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Cost-utility analysis of ruxolitinib versus best available therapy for the treatment of hydroxyurea resistant/intolerant polycythemia vera without splenomegaly in the United States

INTRODUCTION

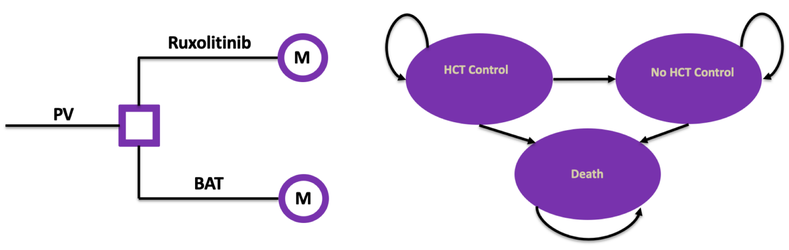
- Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by an abnormal increase in red blood cell mass due to a mutation in the *Janus kinase 2* (JAK2) gene.[1]
- Ruxolitinib is a JAK 1/2 inhibitor which showed 7.3 times greater odds than best available therapy (BAT) (95% confidence interval 3.4-15.5) in achieving hematocrit control in patients with hydroxyurea resistant/intolerant PV. [2-5]
- To date, there are no published US economic analyses of ruxolitinib in PV.
- The aim of this study was to assess the cost-utility of ruxolitinib versus BAT for the treatment of hydroxyurea resistant/intolerant PV without splenomegaly from the perspective of a commercial payer in the United States.

METHODS

Study Design and Participants

- A decision tree was used to assign half of the cohort to ruxolitinib and the other half to BAT; after treatment assignment patients entered a three-state Markov model (**Figure 1**)
  - A 15-year time horizon with 3-month cycles was used; costs and outcomes were discounted 3% annually
- Transition probabilities between alive states were obtained from the RESPONSE-2 clinical trial; second transition period between month 7 and 20 of RESPONSE-2 follow-up was held constant beyond cycle 2 to capture waning treatment efficacy in both arms[4]
- Transition probabilities between alive and dead states were not reported in RESPONSE-2 and were obtained by fitting Weibull and lognormal distributions to survival curves from a retrospective study assessing the impact of median HCT value on survival in 226 PV patients over 13-years of follow-up[6]
- Treatment composition of the BAT group was obtained from the RESPONSE-2 clinical trial and assumed to remain constant since BAT includes the option for patients to be on or off PV treatments
  - Patients in the 'No HCT control' state were assumed to be on BAT regardless of which group they originated from since trial data was not collected after ruxolitinib discontinuation

Figure 1. Decision tree and Markov model



BAT = best available treatment; HCT = hematocrit; M = Markov model; PV = polycythemia vera

Model Inputs

- No PV-specific health state utility values were published; multiple studies suggest effects of PV on quality of life are similar to those reported with other MPNs such as myelofibrosis (MF), therefore, utility values were obtained from a study which mapped EuroQol five-dimensions questionnaire (EQ-5D) utility values from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer (QLQ-C30) in myelofibrosis (MF)[7-9] (**Table 2**)
- Unit costs (USD) were derived from IBM Micromedex® Red Book and a retrospective study describing health care resource utilization and costs associated with thromboembolic events in hydroxyurea-treated patients with PV[10] (**Table 3**)
- Safety and efficacy parameters were generated from the RESPONSE-2 clinical trial[4,5]

Table 2. Health state utility values

Health state	EQ-5D utility value (SE)
HCT control	0.843 (0.015)
No HCT control	0.785 (0.012)

EQ-5D = EuroQol five-dimensions questionnaire; HCT = hematocrit; SE = standard error

Table 3. Resource use and cost inputs

	Input	Source
Drug unit costs[a]		
Ruxolitinib, 20 mg tablet	$270.08	IBM Micromedex Red Book
Hydroxyurea, 500 mg capsule	$1.47	
Peginterferon, 180 mcg / 5 ml solution	$2,451.58	
Lenalidomide, 20 mg capsule	$863.78	
Resource use and costs associated with PV by presence of TEs		
Proportion of HCT control patients with TEs	17.4%	Crisa et al 2010
Proportion of HCT control patients without TEs	82.6%	
Proportion of no HCT control patients with TEs	32.4%	
Proportion of no HCT control patients without TEs	67.6%	
Annual inpatient costs for PV patients with TEs, mean (SD)	$18,952 ($44,039)	Parasuraman et al 2018
Annual inpatient costs for PV patients without TEs, mean (SD)	$4,794 ($18,969)	
Annual outpatient costs for PV patients with TEs, mean (SD)[b]	$20,844 ($77,974)	
Annual outpatient costs for PV patients without TEs, mean (SD)[b]	$8,046 ($11,962)	

PV = polycythemia vera; TE = thromboembolic events
All costs were adjusted for medical-care inflation to 2018 dollars
[a]Unit costs presented as 2019 average wholesale price prior to any rebate
[b]Outpatient costs exclude pharmacy costs

RESULTS

- In the probabilistic sensitivity analysis (PSA) utilizing a second-order Monte Carlo simulation with 5,000 iterations, patients in the ruxolitinib arm accumulated a mean of 28.5 QALYs compared to 27.3 QALYs in the BAT group; mean total costs in the ruxolitinib arm were $526,100 compared to $371,700 with BAT; mean ICER of $128,600 (**Table 4**)
- PSA suggested a 73% probability that the ICER would be cost-effective using a willingness-to-pay (WTP) threshold of $150,000/QALY (**Figure 2**)
- One-way sensitivity analysis showed the most impactful parameter was the 3-month probability of maintaining HCT control after month 6 (**Figure 3**)

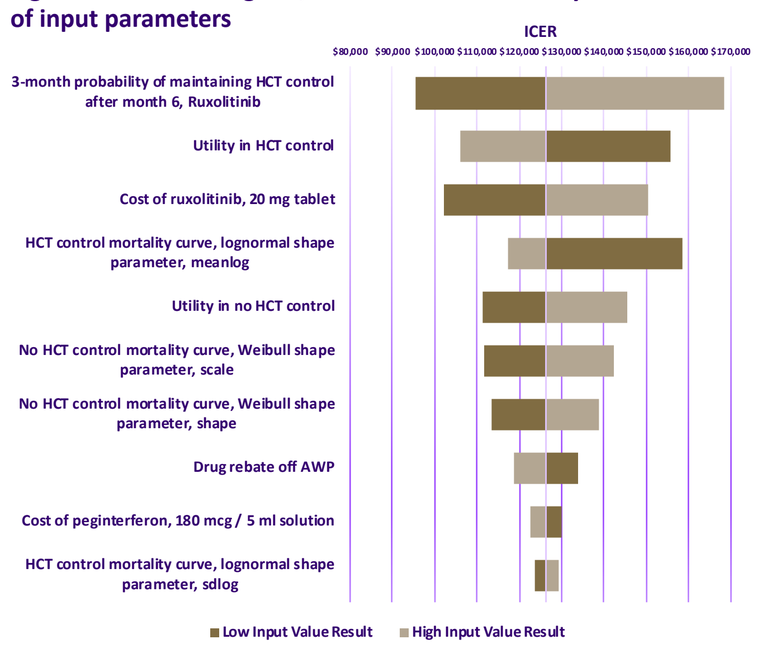
Table 4. Probabilistic results, mean (95% credible range)

Tx group	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Rux	**$526,100** ($428,700 - $623,800)	**28.5** (24.9 – 30.6)	**$154,400** ($91,200 - $271,600)	**1.2** (0.5 – 2.8)	**$128,600** ($82,700 - $215,400)
BAT	**$371,700** ($310,800 - $381,600)	**27.3** (23.7 – 27.0)			

BAT = best available treatment; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; Rux = ruxolitinib; SD = standard deviation

Figure 2. Cost-effectiveness acceptability curve

Figure 3. Tornado diagram, ICER variation caused by individual variation of input parameters



CONCLUSION

> Our results suggest ruxolitinib is cost-effective when compared to best available therapy in patients with hydroxyurea resistant/intolerant PV without splenomegaly using a WTP threshold of $150,000/QALY.

> Additional research is needed in defining PV-specific utilities and establishing an appropriate surrogate endpoint for survival

REFERENCES

1. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114(5):937-951.
2. Vannucchi AM. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med.* 2015;372(17):1670-1671.
3. Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. *Haematologica.* 2016;101(7):821-829.
4. Griesshammer M, Saydam G, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. *Ann Hematol.* 2018;97(9):1591-1600.
5. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol.* 2017;18(1):88-99.
6. Crisà E, Venturino E, Passera R, et al. A retrospective study on 226 polycythemia vera patients: impact of median hematocrit value on clinical outcomes and survival improvement with anti-thrombotic prophylaxis and non-alkylating drugs. Ann Hematol. 2010;89(7):691-699.
7. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer. 2007;109(1):68-76.
8. Abelsson J, Andréasson B, Samuelsson J, et al. Patients with polycythemia vera have worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. Leuk Lymphoma. 2013;54(10):2226-2230.
9. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol. 2012;30(33):4098-4103.
10. Parasuraman SV, Shi N, Paranagama DC, Bonafede M. Health Care Costs and Thromboembolic Events in Hydroxyurea-Treated Patients with Polycythemia Vera. J Manag Care Spec Pharm. 2018;24(1):47-55.