Cost-effectiveness of ruxolitinib vs. Best Available Therapy in the treatment of myelofibrosis in Spain

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Introduction

- Primary myelofibrosis (MF) is a rare philadelphia-negative myeloproliferative neoplasm. Its prevalence is generally established at 2/100,000 people, yielding an estimation of approximately 1,400 patients in Spain[1].
- MF is associated with significant symptom burden which reflects on high healthcare costs. Recently, direct annual cost of managing MF was estimated at $34,690 (€25,972) per patient in the US[2]. Furthermore, a Spanish study reported a mean indirect cost of €86,315 per patient (€168,459 for more symptomatic patients)[1].
- Ruxolitinib is the first JAK1/JAK2 inhibitor approved for the treatment of disease-related splenomegaly or symptoms in patients with MF, with evidence of rapid and sustained splenomegaly reduction, symptom improvement and overall survival (OS) increase [3–6].

Objective

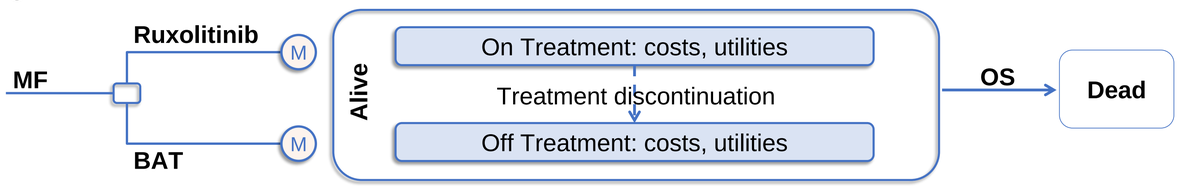
- To assess the cost effectiveness of ruxolitinib vs. best available therapy (BAT) in MF patients in Spain from a societal perspective.

Materials and methods

Model structure

- A global model built in Microsoft Excel® was adapted to the Spanish setting. The model is structured in two main parts: a decision tree and a 3-health states Markov model (**Figure 1**).

Figure 1 Decision tree and Markov model health states



- A lifetime horizon of 15 years was considered, based on the NICE ERG recommendations[7]. Cycle length was 28 days. Costs and benefits were discounted at an annual rate of 3%[8].
- Main outputs of the model include incremental cost-effectiveness (ICER) and cost-utility ratio (ICUR) based on the following outcomes: life years (LYs) gained, quality adjusted life years (QALYs) and total costs.
- Key assumptions and main inputs (**Table 1**-**Table 3**) were validated by clinicians experienced in the treatment of MF.

Table 1 BAT composition considered in the model

	Patients (%)		Patients (%)
Other antineoplastic agents	50,7%	Antigonadotropins and similar agents	17,5%
Hydroxyurea	46,6%	Interferons	2,0%
Anagrelide	5,5%	Nitrogen mustard analogs	2,7%
Glucocorticoids	22,5%	Pyrimidine analogs	7,5%
Other antianemia preparations	25%	No Therapy	32,9%
Other immunomodulatory agents	2,7%	BAT combined	169,0%*
Purine analogs	5,5%		

**The sum of percentages exceed 100% as polymedication was allowed* *Source: Expert validation[6]*

Clinical effectiveness

- Transition probabilities were obtained from the OS curves of the COMFORT II-5 years[9] clinical trial (CT), adjusted to account for the crossover between treatment arms. Parametric extrapolation methods were used to project survival over the 15-year time horizon.
- Utilities were derived from the COMFORT-I CT[10].

Costs estimation

- Costs included pharmacological treatment, resource use, as well as adverse events (grade 3-4) management, loss of productivity, transformation to AML, and end-of-life costs (**Table 2**, **Table 3**). Unit costs were derived from Spanish healthcare cost databases[11,12]. Frequency of use was obtained from the literature[5,13] and the experts' opinion.
- Loss of productivity was estimated based on the age distribution of patients in the COMFORT-II CT[9] and the average annual income from the Spanish National Institute of Statistics[14]. A proportion of 25.1% of patients was assumed to be working in both treatment arms. Mean number of worked days/year was estimated in 255 and 250 for ruxolitinib and BAT respectively[15], yielding a cost per cycle of 263.04 and 231.41 € in each treatment arm.

Table 2. Unit cost, frequency and percentage of patients requiring use of resources.

	Patients requiring (%)	Frequency (times per year)	Frequency (times per cycle)	Unit cost (€)	Cost per cycle (€)	Source
Resource use						
Monitoring of lab. values	100%	11.02	0.85	4.99	4.24	Expert consensus, 12,13
Emergency visit	100%	1*	0.15	73.00	11.19	
Hospital stay	100%	2*	0.08	4,753.93	364.44	
Outpatient visit	100%	11.02*	0.85	65.03	55.28	

*as per expert consensus.

Table 3. Adverse events, AML transformation and end of life related costs.

	(%) with ruxolitinib	% with BAT	Frequency (times per 48 weeks)*	Frequency (times per cycle)	Unit cost (€)	Cost per cycle (€)	Source
Grade 3-4 adverse event							
Thrombocytopenia	4.1%	4,1%	1	0.08	1,404.62	117.05	Expert consensus, 12,16
Anemia	30.0%Ŧ	30.0%Ŧ	1Ŧ	0.08	1,654.48	137.87	
Pyrexia	2.1%Ŧ	0,0%Ŧ	0.46Ŧ	0.04	632.05	52.67	
Pneumonia	1.4%Ŧ	4,1%Ŧ	1Ŧ	0.08	2,688.66	224.05	
Other							
AML transformation	2.33%	1.21%	-	-	1,864.82	-	5,17
End of life	-	-	-	-	2,657.90	-	5,18

*assumed one event per 48 Weeks for both treatments as reported in COMFORT-II; Ŧ as per expert consensus.

Sensitivity analysis

- A One-Way Sensitivity Analysis (OWSA) and a Probabilistic Sensitivity Analysis (PSA) were run to evaluate the consistency of the results under the uncertainty of the input data.
- The OWSA sequentially introduces a variation of ±20% of the base case value for each input parameter. The Spanish National Health System perspective was also considered as an alternative scenario.
- The PSA runs a Monte Carlo simulation with 1,000 iterations while varying the input values according to a predefined probability distribution and its corresponding parameters. For the parameterized survival curves, a Cholesky decomposition of the variance/covariance matrix was used to vary the defining parameters. Gamma distributions were used for costs; proportions and utilities were sampled form beta distribution, while a normal distribution was used for baseline utility.

Results

- The ICER and the ICUR of ruxolitinib vs. BAT were €47,119/LYG and €55,616/QALY respectively (**Table 4**).

Table 4 Cost-effectiveness results

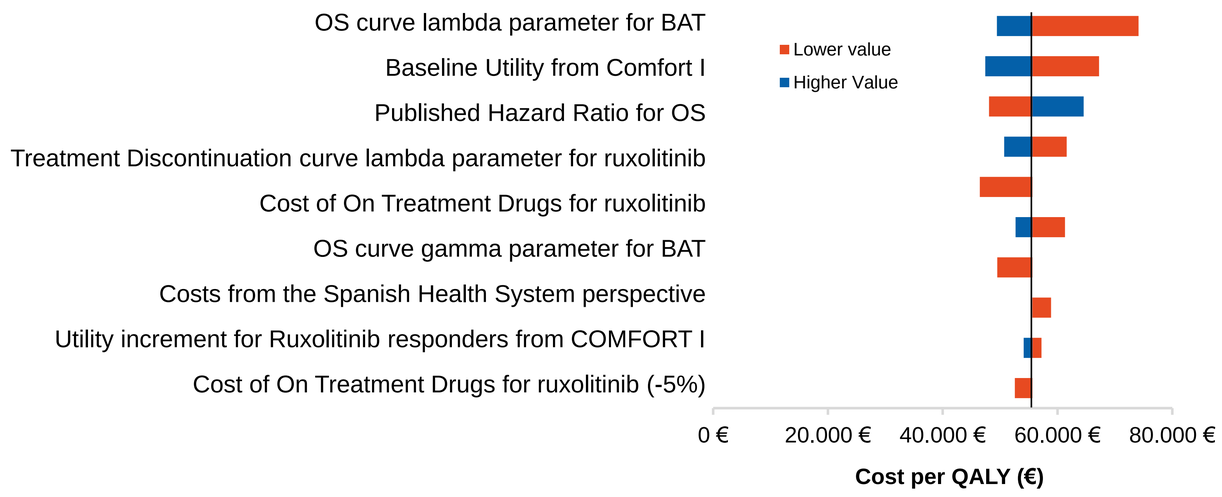
	Cost per patient (€)	LYG	QALYs	ICER	ICUR
Ruxolitinib	164,964	6.1	4.4	47,119	55,616
BAT	43,425	3.5	2.2	-	-
Difference	121,539	2.6	2.2	-	-

Sensitivity analysis

OWSA

- The OS curve lambda parameter for BAT and the baseline utility values had the greatest impact on the ICUR (**Figure 2**).

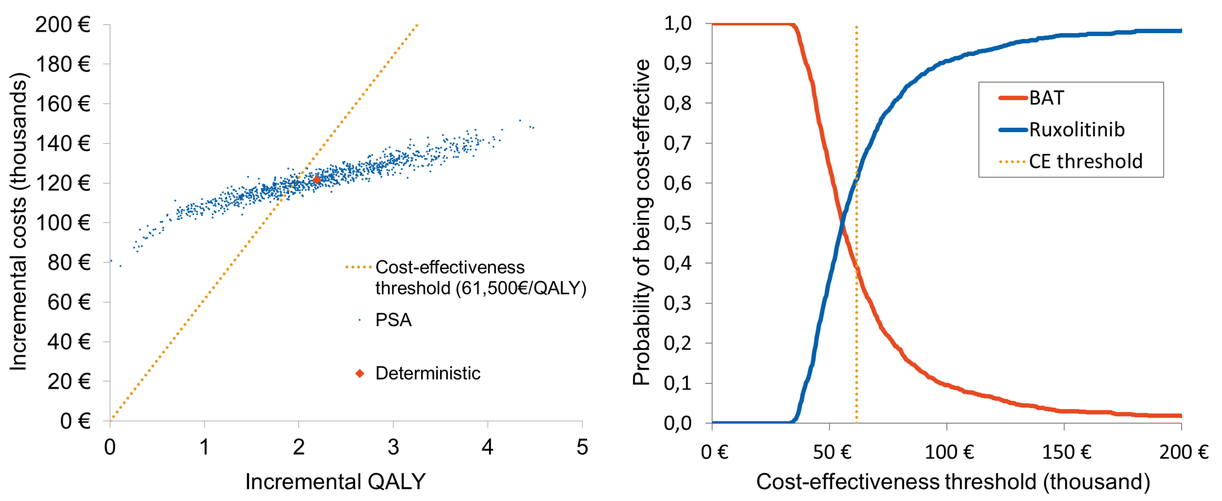
Figure 2 Tornado diagram: ICUR (cost/QALY) variation caused by individual variations of the input parameters



PSA

- The PSA showed that 99.8% of the iterations fall into the upper-right quarter of the cost-effectiveness plane, meaning that ruxolitinib is more effective and more costly than BAT (**Figure 3a**).
- Ruxolitinib has 61% probabilities of being cost-effective at the threshold established by the NICE for oncology drugs that meet 'End-of-Life' (EoL) criteria (€61,500/QALY)[19] (**Figure 3b**).

Figure 3 Cost-effectiveness scatterplot (a) and acceptability curves (b) of ruxolitinib vs BAT



Conclusions

- **According to this analysis ruxolitinib is an effective therapeutic option and can be regarded as cost-effective in comparison with BAT for the treatment of MF-related symptoms in Spain.**

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