BC Cancer Protocol Summary for Therapy of Myelodysplastic Syndrome using Decitabine-Cedazuridine

Protocol Code	*ULKMDSDC*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Tom Nevill*

ELIGIBILITY:

Patients must have:
- Myelodysplastic syndrome (MDS) including all French-American-British (FAB) subtypes (e.g. refractory anemia [RA], chronic myelomonocytic leukemia [CMML]),
- International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2, or high-risk, and
- A BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:
- ECOG 0-2

Note:
- For IPSS intermediate risk or higher, patients are eligible to receive decitabine-cedazuridine (ULKMDSDC) OR azaCITIDine (LKMDSA) but not sequential use of these agents except for intolerance or contraindications.
- Patients who were started on LKMDSA prior to 1 November 2022 and have not progressed may switch to ULKMDSDC if all other eligibility are met. However, there is no data to support that the level of response to azaCITIDine will be maintained with a switch to decitabine-cedazuridine.
- Patients with deletion 5q MDS who have progressed on LKMDSL may be treated with decitabine-cedazuridine (ULKMDSDC) if all other eligibility are met.

EXCLUSIONS:

- Patients who experienced progression during treatment with azaCITIDine (LKMDSA)
- IPSS low-risk MDS
- Acute myeloid leukemia (AML)
- Patients who relapse post allogeneic SCT

TESTS:

- Baseline: CBC and differential, platelets, bilirubin, ALT, alkaline phosphatase, creatinine, pregnancy test prior to treatment in females of child-bearing potential
- 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
- Weekly for the first cycle: CBC and differential, platelets
- Prior to day 1 of each cycle: CBC and differential, platelets, bilirubin, ALT, alkaline phosphatase, creatinine

PREMEDICATIONS:

- ondansetron 8 mg PO 30 minutes prior to decitabine-cedazuridine
- If there has been no nausea and/or vomiting during the first two cycles, antiemetic prophylaxis may be omitted

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
decitabine-cedazuridine	35 mg-100 mg once daily on Days 1 to 5	PO

* It is recommended that patients with initial ANC less than 1.0 x 10^9/L start cycle 1 at dose level -2 (see dose levels, below)

Repeat every 28 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Dose Levels for Toxicities

Drug	Dose Level 0 (starting dose)	Dose Level -1	Dose Level -2	Dose Level -3
decitabine-cedazuridine 35 mg-100 mg	once daily on Days 1 to 5	once daily on Days 1 to 4	once daily on Days 1 to 3	once daily on Days 1, 3, and 5

Hematologic:

Patients with MDS can be cytopenic because of the disease and should receive treatment regardless of their ANC and platelet count during initial therapy.

Dose modification generally not recommended until after cycle 2.

ANC ($x 10^9$/L)		Platelets ($x 10^9$/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 50	100%
less than 1.0	and	less than 50	Delay next cycle until recovery to ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 50 x 10^9/L. If recovery occurs **within** 2 weeks of last cycle, restart at same dose level
			If recovery takes **greater than** 2 weeks from last cycle, delay treatment for up to 2 additional weeks and restart at next lower dose level

Non-Hematologic:*

Renal toxicity:

- If creatinine 177 micromol/L or greater, delay treatment with decitabine-cedazuridine.

Hepatic:

- If bilirubin 2 x ULN or ALT 2 x ULN or greater, delay treatment with decitabine-cedazuridine.

Active or uncontrolled infection:

- Delay treatment with decitabine-cedazuridine. Treat as per local guidelines.

** Consider a dose reduction once recovered. Provider to determine restart parameters and doses*

PRECAUTIONS:

1. **Infections:** serious and fatal **infections** have occurred during treatment; consider prophylactic anti-infective therapies if the patient has a history of neutropenic infections or otherwise clinically indicated

2. **Neutropenia (grade 3 to 4)**: occurs in 71% of patients. Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
3. **Thrombocytopenia (grade 3 to 4):** occurs in 76% of patients. Monitor for signs of bleeding.
4. **Hypersensitivity**: hypersensitivity has been reported with intravenous decitabine and oral decitabine-cedazuridine use. Discontinue decitabine-cedazuridine for serious hypersensitivity reactions and initiate supportive treatment.
5. **Oral decitabine-cedazuridine is not interchangeable with decitabine for injection**. **DO NOT SUBSTITUTE** with or for other decitabine formulations.
6. **Interactions:** gastric pH modifying drugs should be avoided, particularly within 4 hours of taking decitabine-cedazuridine. Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme. Concomitant administration of drugs metabolized by CDA with cedazuridine may result in increased exposure and toxicity of these drugs. Avoid concurrent use. Examples of drugs metabolized by CDA: cytarabine, gemcitabine, azaCITIDine, zalcitabine, zidovudine, telbivudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine, apricitabine, tenofovir, adefovir, idoxuridine, entecavir, trifluridine, vidarabine.
7. **Renal Impairment**: Monitor for increased risk of adverse reactions in patients with CrCl less than 60 mL/minute. No dose adjustment necessary for CrCl greater than or equal to 30 mL/min.
8. **Hepatic Impairment**: No dose adjustment necessary for bilirubin less than or equal to 1.5 X ULN. No data available in moderate or severe hepatic impairment.
9. **Fetal risk**: adverse developmental outcomes were observed in humans taking decitabine-cedazuridine. Patients of childbearing potential should use effective contraception during treatment and for 6 months following the last dose. Males with female partners of childbearing potential should use effective contraception during treatment and for 3 months following the last dose.

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

References:

1. Garcia-Manero, Griffiths, Steensma, Roboz, Wells, McCloskey, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020 Aug 6;136(6):674-683.
2. Patel, Cahill, Saygin, Odenike. Cedazuridine/decitabine: from preclinical to clinical development in myeloid malignancies. Blood Adv. 2021 Apr 27;5(8):2264-2271.