Estimated cardiac deaths associated with treating chronic lymphocytic leukemia with ibrutinib versus zanubrutinib in the United States

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ABSTRACT

Introduction: Efficacy of the Bruton tyrosine kinase inhibitors zanubrutinib and ibrutinib as first-line (1L) treatments for chronic lymphocytic leukemia (CLL) has been shown in the SEQUOIA (NCT03336333) and RESONATE-2 (NCT01722487) pivotal trials, respectively, while the efficacy and safety of zanubrutinib and ibrutinib in second-line or later (2L+) treatment were compared in the randomized phase 3 ALPINE trial (NCT03734016) showing superior efficacy for zanubrutinib. Ibrutinib is associated with a higher risk of sudden/cardiac deaths as reported in the RESONATE-2 and ALPINE clinical trials compared to zanubrutinib. However, there are limited real-world data on cardiac deaths of patients treated with zanubrutinib and ibrutinib. The objective of this study was to conduct a modeling analysis to estimate the number of cardiac deaths in clinical practice in the US that could be avoided by using zanubrutinib instead of ibrutinib for 2L+ CLL treatment based on the published cardiac death rate in the head-to-head data from ALPINE. Additionally, an exploratory analysis was conducted to investigate the number of cardiac deaths that could be avoided in clinical practice with 1L use of zanubrutinib vs ibrutinib using data from SEQUOIA and RESONATE-2, respectively. RESONATE-2 was considered in this analysis as the cardiac death risk reported in this trial is consistent with other phase 3 ibrutinib-containing trials.

Methods: A model analysis of number needed to treat (NNT) was conducted to assess how many patients would need to be treated with zanubrutinib vs ibrutinib to prevent an incremental cardiac death in the 2L+ and 1L settings. NNT was calculated as the reciprocal of the absolute cardiac death risk increase for ibrutinib when compared with zanubrutinib (1/ [cardiac death risk in ibrutinib – cardiac death risk in zanubrutinib]). Cardiac death rates for zanubrutinib and ibrutinib in 2L+ and 1L treatment of CLL were extracted from the ALPINE study (0% for zanubrutinib vs 1.852% for ibrutinib), SEQUOIA (0.833% for zanubrutinib) and RESONATE-2 (2.963% for ibrutinib), respectively. The US Symphony Integrated Dataverse database was used to estimate the number of CLL patients receiving ibrutinib in the real-world setting from 2014 to 2024 (10-year period). To estimate the potential total number of avoidable deaths over a 10-year period, NNT to avoid incremental cardiac death in 2L+ and 1L treatment of CLL was calculated by applying the risks of cardiac death by time on treatment period (0- 12 months; 12 – 36 months; 36 – 60 months; >60 months) to the number of real-world CLL patients receiving ibrutinib.

Results: A total of 39,738 CLL patients treated with ibrutinib were identified in the Symphony Integrated Dataverse database, with 17,213 in 2L+ setting and 22,525 patients in 1L setting. The NNT model estimated that up to 255 cardiac deaths may be avoided over a 10-year period in the US if 2L+ CLL patients were treated with zanubrutinib instead of ibrutinib. Additionally, for every 54 patients treated with zanubrutinib instead of ibrutinib for 2L+ CLL, one additional cardiac death can be prevented over ten years. Exploratory NNT analysis conducted in the 1L setting suggested that up to 266 deaths may be avoided over a 10-year period if CLL patients were treated with zanubrutinib instead of ibrutinib. In this same 10-year period, for every 46 patients treated with zanubrutinib instead of ibrutinib, one additional cardiac death can be prevented.

Conclusion: This model estimates that treating patients with zanubrutinib instead of ibrutinib for CLL could potentially prevent approximately 255 cardiac deaths in the second-line or later (2L+) setting and 266 in the first-line (1L) setting over a 10-year period. The study findings should be interpreted based on model assumptions and data inputs including potential differences in the patient populations treated in the clinical trials vs in the real world. Additional real-world studies are required to further validate the cardiac death risk of treating CLL patients with ibrutinib compared to zanubrutinib.