BC Cancer Protocol Summary for Therapy of Acute Myeloid Leukemia using azaCITIDine and Ivosidenib

Protocol Code	*ULKAMLAZIV*
Tumour Group	*Leukemia/BMT*
Contact Physicians	*Dr. Ryan Stubbins*

ELIGIBILITY:
Patients must have:
- Previously untreated, newly diagnosed acute myeloid leukemia (AML),
- Presence of IDH1 R132 mutation,
- Ineligibility for standard intensive induction chemotherapy and meet at least one of the following criteria:
  - Age 75 years or older, or
  - Age less than 75 years with significant comorbidities or ineligible for intensive chemotherapy as determined by the treating physician
- A Compassionate Access Program (CAP) approval prior to the initiation of treatment

Patients should have:
- QTc interval less than 450 msec. Patients with a prolonged QTc that has resolved on subsequent ECGs are eligible.

Note:
- Patients who initiated LKMDSA prior to 1 Mar 2026 may switch to ULKAMLAZIV if disease has not progressed and all other eligibility criteria is met.
- Patients who were intolerant of ULKAMLAVEN may switch to ULKAMLAZIV provided all eligibility criteria is met. Switching after progression is not funded.
- Patients should be provided with an ivosidenib patient alert card supplied with the product packaging and instructed to carry it with them at all times.

EXCLUSIONS:
Patients must not have:
- Prior treatment for AML, except for treatments to stabilize disease such as hydroxyurea
- QT/QTc interval greater than 500 msec regardless of correction method used
- Congenital long QT syndrome
- Family history of sudden cardiac death or polymorphic ventricular arrythmia
- Use of concurrent strong CYP3A4 inducers or dabigatran
- Acute promyelocytic leukemia (APL)
- Advanced hepatic tumours

CAUTIONS:
- QTc interval between 450 to 500 msec

TESTS:

- **Baseline (within 72 hours of Cycle 1 Day 1)**: CBC & Diff, creatinine, sodium, potassium, chloride, serum bicarbonate, calcium, magnesium, phosphate, urea, total bilirubin, ALT, LDH, GGT, alkaline phosphatase, albumin, INR, PTT, pregnancy test if of childbearing potential, ECG
- **Baseline:** (required but results do not have to be available to proceed with first treatment, results must be checked before proceeding with Cycle 2): HIV, HBsAg, HBsAb, HBcAb, HCAb, HSV 1 and 2 Ab, VZV Ab

- **Cycle 1:**
  - **Optional on Day 3 and 5:** CBC & Diff
  - **Days 8, 15, 22:** CBC & Diff, creatinine, sodium, potassium, chloride, serum bicarbonate, calcium, magnesium, phosphate, uric acid, total bilirubin, ALT, alkaline phosphatase, GGT, LDH, INR, PTT, creatine kinase, ECG
- **Cycles 2 onwards:**
  - **Prior to Day 1:** ECG
  - **Days 1 and 15:** CBC & Diff, creatinine, sodium, potassium, chloride, serum bicarbonate, calcium, magnesium, phosphate, uric acid, total bilirubin, ALT, alkaline phosphatase, GGT, LDH, INR, PTT
  - **If clinically indicated, Days 8 and 22:** CBC & Diff, creatinine, sodium, potassium, chloride, serum bicarbonate, calcium, magnesium, phosphate, uric acid, total bilirubin, ALT, alkaline phosphatase, GGT, LDH, INR, PTT
- **Bone marrow biopsy to assess response:** recommended between Cycles 4 to 6 of therapy, as responses to ivosidenib and azaCITIDine may take up to 6 months
- **If clinically indicated:** HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA)
- prochlorperazine 10 mg PO 30 minutes prior to azaCITIDine
- If required: ondansetron 8 mg PO 30 minutes prior to azacitidine. Be aware that ondansetron increases the risk of QTc interval prolongation; if it is used, ensure appropriate QTc monitoring is in place.

SUPPORTIVE MEDICATIONS:

- Moderate risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Anti-bacterial and anti-fungal prophylaxis is not universally recommended in patients receiving ivosidenib and azaCITIDine. In patients at high risk of infection with a neutrophil count of less than 0.5 x 10^9/L, the use of levoFLOXacin 500 mg PO daily may be considered with appropriate QTc monitoring.
- If HSV or VZV seropositive: valACYclovir 500 mg PO BID for duration of treatment

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
azaCITIDine	Standard regimen (preferred): 75 mg/m^2/day on Days 1 to 7 **OR** Alternative regimen (if treatment must be interrupted by weekends†): 75 mg/m^2/day on Days 1 to 5, 8 and 9	subcutaneous*
ivosidenib	500 mg once daily	PO

* Administer doses greater than 4 mL as two syringes at two separate sites

† May interrupt for more than 2 days but every effort should be made to avoid scheduling over long weekends (e.g. over 3-4 days) or statutory holidays during the week. If unavoidable, should aim to deliver a total of 7 days of treatment out of about 10 consecutive days; having breaks in therapy over these circumstances do not require CAP approval.

Repeat every 28 days for a minimum of 6 cycles, or until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. Differentiation Syndrome:

Severity	Management
If differentiation syndrome is suspected	• Admission to hospital for monitoring and management is recommended. Initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Administer systemic corticosteroids (dexamethasone 10 mg IV q12h) for a minimum of 3 days and taper only after symptom resolution. Premature discontinuation may result in recurrence. • Control leukocytosis by maintaining the total WBC below 10 x 10^9/L with hydroxyurea or other cytoreductive agents. • Closely monitor volume status and weights with diuresis to maintain euvolemia. • Withhold ivosidenib treatment and resume once signs or symptoms are moderate or lower and upon improvement in clinical condition.
Leukocytosis (WBC count greater than 25 x 10^9/L or an absolute increase in total WBC greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea or other cytoreductive agent. • Taper hydroxyurea only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence. • Withhold ivosidenib treatment if leukocytosis has not improved after initiation of hydroxyurea. • Resume ivosidenib treatment when leukocytosis has resolved.

2. Hematological

For azaCITIDine:

Nadir count: (nadir: days 10-17; recovery: days 28-31)

Patient not in remission	
Continue with dose as written	
Patient in remission	
ANC (x10^9/L)	**Dose**
Greater than 0.5	100%
Duration of ANC nadir below 0.5	
4 weeks or less	100%
More than 4 weeks but less than 6 weeks	Extend dosing interval to 5 weeks
• 6 weeks or more • After interval extension and duration of nadir is still greater than 4 weeks.	Dose reduction to 50 mg/m^2/day x 7 days or 37.5 mg/m^2/day x 7 days
8 weeks or greater	Bone marrow biopsy

For ivosidenib:

Patient not in remission	
Continue with dose as written	
Patient in remission	
Severity	**Management**
Grade 3 ANC 0.5 to 0.99 x 10^9/L OR Platelets 25 to 49 x 10^9/L OR WBC 1.0 to 1.9 x 10^9/L	• Withhold ivosidenib treatment until toxicity resolves to less Grade 1 or baseline, then resume treatment at 500 mg once daily • For second occurrence of Grade 3 hematological toxicity, consider reducing ivosidenib dose to 250 mg once daily until toxicity resolves, then resume 500 mg once daily dosing • For third occurrence of Grade 3 toxicity despite dose reduction, consider discontinuing ivosidenib
Grade 4 ANC less than 0.5 10^9/L OR platelets less than 25 x 10^9/L OR WBC less than 1.0 x 10^9/L	• Withhold ivosidenib treatment until toxicity resolves to less Grade 1 or baseline, then resume treatment at 250 mg once daily • If Grade 4 toxicity recurs despite dose reduction, permanently discontinue ivosidenib

3. QTc Interval Prolongation

QTc Interval* (msec)	Management
Greater than 480 to 500	• Withhold ivosidenib treatment until QTc interval returns to less than or equal to 480 msec • Monitor and supplement electrolyte levels as clinically indicated • Review and adjust concomitant medications with known QTc interval-prolonging effects • Resume ivosidenib treatment at same dose once QTc interval returns to less than or equal to 480 msec. Monitor ECGs at least weekly for 2 weeks.
Greater than 500	• Withhold ivosidenib treatment and monitor ECG every 24 hours until QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • If QTc interval is greater than 550 msec, also consider placing patient under continuous electrocardiographic monitoring until QTc returns to less than 500 msec. • Resume ivosidenib treatment at 250 mg once daily once QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. Monitor ECGs at least weekly for 2 weeks. • If alternative etiology for QTc interval prolongation is identified, ivosidenib dose may be increased to 500 mg once daily.
QTc interval prolongation with signs or symptoms of life-threatening ventricular arrhythmia	• Permanently discontinue ivosidenib treatment

*Calculated using the Fridericia formula.

4. Other Non-Hematological Toxicity:

For ivosidenib:

Severity	Management
Grade 3	• Withhold ivosidenib treatment until toxicity resolves to Grade 1 or lower, or baseline, then resume treatment at 500 mg once daily • For second occurrence of Grade 3 toxicity, reduce ivosidenib dose to 250 mg once daily until the toxicity resolves, then resume at 500 mg once daily • For third occurrence of Grade 3 toxicity, permanently discontinue ivosidenib
Grade 4	• Withhold ivosidenib treatment until toxicity resolves to Grade 1 or lower, or baseline, then resume treatment at 250 mg once daily • If Grade 4 toxicity recurs, permanently discontinue ivosidenib

For azaCITIDine:

Severity	azaCITIDine Management
Grade 2 or less	100 %
Grade 3 or greater	Hold until improves to Grade 1 or baseline, then resume at reduced dose

5. Hepatic impairment:
azaCITIDine: Has not been studied in patients with hepatic impairment.
ivosidenib: No dose modifications for mild impairment (Child Pugh A). No recommendation found on dose modification for moderate to severe hepatic impairment (Child Pugh B and C).

6. Renal impairment:
azaCITIDine: If unexplained increases in BUN or serum creatinine occur, delay until improves to baseline or normal, then reduce dose by 50% for next treatment course. If unexplained reduction in serum bicarbonate levels to less than 20 mmol/L occur, the dose should be reduced by 50% for the next cycle.
ivosidenib: No dose modifications for mild or moderate renal impairment (creatinine clearance greater than or equal to 30 mL/min). No recommendation found for severe renal impairment (creatinine clearance less than 30 mL/min).

PRECAUTIONS:

1. **Differentiation syndrome** has been reported with ivosidenib. Clinical presentation may include leukocytosis, fever, dyspnea, cough, rash, hypotension, pleural or pericardial effusion, peripheral edema, rapid weight gain and renal dysfunction. Differentiation syndrome may be fatal if not treated. Median time to onset is 15-29 days. Patients should be informed of the signs and symptoms of differentiation syndrome and to contact their health care provider immediately if these occur. Patients should also be provided with an ivosidenib patient alert card supplied with the product packaging and instructed to carry it at all times. Admission is generally recommended if differentiation syndrome is suspected.

Management may include corticosteroid therapy, hemodynamic monitoring, hydroxyurea or other cytoreductive measures, and ivosidenib dose interruption.

2. **QT Interval Prolongation** is a reported concentration-depended effect of ivosidenib. Ventricular fibrillation may also occur. Ensure regular electrolyte and ECG monitoring of QTc interval is completed during ivosidenib treatment. More frequent monitoring may be required for patients with known risk factors for QT prolongation. Use caution in combination with other medications known to prolong the QTc interval. Management of QT prolongation may include ivosidenib dose interruption and/or dose reduction.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
4. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
5. **Hepatotoxicity**: azaCITIDine may be hepatotoxic, with progressive hepatic coma leading to death having been rarely reported in patients with extensive tumor burden, especially those with a baseline albumin less than 30 g/L. It is contraindicated in patients with advanced malignant hepatic tumours.
6. **Renal toxicity**: azaCITIDine as part of combination therapy, has been associated with serum creatinine elevations, renal tubular acidosis, and renal failure.
7. **Drug interactions:** ivosidenib is a CYP3A4 substrate and induces CYP3A4, 2B6, 2C8, 2C9 and 2C19. Avoid concurrent use with strong or moderate CYP3A4 inhibitors. If coadministration cannot be avoided, decrease ivosidenib dose to 250 mg once daily and monitor for toxicity. CYP3A4 inducers decrease ivosidenib plasma concentration. Concurrent use with strong CYP3A4 inducers should be avoided. If co-administration with CYP3A4 substates is necessary, monitor closely for reduced efficacy of substrate. Ivosidenib also inhibits P-gp and has potential to induce P-gp. If coadministered with a P-gp substrate with a narrow therapeutic index, monitor for toxicity and efficacy of the substrate.

Concomitant Medication	Recommended ivosidenib Dose
None	500 mg PO once daily
Strong CYP3A4 inhibitor	250 mg PO once daily
Moderate CYP3A4 inhibitor	250 mg PO once daily
Weak CYP3A4 inhibitor	500 mg PO once daily
After discontinuation of CYP3A4 inhibitor	Resume 500 mg PO once daily after ≥ 5 half-lives of CYP3A4 inhibitor

Contact the Leukemia/BMT Physician at your regional cancer centre or Dr. Ryan Stubbins with any problems or questions regarding this treatment program.

References:

1. Montesinos P, Récher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. N Engl J Med. 2022;386(16):1519-1531.
2. Montesinos P, Marchione DM, Récher C, Heuser M, Vives S, Zarzycka E, et al. Long-term results from the AGILE study of azacitidine plus ivosidenib vs placebo in newly diagnosed IDH1-mutated AML. Blood Adv. 2025 Oct 28;9(20):5177-5189.
3. Ivosidenib (Tibsovo) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. October 2024; 4(10): 1-32.