BC Cancer Protocol Summary for Treatment of Symptomatic Myelofibrosis with Ruxolitinib

Protocol Code	*ULKMFRUX*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Donna Forrest*
	Dr. Lynda Foltz

ELIGIBILITY:

- Primary myelofibrosis, post-essential thrombocythemia myelofibrosis and post-polycythemia vera myelofibrosis
- Splenomegaly or other symptoms related to myelofibrosis
- DIPSS score:
  - Intermediate-1, intermediate-2 or high risk, OR
  - Low risk with symptomatic splenomegaly
- ECOG 0 to 3
- 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. Approval through CAP is valid until disease progression.

TESTS:

- CBC, platelets, differential
  - Baseline
  - During dosage titration: (physician will be responsible to 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

PREMEDICATIONS:

None

TREATMENT:

Drug	Platelet* ($x 10^9$/L)	Starting dose**	Maintenance dose	BC Cancer Administration Guideline
ruxolitinib	greater than 200	20 mg BID	Adjust according to platelet (max. 25 mg BID)	PO
	100 to 200	15 mg BID		
	50 to 99	5 mg BID		

* plus ANC greater or equal 1.0 x 10^9/L

** consider lower starting dose (followed by optional upward dose titration) for patients unable to tolerate a decline in hemoglobin.

- No dose increase in the first month, thereafter no more than at 2-week intervals
- Discontinue if no reduction of spleen size or improvement of constitutional symptoms at 6 months
- Discontinue if disease progression
- If treatment is stopped, taper dose to prevent a rapid return of symptoms of myelofibrosis, e.g., reduce dose by 5 mg BID every 3 days

DOSE MODIFICATIONS:

1. Hematological:

Existing dose	New dose		
	Platelet 100-125 ($x 10^9$/L)	Platelet 75-99 ($x 10^9$/L)	Platelet 50-74 ($x 10^9$/L)
25 mg BID	20 mg BID	10 mg BID	5 mg BID
20 mg BID	15 mg BID	10 mg BID	5 mg BID
15 mg BID	15 mg BID	10 mg BID	5 mg BID
10 mg BID	10 mg BID	10 mg BID	5 mg BID
5 mg BID	5 mg BID	5 mg BID	5 mg BID

If ANC less than 0.5 x 10^9/L or platelet less than 50 x 10^9/L, consult with prescribing physician (may need to consider holding dose)

Restarting or increasing dose after dose modifications

Current Platelet (x 10^9/L)		Current ANC (x 10^9/L)	Maximum dose*
Less than 50	or	Less than 0.5	Continue to hold
50 to less than 75	or	0.5 to less than 0.75	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
75 to less than 100	or	0.75 to less than 1.0	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
100 to less than125	or	Greater than or equal to 1.0	15 mg BID
Greater or equal to 125	or	Greater than or equal to 1.5	20 mg BID

* Should not exceed 5 mg BID LESS than the original dose which resulted in platelet less than 100 x 10^9/L or ANC less than 0.5 x 10^9/L. If original dose was 5 mg BID, may resume at 5 mg BID when platelet greater than 50 x 10^9/L and ANC greater than 0.5 x 10^9/L

2. Renal dysfunction:

Creatinine clearance (mL/min)	Platelet (x 10^9/L)	Starting dose
less than 50	greater than or equal to 100	10 mg BID
	less than 100	Avoid

End stage renal disease	Platelet (x 10^9/L)	Single dose after hemodialysis
with dialysis	greater than 200	20 mg
	100 to 200	15 mg
	less than 100	Avoid
without dialysis		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).

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

References:

1. Verstovsek S, Mesa RA, Gotlib J et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366(9):799-807.
2. Harrison C, Kiladjian JJ, Al-Ali HK et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366(9):787-98.