pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Ruxolitinib (Jakavi) for Myelofibrosis

January 14, 2013

DISCLAIMER

Not a Substitute for Professional Advice
This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability
pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of ruxolitinib on patient outcomes compared with standard therapies, placebo, or best supportive care in the treatment of patients with splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two multinational, phase 3, randomized controlled trials, COMFORT I (309 patients) and COMFORT II (219 patients), were identified that compared ruxolitinib (15 or 20 mg BID, dosed according to platelet counts) to placebo or best available therapy, respectively. Enrollment criteria were similar between trials and had patients ≥18 years old with myelofibrosis (PMF, PPVMF, or PETMF subtype). COMFORT I included patients who were either refractory or intolerant to prior therapy, while COMFORT II inlcued patients who were still eligible for some available treatments but unsuitable for ASCT. In both trials, patients had ECOG PS of ≤ 3, and featuring palpable splenomegaly ≥ 5cm below left costal margin. In both trials, the majority of patients studied were Caucasian (~90%), high-risk (~60%), with ECOG PS ≤1 (~86%), and had previous exposure to hydroxyurea therapy (~66%); PMF was diagnosed in about half of all patients. Cross-over was permitted in both trials in the event of protocol-specified progression criteria were met; in COMFORT I, cross-over could occur before or after the data-lock at 24 weeks while in COMFORT II cross-over could occur either at 24 weeks or 48 weeks, depending upon the achievement of primary or secondary endpoints.

The primary outcome of COMFORT I was the proportion of patients with >35% reduction in spleen volume by MRI at week 24 while the major secondary outcome was the proportion of patients with a >50% reduction in total symptom score based on the modified Myelofibrosis Symptom Assessment Form (MSAF) at week 24. In COMFORT I, a higher proportion of patients in the ruxolitinib group compared with the placebo group achieved the primary endpoint of >35% reduction in spleen volume at 24 weeks (41.9% vs 0.7%, respectively); 1 percent difference between groups of 41.2% (95% CI: 32.8% to 48.7% according to the FDA statistical review14). A higher proportion of patients in the ruxolitinib group compared with the placebo group achieved ≥50% reduction in total symptom score from the MFSAF at week 24 (68/148, 45.9% vs 8/152, 5.3%, respectively) (P<0.001). In COMFORT II, the proportion of patients with >35% reduction in spleen volume by MRI was examined as the primary outcome at week 48 and at week 24 as the major secondary outcome. In COMFORT II, 28% of patients in the ruxolitinib group compared with none from the best available therapy group achieved the primary endpoint of ≥35% reduction in spleen volume at 48 weeks (percent difference of 28%; 95% CI: 19.3% to 34.8% according to the FDA statistical review). At 24 weeks, 31.9% of patients from the ruxolitinib group compared with none from the best available therapy group achieved ≥35% reduction in spleen volume (31.9%; 95% CI: 22.5 to 38.4).

Deaths related to adverse events were similar between ruxolitinib and control in both COMFORT I (6% vs 7%) and II (3% vs 4%). (Table 8) Non-fatal SAEs were slightly lower in the

ruxolitinib group compared with placebo in COMFORT I (27.7% vs 35.1%), but similar in COMFORT II. The occurrence of grade 3-4 adverse events was similar between ruxolitinib and placebo in COMFORT I, but was numerically higher in ruxolitinib-treated patients compared with best available therapy in COMFORT II (42% vs 25%). Withdrawals due to adverse events were not different between groups in both COMFORT I and II trials.

1.2.2 Additional Evidence

pCODR received input on ruxolitinib from the following patient advocacy groups, The Chronic Myelogenous Leukemia (CML) Society of Canada and Canadian Myeloproliferative Neoplasms (MPN) Network. Provincial Advisory group input was obtained from the six provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

1.2.3 Interpretation and Guidance

Myelofibrosis (MF) is a myeloproliferative disorder that is uncommon, with an annual incidence rate of 0.2 – 1.5 cases per 100 000 per year. The burden of illness of patients affected by myelofibrosis is profound, with majority of patients experiencing poor or very poor quality of life. Current treatments do little to improve quality of life in this disease.

The only curative therapy at this time is allogeneic stem cell transplant which is not available to most individuals because of age, co-morbidity or availability of donor. For the vast majority of patients, therapy is relegated to trying to reduce the symptoms related to splenomegaly and cytokine release. Thus available treatments are either not effective (splenectomy, cytoreductive therapy, supportive care with transfusions) or hard to apply generally to the MF patient population (ASCT). As current treatments palliate symptoms and have limited duration of response, there is clear clinical need for more effective treatment of MF.

Two phase 3 studies, COMFORT-I and COMFORT-II compared ruxolitinib to placebo in the first line setting and ruxolitinib to best available therapy in the second line setting, respectively. In both trials, there was significant improvement in spleen volume, albeit with large overlapping confidence intervals, as measured by imaging in 40% of the patients. Significance was defined as a 35% reduction in spleen volume for purposes of a statistical end point. If spleen reduction of any kind was included, then there were far more patients found in the ruxolitinib arms, in keeping with the frequency found in previous phase 2 studies. In neither trial was there enough power to demonstrate any survival advantage, although secondary analysis attempts have been used to suggest that there is, at least in COMFORT I the placebo-controlled study. Responses if they occurred were in the first 24 weeks, although it is suggested that 48 weeks were necessary to demonstrate response or more correctly treatment failure.

Overall discontinuation due to adverse events (AE) in Comfort I and COMFORT II was low and not different between the experimental and control arms. Grade 3/4 cytopenias were common with ruxolitinib but prescribers of this drug are comfortable managing patients with severe cytopenias. Treatment interruptions are associated with rapid return of symptoms of myelofibrosis, including return of splenomegaly and systemic symptoms. The concern about a withdrawal syndrome has been raised in the literature and will require education of patients and prescribers.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to ruxolitinib in treatment of patients with myelofibrosis. The Clinical Guidance Panel had major concerns with the definition of response used in Comfort I and COMFORT II, and was not convinced of it being a satisfactory surrogate for survival and symptom control. The different response criteria used in the two arms of the studies also introduce significant bias and makes drawing firm conclusions difficult. The Clinical Guidance Panel recognized that in the absence of other available options for individuals with MF and symptoms related to either splenomegaly or cytokine expression that impact on QoL, ruxolitinib is a suitable treatment option.The Clinical Guidance Panel considered stem cell allografting as the only option for cure and only if the patient is a suitable candidate.

The CGP also concluded that from a clinical perspective

- Ruxolitinib may be used with a 24 week observation period where an absence of response within this time period should be a marker for discontinuation and movement to other forms of therapy such as palliation or experimental therapy.
- The duration of ruxolitinib therapy is indefinite at this time. Regular monitoring for the duration of therapy, spleen size, blood counts, evidence of transformation and transfusion requirements is essential. Transfusion requirements may increase at least initially for patients and as such careful monitoring for this possibility should be undertaken
- Discontinuation of therapy should be through a tapering routine if possible and will require careful monitoring because of the potential for significant rebound symptoms. Consideration of patients with thrombocytopenia for ruxolitinib therapy has not been examined carefully and should not necessarily be a contraindication to inclusion. However, extra vigilance will be required in monitoring patients with MF and concurrent thrombocytophenia.
- Disease control for patients receiving ruxolitinib therapy has the biological plausibility to take patients from allograft ineligibility to eligibility and/or result in improvement of outcome and should be re-evaluated for ASLT as therapy progresses.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ruxolitinib for myelofibrosis. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature ruxolitinib in myelofibrosis conducted by the Myelofibrosis Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ruxolitinib in myelofibrosis and a summary of submitted Provincial Advisory Group Input on ruxolitinib in myelofibrosis are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Ruxolitinib is an oral tyrosine kinase inhibitor selective for Janus kinase 1 and 2 (JAK1/JAK2); it is the first JAK inhibitor to be approved for use in myelofibrosis.[1] Myelofibrosis is distinguished molecularly by a gain of function mutation (JAK2 V617F) in the JAK2 gene resulting in overactive (constitutive) JAK2 expression;[2] this JAK2 V617F mutation can be found in approximately 50% of patients with primary myelofibrosis.[2] Although not selective for JAK2 V617F, by targeting the JAK-STAT pathway, JAK inhibitors are thought to reduce proinflammatory cytokine burden through their anti-JAK1 activity, which, unsuppressed, is believed to contribute to the constitutional symptoms and organomegaly (particularly, splenomegaly) that patients with myelofibrosis experience.[1,3] However, JAK inhibitor non-selectivity can result in dose-limiting myelosuppression from inhibition of wild-type JAK2.[1] Interestingly, in clinical trials, JAK inhibition lowers the level of circulating JAK2 V617F allele, but not to any appreciable degree.[3, 5]

As a complex, heterogeneous myeloproliferative neoplasm involving multiple oncogenic pathways, it is thought that a multi-pronged therapeutic intervention targeting the various signaling perturbations would hold the most promise at effectively modifying disease in myelofibrosis rather than an approach of targeting a single pathway, which may only be palliative.[1] Prior to the availability of the JAK inhibitor class, patients with myelofibrosis had few therapeutic options, all of which were only palliative.[3]

Ruxolitinib is the first JAK inhibitor approved by Health Canada for the treatment of patients with splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.[4] The recommended dose of ruxolitinib is 15 or 20 mg administered orally twice daily, adjusted according to platelet counts.[4]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of ruxolitinib on patient outcomes compared with standard therapies, placebo, or best supportive care in the treatment of patients with splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

2.1.3 Highlights of Evidence in the Systematic Review

The efficacy and safety of ruxolitinib 15 or 20 mg orally twice daily in in the treatment of adults with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), or post-essential thrombocythemia myelofibrosis (PETMF) was evaluated in two multinational, phase 3, randomized controlled trials known as COMFORT I and II.

COMFORT I[5] was a double-blind, placebo-controlled trial of North American and Australian patients (n= 309) while COMFORT II[6] was an open-label, active-controlled (best available therapy) trial of European patients (n=219). Only COMFORT II was stratified according to baseline International Working Group (IWG) risk category (i.e., intermediate-2 vs high risk). The primary outcome of COMFORT I was the proportion of patients with $\geq$35% reduction in spleen volume by MRI at week 24 while the major secondary outcome was the proportion of patients with a $\geq$50% reduction in total symptom score based on the modified Myelofibrosis Symptom Assessment Form (MSAF) at week 24. In COMFORT II, the proportion of patients with $\geq$35% reduction in spleen volume by MRI was examined as the primary outcome at week 48 and as the major secondary outcome at week 24.

Enrollment criteria were similar between trials. Eligible adults were $\geq$18 years old with myelofibrosis (PMF, PPVMF, or PETMF subtype). **COMFORT I included patients who were either refractory or intolerant to prior therapy, while COMFORT II inlcued patients who were still eligible for some available treatments but unsuitable for ASCT. In both trials, patients had MF** classified as intermediate-2 or high risk by IWG criteria, with Eastern Cooperative Oncology Group performance status (ECOG PS) of $\leq$ 3, and featuring palpable splenomegaly $\geq$ 5cm below left costal margin. Key exclusion criteria were platelets < 100 x 10^9/L; absolute neutrophil count $\leq$ 1 x 10^9/L; liver or renal impairment; splenic irradiation in the preceding 12 months; or concomitant investigational or myelofibrosis treatments (COMFORT I).[5,6]

In both trials, the majority of patients studied were Caucasian (~90%), high-risk (~60%), with ECOG PS $\leq$1 (~86%), and had previous exposure to hydroxyurea therapy (~66%); PMF was diagnosed in about half of all patients. Slightly more patients > 65 years old were studied in COMFORT I than in COMFORT II (60.5% vs 52.1%). COMFORT I, which was not risk-stratified, did not appear to be as well balanced between treatment and control groups at baseline as COMFORT II, which was risk-stratified; as a result, some allocation imbalances were noted in COMFORT I baseline demographics including with gender, age, MF subtype, and risk category.

In each trial, the intervention consisted of ruxolitinib 15 or 20 mg BID, dosed according to platelet counts. Cross-over was permitted in both trials in the event of protocol-specified progression criteria were met; in COMFORT I, cross-over could occur before or after the data-lock at 24 weeks while in COMFORT II cross-over could occur either at 24 weeks or 48 weeks, depending upon the achievement of primary or secondary endpoints.

There were a total of 24 deaths at the time of data cut-off in the COMFORT I trial; 10 in the ruxolitinib group and 14 in the placebo group (HR=0.67; 95% CI, 0.30 to 1.50; p=0.33).[5] At an updated survival analysis, with 4 additional months of follow-up, the total number of deaths increased to 37; 13 in the ruxolitinib group and 24 in the placebo group (HR=0.50; 95% CI, 0.25 to 0.98; p=0.04). In COMFORT II, a total of 10 deaths were recorded; six in the ruxolitinib group and four in the best available therapy group.[6] In COMFORT I, a total of 36 patients crossed over from placebo to open-label ruxolitinib treatment; of these 36 patients, 16 patients crossed over before week 24 and 20 patients after week 24.[8] In COMFORT II, 18 patients in the best-available treatment group crossed over to ruxolitinib and entered the extension phase of the trial.[9]

Major limitations and sources of bias associated with the COMFORT I and II trials were as follows:

- COMFORT I and II were not designed or powered to detect a difference in overall survival or progression-free survival between treatment groups. Hence, conclusions based on the results for these analyses should be drawn with caution.
- In COMFORT I, cross-overs could occur prior to the data-lock (i.e., 24 weeks); the permission of early cross-over confounds the interpretation of the absolute benefit of ruxolitinib therapy, particularly for survival outcomes.
- Randomization of patients in COMFORT I was not stratified by IPSS, although COMFORT II was stratified. Thus, treatment groups appeared to be better balanced regarding IPSS in COMFORT II than COMFORT I.
- It is unclear whether a change in spleen size as a surrogate endpoint is a reasonable predictor of improvement in patient survival or quality of life (see section 2.1.4). Furthermore, the manufacturer's assertion that a reduction of ≥35% in spleen volume as assessed by imaging is correlated with the IWG-MRT value of ≥50% in spleen length is based on data from a manufacturer-sponsored phase 1/2 study of ruxolitinib for myelofibrosis and has not have been replicated or validated by other investigators to date.
- In COMFORT I, only half of all ruxolitinib-treated patients who achieved a ≥35% reduction in spleen volume (SVR) also achieved a ≥50% reduction in total symptom score (TSS) and vice versa.
- A modified version of the Myelofibrosis Symptom Assessment Form (MFSAF) was used daily in COMFORT I; the MSAF has been validated at a single time point while the modified version has not been validated.[10]
- The EORTC QLQ-C30 is a common quality of life instrument that was used in both COMFORT I and II; it assesses quality of life for cancer generally, but not MF specifically. Evaluation of quality of life data for this review was limited as incomplete data were publically available for each trial.

A summary of the major efficacy and harms outcomes is provided below.

Summary of Key Efficacy and Harms Outcomes				
	COMFORT I (24 weeks)		**COMFORT II (48 weeks)**	
Outcome	RUX (n=155)	PB (n=154)	RUX (n=146)	BAT (n=73)
Efficacy				
Overall survival (number	10 (6.5%)	14 (9.1%)	6 (4.1%)	4 (5.5%)

Summary of Key Efficacy and Harms Outcomes				
	COMFORT I (24 weeks)		**COMFORT II (48 weeks)**	
of deaths, %)[5,6,11]	HR*: 0.67 (0.30-1.50)		HR*†: 0.70 (0.20-2.49)	
	P=0.33		P=0.58†	
Progression-free survival (number of events, %)[6,11]	NR		44 (30.1%)	19 (26.0%)
			HR*†: 0.81 (0.47-1.39)	
			P=0.46†	
Patients with ≥35% spleen volume reduction‡, n (%) [95% CI][5,12]	24 weeks[¶]			
	N=155	N=153	N=146	N=73
	65 (41.9%) [NR]	1 (0.7%) [NR]	46 (31.9%) [NR]	0
	P<0.0001[§]		P<0.0001[δ]	
	48 weeks			
	NA		N=144	N=72
			41 (28.1%) [NR]	0
			P<0.0001[†§]	
Quality of life (EORTC QLQ-C30), mean (SD) change from baseline	N=136	N=104	N=NR	N=NR
	12.3 (25.4)	-3.4 (21.5)	9.1 (NR)	3.4 (NR)
	P-value: NR		NR	
Harms[11]				
	RUX (n=155)	PB (n=151)	RUX (n=146)	BAT (n=73)
Serious adverse events	28%	35%	30%	29%
Adverse events, Grade 3-4	47%	44%	42%	25%
Withdrawals due to adverse events	11%	11%	8%	8%

BAT= Best Available Therapy; **CI**=confidence interval; **HR**=hazard ratio; **NA**=Not applicable; **NR**=Not reported; **PB**= placebo; **RUX**= ruxolitinib;

* Survival curves estimated using the Kaplan-Meier method; HRs calculated using Cox proportional hazards model
† Adjusted for baseline IPSS score
‡ Only patients with baseline data were included in this analysis
§ Calculated using Fisher's exact test (COMFORT I) or the exact Cochrane-Mantel-Haenszel test (COMFORT II)
[¶]Secondary outcome in COMFORT II, p.13-table-9 FDA stats rev
[δ]Fisher's Exact test

2.1.4 Comparison with Other Literature

Long-term outcomes of 107 patients with MF receiving ruxolitinib

Verstovsek et al.[13] conducted a matched historical control analysis to assess the long-term efficacy (including survival) and safety of ruxolitinib in patients with myelofibrosis who were enrolled in a phase 1/phase 2 study[14] at one of the two study sites in the U.S. (the MD Anderson Cancer Center, Houston). Patients in the open-label, non-randomized, phase 1/phase 2 study were those with myelofibrosis who were either refractory or intolerant to prior therapy; newly diagnosed patients with palpable splenomegaly (≥10 cm below the left costal margin) were also eligible. Patients were also enrolled in the phase 1/ phase 2 study with an ECOG performance status of ≤2, intermediate or high risk prognostic score, with the following hematologic and blood protein criteria: ANC >1.5x10^9/L, platelet count >100x10^9/L, bilirubin ≤2.0 mg/dL, alanine aminotransferase ≤2.5 times the upper

limit of normal, and serum creatinine ≤2.5 mg/dL.[14] Of the 153 patients enrolled in the phase 1/phase 2 study, 107 were enrolled at the single site. The historical controls (n=310) were identified from three large databases of myelofibrosis patients; patients were those who would have met enrollment criteria for the phase 1/phase 2 study. Controls were matched to the 107 patients from the phase 1/phase 2 study based on the study eligibility criteria.[13]

The ruxolitinib-treated patients were younger than the historical controls (51% were older than 65 years versus 69% in the control group; median age [range]: 66 [40–83] versus 70 [30–87] years) and had a somewhat higher mean hemoglobin (10.2 [7.2–16.9] versus 9.7 [5.3–16.9] g/dL) at baseline. White blood cell count was higher ($18.9x10^9$/L [2.5–202] versus $12.0x10^9$/L [2.6–361]), and median spleen length larger (19 [0.0–36.0] versus 6 [1.0–36.0] cm) among ruxolitinib-treated patients compared with control patients. Fifty-nine percent (63/107) of patients treated with ruxolitinib were high risk and 32% (34/107) were intermediate-2 risk. In the historical control group, 53% (163/310) of patients were high risk and 47% (145/310) were intermediate-2 risk. In the historical control group, 88% received ≥1 therapies for myelofibrosis during the follow-up period, although the types of therapies were not described.[13]

Initial doses of ruxolitinib in the phase 1/phase 2 study ranged from 10 mg twice daily (BID) to 50 mg BID and from 25 mg daily to 200 mg daily.[14] Seventy-nine of the 107 patients (74%) from MDACC began the study using BID dosing regimens (range 10 mg to 50 mg BID), while the remaining 28 patients began dosing at 50 mg daily (n=19), 100 mg daily (n=6), and 200 mg daily (n=3).

At the time of data analysis, 58 of the 107 patients (54%) were still receiving ruxolitinib therapy. Discontinuation rates at 1, 2, and 3 years were 24%, 36%, and 46%, respectively. The overall survival results are the focus of this summary.[13]

The median follow-up time for survival was 32 months and 55 months for ruxolitinib-treated patients and historical controls, respectively.[13] There were 33 deaths in the ruxolitinib group and 187 deaths in the control group, for overall survival rates of 69% and 40%, respectively (hazard ratio adjusted for IPSS risk: 0.58; 95% CI: 0.39 to 0.85). When the analysis was stratified by IPSS risk status, there were 21 deaths in the high risk ruxolitinib-treated group (N=63) and 111 deaths in the control group (N=165) (hazard ratio: 0.50; 95% CI: 0.31 to 0.81). There were 10 deaths in the intermediate-2 risk ruxolitinib-treated group (N=34) and 76 deaths in the control group (N=145). Although the hazard ratio for the intermediate-2 risk subgroup favored ruxolitinib, the result was not statistically significant (hazard ratio: 0.85; 95% CI: 0.43 to 1.71).[13]

Although this study indicates a survival advantage with ruxolitinib, there are several limitations that reduce the robustness of the results. First, although the use of an historical control group is a reasonable approach, the study is, nevertheless, observational in design. Consequently, the overall quality of evidence is lower versus a RCT, of which there are two examples with survival data: COMFORT I and COMFORT II. Secondly, there were imbalances in the baseline characteristics between the ruxolitinib group and the historical controls that could affect survival, namely older age (almost 70% older than 65 years which is an independently associated with decreased survival[15]) and somewhat lower hemoglobin level for the historical controls, versus a larger proportion of ruxolitinib-treated patients in the

high risk IPSS category, with a higher median white blood count, and a much larger median palpable spleen length (more than 3 times that for the historical controls). Thirdly, it was not described in the published article the types of therapies (if any) the historical control group received. Hence, it is unclear as to exactly what ruxolitinib was being compared with.

The results of the Vertovsek et al. study[13] are suggestive of a significant survival benefit with ruxolitinib. The results are also consistent with those of both RCTs, COMFORT I and COMFORT II, in which the hazard ratios trended (non-significantly at weeks 24 and 48, respectively) in favour of ruxolitinib versus placebo or best available therapy. Nevertheless, given the aforementioned limitations of the findings, caution should be used when drawing conclusions about the favourable results presented in the analysis.

Validity of Outcome Measure: Spleen Size

It has not been determined if a reduction in spleen volume of ≥35% (as assessed by MRI)–the primary outcome used in the clinical trials of ruxolitinib for myelofibrosis, COMFORT I[5] and COMFORT II[6]–is a valid outcome measure. In particular, it is unclear whether this endpoint is an appropriate surrogate for beneficial effect in the natural history of myelofibrosis, such as improved survival.

In a phase 1/phase 2 dose finding study by Verstovsek et al,[14] a subset of 24 patients receiving ruxolitinib 15 mg PO twice daily underwent MRI measurement of spleen and liver volume in order to objectively measure response to treatment. After 6 months of therapy, the median reduction in MRI observed spleen volume was 33% and the median reduction in palpable spleen length was 52%. Investigators concluded that a 50% reduction in palpable spleen length correlated to a 35% reduction in spleen volume on MRI.[14] This finding, therefore, provided the rationale for the using a reduction in spleen volume of ≥35% as the primary outcome for both ruxolitinib phase 3 RCTs.[5,6] However, these results have yet to replicated or validated by others.

Symptomatic splenomegaly is a common occurrence in the clinical course of myelofibrosis and a source of substantial morbidity. As such, the IWG-MRT developed consensus criteria defining treatment response in myelofibrosis.[16] The criteria describe six categories: Complete Remission (CR), Partial Remission (PR), Clinical Improvement (CI), Progressive Disease (PD), Stable Disease (SD), and Relapse.[16] Within these categories, specific changes in spleen size are identified as a variable of symptom burden. For complete response, partial response, and clinical improvement, this is defined as a minimum 50% reduction in palpable splenomegaly of a spleen that was at least 10 cm in length at baseline or a spleen that is palpable at more than 5 cm at baseline becomes non-palpable.[16] Hence, for these criteria spleen size is based on length, not volume. Moreover, reduction in splenomegaly is only one criterion used to define complete and partial response according to the IWG-MRT criteria, which incorporate hematological and bone marrow histology (for complete response only) as the other necessary criteria. A ≥50% reduction in palpable spleen length, however, may be used as a single criterion in defining clinical improvement.[16]

Splenomegaly is an important clinical consequence in myelofibrosis, yet its presence and the degree of enlargement do not appear to be a prognostic factors in terms of overall survival.[3] While reductions in spleen length or volume as endpoints may be clinically useful, they are to some extent arbitrary, and it remains to be determined if they reflect the disease-modifying activity of anti-myelofibrosis drugs.[3]

Additional FDA subgroup analyses

In a published FDA subgroup analysis,[12] it was noted that a statistically significantly higher proportion of women treated with ruxolitinib compared with men (45/76, 59% vs 20/79, 25%) achieved ≥35% reduction in spleen volume at 24 weeks in COMFORT I; the FDA reviewer noted a similar, but smaller effect of gender in COMFORT II (21/63, 33% vs 20/81, 25%) at 48 weeks favoring women.

In another subgroup analysis,[12] JAK2 V617F mutation status was examined in ruxolitinib-treated patients who achieved ≥35% reduction in spleen volume.[7] A higher proportion of JAK2 V617F positive patients achieved ≥35% reduction in spleen volume at 24 weeks compared with JAK2 V617F negative patients in COMFORT I (54/113, 48% vs 11/40, 28%); a similar treatment difference was observed in JAK2 V617F positive compared with negative patients at 48 weeks in COMFORT II (36/108, 33% vs 5/35, 14%). The FDA reviewer noted the trend but concluded that was no difference in distribution of patients with different degree of positivity for the V617F mutation.

Although only a forest plot is provided and only for COMFORT I, a statistically significantly higher proportion of ruxolitinib-treated patients started on a dose of 20 mg BID was found to achieve ≥35% reduction in spleen volume at 24 weeks compared with 15 mg BID (~54% vs ~23%).[11]

2.1.5 Summary of Supplemental Questions

There were no supplemental questions identified for this review.

2.1.6 Other Considerations

Patient Advocacy Group Input

PAG Input

Other

Ruxolitinib Withdrawal Syndrome

Tefferi et al[17] describe a type of severe drug withdrawal syndrome requiring hospitalization that occurred in five patients upon discontinuation of ruxolitinib therapy. These patients belonged to a cohort of 51 patients from a single clinical site, who had participated in the first ruxolitinib clinical (Phase I/II) study in myelofibrosis.[14] At the time of publication, ruxolitinib had been discontinued in 47 (92%) patients from this cohort; four of these patients had a diagnosis of post-polycythemia vera myelofibrosis and one had a diagnosis of primary myelofibrosis. Three of these patients were women and two were men with ages ranging from 44 to 69 years old. The withdrawal syndrome was noted even in patients who had undergone a dose-tapering schedule. Reported withdrawal symptoms included: severe anemia, respiratory distress, symptomatic splenomegaly, septic shock-like syndrome with

severe hypoxia, hypotension, fever, confusion. One patient died, but this was attributed to co-morbidities. The authors speculate a cytokine rebound at the core of this systemic inflammatory response syndrome as the mechanism for triggering this apparent ruxolitinib withdrawal syndrome. They recommend full disclosure of this potential withdrawal reaction to patients and that any drug discontinuation be carried out using a tapering schedule under close medical supervision.[17]

In a poster presented at the 2012 American Society of Clinical Oncology,[18] adverse event data were examined in a subgroup analysis of myelofibrosis patients who had had their treatment interrupted (n=103) or discontinued (n=58) while participating in the COMFORT I trial. (Table 1) While the number of patients in whom treatment was interrupted was similar between groups, a numerically higher number of days of treatment interruption was noted in the ruxolitinib compared with the placebo group (16 vs 9 days). The frequency of grade ≥3 adverse events and serious adverse events were similar, however, between groups. A numerically lower proportion of ruxolitinib-treated patients had treatment discontinued compared with placebo (13.5% vs 24.5%). The frequency of grade ≥3 adverse events and serious adverse events appeared balanced, however, between groups.

Table 1. Adverse events among patients whose treatment was interrupted or discontinued during the COMFORT I trial[18]

	RUX (n=155)	PB (n=151/154)
Treatment interruption		
n (%)	49 (31.6)	54 (35.8)
Mean duration, days	16	9
Grade ≥3 AEs, n (%)	8 (5.2)	7 (4.6)
SAEs, n (%)	3 (1.9)	3 (2.0)
SAE type	Gastrointestinal hemorrhage; Fatigue and neutropenic fever; Urosepsis	Anemia; Pulmonary edema; Hepatic encephalopathy and acute gout
Treatment discontinuation		
n (%)	21 (13.5)	37 (24.5)
Grade ≥3 AEs, n (%)	12 (7.7)	17 (11.3)
SAEs, n (%)	10 (6.5)	13 (8.6)
SAE type	NR	NR

AE= adverse event; **NR**=not reported; **PB**=placebo; **RUX**=ruxolitinib; **SAE**=serious adverse event;

2.2 Interpretation and Guidance

Burden of Myelofibrosis Disease

Myelofibrosis (MF) is a myeloproliferative disorder that is uncommon, with an annual incidence rate of 0.2 – 1.5 cases per 100 000 per year. MF can be primary or develop

secondarily to other disorders such as essential thrombocytosis (ET) or polycythemia rubra vera (PRV) or rarely other diseases such as chronic myelogenous leukemia (CML). The burden of illness of patients affected by myelofibrosis is profound, with majority of patients experiencing poor or very poor quality of life (Johansson et al., Leuk Lymphoma 53: 441-44). With the exception of CML, preventing the development of disease is generally not possible and thus therapy is based on the appropriate diagnosis.[19] Current treatments do little to improve quality of life in this disease.

Need

For most, medical intervention occurs when symptoms arise, as early intervention in the vast majority of cases has little benefit. The only curative therapy at this time is allogeneic stem cell transplant which is not available to most individuals because of age, co-morbidity or availability of donor. Only alpha-interferon therapy, if instituted very early in disease identification and in a very small subset of young patients, has the potential to change the natural history of disease. For the vast majority of patients, therapy is relegated to trying to reduce the symptoms related to splenomegaly and cytokine release. Thus available treatments are either not effective (splenectomy, cytoreductive therapy, supportive care with transfusions) or hard to apply generally to the MF patient population (ASCT). At this point in time, the ability to prevent transformation to acute leukemia, extensive or symptomatic extramedullary hematopoiesis, or to reduce problems related to pancytopenias, those that result in the deaths of these patients, with any other form of therapy including newer ones such as described here, have not been convincingly demonstrated. As current treatments palliate symptoms and have limited duration of response, there is clear clinical need for more effective treatment of MF.

Ruxolitinib is a new type of drug in the therapy of myelofibrosis that recently received Health Canada approval. It is the first in the class of Janus Kinase 2 (JAK2) inhibitors. Ruxolitinib has activity in both JAK1 and JAK2 targets and while JAK2 is involved in normal hematopoiesis and its implications in MF are not fully understood, JAK2 is believed to be an important target in MF. In a phase I/II study,[14] ruxolitinib was demonstrated to have low toxicity, with rapid symptom improvement, about 50% reduction in spleen size, normalization of thrombocytosis and leukocytosis in about 50% of patients, and either worsening or improvement in transfusion requirements in about 14% of patients. Patients who were quite cytopenic were not included. There was no demonstrated survival benefit and the allele burden of JAK2V617F, the mutation associated with MF was not changed to any significant degree. In this study, the improvements were seen in both primary and secondary MF regardless of the presence of the JAK2 mutation.

Efficacy Interpretation

Two phase 3 studies, COMFORT-I[5] and COMFORT-II[6] compared ruxolitinib to t placebo in the first line setting and best available therapy in the second line setting, respectively. These studies were the basis for funding request for the use of ruxolitinib in MF. Interestingly, where the previous phase 2 study suggested improvement in both de novo MF and MF secondary to ET/PRV and in JAK 2 positive and negative patients, the phase 3 studies showed less of a response in the JAK2 negative patients. In both trials, there was significant improvement in spleen volume, albeit with large overlapping confidence intervals, as measured by imaging in 40% of the patients. Significance was defined as a 35% reduction in spleen volume for purposes of a statistical end point. A majority of patients did achieve spleen size reductions as documented by waterfall analysis that were less than the 35% threshold and hence for purposes of analysis would be considered a "failure" and

hence the large confidence intervals. If spleen reduction of any kind was included, then there were far more patients found in the ruxolitinib arms, in keeping with the frequency found in the phase 2 studies. Both COMFORT-I and COMFORT-II included patients with IWG risk category of intermediate-2 or higher. It is unknown the degree to which patients with low-risk disease would want or benefit from ruxolitinib. However, patients in the risk category of intermediate-1 may have constitutional symptoms for which ruxolitinib is, based on expert opinion, the best available treatment option, given the limited efficacy of radiotherapy and hydroxyurea. As such, it may be reasonable, from a clinical perspective, to include at least patients with Int-1 disease who are very symptomatic (e.g. enlarged spleen etc) in the treatment population.

The use of ruxolitinib to prevent symptoms or complications of myelofibrosis has not been studied in randomised trials and the net benefit is unproven.

More notable was the improvement in quality of life as measured with standardized QoL tools in the ruxolitinib arm. This goes beyond the improvement that might be expected just by reduction in the spleen size and likely represents reduction in cytokine induced manifestation of the disease. In neither trial was there enough power to demonstrate any survival advantage, although secondary analysis attempts have been used to suggest that there is, at least in the placebo-controlled study, COMFORT I. Responses if they occurred were in the first 24 weeks, although it is suggested that 48 weeks were necessary to demonstrate response, or more correctly treatment failure.

Safety

Overall discontinuation due to adverse events (AE) in COMFORT 1 and Comfort 2 was low and not different between the experimental and control arms. AEs were common with ruxolitinib, and included diarrhea and headache. Grade 3/4 cytopenias were common with ruxolitinib but prescribers of this drug are comfortable managing patients with severe cytopenias. Treatment interruptions are associated with rapid return of symptoms of myelofibrosis, including return of splenomegaly and systemic symptoms. The concern about a withdrawal syndrome has been raised in the literature and will require education of patients and prescribers. There were few deaths in both arms of COMFORT 1 and Comfort 2.

Limitations

These studies had several issues that could not be addressed. With regards to red cell transfusions, at least one showed an initial increase and then perhaps a decrease in requirements as the study progressed. Overall however, there was no definite evidence of decrease and in fact, the closing of the gap may have been due to transfusion differences in the control arm. In terms of platelets, there was no definite reduction in platelet transfusion requirements with ruxolitinib. Patients with significant thrombocytopenia were excluded from the studies and thus the impact of ruxolitinib on thrombocytopenia both in terms of any improvement and definitely in terms of risk was not assessable.

Transformation to acute leukemia could not be evaluated in terms of whether ruxolitinib therapy improved this. Historically, more acute leukemia is seen in JAK2 negative MF patients. Also not evaluated was any observed difference in thrombotic events. Finally,

there was no observed benefit in disease burden as measured by JAK2 burden, which could be deemed a surrogate marker for overall disease burden.

Of particular concern is the recurrence of symptoms that accompanies cessation of ruxolitinib therapy. In these instances any improvement noted in spleen size or symptoms related to cytokines, seemed to recur somewhat rapidly within a week or so, and in some cases with a significant cytokine-like storm that requires monitoring and early intervention. In virtually none of the reported cases has there been any durability in response unless therapy was continued indefinitely.

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to ruxolitinib in treatment of patients with myelofibrosis. The Clinical Guidance Panel had major concerns with the definition of response used in COMFORT 1 and Comfort 2, and was not convinced of it being a satisfactory surrogate for survival and symptom control. The different response criteria used in the two arms of the studies also introduce significant bias and makes drawing firm conclusions difficult. The Clinical Guidance Panel recognized that in the absence of other available options for individuals with MF and symptoms related to either splenomegaly or cytokine expression that impact on QoL, ruxolitinib is a suitable treatment option.The Clinical Guidance Panel considered stem cell allografting as the only option for cure and only if the patient is a suitable candidate.

The CGP also concluded that from a clinical perspective

- Ruxolitinib may be used with a 24 week observation period where an absence of response within this time period should be a marker for discontinuation and movement to other forms of therapy such as palliation or experimental therapy.
- The duration of ruxolitinib therapy is indefinite at this time. Regular monitoring for the duration of therapy, spleen size, blood counts, evidence of transformation and transfusion requirements is essential. Transfusion requirements may increase at least initially for patients and as such careful monitoring for this possibility should be undertaken
- Discontinuation of therapy should be through a tapering routine if possible and will require careful monitoring because of the potential for significant rebound symptoms. Consideration of patients with thrombocytopenia for ruxolitinib therapy has not been examined carefully and should not necessarily be a contraindication to inclusion. However, extra vigilance will be required in monitoring in patients with MF and concurrent thrombocytophenia.
- Disease control for patients receiving ruxolitinib therapy has the biological plausibility to take patients from allograft ineligibility to eligibility and/or result in improvement of outcome and should be re-evaluated for ASCT as therapy progresses.
- Given the limited efficacy of radiotherapy and hydroxyurea, patients in the risk category of intermediate-1 may have constitutional symptoms for which ruxolitinib is the best available treatment option. As such it may be reasonable, from a clinical

perspective, to include patients with Int-1 disease who are very symptomatic (e.g. enlarged spleen etc) in the treatment population.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Myelofibrosis Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Myelofibrosis is a myeloproliferative neoplasm characterized by clonal hematopoiesis, proliferation of abnormal-appearing megakaryocytes within the bone marrow and reactive bone marrow fibrosis with extramedullary hematopoiesis.[20] Abnormal karyotype and an increased tendency toward acute leukemia suggest that genomic instability may play an important role in the development and progression of myelofibrosis. Myelofibrosis may arise de novo, in which case it is referred to as primary or idiopathic myelofibrosis. It may also develop in a patient with prior essential thrombocytosis or polycythemia rubra vera, in which cases the terms post-ET and post-polycythemic myelofibrosis are used.[21] Myelofibrosis is uncommon, with an annual incidence rate of 0.2 – 1.5 cases per 100 000 per year.

A diagnosis of myelofibrosis may be suspected when unexplained splenomegaly is detected on physical examination. In other cases the diagnosis is discovered upon investigation of abnormal blood counts (anemia, leucopenia or leucocytosis, thrombocytopenia or thrombocytosis). The peripheral blood film demonstrates characteristic abnormalities, including increased numbers of erythroid and granulocytic precursors (the so-called leukoerythroblastic blood picture), eosinophilia and/or basophilia, tear-drop shaped erythrocytes (dacryocytes) and increased numbers of blasts. Physical examination will usually confirm the presence of splenomegaly, which may be massive.[22]

Confirmation of diagnosis requires a combination of clinical, morphological, cytogenetic and molecular features (see Table 1). The typical bone marrow features of advanced myelofibrosis include a hypocellular bone marrow with dense reticulin and collagen fibrosis. Atypical megakaryocytes may be a prominent feature, with dense focal clustering of these cells within the background of fibrotic change. Increased vascularity of the bone marrow may be demonstrated by staining biopsy sections for von Willebrand factor. Earlier in the course fibrosis may be less pronounced (prefibrotic myelofibrosis): In these cases the bone marrow biopsy is typically described as being hypercellular and with clustered, atypical megakaryocytes.[23] Cytogenetic abnormalities are present in up to 30% of patients with primary myelofibrosis: Abnormalities such as del (20q), +8, +9 or del(13q) are commonly described in this condition. Abnormalities of chromosome 5 or 7 may appear late in the illness, and likely reflect the use of cytotoxic chemotherapy earlier in the disease course.

Abnormal cellular signaling likely underlies much of the pathogenesis of this disorder. The most commonly described molecular abnormality in primary myelofibrosis (present in approximately 50% of patients) is a gain of function mutation of JAK-2 (JAK-2 V617F). Under normal circumstances JAK-2 transduces proliferation and survival signals from growth factor and cytokine receptors on the cell surface to the nucleus. A similar gain of function mutation involving MPL (MPL W515L/K) also results in constitutive activation of the JAK-STAT pathway, with similar results.[24] Myeloproliferation affecting mainly the megakaryocytic lineage occurs, with secretion of growth factors for fibroblasts as well as other cytokines. Reactive fibrosis develops within the marrow, promoting migration of hematopoiesis to secondary sites such as liver and spleen. Abnormal cytokine secretion likely accounts for many of the systemic symptoms experienced by patients with this disorder.

Many patients with myelofibrosis are asymptomatic at the time of diagnosis, and may remain free of symptoms of for many years. Early in the course symptoms may develop as a result of abnormal blood counts, including bleeding and thrombosis related to extreme thrombocytosis or fatigue as a result of anemia. As the disease becomes more advanced, however, symptoms of massive

splenomegaly may occur, including early satiety, left upper quadrant abdominal pain and hypersplenism. Portal hypertension may occur as a result of high blood flow through a massively enlarged spleen, and pulmonary hypertension is well described in this condition. Extramedullary hematopoiesis may impair organ function if it occurs in anatomically important areas such as the retrooribital or paravertebral spaces. Systemic symptoms such as anorexia, weight loss, muscle wasting, fever, night sweats and fatigue occur commonly. Patients with advanced myelofibrosis experience extremely poor quality of life as a result of their disease. Deaths due to myelofibrosis occur as a result of bleeding, thrombosis, bone marrow failure and transformation to acute leukemia.

The clinical course of myelofibrosis is variable. Several prognostic scores for myelofibrosis exist: Prognosis is based on features such as bone marrow karyotype, blast count and blood counts. The most recently developed scoring system, the Dynamic International Prognostic Scoring System-Plus (DIPPS-Plus) (Table 2), can be applied at any time in the course of the disease.[25] These scoring systems under-represent the burden of illness on patients with myelofibrosis. A recent quality of life study by a Swedish group identified fatigue in 88% of patients with myelofibrosis. Interestingly, blood values, disease duration and use of cytoreductive therapies did not correlate with improved quality of life, and higher hemoglobin levels were associated with an increasing sense of sadness and hoplessness.[26] Quality of life in advanced MF has been reported to be similar to that of patients with metastatic carcinoma and acute myelogenous leukemia.[27]

3.2 Accepted Clinical Practice

Treatment of myelofibrosis remains unsatisfactory. Bone marrow transplantation remains the only curative treatment for this disease, but the majority of patients with myelofibrosis are never considered for transplantation due to older age, poor overall health and lack of suitable donors. Many patients who undergo stem cell transplantation for this indication experience a very difficult course due to delayed engraftment and high rates of graft-versus-host disease. Treatment-related mortality in transplantation for myelofibrosis is between 10-40% with long-term survival of less than 50%.[28-32]

The long list of therapeutic needs in myelofibrosis remains unmet. No one treatment has adequately addressed all potential therapeutic targets in this disease, and frequently treatment of one problem exacerbates another. Treatment is guided by risk stratification and the patient's individual clinical needs, which may include shortened survival, increased risk of leukemic transformation, severe cytopenias, marked hepatosplenomegaly, non-hepatosplenic extramedullary hematopoiesis, thrombohemorrhagic complications, profound constitutional symptoms and recurrent gout.[19]

Several interventions have been tested to improve symptoms of abnormal blood counts, primarily anemia. Anemia in MF is most often multifactorial, related to iron, B12 or folate deficiency, hypersplenism, ineffective erythropoiesis, and hemolysis (immune or due to small paroxysmal nocturnal hemoglobinuria clones). Hematinic therapy may result in improvements of hemoglobin, particularly in patients with post-polycythemic myelofibrosis who are iron deficient due to previous phlebotomies.[33] Administration of corticosteroids may improve red blood cell survival and decrease transfusion requirements in patients with anemia related to hemolysis. Androgens have been given to patients with myelofibrosis and responses, defined as a decrease or elimination of transfusion requirements, are reported in 37-50% of patients.[34-36] Corticosteroids and androgens may be associated with significant side effects, which often limits the duration of therapy with these agents. Erythropoiesis-stimulating agents may decrease transfusion requirements in myelofibrosis and seem to be more effective in patients with low endogenous levels of erythropoietin.[37] Evidence in favor of thalidomide and lenalidomide is accumulating in myelofibrosis, although reported series contain small numbers of patients and response rates of ~ 40% are described.[38] A multi-center trial concluded that lenalidomide and low-dose prednisone were only modestly effective but

myelosuppressive in MF.[39] Later generation immunomodulatory drugs such as pomalidomide do not appear to be more effective.[40]

Management of massive splenomegaly is challenging in MF. Hydroxyurea has been used frequently to control symptoms of splenomegaly, although evidence supporting its use is lacking. Symptomatic splenomegaly improves in 45% of patients treated with hydroxyurea.[41] Low-dose thalidomide and prednisone may be effective in controlling massive splenomegaly, although responses are infrequent and in most cases transient.[42] Cladribine may be used to decrease massive splenomegaly and to control extramedullary hematopoiesis, although treatment is associated with significant cytopenias.[43] The option of splenectomy should be considered carefully in patients with MF. Even in carefully-selected patients treated in experienced centers splenectomy is associated with high rates of post-operative morbidity and mortality. Patients' clinical status should be optimized in advance of surgery, with careful attention paid to coagulation abnormalities, correction of abnormal platelet counts and assessment of cardiopulmonary, renal and hepatic reserve.[44-46] Given the significant delay in neutrophil and platelet engraftment seen in patients with massive splenomegaly undergoing stem cell transplantation, splenectomy is frequently considered for these patients. Randomized trials of splenectomy have not been carried out in this context, and the practice is not universally endorsed.[22,47] Patients who are not candidates for surgery may elect to undergo splenic radiotherapy, although responses are usually transient.[48]

Blast phase myelofibrosis (MF-BP) occurs in 5-30% of cases and carries an especially poor prognosis. The diagnosis of MF-BP can be confirmed if the bone marrow blast count exceeds 20% or if peripheral blood blasts exceed 20% of the total white blood cell count for more than 8 weeks. Treatment of MF-BP with induction chemotherapy for acute myelogenous leukemia may result in achievement of a new chronic phase of MF, although such remissions are typically short-lived. Frequent complications, such as prolonged cytopenias, infection and organ dysfunction, occur and remissions are less frequent than in de novo AML. Rapid transition of patients who achieve a stable second chronic phase to stem cell transplantation may be curative, although high relapse rates and TRM limit this possibility to highly selected patients. Palliative management of patients with MF-BP may include use of azacytidine, which can produce stabilization of disease for several months, with limited toxicity.[49]

3.3 Evidence-Based Considerations for a Funding Population

The following information in Table 1 and Table 2 pertain to diagnostic criteria and prognostic risk factors for Myelofibrosis, respectively.

Table 1. World Health Organization diagnostic criteria for primary myelofibrosis. Diagnosis requires all three major and two minor criteria.[20]

Major Criteria
1. Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis **or** In the absence of significant fibrosis the megakaryocyte changes must be accompanied by an increase in bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis. 2. Not meeting WHO criteria for polycythemia vera, BCR-ABL1 + chronic myelogenous leukemia, myelodysplastic syndrome or other myeloid neoplasm. 3. Demonstration of JAK2 V617F or other clonal marker (e.g. MPL W515K/L) **or**, in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy or toxic myelopathies.

Minor Criteria
1. Leukoerythroblastosis 2. Increase in serum lactate dehydrogenase level 3. Anemia 4. Splenomegaly

Table 2. The Dynamic International Prognostic Scoring System-Plus (DIPPS-Plus).

Risk Factors		
Age > 65 Hemoglobin < 100 Constitutional Symptoms Leukocytes > 25/nl RBC Transfusion Requirement Platelets < 100/nl Unfavourable karyotype (complex or -5/5q-, -7, 7q-, +8, abnormal 11q23, inv(3), 12p-, i(17q)) Circulating blasts > 1%		
Prognostic Group	Number of Risk Factors	Median OS (years)
Low	0	15.4
Intermediate-1	1	6.5
Intermediate-2	2-3	2.9
High	>3	1.3

3.4 Other Patient Populations in Whom the Drug May Be Used

Ruxolitinib is being actively studied for the treatment of polycythemia vera and essential thrombocythemia (http://ClinicalTrials.gov).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on ruxolitinib for myelofibrosis; their input is summarized below:

- The Chronic Myelogenous Leukemia (CML) Society of Canada
- Canadian Myeloproliferative Neoplasms (MPN) Network

The CML Society of Canada conducted an online survey and one-on-one telephone interviews to gather information about patient experiences with myelofibrosis. Internet chat groups for patients with MPN were identified and patients were recruited with the help of the chat group moderators. The number of respondents and people interviewed was not provided.

The Canadian MPN Network conducted interviews with two patients who had direct experience with ruxolitinib. Based on the information provided by these patients, an online survey was developed. The survey was sent through the Canadian MPN Network, to other support groups (located throughout Canada and the United States) and to physicians treating patients with MPN. There were a total of 8 respondents (6 with direct experience with ruxolitinib) and 3 family caregivers (none with direct experience with ruxolitinib).

From a patient perspective, increasing quality of life and reducing adverse effects are important aspects when consideration is given to treatment. Currently available treatment options in Canada for myelofibrosis are limited, providing little to no improvement in quality of life. Given that the symptoms of the disease are crippling to a patient's ability to carry out activities of daily living, more treatment options that help alleviate symptoms are welcomed by patients. Patients indicated that they are willing to try new treatments associated with side effects if there is the potential to prolong time spent with loved ones and to increase quality of life.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Myelofibrosis

Patients with myelofibrosis experience a number of symptoms that significantly interfere with daily activities. Symptoms usually include: night sweats, fatigue, shortness of breath, pain, enlarged spleen resulting in abdominal swelling, loss of appetite, weight loss, rash/itching and fever. These typically translate to a substantial reduction in patient autonomy and quality of life.

The disease affects not only the patient, but their families and household as well. Patients rely more on their spouse and/or other family members for support which can create significant stress on the whole family and lead to household instability and financial hardships.

The Canadian MPN Network noted that 40% of survey respondents agreed that they were "very much" affected by night sweats and that 20% felt that they were "much" affected. Moreover, 80% indicated that they were "much" affected by fatigue, itching and inability to carry out daily activities. Lastly, 40% of respondents noted that their work performance and/or social and family life was "much" affected by the condition.

Patients ultimately experience a sense of hopelessness and feel a loss of self-worth as they are increasingly unable to carry out day-to-day activities and lead the lives they once did.

4.1.2 Patients' Experiences with Current Therapy for Myelofirbrosis

Current therapies for myelofibrosis include splenectomy, blood transfusion, bone marrow transplant, chemotherapy and other medication therapy to increase red blood cell production.

Patient input highlighted that the currently available therapies provide time-limited relief (some patients note improvement in symptoms from weeks to years until disease progression and/or symptom worsening) or that therapies are inconsistent at maintaining relief (one patient noted that some days the medication appears to make no difference at all). Patients note that currently available therapies prolong life at best, however, provide very little or no increase in quality of life. Moreover, patients expressed concerns of secondary infections, risk of death, and other complications that may arise from invasive interventions such as splenectomy or transplants.

Patients also note concerns with some of the currently available medications and their side effects. Patients cite that nausea, fatigue, diarrhea, abnormal liver function tests ,and abnormal blood cell counts are side effects of currently available treatment options that are the most concerning. Moreover, patient input highlighted that the more difficult side effects to tolerate include: extreme fatigue, pneumonia, heart murmurs, anxiety, high persistent fever, and a persistent itchy rash. Despite these concerns, patients indicated that they are willing to explore other potential treatment options associated with side effects provided that they understand the potential benefits with respect to their quality of life.

Although patients generally note that the currently available therapies are readily accessible and in some cases, paid for by provincial reimbursement programs, there is consensus that the treatment options are not well suited for all patients and thus access to more treatment options is a priority.

Patients also indicated that an area of unmet need is a "cure" for myelofibrosis. A reference is made to Gleevec (imatinib) and its ability to induce remission in patients suffering from CML. Patient input noted that they are aware of patients who are in remission and living medication free, in the setting of CML, and suggest that this is may be a possibility with ruxolitinib.

4.1.3 Impact of Myelofibrosis and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of myelofibrosis on caregivers and families is significant. Caregivers report that there is a detrimental effect on their quality of life as they are required to increase their provision of care as the patient's clinical condition declines. Moreover, family life and marriages suffer as a result of strain put on relationships. The cost of therapy and the inability to earn income compound financial strain and result in stress for patients and their families. One patient noted that their caregiver abandoned them upon the diagnosis of myelofibrosis and that the lack of understanding of the condition in the general public results in increased strain on personal relationships. Patient input noted that treatments that can increase patient autonomy could help alleviate the strain imposed on families and caregivers alike.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Ruxolitinib

Input from patients without direct experience with ruxolitinib highlighted that there are few effective treatment options available in Canada for myelofibrosis and that many offer little to no improvement in quality of life. Although patients recognize that ruxolitinib does not represent a cure for myelofibrosis, they would welcome it as an effective long term therapeutic option to assist in alleviating symptoms and improving quality of life. Some patients indicated that if presented with the option to undergo therapy with ruxolitinib or attempt a bone marrow transplant, they would opt for ruxolitinib instead as they recognize the great risks involved in a transplant.

Patients expect that their lives will be improved by ruxolitinib through the reduction of debilitating symptoms. Although patients recognize that they will likely continue to receive blood transfusions, they indicated that they will feel less fatigue in between each transfusion.

Patient advocacy group input highlighted that many of the respondents surveyed feel that they will benefit from ruxolitinib and that the potential benefits from the drug outweigh the risks given that there is an opportunity to improve quality of life and allow patients to regain the ability to conduct activities of daily living. This could also translate to fewer physician and hospital visits and a reduction in time spent away from family and work.

Patients with direct experience with ruxolitinib indicated that they experienced a significant improvement in quality of life that allowed them to continue to work and spend time with their families. Moreover, patients indicated that ruxolitinib was more effective than any other therapy they had previously undergone and that overall, it was very well tolerated. Patients also indicated the oral dosage route facilitated ease of administration and was very favourable.

One patient advocacy group noted that 5 of 6 respondents who had experience with ruxolitinib had an overwhelmingly positive experience with the medication. Some patients reported experiencing a reduction in spleen size, pain and fatigue. Several patients described their ability to return to work and engage in physical activity with loved ones after weeks of therapy. The 5 patients with positive symptom management also reported no serious adverse effects although they acknowledge that there is a risk. It was noted that 1 patient did not respond well to ruxolitinib and experienced no benefit with dose increases.

The other patient advocacy group indicated that 1 patient with experience with ruxolitinib described adverse effects associated with the medication. This included: return of night sweats after a month of therapy, low red cell count, low platelet count, diarrhea, nausea, fatigue, edema, pneumonia, heart murmur, headaches, shortness of breath, itchy rash, fever, and anxiety. Additionally, it was reported that 2 patients experienced significant increases in energy and 1 patient had a reduction in spleen size.

The concern with cost is also noted as some patients currently receive ruxolitinib via a clinical trial and are unsure of how to finance the medication after the trials are completed. The patient advocacy group noted that the cost of therapy is an enormous burden that places families in financial jeopardy.

4.3 Additional Information

One of the patient advocacy groups noted that during the course of their research, they discovered that patients possessed a high level of understanding about the disease and available treatments. The advocacy group noted that many patients cope with their disease through involvement and by allowing patients to get involved in the drug review process, it allows for a stronger partnership between clinician and patient. The advocacy group hopes that in the future, the pCODR process will allow patients to provide input into the pharmacoeconomic model in order to ensure that it captures the elements that matter most to families and households.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for ruxolitinib (Jakavi) for myelofibrosis. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the ruxolitinib (Jakavi) review was obtained from six of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, ruxolitinib was noted to be the first novel product specifically approved for the treatment of myelofibrosis, which was considered an enabler for implementing a funding decision for this particular agent. PAG also identified that there would likely be a small population of patients accessing ruxolitinib for this indication, as myelofibrosis is considered an uncommon blood cancer. As ruxolitinib is orally administered, PAG identified that it would likely be a more convenient treatment option for patients, and would also be beneficial to patients who live in rural or remote areas, as it may be easier for these patients to access the medication. PAG also noted that there could be situations where the dosage of ruxolitinib would have to be adjusted, either up or down, which may require additional monitoring. In addition, PAG noted that ruxolitinib may add additional workload on chemotherapy clinics, as many myelofbrosis patients are not typically seen in these types of clinics presently.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG recognized that there are very few specific agents available for the treatment of myelofibrosis and symptomatic management remains the main treatment strategy. Ruxolitinib would be the first novel product specifically approved for the treatment of myelofibrosis, which would be an enabler for implementing a funding recommendation for ruxolitinib.

PAG recognized that a stem cell transplant would be a potential comparator that may offer a cure, but many patients with myelofibrosis would not be considered appropriate candidates to receive this particular treatment.

5.2 Factors Related to Patient Population

PAG noted that there would likely be a small patient population accessing ruxolitinib for this indication, as myelofibrosis is considered an uncommon blood cancer.

5.3 Factors Related to Accessibility

PAG noted that ruxolitinib is an oral medication, and in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in

those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

It is anticipated that there will be five different strengths of ruxolitinib available on the market (5mg, 10mg, 15mg, 20mg, and 25mg) which may indicate that dosages would have to be adjusted and that there is a potential that a patient will have many different strengths of the same medication in their home, increasing the risk for medication mix-ups and increased costs.

5.4 Factors Related to Dosing

As ruxolitinib is an orally administered medication, PAG identified that this would likely be a more convenient option for patients, which would be an enabler for ruxolitinib therapy. In addition, an oral treatment option may be beneficial to patients who live in rural or remote areas, as it may be easier for these patients to access the medication.

PAG also identified that there may be several situations where the dose of ruxolitinib would have to be adjusted, indicating that there may be some variability in dosing that would require extra attention and monitoring. It was noted that the dose of ruxolitinib may be increased based on the patients response, up to a maximum of 25mg twice daily and in one drug information reference, it suggests that the ruxolitinib dose can be as high as 25mg BID for six months in patients not experiencing a response, before the therapy is deemed to be ineffective. Furthermore, PAG noted that it is recommended that ruxolitinib be gradually tapered when it is discontinued, which would be a novel concept in the chemotherapy setting that many practitioners would not be accustomed to doing. In addition, PAG noted that patients who receive ruxolitinib in combination with CYP3A4 inhibitors would require closer monitoring due to the potential for drug interactions.

5.5 Factors Related to Implementation Costs

PAG noted that monitoring ruxolitinib for dose adjustments, adverse effects and drug interactions would add additional workload on chemotherapy clinics, as many myelofbrosis patients are not typically seen in these types of clinics presently.

5.6 Other Factors

PAG noted that chemotherapy clinics do not typically see many myelofibrosis patients because there are currently no approved cancer drugs for these patients.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of ruxolitinib on patient outcomes compared with standard therapies, placebo, or best supportive care in the treatment of patients with splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Adult patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis *Subgroups:* IPSS prognostic category	Ruxolitinib in monotherapy at the recommended dose	Placebo Best supportive care Hydroxyurea	• Overall survival • Progression-free survival • **Quality of life** • **Total symptom score** (from MFSAF) • Response rate (IWG-MRT response criteria for CR+PR) • Spleen size • AML/leukemia transformation • Thrombosis Harms • **SAEs** • **AEs** (e.g., thrombocytopenia, anemia, etc.) • WDAEs

AE=adverse event; **AML**=acute myeloid leukemia; **CR**=complete remission; **IPSS**=International Prognostic Scoring System; **IWG-MRT**= International Working Group-Myelofibrosis Research and Treatment; **MSAF**=Myelofibrosis Symptom Assessment Form**; PR**=partial remission; **RCT**=randomized controlled trial; **SAE**=serious adverse event; **WDAE**=withdrawal due to adverse event

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 9) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was ruxolitinib (Jakavi).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or language.

The search is considered up to date as of October 3, 2012.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

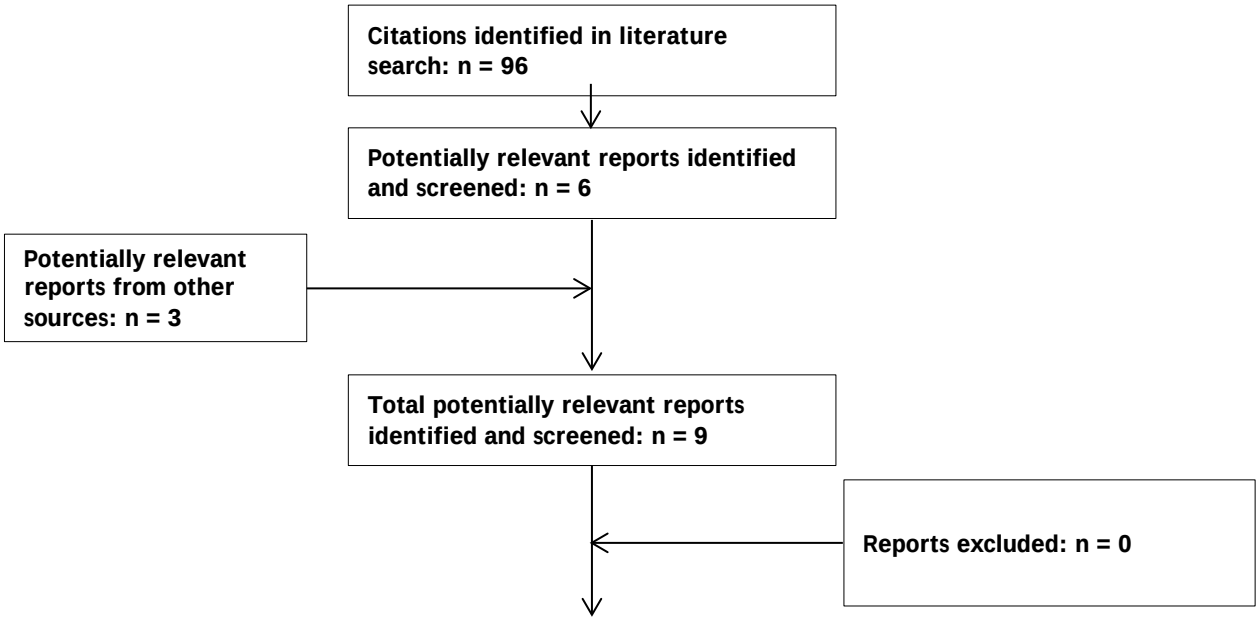
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 96 potentially relevant reports identified, 9 reports were included in the pCODR systematic review[5,6,11,12,50-54] and no studies were excluded.

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



9 reports presenting data from 2 studies

COMFORT I:
Verstovsek et al.[5]

Verstovsek et al.[50] (abstract)
Verstovsek et al.[51] (abstract)

COMFORT II :
Harrison et al.[6]

Harrison et al.[52] (abstract)
Harrison et al.[53] (abstract)

Additional reports:
pCODR submission[54]
FDA reports[11,12]

6.3.2 Summary of Included Studies

Two randomized controlled trials were included in this systematic review (Table 1); one of which was a double-blind, placebo-controlled trial (COMFORT I)[5] and the other an open-label, active-comparator trial (COMFORT II).[6] Both were multicentre-multinational, manufacturer-funded trials. In the event data were not available from these primary studies, the FDA report was used as a secondary data source.[11,12]

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial Characteristics of COMFORT I Study[5,8,11]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
COMFORT I 89 centers in 3 countries (Canada, US, Australia) September 2009 to April 2010* DB, PC, RCT (1:1) n= 309 (ITT) n=306 (Safety analysis) Funded by Novartis	• Patients ≥ 18 years old with PMF, PPVMF, or PETMF, in need of treatment, who were resistant, refractory, intolerant of, or not candidates for available therapy • Life expectancy ≥ 6 months • ECOG PS ≤3 • Spleen length ≥ 5 cm below left costal margin • IWG risk category of intermediate-2 or high risk • Peripheral blood blast count < 10% • CD34+ cell count > 20 $x10^6$/L • Platelet count ≥ 100 $x10^9$/L **Exclusion criteria:** • ANC ≤ $1x10^9$/L • Platelet count < $100x10^9$/L • Direct bilirubin ≥ 2xULN • ALT ≥2.5xULN • Creatinine >2.0mg/dL • History of malignancy within previous 5 years (except for cured basal cell or squamous cell skin cancer) • Splenic irradiation within 12 months prior to randomization • Any prior therapy with JAK inhibitors • Concomitant investigational or myelofibrosis treatments	Ruxolitinib 15 or 20 mg orally twice daily vs. matching placebo *Note:* Treatment interruption or dose adjustment** were permitted in case of adverse events	Primary • Proportion of patients with ≥ 35% in SVR from baseline to week 24 Secondary • Proportion of patients with ≥ 50% reduction in TSS after 24 weeks of treatment • Duration of spleen volume reduction • Proportion of patients with a reduction in total symptom score on modified MFSAF of ≥ 50% from baseline to week 24 • Change in total symptom score on modified MSAF of ≥ 50% from baseline to week 24 • Overall survival

ALT=alanine aminotransferase; **ANC**= absolute neutrophil count; **CR**= complete response; **DB**= double-blind; **ECOG PS**= Eastern Cooperative Oncology Group performance scale; **Hgb**=hemoglobin; **ITT**=intention-to-treat; **IWG**=International Working Group; **MFSAF**= Myelofibrosis Symptom Assessment form; **PC**= placebo controlled; **PETMF**= post-essential thrombocythemia myelofibrosis; **PMF**=primary myelofibrosis; **PPVMF**= post-polycythemia vera myelofibrosis; **PR**= partial response; **RCT**= randomized controlled trial; **SCT**=stem cell transplant; **SVR**= spleen volume reduction; **TSS**= total symptom score; **ULN**=upper limit of normal

* Patient enrollment period
** The dose could be reduced or interrupted depending on platelet count or ANC.

Table 3. Summary of Trial Characteristics of COMFORT II Study[6,9,11]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
COMFORT II 56 centers in 9 European countries July 1, 2009 to January 22, 2010* OL, AC, randomized trial (2:1) stratified by IWG risk category (high vs intermediate-2), n= 219 (ITT), n= 219 (Safety analysis) Funded by Novartis	• Patients ≥ 18 years old with PMF, PPVMF, or PETMF, in need of treatment but ineligible for SCT • Life expectancy ≥6 months • ECOG PS ≤3 • Spleen length ≥ 5 cm below left costal margin • IWG risk category of intermediate-2 or high risk • Peripheral blood blast count <10% • ANC ≥1 x10^9/L • Platelet count ≥100 x10^9/L • No prior treatment with a JAK inhibitor **Exclusion criteria:** • Any history of platelet counts <50 x10^9/L • Any history of ANC <0.5 x10^9/L • History of malignancy in last 5 years excluding early-stage squamous or basal cell skin cancer • Pregnancy or women of child-bearing age unwilling to take measures to prevent pregnancy • Inadequate liver or renal function (i.e., direct bilirubin > 2.0xULN, ALT >2.5xULN, serum creatinine >2.0 mg/dL) • Splenic irradiation within 12 months prior to screening	Ruxolitinib 15 or 20 mg orally twice daily vs. Best Available Therapy *Note:* Treatment interruption or dose adjustment** were permitted in case of adverse events	Primary • Proportion of patients with ≥ 35% in SVR from baseline to week 48 Secondary • Proportion of patients with ≥ 35% in SVR from baseline to week 24 • Durability of ≥ 35% in SVR • Time to ≥ 35% in SVR • Progression-free survival • Leukemia-free survival • Overall survival • Transfusion dependency • Change in bone marrow histo-morphology

AC=active comparator; **ALT**= alanine amino transferase; **ANC**= absolute neutrophil count; **CR**= complete response; **DB**= double-blind; **ECOG PS**= Eastern Cooperative Oncology Group performance scale; **ITT**=intention-to-treat; **IWG**=International Working Group; **OL**= open-label; **PC**= placebo controlled; **PETMF**= post-essential thrombocythemia myelofibrosis; **PMF**=primary myelofibrosis; **PPVMF**= post-polycythemia vera myelofibrosis; **PR**= partial response; **RCT**= randomized controlled trial; **SCT**=stem cell transplant; **SVR**= spleen volume reduction; **TSS**= total symptom score; **ULN**=upper limit of normal

*Randomization period

** The dose could be reduced or interrupted depending on platelet count or ANC.

6.3.2.1 Detailed Trial Characteristics

a) Trials

COMFORT I[5] randomized 309 patients from 89 sites in Canada, the United States, and Australia (1:1) to ruxolitinib (n=155) or placebo (n=154). COMFORT II[6] randomized 219 patients from 56 sites in nine European countries (2:1, stratified according to IPSS score at baseline) to ruxolitinib (n=146) or active comparator (best available therapy; n=73).[11]

Eligibility criteria were similar between trials. Both enrolled adults ≥18 years old with myelofibrosis of either primary, post-polycythemia vera, or post-essential thrombocythemia subtype, who were in need of treatment. COMFORT I included patients who were either refractory or intolerant to prior therapy, while COMFORT II inlcued patients who were still eligible for some available treatments but unsuitable for ASCT. Additionally, patients in either trial needed to have a life expectancy of at least 6 months, a palpable spleen length of at least 5 cm below the left costal margin, an ECOG PS between 0 to 3, an IPSS risk category of intermediate-2 or high, and a platelet count ≥100 x10^9/L. Patients were excluded from the trials if they had renal or liver impairment, splenic irradiation in the past 12 months, or a past history of cancer (other than cured or early-stage squamous or basal cell skin cancer).

The primary outcome of COMFORT I was the proportion of patients with ≥35% reduction in spleen volume by MRI at week 24. The major secondary outcome was the proportion of patients with a ≥50% reduction in total symptom score based on the modified Myelofibrosis Symptom Assessment Form (MSAF) at week 24. In COMFORT II, the proportion of patients with ≥35% reduction in spleen volume by MRI was examined as the primary outcome at week 48 and as the major secondary outcome at week 24.

COMFORT I was designed to have 97% power to detect a between-group treatment difference on the outcome of spleen volume decrease based on a response rate of at least 30% in the treatment group and no more than 10% in the placebo group from baseline to week 24. For COMFORT II, it was assumed that at least 35% of patients on ruxolitinib and no more than 10% in the control (best available therapy) group would achieve a 35% reduction from baseline to week 48 with at least 90% power to detect this difference. Both trials used a two-sided alpha level of 0.05.

b) Populations

In COMFORT I, slightly more females were randomized to the ruxolitinib group (49.0%) compared with the placebo group (42.2%), while the proportions were well balanced in the COMFORT II trial (Table 4).

A majority of patients aged > 65 years were enrolled in the trials, with a higher proportion in COMFORT I (60.5%) compared with COMFORT II (52.1%). Within the trials, COMFORT I had a greater proportion of patients > 65 years in the placebo group and a greater proportion < 65 years in the ruxolitinib group; in COMFORT II, the proportions appeared well balanced between groups.

Participants in both trials were predominantly white (~90%) with about half of myelofibrosis cases being 'primary' in etiology; about two-thirds of patients had previously been treated with hydroxyurea. Myelofibrosis subtypes were well balanced between groups in COMFORT II, but there was a larger proportion of patients with primary myelofibrosis in the placebo group (54.5%) versus the ruxolitinib group (45.2%) in COMFORT I. Most patients (~60%) in both trials were categorized as high risk by IPSS; the distribution of risk was well balanced between groups in COMFORT II, while in COMFORT I there appeared to be a slightly higher number of high-risk patients in the placebo group and a slightly higher number of intermediate-2 risk patients in the ruxolitinib group. The majority of patients in either trial had an ECOG PS of 0 or 1, accounting for 82% of patients in COMFORT I and 91% in COMFORT II. JAK2 V617F mutation was present in a majority of patients

in both trials, having been identified in 76% of patients in COMFORT I and 71% of patients in COMFORT II.

It should be noted that a request had been made by the Methods Team to the manufacturer to obtain baseline hematologic data that were unavailable through the published literature. At present, these missing data remain outstanding and are denoted in Table 4 as 'not reported' (NR).

Table 4. Baseline Characteristics of Patients in COMFORT I, II trials

Variable	COMFORT I[5,12]		COMFORT II[6,12]	
	RUX (n=155)	PB (n=154)	RUX (n=146)	BAT (n=73)
Age (yr)[5,8]				
Median (range)	66 (43-91)	70 (40-86)	67 (35-83)	66 (35-85)
≤ 65 yr, n (%)	70 (45.2%)	52 (33.8%)	69 (47.2%)	36 (49.3%)
> 65 yr, n (%)	85 (54.8%)	102 (66.2%)	77 (52.8%)	37 (50.7%)
Sex (%)[12]				
Male	79 (51.0%)	88 (57.1%)	83 (56.8%)	42 (57.5%)
Female	76 (49.0%)	65 (42.2%)	63 (43.2%)	31 (42.5%)
Unknown	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)
Race, n(%)[12]				
White	138 (89.0%)	139 (90.3%)	118 (80.8%)	67 (91.8%)
Black or African American	6 (3.9%)	7 (4.5%)	0	0
Asian	5 (3.2%)	4 (2.6%)	0	0
Other	6 (3.8%)	4 (2.6%)	0	1 (1.4%)
Myelofibrosis subtype (%)[7]				
PMF	70 (45.2%)	84 (54.5%)	77 (52.7%)	39 (53.4%)
PPVMF	50 (32.3%)	47 (30.5%)	48 (32.9%)	20 (27.4%)
PETMF	35 (22.6%)	22 (14.3%)	21 (14.4%)	14 (19.2%)
Unknown	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)
IPSS risk status (% of patients)[12]				
High	90 (58.1%)	99 (64.3%)	60%	59%
Intermediate-2	64 (41.3%)	54 (35.1%)	40%	40%
Unknown	1 (0.6%)	1 (0.6%)	0%	1%
ECOG PS (%)[12]				
0	47 (31.1%)	38 (25.5%)	40%	36%
1	87 (57.6%)	82 (55.0%)	53%	51%
2	14 (9.3%)	25 (16.8%)	7%	12%
3	3 (2.0%)	4 (2.7%)	1%	1%
Unknown	4 (2.6%)	5 (3.3%)	—	—
Palpable spleen length below costal margin (cm)				
Median (range)	16 (0-33)[a]	16 (5-34)	14 (5-30)	15 (5-37)
Spleen volume (cm^3)				
Median (range)	2598 (478-7462)	2566 (521-8881)	2408 (451-7766)	2318 (728-7701)
Previous myelofibrosis therapy (%)				
Hydroxyurea	104 (67.1%)	87 (56.5%)	110 (75.3%)	50 (68.5%)
Splenic radiotherapy	1 (0.6%)	NR	0 (0%)	4 (5.5%)
Presence of	NR	NR	69%	63%

constitutional symptoms				
Platelet count ($x10^9$/L)				
Median (range)	262 (81-984)	238 (100-887)	244	228
Hemoglobin (g/L)				
Median (range)	105 (66-170)	105 (35-173)	NR	NR
Hemoglobin < 100 g/L	NR	NR	45%	52%
Neutrophil count ($x10^9$/L)				
Median (range)	NR	NR	11.3	9.4
History of leukocyte count > $25x10^9$/L	NR	NR	38%	36%
Circulating blasts ≥1%	NR	NR	76%	74%
JAK2 V617F mutation status at screening (%)[12]				
Positive	113 (72.9%)	123 (79.9%)	108 (74.0%)	48 (65.8%)
Negative	40 (25.8%)	27 (17.5%)	36 (24.7%)	24 (32.9%)
Unknown	1 (0.6%)	4 (2.6%)	2 (1.4%)	1 (1.4%)

BAT= Best Available Therapy; **ECOG PS**= Eastern Cooperative Oncology Group performance scale; **IPSS**= International Prognostic Scoring System; **NR**= Not reported; **PB**= Placebo; **PETMF**= post-essential thrombocythemia myelofibrosis; **PMF**=primary myelofibrosis; **PPVMF**= post-polycythemia vera myelofibrosis; **RUX**= Ruxolitinib;

[a]One patient had a baseline spleen length recorded as nonpalpable in error but had a prior measurement of 16 cm and a baseline spleen volume of 2450 cm^3.

c) Interventions

In COMFORT I,[5] ruxolitinib 15 or 20 mg po BID was compared with matching placebo; no concomitant supportive therapies for myelofibrosis were permitted.[8] COMFORT II[6] compared ruxolitinib 15 or 20 mg po BID with best available therapy. In the case of best available therapy,[6] the investigator was permitted to use any commercially-available treatments at his/her discretion for monotherapy or combination therapy, or could elect no therapy at all; adjustments to the regimen were permitted throughout the treatment phase of the trial.

For each trial, the starting dose of ruxolitinib was dependent on the baseline platelet count, such that patients with a platelet count above 200 $x10^9$/L were begun on a regimen of 20 mg po BID, while patients with a platelet count between 100 $x10^9$/L and 200 $x10^9$/L were started on 15 mg po BID.

A dosing nomogram was followed for reducing the dose of ruxolitinib in the event of falling platelet counts.[8] Likewise, a dosing algorithm was developed for restarting or escalating the dose of ruxolitinib following dose reduction or interruption.[8] In the case of inadequate efficacy after 4 weeks of treatment, the dose could be increased by 5 mg, depending on the platelet count and absolute neutrophil level.[8]

Cross-over was permitted in COMFORT I,[8] where placebo-assigned patients who experienced a symptomatic increase in spleen volume of ≥25 % from baseline were eligible for early unblinding and cross-over to ruxolitinib. In COMFORT II,[6] patients were permitted to cross over after week 24 once superiority of ruxolitinib had been demonstrated on the primary (week 48) or key secondary outcomes (week 24)[55] and if protocol-specified progression criteria were met (i.e., splenectomy or increased

spleen volume of ≥25 % from nadir or baseline); however, if patients experienced leukemic transformation or underwent splenic irradiation, they were withdrawn from the study.[6]

Starting doses were similar in ruxolitinib arms between COMFORT I and II studies (Table 5).[11] Overall, about 36% of patients were initiated on the 15 mg dose. Dose adjustments occurred more often in the ruxolitinib groups (51% and 64%) compared with the placebo (26%) or best available therapy (15%) groups in COMFORT I and II, respectively, as a result of thrombocytopenia of all grades.[11] In COMFORT II, ruxolitinib was dosed at a median intensity of 30mg/day (range: 10-49 mg/day) over the 48-week study period.[6] No published data on median dose intensity was available for COMFORT I.

Table 5. Exposure to RUX by Starting Dose Category in COMFORT I, II trials[11]

	COMFORT I (RUX arm)		COMFORT II (RUX arm)	
Dose (BID)*	Patients (n=155)	Patient-months	Patients (n=146)	Patient- months
15 mg	54 (34.8%)	423.6	55 (37.7%)	578.1
20 mg	101 (65.2%)	856.0	91 (62.3%)	1007.0

BID= twice daily; **RUX**= ruxolitinib

*Starting dose based on baseline platelet count: 20 mg if >200 x10^9/L; 15 mg if between 100 x x10^9/L to 200 x10^9/L.

d) Patient Disposition

In COMFORT II, the same numbers of patients made up both the efficacy and safety analysis sets while in COMFORT I, the safety analysis set comprised three fewer patients in the placebo group. (Table 6)

A smaller proportion of patients discontinued ruxolitinib in COMFORT I and COMFORT II, respectively compared with control (13.5% vs 48.3% and 37.7% vs 57.5%).[12]

There were a total of 24 deaths at the time of data cut-off in the COMFORT I trial; 10 in the ruxolitinib group and 14 in the placebo group (HR=0.67; 95% CI, 0.30 to 1.50; p=0.33).[5] At an updated survival analysis, with 4 additional months of follow-up, the total number of deaths increased to 37; 13 in the ruxolitinib group and 24 in the placebo group (HR=0.50; 95% CI, 0.25 to 0.98; p=0.04). In COMFORT II, a total of 10 deaths were recorded; six in the ruxolitinib group and four in the best available therapy group.[6]

In COMFORT I, a total of 36 patients crossed over from placebo to open-label ruxolitinib treatment; of these 36 patients, 16 patients crossed over before week 24 and 20 patients after week 24.[8] In COMFORT II, 18 patients in the best-available treatment group crossed over to ruxolitinib and entered the extension phase of the trial.[9]

Table 6. Patient Disposition in COMFORT I, II trials[5, 6,11]				
	COMFORT I[5,11]		COMFORT II[6, 11]	
	RUX	PB	RUX	BAT
Efficacy analysis set (ITT)[12]	155 (100%)	154 (100%)	146 (100%)	73 (100%)
Safety analysis set[12]	155 (100%)	151 (98.1%)	146 (100%)	73 (100%)
Continue on treatment	134 (86.5%)	78 (51.7%)	91 (62.3%)	31 (42.5%)
Discontinued treatment	21 (13.5%)	73 (48.3%)	55 (37.7%)	42 (57.5%)
Reasons for withdrawal				
Death	9 (5.8)	9 (6.0)	6 (4.1%)	4 (5.5%)
Adverse event	8 (5.2%)	8 (5.3%)	12 (8.2%)	4 (5.5%)
Consent withdrawn	1 (0.6%)	3 (2.0%)	2 (1.4%)	9 (12.3%)
Protocol deviation	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Disease progression	3 (1.9%)	12 (7.9%)	1 (0.7%)	3 (4.1%)
Non-compliance meds	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Non-compliance with study procedures	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Other	0 (0.0%)	3 (2.0%)	7 (4.8%)	7 (9.6%)
Crossed over to ruxolitinib from PB or BAT	NA	36 (23.8%)[8]	NA	18 (24.7%)[9]
Continued in extension	NA	NA	29 (19.9%)	18 (24.7%)
BAT= Best Available Therapy; **NA**= not applicable; **NR**=not reported; **PB**= placebo; **RUX**= ruxolitinib				

e) Limitations/Sources of Bias

- COMFORT I and II were not designed or powered to detect a difference in overall survival or progression-free survival between treatment groups. Hence, conclusions based on the results for these analyses should be drawn with caution.
- In COMFORT I, cross-overs could occur prior to the data-lock (i.e., 24 weeks); crossed-over patients were deemed to have not had a response to treatment in analyses of spleen volume and total symptom scores. While this approach would have guarded against overestimates of response to treatment, the permission of early cross-over confounds the interpretation of the absolute benefit of ruxolitinib therapy, particularly for survival outcomes. In COMFORT II, cross-overs could only occur after superiority of treatment was demonstrated on the primary outcome (at 48 weeks) or key secondary outcome (at 24 weeks), which coincided with pre-specified data-lock points.[55]
- It is unclear whether a change in spleen size as a surrogate endpoint is a reasonable predictor of improvement in patient survival or quality of life (see section 2.1.4). Additionally, the use of spleen size as the sole measure of response differs from the IWG-MRT recommended definition of response, which also uses blood cell counts ('complete' or 'partial' remission) and bone marrow histology ('complete' remission).[16] However, the use of a single criterion, such as reduction in spleen size, is consistent with the IWG-MRT recommended definition of clinical improvement. Furthermore, the manufacturer's assertion that a reduction of ≥35% in spleen volume as assessed by imaging is correlated with the IWG-MRT value of ≥50% in spleen length is based on data from a manufacturer-sponsored phase 1/2 study of ruxolitinib for myelofibrosis and has not been replicated or validated by other investigators to date. Whether IWG-MRT defined 'clinical

improvement' can be said to have occurred in COMFORT I and II with respect to spleen response is dependent upon the acceptance of spleen volume (as measured by MRI) as a valid alternative surrogate outcome for palpable spleen length.

- In COMFORT I, only half of all ruxolitinib-treated patients who achieved a ≥35% reduction in spleen volume (SVR) also achieved a ≥50% reduction in total symptom score (TSS) and vice versa. In a series of sensitivity analyses (i.e., baseline spleen volume, V617F JAK2 mutation status, IPSS risk category, MF subtype, individual symptom scores, and magnitude of SVR and TSS change) performed by the FDA to try to explain this disparity, no obvious driver(s) were identified.
- Randomization of patients in COMFORT I was not stratified by IPSS, although COMFORT II was stratified. Thus, treatment groups appeared to be better balanced regarding IPSS in COMFORT II than COMFORT I; a larger percentage of controls in COMFORT I had a "high" IPSS score versus ruxolitinib-treated patients.
- A modified version of the Myelofibrosis Symptom Assessment Form (MFSAF) was used as a daily symptom diary that patients in COMFORT I, but not COMFORT II, were asked to complete nightly. The original MFSAF has been validated at a single time point; the modified version of the MFSAF has not been validated. Of note, no information is available with respect to minimally clinically important differences in scores.[10]
- The EORTC QLQ-C30 is a common quality of life instrument that was used in both COMFORT I and II; it assesses quality of life for cancer generally, but not MF specifically. Evaluation of quality of life data for this review was limited as incomplete data were publically available for each trial. For COMFORT II, only the comparative scores for role functioning were publically available from the EORTC QLQ-C30's function subscale; it should be noted that previous work[56] has demonstrated that of the five function subscales, role functioning did not meet the minimum criteria for reliability (Cronbach's alpha coefficient ≥0.70).
- In COMFORT I, potential for unblinding existed as a consequence of observable reductions in spleen size which would have been noted upon physical examination at clinical assessments.

- In both COMFORT I and II, the majority of patients studied had a low ECOG PS score (≤1 in 85% and 82%, respectively) implying the recruitment of generally 'healthier' patients. It is therefore unclear to what extent the study findings would apply to sicker patients. Moreover, a low baseline ECOG PS score may confound the ability of quality of life instruments to demonstrate a clinically meaningful change in quality of life as a function of treatment.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Results are presented according to the hierarchy of outcomes established in the systematic review protocol (section 6.2.1). The data cut-off dates for the primary outcome in COMFORT I and COMFORT II were, respectively, November 2, 2010 and

January 4, 2011, representing follow-up durations of 24 and 48 weeks per trial. For COMFORT I, however, a data cut-off date of March 1, 2011 was used for the overall survival analysis, giving an additional 12 weeks of follow-up beyond that for the primary outcome. As of the primary study cut-off dates, the median durations of treatment were 32 and 52 weeks (ranges not reported) in COMFORT I and COMFORT II for all treated patients, respectively.

Patients who left the trial, or for whom the response evaluations were missing were considered to be failure events. There were no imputations for missing data performed.

Table 7. Summary of Key Efficacy and Harms Outcomes				
	COMFORT I (24 weeks)		COMFORT II (48 weeks)	
Outcome	RUX (n=155)	PB (n=154)	RUX (n=146)	BAT (n=73)
Efficacy				
Overall survival (number of deaths, %)[5,6,11]	10 (6.5%)	14 (9.1%)	6 (4.1%)	4 (5.5%)
	HR*: 0.67 (0.30-1.50)		HR*†: 0.70 (0.20-2.49)	
	P=0.33		P=0.58†	
Progression-free survival (number of events, %)[6,11]	NR		44 (30.1%)	19 (26.0%)
			HR*†: 0.81 (0.47-1.39)	
			P=0.46†	
Patients with ≥35% spleen volume reduction‡, n (%) [95% CI][5,12]	24 weeks[¶]			
	N=155	N=153	N=146	N=73
	65 (41.9%) [NR]	1 (0.7%) [NR]	46 (31.9%) [NR]	0
	P<0.0001[§]		P<0.0001[δ]	
	48 weeks			
	NA		N=144	N=72
			41 (28.1%) [NR]	0
			P<0.0001[†§]	
Quality of life (EORTC QLQ-C30), mean (SD) change from baseline	N=136	N=104	N=NR	N=NR
	12.3 (25.4)	-3.4 (21.5)	9.1 (NR)	3.4 (NR)
	P-value: NR		NR	
Harms[11]				
	RUX (n=155)	PB (n=151)	RUX (n=146)	BAT (n=73)
Serious adverse events	28%	35%	30%	29%
Adverse events, Grade 3-4	47%	44%	42%	25%
Withdrawals due to adverse events	11%	11%	8%	8%

BAT= Best Available Therapy; **CI**=confidence interval; **HR**=hazard ratio; **NA**=Not applicable; **NR**=Not reported; **PB**= placebo; **RUX**= ruxolitinib;

* Survival curves estimated using the Kaplan-Meier method; HRs calculated using Cox proportional hazards model
† Adjusted for baseline IPSS score
‡ Only patients with baseline data were included in this analysis
§ Calculated using Fisher's exact test (COMFORT I) or the exact Cochrane-Mantel-Haenszel test (COMFORT II)
[¶]Secondary outcome in COMFORT II, p.13-table-9 FDA stats rev
[δ]Fisher's Exact test

Overall Survival

COMFORT I

Overall survival was a secondary endpoint in COMFORT I. It was evaluated at two time points: an analysis at 24 weeks (the prespecified primary-cutoff date for the study [November 2, 2010]) and an updated analysis at 36 weeks (the prespecified 4 month safety follow-up [March 1, 2011]).

A total of 24 deaths were recorded at 24 weeks, with 10 deaths (6.5%) occurring in the ruxolitinib group and 14 deaths (9.1%) in the placebo group (HR: 0.67; 95% CI: 0.30 to 1.50; P=0.33; Table 7).[5]

At the time of the updated overall survival analysis at 36 weeks (median follow-up=51 weeks), 13 additional deaths were recorded bringing the total to 37; 13 deaths (8.4%) occurred in the ruxolitinib group and 24 deaths (15.6%) occurred in the placebo group (HR: 0.50; 95% CI: 0.25 to 0.98; P=0.04).[5] Median overall survival had not yet been reached by the final analysis date.

Crossover was permitted both before and after the data-lock at week 24. A total of 36 patients crossed over to ruxolitinib from placebo: 16 patients crossed over before week 24 and 20 crossed over after week 24.[8]

COMFORT II

Overall survival was also a secondary endpoint in COMFORT II. At the planned week 48 cut-off date (January 4, 2011; median follow-up=52 weeks), there were 10 deaths recorded; 6 (4.1%) occurred in the ruxolitinib group and 4 (5.5%) occurred in the best available therapy group (HR: 0.70; 95% CI: 0.20 to 2.49; P=0.58; Table 7).[6,9,11]

In a planned safety update (median=61 weeks) that included two extra months of follow-up data (data cut-off date March 1, 2011), a total of 15 deaths were recorded; 11 deaths (7.5%) in the ruxolitinib group and 4 (5.5%) in the best available therapy group (HR: 1.01; 95% CI: 0.32 to 3.24).[6]

Cross-over was permitted after week 24 once superiority of ruxolitinib had been demonstrated on the primary (week 48) or key secondary outcomes (week 24).[55]

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Progression-free survival

COMFORT I

Progression-free survival was not evaluated as an outcome in COMFORT I.

COMFORT II

Progression-free survival was a secondary outcome in COMFORT II. After 48 weeks of follow-up, progression events were documented in 44 patients (30.1%) in the ruxolitinib group compared with 19 patients (26.0%) in the best available therapy group (HR: 0.81; 95% CI: 0.47 to 1.39; Table 7).[6]

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Quality of life

Quality of life was studied as a secondary endpoint in COMFORT I[5,8] and II[6] using the European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30).[8] The EORTC QLQ-C30 consists of five subscales on function (i.e., physical, role, emotional, cognitive, social), a global health status and quality of life composite score, and individual symptom subscales (e.g., fatigue, pain, nausea).[8] Of note, previous work[56] has demonstrated that of the five function subscales, role functioning was not found to meet the minimum criteria for reliability (Cronbach's alpha coefficient ≥0.70).

COMFORT I

Mean changes in EORTC QLQ-C30 functional subscales from baseline to week 24 were reported to show a statistically significant improvement in ruxolitinib-treated patients for all subscales (P<0.001) except cognitive functioning; by contrast, a worsening in each subscale was reported for patients in the placebo group.[8] Except for cognitive functioning, all of the observed placebo-subtracted changes (global health status and quality of life composite score; physical, emotional, social, and role function subscales) were in excess of five points, which is the threshold for minimal clinical improvement.[8,57] No published data were available for individual symptom scores.[8]

COMFORT II

Limited EORTC QLQ-C30 data were reported in COMFORT II.[6] A numerically greater improvement in the global health status and quality of life composite score was noted in the ruxolitinib group compared with the best available therapy (BAT) group,[6] with the BAT-subtracted change (5.7) slightly above the five-point threshold for minimal clinical improvement. Although comparative statistics were not presented, only the role functioning subscale was reported to show a statistically significant improvement with ruxolitinib treatment compared with BAT; the BAT-subtracted changes (15.3) were well above the five-point threshold for minimal clinical improvement, contributed in part by a worsening in role functioning that occurred in the BAT group from baseline.[6] Changes in the other four subscales were reported as not being statistically significant between groups.[6]

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Total symptom score

COMFORT I

In COMFORT I, the number of evaluable patients with a reduction of ≥50% in the total symptom score from baseline to week 24 (secondary outcome), as measured using the modified Myelofibrosis Symptom Assessment Form (MFSAF), was 149 (96.1%) for the ruxolitinib group and 152 (98.7%) for the placebo group.[5] A higher proportion of patients in the ruxolitinib group (68/148, 45.9%) compared with the placebo group (8/152, 5.3%) achieved ≥50% reduction in total symptom score from

the MFSAF at week 24 (P<0.001).[5] Individual symptom scores (i.e., abdominal discomfort, pain under the left ribs, early satiety, night sweats, itching, bone or muscle pain, and inactivity) were consistent directionally in showing a reduction in symptoms with ruxolitinib therapy compared with a worsening (increase) in symptoms with placebo. Placebo-subtracted changes from baseline were also reported to be statistically significant at P<0.01 for all comparisons.[5] However, it should be noted that no threshold for a minimally clinically important difference has been established for the MFSAF (see section 2.1.4). Moreover, the MFSAF, though only validated in a single time point study, (see section 2.1.4) was self-administered daily in COMFORT I.[5]

COMFORT II

Total symptom score from the MFSAF was not evaluated as an outcome in COMFORT II. However, selected individual symptom scores were reported for fatigue, pain, dyspnea, insomnia, and appetite loss from the nine-item symptom scale of the EORTC QLQ-C30.[6] All best available therapy (BAT)-subtracted changes in these selected symptoms scores were above the five-point threshold for minimal clinical improvement except pain;[6] however, no comparative statistics were provided. Of note, an apparent worsening of symptoms in the best available therapy (BAT) group was consistently noted across symptom scores. This may be related in part to the fact that 33% of BAT-assigned patients received no medication.[9]

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Response rate

COMFORT I

Response rate, as based on the IWG MRT criteria for 'clinical improvement' was reported for spleen response only in the COMFORT I trial. There was no treatment response rate reported for either of the IWG MRT criteria for 'complete' or 'partial' remission specified in the protocol for the systematic review.

COMFORT II

Response rate, as based on the IWG MRT criteria for 'clinical improvement' was reported for spleen response only in the COMFORT II trial. There was no treatment response rate reported for either of the IWG MRT criteria for 'complete' or 'partial' remission specified in the protocol for the systematic review.

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Spleen volume response

COMFORT I

In COMFORT I, a higher proportion of patients in the ruxolitinib group (41.9%) compared with the placebo group (0.7%) achieved the primary endpoint of ≥35% reduction in spleen volume at 24 weeks;[5] percent difference between groups of 41.2% (95% CI: 32.8% to 48.7% according to the FDA statistical review[7]).

COMFORT II

In COMFORT II, no patients from the control (best available therapy) group achieved ≥35% reduction in spleen volume, either at 48 weeks (primary endpoint) or 24 weeks (secondary endpoint).[6]

In COMFORT II, 28% of patients in the ruxolitinib group compared with none from the best available therapy group achieved the primary endpoint of ≥35% reduction in spleen volume at 48 weeks (percent difference of 28%; 95% CI: 19.3% to 34.8% according to the FDA statistical review[7]).

At 24 weeks, 31.9% of patients from the ruxolitinib group compared with none from the best available therapy group achieved ≥35% reduction in spleen volume (31.9%; 95% CI: 22.5 to 38.4).[7]

Subgroup – IPSS risk category

A subgroup analysis by IPSS risk category of ruxolitinib-treated patients who achieved ≥35% reduction in spleen volume at 24 weeks is available for both trials only through the FDA statistical review.[7]

In this subgroup analysis,[7] 'intermediate' and 'high' risk groups were compared. In both COMFORT I and COMFORT II, a higher proportion of intermediate risk (33/64, 52%; 24/74, 32%, respectively) compared with high risk patients (32/90, 36%; 17/70, 24%, respectively) treated with ruxolitinib achieved ≥35% reduction in spleen volume at 24 weeks. The percent differences between ruxolitinib and placebo in COMFORT I were 52% (95% CI: 22% to 53%) for intermediate risk patients versus 35% (95% CI: 32% to 50%) for high risk patients. In COMFORT II, the percent differences between ruxolitinib and best available therapy were 32% (95% CI: 19% to 42%) for intermediate risk patients versus 24% (95% CI: 11% to 34%) for high risk patients.

Leukemic transformation

COMFORT I

Leukemia-free survival was evaluated as a secondary endpoint in COMFORT I. Two patients (1.3%) in the ruxolitinib group compared with none (0%) in the placebo group underwent leukemic transformation. The two patients from the ruxolitinib group were described as being predisposed by having both elevated blast counts and a chromosone 8 abnormality prior to starting ruxolitinib therapy.[11]

COMFORT II

In COMFORT II, leukemia-free survival was evaluated as a secondary endpoint. No patients (0%) underwent leukemic transformation in the ruxolitinib group compared with two (2.7%) in the best available therapy group.[11]

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Thrombosis

COMFORT I

No published data are available for this outcome.

COMFORT II

No published data are available for this outcome.

Subgroup – IPSS risk category

No published subgroup analysis by IPSS risk category is available for this outcome.

Harms Outcomes

Deaths

In COMFORT I, a total 24 deaths were observed; 10 deaths were recorded in the ruxolitinib group compared with 14 in the placebo group. Of the 10 ruxolitinib arm deaths, nine occurred on-study while one death was recorded during follow-up (i.e., > 28 days after last dose of study medication). In the placebo arm, 11 of the 14 deaths occurred on-study while one occurred after cross-over during extension and two deaths were recorded during follow-up.[11]

In COMFORT II, a total of 10 deaths were observed; six deaths were recorded in the ruxolitinib group compared with four in the best available therapy (control) group. Of the six ruxolitinib arm deaths, four occurred on-study while two occurred during follow-up. In the best available therapy arm, three of the four deaths occurred on-study while one was recorded after cross-over during extension.[11]

Serious Adverse Events

Deaths related to adverse events were similar between ruxolitinib and control in both COMFORT I (6% vs 7%) and II (3% vs 4%). (Table 8) Non-fatal SAEs were slightly lower in the ruxolitinib group compared with placebo in COMFORT I (27.7% vs 35.1%), but similar in COMFORT II. The occurrence of grade 3-4 adverse events was similar between ruxolitinib and placebo in COMFORT I, but was numerically higher in ruxolitinib-treated patients compared with best available therapy in COMFORT II (42% vs 25%). Withdrawals due to adverse events were not different between groups in both COMFORT I and II trials.

The frequency of anemia appeared balanced between groups in both COMFORT I and II; thrombocytopenia events were infrequent in the two trials. Serious bleeding events were similar between groups in COMFORT I, but were numerically more frequent in the ruxolitinib-treated patients compared with control in COMFORT II (4.2% vs 0%). Pneumonia was numerically more frequent in the ruxolitinib-treated patients compared with control in COMFORT I (6.5% vs 3.3%), but was numerically lower in ruxolitinib-treated patients compared with control in COMFORT II (0.7% vs 5.5%).

Table 8. Deaths, Non-Fatal SAEs and AEs as Percentage of Total in COMFORT I, II trials[11]

	COMFORT I		COMFORT II	
Adverse event type	RUX (n=155)	PB (n=151/154)	RUX (n=146)	BAT (n=73)
Death related to AEs (Grade 5) <28 days*	6%	7%	3%	4%
SAEs (non-fatal)	43 (27.7%)	53 (35.1%)	44 (30.1%)	21 (28.8%)
Anemia	5 (3.2%)	3 (2.0%)	7 (4.8%)	3 (4.1%)
Pneumonia	10 (6.5%)	5 (3.3%)	1 (0.7%)	4 (5.5%)
Thrombocytopenia	3 (1.9%)	1 (0.7%)	0 (0.0%)	1 (1.4%)
Bleeding	7 (3.7%)	7 (4.1%)	6 (4.2%)	0 (0.0%)
GI Bleed	2 (1.3%)	2 (1.3%)	2 (1.4%)	0 (0.0%)
CNS Bleed	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Post-procedure bleed	1 (0.6%)	1 (0.7%)	1 (0.7%)	0 (0.0%)
UGI bleed	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Epistaxis	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Retroperitoneal bleed	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Splenic bleed	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subdural hematoma	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Grade 3-4 AEs*	47%	44%	42%	25%

AE= adverse event; **BAT**= Best Available Therapy; **CNS**= central nervous system; **GI**= gastrointestinal; **PB**= placebo; **RUX**= ruxolitinib; **SAE**= Serious Adverse Event; **UGI**= upper gastrointestinal tract; **UTI**=urinary tract infection

*Only percentages provided since actual raw numbers not reported.

Adverse Events

The overall frequency of adverse events of any type was not publically available for either COMFORT I or II. Adverse events leading to a dose reduction were more frequent in the ruxolitinib-treated patients compared with control in both COMFORT I (51% vs 26%) and II (64% vs 15%); thrombocytopenia was most often responsible for these dose adjustments.[11]

The frequency of anemia and thrombocytopenia of any grade was only publically available for COMFORT I (Table 10): both anemia (96.1% vs 86.8%) and thrombocytopenia (69.7% vs 30.5%) of any grade were numerically more prevalent in ruxolitinib-treated patients compared with placebo. Of the instances of anemia noted in COMFORT I among ruxolitinib-treated patients, 45.2% were rated grade 3 or 4 in severity compared with 19.2% in the placebo group.[5] Likewise, the prevalence of neutropenia (18.7% vs 4.0%), ecchymosis (18.7% vs 9.3%), and dizziness (14.8 vs 6.6%) were only reported for COMFORT I and were more frequent in ruxolitinib-treated patients. Headache was numerically more frequent in ruxolitinib-treated patients compared with control in both COMFORT I (14.8% vs 5.3%) and II (10.3% vs 4.1%). Abdominal pain (10.3% vs 41.1%) and fatigue (25.2% vs 33.8%) were both numerically less frequent in ruxolitinib-treated patients compared with placebo in COMFORT I, and not different between groups in COMFORT II.

Table 9. Adverse Events Observed in ≥10% of Patients Who Received Ruxolitinib in COMFORT I, II[5,6]

Adverse event	COMFORT I				COMFORT II			
	RUX (n=155)		PB (n=151/154)		RUX (n=146)		BAT (n=73)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
% of patients								
Any	NR	NR	NR	NR	NR	NR	NR	NR
Anemia*	96.1	45.2	86.8	19.2	NR	NR	NR	NR
Thrombocytopenia*	69.7	12.9	30.5	1.3	NR	NR	NR	NR
Fatigue	25.2	5.2	33.8	6.6	12.3	0.7	8.2	0
Diarrhea	23.2	1.9	21.2	0	23.3	1.4	12.3	0
Neutropenia*	18.7	7.1	4.0	2.0	NR	NR	NR	NR
Peripheral edema	18.7	0	22.5	1.3	21.9	0	26.0	0
Ecchymosis	18.7	0	9.3	0	NR	NR	NR	NR
Dyspnea	17.4	1.3	17.2	4.0	15.8	0.7	17.8	4.1
Dizziness	14.8	0.6	6.6	0	NR	NR	NR	NR
Nausea	14.8	0	19.2	0.7	13.0	0.7	6.8	0
Headache	14.8	0	5.3	0	10.3	1.4	4.1	0
Constipation	12.9	0	11.9	0	NR	NR	NR	NR
Vomiting	12.3	0.6	9.9	0.7	NR	NR	NR	NR
Pain in extremity	12.3	1.3	9.9	0	11.6	0.7	4.1	0
Insomnia	11.6	0	9.9	0	NR	NR	NR	NR
Arthralgia	11.0	1.9	8.6	0.7	12.3	0.7	6.8	0
Pyrexia	11.0	0.6	7.3	0.7	13.7	2.1	9.6	0
Abdominal pain	10.3	2.6	41.1	11.3	11.0	3.4	13.7	2.7

BAT=best available therapy; **NR**=Not reported; **RUX**= ruxolitinib; **PB**=placebo

*Hematologic abnormalities are based on laboratory values. The data shown are for events of the worst grade during the study, regardless of whether this grade was a change from baseline grade.

Withdrawal due to Adverse Events

Withdrawals due to adverse events were infrequent in both trials, including discontinuations due to hematologic adverse events such as thrombocytopenia, neutropenia, and anemia.

Table 10. Individual Causes of Discontinuations due to AEs in COMFORT I, II trials[11]

	COMFORT I		COMFORT II	
Adverse event type	RUX (n=155)	PB (n=151/154)	RUX (n=146)	BAT (n=73)
AEs leading to discontinuation	11%	11%	8%	8%
Thrombocytopenia	1%	1%	1%	1%
Neutropenia	1%	0%	0%	0%
Anemia	1%	1%	0%	0%
Diarrhea	1%	0%	0%	0%
Septic shock	1%	0%	0%	0%
Subdural hematoma	1%	0%	0%	0%
Retroperitoneal hemorrhage	1%	0%	1%	0%

AE= adverse event; **BAT**= Best Available Therapy; **PB**= placebo; **RUX**= ruxolitinib;

Only percentages provided since actual raw numbers not reported.

6.4 Ongoing Trials

One ongoing trial was identified through a search of the clinical trials registry (clinicaltrials.gov). The study (NCT01243944) is a manufacturer sponsored phase III, randomized, open-label, multicenter trial designed to compare the efficacy and safety of ruxolitinib (starting dose of 10 mg BID with individualized dose titration ranging from 5 mg QD to 25 mg BID based on safety and efficacy) with best available therapy in patients with polycythemia vera who are resistant to or intolerant of hydroxyurea. Additional key eligibility criteria include: age ≥18 years, a phlebotomy requirement, palpable splenomegaly and a spleen volume of ≥450 cubic centimeters, and an ECOG performance status of ≤2. The primary endpoint is the absence of phlebotomy eligibility and reduction in spleen volume over 32 weeks. The study started enrolling patients October 2010 and is planned to end March 2014, enrolling at least 200 patients in total.

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Myelofibrosis Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ruxolitinib for myelofibrosis. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations or in this publicly available document.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Myelofibrosis Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Embase 1980-2012 Oct 2 (oemezd); Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	(ruxolitinib* or Jakavi* or Jakafi* or INCB018424 or INCB-018424 or INCB18424 or INCB-18424 or INCB424 or INCB-424 or INC424 or INC-424).ti,ot,ab,sh,rn,hw,nm.	430
2	941678-49-5.rn,nm.	161
3	or/1-2	430
4	3 use pmez	94
5	*ruxolitinib/	67
6	(ruxolitinib* or Jakavi* or Jakafi* or INCB018424 or INCB-018424 or INCB18424 or INCB-18424 or INCB424 or INCB-424 or INC424 or INC-424).ti,ab.	221
7	or/5-6	229
8	conference abstract.pt.	855535
9	7 not 8	162
10	9 use oemezd	83
11	4 or 10	177
12	remove duplicates from 11	97

2. Literature search via PubMed

Search	Add to builder	Query	Items found
#5	Add	Search **#3 AND #4**	5
#4	Add	Search **publisher[sb]**	422647

Search	Add to builder	Query	Items found
#3	Add	Search **#1 OR #2**	80
#2	Add	Search **ruxolitinib*[tiab] OR Jakavi*[tiab] OR Jakafi*[tiab] OR 941678-49-5[rn] OR INCB018424[tiab] OR INCB-018424[tiab] OR INCB18424[tiab] OR INCB-18424[tiab] OR INC424[tiab] OR INC-424[tiab] OR INCB424[tiab] OR INCB-424[tiab]**	68
#1	Add	Search **"INCB018424" [Supplementary Concept]**	42

3. Cochrane Central Register of Controlled Trials (Central)

Search for trials. Issue 9 of 12, Sept 2012.

ID	Search	Hits	Edit	Delete
#1	(ruxolitinib* OR Jakavi* OR Jakafi* OR 941678-49-5 OR INCB018424 OR INCB-018424 OR INCB18424 OR INCB-18424 OR INC424 OR INC-424 OR INCB424 OR INCB-424):ti,ab,kw	5	edit	delete

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: ruxolitinib OR Jakavi OR Jakafi

Select international agencies including:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: ruxolitinib OR Jakavi OR Jakafi

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://bloodjournal.hematologylibrary.org/site/misc/ASH_Meeting_Abstracts_Info.xhtml

Search terms: ruxolitinib OR Jakavi OR Jakafi (2007-2012)

REFERENCES

1. Tefferi A. JAK inhibitors for myeloproliferative neoplasms: clarifying facts from myths. Blood [Internet]. 2012 Mar 22 [cited 2012 Jun 26];119(12):2721-30. Available from: http://bloodjournal.hematologylibrary.org/content/119/12/2721.full.pdf+html

2. Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib for the treatment of myelofibrosis. Drugs Today (Barc). 2011 Nov;47(11):817-27.

3. Pardanani A. Ruxolitinib for myelofibrosis therapy: current context, pros and cons. Leukemia. 2012;26(7):1449-51.

4. Jakavi® (ruxolitinib tablets) 5 mg, 15 mg and 20 mg [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2012 Jun 15.

5. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012 Mar 1;366(9):799-807.

6. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012 Mar 1;366(9):787-98.

8. Supplement to: Verstovsek S, Mesa RA, Gotlib J et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366:799-807.

9. Supplement to: Harrison C,Kiladjian J-J, Al-Ali HK et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366:787-98.

10. Pardanani A, Vannucchi AM, Passamonti F, Cervantes F, Barbui T, Tefferi A. JAK inhibitor therapy for myelofibrosis: critical assessment of value and limitations. Leukemia. 2011 Feb;25(2):218-25.

11. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Jakafi (ruxolitinib). Company: Incyte Corporation. Application no.: NDA 202192. Approval date: 11/16/2011. Rockville (MD): The Center; 2011 [cited 2012 Jun 21]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202192Orig1s000TOC.cfm.

12. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Jakafi (ruxolitinib). Company: Incyte Corporation. Application no.: NDA 202192. Approval date: 11/16/2011. Rockville (MD): The Center; 2011 [cited 2012 Jun 21]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202192Orig1s000TOC.cfm.

13. Verstovsek S, Kantarjian HM, Estrov Z, Cortes JE, Thomas DA, Kadia T, et al. Long term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. Blood. 2012 Jun 20;120(6):1202-9.

14. Verstovsek S, Kantarjian H, Mesa RA, Pardanani AD, Cortes-Franco J, Thomas DA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med [Internet]. 2010 Sep 16 [cited 2012 Jun 25];363(12):1117-27. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1002028

15. Cervantes F, Dupriez B, Passamonti F, Vannucchi AM, Morra E, Reilly JT, et al. Improving survival trends in primary myelofibrosis: an international study. J Clin Oncol. 2012 Jul 23;30(24):2981-7.

16. Tefferi A, Barosi G, Mesa RA, Cervantes F, Deeg HJ, Reilly JT, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood [Internet]. 2006 Sep 1 [cited 2012 Jul 16];108(5):1497-503. Available from: http://bloodjournal.hematologylibrary.org/content/108/5/1497.full.pdf+html

17. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc [Internet]. 2011 Dec [cited 2012 Jun 25];86(12):1188-91. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228619/pdf/mayoclinproc_86_12_010.pdf

18. Verstovsek S, Mesa RA, Gotlib JR, Gupta V, DiPersio JF, Catalano JV, et al. Adverse events (AEs) and the return of myelofibrosis (MF)-related symptoms after interruption or discontinuation of ruxolitinib (RUX) therapy [abstract]. J Clin Oncol [Internet]. 2012 [cited 2012 Aug 15];30 Suppl:6624. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=93750

19. Vannucchi AM. Management of myelofibrosis. Hematology Am Soc Hematol Educ Program. 2011;2011:222-30.

20. Thiele J, Kvasnicka HM, Tefferi A, Barosi G, Orazi A, Vardiman JW. Primary myelofibrosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, editors. WHO classification of tumours of hematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer; 2008.

21. Tefferi A. Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012 Mar;87(3):285-93.

22. Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, et al. Guideline for the diagnosis and management of myelofibrosis. Br J Haematol [Internet]. 2012 [cited 2012 Jul 12];158(4):453-71. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09179.x/pdf

23. Orazi A. Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes, and myelodysplastic/myeloproliferative diseases. Pathobiology. 2007;74(2):97-114.

24. Klco JM, Vij R, Kreisel FH, Hassan A, Frater JL. Molecular pathology of myeloproliferative neoplasms. Am J Clin Pathol. 2010 Apr;133(4):602-15.

25. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010 Mar 4;115(9):1703-8.

26. Johansson P, Mesa R, Scherber R, Abelsson J, Samuelsson J, Birgegard G, et al. Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. Leuk Lymphoma. 2012 Mar;53(3):441-4.

27. Scherber R, Dueck AC, Johansson P, Barbui T, Barosi G, Vannucchi AM, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood. 2011 Jul 14;118(2):401-8.

28. Guardiola P, Anderson JE, Bandini G, Cervantes F, Runde V, Arcese W, et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European Group for Blood and Marrow Transplantation, Societe Francaise de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center Collaborative Study. Blood. 1999 May 1;93(9):2831-8.

29. Snyder DS, Palmer J, Stein AS, Pullarkat V, Sahebi F, Cohen S, et al. Allogeneic hematopoietic cell transplantation following reduced intensity conditioning for treatment of myelofibrosis. Biol Blood Marrow Transplant. 2006 Nov;12(11):1161-8.

30. Kroger N, Thiele J, Zander A, Schwerdtfeger R, Kobbe G, Bornhauser M, et al. Rapid regression of bone marrow fibrosis after dose-reduced allogeneic stem cell transplantation in patients with primary myelofibrosis. Exp Hematol. 2007 Nov;35(11):1719-22.

31. Abelsson J, Merup M, Birgegard G, WeisBjerrum O, Brinch L, Brune M, et al. The outcome of allo-HSCT for 92 patients with myelofibrosis in the Nordic countries. Bone Marrow Transplant. 2012 Mar;47(3):380-6.

32. Nivison-Smith I, Dodds AJ, Butler J, Bradstock KF, Ma DD, Simpson JM, et al. Allogeneic hematopoietic cell transplantation for chronic myelofibrosis in Australia and New Zealand: older recipients receiving myeloablative conditioning at increased mortality risk. Biol Blood Marrow Transplant. 2012 Feb;18(2):302-8.

33. Hoffman R, Xu M, Barosi G. Primary myelofibrosis. In: Hoffman R, Benz EJ Jr, Shattil SJ, Furie B, Silberstein LE, Heslop H, editors. Hematology: basic principles and practice. 5th ed. Philadelphia (PA): Churchill Livingstone; 2008. p. 1125-47.

34. Shimoda K, Shide K, Kamezaki K, Okamura T, Harada N, Kinukawa N, et al. The effect of anabolic steroids on anemia in myelofibrosis with myeloid metaplasia: retrospective analysis of 39 patients in Japan. Int J Hematol. 2007 May;85(4):338-43.

35. Cervantes F, Alvarez-Larran A, Domingo A, Arellano-Rodrigo E, Montserrat E. Efficacy and tolerability of danazol as a treatment for the anaemia of myelofibrosis with myeloid metaplasia: long-term results in 30 patients. Br J Haematol. 2005 Jun;129(6):771-5.

36. Cervantes F, Hernandez-Boluda JC, Alvarez A, Nadal E, Montserrat E. Danazol treatment of idiopathic myelofibrosis with severe anemia. Haematologica. 2000 Jun;85(6):595-9.

37. Cervantes F, Alvarez-Larran A, Hernandez-Boluda JC, Sureda A, Granell M, Vallansot R, et al. Darbepoetin-alpha for the anaemia of myelofibrosis with myeloid metaplasia. Br J Haematol. 2006 Jul;134(2):184-6.

38. Jabbour E, Thomas D, Kantarjian H, Zhou L, Pierce S, Cortes J, et al. Comparison of thalidomide and lenalidomide as therapy for myelofibrosis. Blood. 2011 Jul 28;118(4):899-902.

39. Mesa RA, Yao X, Cripe LD, Li CY, Litzow M, Paietta E, et al. Lenalidomide and prednisone for myelofibrosis: Eastern Cooperative Oncology Group (ECOG) phase 2 trial E4903. Blood. 2010 Nov 25;116(22):4436-8.

40. Begna KH, Pardanani A, Mesa R, Litzow MR, Hogan WJ, Hanson CA, et al. Long-term outcome of pomalidomide therapy in myelofibrosis. Am J Hematol. 2012 Jan;87(1):66-8.

41. Martinez-Trillos A, Gaya A, Maffioli M, Arellano-Rodrigo E, Calvo X, Diaz-Beya M, et al. Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. Ann Hematol. 2010 Dec;89(12):1233-7.

42. Thapaliya P, Tefferi A, Pardanani A, Steensma DP, Camoriano J, Wu W, et al. International working group for myelofibrosis research and treatment response assessment and long-term follow-up of 50 myelofibrosis patients treated with thalidomide-prednisone based regimens. Am J Hematol. 2011 Jan;86(1):96-8.

43. Faoro LN, Tefferi A, Mesa RA. Long-term analysis of the palliative benefit of 2-chlorodeoxyadenosine for myelofibrosis with myeloid metaplasia. Eur J Haematol. 2005 Feb;74(2):117-20.

44. Mishchenko E, Tefferi A. Treatment options for hydroxyurea-refractory disease complications in myeloproliferative neoplasms: JAK2 inhibitors, radiotherapy, splenectomy and transjugular intrahepatic portosystemic shunt. Eur J Haematol. 2010 Sep;85(3):192-9.

45. Mesa RA, Nagorney DS, Schwager S, Allred J, Tefferi A. Palliative goals, patient selection, and perioperative platelet management: outcomes and lessons from 3 decades of splenectomy for myelofibrosis with myeloid metaplasia at the Mayo Clinic. Cancer. 2006 Jul 15;107(2):361-70.

46. Mesa RA, Tefferi A. Surgical and radiotherapeutic approaches for myelofibrosis with myeloid metaplasia. Semin Oncol. 2005 Aug;32(4):403-13.

47. Ciurea SO, Sadegi B, Wilbur A, Alagiozian-Angelova V, Gaitonde S, Dobogai LC, et al. Effects of extensive splenomegaly in patients with myelofibrosis undergoing a reduced intensity allogeneic stem cell transplantation. Br J Haematol. 2008 Apr;141(1):80-3.

48. Pardanani A, Brown P, Neben-Wittich M, Tobin R, Tefferi A. Effective management of accelerated phase myelofibrosis with low-dose splenic radiotherapy. Am J Hematol. 2010 Sep;85(9):715-6.

49. Thepot S, Itzykson R, Seegers V, Raffoux E, Quesnel B, Chait Y, et al. Treatment of progression of Philadelphia-negative myeloproliferative neoplasms to myelodysplastic syndrome or acute myeloid leukemia by azacitidine: a report on 54 cases on the behalf of the Groupe Francophone des Myelodysplasies (GFM). Blood. 2010 Nov 11;116(19):3735-42.

50. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF. Consistent benefit of ruxolitinib over placebo in spleen volume reduction and symptom improvement across subgroups and overall survival advantage: results From COMFORT-I [abstract]. Blood [Internet]. 2011 [cited 2012 Jun 29];118(21):278. Available from: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/278

51. Verstovsek S, Mesa RA, Gotlib JR, Levy RS, Gupta V, DiPersio JF, et al. Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF) [abstract]. J Clin Oncol [Internet]. 2011 [cited 2012 Jun 29];29 Suppl:6500. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=82278

52. Harrison CN, Kiladjian JJ, Gisslinger H, Niederwieser D, Passamonti F, Waltzman RJ. Ruxolitinib provides reductions in splenomegaly across subgroups: an analysis of spleen response in the COMFORT-II Study [abstract]. Blood [Internet]. 2011 [cited 2012 Jun 29];118(21):279. Available from: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/279

53. Harrison CN, Kiladjian J, Al-Ali HK, Gisslinger H, Waltzman RJ, Stalbovskaya V, et al. Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). J Clin Oncol [Internet]. 2011 [cited 2012 Jun 29];21 Suppl:LBA6501. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=82446

54. pan-Canadian Oncology Drug Review manufacturer submission: Jakavi® (ruxolitinib tablets); Company: Novartis Pharmaceuticals Canada. Dorval (QC): Novartis; 2012 Jun 20.

55. Protocol for: Harrison C, Kiladjian J-J, Al-Ali HK et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366:787-98.

56. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

57. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.