Number of cardiac deaths associated with ibrutinib versus zanubrutinib for the treatment of chronic lymphocytic leukemia: a European risk-based estimation

Authors: Talha Munir[1], Paolo Sportoletti[2], Andrea Visentin[3], Leyla Mohseninejad[4], Lianne Barnieh[4], Keri Yang[4], Wassim Aldairy[4], Sheila Mpima[5], Vicky Casey[6], Rhys Williams[4], Raul Diez Fernandez[7], Francisco Javier Diaz Galvez[8], Vincent Levy[9]

Affiliations: [1] Leeds Teaching Hospital, Leeds, UK; [2] Hematology and Clinical Immunology Section, Department of Medicine and Surgery, Center for Hemato-Oncological Research (CREO), Universita Delgi Studi di Perugia, Perugia, Italy; [3] Hematology Unit, Azienda Ospedale-Universita Padova, Padova, Italy; [4] BeOne Medicines Ltd., USA, San Carlos, USA; [5] IQVIA, Atlanta, USA; [6] IQVIA, London, UK; [7] Hospital Universitario de Getafe, Getafe, Spain; [8] Salud de Castilla y Leon, Valladolid, Spain; [9] Département de recherche clinique, Hôpital Avicenne, APHP, Bobigny, France

ABSTRACT

Introduction

Bruton tyrosine kinase inhibitors include ibrutinib (first generation) and zanubrutinib (next-generation) are approved treatments of chronic lymphocytic leukemia (CLL) in the EU. They have demonstrated efficacy as monotherapy for the treatment of CLL in the first-line (1L) setting (zanubrutinib in SEQUOIA [NCT03336333] and ibrutinib in RESONATE-2 [NCT01722487]). In the second-line or later (2L+) setting, in the ALPINE trial (NCT03734016) zanubrutinib demonstrated superiority over ibrutinib in preventing progression, relapse or death; further, treatment with ibrutinib led to more cardiac deaths compared to zero cardiac deaths with zanubrutinib. Real-world data on cardiac deaths in CLL remain limited. This study estimates how many cardiac deaths could have been avoided if patients had received zanubrutinib instead of ibrutinib.

Methods

The number of cardiac deaths associated with ibrutinib versus zanubrutinib in the 2L+ (base case) and 1L (sensitivity analysis) CLL setting was estimated using a number needed to treat (NNT) model. The 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]). To estimate the potential total number of avoidable deaths over a 5-year treatment period, the NNT to avoid an incremental cardiac death was calculated by applying the risks of cardiac death by treatment period (0-12 months; 12–36 months; 36–60 months; >60 months) to the number of real-world CLL patients receiving ibrutinib. For the base case analysis, the cumulative cardiac death risk for zanubrutinib and ibrutinib in the 2L+ CLL setting was extracted from the ALPINE study (0% for zanubrutinib vs 1.852% for ibrutinib); for the sensitivity analysis in the 1L CLL setting risk of cardiac death was taken from SEQUOIA (0.833% for zanubrutinib) and RESONATE-2 (2.963% for ibrutinib monotherapy). The number of new CLL patients receiving ibrutinib monotherapy in the real-world setting was obtained from the IQVIA Oncology Dynamics database. To reflect treatment uptake while both zanubrutinib and ibrutinib were

available, new patient starts of ibrutinib were calculated starting from the date of availability of zanubrutinib for CLL in each respective country (2022–2024; France, Germany, Italy, Spain and the United Kingdom).

Results

In the base case analysis, there were an estimated 1,555 2L+ CLL patients starting on ibrutinib monotherapy across the five countries. Based on the NNT model, a total of 20 cardiac deaths may have been avoided since the availability of zanubrutinib if 2L+ CLL patients had been treated with zanubrutinib instead of ibrutinib. The sensitivity analyses for ibrutinib monotherapy in the 1L CLL setting estimated that 19 cardiac deaths may be avoided if patients were treated with zanubrutinib instead of ibrutinib monotherapy.

Conclusion

This NNT model demonstrated that when both zanubrutinib and ibrutinib are available for treatment for CLL, treatment with zanubrutinib instead of ibrutinib monotherapy would have prevented cardiac deaths in CLL patients in Europe. 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.