BC Cancer Protocol Summary for Treatment of Polycythemia Vera with Ruxolitinib

Protocol Code	*ULKPCVRUX*
Tumour Group	*Leukemia/BMT*
Contact Physicians	*Dr. Lynda Foltz* *Dr. Donna Forrest*

ELIGIBILITY:

- Polycythemia vera resistant or intolerant to hydroxyurea defined as below:
  - Resistance: after 3 months of hydroxyurea at the maximally tolerated dose, patients show one of the followings:
    - need for phlebotomy to maintain HCT below 45%, or
    - platelet > 400 × 10^9 /L and WBC > 10 × 10^9 /L, or
    - failure to reduce splenomegaly extending greater than 10 cm below the costal margin by > 50%, as measured by palpation
- Intolerance: one of the following after any dose of hydroxyurea:
  - ANC < 1.0 × 10^9 /L or platelet < 100 × 10^9 /L or hemoglobin < 100 g/L at the lowest hydroxyurea dose required to achieve a response, defined as:
    - HCT < 45% without phlebotomy, and/or all of the followings: platelet ≤ 400 × 10^9 /L, WBC ≤ 10 × 10^9 /L and non-palpable spleen
  - Grade 3 to 4 non-hematologic toxicities (e.g., leg ulcers, mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea)
  - More than 1 week of grade 2 toxicities, permanent discontinuation of hydroxyurea, interruption of hydroxyurea until toxicity resolved, or hospitalization due to hydroxyurea toxicity
- A BC Cancer "Compassionate Access Program" (CAP) request with appropriate clinical information (bone marrow report, cytogenetic report [if done], recent complete blood count and recent clinic progress note) for each patient must be approved prior to treatment. Initial CAP approval for 24 weeks. To continue treatment, apply to CAP for re-approval. Subsequent approval through CAP is valid until disease progression.

TESTS:

- CBC, platelets, differential
  - Baseline
  - During dosage titration: (physician will check and advise patient on dose adjustment)
    - First 3 months: every 1-2 weeks
    - 3-6 months: every 2-4 weeks
  - After 6 months of therapy: every 1-3 months

- Serum creatinine
  - baseline
  - regularly for patients with renal impairment
- Bilirubin, ALT
  - baseline
  - regularly for patients with hepatic impairment
- ECG – baseline and as clinically indicated
- HBsAg, HBcoreAb at baseline (results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment)

SUPPORTIVE MEDICATIONS:
If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

PREMEDICATIONS:
None

TREATMENT:

Drug	Platelet* (x 10^9/L)	Dose**	BC Cancer Administration Guideline
ruxolitinib	100 or greater	Start at 10 mg BID	PO
	50 to less than 100	Start at 5 mg BID	

* Plus ANC greater or equal 1.0 x 10^9/L
** May increase dose 8 weeks after initiation, and then at intervals of 2 weeks or longer. Platelet should be 125 x 10^9/L or higher and ANC 0.75 x 10^9/L or higher. Dose may be ***increased by*** a maximum of 5 mg BID up to ***a dose of*** 25 mg BID.

Assess response after 24 weeks.

DOSE MODIFICATIONS:

1. Hematological:

Hemoglobin (g/L)		Platelet (x 10^9/L)		ANC (x 10^9/L)	Total daily dose
Less than 80	or	Less than 50	or	Less than 0.5	Hold until recovery of blood counts, then restart at 5 mg BID

Dosing recommendations for thrombocytopenia

Platelet Count (x 10^9/L)	Dose at Time of Platelet Decline				
	25 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
	New dose ↓	New dose ↓	New dose ↓	New dose ↓	New dose ↓
100 to less than 125	20 mg BID	15 mg BID	No change	No change	No change
75 to less than 100	10 mg BID	10 mg BID	10 mg BID	No change	No change
50 to less than 75	5 mg BID	5 mg BID	5 mg BID	5 mg BID	No change
Less than 50	Hold until recovery, then restart at 5 mg BID				

2. Renal dysfunction:

Renal dysfunction	Platelet (x 10^9/L)	Dosing
Creatinine clearance less than 50 mL/min	greater than or equal to 100	5 mg BID starting dose
	less than 100	Avoid
On dialysis	100 or greater	10 mg single dose after hemodialysis
	less than 100	Avoid

PRECAUTIONS:

1. **Anemia and thrombocytopenia:** patients may require dose adjustment (see above) and transfusion support. Platelet nadir at approx 4 weeks, hemoglobin nadir at approximately 12 weeks.
2. **Arrhythmia:** A decrease in heart rate and prolongation of PR interval was noted on ECG in ruxolitinib treated patients. The clinical significance of these findings remains unclear.
3. **Hepatic dysfunction:** consider reducing dose in patients with hepatic impairment (e.g., start at 10 mg BID).
4. **Infections:** hepatitis B, tuberculosis, JC virus and herpes zoster infections have been reported. Incidence of herpes zoster in ruxolitinib treated polycythemia vera patients was 6.4% over 32 weeks.
5. **Progressive multifocal leukoencephalopathy (PML)**: has been reported.

6. **Non-melanoma skin cancer (NMSC)**: includes basal call, squamous cell, and Merkel cell carcinoma. Most patients had previously treated with long duration of hydroxyurea and prior history of NMSC or pre-malignant skin lesions. Patients should minimize exposure to risk factors for skin cancer while on ruxolitinib.
7. **Lipid abnormalities**: include increases in total cholesterol, LDL, cholesterol, and triglycerides.

Call Dr. Donna Forrest or tumour group delegate at (604) 875-4337 with any problems or questions regarding this treatment program.

References:

Alessandro M. Vannucchi AM, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015;372:426-35.