Cost-Offset Analysis Performed Utilizing cBTKi Safety Profiles Among Medicare Patients with Chronic Lymphocytic Leukemia

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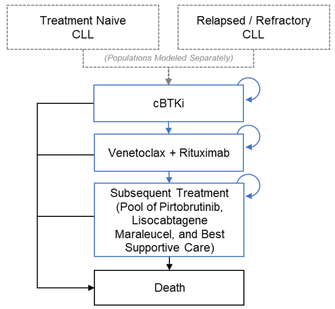
Introduction

- Chronic lymphocytic leukemia (CLL) has had a number of recent treatment innovations including the FDA-approved covalent Bruton's tyrosine kinase inhibitors (cBTKis) ibrutinib, acalabrutinib, and zanubrutinib, which have demonstrated increased efficacy vs. previous standard of care therapies.[1-4]
- Acalabrutinib has shown lower rates of toxicity compared to ibrutinib in a randomized clinical trial (RCT) and matching-adjusted indirect comparison (MAIC) and compared to zanubrutinib in MAICs.[5-8]
- Given the importance of mitigating the high cost of cancer-care, it is important to assess how the selection of different cBTKi treatments impacts the total cost of care.
- **Objective**: To estimate the potential cost savings associated with choice of cBTKi across treatment naïve (TN) and relapsed refractory (RR) Medicare patients with CLL.

Methods

- An economic model was constructed to simulate health and economic outcomes among Medicare Patients with CLL (both TN and RR) initiating cBTKi therapy (ibrutinib, acalabrutinib, or zanubrutinib).
- Population: Modeled population included patients with CLL who are TN and eligible to initiate treatment (excludes "watch and wait" patients) and patients with CLL who are cBTKi-naïve RR in second or third-line (2L-3L) treatment.
- Model structure: A Markov model approach simulated transitions between 4 treatment pathway health states in 28-day monthly cycles: cBTKi, venetoclax + rituximab, subsequent treatment (pooled pirtobrutinib, lisocabtagene maraleucel, best supportive care), and death (**Figure 1**).
- Treatment Efficacy: Treatments were dosed according to FDA labels and efficacy was assumed to be identical across cBTKis.
- Inputs: Cumulative grade ≥3 adverse event (AE) rates for cBTKis were obtained from extended follow-up data of phase III RCTs to ensure similar follow-up duration **(Table 1).**[1,5,9-12] Drug prices were based on 2024 wholesale acquisition costs (WACs),[13] adjusted to reflect Medicare Part D reimbursement using commercial-to-Medicare reimbursement ratio from literature;[14] medical costs associated with treatment of AEs[15] were adjusted for Medicare Part A and B reimbursement rates[17] (**Table 2**).
- Time horizon: 1, 3, and 5 years.
- Outcomes: Total change in cost from cBTKi treatment choice over a 1-year time period.
- Scenario and sensitivity analyses:
  - Subgroup analysis examined outcomes for patients with CLL in Center of Medicare and Medicaid Services (CMS) special subpopulations (disabled, end-stage renal disease (ESRD), and terminally ill (life expectancy <6 months)).[17,18]
  - A sensitivity analysis was conducted using MAIC results to inform AE rates.[6-8] Alternate population scenarios examined outcomes when (1) RR included 2L only, and (2) all newly diagnosed patients were assumed eligible to start treatment (no "watch and wait") and RR included 2L only.
  - Uncertainty in the model was tested through deterministic and probabilistic sensitivity analysis (DSA, PSA).

Figure 1. Model structure



Subsequent treatment state consisted of a pool of pirtobrutinib, lisocabtagene maraleucel, and best supportive care, weighted by real-world US distribution. cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitors; CLL – Chronic Lymphocytic Leukemia.

Table 1. Grade ≥3 AE rates for cBTKis

Grade ≥3 AE Rates	Treatment-Naïve			Relapsed/Refractory		
	Acalabrutinib	Ibrutinib	Zanubrutinib	Acalabrutinib	Ibrutinib	Zanubrutinib
Neutropenia	11.2%	12.6%	12.5%	20.0%	23.0%	22.2%
Thrombocytopenia	1.1%	4.0%	2.1%	10.0%	7.0%	3.7%
Atrial fibrillation	1.1%	5.2%	1.3%	5.0%	4.0%	3.1%
Hypertension	2.8%	8.1%	9.2%	4.0%	9.0%	16.4%
Hemorrhage	2.8%	6.7%	5.8%	4.0%	5.0%	3.7%
Infections	16.2%	20.6%	23.8%	31.0%	30.0%	35.5%
Diarrhea	0.6%	4.4%	1.7%	1.0%	5.0%	1.5%
Source	ELEVATE-TN[9]	RESONATE-2[1,10]	SEQUOIA[11]	ELEVATE-RR[5]	ELEVATE-RR[5]	ALPINE[12]
Follow-up Months	46.9	48	43.7	40.9	40.9	40.3

AE – Adverse Event; cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitors.

Table 2. Model parameters

Clinical	Value	Source
cBTKi Discontinuation Rate, Monthly (TN / RR)	4.92% / 5.35%	20 / 21
cBTKi Mortality Rate, Monthly (TN / RR)	0.70% / 1.09%	22 / 23
Cost	**Value, 2024 USD**	**Source**
Acalabrutinib Drug Acquisition Cost, Monthly	$9,770	13
Ibrutinib Drug Acquisition Cost, Monthly	$11,165	13
Zanubrutinib Drug Acquisition Cost, Monthly	$9,578	13
cBTKi Medical Care Cost (Exclusive of AE Costs)	$1,110	24
Grade ≥3 AE Incremental Cost, Per Event		
Atrial Fibrillation	$32,161	15
Hypertension	$33,652	
Neutropenia	$21,896	
Thrombocytopenia	$28,927	
Infections	$27,947	
Hemorrhage	$27,861	
Diarrhea	$21,041	
Epidemiology	**Value**	**Source**
Annual Incidence of CLL in Medicare	27.5 per 100,000	25
Newly-Diagnosed CLL Eligible to Initiate Treatment	44%	26
Real-World Annual Relative Distribution of TN vs. RR CLL		25, 26
TN / RR (2L-3L)	44% / 56%	
TN / RR (2L Only)	74% / 26%	
Prevalence of Disability in CLL (TN / RR)	7.2% / 5.2%	26
Prevalence of Terminal Illness in CLL	13.47%	27
Prevalence of ESRD in CLL (TN / RR)	4.7% / 3.6%	26

AE – Adverse Event; cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitors; CLL – Chronic Lymphocytic Leukemia; ESRD – End-Stage Renal Disease. RR – Relapsed/Refractory; TN – Treatment-Naive; USD – United States Dollars; 2L – Second-Line Therapy; 3L – Third-Line Therapy.

Results

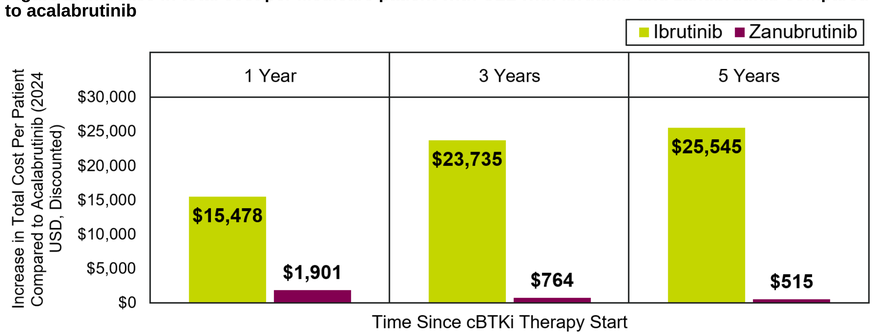
Base case

- A cohort of 13,726 CLL patients was modeled (44% TN, 56% RR) to reflect a real-world Medicare CLL population eligible to initiate cBTKi therapy.
- Compared to ibrutinib, acalabrutinib showed **cost savings of $15,478 per patient** ($212 million across all Medicare patients with CLL) over 1 year since treatment start, driven by lower treatment cost ($12,076 decrease) and lower AE cost ($3,402 decrease) (**Figure 2**).
  - Differences in AE costs were driven by differences in AE rates from extended follow-up of pivotal cBTKi clinical trials of grade ≥3 atrial fibrillation (1.1% acalabrutinib vs. 5.2% ibrutinib), hypertension (2.8% vs. 8.1%), and infections (16.2% vs. 20.6%) in TN, and hypertension (4% vs. 9%), diarrhea (1% vs. 5%) and neutropenia (20% vs. 23%) in RR.
- Compared to zanubrutinib, acalabrutinib showed **cost savings of $1,901 per patient** ($26 million across all Medicare patients with CLL). Higher acalabrutinib treatment cost vs. zanubrutinib ($1,663 increase) was offset by savings from lower AE cost ($3,563 decrease) (**Figure 2**).
  - Differences in AE costs were driven by differences in hypertension and infections in TN (2.8% acalabrutinib vs. 9.2% zanubrutinib; 16.2% vs. 23.8%) and hypertension and infections in RR (4.0% vs. 16.4%; 31.0% vs. 35.5%).
- Overall cost savings per CLL patient vs. ibrutinib and zanubrutinib were **maintained** over 3 ($23,735; $764) and 5 ($25,545; $515) year horizons (**Figure 2**).

Scenario and sensitivity analyses

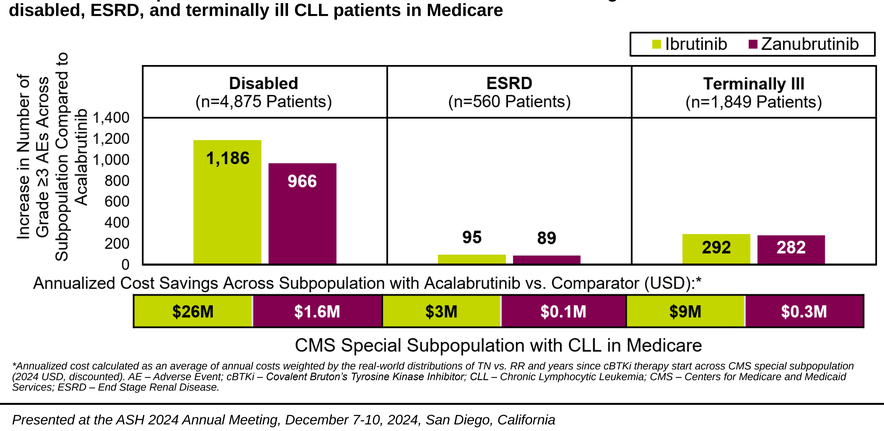
- Acalabrutinib treatment of disabled, ESRD, and terminally ill Medicare CLL patients was associated with **reduced** grade ≥3 AEs vs. ibrutinib (1,186, 95, and 292 fewer, respectively) and vs. zanubrutinib (966, 89, and 282 fewer), resulting in cost savings with acalabrutinib of $87 million, $9 million, and $29 million vs. ibrutinib, and $14 million, $1 million, and $4 million vs. zanubrutinib across disabled, ESRD, and terminally ill, respectively (**Figure 3**).
- Sensitivity analysis using MAIC AE rates and scenario analysis for modeled populations similarly showed **cost savings** over 1, 3, and 5-year horizons (**Table 3**).
- In DSA, acalabrutinib cost savings were sensitive only to cBTKi drug prices. In PSA, lower AE cost with acalabrutinib was maintained in 100% scenarios and lower pharmacy cost maintained in 68.0% and 46.8% scenarios vs. ibrutinib and zanubrutinib, respectively.

Figure 2. Increase in total cost per Medicare patient with CLL with ibrutinib and zanubrutinib compared to acalabrutinib



Positive numbers indicate cost saving with acalabrutinib; negative numbers indicate increased cost with acalabrutinib. AE – Adverse Event; cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitor; CLL – Chronic Lymphocytic Leukemia.

Figure 3. Increase in number of grade ≥3 AEs in year 1 of cBTKi treatment with ibrutinib and zanubrutinib compared to acalabrutinib and total annualized cost savings with acalabrutinib across disabled, ESRD, and terminally ill CLL patients in Medicare



**Annualized cost calculated as an average of annual costs weighted by the real-world distributions of TN vs. RR and years since cBTKi therapy start across CMS special subpopulation (2024 USD, discounted). AE – Adverse Event; cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitor; CLL – Chronic Lymphocytic Leukemia; CMS – Centers for Medicare and Medicaid Services; ESRD – End Stage Renal Disease.*

Table 3. Scenario and sensitivity analysis results

Scenario/Sensitivity Analysis	Time Since cBTKi Start	Difference in Total Cost with Acalabrutinib vs. Comparator (2024 USD, Discounted)			
		Ibrutinib		Zanubrutinib	
		Per Patient	Across Population	Per Patient	Across Population
Using MAIC-informed grade ≥3 AE rates	1 Year	-$15,142	-$208 M	-$1,501	-$21 M
	3 Years	-$23,398	-$321 M	-$365	-$5 M
	5 Years	-$25,209	-$346 M	-$115	-$2 M
Alternate population scenario: RR includes 2L only (8,139 patients modeled, 74% TN, 26% RR)	1 Year	-$16,919	-$138 M	-$2,529	-$21 M
	3 Years	-$25,615	-$208 M	-$1,331	-$11 M
	5 Years	-$27,635	-$225 M	-$1,053	-$9 M
Alternate population scenario: all newly diagnosed assumed eligible to start treatment and RR includes 2L only (18,474 patients modeled, 74% TN, 26% RR)	1 Year	-$16,919	-$313 M	-$2,529	-$47 M
	3 Years	-$25,615	-$473 M	-$1,331	-$25 M
	5 Years	-$27,635	-$511 M	-$1,053	-$19 M

Negative numbers indicate cost saving with acalabrutinib; positive numbers indicate increased cost with acalabrutinib. AE – Adverse Event; cBTKi – Covalent Bruton's Tyrosine Kinase Inhibitor; CLL – Chronic Lymphocytic Leukemia; M – Millions of US Dollars; RR – Relapsed/Refractory; TN – Treatment Naive; 2L – Second-Line Therapy.

Conclusions

- Acalabrutinib yielded cost savings compared to ibrutinib and zanubrutinib for Medicare patients with CLL due to lower treatment cost than ibrutinib and fewer AEs than both ibrutinib and zanubrutinib.

Limitations

- Model health states represented treatment pathways rather than disease progression states, and the model structure represented one treatment pathway for both TN and RR CLL as informed by the consensus guidelines of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL).[19]
- Efficacy differences were not modeled to focus on cost differences from cBTKi safety profiles.
- Unadjusted AE rates from extended follow-up of pivotal cBTKi clinical trials were modeled.
- All cBTKis were evaluated as monotherapy only.

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