EE713

The Impact of Delaying Access to Innovative Therapies in Emerging Markets for Chronic Lymphocytic Leukemia: A Modeling Study

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CONCLUSIONS

- Our analysis showed that delaying access to innovative therapies, such as zanubrutinib, increased the number of progressions and QALY losses in patients with TN or R/R CLL
- Across all four included countries, QALYs were higher when zanubrutinib was available without delay compared with the scenario of SOC alone during the delay time, followed by zanubrutinib
- Providing immediate access to zanubrutinib also resulted in fewer disease progressions. In both TN and R/R CLL, when zanubrutinib was not delayed, more progressions were averted versus both FCR and ibrutinib
- Scenario analyses confirmed that QALYs lost, HEI, and number of progressions averted increased with a longer delay time
- In the one-way sensitivity analyses, HRs had the highest influence
- Understanding the health impact of access delays is crucial to informing policy decisions aimed at improving the timely availability of innovative therapies for patients

INTRODUCTION

- Chronic lymphocytic leukemia (CLL) is one of the most prevalent types of leukemia, leading to impaired immune function and progressive accumulation of abnormal cells in the blood, bone marrow, and lymphoid tissues[1,2]
- Both chemotherapy and targeted therapies are used to treat CLL; however, the standard of care (SOC) varies across countries.[3] Although chemotherapy effectively kills rapidly dividing cells, its broad effect can lead to widespread side effects.[3] Targeted therapies specifically block cancer-causing proteins, offering a more precise attack with fewer side effects[3]
- Zanubrutinib is an innovative, targeted next-generation Bruton tyrosine kinase inhibitor that has demonstrated superior efficacy in both treatment-naïve (TN) and relapsed/refractory (R/R) CLL[4,5]
- Access to novel therapies after regulatory approval varies in emerging markets. Delays in access may significantly impact patient outcomes

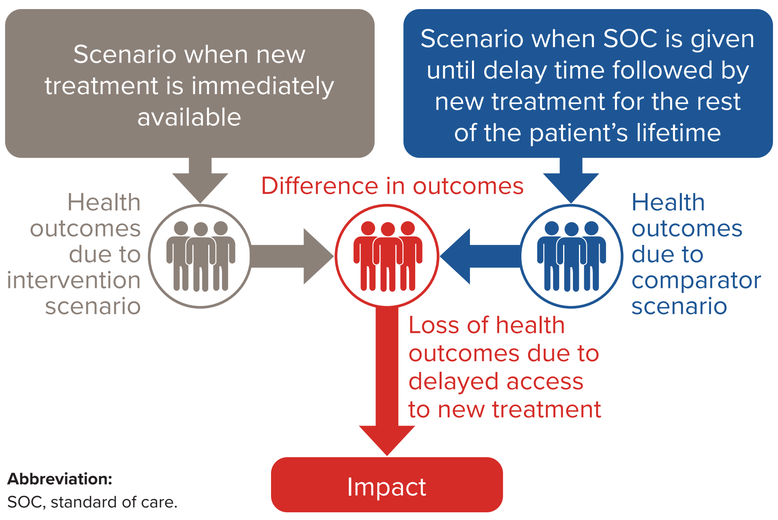
OBJECTIVE

- This study explores the impact of delaying access to innovative therapies in patients with TN and R/R CLL in emerging markets, where access to new medicines may be delayed

METHODS

- A partitioned-survival model with three health states (progression-free, progressed-disease, and death) was developed to compare health outcomes between a "world with" scenario (where patients receive zanubrutinib without delay) and a "world without" scenario (where patients are first treated with SOC during a delay period, prior to receiving zanubrutinib) (**Figures 1** and **2**)
- SOC included ibrutinib in Turkey and Argentina; and fludarabine, cyclophosphamide, and rituximab (FCR) in Brazil and South Africa
- In the comparator scenario, patients start on SOC and then switch to zanubrutinib after a set delay time. After the switch, their hazard ratios (HRs) align with those in the intervention scenario, where zanubrutinib is given from cycle 0

Figure 1. Model Structure



Abbreviation: SOC, standard of care.

Inputs

- Parametric survival analyses were used to extrapolate overall survival (OS) and progression-free survival (PFS) beyond the follow-up period of the clinical studies. The best-fitting distributions (based on the Akaike Information Criterion and Bayesian Information Criterion scores) were selected in the base case analysis
- PFS and OS inputs for zanubrutinib were derived through survival analysis of Kaplan–Meier data from the SEQUOIA and ALPINE trials[4,5]
- For PFS, HRs from clinical trials were applied to zanubrutinib PFS to calculate the comparator PFS (**Table 1**).[6-8] Given the absence of statistically significant differences in OS between zanubrutinib and ibrutinib, and between zanubrutinib and FCR, an OS HR of 1.0 was conservatively applied in the model

Figure 2. Model Specifications

Population	TN and R/R CLL	Time horizon	Lifetime
Perspective	Healthcare provider/payer	Cycle length	4 weeks
Delay time definition	Access delay was defined as the period from regulatory approval of zanubrutinib to patient access in the specific country of interest. Delay time duration of 1 to 5 years was considered in the model.		
Outcomes	QALYs, HEI due to QALYs lost, and the number of progressions averted had zanubrutinib not been delayed, per 1000 patients.		

Abbreviations: CLL, chronic lymphocytic leukemia; HEI, health economic impact; QALY, quality-adjusted life years; R/R, relapsed/refractory; TN, treatment-naïve.

Table 1. Model PFS Inputs

Setting	Comparator	HR (95% CI) Zanubrutinib vs Comparator	HR (95% CI) Comparator vs Zanubrutinib
TN CLL	Ibrutinib	0.59[a] (0.79-0.44)	1.69 (1.27-2.27)
	FCR	0.33[b] (0.69-0.16)	3.03 (1.45-6.25)
R/R CLL	Ibrutinib	0.66[b] (0.84-0.52)	1.52 (1.19-1.92)
	FCR[c]	0.12[b] (0.26-0.05)	8.33 (3.85-20.00)

[a]Time to next treatment (TTNT) has been used as proxy for PFS; [b]COVID-adjusted model; [c]BR data used as proxy as no FCR data available R/R CLL.
Abbreviations: BR, bendamustine and rituximab; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID, coronavirus disease; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naïve; TTNT, time to next treatment.

- Utility values, country-specific discount rates, and mortality rates were sourced from published literature[9]
- The health economic impact (HEI) resulting from delayed access was assessed by multiplying country-specific age-standardized incidence rates (ASIRs) of TN and R/R CLL, estimates of gross domestic product (GDP) per capita, and the per-patient estimates of incremental quality-adjusted life-years (QALYs)[10]

Analyses

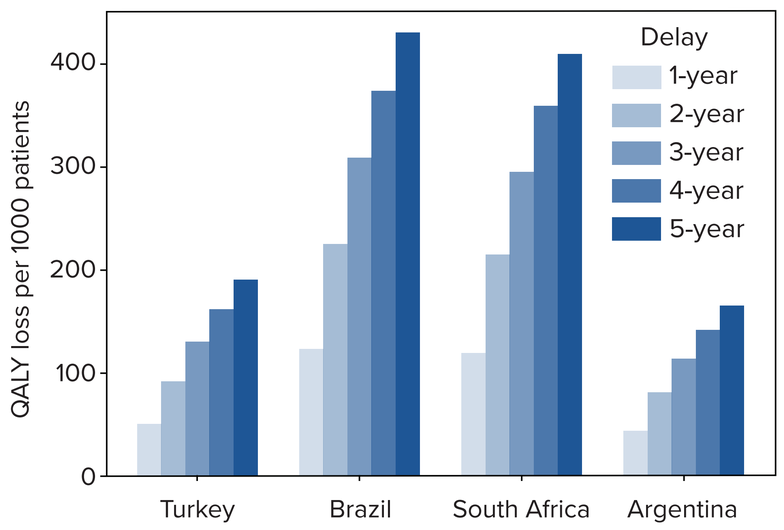
- Scenario analyses assessed the impact of variations in country-specific ASIRs and GDP per capita thresholds used to calculate the HEI.[10] The analyses considered both 1-year and 5-year delay periods across countries and patient populations

RESULTS

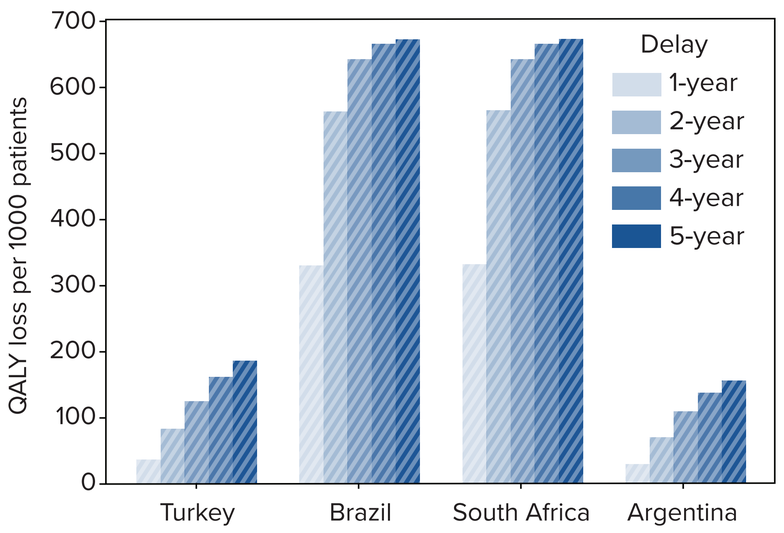
- In TN CLL, a 1-year delay in access to zanubrutinib resulted in a QALY loss ranging from 43 to 123, while a 5-year delay resulted in a loss ranging from 165 to 431. The number of progressions averted if zanubrutinib had not been delayed ranged from 26 to 75 for a 1-year delay and from 106 to 273 for a 5-year delay

Figure 3. QALY Loss Per 1000 Patients Resulting From Delay of Access to Zanubrutinib in the Base Case Analysis

A. TN CLL



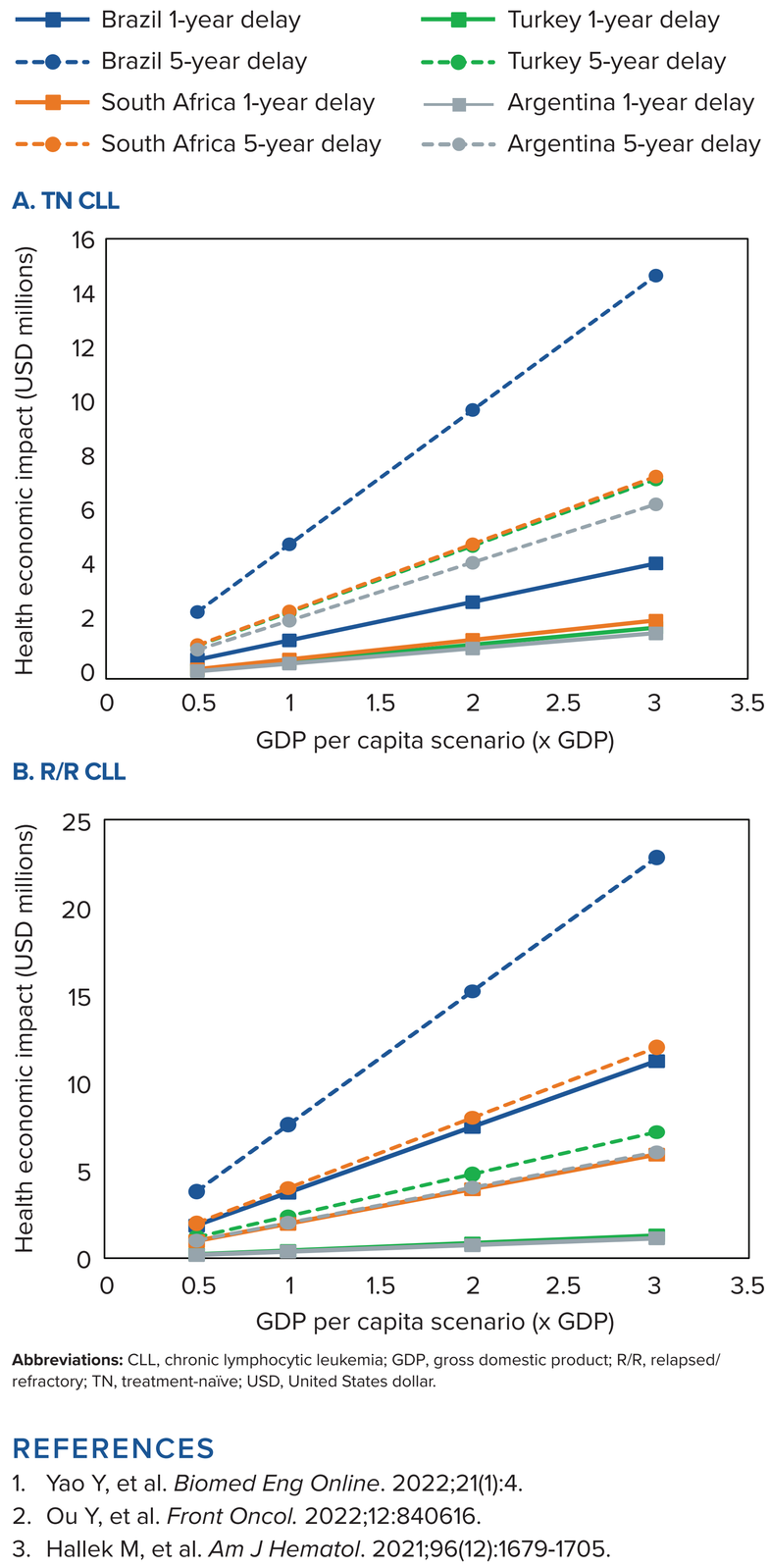
B. R/R CLL



Abbreviations: CLL, chronic lymphocytic leukemia; QALY, quality-adjusted life years; R/R, relapsed/refractory; TN, treatment-naïve.

- In R/R CLL, a 1-year delay resulted in QALY losses ranging from 29 to 330, while ranging from 157 to 671 with a 5-year delay. Progressions averted were higher in Brazil and South Africa (396 [1Y delay] to 507 [5Y delay], respectively) than in Turkey and Argentina (36 [1Y delay] to 149 [5Y delay], respectively) (**Figure 3**)
- Across all four countries, a 1-year delay in access to zanubrutinib for TN CLL patients lead to an HEI (assuming a cost-effectiveness threshold of 1x GDP per capita) that ranged from $0.5 to 1.4 million (M), and increased to $2.1 to 4.9 M with a 5-year delay. For R/R CLL patients, losses ranged from $0.3 to 3.7 M with a 1-year delay and from $2.0 to 7.6 M with a 5-year delay
- One-way sensitivity analyses indicated that the PFS HRs and utility values ranked among the most influential parameters on model outcomes across all countries for both TN and R/R CLL patients
  - The HR for PFS of FCR and ibrutinib over zanubrutinib was the main driver of outcomes when assuming a 1- or 5-year delay time. In R/R CLL, versus ibrutinib, both PFS and OS HRs were highly influential, while in TN CLL, only the PFS HR was influential
- Scenario analyses exploring the lower and upper values of projected ASIRs for 1- and 5-year delay time showed that QALYs lost, HEI, and the number of progressions averted increased with longer delay time
- The HEI increased as GDP per capita increased (ranging from 0.5 to 3) (**Figure 4**)

Figure 4. Scenario Analysis Results on Health Economic Impact Resulting From Delay of Access to Zanubrutinib[8]



Abbreviations: CLL, chronic lymphocytic leukemia; GDP, gross domestic product; R/R, relapsed/refractory; TN, treatment-naïve; USD, United States dollar.

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