Estimating the Cardiac Deaths Associated With Treating Chronic Lymphocytic Leukemia With Ibrutinib Versus Zanubrutinib in the United States

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CONCLUSIONS

- This model suggests that by switching from ibrutinib to zanubrutinib for chronic lymphocytic leukemia (CLL) treatment, an estimated 61 and 64 cardiac deaths may potentially be prevented over a 5-year period in second-line or later (2L+) and first-line (1L) settings, respectively
- Results from the study should be interpreted based on model assumptions and data inputs

INTRODUCTION

- Bruton tyrosine kinase inhibitors zanubrutinib and ibrutinib have demonstrated efficacy in the 1L CLL setting in SEQUOIA (NCT03336333) and RESONATE-2 (NCT01722487) trials, respectively, while the efficacy and safety of zanubrutinib and ibrutinib were compared in patients receiving 2L+ treatment in the phase 3 ALPINE trial (NCT03734016)[1-4]
- However, there are limited real-world head-to-head comparative data on the risk of cardiac death among patients treated with zanubrutinib and ibrutinib for CLL

OBJECTIVES

- The objective of this study was to conduct a modeling analysis to estimate the number of cardiac deaths in the US that could be avoided by treating patients with zanubrutinib instead of ibrutinib for 2L+ CLL treatment based on published head-to-head data from ALPINE
- Additionally, an exploratory analysis was conducted to investigate the number of cardiac deaths that could be avoided for the 1L treatment of CLL with use of zanubrutinib vs ibrutinib

METHODS

- A number needed to harm (NNH) modeling analysis was conducted to assess how many patients with CLL would need to be treated with ibrutinib vs zanubrutinib to be associated with an incremental cardiac death in the 2L+ and 1L settings
- In the 2L+ CLL treatment setting, treatment-related cardiac death data for zanubrutinib and ibrutinib were extracted from the ALPINE study; cardiac death risks extracted for the time on treatment periods are shown in **Table 1**
- In the 1L CLL treatment setting, the number of cardiac deaths among patients treated with zanubrutinib was obtained from SEQUOIA and the number of cardiac deaths among patients treated with ibrutinib from RESONATE-2; cardiac death risks extracted for the time on treatment periods are shown in **Table 1**

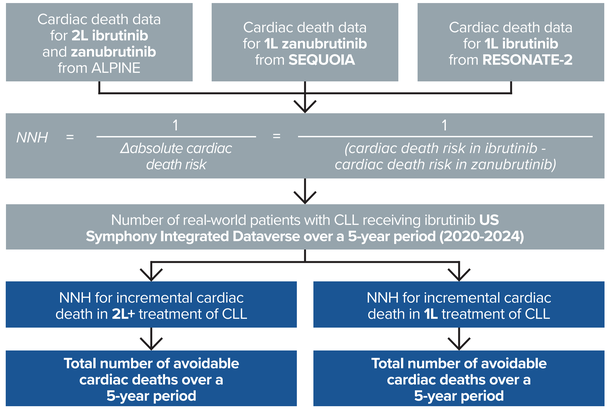
Table 1. Cardiac Death Risks With Zanubrutinib and Ibrutinib in the 2L+ and 1L CLL Settings

2L+ CLL setting	Zanubrutinib – ALPINE	Ibrutinib – ALPINE
0–12 months	0%	0.926%
>12–36 months	0%	1.852%
>36–60 months	0%	1.852%
>60 months	0%	1.852%
1L CLL setting	**Zanubrutinib – SEQUOIA**	**Ibrutinib – RESONATE-2**
0–12 months	0%	0.735%
>12–36 months	0.417%	1.471%
>36–60 months	0.833%	2.206%
>60 months	0.833%	2.941%

1L, first-line; 2L+, second-line or later; CLL, chronic lymphocytic leukemia.

- To estimate the potential total number of avoidable deaths over a 5-year period, the NNH for an incremental cardiac death in 2L+ and 1L treatment of CLL was calculated by applying the cardiac death data from ALPINE (2L+) and RESONATE-2 and SEQUOIA (1L) to the number of real-world patients with CLL receiving ibrutinib (**Figure 1**)
  - The number of patients with CLL receiving ibrutinib in the real-world setting was estimated from a retrospective analysis of the US Symphony Integrated Dataverse database from 2020 to 2024
    - Approximately 30%-50% of the US patients with CLL are represented in the Symphony database
  - The NNH to avoid a cardiac death was calculated by time on treatment period: 0–12, >12–36, >36–60, and >60 months

Figure 1. NNH and Total Number of Avoidable Deaths Over a 5-Year Period



1L, first-line; 2L+, second-line or later; CLL, chronic lymphocytic leukemia; NNH, number needed to harm.

RESULTS

Treatment Utilization of Ibrutinib in the US

- During the 5-year period, a total of 10,884 patients with CLL treated with ibrutinib were identified in the Symphony database: 4,419 in the 2L+ setting and 6,465 patients in the 1L setting
- Ibrutinib data analyzed by time on treatment period is shown in **Table 2**

Table 2. US Real-World Utilization of Ibrutinib for the Treatment of CLL

	Time on Treatment (months)				
	0–12	>12–36	>36–60	>60	Total
2L+ ibrutinib	2,111	1,434	814	60	4,419
1L ibrutinib	2,812	2,097	1,461	95	6,465

1L, first-line; 2L+, second-line or later; CLL, chronic lymphocytic leukemia.

NNH Results for 2L+ CLL

- The NNH with ibrutinib vs zanubrutinib in 2L+ CLL resulting in an incremental cardiac death was calculated for each time-on-treatment period using cardiac death data from the ALPINE study (**Table 3**)

Table 3. NNH Results of Ibrutinib vs Zanubrutinib in 2L+ CLL

		Time on Treatment (months)			
		0–12	>12–36	>36–60	>60
Ibrutinib cardiac death risk		0.926%	1.852%	1.852%	1.852%
Zanubrutinib cardiac death risk		0.000%	0.000%	0.000%	0.000%
NNH		**108**	**54**	**54**	**54**
Cardiac deaths avoided with zanubrutinib	Per treatment period	19	26	15	1
	Total	**61**			

2L+, second-line or later; CLL, chronic lymphocytic leukemia; NNH, number needed to harm.

- The NNH for 1 incremental cardiac death with ibrutinib vs zanubrutinib was 54 among patients treated for a duration of more than 1 year (**Figure 2**)

Figure 2. Schematic Showing Cardiac Death Risk From 2L+ (ALPINE) Patients With CLL

2L+, second-line or later; CLL, chronic lymphocytic leukemia; NNH, number needed to harm.

- Modeling NNH for ibrutinib vs zanubrutinib to US real-world treatment utilization, an estimated 61 cardiac deaths may be avoided over a 5-year period if 2L+ patients with CLL were treated with zanubrutinib

NNH Results for 1L CLL

- An exploratory analysis for the NNH with ibrutinib vs zanubrutinib in 1L CLL to result in 1 incremental cardiac death was calculated for each time-on-treatment period using cardiac death risk data from the SEQUOIA and RESONATE-2 studies (**Table 4**)

Table 4. NNH Results of Ibrutinib vs Zanubrutinib 1L CLL

		Time on Treatment (months)			
		0–12	>12–36	>36–60	>60
Ibrutinib cardiac death risk		0.741%	1.481%	2.222%	2.963%
Zanubrutinib cardiac death risk		0.000%	0.417%	0.833%	0.833%
NNH		**135**	**93**	**72**	**46**
Cardiac deaths avoided with zanubrutinib	Per treatment period	20	22	20	2
	Total	**64**			

1L, first-line; CLL, chronic lymphocytic leukemia; NNH, number needed to harm.

- The NNH for 1 incremental cardiac death with ibrutinib vs zanubrutinib in the 1L CLL setting was 46 among those who had received treatment for 5 years or more
- Modeling NNH for ibrutinib vs zanubrutinib to US real-world treatment patterns, an estimated 64 cardiac deaths may be avoided over a 5-year period if 2L+ patients with CLL were treated with zanubrutinib

DISCUSSION

- Based on this model, switching from ibrutinib to zanubrutinib for CLL treatment may avoid an estimated 61 and 64 cardiac deaths over a 5-year period in 2L+ and 1L settings, respectively
- To the best of our knowledge, this is the first study to quantify the NNH for cardiac death in patients with CLL, comparing ibrutinib and zanubrutinib
- Study results should be interpreted in consideration of differences in study populations and reporting of cardiac-related deaths that may potentially limit comparability of outcomes across trials
- Further real-world studies are needed to evaluate the broader impacts of treatment with zanubrutinib and ibrutinib beyond risk of cardiac death

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DISCLOSURES

TM: Consulting or advising roles for Janssen-Cilag, AstraZeneca, BeOne, SOBI, Roche, AbbVie, Alexion Pharmaceuticals, and Lilly; speakers' bureau participation for AbbVie, Janssen-Cilag, Gilead Sciences, Alexion Pharmaceuticals, AstraZeneca, and SOBI; and travel, accommodations, or expenses from Janssen-Cilag, AbbVie, Alexion Pharmaceuticals, and AstraZeneca. **RW**: Employment and equity holder in BeOne. **DC**: Employment with Curta. Curta received funding for the study. **SC**: Employment and equity holder in BeOne. **QF**: Employment and equity holder in BeOne. **MX**: Employment and equity holder in BeOne. **KY**: Employment and equity holder in BeOne. **AL**: Consulting fees from AstraZeneca, AbbVie, Synthekine, Lilly, and BeOne.

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