EE91

Clinical Outcomes and Associated Costs of Treating Patients With Chronic Lymphocytic Leukemia With Bruton Tyrosine Kinase Inhibitors in the First-Line and Relapsed/Refractory Settings

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OBJECTIVE

To evaluate clinical benefits and associated treatment-related costs of the Bruton tyrosine kinase inhibitors (BTKis), ibrutinib, acalabrutinib, and zanubrutinib using data from United States prescribing information, clinical trials, and real-world evidence

CONCLUSIONS

Using conservative assumptions, results suggest clinical benefits and costs are similar for treatment of chronic lymphocytic leukemia (CLL), exclusive of treatment acquisition costs across BTKis in first-line and relapsed/refractory (R/R) settings

Scenario analyses examining efficacy using clinical trial data derived from head-to-head trials and a match-adjusted indirect treatment comparison support the comparable value of ibrutinib relative to other BTKis

Treatment-related costs (exclusive of drug costs) were similar among patients with R/R CLL, and adverse event (AE) costs were similar across BTKis after accounting for lower AE costs resulting from potential ibrutinib dose reductions among eligible patients

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INTRODUCTION

- The first-in-class Bruton tyrosine kinase inhibitor (BTKi), ibrutinib, and follow-on BTKis acalabrutinib and zanubrutinib, are approved treatments for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in both first-line (1L) and relapsed/refractory (R/R) settings[1-3]
- Previous phase 3 clinical trials have demonstrated a significant progression-free survival (PFS)[4-9] and overall survival (OS)[4,5,8,9] benefit with ibrutinib versus chemotherapy/ chemoimmunotherapy in both previously untreated and R/R CLL/SLL
- Long-term follow-up for ≤8 years has demonstrated sustained benefit with 1L ibrutinib therapy[10,11]
- Prescribing information for ibrutinib includes guidelines for dose reductions (DRs) for management of different types and grades of adverse events (AEs)[1]
- Data from clinical trials showed similar efficacy in patients with DR, which was subsequently demonstrated in studies based on real-world evidence (RWE)[12,13]
- Here we examined clinical benefits and associated treatment-related costs (exclusive of BTKi comparator and subsequent treatment acquisition costs) among BTKis using published clinical trial data, RWE, and indirect treatment comparisons

METHODS

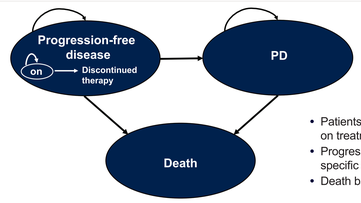
- A semi-Markov model was used to examine clinical and economic outcomes associated with 1L and R/R CLL; model features and parameters are described below
- Medical costs (physician visits and monitoring) and AE-related costs were estimated over 1-year and 5-year time horizons (THs). AE costs per treated patient per month (PTPPM) were applied over a 1-year TH due to inconsistent reporting across trials at longer time points and in an attempt to abstract AE rates across similar time points among multiple trials
- Base case analyses (1L and R/R CLL) of ibrutinib, acalabrutinib, and zanubrutinib were modeled using efficacy data from pivotal trials[5, 14–17]
  - AE rates were taken from trials reported in United States prescribing information (USPI) and supplemented by values from the literature where AE-specific data were missing from PIs
- Scenario analyses (for R/R CLL) examined efficacy and safety from head-to-head trials and a match-adjusted indirect comparison (MAIC, **Supplementary Table 1**)
- The impact of ibrutinib DR on AE costs was examined in scenario analyses for both 1L and R/R CLL using assumptions based on RWE
- 1 way sensitivity analyses were conducted assuming a ±20% range in values, and were reported based on top 5 largest impacts among AE-related costs
- Probabilistic sensitivity analyses were conducted on the incremental PTPPM costs of ibrutinib relative to acalabrutinib and zanubrutinib

Semi-Markov Model Features and Parameters

Perspective	Payer with Medicare population
TH	1 year and 5 years
Cycle length	Weekly
Discount rate	Undiscounted for clinical outcomes; 3.0% for costs
Mortality	Trial mortality data were used up to a common OS time point; thereafter, the highest mortality from trial data or background mortality (from National Vital Statistics System) were used, as opposed to using aggregate mortality data between National Vital Statistics System or published trials
Discontinuation	Patients who discontinued treatment remained progression free until the transition to PD, based on delta between time to treatment discontinuation and median PFS; in some instances the risk of discontinuation was limited to the number of patients discontinuing the clinical trial. Discontinuation was defined in trial by patients ceasing treatment due to PD or toxicity
Population	Patients with 1L or R/R CLL were analyzed separately
Population, baseline characteristics	Average age (67 years), sex (female, 33.8%), and body weight (79 kg) were generally consistent with the RESONATE-2 population and were assumed to be similar across both 1L and RR CLL patients
Comparators	Ibrutinib, acalabrutinib, and zanubrutinib (treated to PD)
Clinical inputs and sources	Efficacy (PFS, OS), safety (grade 3+ AEs), and discontinuation taken from pivotal trials reported in USPIs for each comparator and corresponding publications, with scenario analyses based on head-to-head trials and published indirect treatment comparisons
Economic inputs	Health-state–related HCRU (based on published treatment guidelines and published CLL models) and grade 3+ AE costs (based on values from economic evaluations from models), accounting for reduced AE costs associated with ibrutinib DR using assumptions based on RWE
Outcomes	Clinical: PFS, PD, and total life years over model TH Economic: treatment-related costs, AE costs, and total incremental costs (exclusive of treatment acquisition) reported as PTPPM

HCRU, healthcare resource utilization; PD, progressive disease.

Semi-Markov Model With Weekly Cycles Consistent With Published Model Structure on Similar Decision Problems



- Patients begin in progression-free disease and remain on treatment until progression or discontinuation
- Progression-free disease transition based on treatment-specific PFS curve
- Death based on OS curve and background mortality

- Shadman et al[12] demonstrated that patients with CLL treated with ibrutinib who had a DR following an AE had a lower mean number of all-cause inpatient hospital admissions (0.05 vs 0.14; *P*<0.001) and lower mean number of emergency department visits (0.10 vs 0.22; *P*=0.043) compared with patients without a DR, leading to 20.7% lower HCRU costs ($12,698 vs $16,006)
- In an RWE study, Rogers et al[13] reported that 19.6% of patients taking ibrutinib in the 1L setting had a DR following an AE
  - Other analyses based on RWE suggest that the proportion of patients qualifying for a DR may range from 34% to 83%[18,19]

Model Assumptions Based on RWE

Model Parameter	Assumption
Impact of ibrutinib DR on AE costs	20.7%
Proportion of patients using ibrutinib potentially qualifying for dose DR	19.6%

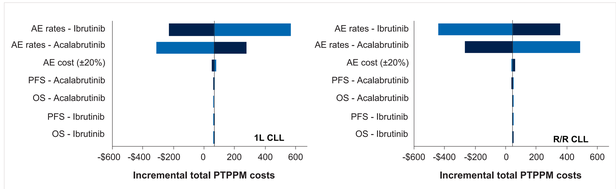
RESULTS

Clinical Results and Estimated Costs

		Clinical Results (years)		Costs (PTPPM)	
Comparator	Clinical Data Source	PFS (1 year/5 years)	Life Year (1 year/5 years)	Treatment Related (1 year/5 years)	AE Costs (1 year)
1L CLL Model					
Ibrutinib	RESONATE-2[5]	0.97/4.16	0.995/4.80	$48/$64	$520/$499 (DR)[a]
Acalabrutinib	ELEVATE-TN[14]	0.97/4.22	0.99/4.68	$46/$58	$457
Zanubrutinib	SEQUOIA[17]	0.96/4.14	0.99/4.65	$46/$60	$489
R/R CLL Model					
Ibrutinib	RESONATE[4]	0.92/3.33	0.96/4.03	$87/$98	$740/$710 (DR)[a]
Acalabrutinib	ELEVATE-RR[15]	0.90/3.06	0.96/4.16	$90/$108	$706
Zanubrutinib	ALPINE[16]	0.94/3.75	0.97/4.35	$86/$93	$570
R/R CLL Scenario Analysis: Head-to-Head Efficacy and Safety					
Ibrutinib	ELEVATE-RR[15]	0.90/3.06	0.96/4.10	$90/$107	$863
Acalabrutinib	ELEVATE-RR[15]	0.90/3.06	0.96/4.16	$90/$108	$822
R/R CLL Scenario Analysis: Head-to-Head Efficacy and Safety					
Ibrutinib	ALPINE[16]	0.90/3.11	0.96/4.13	$89/$106	$581
Zanubrutinib	ALPINE[16]	0.94/3.75	0.97/4.35	$86/$93	$570
R/R CLL Scenario Analysis: MAIC (ALPINE-like Populations)					
Ibrutinib	ALPINE-like RESONATE	0.95/3.89	0.96/4.03	$82/$82	$740
Acalabrutinib	ALPINE-like ASCENT	0.93/3.62	0.96/4.16	$86/$92	$706
Zanubrutinib	ALPINE[16]	0.94/3.75	0.97/4.35	$86/$93	$570

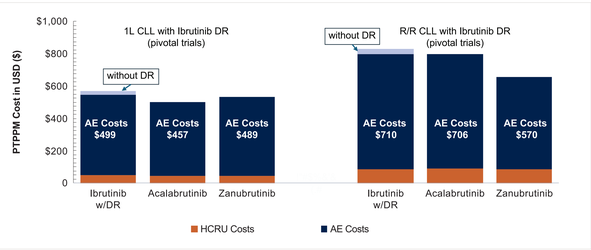
[a]Ibrutinib AE-related costs are without/with DR.

Incremental Total Costs for Ibrutinib Versus Acalabrutinib Are Most Sensitive to AE Rates in 1-Way Sensitivity Analyses



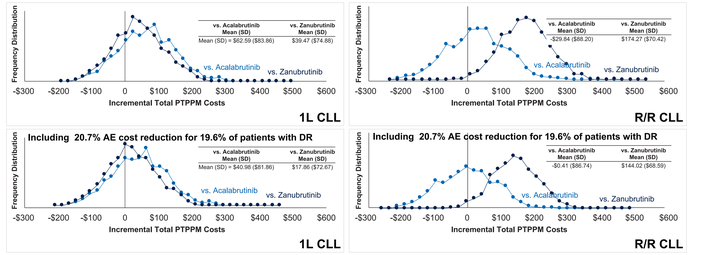
Comparisons based on base case and calculated over a 1-year TH.

Ibrutinib DR Lowered Ibrutinib AE Costs by 4.1%, Suggesting Similar Total Costs for Ibrutinib Relative to Acalabrutinib and Zanubrutinib



Based on modeled AE costs over a 1-year TH. Model applied assumptions for DR of ibrutinib based on pivotal trials and RWE. Based on patients who may have qualified for DR, reduction in AE-related costs could approach 17.2%.

Cost Reductions Associated With Ibrutinib DR May Shift Incremental Total Costs Toward Cost Savings With Ibrutinib Relative to Acalabrutinib or Zanubrutinib



- Cost reductions associated with ibrutinib DR may shift incremental total costs toward cost savings with ibrutinib relative to acalabrutinib or zanubrutinib among patients who may be eligible for DR following and AE (**Supplementary Figure 1**)

LIMITATIONS

- In cases where PFS and OS curves are similar, the implementation of conditional risk of progression relative to survival can produce counterintuitive results, although no standard alternative is considered totally acceptable without the use of individual patient data
- The cost of AEs only applies to the first modeled year, due to the lack of consistent and quality data for long-term AEs
- The impact of DR is modeled as a reduction in AE costs only due to a lack of data regarding not only the relationship between treatment persistence and efficacy but also the relationship between AEs and real-world discontinuation

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