Budget Impact Analysis of Zanubrutinib for Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma in the United States

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Background

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a predominantly slow growing form of cancer in which blood stem cells create too many abnormal lymphocytes.[1] An estimated 20,160 new cases of CLL were diagnosed in the United States in 2022, and the 5-year relative survival was 87.9% based on 2012-2018 data.[2]
- Refractory disease is defined as disease progression or no objective response within six months of the last treatment; relapsed disease is defined as progression or relapse >6 months after the last treatment.[3] The majority of relapses are diagnosed relatively early on because patients are monitored regularly after first-line (1L) or second line (2L) treatment.
- Inhibition of Bruton's tyrosine kinase (BTK) has become a strategy for targeting B-cell malignancies. However, not all patients respond to treatment with BTK inhibitors and adverse events are the most common reason for treatment discontinuation.
- A recent update to the National Comprehensive Cancer Network (NCCN) clinical guidelines included zanubrutinib, a next-generation BTK inhibitor (BTKi), as the preferred treatment for R/R CLL/SLL.[4] The phase 3 ALPINE trial (NCT03734016) compared the efficacy and safety of ibrutinib, a first-generation BTKi, with zanubrutinib, a novel highly selective BTKi, in patients with relapsed or refractory (R/R) CLL/SLL.
- This study conducts a budget impact analysis to estimate the incremental costs associated with using zanubrutinib in R/R CLL/SLL patients from the US payer perspective.

Methods

Model Design

- A budget impact model (BIM) was developed to estimate the economic impact of providing adult R/R CLL/SLL patients access to zanubrutinib within a hypothetical blended United States (US) health plan with one million members.
- The model analysis compared a reference scenario with the "current market mix" (i.e., before the introduction of zanubrutinib) and an alternative scenario with a "revised market mix" where the uptake of zanubrutinib was included (i.e., after zanubrutinib entry).
- The targeted patient population entering the model was estimated based on US-specific epidemiological inputs.
- Comparators included ibrutinib, acalabrutinib, venetoclax ± rituximab, bendamustine + rituximab, idelalisib + rituximab, chlorambucil ± rituximab, and obinutuzumab + chlorambucil (**Table 1**).

Table 1. Treatment Regimens

BTKi	Zanubrutinib (uptake assumed proportionally taken from all other existing treatment options), acalabrutinib, and ibrutinib
Venetoclax-based therapy	Venetoclax monotherapy and venetoclax + rituximab combination assumed based on the market share data
Phosphatidylinositol 3 kinase inhibitor (PI3Ki)	Idelalisib + rituximab
Chemotherapy ± anti-CD20 therapy	Bendamustine ± other (i.e., bendamustine + rituximab), chlorambucil ± other (i.e., chlorambucil and chlorambucil + rituximab assumed), and obinutuzumab ± other (i.e., obinutuzumab + chlorambucil)

BTKi = Bruton's Tyrosine Kinase Inhibitor; PI3Ki = phosphatidylinositol 3 kinase inhibitor

- Zanubrutinib was assumed to treat until disease progression; the treatment duration was informed by the progression-free survival (PFS) extrapolated from the ALPINE trial observed data. Treatment duration of other regimens were estimated based on the constant hazard ratios derived based on a standard NMA analysis or modeled as a fixed duration based on drug labels.[5]
- After treatment discontinuation or disease progression, patients could receive active subsequent treatments; therefore, a one-time cost will be applied. Cost was calculated as a weighted average by the distribution of treatment options that are considered appropriate for R/R patients after progression on 2L or later line treatment. This included venetoclax + rituximab for those who progressed following BTKi whilst ibrutinib for those who progressed following chemoimmunotherapy or other combination regimens, or alternatively fludarabine + cyclophosphamide + rituximab (FCR).
- The model reported outputs as the total, per-member-per-month (PMPM), and per-treated-member-per-year (PTMPY) budget impact, estimated using the base-case scenarios of clinical practice with and without zanubrutinib. A one-way sensitivity analysis (OWSA) was conducted by varying each input by ± 20% to assess parameter uncertainties and explore key model drivers.

Model Inputs and Assumptions

- The number of eligible patients entering the model in each year was derived from a hypothetical plan size of one million, annual incidence and progression, and proportion of patients eligible and receiving active 2L+ treatment (**Table 2**).

Table 2. Epidemiology Inputs for the BIM

Parameter	Value	Source
Total plan size (N)	1,000,000	Assumption
Annual incidence rate of TN CLL/SLL (per 100,000)—Commercial	4.91	SEER 21 areas (all age)[6]
Annual incidence rate of TN CLL/SLL (per 100,000)—Medicare	27.50	SEER 21 areas (age 65 and over)[6]
Of which, percent eligible and receiving active 1L treatment (e.g., symptomatic)	32.6%	Calculated from Mato et al. 2018[7] (sample size of 3,214 and 1,047 received 1L)[7]
Annual progression to R/R	15.1%	Calibrated based on SEQUOIA (NCT03336333) trial data (a pooled proportion of progression for zanubrutinib and BR: 38.85% at 36-month; converted to annual probability)[8]
Of which, % eligible and receiving active 2L+ treatment	41.7%	Calibrated based on Kabadi 2020[9]

BR = bendamustine + rituximab; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; R/R = relapsed or refractory; SEER = Surveillance Epidemiology, and End Results; TN = treatment-native;

- Market share data for the current market mix were sourced from BeiGene market research. Zanubrutinib uptake was assumed to be 10% and obtained proportionally from the current market mix. The market share values in both scenarios were assumed to be constant throughout the time horizon.
- Drug dosing information was extracted from clinical trials or relevant US prescribing information (USPI). Listed prices of drugs were taken from wholesale acquisition costs (WAC) reported in REDBOOK and average selling price (ASP) published on CMS.gov, for commercial and Medicare, respectively. Drug wastage was considered for treatments that were dependent on weight or body surface area (BSA), as well as with relative dose intensity adjusted. Other cost inputs, including administration, disease management, and treatment monitoring were also derived from US-specific public dataset. (**Table 3** and **Table 4**)
- Adverse event (AE) management costs were applied at the start of each treatment; only grade 3 or higher AEs reported in at least 5% of patients for at least one treatment were included. AE incidences were extracted from trial publications.

Methods (Cont'd)

Table 3. Cost Categories and Sources

Drug administration costs	Oral administration cost was assumed to be $0; chemotherapy administration costs were informed by 2021 Physicians' Fee & Coding Guide (inflated to 2022) for commercial costs;[10] CMS.gov Medicare Physician Fee Schedule 2022 and Medicare Hospital Outpatient PPS File for Medicare costs.[11]
Medical resource use (MRU) costs	MRU costs per month (e.g., hospitalization, emergency department visit, physician's office visit, and lab tests) were extracted from Kabadi 2020, a retrospective database analysis for patients without AEs, and inflated to 2022.[9] TLS one-off costs were calculated based on risk category as reported in MURANO trial.[12]
AE management costs	Costs per AE were derived from CMS.gov Medicare Acute Inpatient PPS 2022 for Medicare and multiplied by a ratio of 2.05 for commercial.[13]

AE = adverse event; HTA = Health Technology Assessment; PPS =Prospective Payment System; TLS = tumor lysis syndrome

Table 4. Cost Inputs by Category

Treatment	Drug acquisition cost			Drug administration cost			AE cost (aggregated)
(cycle = 28-day)	**Cycle 1**	**Cycle 2–7**	**Cycle 8+**	**Cycle 1**	**Cycle 2–7**	**Cycle 8+**	**One-off cost**
Zanubrutinib	$13,025	$13,025	$13,025	$0	$0	$0	$4,519
Ibrutinib	$14,956	$14,956	$14,956	$0	$0	$0	$4,401
Acalabrutinib	$13,257	$13,257	$13,257	$0	$0	$0	$6,120
Venetoclax ± Other	$4,703	$14,266	$12,212	$145	$70	$0	$14,470
Bendamustine ± Other	$14,907	$13,901	$0	$440	$211	$0	$13,425
Idelalisib + rituximab	$17,207	$17,726	$11,601	$440	$211	$0	$2,505
Chlorambucil ± Other	$3,722	$3,846	$0	$220	$106	$0	$1,469
Obinutuzumab ± Other	$20,619	$6,270	$0	$862	$211	$0	$11,884

BTKi = Bruton's Tyrosine Kinase Inhibitor; PI3Ki = phosphatidylinositol 3 kinase inhibitor

Results

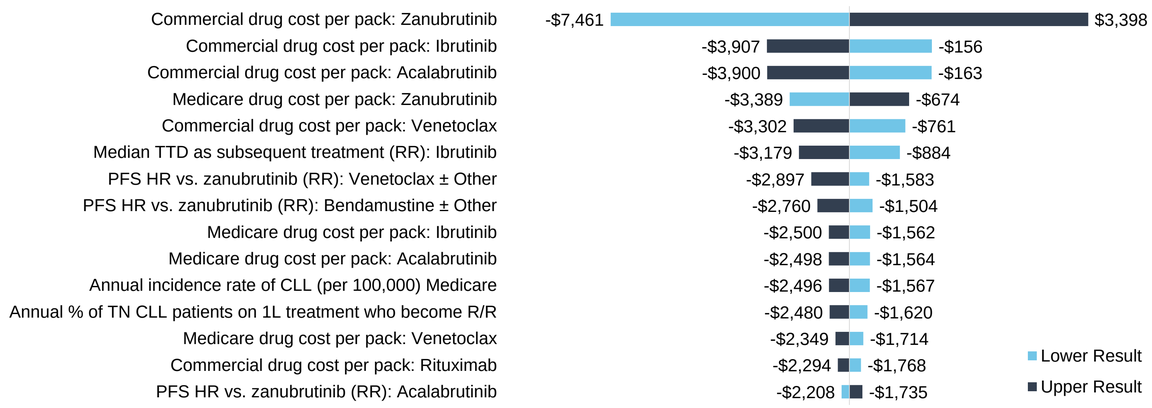
Base Case Analysis

- In a hypothetical one-million-member health plan, two patients were estimated to have R/R CLL/SLL and initiated treatment.
- Total healthcare costs were $412K with zanubrutinib and $414K without, suggesting that adding zanubrutinib is associated with a cost-saving of $2,031 over 1 year (PMPM <-$0.001; PTMPM: -$88).

One-way sensitivity analysis (OWSA)

- OWSA showed that the budget impact on healthcare costs over a one-year time horizon were most sensitive to zanubrutinib wholesale acquisition cost (**Figure 4**).

Figure 4. OWSA Tornado Chart (Top 15 Key Drivers)



BSA = Body surface area; HR = Hazard ratio; PFS = Progression-free survival; RR = relapsed/refractory; TN = treatment-native; TTD = Time to treatment discontinuation

Limitations

- Data on the annual progression to R/R was calibrated based on SEQUOIA trial data rather than real-world registry data. However, progression was validated by comparing SEQUOIA trial data to the 7-year follow-up data reported in RESONATE2 trial.[14]
- Market uptake for zanubrutinib was based on BeiGene forecasts and may be subject to future updates according to real-world utilization.
- Where treatment options could be defined as a mixed basket of monotherapy and combination therapies, changes to the default inputs impacted acquisition and administration costs but not efficacy.

Conclusions

Results from the economic analysis suggests that providing access to zanubrutinib for patients with R/R CLL/SLL is associated with cost savings to a US health plan.

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