BC Cancer Interim Protocol Summary for Ropeginterferon Alfa-2b Therapy of Chronic Myeloid Neoplasms and Hypereosinophilic Syndrome

Protocol Code	*ULK0*
Tumour Group	*Myeloid*
Contact Physician	*Dr. Lynda Foltz*

NOTE:
This interim protocol is only to be used during the drug shortage of peginterferon alfa-2a (PEGASYS). Once the drug shortage of peginterferon alfa-2a (PEGASYS) is resolved, patient must transition to treatment with LKPEGIFN protocol.

ELIGIBILITY:
Patient must:
- Be eligible for LKPEGIFN protocol, with no other satisfactory treatment options
- Have a BC Cancer Compassionate Access Program request approval prior to treatment

EXCLUSIONS:
Patient must not have:
- Uncontrolled pre-existing thyroid disease
- Existence or history of severe psychiatric disorder
- History or presence of active serious or untreated autoimmune disease
- History of transplant, currently receiving immunosuppressive medication
- End-stage renal disease
- Hepatic impairment (Child-Pugh B or C)

CAUTIONS:
- Avoid use in patients with severe, acute or unstable cardiovascular disease
- Renal impairment: avoid use in patients with eGFR <30 mL/min

TESTS:
- **Baseline:** CBC & Diff, creatinine, ALT, GGT, alkaline phosphatase, total bilirubin, LDH, TSH, triglycerides
  - Consider prescriber screening for depression (PHQ-2, PHQ-9, Beck Depression Inventory, GDS-15, etc.), especially in patients with high risk of mood disorders. Recommended and prescriber responsible to review results.
- **During treatment:**
  - CBC & Diff, ALT, GGT, total bilirubin, TSH
    - First 3 months: every 2 weeks
    - After 3 months: every 3 months
  - If clinically indicated: creatinine, AST, alkaline phosphatase, LDH, triglycerides, random glucose

PREMEDICATIONS:
- Pre-medication is not required routinely

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
ropeginterferon alfa-2b	100 mcg* every 2 weeks, increase by 50 mcg every 2 weeks** Maximum: 500 mcg every 2 weeks	Subcutaneously

* Patients transitioning from hydroxyurea, start at 50 mcg every 2 weeks and escalate by 50 mcg every 2 weeks to maximum 500 mcg. Taper off the hydroxyurea by reducing the total biweekly dose by 20-40% every two weeks during Weeks 3-12. Discontinue hydroxyurea by week 13.

**Increase the dose of ropeginterferon alfa-2b by 50 mcg every two weeks (up to a maximum of 500 mcg), until a satisfactory hematologic response is achieved.

Continue until peginterferon alfa-2a supply available, disease progression or unacceptable toxicities.

For patients transitioning from peginterferon alfa-2a:

Peginterferon alfa-2a weekly (or every 2 weeks) dose	Suggested ropeginterferon alfa-2b every 2 weeks (or every 4 weeks) dose*
45 mcg	65 to 125 mcg
90 mcg	125 mcg
135 mcg	200 mcg
180 mcg	250 mcg

*dose of ropeginterferon alfa-2b = approx. 70% dose of peginterferon alfa-2a.
Dose of ropeginterferon alfa-2b every 4 weeks = approx. 70% dose of peginterferon alfa-2a every 2 weeks. Doses should be adjusted according to hematological response.

DOSE MODIFICATIONS:

1. Hematological (neutropenia, thrombocytopenia and anemia):

Neutropenia:

ANC ($x10^9$/L)	Dose
Greater than or equal to 0.8	Current dose
Greater than or equal to 0.5 to less than 0.8	Decrease dose by 50 mcg every 2 weeks until ANC greater than or equal to 0.8. If the interrupted dose is 50 mcg, hold treatment until ANC greater than or equal to 0.8
Less than 0.5	Hold treatment until improvement to ANC greater than or equal to 0.8. Reduce the dose by 50 mcg upon recovery. Consider permanent discontinuation if neutropenia persists after 4 dose reductions

Thrombocytopenia:

Platelets ($x10^9$/L)	Dose
Greater than or equal to 50	Current dose
Greater than or equal to 25 to less than 50	Decrease dose by 50 mcg every 2 weeks until platelets greater than 75. If the interrupted dose is 50 mcg, hold treatment until platelets greater than 75
Less than 25	Hold treatment until improvement to platelets greater than 75. Reduce the dose by 50 mcg upon recovery. Consider permanent discontinuation if thrombocytopenia persists after 4 dose reductions

Anemia:

Hemoglobin (g/L)	Dose
Greater than or equal to 80	Current dose
Less than 80	Decrease dose by 50 mcg 2 weeks until hemoglobin greater than 100. If the interrupted dose is 50 mcg, hold treatment until hemoglobin greater than 100
Life threatening anemia, or urgent intervention required	Hold treatment until improvement greater than 100. Reduce the dose by 50 mcg upon recovery. Consider permanent discontinuation if anemia persists after 4 dose reductions

2. Hepatotoxicity during treatment:

ALT or AST or GGT	Dose
Any increase above baseline and ULN to less than or equal to 5 x ULN **without** concomitant total bilirubin above baseline and ULN	Current dose
Any increase above baseline and ULN **with** concomitant total bilirubin above baseline and ULN	**Hold treatment** until return to baseline and less than or equal to ULN, then restart at 50 mcg lower than the interrupted dose. If the interrupted dose is 50 mcg, hold treatment until return to baseline and less than or equal to ULN. Consider permanent discontinuation if toxicity persists after 4 dose reductions
Greater than 5 x ULN but less than or equal to 20 x ULN	**Decrease dose** by 50 mcg every 2 weeks until ALT recovers to less than 3 x ULN (if baseline normal); 3 x baseline (if baseline abnormal), and GGT less than 2.5 x ULN (if baseline normal); 2.5 x baseline (if baseline abnormal). If the interrupted dose is 50 mcg, hold treatment until recovery as above
Greater than 20 x ULN	**Hold treatment** until ALT recovers to less than 3 x ULN (if baseline normal); 1.5 x baseline (if baseline abnormal), and GGT less than 2.5 x ULN (if baseline normal); 2 x baseline (if baseline abnormal). Consider permanent discontinuation if toxicity persists after 4 dose reductions

3. Depression:

Severity	Dose Modification
Mild (without suicidal ideation)	Consider psychiatric consultation if persistent (>8 weeks)
Moderate (without suicidal ideation)	Consider dose reduction and psychiatric consultation
Severe (or any severity with suicidal ideation)	Discontinue therapy, recommend psychiatric consultation

PRECAUTIONS:

1. **Neuropsychiatric reactions:** Neuropsychiatric reactions, including depression and suicidal ideation, have been reported in patients being treated with ropeginterferon alfa-2b. These reactions may occur in patients with or without history of psychiatric illness. Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment should they occur. Discontinue treatment with persistently severe or worsening signs or symptoms
2. **Endocrine Toxicity:** May include worsening hypothyroidism and hyperthyroidism, autoimmune thyroiditis and hyperglycemia (including new onset type 1 diabetes). Discontinue treatment if endocrine disorders occur that cannot be managed by appropriate medical care.
3. **Cardiovascular toxicity:** Avoid use in patients with severe, acute or unstable cardiovascular disease. Cardiovascular toxicity, including cardiomyopathy, myocardial infarction and atrial fibrillation may occur. Patients with a history of cardiovascular disorders should be closely monitored for toxicity.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Hypersensitivity Reactions:** Hypersensitivity reactions have occurred in patients receiving interferon alfa products. Ropeginterferon alfa-2b is contraindicated in patients with hypersensitivity reactions to interferon products or any of the inactive ingredients. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes may not require interruption of treatment.
6. **Pancreatitis:** Pancreatitis has occurred in patients receiving interferon alfa products. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal and/or hepatic function. Hold treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of treatment in patients with confirmed pancreatitis.

7. **Colitis:** Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases occurring as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue treatment in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.
8. **Pulmonary toxicity:** Pulmonary toxicity has occurred in patients treated with ropeginterferon alfa-2b. Monitor patients closely for symptoms including dyspnea, pulmonary infiltrates, pneumonia, interstital pneumonitis and pulmonary hypertension. Discontinue ropeginterferon alfa-2b treatment if pulmonary infiltrates seen on imaging or pulmonary function impairment.
9. **Ophthalmologic toxicity:** Eye disorders such as retinopathy, retinal haemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion have occurred. Advise patients to have eye examinations before and during treatment. Evaluate reported eye symptoms promptly and discontinue ropeginterferon alfa-2b treatment if new or worsening eye disorders develop.
10. **Hyperlipidemia:** Elevated triglycerides may result in pancreatitis (see precaution 5 above). Monitor serum triglycerides before treatment starts and intermittently during therapy and manage when elevated. Consider discontinuation of treatment with persistently, markedly elevated triglycerides.
11. **Hepatotoxicity:** Hepatotoxicity, characterized by elevated ALT, AST, GGT and total bilirubin has occurred in patients treated with ropeginterferon alfa-2b. Monitor liver function regularly throughout treatment and manage per Dose Modification section above. Treatment should be discontinued for progressive liver enzyme elevation despite dose reduction.
12. **Dental toxicity:** Dental and periodontal disorders have been reported with interferon alfa products, which may lead to loss of teeth. In addition, dry mouth could have damaging effects on teeth and oral mucous membranes during long-term treatment. It is important to have good oral hygiene and regular dental examinations.
13. **Dermatologic toxicity:** Skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis and hyperhidrosis have been reported. Consider discontinuing if clinically significant dermatologic toxicity develops.

Call Dr. Lynda Foltz or any member of the Myeloid Tumour Group at 236-317-3083 with any problems or questions regarding this treatment program.

References:

1. PharmaEssentia Corp. BESREMi® full prescribing information. Burlington, MA, USA; April 2024.
2. NHS England. Urgent Interim Commissioning Policy Proposition: Peginterferon alfa-2a and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (all ages) [2420]. 23 October 2024.
3. European Medicines Agency (EMA). (2019). Besremi – Product information. 23 December 2023.