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

Protocol Code	*ULKAMLAVEN*
Tumour Group	*Leukemia/BMT*
Contact Physicians	*Dr. David Sanford*

ELIGIBILITY:
Patients must have:
- Acute myeloid leukemia (AML), previously untreated,
- Ineligible for standard intensive induction chemotherapy:
  - Age 75 years or older with ECOG 0-2, or
  - Age less than 75 years with significant comorbidities or ineligible for transplant, and
- A Compassionate Access Program (CAP) approval prior to the initiation of treatment

Note: Patients who initiated azacitidine within 6 months may switch to combination therapy with venetoclax if disease has not progressed.

EXCLUSION:
Patients must not have:
- Acute promyelocytic leukemia (APL)
- Advanced hepatic tumors

CAUTION:
- White blood cell (WBC) count greater than 25 x 10^9/L (cytoreduction with hydroxyurea permitted)
- Concurrent therapy with moderate or strong CYP3A4 inhibitors (see dose modifications)
- Creatinine clearance less than 30 mL/min
- Bilirubin greater than 3 x upper limit of normal (ULN)

TESTS:
- **Baseline** (within 72 h of first treatment): CBC and differential, platelets, sodium, potassium, chloride, serum bicarbonate, calcium, magnesium, phosphate, uric acid, creatinine, urea, bilirubin, ALT, LDH, GGT, alkaline phosphatase, albumin, INR, PTT, pregnancy test prior to treatment in females of child-bearing potential
- **Baseline:** HIV, HBsAg, HBsAb, HBcAb, HCAb, HSV1 and 2 Ab, VZV
- **Cycle 1:**
  - **Tumour lysis syndrome (TLS) monitoring:** potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin
    - Inpatient (higher risk for TLS): Q8H on days 1 to 4, starting prior to first dose of venetoclax
    - Outpatient (lower risk for TLS): Prior to treatment on days 1 to 4 (prescriber responsible to monitor results and advise on supportive treatment)
  - **Days 1 to 4:** CBC and differential, platelets (prescriber responsible to monitor results and advise on supportive treatment)
  - **Days 8, 11, 15, 18, 22, 25:** CBC and differential, platelets, creatinine, sodium, potassium, chloride, serum bicarbonate, bilirubin, ALT, alkaline phosphatase, GGT, LDH, INR, PTT

- **Subsequent cycles:**
  - **Prior to each cycle:** CBC and differential, platelets, creatinine, sodium, potassium, chloride, serum bicarbonate, bilirubin, ALT, alkaline phosphatase, GGT, LDH, INR, PTT
  - **Weekly on Days 8, 15, and 22:** CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, GGT, LDH
- It is recommended to arrange bone marrow aspirate and biopsy approximately day 22 to 28 following cycle 1. Best response with this combination occurs within 1-2 cycles in most patients, and this guides the timing of cycle 2 if count recovery has not occurred at this time.

PREMEDICATIONS:
- Antiemetic protocol for low-moderate emetogenic chemotherapy (see SCNAUSEA)
- ondansetron 8 mg PO 30 minutes prior to azaCITIDine
- If required: prochlorperazine 10 mg PO 30 minutes prior to azaCITIDine

SUPPORTIVE MEDICATIONS:

Tumour lysis syndrome (TLS) may occur with venetoclax. Patients should be assessed for level of TLS risk. For patients with high risk factors for TLS (e.g. elevated WBC >25 x 10^9/L at presentation, extramedullary disease, elevated LDH, hyperuricemia, elevated creatinine or spontaneous TLS present prior to starting treatment, chronic renal impairment) should be planned for increased laboratory monitoring and hospitalization for treatment initiation during the ramp-up phase until 24 hours after reaching maximum venetoclax dose.

TLS prophylaxis:
- WBC count should be less than 25 x 10^9/L prior to starting venetoclax. Cytoreduction may be required
- Hydration: Start 48 h prior to 1st dose, and continue throughout initial dose ramp-up phase
  - 1.5 to 2 L daily (8 glasses) orally, and consider additional IV fluids as needed
- Anti-hyperuricemic agents: Start 48 to 72 h prior to 1st dose
  - Allopurinol 300 mg PO daily for 7 days or until dose ramp-up complete and at physician discretion
  - Consider rasburicase 3 mg IV x 1, may repeat Q24H prn
    - For patients on rasburicase, blood sample for uric acid must be placed on ice while awaiting assay
- Correct preexisting blood chemistry abnormalities prior to treatment initiation

Antimicrobial prophylaxis:
- If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines
- Antifungal and anti-bacterial prophylaxis is recommended if ANC less than 0.5 x 10^9/L during cycle 1. This should also be considered during subsequent cycles if prolonged neutropenia occurs. Recommended prophylactic agents include fluconazole 400 mg PO daily (venetoclax dose modification required – see drug interactions section below) and levofloxacin 500 mg PO daily. Physician may select alternatives based on organ function, allergy status, etc.
- If HSV or VZV seropositive: valACYclovir 500 mg PO BID for duration of treatment

TREATMENT:

Cycle 1:
(Outpatients must start on a Monday or Tuesday)

Drug	Dose	BC Cancer Administration Guideline
azaCITIDine	Standard regimen (preferred): 75 mg/m^2/d on days 1 to 7 **OR** Alternative regimen (if treatment must be interrupted by weekends†): 75 mg/m^2/d on days 1 to 5, 8 and 9	subcutaneous*
venetoclax¥	Ramp-up: 100 mg on day 1, then 200 mg on day 2, then 400 mg daily on days 3 to 28	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.

¥ Dose modifications are required for concomitant use of strong or moderate CYP3A4 inhibitors – see drug interactions section below.

Cycle 2 onwards:

Drug	Dose	BC Cancer Administration Guideline
azaCITIDine	Standard regimen (preferred): 75 mg/m^2/d on days 1 to 7 **OR** Alternative regimen (if treatment must be interrupted by weekends†): 75 mg/m^2/d on days 1 to 5, 8 and 9	subcutaneous*
venetoclax¥	400 mg daily on days 1 to 28	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.

¥ Dose modifications are required for concomitant use of moderate or strong CYP3A4 inhibitors – see drug interactions section below.

Repeat every 28 days until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Dosing levels:

	azaCITIDine
Starting dose	75 mg/m^2
Dose level -1	50 mg/m^2
Dose level -2	37.5 mg/m^2

1. Tumour Lysis Syndrome (TLS)

If patient meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution. During ramp-up, monitor for evidence of TLS, and manage abnormalities of creatinine and electrolytes promptly

- Changes in blood chemistries that require prompt management can occur as early as 6 to 8 hours after the first dose of venetoclax and after each dose increase
- Reduced renal function (CrCl ≤ 80 mL/min) increases the risk for TLS
- Electrolytes must be corrected to within normal limits prior to proceeding with next dose of venetoclax during the ramp-up phase
- See **Appendix I** for TLS management strategies

2. Hematological

It is not suggested to interrupt treatment due to cytopenias prior to achieving remission unless there is associated severe infection.

After remission is achieved (ie, patient in remission):

For Day 1 treatment:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Doses (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 50	100 %
Less than 1.0	or	Less than 50	Delay

During cycle:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Doses (both drugs)
Less than 0.5	or	Less than 25	<u>For any occurrences after remission, lasting 7 days or longer:</u> Hold until recovery to Grade 2 or better (ANC > 1.0 and platelets > 50); then resume same dose of venetoclax and azacitidine but reduce venetoclax duration by 7 days during each subsequent cycle (e.g. for the second occurrence reduce to 21 days instead of 28 days, for the third occurrence reduce to 14 days, for the fourth occurrence reduce to 7 days). Earlier or more rapid duration reductions can be considered, if warranted by individual patient circumstance (*e.g.,* high risk of infectious complications). For patients with prolonged cytopenias despite modification of venetoclax duration to 14 days or less, consider reduction of azaCITIDine by one dose level. In this instance, it can be considered to increase the cycle dosing interval to 5 or 6 weeks. Growth factor support with GCSF can be used following remission to hasten ANC recovery.

3. Drug Interactions

Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are **strong or moderate CYP3A4 inhibitors** increases venetoclax exposure and risk of toxicities, including the risk for TLS at initiation and during ramp-up. Venetoclax dose modifications during initiation, ramp-up and post ramp-up are required.

CYP3A4 inducers may decrease serum concentration of venetoclax.
P-glycoprotein inhibitors (P-gp) may increase serum concentration of venetoclax.

Agent Initiated	At initiation and dose ramp-up	After dose ramp-up is completed
Strong CYP3A4 inhibitors (e.g. posaconazole, voriconazole, clarithromycin, ritonavir)	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 75% as follows: Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less	• Reduce venetoclax dose by 75%. • Monitor patients more closely for signs of toxicities. • Resume standard venetoclax dosing 2 to 3 days after CYP3A4 inhibitor is discontinued.
Moderate CYP3A4 inhibitors (e.g. fluconazole, isavuconazole, ciprofloxacin, diltiazem)	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50% as follows: Day 1 – 50 mg Day 2 – 100 mg Day 3 – 200 mg or less	• Reduce venetoclax dose by at least 50%. • Monitor patients more closely for signs of toxicities. • Resume standard venetoclax dose 2 to 3 days after CYP3A4 inhibitor is discontinued.
Weak CYP3A4 inhibitors	No dose adjustment needed	
Strong and moderate CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine)	Avoid. Consider alternative treatments with less CYP3A4 induction.	
P-glycoprotein inhibitors (e.g. clarithromycin, cyclosporine)	• Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50%. • Monitor patients more closely for signs of toxicities. • Resume standard dose 2 to 3 days after discontinuation of P-gp inhibitor. **Note:** an exception is made for **azithromycin**, where dose adjustments of venetoclax are not required.	

4. Non-Hematological:

Severity	Venetoclax Dose	azaCITIDine Dose
Grade 2 or less	100 %	100 %
Grade 3 or greater	Hold if not resolved with supportive care. Once improves to Grade 1 or baseline, resume same dose	Hold until improves to Grade 1 or baseline, then resume at reduced dose

5. Hepatic:

azaCITIDine: Has not been studied in patients with hepatic impairment.

Venetoclax: No dose modifications for mild or moderate hepatic impairment. A 50% dose reduction of venetoclax during and after the ramp-up period as well as more frequent monitoring for signs of toxicity are recommended for patients with severe hepatic impairment.

6. Renal:

azaCITIDine: If increases in BUN or serum creatinine (unexplained) occur, delay until improves to baseline or normal, then reduce dose by 50% for next treatment course.

Venetoclax: No dose modifications for mild or moderate renal impairment (CrCl 30 mL/min). Dosing has not been determined for severe renal impairment or patients on dialysis.

7. Gastrointestinal toxicity:

Severity	azaCITIDine Dose
Grade 0 – 2	100 %
Grade 3 or greater	Reduce one dose level

PRECAUTIONS:

1. **Tumour lysis syndrome (TLS):** TLS has been reported and the risk is greatest during the venetoclax dose ramp-up phase. All patients require prophylaxis for TLS using hydration beginning 48 hours and anti-hyperuricemic agents beginning 48 to 72 hours prior to initiation of therapy. Hospitalization may be considered for those with additional risk factors for TLS (elevated WBC >25 x 10^9/L at presentation, extramedullary disease, elevated LDH, hyperuricemia, elevated creatinine or spontaneous TLS present prior to starting treatment, CrCl ≤ 80 mL/min, unable to drink 1.5-2 L per day, unsuitable for outpatient treatment and lab monitoring, or at physician discretion). It is mandatory that electrolytes are monitored as TLS requires prompt management (see **Appendix I** for management recommendations).

2. **Neutropenia**: The combination of azaCITIDine and venetoclax can often result in more severe thrombocytopenia and neutropenia of longer duration as compared to single agent azaCITIDine. As such, patients may be at increased risk for infectious complications and possibly bleeding events, particularly during the first 1-2 cycles prior to achieving remission. In case of worsening cytopenias that do not resolve between cycles, bone marrow exam is recommended to assess if related to disease progression versus drug-effect. It is recommended to start antibiotic and antifungal prophylaxis when ANC < 0.5 $x10^9$/L and HSV/VZV prophylaxis while on treatment to prevent infection. Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines. Following the attainment of remission, in patients with febrile neutropenia and evidence of moderate to severe infection it is suggested to temporarily hold venetoclax treatment until this is treated.
3. **Hepatitis B Reactivation:** All patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
4. **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.
5. **Renal toxicity**: azaCITIDine in combination with chemotherapy have been associated with serum creatinine elevations, renal tubular acidosis, and renal failure.
6. **Drug interactions:** Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are strong or moderate CYP3A4 inhibitors should be avoided during initiation and during the dose ramp-up phase, due to increased serum concentration of venetoclax and potential increased risk of TLS. See Drug Interactions in Dose Modification section above.
7. **Pregnancy:** Venetoclax is not recommended for use in pregnancy. Fetotoxicity is likely. Women of childbearing potential should undergo pregnancy testing before initiating treatment and use adequate contraception during treatment and for at least 30 days after the last dose.
8. **GI Toxicity:** azaCITIDine is associated with GI toxicity including nausea, vomiting, diarrhea, and constipation. Use of prophylactic 5-HT3 antagonists (e.g. ondansetron) is also associated with constipation. Patients should be made aware of potential GI toxicities prior to starting azaCITIDine.

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

References:

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020; 383(7):617-29.
2. AbbVie Corporation. VENCLEXTA® product monograph. St-Laurent, Quebec; 21 January 2021
3. AbbVie Inc. VENCLEXTA® product monograph. North Chicago, IL; December 2021.
4. Howard et al. the Tumor Lysis Syndrome. NEJM 2011; 364(19): 1844-1854
5. Coiffer et al. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. JCO 2008; 26(16): 2767-2778
6. Tumor Lysis Syndrome (TLS) in Adult Patients from MD Anderson Centre. https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-tumor-lysis-web-algorithm.pdf
7. Agarwal et al. Effect of Azithromycin on Venetoclax Pharmacokinetics in Health Volunteers: Implications for Dosing Venetoclax with P-gp Inhibitors. Advances in Therapy 2018; 35(11):2015-2023

APPENDIX I:

Manage Tumour Lysis Syndrome (TLS) according to institution guidelines. If no local guidelines, may use the following. Consider hospital admission, if needed for cardiac monitoring or IV medications/hydration.

Suggested Guide for Management of Tumour Lysis Syndrome (TLS) (adapted from MD Anderson TLS guidelines[6])

Electrolyte Abnormality	Management Recommendations
Hyperkalemia	

Mild
 	
(greater than upper limit of normal to less than 6 mmol/L)
	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake)
	• Sodium polystyrene (Kayexalate®)
	  ○ 15-30 grams PO
	  ○ Repeat as needed depending on follow-up potassium levels
	• Consider ECG and cardiac rhythm monitoring at physician discretion

Moderate
 	
(6-7 mmol/L) **and** asymptomatic
	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake)
	• ECG and cardiac rhythm monitoring
	• Sodium polystyrene (Kayexalate®)
	  ○ 15-30 grams PO
	  ○ Repeat every 4 to 6 hours depending on follow-up potassium levels

Severe
 	
(greater than 7 mmol/L **and/or** symptomatic)
	Same as moderate plan plus:
	• Concurrent ECG changes: calcium gluconate 1 g via slow IV infusion; may be repeated after 5-10 minutes if ECG changes persist
	• To temporarily shift potassium intracellularly:
	  • IV insulin and dextrose
	  ➢ Give 10 units of regular insulin in 500 mL of D10W infused IV over 60 minutes
	  ➢ Monitor blood glucose closely
	  • Sodium bicarbonate
	  ➢ Give 50 mEq via slow IV infusion
	  ➢ Can be used if patient is acidemic; however sodium bicarbonate and calcium should not be administered through the same lumen
	  • Salbutamol
	  ➢ Give 10-20 mg in 4 mL saline via nebulizer over 20 minutes or 10-20 puffs via inhaler over 10-20 minutes
	  ➢ Avoid in patients with acute coronary disease

Electrolyte Abnormality	Management Recommendations
Hyperphosphatemia	

Moderate
(greater than or equal to 1.94 mmol/L)
	• Restrict phosphorus intake (avoid IV and PO phosphorus; limit dietary sources)
	• Administer phosphate binder:
	  ○ Sevelamer (Renagel®, Renvela®) 800-1600 mg PO three times a day with meals
	  ○ Lanthanum carbonate (Fosrenol®) 500-1000 mg PO three times a day with meals
	  ○ Aluminum hydroxide tablet 300 mg PO three times a day with meals, may increase dose to 600 mg PO three times a day (avoid in patients with renal dysfunction)
	  ○ Aluminum hydroxide 64 mg/mL suspension 15 mL PO three times a day with meals, may increase dose to 30 mL four times a day based on phosphate level (avoid in patients with renal dysfunction)

Severe	Dialysis may be needed in severe cases
Hypocalcemia (calcium less than or equal to 1.75 mmol/L or ionized calcium less than or equal to 0.8 mmol/L)	
Asymptomatic	• No therapy • To avoid calcium phosphate precipitation, asymptomatic patients with acute hypocalcemia and hyperphosphatemia should not be given calcium repletion until phosphorous level has normalized
Symptomatic	Calcium gluconate 1 g via slow IV infusion with ECG monitoring
Uremia (renal dysfunction)	
	• Fluid and electrolyte management • Uric acid and phosphate management • Adjust doses for renally excreted medications • Dialysis