Poster PCN101

Real-World Economic Outcomes of First-Line (1L) Ibrutinib Treatment in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Swetha Challagulla, MS[1]; Philip Lee, PharmD[1,2]; Kristin Kistler, PhD[3]; Luc Douyon, MS[3]; Dominic Lai, PharmD[1]; Reethi Iyengar, PhD, MBA, MHM[1]

[1]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [2]Keck Graduate Institute School of Pharmacy, Claremont, CA, USA; [3]Xcenda, Palm Harbor, FL, USA

INTRODUCTION

- Ibrutinib is an oral, once-daily Bruton's tyrosine kinase (BTK) inhibitor that received FDA approval in March 2016 as a 1L treatment for CLL/SLL.
- Ibrutinib is the only targeted therapy to demonstrate both significant progression-free survival (PFS)[1-7] and overall survival (OS)[1,5-8] benefits vs chemotherapy and/or immunotherapy regimens in multiple randomized phase 3 studies in both previously untreated and relapsed/refractory CLL/SLL.
- Several real-world studies have evaluated economic outcomes of 1L ibrutinib use in CLL/SLL. It is therefore imperative to understand the totality of published evidence and economic implications of utilizing ibrutinib across diverse populations.

OBJECTIVE

- To systematically collate and summarize economic outcomes associated with 1L ibrutinib use for patients with CLL/SLL

METHODS

- A systematic literature review (SLR) was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.
- Embase, Medline, and relevant conference websites (Society of Hematologic Oncology [SOHO], Association of VA Hematology/Oncology [AVAHO], International Workshop on Chronic Lymphocytic Leukemia [iwCLL], National Comprehensive Cancer Network [NCCN], and Academy of Managed Care Pharmacy [AMCP]/AMCP Nexus annual meetings) were searched for abstracts and full-text publications indexed January 2014–June 2020.
- Publications were selected for inclusion based on pre-defined PICOS (population, intervention, comparator, outcomes, study design) criteria (**Table 1**) via a dual-screening process.
- Eligible studies reporting healthcare resource utilization (HRU) and total direct cost of care were descriptively summarized.

Table 1. Inclusion and Exclusion Criteria

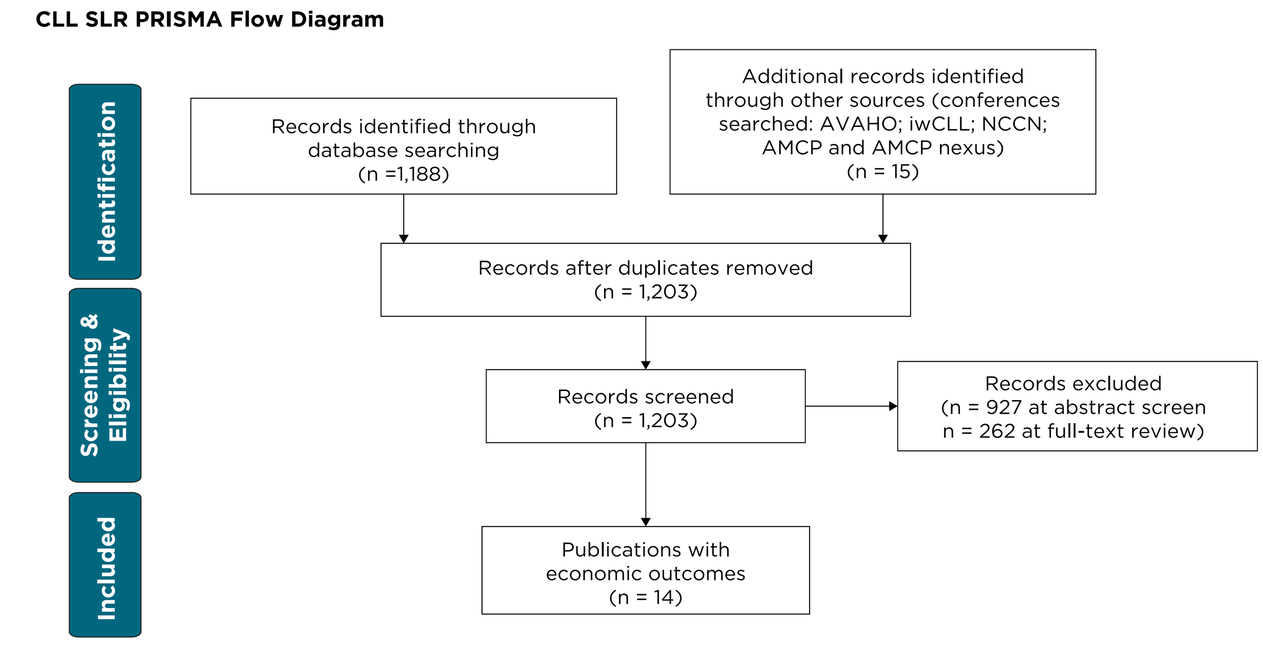
PICOS	Inclusion	Exclusion
Population	• Adult (≥18 years old) patients with CLL/SLL	• Non-human studies • <18-year-old patients • Individuals without CLL/SLL
Intervention Comparator	• Ibrutinib • Any/all/no comparators	• No ibrutinib exposure
Outcome	• HRU • Direct and indirect costs	• Outcomes not specified in the Inclusion column
Study Design	• Real-world observational studies (eg, prospective and retrospective, surveys, and cross-sectional studies) • SLRs and/or meta-analyses (for reference checking)	• Interventional studies • Non-systematic reviews • Case reports • Case series (n<10) • Animal studies • Letters • Editorials
Timeframe	• January 1, 2014 – June 30, 2020	• ≤2013; >June 30, 2020

RESULTS

Characteristics of Included Studies

- A total of 1,203 citations were screened. Direct medical costs and/or HRU associated with 1L ibrutinib were investigated in 12 studies and reported in 14 publications, including 3 full-text manuscripts, 6 posters, and 5 abstracts (**Figure 1**).

Figure 1. Literature Selection and Review Process



[a]These excluded publications also include abstracts excluded during data extraction as a result of a protocol amendment.
[b]n=139 are included in SLR as they report outcomes other than economics (the full SLR included outcomes of patient characteristics, effectiveness, and treatment patterns).

Table 2. Characteristics Across 12 Studies (Reported in 14 Publications) of CLL Patients Treated With 1L Ibrutinib and Reporting Economic Outcomes

	Publication Author, Date	Sponsorship	Data Source	Study Start-End	Adjusted for Potential Baseline Imbalances	Treatment Arms[a]	Number of Ibrutinib- and CIT-Treated Patients[a]	Median Age, Years[a]	Male (%)[a]
MANUSCRIPTS	Emond, 2019[9]	Janssen	Optum	Feb 2014-Jun 2017	✓	Ibrutinib CIT	583 578	72 71	61 62
	Kabadi, 2020[10]	AstraZeneca	PharMetrics	Nov 2012-Jun 2018	✓	Ibrutinib BR, RM, or FCR	429 1,150	NR	NR
	Huang, 2020[11]	Janssen	US VHA	Apr 2013-Mar 2018	✓	Ibrutinib CIT	614 614	72[b] 71[b]	99 99
POSTERS	Huang, 2020[12]	Janssen	CMS & Optum	Mar 2016-Dec 2017	✓	Ibrutinib CIT	2,307 2,353	74 74	58 58
	Nero, 2017[13,c]	Independent	MORE[2]	Jan 2014-Sept 2016	X	Ibrutinib Other	295 2,047	64[d] 66[d]	69 58
	Iyengar, 2019[14]	Pharmacyclics	informCLL registry	NR	No comparative results reported	Ibrutinib	457	69	64
	Iyengar, 2019[15]	Pharmacyclics	MarketScan	Feb 2014-Dec 2017	✓	Ibrutinib CIT	107 326	69[b] 69[b]	59 59
	DaCosta Byfield, 2018[16] Matasar, 2017[17]	Genentech	Optum	May 2013-Jun 2015	X	Ibrutinib BR, FCR, or Ob+/Chl	46 142	69[b] 67[b]	63 74
ABSTRACTS	Irwin, 2019[18] Irwin, 2018[19]	Teva Pharma	MarketScan	Feb 2014-Aug 2017	X	Ibrutinib BR	1,157 729	69[b] 66[b]	64 68
	Irwin, 2017[20]	Teva Pharma	MarketScan	NR	✓	Ibrutinib Bendamustine[e]	622 570	68[b] 66[b]	66 67
	Nabhan, 2017[21]	Independent	MORE[2]	Feb 2014-Sept 2016	X	Ibrutinib CIT	178 908	65 65	64 64
	Nabhan, 2018[22]	Independent	Symphony	Jan 2014-Dec 2017	X	Ibrutinib CIT	4,368 2,176	68[b,d] 63[b,d]	NR

n<1000 n=1000-2000 n>2000

[a]If data were adjusted for potential baseline imbalances, weighted data are presented.
[b]Mean age.
[c]Abstract states "Among the 2,342 CLL patients, 295 patients were treated with ibrutinib while 2,047 patients were not." Poster presents as "other treatment."
[d]Age at diagnosis.
[e]Approximately 92% of patients received BR.
BR, bendamustine/rituximab; Chl, chlorambucil; CIT, chemoimmunotherapy; CMS, Centers for Medicare and Medicaid Services; FCR, fludarabine, cyclophosphamide, rituximab; FFS, fee-for-service; MA, Medicare Advantage; MORE[2] database, Medical Outcomes Research for Effectiveness and Economics Registry payer claims and remittance database; NR, not reported; Ob, obinutuzumab; Optum, Optum Informatics Extended DataMart de-Identified database; PharMetrics, IQVIA PharMetrics Plus database; RM, rituximab monotherapy; Symphony, Symphony Health's Integrated Dataverse; US VHA, United States Veterans Health Administration.
Note: All data were from the United States.

RESULTS (CONT.)

- Study and patient characteristics are displayed in **Table 2**.
  - Across the 12 studies, the number of patients with CLL treated with 1L ibrutinib ranged from 46 to 4,368.
- With the exception of one analysis using data from a prospective registry (the informCLL™ registry),[14] the studies were retrospective analyses of data from health insurance claims databases.
- Comparisons of all-cause HRU and/or costs between 1L ibrutinib and other 1L therapies were reported in 13 of the 14 publications.
  - In 11 studies, ibrutinib was compared to CIT (2 studies included comparisons to both chemotherapy and CIT); in 1 study, ibrutinib was compared to bendamustine (92% of patients in the bendamustine arm received BR); and in the remaining study, the comparison group was stated as "not on ibrutinib."
- Full-text manuscripts (n=3) or posters (n=5) were available for 8 of the 14 publications for which quality was evaluated and deemed acceptable using the ISPOR checklist.[23]

Healthcare Resource Utilization (PPPM)

Table 3. Ranges in All-Cause Healthcare Visits PPPM[a]

HRU Category	Rate Ratio (Ibrutinib vs CIT)	
	Lower	Upper
Outpatient Visits[b]	0.47	0.86
Office Visits[c]	0.75	1.00
Outpatient Service Related to Antineoplastic Drug Administration	0.02	0.13
Other Outpatient[d]	0.42	1.01
ER Visits[e]	0.57	1.22
Inpatient Admissions[f]	0.38	1.40
Length of Stay	0.46	0.96

[a]Includes posters/full-text publications only.
[b]DaCosta Byfield, 2018, reported mean hospital outpatient visits over a fixed 9-month period (ibrutinib: 1.39; BR: 1.48; FCR: 1.67; Ob±Chl: 1.45), which were not included in the ranges shown.
[c]DaCosta Byfield, 2018, reported mean office visits over a fixed 9-month period (ibrutinib, 2.9; BR, 2.8; FCR, 3.2; Ob±Chl, 2.5), which were not included in the ranges shown.
[d]Other Outpatient includes antineoplastic drug administration services.
[e]DaCosta Byfield, 2018, gave mean ER visits over a fixed 9-month period (ibrutinib, 0.09; BR, 0.11; FCR, 0.12; Ob±Chl, 0.10), which were not included in the ranges shown.
[f]DaCosta Byfield, 2018, gave mean inpatient visits over a fixed 9-month period (ibrutinib, 0.04; BR, 0.06; FCR, 0.03; Ob±Chl, 0.06), which were not included in the ranges shown.
ER, emergency room.
Note: Outpatient categories may not be defined consistently across studies.

- Ibrutinib was associated with significantly lower outpatient HRU and similar inpatient and ER HRU vs CIT (rate ratios range: outpatient 0.47–0.86, *P*<0.05; inpatient 0.38–1.4, *P*>0.05; ER 0.57–1.22, *P*>0.05; **Table 3**).

Table 4. Summary of All-Cause HRU for Ibrutinib vs CIT Across all Publications

Outpatient Visits	ER Visits	Inpatient Admissions	Inpatient Length of Stay
Full-text/Poster Data Only: ■■■■■■▨	Full-text/Poster Data Only: ■■■■▨	Full-text/Poster Data Only: ■■■■■▨	Full-text/Poster Data Only: ■■■■
All Sources: ■■■■■■▨■■■	All Sources: ■■■■▨■■■	All Sources: ■■■■■▨■■■	All Sources: ■■■■■■■

Color Key:
■ Ibrutinib significantly greater HRU (*P*<0.05).
■ Similar HRU (*P*>0.05).
■ Ibrutinib significantly lower HRU (*P*<0.05).
▨ *P*-value not reported.

Each square represents a unique study reporting relevant outcomes.

- HRU results identified from publications with a full-text manuscript or poster tended to be congruent with overall publications (**Table 4**).

Healthcare Direct Costs (PPPM)

Table 5. Ranges in Mean All-Cause PPPM Costs[a]

HRU Category	Mean Monthly Cost Difference (MMCD)	
	Lower ($)	Upper ($)
Inpatient Admissions	-5	+2,412
Outpatient Visits	-223	-32,764
ER Visits	-4	-216 (vs BR)
Total Medical	-5,888	-18,717
Pharmacy	+4,878	+12,232[b]
Total Healthcare	-996	-17,104

[a]Includes posters/full-text publications only.
[b]Outpatient prescriptions; CLL-related lower for ibrutinib.
Note: Mean dollar amounts are not reported in every study. Therefore, ranges may be based on only one study. For example, for Medicare data, ranges were reported across time (ie, during 1L or 1L oncology care model) and type (FFS vs MA). Matasar & DeCosta Byfield, both reporting on the same study, report only the mean amount over 9 months, and were not included in the summarized ranges.

- Ibrutinib had significantly lower medical costs (MMCD: -$5,888 to -$18,717, *P*<0.05) and significantly higher pharmacy costs vs CIT (MMCD: $4,878 to $12,232, *P*<0.05; **Table 5**).
- The total net direct healthcare cost for ibrutinib was significantly lower than for CIT (MMCD: -$996 to -$17,104, *P*<0.05; **Table 5**).

Table 6. Summary of All-Cause Costs for Ibrutinib vs CIT Across All Publications

Inpatient Costs	Outpatient Costs	ER Costs	Total Medical Costs	Pharmacy Costs	Total Healthcare Costs
Full-text/Poster Data Only: ■■■■■	Full-text/Poster Data Only: ■■■■■	Full-text/Poster Data Only: ■■■■	Full-text/Poster Data Only: ■■■▨	Full-text/Poster Data Only: ■■■■	Full-text/Poster Data Only: ■■■■
All Sources: ■■■■■■■■■	All Sources: ■■■■■■■■■	All Sources: ■■■■■▨	All Sources: ■■■▨	All Sources: ■■■■■▨	All Sources: ■■■■■■

Color Key:
■ Ibrutinib significantly greater cost (*P*<0.05).
■ Similar cost (*P*>0.05).
■ Ibrutinib significantly lower cost (*P*<0.05).
▨ *P*-value not reported.

Note: Each square represents a unique study reporting relevant outcomes.

- Direct cost of care results extracted from publications with a full-text manuscript or poster tended to be congruent with overall publications (**Table 6**).

LIMITATIONS

- A limitation of any SLR is that relevant publications may be missed in the search. To mitigate this possibility, relevant congress websites were searched to capture all relevant studies.
- Heterogeneity in study designs and study populations was not adjusted for in this literature review.
- There were limited data available in full-text format. However, HRU/costs results tended to be congruent across publication types (full-texts, posters, abstracts).

CONCLUSIONS

- This systematic literature review of real-world evidence suggests that 1L ibrutinib for CLL/SLL is associated with lower healthcare resource utilization when compared to CIT.
- Correspondingly, higher ibrutinib pharmacy costs were observed to be completely offset by lower overall medical costs, resulting in total net savings associated with 1L ibrutinib use vs CIT for CLL/SLL.

REFERENCES

1. Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-23.
2. Burger JA, et al. *Leukemia*. 2020;34(3):787-98.
3. Moreno C, et al. *Lancet Oncol*. 2019;20(1):43-56.
4. Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-28.
5. Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-43.
6. Fraser GAM, et al. *Leuk Lymphoma*. 2020;61(13):3188-97.
7. Munir T, et al. *Am J Hematol*. 2019;94(12):1353-63.
8. Burger JA, et al. *N Engl J Med*. 2015;373(25):2425-37.
9. Emond B, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(12):763-75.e2.
10. Kabadi SM, et al. *Adv Ther*. 2020;37(7):3129-48.
11. Huang Q, et al. *J Manag Care Spec Pharm*. 2020;26(10):1266-75.
12. Huang QL, et al. *Value Health*. 2020;23(suppl 1):S44-S5.
13. Nero D, et al. *Value Health*. 2017;20(9):A414.
14. Iyengar R, et al. *J Manag Care Spec Pharm*. 2019;25(10-a Suppl):S35.
15. Iyengar R, et al. *Journal of Manag Care Spec Pharmacy*. 2019;25(10-a Suppl):S36.
16. DaCosta Byfield S, et al. *Journal of Manag Care Spec Pharm*. 2018;24(4-a Suppl):S29.
17. Matasar MJ, et al. *J Clin Oncol*. 2017;35(8_suppl):15.
18. Irwin D, et al. *J Manag Care Spec Pharm*. 2019;25(3-a Suppl):S32.
19. Irwin D, et al. *Blood*. 2018;132(Supplement 1):3548.
20. Irwin D, et al. *Blood*. 2017;130(Supplement 1):5618.
21. Nabhan C, et al. *Blood*. 2017;130(Supplement 1):2111.
22. Nabhan C, et al. *Blood*. 2018;132(Supplement 1):4757.
23. Motheral B, et al. *Value Health*. 2003; 6(2):90-7.

DISCLOSURES

SC: employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; **PL:** employment with Pharmacyclics LLC, an AbbVie Company; travel expenses from Celgene and Novartis; **KK & LD:** employment with Xcenda, LLC; research funding from Pharmacyclics LLC, an AbbVie Company; **DL:** employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie and Bristol Myers Squibb; **RI:** employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; patents, royalties, or other intellectual property with Express Scripts.

ACKNOWLEDGMENTS

This study was sponsored by Pharmacyclics LLC, an AbbVie Company. Editorial support was provided by Michelle Jones, PhD, MWC, and funded by Pharmacyclics LLC, an AbbVie Company.

To submit a medical question, please visit www.pharmacyclicsmedinfo.com