Zanubrutinib versus Ibrutinib to Treat Adults with Relapsed or Refractory Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (CLL/SLL): A Cost per Responder Model from a Payer Perspective in the United States

Sizhu Liu[1], Keri Yang[1], David Campbell[2], Kristen Migliaccio-Walle[2], Kevin Li[2], Fan Wu[2], Boxiong Tang[1]

[1]BeiGene USA, San Mateo, CA; [2]Curta, Seattle, WA

Background

- As the most common form of leukemia in adults, chronic lymphocytic leukemia (CLL) accounts for approximately 38% of cases, with an incidence rate in the United States of 4.2 per 100,000 across all ages and a rate of 23.1 per 100,000 among those ≥65 years.[1,2]
- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling.[3]
- The efficacy of Bruton's tyrosine kinase (BTK) inhibitors over anti-CD20 mAb and conventional immuno-chemotherapy for the treatment of relapsed or refractory CLL/SLL has been demonstrated in several phase III studies.[4,5]
- BTK inhibitors are now the most commonly used treatment for relapsed or refractory CLL/SLL.[6]
- Zanubrutinib is an irreversible, potent, and specific next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of tyrosine kinases which are thought to cause adverse effects.[3]
- The randomized, phase 3 ALPINE trial (NCT03734016) compared the efficacy and safety of ibrutinib, a first-generation BTK inhibitor, with zanubrutinib, a novel highly selective BTK inhibitor, in patients with relapsed or refractory CLL/SLL.[7]

Objective

- This study aimed to estimate the cost per responder (CPR) for zanubrutinib versus ibrutinib in relapsed or refractory CLL/SLL from a payer perspective in the United States (US).

Methods

Model Structure

- A Microsoft Excel-based model was developed to compare the cost per responder with zanubrutinib versus ibrutinib to treat relapsed or refractory CLL/SLL patients over a 1-year time horizon.

Model Inputs

- Treatment response was based on the investigator-assessed overall response rate (ORR) at the interim 12-month analysis of the ALPINE trial (data cut-off Dec 2020).
- Responders are defined as patients with a best overall response of partial response or higher.
- Total cost per patient included costs of drug acquisition and adverse event management.
- Daily drug costs were calculated using the published wholesale acquisition cost (WAC), duration of treatment, and dosing from the ALPINE trial (**Table 1**).
  - The WAC costs for zanubrutinib and ibrutinib were obtained from IBM Micromedex RED BOOK Online®.[8]
  - Patients are assumed to be diagnosed at the beginning of the year and assumed to be treated for all 365 days of the year.
- Adverse event (AE) management costs were estimated based on the incidence of BTK inhibitor AEs of interest (grade ≥3) from the ALPINE trial and costs per AE as reported by the Healthcare Cost and Utilization Project (HCUP).[9,10]
  - Probabilities for the following grade ≥3 AEs were extracted from the ALPINE trial and included in the model: atrial fibrillation/flutter, hemorrhage, hypertension, infection, neutropenia, and secondary malignancy (**Table 2**).
  - Cost per AE from HCUP was adjusted from 2015 to 2021 United States dollars using the medical care component of the Consumer Price Index.[11]

Model Outputs

- The cost per responder outcome was calculated as the total cost of each treatment group divided by the proportion of people who achieved ORR in that treatment group.
- A breakeven analysis was conducted for the treatment with a higher cost per responder to determine the discount needed from WAC to achieve a parity in cost per responder outcome.
- One-way sensitivity analyses were conducted to identify the impact of parameter uncertainty and key drivers of model outcomes.

Table 1. Treatment Costs

Drug Costs	Zanubrutinib	Ibrutinib
WAC per package	$13,997	$14,956
Daily cost	$467	$534

Abbreviations: WAC, wholesale acquisition cost

Table 2. Treatment Related Adverse Event Costs

Adverse events	Zanubrutinib	Ibrutinib	Cost per Episode
Atrial fibrillation/flutter	1.0%	1.9%	$10,261
Hemorrhage[a]	2.9%	2.9%	$19,498
Hypertension	10.8%	10.6%	$3,819
Infection	12.7%	17.9%	$6,761
Neutropenia[b]	18.6%	15.0%	$14,430
Secondary primary malignancy[c]	4.9%	1.9%	$24,724

[a] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades
[b] Includes neutropenia, neutrophil count decreased, and febrile neutropenia;
[c] Defined as: Ultra-violet light mediated skin cancers (i.e., basal cell carcinoma, squamous cell carcinoma of skin, Bowen's disease, skin cancer, malignant melanoma)

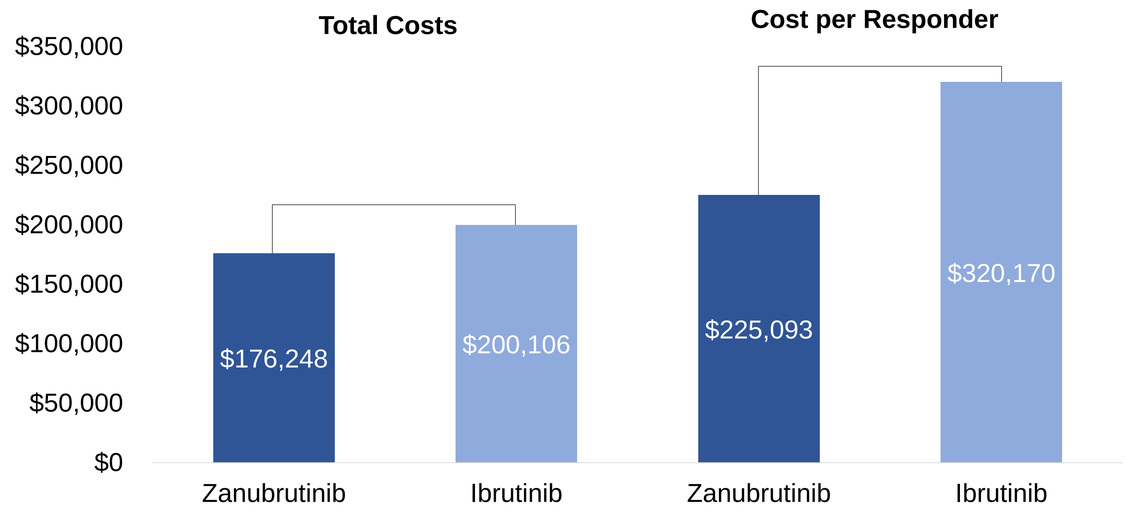
Results

- Among zanubrutinib patients, the total direct medical cost per modeled patient was $176,248 (drug acquisition: $170,413; adverse events: $5,835) (**Table 3, Figure 1**).
- Among ibrutinib patients, the total direct medical cost per patient was $200,106 (drug acquisition: $195,097; adverse events: $5,010).
- The modeled cost per responder was $225,093 for those treated with zanubrutinib and $320,170 for those treated with ibrutinib.
- Zanubrutinib was associated with lower direct medical costs and lower cost per responder.

Table 3. Model Results

an	Zanubrutinib	Ibrutinib
Response rate (ORR)[7]	78%	63%
Drug acquisition cost	$170,413	$195,097
Adverse event cost	$5,835	$5,010
Total costs	$176,248	$200,106
Cost per responder	**$225,093**	**$320,170**

Figure 1. Summary of Direct Treatment Costs and Cost per Responder



Sensitivity Analysis

- A breakeven analysis found that the WAC of ibrutinib (strength: 420 mg, package size: 28) would need to be reduced by 30% (i.e., from $14,956 to $10,401) to match the cost per responder of zanubrutinib.
  - This reduction in price is similar to the 36% reduction in WAC of ibrutinib reported in a previous cost per responder analysis in Waldenström macroglobulinemia to match the cost per responder of with zanubrutinib.[12]
- With a parameter range of +/- 10%, the cost per responder for zanubrutinib was most sensitive to the zanubrutinib response rate, WAC per package, daily dosage.

Discussion

- Zanubrutinib offers an important treatment option for adult patients with relapsed or refractory CLL/SLL who required treatment based on consensus criteria.
- This cost per responder analysis found zanubrutinib was both clinically more effective and associated with lower direct medical costs and cost per responder.
- Future research is warranted to validate the results based on real world outcomes and longer follow-up.

Limitations

- The clinical inputs were derived from the first 12-month interim analysis of the phase 3 ALPINE study, which may underestimate the number of long-term adverse events and increase the variability in estimates of treatment effects.
- Only Grade ≥3 AE categories of interest (BTK inhibitor Class AEs) were chosen to be in the model because these are the most relevant to the relative safety profiles of the two treatments.

Conclusion

In adult patients with relapsed or refractory CLL/SLL, zanubrutinib represents a cost saving option to achieve clinical response, with a lower cost per responder compared to ibrutinib from a US payer perspective.

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Correspondence: keri.yang@beigene.com

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