Cost-effectiveness of Ibrutinib as Frontline Treatment For Adult Patients With Chronic Lymphocytic Leukaemia in Belgium

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BACKGROUND AND OBJECTIVE

- Chronic lymphocytic leukemia (CLL) is an incurable and life-threatening orphan disease that most commonly affects the elderly. Choice of treatment, especially for those with comorbidities, requires a trade-off between efficacy and toxicity. This study assessed the cost-effectiveness—from a Belgian healthcare payer perspective—of ibrutinib, a first-in-class covalent Bruton’s tyrosine kinase inhibitor associated with significant improvement in progression-free survival (PFS) and overall survival (OS) in frontline treatment of elderly/unfit patients with CLL in terms of projected life-years (LY), quality-adjusted LYs (QALY), and incremental cost-effectiveness ratios (ICER).

METHODS

- A survival partition model with three health states (PFS, post-progression survival [PPS], and death) was developed to evaluate the health and cost consequences of CLL treatment (Figure 1) with ibrutinib vs. chlorambucil monotherapy, chlorambucil + obinutuzumab (Ch+O), bendamustine + rituximab (BR), and physician’s choice (PC), a mixed basket of the above treatments, as used in Belgian clinical practice.
- A cohort of elderly, unfit, treatment-naïve patients were followed for 25 years (reflective of a lifetime time horizon), and health and cost outcomes were discounted by 1,5% and 3,0%, respectively.¹ Patients entered the model and initiated frontline treatment for CLL. Upon progression, patients transitioned to PPS, where they were modelled to receive a subsequent line of active treatment that impacted cost but not patient survival. Patients could die at any time in the model.

Data Sources

- Efficacy of ibrutinib and chlorambucil was informed by RESONATE-2 trial data.² Efficacy of comparators were based on a Bayesian network meta-analysis (NMA) that estimated the treatments’ relative efficacy (PFS and OS hazard ratios [HR]) based on data from a systematic literature review (SLR) (Table 1).³ Baseline utility and changes in utility associated with ibrutinib treatment were based on EuroQoL–Five Dimensions data collected in RESONATE-2 (Table 2). Other utility values were based on published sources identified through the SLR.
- Medical resource use was informed by clinical expert opinion, and unit costs were sourced from Belgian cost databases.

Projection of OS and PFS

- PFS and OS outcomes were projected from clinical trials using standard parametric fittings to establish reference curves that represent the underlying risk of progression and/or death. PFS and OS HRs derived from the NMA were applied to the reference curve to estimate the relative efficacy in terms of PFS and OS for each treatment arm in the model.³
 - PFS reference curve: CLL11 chlorambucil PFS curve, Weibull projection (best fit per Akaike and Bayesian Information Criterion statistics)
 - OS reference curve: RESONATE-2 ibrutinib OS curve, capped by the Belgian general population mortality.

Figure 1. Model Diagram

Table 1. Comparative Efficacy based on NMA

vs. Chlorambucil	OS HR [95% CI]	PFS HR, [95% CI]	Reference
Ibrutinib	0,16 [0,05, 0,55]	0,16 [0,09, 0,28]	Xu Y et al. 2017 ³
Ch+O	0,41 [0,23, 0,74]	0,19 [0,14, 0,27]	
BR	0,64 [0,28, 1,50]	0,24 [0,14, 0,40]	

Table 2. Utility Values Used in Model

	Mean Utility	Reference
Baseline utility, frontline PFS	0,780	RESONATE-2 EQ-5D ⁴
Utility change due to ibrutinib treatment	0,036	RESONATE-2 EQ-5D ⁴
Utility change due to IV administration	-0,040	Obinutuzumab NICE ERG ⁵
Utility change due to hospital visits*	-0,120	Obinutuzumab NICE ERG ⁵
*applied first administration of Ch+O only		

RESULTS

- Deterministic results indicated that ibrutinib was associated with health gains of up to 7,13 LYs and 4,74 QALYs, and higher costs, which were largely driven by ibrutinib’s superior PFS (i.e., longer time on treatment) (Table 3). Deterministic sensitivity analyses indicated that model results were sensitive to key drivers, including discount rates for health and cost outcomes, and ibrutinib treatment duration.

Table 3. Results: Incremental Outcomes vs. Ibrutinib

Ibrutinib vs. Comparator	Chlorambucil	BR	Ch+O	PC
Incremental cost (€)	244.862	226.063	203.062	217.174
Incremental LYs	7,13	5,72	4,11	5,11
Incremental QALYs	4,74	3,68	2,66	3,30
ICER per LY gained (€)	34.361	39.523	49.424	42.540
ICER per QALY gained (€)	51.641	61.506	76.451	65.760

CONCLUSIONS

- Results indicate that ibrutinib offers a pronounced benefit over comparators for frontline treatment of CLL.
- ICERs are well within 1–3-times Belgium’s gross domestic product (€42.120 – €126.359),^{6,7} a standard metric of value for money,⁸ demonstrating that ibrutinib is a cost-effective resource for elderly/unfit frontline-treated CLL patients..

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