Cost-Effectiveness Analysis of Ruxolitinib vs Best Available Therapy for the Treatment of Myelofibrosis in the United States

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BACKGROUND

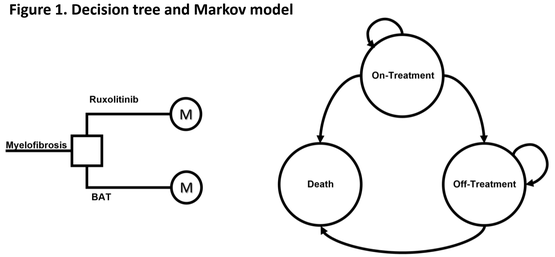
- Myelofibrosis is a Philadelphia chromosome-negative myeloproliferative neoplasm characterized by Janus Kinase (JAK) mutations that cause the overproduction of hematocytes in the bone marrow.[1]
- Myelofibrosis has a 5.9-year median overall survival (OS) and clinical manifestations include splenomegaly, anemia, and a multitude of constitutional symptoms such as fatigue, night sweats, and fever.[2, 3]
- Ruxolitinib is a JAK 1/2 inhibitor that has been shown to significantly reduce spleen volume, decrease constitutional symptoms and improve OS compared to best available therapy (BAT).[4]
- In 2011, Ruxolitinib became the first targeted therapy approved by the FDA for the treatment of intermediate and high-risk myelofibrosis.[5]
- Currently, the cost-effectiveness of ruxolitinib for the treatment of myelofibrosis in the U.S. is unknown
- The aim of this study was to assess the cost-effectiveness of ruxolitinib versus BAT for the treatment of intermediate and high-risk myelofibrosis from a healthcare perspective in the United States.

METHODS

Study Design and Participants

- Using a decision tree, half of the cohort was assigned to a ruxolitinib arm and the other half to a BAT arm. Patients then entered a Markov model with three health states: on-treatment, off-treatment, and death (Figure 1)
  - A 15-year time horizon with a cycle length of 28 days was chosen; costs and outcomes were discounted at a 3% annual rate.
  - The model was built using TreeAge Pro, version 2022 R1.0
- Alive-to-dead transition probabilities were not reported in the COMFORT II clinical trial and were obtained by fitting lognormal distributions to the ruxolitinib and crossover-adjusted BAT OS curves that were reconstructed from COMFORT II through digitization and recreation of the time-to-event data.[6, 7]
  - Crossover from BAT to ruxolitinib was accounted for in COMFORT II by including an adjusted BAT OS curve using the rank-preserving structural failure time method.[4]
- Treatment discontinuation was only reported at the 3 and 5-year time point in COMFORT II, so on-to-off treatment transition probabilities were estimated by fitting a Gompertz distribution to the available time points and incorporating a large range of uncertainty (±50%) in the sensitivity analysis.[4, 8]
- BAT treatment composition was obtained from COMFORT II and assumed to remain constant since the composition includes "no treatment" as an option.[9]

Figure 1. Decision tree and Markov model



BAT = best available therapy; M = Markov model

Model Inputs

- Unit costs (USD) were derived from the VA federal supply schedule (FSS) and several cost of illness studies that characterized healthcare utilization and costs associated with myelofibrosis as well as the most common adverse effects of ruxolitinib and BAT treatment, acute myeloid leukemia (AML) transformation, and end of life (EOL) care (Table 1).[10-16]
- Health state utility values were obtained from a study that derived on and off-treatment utility values for ruxolitinib and BAT using the standard gamble technique (Table 2).[17]

Sensitivity Analysis

- A one-way sensitivity analysis (OWSA) was carried out by varying the on-to-off treatment parameters by ± 50%, varying drug unit costs based on the range of VA FSS prices and varying all other base case values by ± 20%.
- A probabilistic sensitivity analysis (PSA) was run with 1,000 iterations that incorporated beta distributions applied to all utility and transition probability parameter inputs and gamma distributions applied to all cost inputs to generate cost effectiveness acceptability curves.

Table 1. Transition probability and cost inputs

	Input		Source
Transition probability parameters			
On-to-off treatment (Ruxolitinib)[a]	λ=0.1630; γ=0.0003		Comfort II 3 & 5-year follow-up
On-to-off treatment (BAT)[a]	λ=0.5766; γ=0.5000		
Alive-to-dead (Ruxolitinib)[b]	LogMean=1.8850; LogSD=1.3670		Comfort II 5-year follow-up
Alive-to-dead (BAT)[b]	LogMean=1.1750; LogSD=1.0850		
Cost inputs (per cycle)			
Ruxolitinib drug cost	$13,476.45		VA FSS
BAT drug cost	$984.35		
Emergency room visit	$99.57		Mehta et al. 2014
Hospital Inpatient	$2,469.53		
Outpatient visits and services	$2,715.19		
Anemia[c]	Rux: $13.45	BAT: $11.39	Ershler et al. 2005
Thrombocytopenia[c]	Rux: $32.83	BAT: $33.41	Liou et al. 2007
Pneumonia[c]	Rux: $0.44	BAT: $1.23	Tong et al. 2018
Cost inputs (one-time)			
AML transformation[d]	$223,316.50		Hagiwara et al. 2018
End of Life	$103,696.48		Chastek et al. 2012

BAT = best available therapy; Rux = ruxolitinib; AML = Acute Myeloid leukemia; SD = standard deviation; VA FSS = Department of Veteran's Affairs Federal Supply Schedule

[a]Lambda and gamma parameter values for Gompertz distribution

[b]Mean and SD parameter values for lognormal distribution

[c]Risk of adverse effects differed for ruxolitinib and BAT arm, leading to different cost inputs

[d]Risk of AML transformation was 1.21% for ruxolitinib arm and 2.33% for BAT arm

Table 2. Health state utility values

Health state	Standard Gamble Utility Values
On treatment (Ruxolitinib)	0.82
Off treatment (Ruxolitinib)	0.58
On treatment (BAT)	0.44
Off treatment (BAT)	0.41

BAT = best available therapy; SD = standard deviation

RESULTS

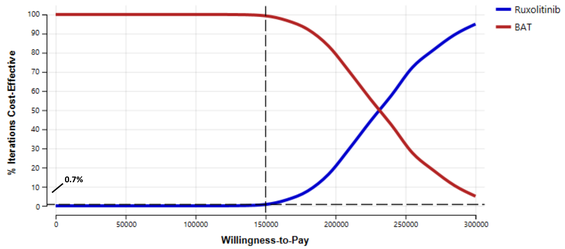
- After running a Monte Carlo microsimulation of 1,000 patients, ruxolitinib treatment was expected to generate 4.71 QALYs at a cost of $1,107,203 while BAT was expected to generate 1.85 QALYs at a cost of $426,355 resulting in an incremental cost effectiveness ratio (ICER) of $238,474/QALY (Table 3)
- The PSA revealed that ruxolitinib had an ICER < $150,000/QALY in 0.7% of iterations. (Figure 2)
- One-way sensitivity analysis showed the most impactful parameter was the drug cost of ruxolitinib. None of the ranges explored yielded an ICER < $150,000/QALY. (Figure 3).

Table 3. Probabilistic results: Costs, QALYs, and ICER

Treatment group	Total		Incremental		ICER
	Cost	QALYs	Cost	QALYs	
Rux	$1,107,202.63	4.71	$680,847.35	2.86	$238,474.00
BAT	$426,355.29	1.85			

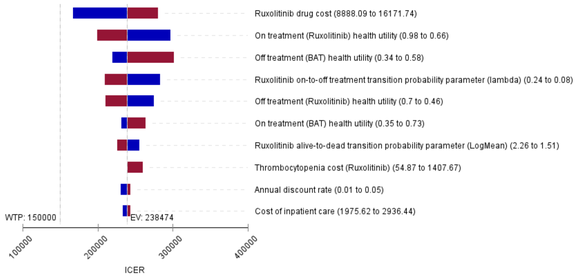
BAT = best available therapy; Rux = ruxolitinib; ICER = incremental cost-effectiveness ratio; QALY = Quality-adjusted life year

Figure 2. Cost-effectiveness acceptability curve



BAT = best available therapy

Figure 3. Tornado diagram: Top 10 parameters influencing ICER variation



BAT = best available therapy; ICER = incremental cost-effectiveness ratio; EV = expected value; WTP = willingness to pay

CONCLUSION

- ✓ **This analysis found that ruxolitinib may extend quality adjusted survival by almost three years but at current prices is unlikely to be a cost-effective option to treat myelofibrosis compared to BAT in the U.S.**
- ✓ **None of the one-way sensitivity analyses nor the probabilistic sensitivity analysis suggested that ruxolitinib would likely have an ICER < $150,000 / QALY.**
- ✓ **Future cost-effectiveness research should employ other payer perspectives to identify and evaluate a broader range of potential benefits and costs of ruxolitinib versus BAT for the treatment of myelofibrosis in the United States.**

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