

# A SYSTEMATIC LITERATURE REVIEW OF PHARMACOECONOMIC EVALUATIONS FOR CHRONIC LYMPHOCYTIC LEUKEMIA IN EUROPE

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## Background

- Chronic Lymphocytic Leukemia (CLL) is the most common form of leukemia <sup>[1]</sup> with global incidence varying geographically, and slightly higher rates in Europe and the United States <sup>[2]</sup>
- Currently there are no systematic literature reviews on economic evaluations of treatment options for CLL available in Europe to inform decision makers

## Objective

- To provide a comprehensive and critical review of the pharmacoeconomic evaluations of CLL treatments in Europe

## Methods

- We conducted a systematic literature review in MEDLINE (PubMed) and EMBASE covering 2015-2020 to identify publications of pharmacoeconomic models evaluating treatments of CLL in Europe; studies included manuscripts and conference abstracts published in English
- Studies were screened by two independent reviewers to identify pharmacoeconomic evaluations including cost-effectiveness, cost-utility, cost-comparison, and budget impact models. All cost outcomes not reported in Euros were converted to Euros using 2020 exchange rates
- Studies were reviewed and data extracted by European country, patient population, intervention(s), clinical, economic, and utility data input, analysis results, and study funding source

## Results

- **Literature Review Results (Table 1)**
  - We identified 721 unique studies and screened for full text/abstract/poster eligibility that matched our objective; 79 were assessed for eligibility; 48 studies used pharmacoeconomic models; and 25 studies took place in Europe. Of these, 21 were cost-effectiveness studies, including 11 abstracts and 10 manuscripts; more than half of the studies (76%) were industry sponsored
  - Geographical distribution of studies was mixed; 7 studies in the United Kingdom, 3 in Russia, 3 in Portugal, 2 in Spain and 10 in other European countries
  - Most economic evaluations used Markov models (55%), followed by partitioned survival models (34%); few studies used decision analytic models (14%)
  - Studies varied in patient populations, with a mixture of different lines of therapy and disease status; in total we found 9 studies in relapse/refractory CLL (r/r CLL). Among the 16 CLL studies 4 are treatment naïve CLL studies
  - Model inputs:
    - Almost all clinical data came from trial data (n=20); other data sources included meta-analysis, published studies, and published literature
    - Economic data came from national data sources (n=21); several studies used expert opinion (n=6)
    - Utility data came from a combination of clinical trials, published literature, published studies, and country-data

## Cost-Effectiveness Evaluations (49 analysis) (Table 2)

- Within the 21 cost-effectiveness studies, 49 separate analysis were carried out evaluating incremental cost-effectiveness ratios (ICERs) using quality-adjusted life-years (QALY) (n=47) and life-years (LYs) (n=21) as outcomes
- Across all studies ICERs for LYs ranged from €9,445-€100,122; ICERs for QALYs ranged from €1,263-€156,676
- For r/r CLL only two analysis reported ICER LYs and these were €14,733 and €32,702; QALYs ranged from €1,263-€64,373 with a median of €20,441
- For treatment naïve CLL, ICER LY ranged from €15,773-€49,424 and ICER QALY ranged from €9,847-€76,451 with a median of €56,574

#### **Budget Impact Models (n=2) (Table 1)**

- Both budget impact analysis were presented as abstracts from Czech Republic (r/r CLL) and Russia (CLL)
- Economic data input came from University sources (Czech Republic) and Registry/clinical data (Russia)
- Within the budget impact models the budget impact ranged from €1.1m (year 1) to €7.2m (year 5) for Ibrutinib in the Czech Republic and €22,200 (year 1) to €66,900 (year 5) for Ibrutinib + Obinutuzumab in Russia

#### **Cost Minimization models (n=2) (Table 1)**

- Cost minimization models were presented as abstracts from Portugal (r/r CLL) and Russia (CLL)
- In Portugal, authors reported expenditure for Venetoclax + Rituximab to be €213,844 and Ibrutinib to be €317,310. In Russia, total direct expenditure for Obinutuzumab + Chlorambucil €57,373 and for Ibrutinib: €194,040

#### **Discussion**

- Beyond the 14 European countries found in the current systematic literature review, there is a lack of published CLL economic evaluations in remaining European countries, particularly in Southern and Eastern Europe
- The heterogenous patient populations in the published pharmacoeconomic studies (treatment naïve, r/r CLL, mixed CLL) with various disease status and line of therapy made comparisons for QALYs particularly challenging; additional studies may consider stratifying by patient population and extending the study period to understand the preferred treatment options in Europe
- Wide range of costs with different economic outcomes might be related to differences in treatment patterns across Europe, and local adaptations of treatment guidelines from the European Society for Medical Oncology (ESMO) guidelines, which might often be caused by different reimbursement status of each treatment regimen and option across countries.
- Most studies looked at comparisons of chemotherapies, and very few included oral medications such as Bruton's tyrosine kinase inhibitors . Additional cost-effectiveness analysis including new oral treatments are needed as treatment patterns evolve
- Most of the publications were conference abstracts, which meant limited technical details and assumptions of the models were available for validation by other researchers

#### **Conclusions**

- Recently published pharmacoeconomic analyses in Europe evaluated different treatment regimens and lines of therapy for CLL in patient populations across 14 different European countries

- Future economic evaluations on a broader range of recent CLL treatment options, including oral Bruton's tyrosine kinase inhibitors in additional European countries are warranted

## TABLES AND FIGURES

**Table 1: Summary of Systematic Literature Review of Pharmacoeconomic Analysis of Treatments in CLL 2015-2020 by country (N=25) (CEA; N=21 BIM; N=4)**

COUNTRY	YEAR	AUTHOR	PATIENT POPULATION	STUDY TYPE	PUBLICATION TYPE	SPONSOR	DATA SOURCE
Belgium	2017	Smet et al. [3]	CLL (First-Line)	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> RESONATE-2; Bayesian Network Meta-Analysis; Systematic Literature Review <b>Utility Data:</b> RESONATE-2; Systematic Literature Review <b>Economic Data:</b> Belgian Costs Databases; Expert Opinion
Bulgaria	2017	Djambazov et al. [4]	r/r CLL ± del17p/TP53	Cost-Effectiveness	Abstract	Non-Industry	<b>Clinical Data:</b> Network Meta-Analysis <b>Utility Data:</b> N/A <b>Economic Data:</b> N/A
Czech Republic	2016	Pribylova et al. [5]	r/r CLL	Budget Impact	Abstract	Industry	<b>Economic Data:</b> University Hospital Brno
England	2017	Hassan et al. [6]	r/r CLL	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> RESONATE; Indirect Treatment Comparison <b>Utility Data:</b> RESONATE EQ-5D; Published Sources <b>Economic Data:</b> British National Formulary and NHS Reference costs
Finland	2016	Soini et al. [7]	CLL Ineligible for Full-Dose Fludarabine	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> CLL11; Knauf et al.; COMPLEMENT 11 CLL10 <b>Utility Data:</b> UK Data <b>Economic Data:</b> Finish Data
France	2016	Plommet & Boissard [8]	CLL Unsuitable for Full-Dose Fludarabine Therapy	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> CLL5 Trial <b>Utility Data:</b> French Time Trade-off Study <b>Economic Data:</b> Literature Review; Databases
Germany	2016	Muller et al. [9]	CLL (First-Line)	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> CLL8-Trial <b>Utility Data:</b> CLL8-Trial <b>Economic Data:</b> German Public Sources
Greece	2017	Kousoulakou et al. [10]	CLL Unsuitable for Fludarabine Therapy	Cost-Effectiveness	Abstract	Industry	<b>Utility Data:</b> Published UK Study <b>Economic Data:</b> Expert Panel; Ministry of Health
Italy	2015	Marchetti et al. [11]	r/r CLL	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> Furman et al. 2014, Byrd et al 2014, Fisher et al. 2011, Cortelezzi et al. 2014, Awan et al. 2014 <b>Utility Data:</b> Beusterien et al. 2010 <b>Economic Data:</b> Published Retrospective Analysis
Macedonia	2017	Kapedanovska Nestorovska et al. [12]	CLL Unsuitable for Full-Dose Fludarabine-Based Therapy	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> CLL 11 <b>Utility Data:</b> Literature <b>Economic Data:</b> Government and hospital pharmacy, publicly available data.
Portugal	2015	Gouveia et al. [13]	r/r CLL	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> Phase 3 Trial <b>Utility Data:</b> Kind et al. 1999 <b>Economic Data:</b> Expert Opinion; DRG; Portuguese Legislation; NHS Reference
Portugal	2017	Paquete et al. [14]	CLL Unsuitable for Full-Dose Fludarabine Therapy	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> CLL11; CLL5 <b>Utility Data:</b> Kosmas et al. <b>Economic Data:</b> Official Sources; Portuguese Experts
Portugal	2019	Miguel et al. [15]	r/r CLL	Total Cost Per Patient	Abstract	Industry	<b>Clinical Data:</b> MURANO <b>Economic Data:</b> Expert Opinion; Portuguese Public Sources
Russia	2015	Yagudina et al. [16]	Elderly CLL (First-Line)	Cost-Effectiveness	Abstract	Non-Industry	<b>Clinical Data:</b> CLL11 <b>Utility Data:</b> N/A <b>Economic Data:</b> National Healthcare System in the Russian Federation
Russia	2017	Kolbin et al. [17]	CLL	Total Direct Expenditures	Abstract	Non-Industry	<b>Clinical Data:</b> CLL-11; RESONATE-2 <b>Economic Data:</b> N/A
Russia	2016	Derkach et al. [18]	CLL	Budget Impact	Abstract	N/A	<b>Clinical Data:</b> Russian Registry / Clinical Studies <b>Economic Data:</b> Russian Registry / Clinical Studies
Scotland	2015	Kumar et al. [19]	r/r CLL & First-Line w/ del17p/TP53	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> Study 116 <b>Utility Data:</b> Published Sources <b>Economic Data:</b> National Databases

Spain	2018	Casado et al. [20]	r/r CLL	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> Clinical Trial <b>Utility Data:</b> England and Scotland Standard Gamble Study <b>Economic Data:</b> Spanish NHS
Spain	2016	Casado et al. [21]	CLL Not Eligible for Fludarabine-Based Therapy	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> CLL11 <b>Utility Data:</b> UK Study <b>Economic Data:</b> Published Spanish Sources
Ukraine	2015	Mandrik et al. [22]	r/r CLL and Treatment-Naïve CLL	Cost-Effectiveness	Manuscript	Non-Industry	<b>Clinical Data:</b> Two Phase 3 Studies <b>Utility Data:</b> UK Data <b>Economic Data:</b> Ukraine Ministry of Health; Local Experts
United Kingdom	2015	Pearson et al. [23]	CLL Not Eligible for Fludarabine-Based Therapy	Cost-Effectiveness	Abstract	Industry	<b>Clinical Data:</b> COMPLEMENT-1 Trial <b>Utility Data:</b> COMPLEMENT-1 Trial <b>Economic Data:</b> BNF; Dept. of Health; Woods et al. 2012
United Kingdom	2016	Becker et al. [24]	CLL Ineligible for Full-Dose Fludarabine	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> Clinical Trial Data; Network Meta-Analysis <b>Utility Data:</b> Utility Elicitation Study <b>Economic Data:</b> Government Sources
United Kingdom	2018	Sinha & Redekop [25]	CLL Unable to Tolerate Fludarabine-Based Therapy	Cost-Effectiveness	Manuscript	Non-Industry	<b>Clinical Data:</b> Clinical Trials <b>Utility Data:</b> UK Elicitation Studies <b>Economic Data:</b> Government Sources
United Kingdom	2017	Hatswell et al. [26]	Double-Refractory CLL	Cost-Effectiveness	Manuscript	Industry	<b>Clinical Data:</b> Hx-CD20-406 (Phase 2) <b>Utility Data:</b> Time Trade-Off Study (Ferguson et al.) <b>Economic Data:</b> NHS Reference Costs
United Kingdom	2019	Vreman et al. [27]	Relapsed CLL	Cost-Effectiveness	Manuscript	Non-Industry	<b>Clinical Data:</b> Phase I/II Data <b>Utility Data:</b> RESONATE <b>Economic Data:</b> British National Formulary

**Table 2: Summary of CEA results (ICER and LY comparison) by treatment across analysis (49 analysis from 21 cost-effectiveness studies)**

COUNTRY	PATIENT POPULATION	INTERVENTION	COMPARATOR	ICER	
				LY	QALY
Belgium	CLL (First-Line)	Ibrutinib	Chlorambucil Monotherapy	€ 34,361	€ 51,641
			Bendamustine + Rituximab	€ 39,523	€ 61,506
			Chlorambucil + Obinutuzumab	€ 49,424	€ 76,451
			Physician's Choice	€ 42,540	€ 65,760
Bulgaria	del 17p/TP53	Venetoclax	Ibrutinib	-----	Dominant
			Idelalisib + Rituximab	-----	€ 6,228
			Rituximab + Benadmustine	-----	€ 10,957
	r/r CLL	Venetoclax	Ibrutinib	-----	Dominant
			Ofatumumab + Benadmustine	-----	€ 5,065
			Rituximab + Benadmustine	-----	€ 19,933
England	r/r CLL	Ibrutinib	Bendamustine + Rituximab	-----	€ 58,828
			Physician's Choice	-----	€ 63,344
			Ofatumumab	-----	€ 63,894
			Idelalisib + Rituximab	-----	€ 64,373
Finland	CLL Ineligible for Full-Dose Fludarabine	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	€ 18,035	€ 20,038
			Chlorambucil Monotherapy	€ 24,474	€ 29,334
France	CLL Unsuitable for Full-Dose Fludarabine Therapy	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	€ 20,493	€ 22,045
			Chlorambucil Monotherapy	€ 25,836	€ 29,149
Germany	CLL (First-Line)	Fludarabine + Cyclophosphamide + Rituximab	Fludarabine + Cyclophosphamide	€ 15,773	€ 17,979

Greece	CLL Unsuitable for Fludarabine Therapy	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	€ 15,679	€ 16,614
			Chlorambucil Monotherapy	€ 17,258	€ 19,269
			Ofatumumab + Chlorambucil	€ 9,587	€ 9,967
			Rituximab + Bendamustine	€ 9,445	€ 10,026
Italy	r/r CLL	Idelalisib + Rituximab	Rituximab	-----	€ 14,376
			Fludarabine + Cyclophosphamide + Rituximab	-----	€ 20,441
			Bendamustine + Rituximab	-----	€ 26,445
			Bendamustine + Ofatumomab	-----	€ 21,466
			Ofatumomab	-----	€ 1,263
Macedonia	CLL Unsuitable for Full-Dose Fludarabine-Based Therapy	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	-----	€ 29,436
Portugal	CLL Unsuitable for Full-Dose Fludarabine Therapy	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	€ 16,696	€ 17,572
			Chlorambucil Monotherapy	€ 18,913	€ 20,397
	r/r CLL	Idelalisib + Rituximab	Rituximab	€ 32,702	€ 15,935
Russia	Elderly CLL (First-Line)	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	-----	-----
Scotland	All Patients	Idelalisib + Rituximab	BSC	-----	€ 38,616
	del17p/TP53 Mutations		BSC	-----	€ 22,848
Spain	CLL Not Eligible for Fludarabine-Based Therapy	Obinutuzumab + Chlorambucil	Rituximab + Chlorambucil	€ 23,314	€ 24,838
	r/r CLL	Idelalisib + Rituximab	Rituximab Monotherapy	€ 14,733	€ 29,990
Ukraine	r/r CLL	Fludarabine + Cyclophosphamide + Rituximab	Fludarabine + Cyclophosphamide	-----	€ 7,747
	Treatment-Naïve CLL		Fludarabine + Cyclophosphamide	-----	€ 9,848
United Kingdom	CLL Ineligible for Full-Dose Fludarabine	Chlorambucil Monotherapy	Benadmustine Monotherapy	-----	€ 23,383
			Chlorambucil + Rituximab	-----	Dominant
			Ofatumumab + Chlorambucil	-----	Dominated
			Bendamustine + Rituximab	-----	Dominant
			Obinutuzumab + Chlorambucil	-----	€ 34,423
	CLL Unable to Tolerate Fludarabine-Based Therapy	Ibrutinib	Chlorambucil + Obinutuzumab	€ 100,122	€ 90,778
	CLL Not Eligible for Fludarabine-Based Therapy	Ofatumumab + Chlorambucil	Chlorambucil Monotherapy	€ 38,192	-----
	Double-Refractory CLL	Ofatumumab	BSC	€ 76,250	€ 156,676
Relapsed CLL	Acalabrutinib	Ibrutinib	-----	€ 74,329	

Conversions rates on January 1, 2020: 1GBP=1.2 EURO; 1USD=0.89 EUROS; 1BGN=0.51 EURO

Abbreviations: CLL= Chronic Lymphocytic Leukemia; ICER=Incremental cost effectiveness ratio; LY= life year; r/r CLL = relapse/refractory chronic lymphocytic leukemia; QALY=Quality adjusted life-year

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