Ruxolitinib for the second-line treatment of myelofibrosis (IPSS intermediate risk-1 or above)

June 2012

Background

Myelofibrosis is a disorder of the bone marrow, in which the marrow is replaced by scar (fibrous) tissue. Myelofibrosis may be primary, or secondary to a number of haematological, malignant, and non-malignant conditions. Two of the most common secondary causes of myelofibrosis are polycythemia vera (a blood disorder in which the bone marrow makes too many red blood cells) and essential thrombocythaemia (a blood disorder characterised by the overproduction of platelets by megakaryocytes in the bone marrow). These disorders are closely linked, and many patients share a common transformation in the early haematopoietic stem cell of the Janus-associated kinase (JAK) 2 gene (JAK2V617F), seen in approximately 95% of people with polycythemia vera and in 50-60% of people with essential thrombocythaemia and primary myelofibrosis. In primary myelofibrosis, transformed haematopoietic cells, thought to release cytokines and growth factors, stimulate bone marrow fibroblasts to secrete excessive collagen, resulting in bone marrow fibrosis, characteristic of these disorders.

As the bone marrow becomes more scarred, it is less able to produce blood cells. To compensate for this, blood cell production occurs in the liver and spleen through a process called extramedullary haematopoeisis, which in turn causes these organs to swell. In the early stages, myelofibrosis can be asymptomatic, but can lead to symptoms including hepatomegaly and splenomegaly which may result in left upper quadrant discomfort. Other symptoms include general malaise, weight loss, night sweats, low grade fever, anaemia, fatigue, pallor, and shortness of breath.

The median survival is 5 years from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival. The median survival from the time of diagnosis is 4 years for patients with intermediate risk-2 disease and 2 years for patients with high-risk disease (7). The peak incidence of primary myelofibrosis is between 50 and 70 years of age. Haematopoietic stem cell transplant is the only potentially curative treatment for myelofibrosis. However, it is only suitable for people who are fit enough to undergo treatment. Other treatment options aim to relieve symptoms and improve the person’s quality of life. These treatments include androgens, splenectomy, chemotherapy (e.g. hydroxyurea, busulfan), splenic embolisation, and radiation therapy. For patients with low erythropoietin levels relative to the degree of anaemia, erythropoietin may increase haemoglobin sufficiently; otherwise, red blood cell transfusion may be necessary (1). Hydroxyurea is widely used in myelofibrosis for controlling splenomegaly, leucocytosis, and thrombocytosis. It has limited efficacy in the management of myelofibrosis-associated anaemia or constitutional symptoms (symptoms affecting the general well-being or general status of the patient e.g. general malaise, weight loss, and night sweats) (2).
Stage of myelofibrosis
International Prognostic Scoring System (IPSS) describes the stage and severity of myelofibrosis. There are four risk categories and they are assigned according to the patient’s score (5):
- Low risk = 0; intermediate risk-1 = 1; intermediate risk-2 = 2; and high risk ≥ 3
- Patients are scored 1 each for:
  - Age >65
  - WBC >25x10⁹ per litre
  - Hb <10g/decilitre
  - Circulating myeloblasts >1%
  - Constitutional symptoms

JAK inhibitors and ruxolitinib
Janus-associated kinases (JAKs) are tyrosine kinases involved in specific cytokine-receptor signalling pathways and are often upregulated in myeloproliferative and inflammatory disorders (1). A number of gene mutations, including the JAK2V617F mutation described above, have been identified in patients with myelofibrosis. Inhibition of wild type JAK 1 is associated with cytokine rebound syndrome and inhibition of wild type JAK 2 is associated with myelosuppression (2). Ruxolitinib (Jakafi, Novartis) is a JAK 1 and 2 inhibitor. Ruxolitinib is currently unlicensed in the UK although it is due to be launched in the UK in the 3rd quarter of 2012 (3). It was licensed in the US in November 2011 for use in high and intermediate risk myelofibrosis (4). The EMEA states in the summary of opinion for ruxolitinib that it will be indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis (9). The line of therapy for ruxolitinib in either document is not mentioned. There are no currently licensed drugs used for this indication and treatment is individualised (for example hydroxycarbamide is used for splenomegaly, erythropoietin is used for anaemia). It is proposed that the place in therapy of ruxolitinib, if accepted via the CDF, would be second-line use in patients not achieving response to a current therapy.

Epidemiology
Myelofibrosis is a relatively uncommon disease, with an annual incidence of approximately 0.75 cases per 100,000 (1). The application to request ruxolitinib via the Cancer Drugs Fund, proposed using ruxolitinib as a second-line therapy in patients not receiving response to a current therapy. The number of patients with myelofibrosis who would be eligible for ruxolitinib as a second-line therapy will be less than 0.75 per 100,000 but it is not clear what the actual figure will be.

Published data

Published guidance
NICE is in the process of reviewing ruxolitinib for the treatment of primary myelofibrosis and myelofibrosis secondary to polycythemia vera and essential thrombocythaemia for whom haematopoietic stem cell transplantation is considered inappropriate. This technology appraisal is expected in June 2013 (1).

Clinical trial evidence
There are two published phase III randomised control trials (COMFORT I and COMFORT II).

COMFORT I
This phase III double blind, placebo controlled trial was conducted in 89 sites in the United States, Australia, and Canada with a total of 309 patients (6). Patients were randomly assigned in a 1:1 ratio to receive oral ruxolitinib tablets or matched placebo. The starting dose of ruxolitinib depended on the baseline platelet count (15mg twice daily for a platelet count of 100x10⁹ to 200x10⁹ per litre, and 20mg twice daily for a count that exceeded 200x10⁹ per litre). Unblinding of the study-drug assignments and crossover from placebo to ruxolitinib were permitted for protocol-defined worsening splenomegaly. After crossover, data for patients who were initially assigned to placebo were not included in the analysis, except for the intention-to-treat analysis of overall survival. Eligibility criteria included:
- Over 18 years of age
- Primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis (9). The line of therapy for ruxolitinib in either document is not mentioned. There are no currently licensed drugs used for this indication and treatment is individualised (for example hydroxycarbamide is used for splenomegaly, erythropoietin is used for anaemia). It is proposed that the place in therapy of ruxolitinib, if accepted via the CDF, would be second-line use in patients not achieving response to a current therapy.

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A total of 155 patients were assigned to ruxolitinib, and 154 patients were assigned to placebo. The median age was 66 years (range 43–91 years) in the ruxolitinib arm and 70 years (range 40–86 years) in the placebo arm. Baseline characteristics were similar in the two groups. The median spleen volume was more than 2500cm\(^3\) (>10 times the median normal spleen volume of 200cm\(^3\)). A total of 38.2% of the patients had IPSS intermediate-2 risk disease, and 61.2% had high-risk disease.

The primary end point of this study was the proportion of patients with a reduction of 35% or more in spleen volume from baseline to week 24. This end-point was selected because 35% spleen volume reduction equates to a 50% reduction on palpable length, which is a response according to international response criteria (10). Secondary end points included the duration of the reduction in spleen volume; the proportion of patients with a reduction in the total symptom score of 50% or more from baseline to week 24, as assessed with the modified Myelofibrosis Symptom Assessment Form (MFSAF); the change in the total symptom score from baseline to week 24; and overall survival. The analysis of overall survival was updated at the time of a planned data-collection cut-off 4 months after the primary analysis. Patients completed the MFSAF every night and it was used to evaluate symptoms of night sweats, itching, abdominal discomfort, pain under the ribs on the left side, a feeling of fullness, muscle or bone pain, and inactivity. Scores ranged from 0 (absent symptoms) to 10 (worst imaginable symptoms), and the total score was the sum of the individual scores, excluding inactivity.

At the point of data cut-off (median follow-up 32 weeks) the main results were as follows:

- 134 patients in the ruxolitinib group (86.5%) and 78 in the placebo group (50.6%) were receiving the randomly assigned study drug. Thirty-six patients in the placebo group (23.4%) crossed over to ruxolitinib (16 before and 20 after week 24)
- The proportion of patients with a reduction of 35% or more in spleen volume at week 24 (primary endpoint) was 41.9% in the ruxolitinib arm and 0.7% in the placebo arm (odds ratio 134.4; 95% CI 18.0–1004.9; P<0.001).
- Among the patients for whom baseline and week 24 data were available, the 139 patients receiving ruxolitinib had a mean reduction in spleen volume of 31.6% (median 33%) at week 24; the 106 patients receiving placebo had a mean increase of 8.1% (median 8.5%).
- The reduction in spleen volume was durable with continued therapy. Among patients who had a reduction of 35% or more in spleen volume, 67% (95% CI 46.4–81.1) had a reduction in spleen volume that was maintained for 48 weeks or more (loss of response was defined as a reduction of <35% from baseline and an increase of ≥25% from the nadir).
- The proportion of patients with a reduction of 50% or more in the total symptoms score from baseline to week 24 was significantly higher in the ruxolitinib arm than in the placebo arm (45.9% vs. 5.3%; odds ratio 15.3; 95% CI 6.9–33.7; P<0.001).
- Among the patients for whom baseline and week 24 data were available, the 129 patients receiving ruxolitinib had a mean improvement of 46.1% (median 56.2%) in the total symptom score at week 24; the 103 patients receiving placebo had a mean worsening of 41.8% (median 14.6%) in the score (P<0.001). There were 10 deaths in the ruxolitinib group (6.5%) compared to 14 deaths in the placebo group (9.1%) (hazard ratio 0.67; 95% CI 0.3–1.5; P=0.33).

After an additional 4 months of follow-up (median follow-up 51 weeks) there were 13 deaths in the ruxolitinib arm (8.4%) and 24 deaths in the placebo arm (15.6%) (hazard ratio 0.5; 95% CI 0.25–0.98; P=0.04).

**COMFORT II**

This phase III randomised controlled trial recruited 219 patients. Patients were randomly assigned, in a 2:1 ratio, to receive ruxolitinib or the best available therapy, which included any commercially available agents (as monotherapy or in combination) or no therapy at all and which could be changed during the treatment phase. Among patients receiving the best available therapy, the most common therapies were antineoplastic agents (51%)—most frequently hydroxyurea (47%)—and glucocorticoids (16%); a total of 33% of patients received no therapy. The starting dose of ruxolitinib tablets was 15mg orally twice daily if the baseline platelet count was 200x10\(^9\) per litre or less and 20mg twice daily if the baseline platelet count was greater than 200x10\(^9\) per litre. The ruxolitinib dose could be escalated to increase efficacy but the maximum dose permitted was 25mg twice daily. Symptoms and quality of life were assessed with the EORTC quality-of-life questionnaire core model (QLQ-C30) and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scale. Patients received treatment in either arm until disease progression. At any time, patients who underwent splenectomy, or had an increase in spleen volume of >25% from the nadir during the study period, discontinued the randomised treatment phase of the study and could enter an extension phase. In the extension phase, patients who
had been randomly assigned to the best available therapy could receive ruxolitinib if they met safety criteria, and patients who had been randomly assigned to ruxolitinib could continue to receive ruxolitinib if they were still deriving a clinical benefit. Eligibility criteria for the trial included:

- Patients 18 years of age or older who had primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocytemia myelofibrosis
- Palpable spleen 5cm or more below the costal margin
- IPSS intermediate-2 risk or high-risk
- Peripheral-blast blast count of 100x10^6 or more per litre
- ECOG performance status of 3 or less

Patients were not considered to be suitable candidates for allogeneic stem-cell transplantation at the time of enrolment.

Randomisation was stratified according to IPSS score. A total of 146 patients were assigned to receive ruxolitinib, and 73 patients assigned to receive the best available therapy (BAT). The baseline characteristics were balanced between the groups. The median age was 67 years in the ruxolitinib arm (range 35–83 years) and 66 years in the BAT arm (range 35–85 years). Approximately half the patients had primary myelofibrosis, approximately one third had post-polycythemia vera myelofibrosis, and the remainder had post-essential thrombocytemia myelofibrosis. Approximately 40% of the patients in each study group were classified as having disease of intermediate-2 risk, and 60% were classified as having high-risk disease.

The primary endpoint was a reduction of 35% or more in spleen volume from baseline at week 48. Spleen volume was assessed by MRI (or CT if patients were not suitable for MRI). Secondary endpoints included a reduction of 35% or more in spleen volume from baseline at week 24, the length of time that a reduction in spleen volume of at least 35% was maintained, the time to reduction in spleen volume of 35% or more from baseline, progression-free survival, leukaemia-free survival, overall survival, and change in marrow histomorphologic features. The efficacy analysis was performed according to the intention-to-treat principle.

Three patients (two in the ruxolitinib arm and one in the BAT arm) had a baseline spleen assessment MRI after randomisation and were not included in the efficacy analysis of spleen volume. At the data cutoff date, a smaller percentage of patients in the ruxolitinib arm than in the BAT arm had discontinued the randomised treatment phase of the study (38% vs. 58%). Of the 55 patients who discontinued the randomised treatment phase who were originally assigned to receive ruxolitinib, 29 (53%) entered the extension phase and continued to receive ruxolitinib. Of the 42 patients originally assigned to BAT who discontinued the randomised treatment phase for any reason, 18 (43%) crossed over to ruxolitinib in the extension phase. The results presented are those from the randomised treatment phase only.

The main results after a median of 12 months follow-up were as follows:

- Only patients in the ruxolitinib arm met the criteria for the primary end point, at least a 35% reduction in spleen volume from baseline at 48 weeks, (28% vs. 0% in the BAT arm; P<0.001).
- At 24 weeks, 32% of patients in the ruxolitinib arm had a reduction of at least 35% in spleen volume compared with 0% in the BAT arm (P<0.001).
- During the 48 week period, almost all patients who were treated with ruxolitinib (97%), compared with 56% given BAT, had a measurable reduction in spleen volume.
- The rates of response (reduction in spleen volume of ≥35%) in the V617F-positive subgroup were 33% (95% CI 25–43) with ruxolitinib and 0% (95% CI 0–7) with the best available therapy; the corresponding rates in the V617F-negative subgroup were 14% (95% CI 5–30) and 0% (95% CI 0–17).
- The median time to the first observation on MRI or CT of a reduction from baseline of 35% or more in spleen volume was 12.3 weeks in the ruxolitinib group.
- Among the 69 patients who had a reduction in spleen volume of at least 35% at any time during the study, the reduction was observed the first assessment (12 weeks) in 44 patients (64%).
- The median duration of response among patients treated with ruxolitinib was not reached, with 80% of patients still having a response after a median of 12 months follow-up.
- At week 48, patients treated with ruxolitinib had a mean decrease in spleen length from baseline of 56%, compared with a mean increase of 4% in patients receiving BAT.
- In a time-to-event analysis, conducted at week 48, there were 44 patients in the ruxolitinib arm (30%) who had progression events compared with 19 (26%) in the BAT arm (hazard ratio for progression with ruxolitinib 0.81; 95% CI 0.47–1.39).
- In the analyses of leukaemia-free survival and overall survival, there were 10 events in total (all of which were deaths): 6 events (4%) with ruxolitinib and 4 events (5%) with the BAT
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(hazard ratio for leukaemia-free survival with ruxolitinib 0.65, 95% CI 0.18–2.31; hazard ratio for overall survival 0.70, 95% CI 0.2–2.49)

- The median survival has not yet been reached.

At week 48, patients receiving ruxolitinib had significant reductions in myelofibrosis-associated symptoms, including appetite loss, dyspnoea, fatigue, insomnia, and pain. Patients receiving BAT had worsening symptoms. Substantial improvements in FACT-Lym scores indicated that patients receiving ruxolitinib had a reduction in myelofibrosis-associated symptoms.

Safety

COMFORT I

Seventeen patients who received ruxolitinib (11%) and 16 patients who received placebo (10.6%) discontinued the study treatment because of adverse events of any grade. Twenty deaths occurred during the study or within 28 days after the last dose was administered (9 deaths in the ruxolitinib arm and 11 deaths in the placebo arm, including 1 death after crossover). Principal causes of death in the ruxolitinib group were muscle weakness and general deterioration, subdural haematoma, renal failure, non-small cell lung cancer, acute myeloid leukaemia (AML), pneumonia (in 2 patients), and sepsis (in 2 patients). Principal causes of death in the placebo group were staphylococcal infection, gastrointestinal haemorrhage, intestinal perforation, multiorgan failure, pneumonia, sepsis (in 2 patients), and disease progression (in 4 patients).

Anaemia and thrombocytopenia were the most frequent haematologic adverse events. Grade 3 or 4 anaemia occurred in 45.2% of patients in the ruxolitinib arm compared to 19.2% in the placebo arm. Grade 3 or 4 thrombocytopenia occurred in 12.9% of patients taking ruxolitinib and 1.3% of patients taking placebo. Adverse events of grade 3 or higher developed in 8 of 49 patients in the ruxolitinib arm (16.3%) and in 7 of 54 patients in the placebo arm (13%) after interruption of the study drug and in 12 of 21 patients in the ruxolitinib arm (57.1%) and 17 of 37 patients in the placebo arm (45.9%) after discontinuation.

COMFORT II

The percentage of patients who discontinued treatment because of adverse events was 8% in the ruxolitinib arm and 5% in the BAT arm. The most frequently reported non-haematologic adverse event of any grade in the ruxolitinib arm was diarrhoea (diarrhoea of any grade occurring in 23% of the patients and grade 3 or 4 diarrhoea occurring in 1%). The most frequently reported grade 3 or 4 non-haematologic adverse events were abdominal pain in the ruxolitinib arm (occurring in 3% of patients) and dyspnoea and pneumonia in the BAT arm (each occurring in 4% of the patients). Adverse events of any grade requiring dose reductions or interruptions occurred more frequently with ruxolitinib than with the best available therapy (in 63% of patients vs. 15%). Thrombocytopenia was the most common cause of dose modifications in both groups (in 41% of the patients in the ruxolitinib arm and 1% in the BAT arm). 5% of the patients in the ruxolitinib arm required dose interruptions or reductions owing to anaemia and 1% owing to neutropenia; the corresponding percentages in the BAT arm were 1% and 0%.

Among the 32 patients who discontinued ruxolitinib, 19 had adverse events 2 weeks or less after discontinuation. Of these 19 patients, 6 patients had at least one symptom related to myelofibrosis, including general deterioration in physical health (1 patient), pyrexia (2), anorexia (2), fatigue (1), weight loss (2), night sweats (1), and pruritus (1).

Tefferi A. and Pardanani A. report on 5 patients among 47 Mayo Clinic patients (11%) who experienced severe withdrawal symptoms during ruxolitinib treatment discontinuation (8). This ‘ruxolitinib withdrawal syndrome’ was characterised by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias, and occasional haemodynamic decompensation, including a septic shock-like syndrome. The United States prescribing information for ruxolitinib states that when discontinuing ruxolitinib for reasons other than thrombocytopenia, gradual tapering of the dose of ruxolitinib may be considered.

Cost

Ruxolitinib is not yet commercially available in the UK. Provisional cost estimates by the manufacturer, Novartis, suggest that the cost per patient per annum will be £40,000–£45,000 (excluding VAT).

Assuming epidemiology of 0.75 patients per 100,000, the cost would be between £30,000 and £33,750 per 100,000 population per year. This is the cost of using ruxolitinib first-line. The application proposed is using ruxolitinib second-line in patients not receiving response to a current therapy. The cost of using ruxolitinib second-line is likely to be slightly lower than this but it is not clear what the actual figure will be.
Issues for consideration

In COMFORT I the proportion of patients with a reduction of 35% or more in spleen volume at week 24 (primary endpoint) was 41.9% in the ruxolitinib arm and 0.7% in the placebo arm (odds ratio 134.4; 95% CI 18.0–1004.9; P<0.001). In COMFORT II only patients in the ruxolitinib arm met the criteria for the primary endpoint, at least a 35% reduction in spleen volume from baseline at 48 weeks, (28% vs. 0% in the best available therapy arm; P<0.001). The reduction in spleen volume was durable with continued therapy. Among patients in COMFORT I who had a reduction of 35% or more in spleen volume, 67% (95% CI 46.4–81.1) had a reduction in spleen volume that was maintained for 48 weeks or more (loss of response was defined as a reduction of <35% from baseline and an increase of ≥25% from the nadir). In COMFORT II the median duration of response among patients treated with ruxolitinib was not reached, with 80% of patients still having a response after a median of 12 months follow-up.

The effect of ruxolitinib on progression free survival and overall survival did not show any significant differences between ruxolitinib treatment and placebo/best available therapy, possibly because crossover was permitted. However, COMFORT II reports that the median survival has not yet been reached. Ruxolitinib is associated with a reduction in myelofibrosis symptoms and patients taking ruxolitinib had improvement in the symptom score compared to patients taking placebo/best available therapy who had a worsening of symptoms.

Thrombocytopenia and anaemia occurred more frequently in the patients receiving ruxolitinib than in patients receiving placebo/best available therapy. There are also reports of a ‘ruxolitinib withdrawal syndrome’ and the U.S prescribing information for ruxolitinib suggests that gradual tapering of the dose when discontinuing ruxolitinib for reasons other than thrombocytopenia may be considered. COMFORT II found that 19 out of 32 patients discontinuing ruxolitinib had adverse events 2 weeks or less after discontinuation. None of these patients had septic shock-like syndrome which was reported by Tefferi A. and Pardanani A. (8).

The application to add ruxolitinib to the Cancer Drugs Fund requests using ruxolitinib in patients with IPSS intermediate-1 risk and above. The randomised control trials both excluded patients with IPSS intermediate-1 risk and included patients with intermediate-2 risk and high-risk only. Patients with IPSS intermediate-1 risk have been included in other studies including a global expanded access study [personal communication with manufacturer].
**References:**

3. UKMI new online drugs report for ruxolitinib (accessed 15/6/12). Available at [www.ukmi.nhs.uk](http://www.ukmi.nhs.uk)

**Details of search strategy:**

NELM
NICE
Cancer Research UK
UKMI

**Search History:**

1. EMBASE; RUXOLITINIB/; 129 results.
2. EMBASE; MYELOFIBROSIS/; 5061 results.
3. MEDLINE; ruxolitinib.ti,ab; 29 results.
4. EMBASE; 1 AND 2; 76 results.
5. MEDLINE; 4 AND 5; 22 results.
6. MEDLINE; MYELOPROLIFERATIVE DISORDERS/ OR PRIMARY MYELOFIBROSIS/; 8247 results.
7. EMBASE,MEDLINE; Duplicate filtered: [1 AND 2], [4 AND 5]; 98 results.