PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ruxolitinib (Jakavi) for Polycythemia Vera

March 3, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of ruxolitinib (Jakavi) compared with standard therapy in adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea (HU).

Ruxolitinib has a Health Canada indication for:

- the treatment of splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-PV myelofibrosis (MF) or post-essential thrombocythemia MF.
- the control of hematocrit (HCT) in adult patients with PV resistant to or intolerant of a cytoreductive agent.

Ruxolitinib is an oral tablet available as 5 mg, 10 mg, 15 mg and 20 mg; it has Health Canada approval in PV for a starting dose of 10 mg orally twice daily for platelet count ≥100,000/mm^3 and 5 mg orally twice daily for platelet count of 50,000 to <100,000/mm^3.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one ongoing, open-label randomized phase III study (RESPONSE) examining the use of ruxolitinib (n=110) versus standard therapy (n=112) in patients with PV who had an inadequate response to or had unacceptable side effects from HU.[2] The definitions of HU resistance and intolerance used in the RESPONSE trial are defined in Section 6.3.2.1.a. The choice of standard therapy was at the discretion of the investigator and could include any of the following single-agent regimens: HU (at a dose that did not cause unacceptable side effects), interferon alpha (INF-a) or pegylated INF-a, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. All patients in both arms received low dose aspirin unless it was contraindicated. The trial permitted patients randomized to standard therapy to crossover to ruxolitinib at or after week 32.

The median age of patients was 60 years (range, 33 to 90 years). The majority of patients had an ECOG PS of 0 (69%). Approximately 54.1% and 45.9% of all patients had unacceptable side effects from or inadequate response to HU, respectively. The median duration of previous HU therapy was 3.1 and 2.8 years in the ruxolitinib and standard therapy groups, respectively. The trial is ongoing and the median duration of ruxolitinib was 34 weeks at week 32, 81 weeks at week 48 and 111 weeks at week 80. Among the 112 patients randomized to standard therapy, the most common initial therapy was HU (59%), no medication (15%), and INF (12%). The median duration of standard therapy was 34 weeks. A total of 96 (86%) patients assigned to standard therapy crossed over to the ruxolitinib arm, with the majority of patients crossing over at week 32, or shortly after.

Potential limitations and sources of bias in RESPONSE included the open-label design where investigators and patients were not blinded to treatment assignment. The risk of performance bias is of particular concern as 59% of patients in the standard therapy arm received HU, a treatment they knew they were intolerant or resistant to. As lack of efficacy would be an expected outcome, it is not surprising a high percentage (87.5%) of patients discontinued treatment due to lack of efficacy. Additionally, at present, longer-

term efficacy and safety of ruxolitinib is limited to an abstract with outcomes reported up to 80 weeks. The limitations of abstract data should be considered as well as the high-level of crossover, which also limits the assessment of longer-term outcomes. Another source of bias includes the three amendments that were made to the protocol over the course of the trial, of which the first resulted in significant changes to the inclusion criteria. Finally, the standard therapy arm included several different treatment regimens, which may not be considered standard of care in some Canadian jurisdictions.

Efficacy

The primary outcome was a composite response endpoint including the proportion of patients who achieved both HCT control and a reduction in spleen volume of ≥35%, as assessed by either MRI or CT imaging, at week 32. Key secondary endpoints included: duration of primary response at week 48, complete hematological response (CHR) at week 32, symptom reduction, and quality of life (QOL).

The composite response rate at week 32 was 20.9% versus 0.9% in the ruxolitinib and standard therapy arms, respectively (OR=28.6, 95%CI: 4.5-1206, p<0.001). Duration of primary response at week 48 was 19.1% versus 0.9% in the ruxolitinib and standard therapy arms, respectively (OR=26.11, 95%CI: 3.98-1080, p<0.0001). CHR was 24% versus 9% in the ruxolitinib and standard therapy arms, respectively (OR=3.35, 95%CI: 1.43-8.35, p=0.003).

Quality of life was measured using the EORTC Quality of Life Questionnaire-Core 30 where a 10-point change in score from baseline to week 32 was considered the minimally important difference (MID). The MID was achieved in 46% and 10% of patients in the ruxolitinib and standard therapy arms. As measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Patient Diary, a 50% reduction in the total symptom score was observed in 49% and 5% in the ruxolitinib and standard therapy arms, respectively. Similar results were reported in the Patient Global Impression of Change instrument, which assessed patients' perception of change in their PV symptoms over time. The Pruritus Symptom Impact Scale indicated an improvement from baseline with ruxolitinib (mean change ranged from -1.5 to -2.2) and standard therapy (mean change ranged from -0.1 to 0.3).

Harms

The rates of grade 3 or 4 adverse events were similar in both study arms; 33% in the ruxolitinib arm and 29% in the standard therapy arm. Treatment-related adverse events of all grades occurred in 59% and 33% of patients in the ruxolitinib and standard therapy groups, respectively. At week 48, 16% and 96% of patients in the ruxolitinib and standard therapy arms discontinued randomized treatment. Patient discontinuations in the standard treatment arm were primarily attributed to lack of efficacy. Follow-up analysis at week 80 indicated 83% of patients had ongoing treatment with ruxolitinib (randomized and crossover). At week 80, few new adverse events were observed. The rate of herpes zoster infection continued to be higher in the ruxolitinib arm and the rate of thromboembolic events continued to be higher in the standard therapy arm.

1.2.2 Additional Evidence

pCODR received input on ruxolitinib from one patient advocacy group (Canadian Myeloproliferative Neoplasms Network). Provincial Advisory Group input was obtained from eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. One supplemental issue was identified during the development of the review on the type and degree of resistance and intolerance to HU that would be considered in order to support a switch in treatment to ruxolitinib.

1.2.3 Interpretation and Guidance

The incidence of PV is estimated to be around 2/100,000/year with the median age of diagnosis of 60 years. The goals of treatment are to decrease the risk of thrombosis and to control symptoms related to PV. Current standard treatments include phlebotomy, low dose aspirin, and HU. Approximately 18 to 22% of these patients will develop resistance or intolerance to HU. Ruxolitinib is the first targeted treatment with proven efficacy to improve disease-related outcomes in patients who have demonstrated intolerance or resistance to standard first-line treatment with HU.

Effectiveness

In the RESPONSE trial,[2] a significantly higher proportion of patients in the ruxolitinib arm compared to the standard therapy arm achieved the composite primary response outcome (both HCT control and a ≥35% reduction in spleen volume). Significant improvements were also seen with ruxolitinib compared to the standard therapy arm for the secondary outcomes of duration of primary response at 32 weeks (19% versus 0.9%) and CHR (24% versus 9%). Improvement in symptom score was also improved with ruxolitinib compared to standard therapy (49% versus 5%) as measured by the MPN-SAF Patient Diary. Quality of life measured in the RESPONSE trial also favoured the ruxolitinib arm.

Safety

There were few grade 3 or 4 adverse events observed in both arms of the RESPONSE trial. Non-clinically significant but notable differences in toxicity included the rate of herpes zoster infection (6.4% vs. 0%) and skin cancers (3.6% vs. 1.8%). There were similar low rates of progression to MF (2.7% vs. 0.9%) and there was no difference in progression to acute myeloid leukemia (AML) in either arm (0.9% vs. 0.9%).

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of ruxolitinib in patients with PV who have specifically demonstrated intolerance or resistance to HU based on one ongoing phase III RCT (RESPONSE). There is a statistically significant and clinically meaningful benefit demonstrated with ruxolitinib in this patient population in controlling the HCT and reducing spleen size. Compared to standard therapy, symptom scores related to PV were also significantly reduced. Grade 3/4 adverse events were uncommon, manageable and the rates were similar across treatment arms. The Clinical Guidance Panel also considered that from a clinical perspective:

- The clinical benefit demonstrated in the RESPONSE trial aligned with what was reported in the patient advocacy input.
- It is noted that the evidence for use of ruxolitinib is only in a specific population of patients with PV in the second-line setting. There is no current data for its use in the first-line setting.
- Ruxolitinib may be used with a 32-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 experimental therapy.
- The duration of ruxolitinib therapy is indefinite at this time. Regular monitoring for the duration of therapy, spleen size, blood counts, and evidence of transformation is essential. Phlebotomy needs may change with treatment with ruxolitinib.
- Discontinuation of therapy should be through a tapering routine if possible and will require careful monitoring because of the potential for significant rebound symptoms.

- There is currently no randomized controlled trial data to inform the use of ruxolitinib in cases of resistance or intolerance to other cytoreductive therapies such as INF, however this may be a very small subset of patients in the Canadian context. Therefore, use of ruxolitinib in this setting should be on a case-by-case basis with the stopping provisions as discussed above.
- Three retrospective cohort studies suggest that elevated white blood cell (WBC) count is associated with worse overall survival in PV, however, it has not been demonstrated that modifying the WBC count changes overall survival. Thus, the CGP felt that based on the current level of evidence, a more appropriate end-point for the submitted cost-effectiveness analysis was CHR.

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 polycythemia vera (PV). 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding ruxolitinib for PV conducted by the Hematology Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); 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 for PV and a summary of submitted PAG Input on ruxolitinib for PV are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Polycythemia vera is one of the chronic myeloproliferative neoplasms (MPNs), which are collectively characterized by clonal proliferation of myeloid cells with variable morphologic maturity and hematopoietic efficiency. PV is distinguished clinically from the other MPNs by the presence of an elevated red blood cell mass. However, an increased red blood cell mass alone is insufficient to establish the diagnosis.[3] The median age at diagnosis is approximately 60 years.[4,5] The incidence of PV is estimated to be around 2/100,000/year.[6] Prevalence of PV is estimated to be 57 per 100,000 in Canada, which suggests there are approximately 20,483 cases in Canada.[7]

Most patients with PV are discovered incidentally when elevated hemoglobin is noted on a complete blood count obtained for another reason. Others present with disease-related symptoms (e.g., headache, dizziness, visual disturbances, pruritus, and early satiety due to enlarged spleen) or complications like thrombosis, bleeding, etc.

The median survival of untreated symptomatic patients with PV was initially estimated at 6 to 18 months from the time of diagnosis,[8] whereas current survival of treated patients is 13 years or more.[9] With treatment, overall mortality is greater than that of an age- and sex-matched normal population.[5,9-11]

Goals of therapy in PV are to reduce thrombosis without increasing bleeding tendency, to ameliorate symptoms and to prolong duration of progression to hematologic complications.

The gold standard for high-risk patients at present is hydroxyurea (HU). In some circumstances interferon (INF) can be used as first-line treatment (e.g. women of childbearing potential or pregnant). When used, side effects (flu-like symptoms, depression, heart, ocular complications) may lead to discontinuation in 20 to 40% of patients. In addition to cytoreductive therapies of HU and INF, regular phlebotomy treatment is used to keep the hematocrit below 45% in men and 42% in women. Low dose aspirin (81mg) is given to all patients unless intolerance, bleeding complications or it is contraindicated for other reasons. Use of cytoreductive treatment also results in a

decrease in phlebotomy requirement. Unfortunately both HU and INF provide only transient relief of other symptoms like pruritus or symptoms due to splenomegaly, etc.

Based on the European Leukemia Net (ELN) consensus definition,[7,12] 18 to 21.8% of patients are intolerant or resistant to HU in the PV treated population. Taking into consideration the Canadian prevalence of PV, approximately 3687 to 4465 patients with PV are intolerant or resistant to HU in Canada.

Second-line agents sometimes used in practice, due to intolerance/toxicity/refractoriness to HU, are INF and busulphan. Busulphan may cause profound and long-lasting cytopenias, marrow aplasia, skin pigmentation, pulmonary fibrosis, and leukemia in patients with PV. Other agents cited in the literature and used in the treatment of PV are anagrelide, pipobroman and ^{32}P with the latter two associated with increased risk of leukemia.

Current therapeutic landscapes for PV is limited to prevention of complications and are not curative. Treatment options for patients who are refractory to HU are inadequate.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the efficacy and safety of ruxolitinib (Jakavi) compared with standard therapy in adult patients with PV who are resistant or intolerant to HU.

Refer to Table 1 in section 6.2.1 for outcomes of interest and appropriate comparators.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One ongoing, open-label, international (92 sites from 18 countries), randomized controlled trial, RESPONSE,[2] compared the efficacy and safety of ruxolitinib to standard therapy in adult patients with PV who are resistant or intolerant to HU. For a more detailed description of trial design characteristics refer to Tables 2 and 3 in the Systematic Review (section 6.3.2.1). Standard therapy included any of the following single-agent regimens: HU (at a dose that did not cause unacceptable side effects), INF-alpha (INF-a) or pegylated INF-a, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. The trial permitted patients randomized to standard therapy to crossover to ruxolitinib at or after week 32.

The primary outcome of the trial was a composite response endpoint including the proportion of patients who achieved both HCT control and a reduction in spleen volume of ≥ 35%, as assessed by either MRI or CT imaging, at week 32. Key secondary outcomes included duration of primary response (and progression-free) at week 48, and complete hematological response (CHR) at week 32 (HCT control, platelet count ≤ 400 x 10^9/litre, and a WBC count ≤10 x 10^9/litre). Other secondary outcomes included response rates of durable spleen volume reduction, HCT control, and CHR at week 48, and symptom reduction, quality of life and safety.

The primary efficacy analyses (for primary and key secondary outcomes) were performed using the intent-to-treat principle and were conducted when all patients reached week 48 or discontinued treatment. The analyses of other secondary outcomes were considered exploratory and non-comparative. A follow-up analysis was pre-planned at week 80 to

assess longer-term efficacy and safety; these data have only been published in abstract form. Patient-reported outcomes, including symptom reduction and quality of life (QOL), were also considered exploratory and were assessed descriptively using four different scales completed from baseline through to week 32. Safety analyses included all patients who received at least one dose of study drug (including those patients who received no drug as part of standard therapy).

A total of 222 patients were randomized in the RESPONSE trial; 110 were randomized to ruxolitinib and 112 to standard therapy. Treatment arms were generally balanced with respect to baseline characteristics and disease history. Median age of patients was 60 years. Median time since PV diagnosis was 8.2 and 9.3 years in the ruxolitinib and standard arms, respectively. Median durations of previous HU therapy were 3.1 years in the ruxolitinib arm and 2.8 years in the standard therapy arm. The percentage of patients deemed HU resistant was 46.4% and 45.5% in the ruxolitinib and standard arms, respectively; while 53.6% and 54.5%, were considered HU intolerant.

All patients randomized to ruxolitinib received treatment at a starting dose of 10 mg twice a day, with a maximum allowed dose of 25 mg twice daily. The median total daily dose of ruxolitinib was 22.3 mg/day and, as treatment with ruxolitinib is ongoing, the median duration of treatment was 34 weeks at week 32, 81 weeks at week 48 and 111 weeks at week 80. The types of initial standard therapy used included HU (in 58.9% of patients), INF (11.6%), anagrelide (7.1%), immunomodulators (4.5%), and pipobroman (1.8%). No medication was administered as standard therapy in 15.2% of patients. Six patients (5.3%) switched the type of standard therapy over the course of the trial. A total of 96 (85.7%) patients assigned to standard therapy crossed over to the ruxolitinib arm, with the majority of crossovers occurring immediately at week 32, or shortly after. Patient discontinuations in the standard arm were primarily attributed to lack of efficacy. At week 80, 82.7% (n=91) of patients randomized to ruxolitinib were continuing treatment versus no patients in the standard therapy arm. Of the 98 patients who crossed over to the ruxolitinib arm, 82.7% (n=81) remained on treatment at week 80.

Key outcomes of the RESPONSE trial are summarized in Table 1. At week 32, the primary outcome of response occurred in a statistically significant higher proportion of patients in the ruxolitinib arm compared to patients receiving standard therapy. Similar response rates were observed by HU status. As well, the individual endpoints comprising primary response, duration of primary response, and CHR all significantly favoured the ruxolitinib arm. At week 80 the primary response rate in the ruxolitinib arm decreased slightly to 19.6% (i.e., one patient lost their response). Among the 60% of patients in the ruxolitinib arm who achieved HCT control at week 32, the probability of maintaining response through to week 80 was 89%. All patients in the ruxolitinib arm who achieved a ≥35% spleen volume reduction maintained their response at week 80.

At week 32, the incidences of any grade adverse events were generally similar between trials arms. Compared to standard therapy, ruxolitinib was associated with a higher frequency of the following hematologic adverse events (all grades): anemia (43.6% vs. 30.6%) and thrombocytopenia (24.5% vs. 18.9%). Standard therapy was associated with a higher frequency of neutropenia (8.1% vs. 1.8%) and lymphopenia (50.5% vs. 43.6%). Non-hematologic adverse events occurring more frequently in patients treated with ruxolitinib included diarrhea (14.5% vs. 7.2%), muscle spasms (11.8% vs. 4.5%), dyspnea (10% vs. 1.8%), and herpes zoster infections (6.4% vs. 0, grade 1 or 2). In the standard therapy arm there were a higher percentage of patients with pruritus (22.5% vs. 13.6%). Thromboembolic events (5.4% vs. 0.9%) were also greater despite a higher incidence of these events in the ruxolitinib arm at baseline. The rates of grade 3 or 4 adverse events were

similar in both study arms; while serious adverse events and adverse events leading to treatment discontinuations were more frequent in patients treated with ruxolitinib.

Through week 32, three patients (3%) in the ruxolitinib arm developed myelofibrosis (MF) and one patient (<1%) developed acute myeloid leukemia (AML). There was one case of MF in the standard therapy arm prior to crossover to ruxolitinib and two cases of transformation to MF after crossover. Two deaths occurred after crossover and were considered to be unrelated to ruxolitinib treatment. New or worsening hematologic adverse events occurring up to week 80 (rates per 100 patient-years) included grade 1 or 2 anemia (27.2) thrombocytopenia (14.9), and lymphopenia (27.2); and non-hematologic adverse event rates appeared similar relative to week 48.

Quality of life was measured using the EORTC Quality of Life Questionnaire-Core 30 where a 10-point change in score from baseline to week 32 was considered the minimally important difference (MID). The MID was achieved in 46% and 10% of patients in the ruxolitinib and standard therapy arms. As measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Patient Diary, a 50% reduction in the total symptom score was observed in 49% and 5% in the ruxolitinib and standard therapy arms, respectively. Similar results were reported in the Patient Global Impression of Change instrument, which assessed patients' perception of change in their PV symptoms over time. The Pruritus Symptom Impact Scale indicated an improvement from baseline with ruxolitinib (mean change ranged from -1.4 to -2.2) and standard therapy (mean change ranged from -0.1 to 0.3).

The major limitations and sources of bias associated with the RESPONSE trial include the following:

- The trial was open label and therefore investigators and patients were not blinded to treatment assignment. Patients in the ruxolitinib arm may have been more likely to adhere to experimental therapy and investigators may have been more likely to discontinue treatment in the standard therapy arm. The risk of performance bias is of particular concern since the majority of patients in the standard therapy arm (58.9%) were either receiving HU (a treatment they knew they were intolerant or resistant to) or no therapy at all (15.2%). Since lack of efficacy would be an expected outcome in these patients it is not surprising such a high percentage of patients (87.5%) discontinued treatment due to lack of efficacy and highlights the possibility that the results may also be attributable to factors other than the intervention of interest.
- Since PV is a chronic malignancy, there is value in assessing the longer-term efficacy and safety of ruxolitinib. At present, long-term data from the RESPONSE trial are limited to 80-week data presented in abstract form. The limitations of abstract data should be considered when interpreting these data and further review should be carried out upon full publication. The high-level of crossover in the trial also limits the assessment of longer-term outcomes.
- The standard therapy arm included several different treatment regimens that were selected at the discretion of the treating investigator. Some of these regimens may not be considered standard of care in some Canadian jurisdictions and thus call into question the appropriateness of the comparator regimens selected in this trial.
- Three amendments to the protocol occurred over the course of the trial. The first included significant changes to the inclusion criteria that took effect after 30 patients were randomized. There is a possibility those 30 patients represent a different population of PV patients relative to patients enrolled after the amendment change.
- Patient-reported symptom reduction was assessed using two scales: a modified version of the MPN-SAF patient diary and the Pruritus Symptom Impact Scale. To the knowledge of pCODR, neither instrument has been validated. The EORTC QLQ-C30 was used to assess QOL. Although this tool is validated and commonly used in cancer, it is

not specific to patients with PV. These aspects combined with the open-label design of the trial make the interpretation of patient-reported outcomes difficult.

Table 7: Key outcomes of the RESPONSE trial[2] comparing ruxolitinib to standard therapy in adult patients with polycythemia vera who are resistant or intolerant to hydroxyurea.

Key Efficacy Endpoints	Ruxolitinib n=110	Standard Therapy n=112
Primary	**% (n)**	**% (n)**
Response rate at week 32: Hematocrit control and ≥ 35% reduction in spleen volume	20.9 (23)	0.9 (1)
	OR=28.6 (95% CI, 4.5-1206) p<0.001	
Response rate by HU status:		
Unacceptable side effects to HU (HU intolerance, n=59 vs. n=61)	22 (13)	0
	OR=NA	
Inadequate response to HU (HU resistance, n=51 vs. n=51)	19.6 (10)	2 (1)
	OR=11.96 (95% CI, 1.59-539.56) p=NR	
Individual components of primary response rate:		
Hematocrit control through week 32	60 (66)	19.6 (22)
≥ 35% reduction in spleen volume at week 32	38.2 (42)	0.9 (1)
Secondary	**% (n)**	**% (n)**
Complete hematologic response	23.6 (26)	8.9 (10)
	OR=3.35 (95% CI, 1.43-8.35) p=0.003	
Duration of primary response (at week 32) maintained at week 48	19.1 (21)	0.9 (1)
	OR=26.11 (3.98-1080) p<0.0001	
Quality of Life (EORTC QLQ-C30)	n=89	n=83
Mean change from baseline in overall global health status at week 32**	10.86	-4.82
Harms (at week 32)	n=110	n=111***
Any grade 3 or 4 adverse event	32.7	28.8
Any serious adverse event	13.6	9
Any treatment-related adverse event	59.1	33.3
Adverse events leading to treatment discontinuation	6.4	0.9

Abbreviations: CI - confidence interval; HU - hydroxyurea; OR - odds ratio; NA - not available; NR - not reported; p - p-value.

Notes:
* Rate includes patients who did not discontinue randomized treatment prior to week 8; and is based on 106 patients in the ruxolitinib arm and 109 patients in the standard therapy arm.
**A higher score (mean change) indicates improvement from baseline.
***One patient withdrew consent and did not receive study treatment.

2.1.4 Comparison with Other Literature

Data from three retrospective cohort studies were used to inform the submitted pharmacoeconomic evaluation for ruxolitinib for patients with PV and intolerant or resistant to HU. Specifically, literature on elevated white blood cell (WBC) count as a prognostic marker for reduced overall survival. A synopsis and critique of each study was conducted in order to better understand and contextualize the data supporting the pharmacoeconomic evaluation. Study patient population, methodology, and overall survival results are the focus of each summary.

Tefferi et al (2013)

Tefferi et al[5] conducted a large international retrospective study to examine survival in patients with PV, which included a comparison of life expectancy between the PV and a control population, and identifying predictors of overall survival.

Study eligibility criteria included adherence to the 2008 WHO diagnostic criteria for PV, availability of clinical and laboratory information obtained within one year from diagnosis and before initiating cytoreductive therapy, a diagnosis after 1970, and patient age ≥ 18 years. Seven centres from Italy, Austria and the United States submitted diagnostic and follow-up data on 1818 patients with PV, of which 1545 met the eligibility criteria and were included in the study. The survival curves of the PV population were compared to the expected survival of an age- and sex-matched US population. Overall survival curves were constructed using the methods of Kaplan-Meier and compared using the log-rank test. Cox-proportional hazards regression was used to identify prognostic predictors of survival. All comparisons were significant at $p<0.05$. The number of evaluable patients ranged from 306 to 1545 depending on the variable of interest. Losses to follow-up were not addressed in the study report.

Among the sample of PV patients, gender distribution was 1:1, median age was 61 years, and approximately a third of patients (range 28.5% to 36%) presented at diagnosis with palpable splenomegaly, pruritus, and vasomotor symptoms. Median values (x 10^9/l) for leukocyte and platelet counts were 10.4 and 466, respectively. Treatment of PV was documented as either cytoreductive (73%, n=1129) or aspirin (84%, n=1281).

Median follow-up of the PV sample was 6.9 years. There were 347 (23%) deaths recorded during the follow-up period. The cause of death was documented for less than half of patient deaths (47%, n=164); the majority of these were attributed to AML (n=36), second malignancies (n=36) and thrombotic complications (n=32). The median survival of the PV sample was 18.9 years, which when compared to the survival of the control population, suggested a trend (p=0.1) towards inferior survival among the patients with PV. The authors attributed the lack of a statistically significant reduction in life expectancy to immature survival data; the percentage of deaths ranged from 5% to 44% among the seven centres. When the analysis was restricted to the centre with the most mature data a sensitivity analysis showed significantly shortened survival among PV patients in both young and older patient groups.

All prognostic variables at diagnosis[a] (significant at the univariate level) were included in a multivariate analysis predicting survival. Age [Hazard ratio (HR)=5.6; 95% CI, 4.1-7.8;

[a] Includes age, various hematologic parameters, palpable spleen, pruritus, cardiovascular risk factors, increase in lactate dehydrogenase, leukoerythroblastic smear, abnormal karyotype, JAK2 mutation, serum erythropoietin, endogenous erythroid colony, increased red cell mass, history of tobacco use, diabetes, hyperlipidemia and hypertension.

p<0.0001)], leukocyte count defined as ≥ 10.5 x 10^9/l (HR=1.9; 95% CI, 1.4-2.6; p<0.0001)[b], venous thrombosis (HR=1.9; 95% CI, 1.2-3.0; p=0.0007) and leukoerythroblastic blood smear (HR=2.1; 95% CI, 1.3-3.4; p=0.003) were significantly associated with inferior survival in PV patients (independent of all other variables in the analysis). Thrombocytosis (HR=0.7; 95% CI, 0.6-0.98; p=0.03) and pruritus (HR=0.7; 95% CI, 0.5-0.95; p=0.02) were significantly associated with improved survival. Inclusion of abnormal karyotype into the survival model, which limits the analysis to 383 patients, resulted in a loss of prognostic significance for thrombocytosis and leukoerythroblastosis. The authors used the results of the multivariate analysis to develop prognostic risk groups. Specifically, optimal cut-off levels for age and leukocyte count were tested in the US cohort. Hazard ratios derived from the test analysis were applied as weights in assigning adverse points to age (≥67 years=5 points; 57-66 years=2 points), leukocyte count (≥15 x 10^9/l=1 point) and venous thrombosis (1 point) in order to derive a prognostic model with low (0 points), intermediate (1 or 2 points) and high-risk categories (≥3 points). The prognostic model was then validated in the entire PV sample. The authors reported excellent discrimination between risk groups. The median survivals of the PV sample, stratified by risk, were as follows: 27.8 years for low-risk (n=503), 18.9 years for intermediate-risk (HR=3.7; 95% CI, 2.6-5.2), and 10.9 years for high-risk (HR=10.7; 95% CI, 7.7-15.0).

The main limitations of this large study of PV patients relate to its retrospective design. Many parameters cannot be controlled when data are gathered retrospectively. Differences in influential parameters (i.e., concomitant study medications, variations in institutional practices) can bias study results. This is particularly relevant in this study, which acquired data from seven centres among three countries. Missing data are also an issue with retrospective design. Data were missing for a majority of variables in this study and quite substantially in an area of potential clinical importance (i.e., abnormal karyotype). The missing data signal a risk of selection bias and reduce the statistical power of some analyses, lowering confidence in some of the results obtained. There are also issues with generalizability to the HU resistant/intolerant population. Life expectancy comparisons were made to a control group from the US and did not include representation from the other countries contributing to the study, even though these patients comprised a majority of the sample (78%). The survival analysis too, was restricted to a smaller subset (n=337) of US patients due to data immaturity among non-US centres. Finally, the reported study methods did not include a description of planned subgroup or sensitivity analyses; however, such analyses were performed and results were presented. The chance of obtaining a significant result is more likely when the number of analyses performed is uncontrolled and a less stringent level of statistical significance is used (i.e., p<0.05).

In summary, the study by Tefferi et al[5] provides comprehensive data on the prognostic value of patient characteristics associated with PV and their impact on survival. The results suggest advanced age, elevated leukocyte count, and venous thrombosis are important independent risk factors associated with significantly shorter survival in US patients with PV. This finding was further demonstrated when these variables were used in a prognostic model discriminating levels of risk for survival. The prognostic importance of abnormal karyotype is a finding that requires further inquiry. The study results should be considered in light of the aforementioned limitations.

[b] This is not the hazard ratio (HR) used in the pharmacoeconomic analysis. The effect estimate used (HR=4.1, 95% CI, 2.4-6.9; p<0.0001) was derived from the test analysis (on Rochester US cohort) where leucocyte count was defined as ≥ 15x10^9/l.[13]

Alvarez-Larran (2012)

Alvarez et al[14] conducted a retrospective study to investigate the prognostic value of the ELN criteria for response[12] and resistance/intolerance[15] to HU in patients with PV, and analyzed whether fulfillment of the criteria impacted overall survival.

Eligible patients included those who met updated WHO criteria and received HU as cytoreductive therapy. The medical charts of all patients diagnosed with PV in five institutions in Spain were reviewed, and diagnosis data were reassessed using the updated criteria of the WHO. The timeframe of patient recruitment was not reported. The primary outcome of interest was survival from diagnosis of PV.

Overall survival curves were generated using the methods of Kaplan-Meier. The survival of PV patients was compared to the expected survival of a control population derived from the general population and matched on age, sex, and calendar year of diagnosis. Cox regression analysis was used to identify significant predictors of survival.

A total of 261 patients were included in the study and 24 (9%) were lost to follow-up. The median time of HU exposure was 4.4 years. Response to HU was measured according to ELN response criteria; 24% (n=62) of patients achieved a complete response, 66% (n=173) achieved a partial response, and 10% (n=25) did not achieve a response after a median of 4.6 months of HU therapy. During follow-up, 38% (n=99) of patients lost their response (25 patients permanently and 74 intermittently). HU was withdrawn due to toxicity or lack of response in 11.4% (n=30) and 6.69% (n=18) of patients, respectively.

At the time of analysis, there were 48 (18%) patient deaths, 8 (3%) and 20 (8%) transformations to AML and MF, respectively, and 35 (13%) second malignancies. Cause of death was attributed to AML or MF (n=19), second malignancy (n=9), cardiac disease (n=6), thrombosis (n=5), infection (n=4), bleeding (n=2) and other (n=3). Follow-up from PV diagnosis was 7.2 years and median survival from diagnosis was 19 years, with a 10-year probability of survival of 81%. When survival was measured from the start of HU therapy, the median survival of patients was 18 years (based on 1726 person years of observation). The percentage of patients meeting at least one of the ELN criteria for resistance was 11.5% (n=30) and 12.6% (n=33) fulfilled the ELN criteria for intolerance.

The following prognostic variables were examined in a multivariate analysis predicting survival: age, male sex, cardiovascular risk factors, hematologic parameters at diagnosis (hemoglobin, WBC >10 x 10^9/l, platelet count >500 x 10^9/l), no response in leukocyte count (defined as persistence of WBC >10 x 10^9/l despite treatment with HU), response and resistance to HU (ELN criteria), and thrombosis and bleeding. Of these, resistance to HU (HR=5.6; 95% CI, 2.7-11.9;p<0.001), age (HR=4.1; 95% CI, 1.9-9.0; p<0.001), no response in leukocyte count (HR=2.7; 95% CI, 1.3-5.4; p=0.007) and male sex (HR=2.0; 95% CI, 1.9-9.0; p=0.03) were significantly associated with an increased risk of death (independent of all other variables in the analysis).

The study by Alvarez-Larran et al[14] was well conducted; however, the same aforementioned limitations of retrospective design also apply, including the risk of bias related to patient selection and uncontrolled parameters (e.g., concomitant medications, variable use of in spleen imaging). Generalizability is also an issue since the study was restricted to Spanish patients from hospital centres (as opposed to the general population). This study suggests that no response in leukocyte count was predictive of worse survival outcomes while ELN criteria for response was not predictive of survival. Unlike the other two studies reviewed, it included resistance to HU as a prognostic

variable; in the multivariate analysis, HU resistance and not venous thrombosis was associated with a statistically significant shortened survival (HR=5.6; 95% CI, 2.7-11.9; p<0.001).

Bonicelli et al (2012)

Bonicelli et al[16] conducted a retrospective study including two population-based cohorts for the purpose of examining prognostic risk factors for survival among patients with PV. The study included all patients registered between 1980 and 2008 in two population registries, one in France and the other in Sweden. Specific study eligibility criteria were not described in the study report. PV diagnosis was made according to PV Study Group criteria between 1980 and 2001, and WHO criteria through to 2008.

Overall survival curves were generated using the methods of Kaplan-Meier. The survival of PV patients was compared to the expected survival of a control population derived from the general population of the two countries matched on country, age, sex and calendar year. Relative overall survival rates were calculated using proportional hazards regression.

A total of 327 patients with PV were included in the study (188 patients from France and 139 from Sweden). Among the sample, the percentage of male patients was 46% and median age was 71 years. The authors noted no differences in disease presentation between patients diagnosed with PV Group versus WHO criteria; however no data in support of this assertion were presented. At diagnosis median hemoglobin (g/l), leukocyte ($x10^9$/l), and platelet ($x10^9$/l) counts were 176, 13, and 515, respectively. Myelofibrosis was present in 37 patients (11%) and transformation to AML had occurred in 30 patients (9%). Median follow-up time was 11 years and 21 patients were lost to follow-up.

During the follow-up period, 244 patients died and the cause of death was documented for 174 (71%) patients. The recorded deaths were related to thrombotic events (21%), secondary AML (17%), solid tumours (17%) and heart failure (15%). Overall median survival, reported by age group for the PV cohort, was 17.5 years for patients <65 years of age and 6.4 years for patients ≥ 65 years. The relative survival rates of the PV cohort at 5, 10 and 20 years were 93%, 72%, and 46%, respectively. The authors noted no difference in survival between the two cohorts of patients.

The following variables (significant at the univariate level) were included in the multivariate analysis predicting survival: age >60 or >70 years, hyperleukocytosis (WBC >11 x 10^9/l), median WBC (WBC >13 x 10^9/l), hemoglobin, HCT, platelet count, and thrombosis at time of diagnosis. Of these, age > 70, hyperleukocytosis, and thrombosis at diagnosis were significantly associated with poor survival outcomes (independent of all other variables in the analysis). Among the subgroup of PV patients <60 years of age, only thrombosis was identified as an independent risk factor for inferior survival. Effect estimates and p-values were not reported. Risk stratification incorporating the variables of age, hyperleukocytosis, and thrombosis was also performed in this study. Risk was determined based on how many risk factors were present: low (none present), intermediate (one present), and high (2 or three present). Ten-year relative survival for the risk groups was 84%, 59%, and 26% for the low-, intermediate- and high-risk groups, respectively (p<0.001).

In addition to the limitations associated with retrospective design, the study by Bonicelli et al suffers from poor reporting. It is difficult to have confidence in the findings reported when important information on methodology (i.e., study eligibility criteria, validity of risk stratification) and key results (i.e., distributions of important patient characteristics,

effect estimates) are missing from the published study report. Barring this in mind, the study is consistent with the findings of the other two studies, suggesting worse survival associated with age, elevated leucocyte count and thrombosis.

2.1.5 Summary of Supplemental Questions

What type and degree of resistance and intolerance to HU would be considered in order to support a switch in treatment to ruxolitinib?

A search was undertaken, at the request of the pCODR Provincial Advisory Group, to identify and summarize existing criteria and/or clinical guideline recommendations that define intolerance and resistance to HU in order to ascertain when in the treatment course of PV it is appropriate to discontinue HU therapy and offer ruxolitinib. The search identified one set of criteria, the ELN Definitions of Resistance/Intolerance to HU in patients with PV,[15] which are based largely on expert opinion and consensus. One retrospective study of 261 patients has assessed the prognostic value of using the criteria for determining when to introduce second-line treatment after HU.[14] The study found that HU resistance as defined by the ELN criteria (but not intolerance) was associated with a significantly higher risk of death and transformation to AML or MF relative to non-resistant patients. The timing and reasons for initiating other therapy after HU, however, were not reported despite being objectives of the study. These results should be interpreted within the context of retrospective study design limitations and requires prospective validation. However, they do suggest HU resistance is an important prognostic factor for patients with PV. The development of HU intolerance, although not of prognostic significance, may be a useful indicator of when to consider switching treatment from HU to other cytoreductive therapy. ELN management guidelines for PV recommend switching first-line therapy at the onset of intolerance in high-risk patients and suggest INF-a as the regimen of choice. The management guidelines were developed before results and publication of the RESPONSE trial became available.

See section 7.1 for more information.

2.1.6 Other Considerations

See section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

One patient advocacy group, the Canadian Myeloproliferative Neoplasms Network (Canadian MPN), provided input on the ruxolitinib (Jakavi) submission as treatment for PV patients who are resistant to or intolerant of HU, and their input are summarized below.

From a patient perspective, there are a number of symptoms associated with PV, which include cognitive impacts (e.g., difficulty concentrating, stress/anxiety), fatigue, itching, night sweats, and pain. Respondents also reported about the impact of PV on their daily living (work and taking care of family). Respondents who had experience with ruxolitinib reported side effects, mainly nausea or abdominal effects (e.g., diarrhea and pain), but none experienced serious effects or problems with the drug under review. According to Canadian MPN, respondents reported a reduction in symptoms; in particular, some respondents said their

spleen size had reduced considerably ("no longer palpable"). Some respondents also stated that they no longer need to rely on phlebotomies and experienced a reduction in stress and anxiety, especially their concern about the risk of blood clots or a heart attack.

PAG Input

The PAG 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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ruxolitinib for PV:

Clinical factors:

- Fills gap in therapy for patients resistant or intolerant to HU
- Indication creep - pressure from clinicians and patients to use in first-line

Economic factors:

- High number of patients deemed intolerant to HU
- Duration of treatment in responding patients not fully elucidated
- High cost of drug

2.2 Interpretation and Guidance

Burden of Disease & Need

Polycythemia vera (PV) is one of the MPNs that is characterized by the presence of an elevated red cell mass. Its incidence is estimated to be around 2 per 100,000 per year with a median age at diagnosis of approximately 60 years. Greater than 95% of these patients have a clonal marker (JAK2 mutation). The goals of treatment are to decrease the risk of thrombosis and to control symptoms. This condition is chronic with no curative treatment available to date. Current standard treatments include, 1) phlebotomy for HCT (<45%); 2) low dose as (for thrombosis prevention); and 3) HU, as first-line pharmacologic intervention for disease control.

About 18 to 21.8% of patients with PV will develop resistance or intolerance to HU. Currently, there is no second-line treatment with proven efficacy in this cohort of patients compared to standard of care options. Based on ELN criteria, patients are considered resistant to HU if 1) they continue to require phlebotomy after being on HU for >3 months at a dose of >2g/day OR; 2) uncontrolled myeloproliferation with platelet count >400 and WBC >10 OR; 3) failure to achieve 50% reduction in splenomegaly or symptoms related to splenomegaly despite >2g/day of HU over >3 months. Intolerance to HU could be due to leg ulcers, grade 3 and persistent or mucocutaneous ulcer, gastrointestinal symptoms, pneumonitis, persistent fever; OR it could be due to absolute neutrophil count of <1.0 and platelet count <100 at the lowest dose of hydroxyurea to achieve hematologic response.

Ruxolitinib is the first targeted treatment with proven efficacy to improve disease-related outcomes in patients that have demonstrated intolerance or resistance to standard first-line treatment with HU.

Effectiveness

The RESPONSE trial is a phase III open label RCT that has addressed the need of second-line treatment in patients with PV who had demonstrated intolerance or resistance to HU (based on ELN criteria). The study population was randomized to ruxolitinib versus standard therapy. Cross over was allowed after 32 weeks if the primary endpoint was not met or in cases of disease progression, 85.7% of patients in the standard of care arm crossed over to the ruxolitinib arm at or after 32 weeks. The comparator arm, standard therapy, included standard treatments that are used in clinical practice. The study population was noted to have a median time since diagnosis of 8.2 and 9.3 years and median duration of previous treatment with HU of 3.1 and 2.8 years in the ruxolitinib and standard therapy arms, respectively. The majority of the patients had an ECOG performance status of 0-1 and had developed either resistance to HU (46.4% vs. 45.5%) or intolerance (53.6% vs 54.5%) in the ruxolitinib and standard therapy arms, respectively.

The primary outcome was a composite primary response outcome, which included both HCT control and a ≥35% reduction in spleen volume. This occurred in a significantly higher proportion of patients in the ruxolitinib arm compared to patients in the standard therapy arm (20.9% vs. 0.9%), a difference that was statistically significant ($p<0.001$). Key secondary outcomes included duration of primary response, among patients in each arm achieving a primary response at week 32, 21 patients (19.1%) in the ruxolitinib arm and one patient (0.9%) in the standard arm maintained a response at week 48 ($p<0.001$). Complete haematological response was achieved in a significantly higher proportion of patients randomized to ruxolitinib; the response rates were 23.6% compared with 8.9% with standard therapy ($p=0.003$). Improvement in symptom score was noted with ruxolitinib compared to standard therapy (49% vs. 5%) as measured by the modified MPN-SAF Patient Diary. Quality of life measured in the RESPONSE trial also favoured the ruxolitinib arm.

Safety

Adverse events were evaluated at week 32 since 85.7% of patients in the standard therapy arm crossed over to the ruxolitinib arm. Both ruxolitinib and standard therapy arms were associated with very few grade 3/4 adverse events. Non-clinically significant but notable differences in toxicity included the rate of herpes zoster infection (6.4% vs. 0%) and skin cancers (3.6% vs. 1.8%). There were similar low rates of progression to myelofibrosis (2.7% vs. 0.9%) and there was no difference in progression to AML in either arm (0.9% vs. 0.9%).

2.3 Conclusions

The CGP concluded that there is a net overall clinical benefit with the use of ruxolitinib in patients with PV who have specifically demonstrated intolerance or resistance to HU based on one ongoing phase III RCT (RESPONSE). There is a statistically significant and clinically meaningful benefit demonstrated with ruxolitinib in this patient population in controlling the HCT and reducing spleen size. Compared to standard therapy, symptom scores related to PV were also significantly reduced. Grade 3/4 adverse events were uncommon, manageable and the rates were similar across treatment arms. The CGP also considered that from a clinical perspective:

- The clinical benefit demonstrated in the RESPONSE trial aligned with what was reported in the patient advocacy input.

- It is noted that the evidence for use of ruxolitinib is only in a specific population of patients with PV in the second-line setting. There is no current data for its use in the first-line setting.
- Ruxolitinib may be used with a 32-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 experimental therapy.
- The duration of ruxolitinib therapy is indefinite at this time. Regular monitoring for the duration of therapy, spleen size, blood counts, and evidence of transformation is essential. Phlebotomy needs may change with treatment with ruxolitinib.
- Discontinuation of therapy should be through a tapering routine if possible and will require careful monitoring because of the potential for significant rebound symptoms.
- There is currently no randomized controlled trial data to inform the use of ruxolitinib in cases of resistance or intolerance to other cytoreductive therapies such as INF, however this may be a very small subset of patients in the Canadian context. Therefore, use of ruxolitinib in this setting should be on a case-by-case basis with the stopping provisions as discussed above.
- Three retrospective cohort studies suggest that elevated WBC count is associated with worse overall survival in PV, however, it has not been demonstrated that modifying the WBC count changes overall survival. Thus, the CGP felt that based on the current level of evidence, a more appropriate end-point for the submitted cost-effectiveness analysis was CHR.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Polycythemia Vera (PV) is one of the chronic myeloproliferative neoplasms (MPNs), which are collectively characterized by clonal proliferation of myeloid cells with variable morphologic maturity and hematopoietic efficiency. Polycythemia vera is distinguished clinically from the other MPNs by the presence of an elevated red blood cell mass. However, an increased red blood cell mass alone is insufficient to establish the diagnosis, since this is also observed in conditions associated with chronic hypoxia and with erythropoietin-secreting tumours.[3]

Polycythemia vera occurs in all populations, and all ages, including children and adolescent. The median age at diagnosis is approximately 60 years.[4,5] Approximately one-quarter of cases present before age 50 years and one-tenth before age 40 years. The incidence of PV is estimated to be around 2/100,000/year.[6] Incidence is lower in Japan than in Europe and North America. Prevalence of PV is estimated to be 57 per 100,000 in Canada, which suggests there are approximately 20,483 cases in Canada.[7]

Most patients with PV are discovered incidentally when elevated hemoglobin is noted on a complete blood count obtained for another reason. Others present with disease-related symptoms (e.g., headache, dizziness, visual disturbances, pruritus, and early satiety due to enlarged spleen) or complications like thrombosis, bleeding, etc.

Diagnosis is established based on WHO criteria for PV, which includes clinical, laboratory evaluation and molecular features.[17]

WHO Criteria for Diagnosis

The two major criteria for diagnosis include, an increased hemoglobin level (>18.5 g/dl in men or >16.5 g/dl in women) or other evidence of increased red cell volume and presence of a JAK2 mutation.[17] Over 95% of patients with PV have JAK2 mutation, a clonal marker, involving either exon 12 or 14. The three minor criteria include typical findings on the bone marrow aspiration/biopsy, a serum EPO level below the reference range for normal, and endogenous erythroid colony formation in vitro. The diagnosis of PV requires the presence of both major criteria and one minor criterion, or the presence of the first major criterion together with two minor criteria. These diagnostic criteria should be applied only to patients who have undergone the appropriate diagnostic evaluation to exclude secondary causes of polycythemia.

In practice, otherwise unexplained elevated hematocrit (HCT), JAK2 mutation and subnormal erythropoietin level establishes the diagnosis. The median survival of untreated symptomatic patients with PV was initially estimated at 6 to 18 months from the time of diagnosis,[8] whereas current survival of treated patients is 13 years or more.[9] With treatment, overall mortality is greater than that of an age- and sex-matched normal population.[5,9-11] In a large multinational prospective study of 1638 patients, the overall mortality rate was 3.7 deaths per 100 persons/year.[18] Thrombotic events (cardiovascular and cerebrovascular thrombosis), solid tumours, and hematologic transformation (acute myeloid leukemia (AML), myelofibrosis (MF)) accounted for 45%, 20%, and 13% of the deaths, respectively.

3.2 Accepted Clinical Practice

Goals of therapy in PV are to reduce thrombosis without increasing bleeding tendency, to ameliorate symptoms and to prolong duration of progression to hematologic complications.

Non-pharmacological interventions include lifestyle modifications to reduce risk of vascular complications. This may consist of advocating for smoking cessation, physical exercise, control of body weight, adherence to medications for hypertension, hypercholesterolemia, diabetes, etc.

Patients with low risk [age <60 years, white blood cell (WBC) <11/13 x10^9/L and no thrombosis history] can be treated with intermittent phlebotomy, low dose aspirin and non-pharmacological interventions as above. Patients with high risk (>60 years, WBC >11/13 x10^9/L and history of thrombosis), in addition to the above, also require cytoreductive therapy. The gold standard at present is HU. The dose of HU is titrated based on blood parameters and is anywhere from 500mg/day to 2 grams per day. In some circumstances interferon (INF) can be used as first-line treatment (e.g. women of childbearing potential or pregnant). When used, side effects (flu-like symptoms, depression, heart, ocular complications) may lead to discontinuation in 20 to 40% of patients.

Based primarily upon the observations and recommendations of the Polycythemia Vera Study Group (PVSG), the goal of phlebotomy is to keep the HCT below 45% in men and 42% in women. Low dose ASA (81mg) is given to all patients unless intolerance, bleeding complications or it is contraindicated for other reasons. Use of cytoreductive treatment also results in decrease in phlebotomy requirement.

Unfortunately both HU and INF provide only transient relief of other symptoms like pruritus or symptoms due to splenomegaly.

Second-line agents sometimes used in practice, due to intolerance/toxicity/refractoriness to HU, are INF and busulphan. Busulphan may cause profound and long-lasting cytopenias, marrow aplasia, skin pigmentation, pulmonary fibrosis, and leukemia in patients with PV. Other agents cited in the literature and used in the treatment of PV are anagrelide, pipobroman and ^{32}P with the latter two associated with increased risk of leukemia.

Current therapeutic landscapes for PV is limited to prevention of complications and are not curative. Treatment options for patients who are refractory to HU are inadequate. Ruxolitinib, a JAK (1,2) inhibitor, is a promising treatment option (based on the RESPONSE trial) for this subset of patients who are resistant to or intolerant of HU. Other agents still undergoing clinical trials are, histone deacetylase inhibitors (HDAC) like givinostat, vorinostat and pegylated INF.

3.3 Evidence-Based Considerations for a Funding Population

Based on the published literature and European Leukemia Net (ELN) consensus definition (refer to table below),[7,12] 18 to 21.8% of patients are intolerant or resistant to HU in the PV treated population. Taking into consideration the Canadian prevalence of PV, approximately 3687 to 4465 patients with PV are intolerant or resistant to HU in Canada. Currently there is a lack of adequate treatment options for this patient population.

Criteria of clinical resistance and intolerance to hydroxyurea in PV based on the European LeukemiaNet (ELN) consensus.	
Type	**Criteria**
Resistance	
1	Need for phlebotomy to keep Hct <45% after 3 months of ≥2 g/day of hydroxyurea, OR
2	Uncontrolled myeloproliferation, i.e., platelet count >400 x 10^9/L AND white blood cell count >10 x 10^9/L after 3 months of ≥2 g/day of hydroxyurea , OR
3	Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly after 3 months of ≥2 g/day of hydroxyurea , OR
Intolerance	
4	Absolute neutrophil count <1.0 x 10^9/L OR platelet count <100 x 10^9/L or Hb <100 g/L at the lowest dose of hydroxyurea required to achieve a complete or partial clinic-hematological response+, OR
5	Presence of leg ulcers or other unacceptable hydroxyurea-related non-hematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea
Notes: *Organ extending by >10 cm from the LCM. +Complete response was defined as Hct <45% without phlebotomy, platelet count ≤400 x 10^9/L, white blood cell count ≤10 x 10^9/L, and no disease-related symptoms. Partial response was defined as Hct <45% without phlebotomy, or response in three or more of the other criteria.	

3.4 Other Patient Populations in Whom the Drug May Be Used

Ruxolitinib use has been approved for use in MF. The Hematology CGP is currently not aware of any other off-label use of ruxolitinib.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, the Canadian Myeloproliferative Neoplasms Network (Canadian MPN), provided input on the ruxolitinib (Jakavi) submission as treatment for polycythemia vera (PV) patients who are resistant to or intolerant of hydroxyurea (HU), and their input is summarized below.

The Canadian Myeloproliferative Neoplasms Network conducted individual interviews and a survey of respondents from within and outside of Canada. According to Canadian MPN, the experiences of the PV patients were similar to those reported by the myelofibrosis (MF) patients, and the survey used previously with MF patients was modified on Survey Monkey in order to be sent out through the Canadian MPN network as well as several USA sites, namely the MPN Forum and MPN Research Foundation. Respondents were recruited through outreach from the MPN network, physician referral to the Canadian MPN network, MPN forum, and the MPN Research foundation. In addition, physicians treating patients with PV and conducting clinical trials with ruxolitinib were also contacted, and were sent PDF copies as well as the link to an online survey to forward to their patients.

Input was requested from respondents that represent PV patients with and without experience with ruxolitinib. Canadian MPN received a total of 24 patient responses. Eight of these patients had experience with ruxolitinib. Of the eight respondents who had experience with ruxolitinib, five were Canadian and the other three were from outside Canada. Four of the Canadian PV patients with ruxolitinib experience were from Ontario and one was from British Columbia. None of the respondents were caregivers. According to Canadian MPN, respondents have been diagnosed from three to 20 years and range in age from 27 to over 64 years of age.

From a patient perspective, there are a number of symptoms associated with PV, which include cognitive impacts (e.g., difficulty concentrating, stress/anxiety), fatigue, itching, night sweats, and pain. Respondents also reported about the impact of PV on their daily living (work and taking care of family). Respondents who had experience with ruxolitinib reported side effects, mainly nausea or abdominal effects (e.g., diarrhea and pain), but none experienced serious effects or problems with the drug under review. According to Canadian MPN, respondents reported a reduction in symptoms; in particular, some respondents said their spleen size had reduced considerably ("no longer palpable"). Some respondents also stated that they no longer need to rely on phlebotomies and experienced a reduction in stress and anxiety, especially their concern about the risk of blood clots or a heart attack.

Please see below for a summary of specific input received from the Canadian MPN. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Polycythemia Vera

Respondents were asked to identify symptoms and issues associated with PV. According to Canadian MPN, most respondents reported that they had experienced symptoms and knew something was wrong at least a couple of years prior to diagnosis. Canadian MPN reported that the most frequent mentioned symptoms were cognitive impacts (e.g., difficulty concentrating, stress/anxiety), fatigue, itching, night sweats and pain. Patients also reported impact on daily living (work and taking care of family). Most respondents also commented that they suffered from all of these symptoms, and rated them as varying from "*some*" to "*very severe*".

Below are some of the key comments gathered from respondents through the Canadian MPN survey:

- *"I have an ever present level of fatigue and low grade migraine. My blood pressure has been high since dx requiring multiple meds at escalating doses. I have persistent tinnitus."*
- *"The fatigue has really impacted my daily routine. …I can barely make it home. Also, the night sweats are all day long and they make me feel week (sic) and breathless. My day usually ends around 3 pm as far as out-of-the-house activity. …Some days I can't even walk through the mall with family or friends because I'm out of breath and have to keep stopping."*
- *"I often feel very frustrated with the pain and side effects of the treatment that hinders my daily activities. … My feet always feel tired and headaches are pretty much daily. I experience itching, increased spleen size and increased body inflammation."*
- *"Can you imagine what it is like to not be able to take a shower or a bath without incredible itching that feels like insects crawling up your legs? The fatigue that means you have to plan and limit yourself to two major activities a day. The migraine headaches that increase as your HCT goes up. Then there is the bone pain that keeps you awake at night. There is also the occasional gout in the big toe. I also suffer from spleen pain as it is enlarging. The social burden of PV is that you don't look sick and people do not understand."*

Canadian MPN reported that 54% (13/24) of respondents stated that they were "*much*" or "*very much*" affected by "*difficulty concentrating*" and nearly half of respondents were "*much*" or "*very much*" affected by "*stress/anxiety*", by "*itching*", and by "*inactivity due to the disease."* In addition, 37.5% (9/24) of the respondents were "*much or very much*" bothered by "*fatigue"* and the impact on their "*work performance*" and/or "*daily activities*." Canadian MPN stated that they were unaware how many of these respondents were the 'same persons' who would have experienced multiple symptoms or whether these were unique.

4.1.2 Patients' Experiences with Current Therapy for Polycythemia Vera

Canadian MPN reported that all of the 24 respondents had or were currently receiving phlebotomy to manage their condition, and all except one had or were also on an aspirin regimen (to reduce red cell count). In addition, approximately three-fourths had or were taking HU, only two were also taking INF (pegylated), and eight also had experience with ruxolitinib.

According to Canadian MPN, respondents reported that phlebotomy (alone) or with aspirin had worked in reducing their blood counts, at least for a while.

One comment gathered from a respondent stated that "*The benefits of aspirin and phlebotomy are that the (sic) temporarily lower my HCT."*

One respondent stated the following:

- *"I didn't really mind the phlebotomies even though it meant going to hospital every two or three weeks, and I really was not able to happy with all of the side*

effects of the hydroxyurea, but I was willing to take it as long as it kept my hematocrit at a normal level. But when that was no longer working, I felt that my life was over."

Canadian MPN noted the following comments among those who had progressed to HU:

- One respondent stated that the HU had not worked at all in relieving his key symptom (itching).
- Some respondents (nearly two-thirds) stated that it had worked "*for a while*" but it was no longer currently as effective or had become *"not at all*" effective.
- Some respondents mentioned that the dosing of HU had been increased.
- One comment gathered from a respondent stated that "*Hydroxyurea has definitely kept my levels under control. The dosage has been increased twice since 2009. I have an enlarged spleen of course but BMB revealed that so far I don't qualify for Jakavi."*
- All respondents mentioned that there were "*some*" to "*much*" side effects with the HU (fatigue, nausea, night sweats, itching) and that they were still receiving phlebotomies while on HU.

Respondents also reported that their experience with INF was limited and was presented as effective in reducing the blood counts but had significant side effects.

Below are some of the key comments gathered from respondents through the Canadian MPN survey and individual interviews who have experienced with INF:

- *"I am currently on Interferon. It has minimized by (sic) itching, headaches and stopped spleen from growing. I seem to still need phlebotomies every 6-8 weeks. The side effects of the drug is nausea and increased inflammation which is hard to take. The CBC's are coming back within the normal range for most of my visits to the doctors."*
- *"I wish there was a pill form of medication for polycythemia. I really don't like the weekly injection of the interferon and I do find it hard on me. I am also concerned that I read that interferon is also considered a carcinogen. This worries me greatly."*

4.1.3 Impact of Polycythemia Vera and Current Therapy on Caregivers

Canadian MPN stated that although there was no direct feedback from caregivers, several respondents mentioned the impact that PV had on the family, especially parents with children or adults who were still of working age but no longer able to work as previously.

One comment gathered from a respondent stated that "*I have young children and I just wish I felt better to fully meet the requirements of being a wife, mom and full time employee."* Another respondent reported: *"I had to retire early and this has put a strain on my husband who has to work full time and also take over the household chores when I am not up to it*."

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with ruxolitinib (Jakavi)

According to Canadian MPN, all of the patients responded that they knew of ruxolitinib, regardless of their personal experience with the drug. Some had only read about it (on the Internet) while others knew of PV patients (or patients with MF or other conditions) who were on ruxolitinib (in Canada or elsewhere).

Canadian MPN reported that respondents who had no direct experience with ruxolitinib expressed the opinion that they understood it was not a cure for PV, although about one-fourth stated that they expect it would slow down progression of their disease. Conversely, about the same number explicitly said it would probably not "keep the disease from progressing."

It was also reported that most of the younger respondents expressed their hope of being able to return to work or to resume their daily activities because their symptoms would be better managed. Some respondents said they anticipate it would reduce their risk of disease progression to MF and other organ damage, or death, although some acknowledged that there were no data on impact on disease progression or survival.

Most respondents anticipate that ruxolitinib would better manage their symptoms and also reduce the size of their spleen and therefore the need for a splenectomy. Another potential benefit that respondents expected was that it could reduce or eliminate the need for regular phlebotomies as well as avoid the side effects of other drugs (HU and/or INF).

To help better illustrate the expectations of the drug under review, below are some of the key comments gathered from respondents through the Canadian MPN survey:

- *"I hope it slows down progression considerably and improves quality of life by eliminating the dreaded symptoms."*
- *"[It will] control blood counts with fewer side effects than other treatments, reduce itching and improve energy levels. Also, hopefully reduce the allele burden."*
- *"I strongly feel it will help so many patients like myself to have an increased quality of life and minimize the harsh side effects of the drugs currently used and the symptoms of the disease."*

Canadian MPN reported that the respondents who were most eager for ruxolitinib to be available were those who said they were no longer responsive to or able to manage the side effects of HU.

One respondent commented the following:

- *"According to the bone marrow biopsy, [in spite of the increases in hydroxyurea], my blood counts are still going up and my spleen has also grown, so I am sure that Jakavi will be in my future."*

Only a few of the respondents indicated that they knew how ruxolitinib worked. When prompted, the patients interviewed said they believed the drug would reduce the production of red blood cells and therefore reduce the risk of blood clots and the enlargement of the spleen.

Canadian MPN reported that most of the respondents indicated that they knew a potential risk of "too low" blood counts, including the risk of anemia, bleeds or infections, but most also said that the benefit of no longer being "dependent on phlebotomy" far outweighed these risks. Respondents also stated their awareness that that there could be other side effects, but most felt that overall the adverse effects of ruxolitinib would be much less than those with their current treatments (e.g., fatigue, nausea, pain).

According to Canadian MPN, the 5 Canadian respondents who had experience with ruxolitinib through the clinical trials were all still on therapy, some now with 2 or more years of experience. Canadian MPN reported that about half of respondents had experienced some side effects, mainly nausea or abdominal effects (diarrhea and pain), but none experienced serious effects or problems with the drug.

The most important benefit reported by respondents was the reduction in symptoms. Some respondents said their spleen size had reduced considerable ("*no longer palpable*"); they had less itching, abdominal pain, increased energy, and less pain.

Below are some of the key comments gathered from respondents through the Canadian MPN survey:

- *"For 2 years I had an itch after my skin was exposed to water that made showering or swimming particularly difficult. After water exposure I need about 15 min of ice packs on my torso to get rid of itch. Since March, when I started the ruxolitinib, I no longer itch after water exposure."*
- *"The doctor said that it is not a cure and that my disease may probably progress, but this is the best I have felt in years."*
- *"I know it is not a cure for PV but for me and my family, it is just about the next best thing. We have our lives back as a family."*

Canadian MPN reported that six out of eight respondents expressed the benefit of no longer needing to rely on phlebotomies and experienced a reduction in stress and anxiety, especially their concern about the risk of blood clots or a heart attack. One respondent stated *"I used to wake up in the middle of the night with bone pain and night sweats, but the biggest benefit of Jakavi is that I am no longer consumed by the fear that I will have a life-ending blood clot or heart attack."*

4.3 Additional Information

None.

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 Polycythemia vera (PV). PAG 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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ruxolitinib for PV:

Clinical factors:

- Fills gap in therapy for patients resistant or intolerant to hydroxyurea (HU)
- Indication creep - pressure from clinicians and patients to use in first-line

Economic factors:

- High number of patients deemed intolerant to HU
- Duration of treatment in responding patients not fully elucidated
- High cost of drug

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

5.1 Factors Related to Comparators

PAG identified that patients in Canada with PV who are resistant or intolerant to HU are treated with interferon (INF), anagrelide, aspirin, no treatment or best supportive care. This is similar to the treatment options in the control arm of the RESPONSE trial.

5.2 Factors Related to Patient Population

PAG noted that ruxolitinib is a new class of drug that provides a new treatment option for patients who are resistant or intolerant to HU. Ruxolitinib would replace current treatments in the second-line setting.

PAG identified that there will be requests from clinicians to use ruxolitinib in the first-line setting, before HU. PAG has concerns that the threshold for intolerance or resistance to HU would be lower with the availability of ruxolitinib.

5.3 Factors Related to Dosing

The flat starting dose and the twice daily administration is similar to HU. These are enablers to implementation.

Although the availability of five different strengths is an enabler for ease of dose adjustments, PAG indicated that the flat pricing (same price for all tablet strengths) would be a barrier to implementation. PAG noted that two 10mg tablets would be twice the cost

of one 20mg tablet with the flat pricing structure. In addition, there would be added costs for dose modifications. For example, a patient whose dose is escalated to 25mg twice daily dose may be dispensed either 20mg tablets plus 5mg tablets (1x20mg + 1x5mg per 25mg dose) or 10mg tablets plus 5mg tablets (2x10mg + 1x5mg per 25mg dose) and the cost of the latter dispensing strategy is higher with the flat pricing.

There are also concerns with the potential for drug wastage for patients who may be dispensed one strength but require dose adjustments to a different strength prior to finishing the original strength dispensed.

5.4 Factors Related to Implementation Costs

As ruxolitinib is administered orally, chemotherapy units and chair time would not be required. In addition, health care professionals are already familiar with ruxolitinib. These are enablers to implementation.

PAG noted that while PV is uncommon, there could be a large prevalent population eligible for treatment with ruxolitinib and the potential for a large number of patients who are deemed intolerant to HU. Given that HU is generally well tolerated, PAG is seeking information on the nature of intolerance to HU that would be considered in order to support switching to ruxolitinib.

In addition, as PV is a chronic condition, PAG is seeking information on the benefits of ruxolitinib compared to phlebotomy and whether treatment with ruxolitinib would decrease the need for phlebotomy.

Additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions.

5.5 Factors Related to Health System

Ruxolitinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they 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 and their families. The other coverage options for patients not eligible for Pharmacare coverage are: private insurance coverage or full out-of-pocket expenses.

5.6 Factors Related to Manufacturer

PAG identified the high cost of the drug and the same price for all strengths would be a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of ruxolitinib (Jakavi) compared with standard therapy in adult patients with polycythemia vera (PV) who are resistant or intolerant to hydroxyurea (HU).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group (PAG) were identified while developing the review protocol and are outlined in section 7.

- What type and degree of resistance and intolerance to HU would be considered in order to support a switch in treatment to ruxolitinib?

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Hematology Clinical Guidance Panel (CGP) 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
Randomized controlled trials	Adult patients (≥18 years) with original diagnosis[§] of PV and resistance or intolerance to HU Subgroups: -Prior DVT vs. none	Ruxolitinib 10 mg bid (starting dose) to a maximum of 25 mg bid (minimum of 5 mg daily)	Standard therapy can include the following: • Cytoreductive agents: o HU (at a tolerated dose likely to provide benefit) o Interferon o Anagrelide o Immunomodulators (e.g., lenalidomide, thalidomide), o Busulfan o Pipobroman o Chlorambucil o Phosphorus-32 • Aspirin • BSC (e.g., phlebotomy as needed, medications for symptom control)	• Response rate • **HCT control/frequency of phlebotomy** • **Spleen volume reduction** • **Hematologic response/remission** • Proportion of patients achieving durable response • **Control of symptoms** (e.g., pruritus, systemic symptoms, sweats, weight-loss) • Adverse events including thrombotic events and flare (of spleen size and blood counts upon drug withdrawal or interruption) • **HRQoL**

Abbreviations: bid - twice daily; BSC - best supportive care; DVT - deep vein thrombosis; HCT - hematocrit; HRQoL - health-related quality of life; HU - hydroxyurea; PV - polycythemia vera.

Notes:
*Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
[§]Excludes patients who have transformed to myelofibrosis.

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 to present) with in-process records & daily updates via Ovid; Embase (1974 to 2015 September 09) via Ovid; The Cochrane Central Register of Controlled Trials (August 2015) via Ovid; 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 concepts were ruxolitinib, Jakavi, Jakafi and polycythemia vera.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of December 3, 2015.

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 – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian 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 additional 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. One member of the pCODR Methods Team independently made the initial selection of studies to be included in the review; any uncertainties regarding eligibility were resolved through discussion with the CGP.

Included and excluded studies (with reasons for exclusion) are identified in section 6.4.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the CGP 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 pCODR Methods Team, the CGP and the pCODR Secretariat:

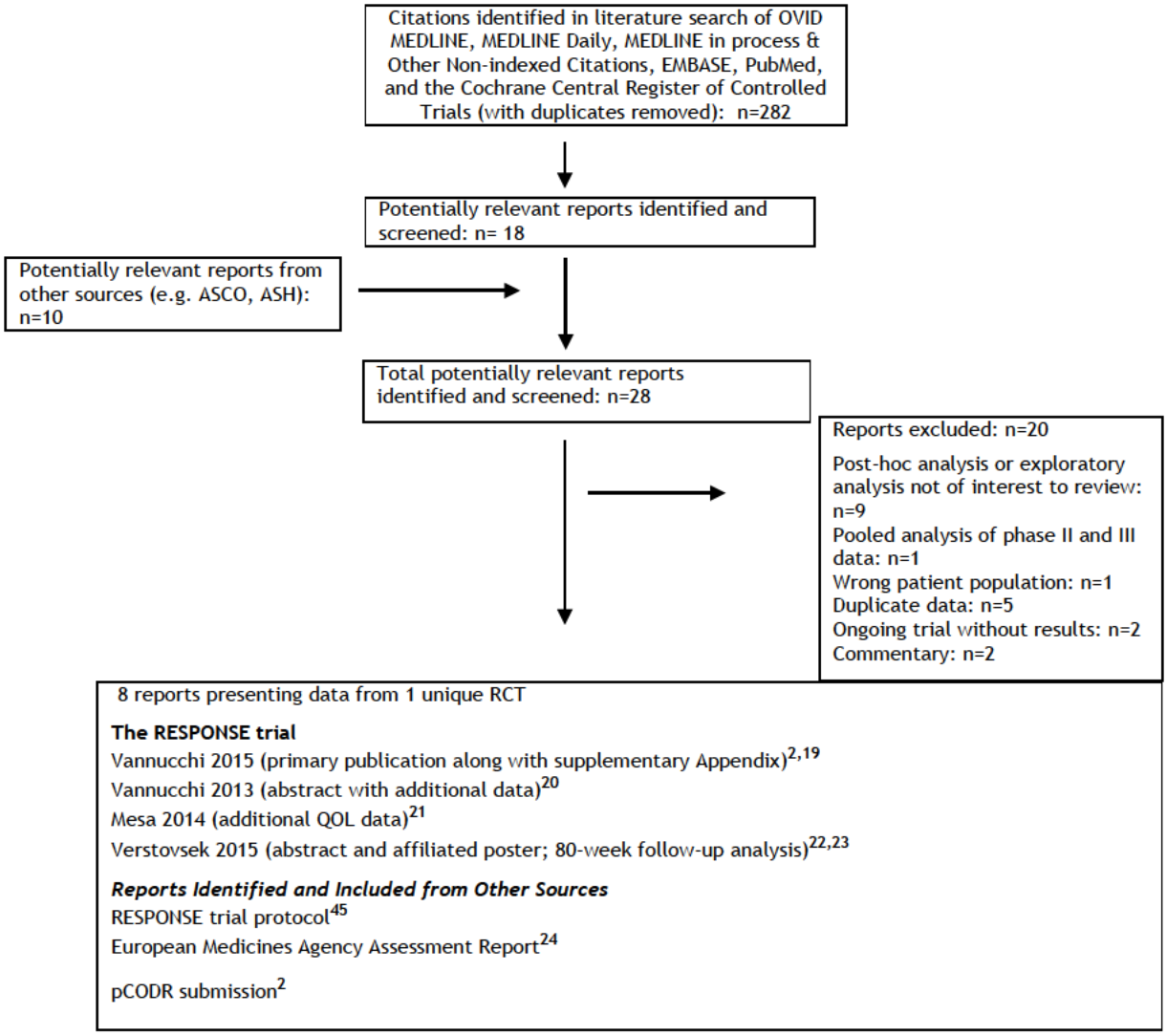
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR CGP wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall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

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant reports identified for full text review (n=26), eight reports were included in the pCODR systematic review[2,19-24] and 20 reports were excluded. Reports were excluded from the review for the following reasons: they were either post-hoc analyses of trial data or exploratory analyses not of interest to this review,[25-33] pooled analyses of phase III and phase II data,[34] included the wrong patient population,[35] provided duplicate data[36-40], describe an ongoing trial without results,[41,42] or were commentary in nature.[43,44]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to the RESPONSE trial were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One randomized controlled trial[2] was identified that met the eligibility criteria of this systematic review. The key characteristics of this trial are summarized in Table 2 and specific features of trial quality are summarized in Table 3.

6.3.3 Detailed Trial Characteristics

Table 2: Summary of trial characteristics of the included RESPONSE trial of ruxolitinib in adult patients with polycythemia vera who are resistant or intolerant to hydroxyurea.

***Response Trial*[2,19,24,45]**

Trial Design	Eligibility Criteria*	Intervention	Comparator	Outcomes
Clinical Trial NCT01243944 Open label phase III RCT Patient enrolment: November 2010 - February 2013 Data cut-off date: January 15, 2014, when all patients reached week 48 or discontinued therapy N randomized = 222 Multicentre (92 sites in 18 countries) Randomized 1:1 ratio, stratified by HU status (inadequate response vs. unacceptable side effects) Funded by Incyte and Novartis	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • Diagnosed with PV for at least 24 weeks prior to trial screening according to WHO criteria (2008) • Requiring phlebotomy[A] for HCT control[B] • Spleen volume of ≥450 cm^3, measured by MRI or CT[C] • Resistance or intolerance to HU according to modified ELN criteria[D] • ANC ≥ 1.5 x 10^9/L and PLT ≥ 100 x 10^9/L • Peripheral blood blast count of 0% • ECOG of 0, 1 or 2 • Therapy for PV must have been on a stable dose and schedule at least 2 weeks before screening and no less than 4 weeks before randomization <u>Exclusion Criteria:</u> • Prior treatment with JAK inhibitor	Ruxolitinib at a starting dose of 10 mg twice daily, to a maximum dose of 25 mg/daily (5 mg minimum daily dose)	Best available (standard) therapy as chosen by treating physician, including: • HU (at a dose not causing unacceptable side effects) • INF or pegylated INF • Pipobroman • Anagrelide • Immunomodulators including lenalidomide or thalidomide • No medication Standard therapy could be changed due to lack of response or toxicity if protocol specific criteria were met Patients could crossover to receive ruxolitinib at week 32 if primary endpoint unmet, or later upon disease progression.	<u>Primary</u>: • Proportion of patients who had *both* HCT control[E] and ≥35% reduction in spleen volume (from baseline) at week 32 as assessed by centrally reviewed MRI or CT <u>Key Secondary</u>: • Proportion of patients with a primary response (i.e., achieving both criteria of primary endpoint) at week 32 that was maintained at week 48. • Proportion of patients with complete hematologic remission (i.e., HCT control, PLT ≤400x10^9 per litre, and white cell count ≤10x10^9 per litre) at week 32 • Duration of response • Symptom reduction (MPN-SF patient diary; Pruritus Symptom Impact Scale) • QOL (EORTC-QLQ-C30; Patient Global Impression of Change) • Safety
		All patients received low-dose aspirin unless it was contraindicated.		

Abbreviations: **ANC** - absolute neutrophil count; **CT** - computed tomography; **ELN** - European LeukemiaNet; **EORTC-QLQ-C30** - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; **HCT** - hematocrit; **HU** - hydroxyurea; **JAK** - janus kinase; **MPN-SF** - Myeloproliferative Neoplasm Symptom Assessment Form; **MRI** - magnetic resonance imaging; **PLT** - platelet; **PV** - polycythemia vera; **QoL** - quality of life; WHO - World Health Organization.

Notes:

*Reflect revised eligibility criteria after protocol amendment 1 (refer to Appendix B for a summary of protocol amendment changes).

[A]Phlebotomy dependence was defined as ≥ 2 phlebotomies within 24 weeks before trial screening, and ≥ 1 phlebotomy within the 16 weeks before screening. The most distant and the most recent phlebotomy within the 24 weeks prior to screening must be at least 4 weeks apart. Patients were also considered phlebotomy dependent if phlebotomy required within 16 weeks before screening and they exhibited a hematocrit > 45% at screening.[19]

[B] Patients with a HCT < 40% or >45% entered a HCT control period before randomization; patients with a HCT between 40 and 45% proceeded directly to randomization.

[C]Splenomegaly was defined as a palpable spleen (or non-palpable due to body habitus) below the costal margin, with spleen enlargement confirmed by MRI/CT at screening, and a volume ≥ 450 cm^3.

[D]Patients with inadequate response to or unacceptable side effects from HU. Refer to Table 4 for definitions of HU resistance and intolerance.

[E]Hematocrit control was defined as ineligibility for phlebotomy from weeks 8 to 32, with no more than 1 instance of phlebotomy eligibility between randomization and week 8. Phlebotomy eligibility was defined as HCT > 45% that was at least 3 percentage points higher than baseline or a HCT > 48%, whichever was lower, regardless of phlebotomy being performed.

Table 3: Selected quality features of the included RESPONSE trial of ruxolitinib in patients with polycythemia vera resistant or intolerant to hydroxyurea.

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
RESPONSE[2]	Ruxolitinib vs. standard therapy	Proportion of patients with HCT control *and* ≥35% reduction in spleen volume (from baseline) at week 32	200 patients required to provide 94% power to detect a 20% difference (using a stratified CMH test and two-sided overall alpha=0.05) in the primary outcome between arms at week 32[A,24]	110 vs. 112	Central IRT, stratified[2] using permuted blocks (block size of 4)	No	Outcome assessment (spleen volume)[B]; data analysis[C]	Yes	No	No	Yes

Abbreviations:
CMH - Cochran-Mantel Haenszel; **IRT** - Interactive Response Technology; **ITT** - intent-to-treat analysis;

Notes:
[A] Based on assumed response rates of 30% and 10% in the ruxolitinib and standard therapy arms, respectively. CMH test stratified by HU status: resistant vs. intolerant. Stratum-specific rates for each treatment arm were obtained assuming a ratio of HU resistance to HU intolerance is 2:1, with response rates 20% higher for patients HU intolerant relative to patients HU resistant (i.e., the response rate in HU intolerant patients equals 1.2 times the response rate in HU resistant patients).
[B] Assessment of HCT was performed locally at each centre using standardized procedures. Spleen volume imaging (via MRI or CT) was assessed centrally by external experts blinded to treatment assessment.[45]
[C] Data analyses were performed by the sponsor; and data analysts were blinded to treatment assignment until database lock.

a) Trials

One randomized controlled trial, RESPONSE,[2] met the inclusion criteria of this systematic review.

The RESPONSE trial is an ongoing, open-label randomized phase III trial that randomized patients with PV intolerant or resistant to HU in a 1:1 ratio to receive treatment with either ruxolitinib or best standard therapy. The choice of best standard therapy was at the discretion of the investigator, and could include any of the following single-agent regimens: HU (at a dose that did not cause unacceptable side effects), interferon alpha (INF-a) or pegylated INF-a, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. Phosphorus-32, busulfan, and chlorambucil were excluded from the trial as standard therapy. The type of standard therapy was permitted to change over the course of the trial according to specific criteria indicative of lack of response or toxicity. All patients in the trial received low dose aspirin unless it was contraindicated. The trial permitted patients randomized to standard therapy to crossover to ruxolitinib at or after week 32.

Patient eligibility requirements included dependence on phlebotomy for hematocrit (HCT) control and a spleen volume of ≥ 450 cm^2 (as measured by MRI or CT), and no previous treatment with a JAK inhibitor. A patient was considered phlebotomy dependent if they required ≥ 2 phlebotomies within 24 weeks of the screening period of the trial and ≥1 phlebotomy 16 weeks prior to screening (see below).

RESPONSE is an international multicentre trial including patients from 18 countries (92 sites) representing North America, Europe, the United Kingdom, and Asia. Patient enrolment occurred between November 2010 and February 2013. Patients were stratified at randomization according to HU status; they were classified as having either an inadequate response to HU (resistant) or unacceptable side effects from HU (intolerance) using modified European LeukemiaNet (ELN) Criteria. The modified ELN criteria used in the trial are summarized in Table 4.

The trial comprised of four distinct phases:[45]

- A screening phase (up to 3 weeks) to determine eligibility and stratify patients by HU status. Patients meeting eligibility requirements at the screening visit proceeded directly to randomization.
- A pre-randomization period (up to four weeks) to achieve HCT control (defined as HCT between 40-45%) in patients with HCT values of <40% and >45% during the screening visit.
- A treatment period (days 1 to week 80), where on day 1 patients were randomized to ruxolitinib or best standard therapy. Patients randomized to standard therapy could crossover to the ruxolitinib arm if they failed to meet the primary endpoint of the trial at week 32, or could occur after week 32 if they did not achieve HCT control or had spleen volume progression (≥ 25% increase relative to volume determined at the time of best documented spleen volume response).
- An extended treatment period (week 80 to week 208) – patients treated with ruxolitinib at week 80 were eligible to continue treatment until week 208. Patients still receiving standard therapy were not eligible to continue on study.

The trial protocol was amended three times over the course the trial; a summary of the amendment changes are summarized in Appendix B.

Table 4: Definitions of hydroxyurea resistance and intolerance used in the RESPONSE trial.[19]		
Criteria Used	**Definition of Resistance**	**Definition of Intolerance**
Modified ELN	An inadequate response to HU was defined as a dose ≥ 2g/day or a maximum tolerated dose < 2g/day resulting in at least 1 of the following: • Need for phlebotomy to maintain HCT < 45% • PLT count > 400 x 10^9/L • Failure to reduce splenomegaly extending > 10cm below the costal margin by > 50%, as measured by palpation	Unacceptable side effects from HU were defined as at least 1 of the following: • ANC < 1.0 x 10^9/l • PLT < 100 x 10^9/l or Hb < 100 g/L (i.e., 10 g/dl) at the lowest dose of HU required to achieve a response. • Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities (such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever an any dose of HU), defined as CTCAE grade 3-4 or > 1 week of CTCAE grade 2, permanent discontinuation of HU, interruption of HU until toxicity resolved, or hospitalization due to HU toxicity.
Abbreviations: ANC - absolute neutrophil count; **CTCAE** - Common Terminology Criteria for Adverse Events, version 3.0; **ELN** - European LeukemiaNet; **Hb** - hemoglobin; **HCT** - hematocrit; **HU** - hydroxyurea; PLT - platelet.		

Novartis and Incyte Pharmaceuticals funded the trial and sponsor staff oversaw its conduct including data analyses and interpretation. It was reported that sponsor staff were unaware of treatment assignment until database lock. One of the trial authors drafted the trial publication with assistance from a medical writer funded by the sponsor. An independent data and safety monitoring board reviewed the trial data and advised on continuation of the trial.

The primary outcome of the trial was a composite response endpoint including the proportion of patients who achieved both HCT control and a reduction in spleen volume of ≥ 35%, as assessed by either MRI or CT imaging, at week 32. Imaging was assessed via central blinded review; however, HCT control was performed locally using the standardized methods of participating centres. No measures were taken to standardize these methods across centres. Hematocrit control was defined as protocol-specified ineligibility for phlebotomy from week 8 to week 32, with no more than one instance of phlebotomy eligibility between randomization and week 8. Thus the primary response endpoint assessed at 32 weeks reflects the initial 8 weeks plus an additional 24 weeks of treatment. A patient was deemed phlebotomy eligible if they had a HCT >45% that was at least 3 percentage points above their HCT at baseline, or a HCT >48%, whichever value was lower regardless of whether phlebotomy was actually performed.

The key secondary outcomes of the trial included the following:

- Duration of primary response at week 48 - the proportion of patients who achieved the primary response outcome and remained progression-free[c] at 48 weeks post-randomization.
- Complete hematological response (CHR) at week 32 – the proportion of patients who achieved HCT control, platelet count ≤ 400 x 10^9/litre, and a white-cell count ≤10 x 10^9/litre.

Other secondary outcomes included response rates of durable spleen volume reduction, HCT control, and CHR at week 48, symptom reduction, quality of life (QOL) and adverse events/safety.

The procedures used to randomize patients were not reported in the trial report. A request was made to the sponsor for this information; they indicated patients were centrally randomized and stratified with the use of Interactive Response Technology.[2] The RESPONSE trial was designed and powered to detect a 20% difference in the primary outcome between trial arms. The estimated trial sample size requirement is detailed in Table 3. A Cochran-Mantel-Haenszel (CMH) test stratified by HU status was used to compare the treatment effect between trial arms, which was estimated using an odds ratio and corresponding 95% confidence interval. The Hochberg procedure was used to control the type 1 error rate for multiple comparisons (i.e., for efficacy analyses of primary and key secondary outcomes). Subgroup analyses were prospectively planned to examine treatment effect in particular subgroups of patients (without formal hypothesis testing)[2] for both the primary and key secondary outcomes of interest using logistic and linear regression methods.

The primary efficacy analyses (for primary and key secondary outcomes) were carried out using the intent-to-treat principle. Data analyses of outcomes assessing changes in values from baseline included all patients with baseline measurements; patients with any missing assessments were considered to have no response. Efficacy analyses included all patients randomized to receive ruxolitinib regardless of the dose received, and included all patients randomized to receive standard therapy regardless of the initial or subsequent type of standard therapy received. The primary efficacy analysis was conducted when all patients reached week 48 or discontinued treatment (data cut-off date of January 15, 2014). The analyses for the other secondary outcomes of interest were considered exploratory and non-comparative. For each of these outcomes durable response rates were calculated (i.e., responders/number of patients) and the duration of responses were estimated using the Kaplan-Meier method.

A follow-up analysis was pre-planned at week 80 to assess longer-term efficacy and safety outcomes; these data have only been published in abstract form.[22,23]

Patient-reported outcomes, including symptom reduction and QOL, were also considered exploratory endpoints and were assessed descriptively using the following scales and measures completed from baseline through to week 32:

- The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) (modified) patient diary (all symptom, symptom cluster, and individual symptom scores)
- The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)
- Pruritus Symptom Impact Scale
- Patient Global Impression of Change (PGIC)

[c] Progression included the occurrence of any one of the following: the first of two consecutive HCT assessments that confirmed phlebotomy eligibility, spleen volume assessment that was reduced < 35% from baseline and ≥ 25% increased relative to the time of best documented spleen response, death due to any cause, development of myelofibrosis as confirmed by bone marrow biopsy, and development of acute myeloid leukemia as confirmed by bone marrow blast counts of ≥ 20% or peripheral blast counts of ≥20% lasting ≥ 2 weeks.

Safety analyses included all patients who received at least one dose of study drug, including those patients who received no drug as part of standard therapy and underwent any post-randomization procedures. The large proportion of patients that crossed over from standard therapy to the ruxolitinib arm resulted in an imbalance of treatment exposure between arms at the data cut-off dates (weeks 48 and 80). Consequently, a comparative assessment of safety was performed for the period from day 1 up to week 32; and for analyses at weeks 48 and 80 the event rates were adjusted for treatment exposure. The adjusted rates were presented as adverse events per 100 patient-years.

b) Populations

A total of 222 patients were randomized in the RESPONSE trial; 110 and 112 were randomized to ruxolitinib and standard therapy, respectively. The authors reported treatment arms were balanced with respect to baseline characteristics and disease history (Table 5). The majority of patients were male in each arm; however, the percentage was higher in the standard therapy arm (71% vs. 60%). Median spleen volume also appeared higher in this arm (1322 cm^3 vs. 1195 cm^3). The median age of patients was 60 years (range, 33 to 90 years). Overall, the patients enrolled in this trial indicate an advanced population of PV patients; with the median time since PV diagnosis in the ruxolitinib and standard therapy arms being 8.2 and 9.3 years, respectively; and the median duration of previous HU therapy being 3.1 and 2.8 years. Apart from HU, other prior medications included interferons (15%), PLT aggregation inhibitors (10%), alkylating agents (3.6%), alkyl sulfonates (3.2%), pyrimidine analogues (1.8%), and nitrosoureas (1.4%).[20] The percentage of patients having an inadequate response to HU (i.e., HU resistant) was 46.4% and 45.5% in the ruxolitinib and standard arms, respectively; while 53.6% and 54.5%, were considered to have unacceptable side effects (i.e., HU intolerant). The percentage of patients with a previous thromboembolic event was 35.5% in the ruxolitinib arm and 29.5% in the standard therapy arm. The incidence of disease complications was not reported by treatment arm.

c) Interventions

All patients randomized to ruxolitinib received treatment at a starting dose of 10 mg twice a day. Dosage was adjusted for each patient (based on the patient demonstrating specific criteria related to inadequate efficacy and hematologic values) such that increases were intended to achieve and maintain a HCT of < 45% in the absence of phlebotomy, reduce spleen size (assessed by palpation), and normalize white cell and platelet counts. Protocol-specified dosing adjustments (reductions or interruptions) were mandated in the trial to ensure hematologic safety. The maximum dose that could be administered was 25 mg twice daily.

It was reported that most ruxolitinib dose adjustments occurred during the first 8 weeks of patients receiving the drug. At week 32, the percentage of patients receiving ruxolitinib at dosages (twice daily) of <10 mg, 10 mg, 15 mg, 20 mg, and 25 mg were 10.2%, 33.7%, 32.7%, 15.3% and 8.2%, respectively. The median total daily dose of ruxolitinib was 22.3 mg/day[24] and the median duration of treatment was 34 weeks at week 32, 81 weeks at week 48 and 111 weeks at week 80.

Among the 112 patients randomized to standard therapy, the types of initial standard therapy used were: HU (in 58.9% of patients), INF (11.6%), anagrelide (7.1%), immunomodulators (4.5%), and pipobroman (1.8%). No medication was administered as standard therapy in 15.2% of patients. A total of six patients (5.3%) switched therapy over the course of the trial and received more than one type of standard therapy. Information on dosing of standard therapies was not reported. The median duration of treatment was 34 weeks.[24] A total of 96 (85.7%) patients assigned to standard

therapy crossed over to the ruxolitinib arm, with the majority of crossovers occurring immediately at week 32, or shortly after.

Table 5: Baseline patient characteristics of included trial of ruxolitinib in adult patients with polycythemia vera who are resistant or intolerant to hydroxyurea.[2]

Baseline Characteristics	Ruxolitinib	Standard Therapy
Response Trial		
N randomized	110	112
Age (years)		
Median	62	60
Range	34-90	33-84
Sex, n (%)		
Male	66 (60)	80 (71.4)
Female	44 (40)	32 (28.6)
Time since diagnosis (years)		
Median	8.2	9.3
Range	0.5-36	0.5-23
Duration of previous HU therapy (years)		
Median	3.1	2.8
Range	<0.1-20.9	<0.1-20.9
ECOG performance status, n (%)		
0	76 (69.1)	77 (68.8)
1	31 (28.2)	34 (30.4)
2	3 (2.7)	1 (0.9)
HU status, n (%)		
Unacceptable side effects (HU intolerance)	59 (53.6)	61 (54.5)
Inadequate response (HU resistance)	51 (46.4)	51 (45.5)
Previous thromboembolic event, n (%)	39 (35.5)	33 (29.5)
Positive status for JAK2 V617F mutation, n (%)	104 (94.5)	107 (95.5)
Allele burden, %	76.2±17.8	75±22.6
Spleen length - below costal margin, cm		
Median	7	7
Range	0-24	0-25
<10 cm, n (%)	71 (64.5)	67 (59.8)
>20 cm, n (%)	2 (1.8)	4 (3.6)
Spleen volume, cm^3		
Median	1195	1322
Range	396-4631	254-5147
HCT - %*		
Mean	43.6 ±2.2	43.9±2.2
Median	43.3	44
Range	39.2-50.5	37.6-50.5
HCT category, n (%)		
40-45%	79 (71.8)	83 (74.1)
>45%	28 (25.5)	25 (22.3)
WBC count - $x10^{-9}$/litre, mean	17.6±9.6	19±12.2
PLT count - $x10^{-9}$/litre, mean	484.5±323.3	499±318.6

No. phlebotomies within 24 week period before screening:		
Median	2	2
Range	1-8	0-16
Abbreviations: ECOG - Eastern Cooperative Oncology Group; HCT - hematocrit; HU - hydroxyurea; PLT - platelet; SD - standard deviation; WBC - white blood cell count; ± - mean plus-minus standard deviation.		
Notes: *The value at the end of the HCT control period before randomization. Patients with a HCT of 40 to 45% within 14 days before day 1 visit could proceed to randomization; however, HCT at baseline may have been higher or lower.		

d) Patient Disposition

The disposition of patients at the time of the primary analysis (week 48) and at a second follow-up analysis (week 80) is provided in Table 6. At week 48 the percentage of patients discontinuing randomized treatment was 15.5% in the ruxolitinib arm versus 96.4% in the standard therapy arm. Patient discontinuations in the standard arm were primarily attributed to lack of efficacy. The other reasons for discontinuing treatment were similar among the two treatment arms.

At week 80, 82.7% (n=91) of patients randomized to ruxolitinib were continuing treatment versus no patients in the standard therapy arm. Of the 98 patients who crossed over to the ruxolitinib arm, 82.7% (n=81) remained on treatment at week 80.[22,23]

The number of major protocol deviations that occurred during the trial was similar between treatment arms (10% vs. 7% in the ruxolitinib and standard arms, respectively).[24]

Table 6: Patient disposition in the RESPONSE trial at the time of primary analysis (week 48)[19] and follow-up analysis (week 80).[22,23]

	Ruxolitinib n (%)	**Standard Therapy** n (%)	
Primary Analysis at week 48:			
Patients randomized	110	112[A]	
Patients continuing randomized treatment	93 (84.5)	3 (2.7)	
Patients discontinuing randomized treatment	17 (15.5)	108 (96.4)	
Primary reason for treatment discontinuation:			
Adverse event	4 (3.6)	2 (1.8)	
Lack of efficacy	0	98 (87.5)	
Disease progression	5 (4.5)	1 (0.9)	
Patient decision	6 (5.5)	5 (4.5)	
Physician decision	2 (1.8)	2 (1.8)	
Major protocol deviations	11(10)	8 (7.1)	
Follow-up Analysis at week 80:	**Ruxolitinib**	**Standard Therapy**	**Crossover**
n	110	112	98
Ongoing treatment	91 (82.7)	0	81 (82.7)
Primary reason for treatment discontinuation:			
Adverse event	5 (4.5)	2 (1.8)	9 (9.2)[B]

Lack of efficacy	0	100 (89.3)	0
Disease progression	6 (5.5)	1 (0.9)	5 (5.1)
Patient decision	6 (5.5)	5 (4.5)	2 (2)
Physician decision	2 (1.8)	2 (1.8)	0
Lost to follow-up	0	0	1 (1.0)
Completed	0	1 (0.9)	0

Notes:
[A] One patient withdrew consent and was not treated on study.
[B] Includes 2 deaths reported after crossover to ruxolitinib (neither considered to be related to study drug).

e) Limitations/Sources of Bias

Refer to Table 3 for a summary of key quality-related features of the RESPONSE trial.[2]

Overall, the RESPONSE trial was well conducted. The methods used to randomize patients and conceal allocation assignment during the randomization process were not reported in the trial publication; however, information provided by the submitter indicated the methods used (central and stratified) were indeed appropriate. The sample size was based on a determination of sufficient power required to test for the desired difference in treatment effect. All efficacy analyses were appropriately performed by assigned treatment. However, the following limitations and biases associated with the trial should be considered when reviewing the trial results:

- The trial was open label, and as such is at risk for a number of different biases that can affect the internal validity of a trial. Investigators and patients were not blinded to treatment assignment. Therefore patients in the ruxolitinib arm may have been more likely to adhere to experimental therapy and investigators may have been more likely to discontinue treatment in the standard therapy arm. The risk of such performance bias is of particular concern in this trial since the majority of patients in the standard therapy arm (58.9%) were either receiving HU (a treatment they knew they were intolerant or resistant to) or no therapy at all (15.2%). Since lack of efficacy would be an expected outcome in these patients it is not surprising such a high percentage of patients (87.5%) discontinued treatment due to lack of efficacy and highlights the possibility that the results may also be attributable to factors other than the intervention of interest.
- Since PV is a chronic malignancy, there is value in assessing the longer-term efficacy and safety of ruxolitinib. At present, long-term data from the RESPONSE trial are limited to 80-week data presented in abstract form. The limitations of abstract data[46] should be considered when interpreting these data and further review of these data should be carried out upon full publication. The high-level of crossover in the trial also limits the assessment of longer-term outcomes.
- The standard therapy arm included several different treatment regimens that were selected at the discretion of the treating investigator using unspecified criteria. Some of these regimens may not be considered standard of care in some Canadian jurisdictions and thus call into question (among some clinical authorities) the appropriateness of the comparator regimens selected in this trial.
- Three amendments to the protocol occurred over the course of the trial (refer to Appendix B). Amendment 1 included significant changes to the inclusion criteria that took effect after 30 patients were randomized. There is a possibility that those 30 patients represent a different population of PV patients relative to patients enrolled after the amendment change.
- The trial used two scales, a modified version of the MPN-SAF patient diary and the Pruritus Symptom Impact Scale, to assess patient-reported symptom reduction. To the knowledge of pCODR, neither instrument has been validated. The EORTC QLQ-C30 was used to assess QOL.

Although this questionnaire is commonly used in cancer, it is not specific to patients with PV. These issues combined with the open-label design of the trial make the interpretation of patient-reported outcomes difficult.

- The trial sponsors Novartis and Incyte funded the trial, and sponsor employees were involved in all aspects of its conduct including design, data collection, analyses and interpretation, as well as writing of the final trial manuscript. Some measures were taken to minimize bias including central review of spleen imaging, blinding of sponsor staff to treatment assignment until database lock and the use of an independent data and safety-monitoring board. However, the extent to which the use of blinded independent investigators and data-analysts would have influenced the results and reporting of the trial is unknown.

6.3.3.1 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A summary of the key efficacy results can be found in Table 7.

Primary Outcome

Primary Response

At week 32, the composite primary response outcome, which included both HCT control and a ≥ 35% reduction in spleen volume, occurred in a significantly higher proportion of patients in the ruxolitinib arm compared to patients receiving standard therapy, 20.9% (n=23) vs. 0.9% (n=1); a difference that was statistically significant (p<0.001).[2] Similar response rates were observed in the subgroups of patients who were HU resistant and HU intolerant. No statistically significant differences in treatment effect were observed among the pre-planned patient subgroup analyses.

The individual endpoints comprising the primary outcome also favoured the ruxolitinib arm. Hematocrit control (60.0% vs. 19.6%) and a reduction of ≥35% spleen volume (38.2% vs. 0.9%) were achieved in significantly more patients treated with ruxolitinib compared to standard therapy.

Efficacy data for the individual endpoints comprising primary response were also reported by initial treatment received in the standard therapy arm. Amongst the 112 patients in the standard therapy arm, HCT control was achieved in 22.7% (15/66) of patients receiving HU, 30.8% (4/13) of patients receiving INF, 12.5% (1/8) of patients receiving anagrelide, 50.0% (1/2) of patients receiving pipobroman and 5.9% (1/17) of patients receiving no medication. Of all patients in the standard therapy arm, only one patient, who received HU, achieved a spleen volume reduction ≥35%.

The number of phlebotomy procedures performed to control HCT (between weeks 8 and 32) was lower among patients in the ruxolitinib arm compared to patients receiving standard therapy (Table 7).

Follow-up at week 80[22,23]

At week 80 the primary response rate in the ruxolitinib arm decreased slightly to 19.6% (i.e., one patient lost their response).[d] For the 60% of patients in the ruxolitinib arm who achieved HCT control at week 32, the probability of maintaining their response through to week 80 was 89%. All patients in the ruxolitinib arm who achieved a ≥35% spleen volume reduction maintained their response at week 80. The percentage of patients in the ruxolitinib arm having 0, 1, 2 and ≥3 phlebotomy procedures between week 32 and week 80 were 89.8%, 7.1%, 0 and 3.1%, respectively.

Key Secondary Outcomes

Duration of Primary Response

Among patients in each arm achieving a primary response at week 32, 21 patients (19.1%) in the ruxolitinib arm and one patient (0.9%) in the standard arm maintained a response at week 48 (p<0.001).[2]

[d] At the time of this review, follow-up data at 80 weeks were published in abstract form. In the poster presentation that accompanied the abstract (insert ref) it was noted that at the 80-week analysis corrections to the original MRI data identified two additional patients with a primary response in the ruxolitinib arm at week 32, bringing the total number of patients with a primary response to 25 (22.7% response rate).

Complete Hematological Response
Complete hematological response was achieved in a significantly higher proportion of patients randomized to ruxolitinib; the response rates at week 32 were 23.6% vs. 8.9% with standard therapy (p=0.003).[2]

Follow-up at week 80[22,23]
The probability that patients in the ruxolitinib arm with an initial primary response at week 32 maintained their response at week 80 was 92%; the probability that patients maintained their CHR was 69%.

Other Secondary Outcomes

Duration of Individual Response Endpoints
Responses for the individual endpoints comprising primary response, HCT control and ≥ 35% spleen reduction, were maintained overtime; at week 48, 54% of patients (n=60) randomized to ruxolitinib maintained a durable HCT and 20.0% (n=22) maintained a durable spleen volume reduction. Durable CHR was obtained in 23.6% (n=60) of patients. The duration of response rates could not be assessed in patients receiving standard therapy since a majority of patients crossed over to the ruxolitinib arm at week 32 or shortly thereafter.[19]

Follow-up at week 80[22,23]
Durable response rates for HCT control and ≥ 35% spleen reduction were not reported in the follow-up analysis.

Table 7: Key efficacy outcomes of the RESPONSE trial[2] comparing ruxolitinib to standard therapy in adult patients with polycythemia vera who are resistant or intolerant to hydroxyurea.		
Key Efficacy Endpoints	**Ruxolitinib n=110**	**Standard Therapy n=112**
Primary	**% (n)**	**% (n)**
Response rate at week 32: Hematocrit control and ≥ 35% reduction in spleen volume	20.9 (23)	0.9 (1)
	OR=28.6 (95% CI, 4.5-1206) p<0.001	
Response rate by HU status:		
Unacceptable side effects to HU (HU intolerance, n=59 vs. n=61)	22 (13)	0
	OR=NA	
Inadequate response to HU (HU resistance, n=51 vs. n=51)	19.6 (10)	2 (1)
	OR=11.96 (95% CI, 1.59-539.56) p=NR	
Individual components of primary response rate:		
Hematocrit control through week 32	60 (66)	19.6 (22)
≥ 35% reduction in spleen volume at week 32	38.2 (42)	0.9 (1)
Secondary	**% (n)**	**% (n)**
Complete hematologic response	23.6 (26)	8.9 (10)
	OR=3.35 (95% CI, 1.43-8.35) p=0.003	
Duration of primary response (at week 32) maintained at week 48	19.1 (21)	0.9 (1)
	OR=26.11 (3.98-1080) p<0.001	
Other Secondary	n=106	n=109
Rate of phlebotomy between weeks 8 and 32*:	%	%
0	80	38
1	13	28
2	4	14
≥3	3	20
Abbreviations: CI - confidence interval; HU - hydroxyurea; OR - odds ratio; NA - not available; NR - not reported; p - p-value.		
Notes: * Rate includes patients who did not discontinue randomized treatment prior to week 8; and is based on 106 patients in the ruxolitinib arm and 109 patients in the standard therapy arm.		

The open-label design of the RESPONSE trial makes interpretation of patient-reported symptom reduction and QOL outcomes difficult. Awareness of treatment assignment unduly influences patient responses on subjective assessment instruments. This limitation should be taken into account for each of the outcomes summarized below.

Symptom Reduction

MPN-SAF Patient Diary
The modified MPN-SAF patient diary, which is a modification to the MPN-SAF patient diary and was developed by Incyte Pharmaceuticals, was the instrument used to assess patient-reported PV symptoms.[2] It is unknown whether the modified version of this instrument has been appropriately validated. The 14-item (symptom) diary includes symptoms particularly bothersome to patients with PV (e.g., itching, early satiety, headache, muscle ache, night sweats, sweats while awake, tiredness, abdominal discomfort, numbness/tingling in hands/feet, concentration) and requires patients to rate their symptoms on a scale from 0 (absent) to 10 (worst imaginable) during the previous 24 hours. In addition to individual symptom scores, symptom data were combined to produce a total symptom score (all 14 items) as well as symptom cluster scores. Patients with complete data at baseline (value >0) and week 32 were included in analyses to assess mean changes from baseline.

The number of patients contributing to these analyses ranged from 63 to 74 in the ruxolitinib arm and 71 to 81 in the standard therapy arm depending on the symptom score (Table 8). A 50% reduction in the total symptom score was observed in 49% of patients receiving ruxolitinib compared to 5% of patients receiving standard therapy [odds ratio (OR)=18.12; 95% CI, 5.73-72.71)]. Ruxolitinib treatment was also associated with greater reductions in all symptom clusters and individual symptom scores relative to standard therapy.

Pruritus Symptom Score
The Pruritus Symptom Impact Scale was used to measure changes in the severity of pruritus symptoms experienced by patients in each treatment arm at baseline and at week 32.[19] The use and validity of this scale among patients with PV is not known. Patients respond to questions on a scale from 0 (not at all) to 10 (worst imaginable) regarding symptom burden (Table 9). A total of five questions comprise the scale. Patients with complete data at baseline and week 32 were included in analyses to assess mean changes from baseline.

The number of patients included in analyses was not reported in the trial report. A request was made to the submitter for this information; they indicated the percentage of patients included in analyses was approximately 75% in the ruxolitinib arm and 69% in the standard therapy depending on the question posed.[1] For each scale question mean changes from baseline favoured treatment with ruxolitinib; mean change ranged from -1.4 to -2.2 among patients receiving ruxolitinib, and ranged from -0.1 to 0.3 for patients receiving standard therapy, where lower scores indicate an improvement from baseline.

Patient Global Impression of Change
The PGIC scale was used in the RESPONSE trial to assess patients' perceptions of change in their PV symptoms over time.[19] At each monthly visit patients were asked to answer the following question: "Since the start of the treatment you've received in this study, your PV symptoms are (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, (7) very much worse."[45] The number of patients included in analyses was not reported in the trial report. A request to the submitter for this information was made; they indicated approximately 85% of patients in the ruxolitinib arm and 92% of patients in the standard therapy arm completed assessments at baseline and week 32.[1] At week 32 a higher proportions of patients receiving ruxolitinib perceived very much or much improvement (68% vs. 13%) in PV

symptoms compared to patients receiving standard therapy. Six percent of patients treated with ruxolitinib compared to 42% of patients treated with standard therapy reported no change in symptoms at week 32.

Quality of Life

EORTC Quality of Life Questionnaire-Core C30
The EORTC QLQ-C30 was used to measure overall QOL and different aspects of patient functioning, encompassing physical, emotional, cognitive, social and role aspects. The scale is commonly used in oncology and assesses QOL in general, but is not specific to MPNs or PV. Mean changes in patient scores from baseline and at week 32 were compared between treatment arms, where higher scores indicate improvements in QOL status and functioning (Table 10). A 10-point change in score from baseline at week 32 was considered the minimally important difference (MID).[21]

The number of patients included in these analyses depended on the specific scale, and ranged from 86 to 90 in the ruxolitinib arm and 80 to 84 in the standard therapy arm.[24] Improvement in the overall health QOL score (mean change from baseline, 10.9 vs. -4.8 for ruxolitinib and standard therapy, respectively) as well as each aspect of functioning was observed among patients in the ruxolitinib arm compared to patients in the standard therapy arm. An MID in the overall health QOL score was achieved in 46% of patients treated with ruxolitinib versus 10% of patients treated with standard therapy.[21]

Table 8: Symptom reduction in the RESPONSE trial, as measured by the modified MPN-SAF (Myeloproliferative Neoplasm Symptom Assessment Form) Patient Diary[2]

	Ruxolitinib	Standard Therapy
*n**	74	81
Total 14 symptom score[A]	49%	5%
*n**	74	80
Cytokine symptom cluster score[A]	64%	11%
Reduction in individual symptoms[B]:		
Tiredness	-49.6	-4.2
Itching	-94.9	-2.1
Muscle ache	-61.1	0.4
Night sweats	-99.5	3.9
Sweating while awake	-100.0	-4.4
*n**	71	80
Hyperviscosity symptom cluster[A]	37%	13%
Reduction in individual symptoms[B]:		
Vision problems	-41.8	10.9
Dizziness	-80.2	7.9
Concentration problems	-44.0	16.7
Headache	-51.5	11.1
Numbness or tingling in hands or feet	-37.1	15.7
Skin redness	-64.1	5.0
*n**	63	71
Splenomegaly symptom cluster[A]	62%	17%
Reduction in individual symptoms[B]:		
Abdominal discomfort	-65.9	1.4
Early satiety - Fullness	-93.9	0
Notes		

* The number of patients included in analyses with data at both baseline (value >0) and week 32.
[A] The percentage of patients with ≥50% reduction in the MPN-SAF total symptom score (maximum score =140) or cluster score at week 32.
[B] Median percentage changes from baseline to week 32. Higher scores indicate greater severity of symptoms; negative values indicate a reduction in severity of symptoms.

Table 9: Assessment of Pruritus in the RESPONSE trial as measured by the Pruritus Symptom Impact Scale.[19]

Scale Questions[A]	Ruxolitinib		Standard Therapy	
	n[B]	Mean change from baseline at week 32[C]	n[B]	Mean change from baseline at week 32[C]
1. How severe was PV-related itching during the past 7 days?	NR	-2.2	NR	0
2. How bothered by PV-related itching during the past 7 days?	NR	-2.0	NR	0
3. How much PV-related itching interfered with daily life during the past 7 days?	NR	-1.5	NR	0.3
4. How bothered by PV-related itching during the past 24 hours?	NR	-1.9	NR	-0.1
5. How much PV-related itching interfered with daily life during the past 24 hours?	NR	-1.4	NR	0.3

Abbreviations: NR - not reported.

Notes:
[A] Responses to scale questions were on a scale from 0 (not at all) to 10 (worst imaginable).
[B] The number of patients included in analyses (data at baseline and week 32) was not reported. A request to the submitter for this information indicated the percentage of patients contributing to analyses was approximately 75% in the ruxolitinib arm and 69% in the standard therapy depending on the question posed.
[C] A lower score (mean change) indicates improvement from baseline.

Table 10: Quality of Life assessment in the RESPONSE trial, as measured by the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30).[21,24]

Scale	Ruxolitinib			Standard Therapy		
	n*	Baseline score	Mean change from baseline at week 32[A]	n*	Baseline score	Mean change from baseline at week 32[A]
Overall global health status/QOL Scale	89	59.6	10.86	83	64.6	-4.82
Symptom and Single-item Scales						
Fatigue	89	37.7	-12.2	81	36.8	0.82
Nausea and vomiting	89	5.2	-1.5	80	4.8	0.21
Pain	86	25.4	-11.1	80	24.4	0.21
Insomnia	89	27.0	-12.0	81	37.0	-7.8
Functioning Scales						
Physical	90	80	6.44	84	83.2	-1.51
Emotional	88	75.9	7.92	80	77.4	1.04
Cognitive	88	76.7	4.17	80	77.9	-3.33
Social	87	81.4	7.66	80	81.3	-0.42
Role	88	78.4	5.3	81	78.2	-0.41

Abbreviations: NR - not reported; QOL - quality of life.

Notes:
* The number of patients included in analyses with data at both baseline and at week 32.
[A] A higher score (mean change) indicates improvement from baseline.

Harms Outcomes

The RESPONSE trial provided data on adverse events at three separate time periods (week 32, and weeks 48 and 80), which are summarized in Tables 11 and 12. The trial did not report data on the flare phenomenon (i.e., flare of spleen size and blood counts upon drug withdrawal or interruption). No statistical comparisons of the differences in the frequency of adverse events rates between trials arms were performed.

Adverse Events at Week 32[2]

At week 32, the incidences of any grade adverse events were generally similar between the ruxolitinib and standard therapy arms (Table 11). Compared to standard therapy, ruxolitinib was associated with a higher frequency of the following hematologic adverse events (all grades): anemia (43.6% vs. 30.6%) and thrombocytopenia (24.5% vs. 18.9%). Standard therapy was associated with a higher frequency of neutropenia (8.1% vs. 1.8%) and lymphopenia (50.5% vs. 43.6%).

Non-hematologic adverse events occurring more frequently in patients treated with ruxolitinib included diarrhea (14.5% vs. 7.2%), muscle spasms (11.8% vs. 4.5%), dyspnea (10% vs. 1.8%), and herpes zoster infections (6.4% vs. 0, grade 1 or 2). In the standard therapy arm there were a higher percentage of patients who experienced pruritus (22.5% vs. 13.6%). Thromboembolic events

(5.4% vs. 0.9%) were also higher in the standard therapy arm despite a higher incidence of these events in the ruxolitinib arm at baseline.

The rates of grade 3 or 4 adverse events appeared similar between the treatment arms (Table 11). Serious adverse events and adverse events leading to treatment discontinuations were more frequent in patients treated with ruxolitinib compared to standard therapy (13.6% vs. 9% and 6.4% vs. 0.9%, respectively). No deaths were reported in either trial arm through week 32.

Through week 32, three patients (3%) in the ruxolitinib arm developed MF. These transformations occurred 5, 9, and 19 years after diagnosis of PV, and 120, 182, and 469 days post-randomization, respectively. One patient (<1%) in this arm developed AML (day 56). There was one case of MF in the standard therapy arm prior to crossover (day 101) and two cases of transformation to MF after crossover to ruxolitinib (on days 308 and 378).

Adverse Events at Week 48 (corrected for cumulative treatment exposure)[19]
The rates of adverse events through to week 48, which were adjusted for cumulative treatment exposure between trial arms, are summarized in Table 12. The number of patient-years of exposure was 170 in the ruxolitinib arm versus 72.8 in the standard therapy arm. The overall adverse event rate per 100 patient-years was higher in the standard therapy arm compared to the ruxolitinib arm for both all grade (145.6 vs. 64.7) and grade 3 or 4 (44 vs. 28.8) adverse events. Refer to Table 12 for the specific rates of individual hematologic and non-hematologic toxicities.

The rate of serious adverse events per 100 patient-years was 15.3 in the ruxolitinib arm versus 13.7 in the standard therapy arm. Two deaths occurred in patients after crossover to ruxolitinib (occurring within 30 days after the last dose of ruxolitinib) and were considered to be unrelated to ruxolitinib treatment. One patient death was due to central nervous system haemorrhage attributable to long-standing poorly controlled hypertension. The other death was attributed to multi-organ failure and hypovolemic shock with a precipitous unexplained drop in hemoglobin (in association with a positive fecal occult-blood test).

Adverse Events at Week 80 (corrected for cumulative treatment exposure)[22,23]
It was reported that after the first six months of treatment, few new adverse events were observed among patients randomized to ruxolitinib (Table 12). New or worsening hematologic adverse events occurring up to week 80 (rates per 100 patient-years) included grade 1 or 2 anemia (27.2) thrombocytopenia (14.9), and lymphopenia (27.2); non-hematologic adverse event rates appeared similar relative to week 48. At week 80, herpes zoster infections continued to be higher in the ruxolitinib arm (5.3 vs. 0 with standard therapy) and thromboembolic events remained higher in the standard therapy arm (8.2 vs. 1.8). The rate of serious adverse events in each treatment arm was not reported for the follow-up analysis; however, five patients in the ruxolitinib arm did experience adverse events leading to treatment discontinuation by week 80. No additional transformations to MF or AML were reported in either arm at the week 80.

Table 11: Summary of adverse events reported in the RESPONSE trial up to week 32.[2,24]				
Adverse Events[A]	**Ruxolitinib (n=110)**		**Standard Therapy (n=111)[B]**	
n (%)	All grade	Grade 3/4	All grade	Grade 3/4
Any adverse event	105 (95.5)	36 (32.7)	104 (93.7)	32 (28.8)
Non-hematologic				
Headache	18 (16.4)	1 (0.9)	21 (18.9)	1 (0.9)
Diarrhea	16 (14.5)	0	8 (7.2)	1 (0.9)
Fatigue	16 (14.5)	0	17 (15.3)	3 (2.7)
Pruritus	15 (13.6)	1 (0.9)	25 (22.5)	4 (3.6)
Dizziness	13 (11.8)	0	11 (9.9)	0
Muscle spasms	13 (11.8)	1 (0.9)	5 (4.5)	0
Dyspnea	11 (10)	3 (2.7)	2 (1.8)	0
Abdominal pain	10 (9.1)	1 (0.9)	13 (11.7)	0
Asthenia	8 (7.3)	2 (1.8)	12 (10.8)	0
Hematologic				
Anemia	48 (43.6)	2 (1.8)	34 (30.6)	0
Thrombocytopenia	27 (24.5)	6 (5.5)	21 (18.9)	4 (3.6)
Lymphopenia	48 (43.6)	18 (16.4)	56 (50.5)	20 (17.9)
Leukopenia	10 (9.1)	1 (0.9)	14 (12.6)	2 (1.8)
Neutropenia	2 (1.8)	1 (0.9	9 (8.1)	1 (0.9)
Other				
Any infection	45 (41)	4 (3.6)	41 (36.9)	3 (2.7)
Herpes zoster infection	7 (6.4)[C]	0	0	0
Thromboembolic events	1 (0.9)		6 (5.4)[E]	
Non-melanoma skin cancer (basal-cell or squamous cell carcinoma)[D]	4 (3.6)		2 (1.8)	
Any serious adverse event	15 (13.6)		10 (9)	
Any treatment-related adverse event	65 (59.1)		37 (33.3)	
Adverse events leading to treatment discontinuation	7 (6.4)		1 (0.9)	

Notes:
[A] Events occurring in at least 10% of patients in either treatment arm.
[B] One patient withdrew consent and did not receive study treatment.
[C] Grade 1 or 2.
[D] All but one patient (in standard therapy group) had a history of non-melanoma skin cancer or precancerous skin lesions. One patient (standard therapy group) was diagnosed with melanoma.
[E] One thromboembolic event occurred after week 32 in the ruxolitinib treatment arm.

Table 12: Summary of Adverse Events in the RESPONSE trial at weeks 48 and 80.[19,22-24]								
Adverse Events	**Week 48***				**Week 80****			
	Ruxolitinib (n=110)		**Standard Therapy (n=111)**		**Ruxolitinib (n=110)**		**Standard Therapy (n=111)**	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Patient-year exposure	170		72.8		222.7		73.6	
Any adverse event:	64.7	28.8	146.6	44	NR	NR	NR	NR
Non-hematologic								
Headache	13.5	1.2	28.8	1.4	10.5	0.9	28.5	1.4
Diarrhea	12.4	0	12.4	1.4	9.7	0	12.2	1.4
Fatigue	11.2	0	23.3	4.1	8.3	0.4	23.1	4.1
Pruritus	11.2	0.6	34.3	5.5	9.7	0.4	32.6	5.4
Dizziness	8.8	0	15.1	0	7.5	0	14.9	0
Muscle spasms	NR	NR	NR	NR	7.9	0.4	9.5	0
Dyspnea	NR	NR	NR	NR	7	1.3	2.7	0
Abdominal pain	7.1	1.2	17.9	0	6.6	0.9	17.7	0
Asthenia	5.9	1.2	16.5	0	NR	NR	NR	NR
Nasopharyngitis	7.6	0	12.4	0	5.7	0	12.2	0
Arthralgia	7.6	0	11.0	1.4	6.1	0	10.9	1.4
Night sweats	5.9	0	12.4	0	NR	NR	NR	NR
Increased weight	NR	NR	NR	NR	7.5	0.4	1.4	0
Cough	NR	NR	NR	NR	5.7	0	8.2	0
Back pain	NR	NR	NR	NR	5.7	0.4	6.8	0
Constipation	NR	NR	NR	NR	5.3	0.4	4.1	0
Pyrexia	NR	NR	NR	NR	5.3	0	6.8	0
Hematologic								
Anemia	15.9	1.2	5.5	0	27.2	0.9	47.6	0
Thrombocytopenia	7.6	2.4	16.5	2.7	14.9	2.6	29.9	5.4
Lymphopenia	NR	NR	NR	NR	27.2	9.7	78.8	27.2
Leukopenia	NR	NR	NR	NR	6.6	0.9	19	2.7
Neutropenia	NR	NR	NR	NR	2.2	0.4	12.2	1.4
Other								
Any infection	NR	NR	NR	NR	29.4	4	58.4	4.1

Herpes zoster infection	NR	NR	NR	NR	5.3	0.9	0	0
Thromboembolic events	NR	NR	NR	NR	1.8	0.9	8.2[E]	2.7
Diagnosis of non-melanoma skin cancer	NR	NR	NR	NR	4.4	NR	2.7[F]	NR
Diagnosis of MF, n (%)	3[A] (2.7)	NR	1[B] (0.9)	NR	3 (2.7)	NR	1[B] (0.9)	NR
Diagnosis of AML, n (%)	1[C] (0.9)	NR	0	NR	1 (0.9)	NR	0	NR
Any serious adverse event [A]	15.3	NR	13.7	NR	NR	NR		NR
Adverse events leading to treatment discontinuation [D]***, n (%)***	9 (8.2)	5 (4.5)	2 (1.8)	1 (0.9)	5 (4.5)	NR	NR	NR

Abbreviations: AML - acute myeloid leukemia; NR - not reported; MF- myelofibrosis.

Notes:
*Adverse event occurring at a rate ≥ 10 per 100 patient-year of treatment exposure.
** Adverse event occurring at a rate ≥ 5 per 100 patient-year of treatment exposure.
[A] Approximately 5, 9, and 19 years after diagnosis of PV and at 120, 182, and 469 days after randomization.
[B] Three patients received a diagnosis of MF; one patient on day 101, and two patients on days 308 and 378 after crossover, with one who had progression to AML.
[C] At day 56.
[D] Does not include patients randomized to standard therapy who crossed over to ruxolitinib.
[E] One patient in the standard therapy arm had two events.
F There were three additional events after crossover, one of these was in a patient with a history of skin cancer/precancer.

6.4 Ongoing Trials

Only one ongoing randomized trial, RESPONSE 2, was identified that met the eligibility criteria of this review. RESPONSE 2 is designed to compare efficacy between ruxolitinib and standard therapy in an expanded population of adult patients with PV who are resistant or intolerant to HU without splenomegaly.[41,47]

Table 13: Ongoing trial of ruxolitinib in adult patients with polycythemia vera who are resistant or intolerant to hydroxyurea.

Trial Design	Key Inclusion Criteria	Interventions and Comparators	Outcomes
Trial NCT02038036 (RESPONSE 2) Multicentre (49 sites), open-label, randomized phase III trial Start date: March 2014 Expected completion date: April 2020 Status: Active (not recruiting patients) Estimated enrolment: 141 Sponsor: Novartis	• ≥ 18 years old • Diagnosis of PV according to WHO criteria • Non-palpable spleen • Phlebotomy dependent • Resistant or intolerant to HU • ECOG 0, 1 or 2 • No previous treatment with a JAK inhibitor	<u>Ruxolitinib</u> Starting at a dose of 10mg twice daily. Dose may be decreased or escalated based on efficacy and safety parameters; maximum allowed dose is 25mg twice daily. vs. <u>Standard therapy:</u> As chosen by investigator from: • HU • IFN/PEG-INF • Pipobroman • Anagrelide • IMIDs • Observation	*Primary:* • HCT control at week 28 *Secondary:* • Peripheral blood count remission at week 28 • Durable HCT control at week 52 • Durable peripheral blood count remission at week 52 • Change in ECOG status from baseline • Change in spleen length from baseline • Partial remission based (ELN criteria) at week 28 • Durable partial remission at week 52 • Symptom reduction as measured by MPN-SAF TSS • QOL (EQ-5D-5L) • Safety

Abbreviations: ECOG - Easter Cooperative Oncology Group; **ELN** - European LeukemiaNet; **EQ**- EurolQol; **HCT** - hematocrit; **HU** - hydroxyurea; **JAK** - janus kinase; **MPN-SAF**- Myeloproliferative Neoplasm Symptom Assessment Form; **PV** - polycythemia vera; **QoL** - quality of life; **WHO** - World Health Organization.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of ruxolitinib in adult patients with polycythemia vera (PV) who are resistant or intolerant to hydroxyurea (HU):

- What type and degree of resistance and intolerance to HU would be considered in order to support a switch in treatment to ruxolitinib?

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Type and Degree of Intolerance and Resistance to Hydroxyurea

7.1.1 Objective

To identify and summarize existing criteria and/or clinical guideline recommendations that define intolerance and resistance to HU in order to ascertain when in the treatment course of PV it is appropriate to discontinue HU therapy and offer ruxolitinib.

Data on the type and degree of HU intolerance were summarized at the request of the Provincial Advisory Group (PAG). The PAG had concerns, that while PV is an uncommon disease, there exists a potential for a large prevalent population of PV patients who may be deemed intolerant to HU. As such, PAG requested information on the nature of intolerance and resistance to HU that could be considered in order to support a switch in treatment to ruxolitinib.

7.1.2 Findings

A search for existing criteria and clinical practice guidelines was undertaken. The search uncovered the European LeukemiaNet (ELN) Definitions of Resistance/Intolerance to HU in patients with PV. These criteria are based on expert opinion and consensus, and thus largely reflect the experience and knowledge of experts within the context of a group decision-making process. No other criteria or clinical guidelines were identified by the search.

In 2011, the ELN developed and published (2011) consensus-based recommendations for the management of myeloproliferative neoplasms (MPNs), including recommendations on therapy changes and second-line therapy in patients with PV with HU intolerance and resistance.[12] It should be noted that these recommendations were made prior to the RESPONSE trial. The ELN recommendations can be summarized as follows:

- In high-risk patients, first-line therapy should be changed when intolerance has been demonstrated (as per the ELN definition of HU intolerance).
- Second-line therapy of PV is INF-a in patients intolerant or resistant to HU
- HU is the second-line therapy of choice for patients intolerant or resistant to INF-a
- Pipobroman, busulfan, and ^{32}P are second-line therapies reserved for patients with short-life expectancy.

The ELN criteria for defining intolerance/resistance were developed by an international working group comprised of 14 members considered experts in MPNs and chaired by a clinician with expertise in clinical epidemiology.[15] Formal consensus methods were used to develop the ELN criteria; however, the specific consensus methodology used and its validity were neither noted nor referenced in the primary publication. Table 14 summarizes the ELN definitions for resistance and intolerance to HU in patients with PV. Of note, a modified version of the ELN

criteria was used to determine HU status in the RESPONSE trial;[2] the specific criteria that were modified in the trial are indicated in the Table 14.

Table 14: ELN Definitions of hydroxyurea resistance and intolerance to hydroxyurea and modifications of these criteria used in the RESPONSE trial.[24]

ELN Definition of Resistance:	Modifications to definition used in the RESPONSE trial:
After 3 months (12 weeks) of at least 2 g/day of HU, the patient shows: • Need for phlebotomy to keep HCT <45%, OR • Uncontrolled myeloproliferation: PLT > 400 x10^9/L and WBC > 10 x 10^9/L, OR • Failure to reduce massive* splenomegaly > 50% as measured by palpation or failure to completely relieve symptoms related to splenomegaly	*Added (bold):* *"After 12 weeks of at least 2g/day of HU **OR at the patient's maximally tolerated HU dose if that dose is <2g/day**.* *Removed:* *"...or failure to completely relieve symptoms related to splenomegaly"*
ELN Definition of Intolerance:	**Modifications to definition used in the RESPONSE trial:**
After any dose of HU, the patient shows: • ANC <1.0 x 10^9/L, OR • PLT <100 x 10^9/L or Hb <100 g/L at the lowest dose of HU required to achieve a response (response defined as HCT <45% without phlebotomy, and/or all of the following: PLT ≤ 400 x 10^9/L, WBC ≤ 10 x 10^9/L, and non-palpable spleen) • Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, GI symptoms, pneumonitis or fever)	*Added (bold):* *"...**fever, defined as CTCAE version 3.0 grade 3 or 4, or >1 week of CTCAE version 3.0 grade 2, or permanent discontinuation of HU, or interruption of HU until toxicity resolved, or hospitalization due to HU toxicity**.*
fAbbreviations: ANC - absolute neutrophil count; **CTCAE** - Common Terminology Criteria for Adverse Events, version 3.0; **ELN** - European LeukemiaNet; **Hb** - hemoglobin; **HCT** - hematocrit; **HU** - hydroxyurea; **PLT** - platelet; **WBC** - white blood cell count.	
Notes: *Organ extending by >10 cm from the costal margin.	

A retrospective study[14] evaluated the use of the original ELN criteria for intolerance and resistance in patients with PV in order to assess their prognostic value for determining when to introduce second-line treatment after HU (refer to section 2.1.4 for a study summary). The study by Alvarez-Larran et al (2012) included 261 patients,[14] of whom 11.5% (n=30) and 12.6% (n=33) fulfilled at least one of the ELN criteria for resistance and intolerance, respectively. In the multivariate analysis predicting survival, resistance to HU was associated with a significantly higher risk of death (HR=5.6, 95% CI, 2.7-11.9; p<0.001) relative to patients without resistance; an effect that was independent of other prognostic factors including age, sex, hematologic values at diagnosis, thrombosis, hemorrhage and leukocyte count. Median survival after

developing resistance to HU was 1.2 years. HU resistance was also significantly associated with transformation to AML or MF after adjusting for other factors (HR=6.8; 95% CI, 3.0-15.4; p<0.001). Of notable interest, primary HU resistance was very rare with the majority of patients developing resistance late in the course of disease. The median time to diagnosis of HU resistance was 6 years. When the individual items included in the definition of resistance were examined, cytopenia at the lowest dose of HU required to achieve a response was the most frequent indicator of resistance. The authors interpreted this finding as indicative that resistance is more a reflection of reduced hematopoietic reserve and impending hematologic transformation as opposed to a dose-dependent process. HU intolerance, as defined by ELN, did not show any association with survival or risk of disease transformation. During the study period 22% of patients (n=57) received other cytoreductive therapies including ^{32}P, anagrelide, busulfan and interferon. The timing and reasons for initiating other therapy were not addressed in the study report despite these being objectives of the study.

Despite the finding that HU resistance is associated with shorter survival, the percentage of patients categorized as resistant and intolerant (11.5% and 12.6 %, respectively) appeared low in this study. This raises the question of whether the number of patients was in fact large enough to detect with confidence the prognostic significance of both ELN criteria. In addition, it is surprising and unfortunate that the study failed to examine the specific factors that lead to a change in therapy after HU; and in what capacity if any these factors relate to those that define resistance and intolerance. Other limitations of this study are summarized in section 2.1.4. In light of the aforementioned limitations, this single study requires validation in prospective evaluations in order determine the true prognostic utility of the ELN Criteria for both HU resistance and intolerance.

7.1.3 Summary

A search was undertaken, at the request of the PAG, to identify and summarize existing criteria and/or clinical guideline recommendations that define intolerance and resistance to HU in order to ascertain when in the treatment course of PV patients it is appropriate to discontinue HU therapy and offer ruxolitinib. The search identified one set of criteria, the ELN Definitions of Resistance/Intolerance to HU in patients with PV, which are based largely on expert opinion and consensus (versus evidence-based). One retrospective study of 261 patients has assessed the prognostic value of using the criteria for determining when to introduce second-line treatment after HU. The study found that HU resistance as defined by the ELN criteria (but not intolerance) was associated with a significantly higher risk of death and transformation to AML or MF relative to non-resistant patients. The timing and reasons for initiating other therapy after HU, however, were not reported despite being objectives of the study. These results should be interpreted within the context of retrospective study design limitations and requires prospective validation but do suggest HU resistance is an important prognostic factor for patients with PV. The development of HU intolerance, although not of prognostic significance, may be a useful indicator of when to consider switching treatment from HU to other cytoreductive therapy. ELN management guidelines for PV recommend switching first-line therapy at the onset of intolerance in high-risk patients and suggest INF-a as the regimen of choice. The management guidelines were developed before results and publication of the RESPONSE trial became available.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Hematology 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 (Jakavi) for polycythemia vera. 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 CADTH website (www.cadth.ca/pcodr).

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.

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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Hematology Clinical Guidance Panel is comprised of 3 hematologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). 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

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2015, **Embase** 1974 to 2015 September 09, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(ruxolitinib* or Jakavi* or Jakafi* or INC 424 or INC424 or "INCB 018424" or INCB018424 or INCB 424 or INCB424 or INCB 18424 or INCB18424 or 941678-49-5 or 82S8X8XX8H).ti,ot,ab,sh,rn,hw,nm,kw.	2020
2	1 use pmez,cctr	494
3	*ruxolitinib/ or (ruxolitinib* or Jakavi* or Jakafi* or INC 424 or INC424 or "INCB 018424" or INCB018424 or INCB 424 or INCB424 or INCB 18424 or INCB18424).ti,ab,kw.	1387
4	3 use oemezd	945
5	2 or 4	1439
6	Polycythemia Vera/ or (polycythemia* or polycythaemia* or erythremia* or erythraemia* or Vasquez disease or postpolycythemia* or postpolycythaemia* or erythremic myelosis or erythrocytemia* or erythrocythaemia* or erythrocytosis megalosplenica or osler disease or osler's disease).ti,ab,kw.	25313
7	5 and 6	397
8	limit 7 to english language	388
9	remove duplicates from 8	301

2. **Literature search via PubMed**

Search	Query	Items found
#3	Search **#1 AND #2 AND publisher[sb]** Filters: **English**	3
#2	Search **polycythemia*[tiab] OR polycythaemia*[tiab] OR erythremia*[tiab] OR erythraemia*[tiab] OR Vasquez disease[tiab] OR postpolycythemia*[tiab] OR postpolycythaemia*[tiab] OR erythremic myelosis[tiab] OR erythrocytemia*[tiab] OR erythrocythaemia*[tiab] OR erythrocytosis megalosplenica[tiab] OR osler disease[tiab] OR osler's disease[tiab]** Filters: **English**	7552
#1	Search **INCB018424 [Supplementary Concept] OR ruxolitinib*[tiab] OR Jakavi*[tiab] OR Jakafi*[tiab] OR INC 424[tiab] OR INC424[tiab] OR INCB 018424[tiab] OR INCB018424[tiab] OR INCB424[tiab] OR INCB 424[tiab] OR INCB 18424 OR INCB18424 OR 941678-49-5[rn] OR 82S8X8XX8H[tiab] OR ruxolitinib*[ot] OR Jakavi*[ot] OR Jakafi*[ot]** Filters: **English**	455

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Jakavi/Jakafi/ruxolitinib

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Jakavi/Jakafi/ruxolitinib

Conference abstracts:

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

European Society for Medical Oncology
http://www.esmo.org/

Search terms: Jakavi/Jakafi/ruxolitinib last 5 years

APPENDIX B: Summary of Trial Protocol Amendments in the RESPONSE Trial

Summary of Trial Protocol Amendments in the RESPONSE Trial.[24]	
Protocol Amendment (Date)	**Summary of Revisions to Response Trial Protocol**
Amendment 1 (August 23, 2011)	This amendment occurred after 30 patients had been randomized and included the following changes to the inclusion criteria: • Criterion requiring a palpable spleen length of >5cm was changed to requiring palpable splenomegaly confirmed by MRI/CT (volume ≥ 450 cm^3). • Criterion requiring patients to have a leukocytosis > $15x10^9$/l and/or thrombocytosis >600 x 10^9/l at screening was removed. • Definition of unacceptable non-hematological toxicities in HU intolerant patients was extended to include events reflecting severe/very severe toxicities leading to treatment discontinuation/interruption and hospitalization. • Phlebotomy requirement prior to study entry was extended from 12 to 16 weeks between the last phlebotomy and screening (for patients with HCT >45% at screening for the evidence of phlebotomy dependence) • Definition of durable response (for the primary endpoint and key secondary endpoints) was changed to 48 weeks after randomization; definition of duration of primary response was maintained as time from initial response. • Bone marrow biopsy was mandated in the event of suspected myelofibrosis or acute leukemia. • Sample size was reduced from 300 to 200 patients, and assumptions on response rates were modified accordingly.
Amendment 2 (April 13, 2012)	This amendment occurred after 98 patients had been randomized (none of them at the week 80 visit) and included an extension to the treatment period of patients receiving ruxolitinib (week 80 was the end of treatment in original protocol). • The treatment phase was extended by 128 weeks, from week 80 to week 208, and was defined as the Extended Treatment Phase. • Patients randomized to ruxolitinib and demonstrating benefit were offered enrolment into the Extended Treatment Phase.
Amendment 3 (June 25, 2013)	This amendment occurred after all patients had been randomized but 6 months prior to database lock for the primary analysis, and included revisions to assessment windows in order to define the use of multiple assessments available within an analysis window, minimize missing data, remove ambiguity and optimize available assessments. • The analysis window for MRI/CT scans was changed from ±7 to ±28 days. • The analysis windows for HCT, WBC and platelets were specified in greater detail for individual study visits.
Abbreviations: CT computed tomography;- HCT - hematocrit; MRI - magnetic resonance imaging; WBC - white blood cell.	

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