BC Cancer Protocol Summary for Treatment of Symptomatic Myelofibrosis with Fedratinib

Protocol Code	*ULKMFFED*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Lynda Foltz*

ELIGIBILITY:

Patients must have:

- Primary myelofibrosis, post-essential thrombocythemia myelofibrosis, or post-polycythemia vera myelofibrosis,
- Splenomegaly or other symptoms related to myelofibrosis,
- Intolerance or contraindication to ruxolitinib,
- DIPSS score: intermediate-2 or high risk, and
- A Compassionate Access Program (CAP) approval prior to the initiation of treatment

Patients should have:

- ECOG 0 to 3
- Adequate hepatic and renal function

EXCLUSION:

Patients must not have:

- Prior progression on ruxolitinib
- Platelet count less than 50 x 10^9/L
- Thiamine deficiency (if thiamine testing is required, refer to your local public health authority lab for guidelines. An application and signed patient consent must be submitted directly to the testing site)

TESTS:

- Baseline: CBC & Diff, ALT, total bilirubin, creatinine
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- During treatment: CBC & Diff, ALT, total bilirubin, creatinine every 4 weeks
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- Thiamine (Vitamin B1) 100 mg PO once daily during fedratinib treatment
- Antiemetic protocol for chemotherapy with moderate emetogenicity (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
fedratinib	400 mg once daily	PO

- Repeat every 28 days until disease progression or unacceptable toxicity
- Discontinue if no response by 6 cycles

DOSE MODIFICATIONS:

Table 1: Dose Reductions for All Toxicities:

Agent	Starting Dose	Dose level -1	Dose level -2
fedratinib	400 mg once daily	300 mg once daily	200 mg once daily

- Discontinue fedratinib in patients who are unable to tolerate a dose of 200 mg daily

1. Hematological:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
greater than or equal to 0.5	and	greater than or equal to 50	100%
less than 0.5	or	less than 50 (with active bleeding), or less than 25	Delay until ANC greater than or equal to 1.0 $x10^9$/L and platelets greater than or equal to 50 $x10^9$/L. Restart at the next lower dose level

2. Renal dysfunction:

Creatinine Clearance (mL/min)	Dose
greater than 60	100%
30 to 59	100%; monitor for toxicity
15 to 29	200 mg PO daily; monitor for toxicity

3. Hepatic dysfunction:

Bilirubin (micromol/L)		ALT	Dose
greater than 3 x ULN	or	greater than 5 x ULN	Delay until resolved and restart at the next lower dose level. Discontinue for recurrence.

- ULN = upper limit of normal

PRECAUTIONS:

1. **Wernicke's encephalopathy:** if suspected, immediately discontinue and initiate parenteral thiamine treatment. Monitor until symptoms resolve and thiamine levels normalize. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia.
2. **Thiamine deficiency:** patients with thiamine deficiency are at increased risk of Wernicke's encephalopathy. Do not initiate fedratinib in patients with thiamine deficiency. All patients should receive thiamine 100 mg PO once daily. If required, may consider thiamine testing monthly for 3 months, then every 3 months during fedratinib therapy (refer to your local public health authority lab for guidelines on thiamine testing).
3. **Anemia**: in patients with hemoglobin less than 80 g/L, consider correction of anemia prior to beginning/continuing fedratinib treatment.
4. **Diarrhea:** antidiarrheal medications are recommended at the first onset of symptoms.
5. **Drug interactions:** fedratinib is a substrate of CYP3A4. Concurrent use of moderate or strong CYP3A4 inhibitors and strong CYP3A4 inducers should be avoided. If the use cannot be avoided, reduce the dose of fedratinib to 300 mg PO once daily with moderate CYP3A4 inhibitor, and to 200 mg PO once daily with strong CYP3A4 inhibitor. If concurrent inhibitor is discontinued, fedratinib may be re-escalated in 100 mg increments as clinically indicated.
6. **Hepatitis B Reactivation:** Low risk for hepatitis B reactivation. See SCHBV protocol for monitoring requirements.

Call Dr. Lynda Foltz or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of Fedratinib in patients with primary or secondary myelofibrosis. JAMA Oncol 2015;1(5):643-651
2. Celgene Inc. INREBIC® product monograph. Montreal, Canada; September 9, 2021