE-2 [NCT01722487]). In the second-line or later (2L+) setting, zanu demonstrated superiority over ibru in preventing progression, relapse or death (ALPINE [NCT03734016]); in ALPINE, ibru was associated with more cardiac deaths than zanu. However, real-world comparative data on CLL cardiac deaths in Europe remain limited.

Aims

This study estimated the number of cardiac deaths avoided if patients were treated with zanu instead of ibru based on real-world patient numbers from France, Germany, Italy, Spain and the UK.

Methods

The number of cardiac deaths avoided by treating with zanu was calculated using a number-needed-to-treat (NNT) model for both the 2L+ (base case) and 1L settings (sensitivity analysis). The NNT was calculated as the reciprocal of absolute cardiac death risk increase for ibru versus zanu (1/ |cardiac death risk with ibru − cardiac death risk with zanu|). To estimate the potential total number of avoidable cardiac deaths, the NNT was applied to the number of real-world CLL patients receiving ibru (number of avoidable deaths = number of patients starting on ibru/NNT). To reflect treatment uptake, new patient starts on ibru were calculated starting from the date of availability of zanu for CLL in each respective country to the end of 2025 (derived from IQVIA Oncology Dynamics database). For the base-case analysis, risk of cardiac death was obtained from the ALPINE study; for the sensitivity analysis, risk of cardiac death for zanu and ibru were obtained from SEQUOIA and RESONATE-2, respectively.

Results

In the base case, the NNT to avoid one cardiac death with treatment with zanu was 54. When considering the time period starting from availability of zanu, new patient starts on ibru across the five countries were estimated to total 1743 in the 2L+ setting and thus a total of 32 deaths would have been avoided if patients were treated with zanu instead of ibru (**Table**). In the sensitivity analysis in the 1L setting, the NNT to avoid one cardiac death with zanu treatment was 46. An estimated total of 52 deaths may have been avoided if these patients were treated with zanu instead of ibru, based on 2428 new patient starts on ibru.

Summary/Conclusion

This NNT analysis demonstrated that treatment with zanu instead of ibru monotherapy could have prevented ~84 cardiac deaths across both 2L+ and 1L CLL settings. The study findings should be interpreted within the context of the model assumptions and data inputs. Further real-world studies using European registry data are needed to confirm these findings.

Table. Number of cardiac deaths avoided by country

Outcome	**Country**				
	France	**Germany**	**Italy**	**Spain**	**UK**
Time period*	**Feb 2024–Dec 2025**	**Nov 2022–Dec 2025**	**Nov 2023–Dec 2025**	**Jun 2023–Dec 2025**	**Oct 2023–Dec 2025**
Base case (2L+)					
Cardiac death risk with zanu	0%				
Cardiac death risk with ibru	1.852%				
NNT	54				
Number of patients	109	602	728	142	162
Number of deaths avoided	2	11	13	3	3
Total deaths avoided	**32**				
Sensitivity analysis (1L)					
Cardiac death risk with zanu	0.833%				
Cardiac death risk with ibru	2.963%				
NNT	46				
Number of patients	337	710	775	267	339
Number of deaths avoided	7	15	17	6	7
Total deaths avoided	**52**				

*Considering the date of zanu availability.