CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Final Recommendation)

Decitabine and Cedazuridine (Inqovi)

Indication: For treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups.

Recommendation: Reimburse with Conditions

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Single Technology

DECITABINE and CEDAZURIDINE (INQOVI— Taiho Pharma Canada, Inc.)

Therapeutic Area: Myelodysplastic Syndromes (MDS)

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that decitabine and cedazuridine should be reimbursed for the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one phase III (ASCERTAIN; n = 133) trial and one phase II (ASTX727-01-B; n = 80) trial demonstrated pharmacokinetic equivalence of oral decitabine and cedazuridine (35 mg and 100 mg, respectively) compared to intravenous (IV) decitabine (20 mg/m^2) when both treatments administered daily for five consecutive days at the beginning of each 28-day treatment cycle. Decitabine and cedazuridine showed evidence of similar clinical efficacy to IV decitabine in terms of overall response rate, complete response, and percentage of patients achieving transfusion independence for any period of 56 or more consecutive days after starting the treatment; however, neither trial was designed to demonstrate superiority or non-inferiority to azacitidine monotherapy, which was identified by pERC as the current standard of care in intermediate to high-risk MDS patients in Canada.

In the absence of direct evidence comparing decitabine and cedazuridine to relevant treatments, the sponsor submitted indirect treatment comparisons (ITC) that considered three possible evidence networks. Results of the ITC suggested that the effect of fixed dose oral treatment with decitabine and cedazuridine compared with azacitidine on overall survival (OS) [redacted]. pERC noted that the patient population included in the indirect comparisons only partially reflects the funding request for decitabine and cedazuridine, as patients with intermediate-1 risk MDS and CMML were not included in the analyses. Overall, pERC was unable to determine the magnitude of clinical benefit of decitabine and cedazuridine compared with appropriate comparators (e.g., azacitidine) with regard to outcomes important to decision-making such as OS and quality of life.

Patients identified a need for effective treatments with minimal side effects, that prolonged quality of life, and were easy to administer. pERC concluded that decitabine and cedazuridine therapy offers an additional treatment option with manageable toxicities for patients with MDS, and acknowledged that the oral route of administration addresses the unmet need for patients to access effective treatment at home without having to visit specialized infusion centres or having to endure the discomfort of injected or infused treatments. No patient-reported data supporting the use of decitabine and cedazuridine were included, thus pERC was unable to comment on the impact of decitabine and cedazuridine on quality of life.

The cost-effectiveness of decitabine and cedazuridine is highly uncertain due to limitations with the sponsor's submitted model and comparative effectiveness data. As such, CADTH was unable to determine a base case cost-effectiveness estimate in adult patients with de novo or secondary MDS who are not considered candidates for hematopoietic stem cell transplantation.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Treatment with decitabine and cedazuridine should be reimbursed in adult patients with MDS who: 1.1. have previously treated or untreated with de novo or secondary MDS, including all FAB subtypes (RA, RARS, RAEB, RAEB-t, and CMML); or 1.2. have IPSS intermediate-1, intermediate-2, or high-risk MDS	Evidence from the ASCERTAIN and ASTX727-01-B trials showed the pharmacokinetic equivalence and similar clinical efficacy and safety of decitabine and cedazuridine therapy when compared to IV decitabine in adult patients with treatment-naïve or previously treated MDS including all FAB subtypes (RA, RARS, RAEB, RAEB-t, and CMML), and those with MDS IPSS intermediate-1, intermediate-2, or high-risk MDS.
2. Patient must have ECOG PS of 0 to 2 and adequate organ function upon treatment initiation with decitabine and cedazuridine.	No evidence was identified to demonstrate effects of decitabine and cedazuridine in adult patients with ECOG PS >2 and impaired organ function at baseline.
Discontinuation	
3. Treatment with decitabine and cedazuridine should be discontinued upon the occurrence of any of the following: 3.1. documented disease progression 3.2. Unacceptable toxicity	In the ASCERTAIN and ASTX727-01-B, treatment with decitabine and cedazuridine was discontinued if a patient experienced disease progression, or intolerable or serious adverse events. This is aligned with discontinuation criteria in the product monograph.
Prescribing	
4. Decitabine and cedazuridine should only be prescribed by clinicians who have been trained in oncology and should be administered under the supervision of a health professionals experienced in the use of antineoplastic agents	To ensure that decitabine and cedazuridine is prescribed only for appropriate patients and adverse effects are managed in a timely manner.
Pricing	
5. Decitabine and cedazuridine should be negotiated to provide cost savings to the CADTH-participating-drug programs for adult patients with de novo or secondary MDS who are not considered candidates for hematopoietic stem cell transplantation relative to azacitidine in jurisdictions that fund azacitidine for this indication.	There is substantial clinical and methodological uncertainty surrounding the comparative efficacy of decitabine and cedazuridine with azacitidine, treatment wastage, and administration costs.

CMML = chronic myelomonocytic leukemia; FAB = French, American, and British subtypes; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-t = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts.

Implementation Guidance

Comparison to currently funded treatments in specific patient subgroups

- Decitabine and cedazuridine compared with azacitidine in higher risk MDS subtypes – pERC noted that the sponsor submitted network meta-analysis (NMA) compared decitabine to azacitidine in intermediate-2 and high-risk MDS patients, however it was subject to a number of limitations resulting in significant uncertainty in the reported results. Thus, the magnitude of the clinical benefit, if any, of decitabine and cedazuridine compared to azacitidine remains unknown.

- Decitabine and cedazuridine compared with azacitidine and hydroxyurea in CMML patients - The sponsor-submitted NMA attempted to include patients with CMML; however, subgroup analyses were not possible and thus, it was assumed the results of the NMA were similar across IPSS subgroups and CMML patients. Hydroxyurea was not included as a comparator. Thus, the comparative effectiveness of decitabine and cedazuridine to azacitidine and hydroxyurea in CMML patients remains unknown.
- Decitabine and cedazuridine compared with lenalidomide in patients with deletion 5q chromosome change MDS – Comparison to lenalidomide was not possible in the sponsor submitted NMA due to its pre-specified population. Trials of lenalidomide were excluded from the NMA as they primarily included patients with low-risk MDS. As such, comparative effectiveness decitabine and cedazuridine versus lenalidomide in patients with deletion 5q remains unknown. The clinical experts consulted by CADTH agree that, for patients with deletion 5q, lenalidomide would be the preferred regimen due to better available evidence.
- Decitabine and cedazuridine compared with HSCT for MDS –The clinical experts consulted by CADTH noted that HSCT is the only curative option for patients with MDS and, as such, decitabine and cedazuridine would not replace HSCT for patients who are transplant-eligible. However, the decitabine and cedazuridine could be used as a bridge to transplant.

Considerations for Initiation of Therapy

- Patients who have received prior hematopoietic stem cell transplant (HSCT) – Patients with a history of HSCT were not excluded from eligibility from the decitabine and cedazuridine trials per protocol; however, none of the trial participants actually received prior HSCT; therefore, pERC was unable to comment on the effectiveness of decitabine and cedazuridine in this patient population.
- Patients who are candidates for intensive induction chemotherapy – pERC agreed with the clinical experts consulted by CADTH that patients who are candidates for intensive induction chemotherapy could be eligible for decitabine and cedazuridine, based on patient preference.
- Patients who are candidates for HSCT – pERC agreed that patients who are candidates for HSCT could use decitabine and cedazuridine as a bridge to transplant.
- Patients previously treated with a hypomethylating agent (HMA) – pERC agreed that patients treated with a HMA who have had a response could switch to decitabine and cedazuridine; however, the committee noted that patients whose disease has progressed on a HMA are not eligible as there is no evidence to support the use of another HMA upon progression.
- Patients with ECOG PS ≥2 – Clinical experts consulted by CADTH agreed that patients with ECOG PS 2 or higher would be eligible for treatment with decitabine and cedazuridine, at the treating clinician's discretion.
- Patients receiving azacitidine (time-limited need) – pERC agreed that, upon implementation of this recommendation, patients who are currently receiving azacitidine and have not had a disease progression may switch to decitabine and cedazuridine, for the convenience of an oral therapy and based on patients' preference.
- Patients with deletion 5q MDS who progress on lenalidomide – pERC agreed that these patients could be considered for treatment with decitabine and cedazuridine due to the limited treatment alternatives for these patients upon disease progression.
- Expansion of the indication for decitabine and cedazuridine:
    - Second line treatment after azacitidine – pERC noted there was no evidence included in this review to support the use of decitabine and cedazuridine in second line after azacitidine.
    - Treatment of acute myeloid leukemia (AML) – pERC noted that patients with AML were excluded from the reviewed trials and, thus, there is no evidence to support the use of decitabine and cedazuridine over azacitidine in this patient population.
    - Low-risk MDS – pERC noted that there is no evidence to support the use of decitabine and cedazuridine in patients with low-risk MDS.

Considerations for continuation or renewal of therapy

- pERC discussed the ideal treatment duration with decitabine and cedazuridine and agreed with the clinical experts consulted by CADTH that patients should be treated for at least 6 months in the absence of progressive disease or unacceptable toxicity. If the patient is stable or shows clinical improvement, then the treatment should continue. Treatment should be discontinued if there is progressive disease, unacceptable toxicity, or due to patient preference.

- pERC discussed dose reductions using single tablet strength and noted that for patients who take decitabine and cedazuridine tablets as indicated in the product monograph (i.e. one tablet daily for 5 consecutive days in the beginning of each 28-day cycle), three dose reductions are possible: (1) one tablet daily through days 1 to 4; (2) one tablet once daily through days 1 to 3; and (3) one tablet daily on days 1, 3, and 5.
- pERC also considered possible drug wastage due to dose reductions that involve reducing the number of tablets per cycle. pERC noted that decitabine and cedazuridine is packaged in a blister pack containing 5 tablets per box. The blister card can be cut by the pharmacy to dispense fewer tablets to accommodate dose reductions. Any remaining blistered tablets that have been cut can be subsequently used for other MDS patients if the tablets remain within the individual blister seal.

Sequencing decitabine and cedazuridine with other treatments (funding algorithm)

- Options after treatment failure with decitabine and cedazuridine – pERC agreed that, while there is no standard of care in this setting, options could include best supportive care, clinical trials, hydroxyurea, and induction chemotherapy.
- Use of decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent) – The clinical experts consulted by CADTH noted that decitabine and cedazuridine could be used as a bridge to HSCT, and possibly intensive chemotherapy, however, the latter is not commonly done.
- Sequencing decitabine and cedazuridine with azacitidine – The clinical experts consulted by CADTH indicated that decitabine and cedazuridine would not be sequenced with azacitidine; failure on one HMA precludes the use in subsequent line.
- Use of decitabine and cedazuridine for patients with deletion 5q- MDS who are currently on lenalidomide and experience disease progression – The clinical experts consulted by CADTH agreed that decitabine and cedazuridine could be used in these patients.
- Use of decitabine and cedazuridine for patients with low risk MDS and have progressed after treatment with erythropoietin (EPO) with or without granulocyte-colony stimulating factor (G-CSF) – pERC noted that it did not review any evidence that supported the use decitabine and cedazuridine in low-risk patients, unless the low-risk patients have progressed to higher risk MDS of intermediate-1 or higher.

pERC's responses to the implementation questions submitted from the public drug plans are also summarized in tabular format in Appendix 1.

Discussion Points

- pERC discussed the results of a Phase III, randomized, open-label, 2-period, 2-sequence crossover (ASCERTAIN) trial that compared oral decitabine and cedazuridine with IV decitabine in adult patients with MDS or CMML. The primary endpoint of the trial was the total 5-day (total cycle) area under the curve (AUC) drug exposures which indicated equivalent decitabine exposure between oral decitabine and cedazuridine and IV decitabine. Based on the trial results, pERC acknowledged that decitabine and cedazuridine convincingly demonstrated pharmacokinetic equivalence to IV decitabine; however, the committee noted that the available evidence did not evaluate superiority or non-inferiority of decitabine and cedazuridine compared to azacitidine monotherapy, which is the current standard of care in intermediate to high-risk MDS patients in Canada. Moreover, by virtue of the study designs, the clinical effectiveness outcomes were secondary, sample size calculations were not based on establishing efficacy, and the trials were not powered to test specific efficacy hypotheses, which did not allow direct comparison to relevant treatments.
- pERC discussed the safety profile of decitabine and cedazuridine and agreed that although serious adverse events were more frequent with oral decitabine and cedazuridine compared to IV decitabine (35.9% vs 28%), there was no clinically notable difference between decitabine ad cedazuridine and IV decitabine with respect to the proportion of patients who experienced any grade adverse events.
- No patient-reported data supporting the use of decitabine and cedazuridine was included in the submitted evidence, thus the committee was unable to comment on the impact of decitabine and cedazuridine on patients' quality of life.
- pERC discussed the results of the sponsor-submitted ITC that had been conducted in a Bayesian framework using three possible evidence networks. pERC noted that two of the network scenarios (including the full network) were based on the equivalence of oral decitabine and cedazuridine to IV decitabine assumption, and that data from the decitabine and

cedazuridine trials were not included in these networks. pERC also considered that the ITC did not evaluate the Intermediate-1 and CMML populations and it was assumed that the results would hold across IPSS groups. Due to these limitations, the committee was unable to make conclusions on the benefit of decitabine and cedazuridine compared with other relevant treatment options, including azacitidine.

- pERC discussed that the schedule for MDS treatments administered intravenously or through injection could impact or limit patients' day-to-day activities. Moreover, patients often must travel to a hospital or clinic to receive their treatment which might require arrangements for lodging to accommodate their infusion schedule. pERC concluded that the oral formulation of decitabine and cedazuridine addresses an unmet need of providing an active therapy in a convenient provides a convenient route of administration and increased patient choice particularly for elderly, patients with disabilities, patients living in remote locations, and those with compromised immune systems who are at a greater risk of acquiring hospital based infections.
- pERC discussed limitations with the submitted economic evaluation; specifically, the limitations with the comparative efficacy analysis, noting the full ITC results indicated the potential that decitabine and cedazuridine may not be as effective as azacitidine, resulting in an ICER above $50,000 per QALY. pERC also discussed that wastage of azacitidine may differ between jurisdictions and sites for azacitidine; analyses assuming no wastage for azacitidine resulted in an incremental total cost of treatment for decitabine and cedazuridine.

Background

Decitabine and cedazuridine has a Health Canada indication as treatment for adult patients with MDS including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk IPSS groups. Decitabine and cedazuridine is a novel, oral, fixed-dose cytotoxic combination antineoplastic composed of decitabine, a DNA methyltransferase inhibitor, and the cytidine deaminase inhibitor cedazuridine. It is available as an oral tablet and the Health Canada approved dose is one tablet containing (35 mg of decitabine and 100 mg of cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of two crossover RCTs in adult patients with MDS or CMML and one sponsor-provided indirect treatment comparison (ITC).
- Patients' perspectives gathered by patient groups, The Leukemia & Lymphoma Society of Canada (LLSC) and Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Three clinical specialists with expertise diagnosing and treating patients with MDS and CMML.
- Input from two clinician groups, including Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee (DAC) and Odette Cancer Centre and Princess Margaret Hospital (OCC/PMH) and an individual oncologist from Alberta.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Advocacy Group Input

The Leukemia & Lymphoma Society of Canada (LLSC) and Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) provided a joint input on decitabine and cedazuridine for MDS. Information was gathered through an online survey created by AAMAC. A total of 42 patients responded to the survey, however two were not included due to incomplete data. Of the remaining 40

respondents, 34 identified as patients with MDS, while six were caregivers of MDS patients. One respondent had experience with decitabine and cedazuridine. Responses to the survey were collected from August 4, 2020, to September 25, 2020.

From the patient perspective, MDS symptoms and receiving intravenous or injected MDS treatments were reported to have a significant or large impact on the ability to travel, exercise, work, conduct household chores, fulfill family obligations, and spend time with family and friends. Most patients had treatment experience with azacitidine, followed by Eprex®, blood transfusion, and stem cell transplant for MDS. Side effects associated with MDS treatments administered intravenously or through subcutaneous injections that were most commonly rated to be completely or relatively intolerable included injection-site rash or pain and bruising; sleep problems; fatigue/lack of energy; constipation; and dry mouth. Overall, patients with MDS value having access to new treatments and seek treatments that are effective, have minimal and tolerable side effects, and prolong quality of life. Patients prefer oral agents over injected/infused treatments as they may be administered at home, which mitigates the need to travel to treatment centres and the pain, discomfort, skin irritation, bruising, and soreness that commonly accompanies injected/infused treatments.

Provincial Advisory Group (PAG) Input

Input was obtained from nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

- Comparison to currently funded treatments in specific patient subgroups
- Considerations for Initiation of Therapy
- Considerations for continuation or renewal of therapy
- Sequencing decitabine and cedazuridine with other treatments

Registered Clinician Input

Three registered clinician inputs were provided for the review of decitabine and cedazuridine for MDS: one from an individual oncologist (Alberta) and two group inputs (Ontario)—two clinicians on behalf of Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee (DAC) and five clinicians from Odette Cancer Centre and Princess Margaret Hospital (OCC/PMH). The two Ontario clinician groups reported having experience administering decitabine and cedazuridine, whereas the Alberta clinician did not have experience. All clinicians noted that the patient population in the reimbursement request aligns with the need in their clinical practice.

Current treatments for MDS are administered based on risk sub-type and cytogenetic or familial pre-dispositions. Erythropoietin stimulating agents (e.g., darbepoetin) are used for low or intermediate-1 risk MDS patients, while azacitidine is used in intermediate-2 or high-risk MDS patients. Lenalidomide may be used for MDS patients with a deletion 5q chromosome change. Azacitidine or hydroxyurea (specifically in patients who are transplant ineligible) may be used for CMML patients. Hematopoietic stem cell transplant or high-dose chemotherapy may be used in MDS patients with good fitness but are not standard treatments. Decitabine has Health Canada approval but is not currently marketed for higher risk MDS in Canada. The OH-CCO DAC and Alberta clinicians noted that decitabine and cedazuridine would replace azacitidine in all eligible patients. However, the OCC/PMH clinicians stated that decitabine and cedazuridine would not supplant current treatments in lower risk disease but could replace azacitidine in the higher risk disease patients and those unable to tolerate or travel to receive azacitidine. All clinicians felt it is clinically reasonable to use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent). The Ontario clinician groups noted there is no evidence to support sequencing of azacitidine and decitabine and cedazuridine; whereas the Alberta clinician stated there is evidence for switching in the setting where azacitidine is still working but not sequencing in the traditional sense of switching due to a lack or loss of response.

Clinical Evidence

The CADTH systematic review included two randomized controlled trials (RCTs); ASCERTAIN (n = 133) and ASTX727-01-B (n = 80).

ASCERTAIN

ASCERTAIN was a Phase III, multicenter, randomized, open-label, 2-period, 2-sequence crossover study comparing oral decitabine and cedazuridine (also referred to as ASTX727 in the study publications) and IV decitabine as treatment for adult patients with MDS or CMML. The primary objective was to establish decitabine AUC equivalence of 5-day dosing between oral decitabine and cedazuridine versus IV decitabine. Eligible patients were randomized to receive either the fixed dose oral decitabine and cedazuridine followed by crossover to IV decitabine, or the opposite sequence.

To be eligible, patients had to have previously treated or untreated, de novo or secondary MDS, including all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML), and subjects with MDS IPSS intermediate-1, intermediate-2, or high-risk MDS, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were permitted to have treatment with one prior cycle of hypomethylating agent (HMA; decitabine or azacitidine), provided that treatment was not within four weeks of study treatment.

Eligible patients were randomized 1:1 to receive oral decitabine and cedazuridine (35 mg and 100 mg, respectively) in Cycle 1 followed by IV decitabine (20 mg/m^2) via 1-hour infusion in cycle 2 (Sequence A), or IV decitabine (20 mg/m^2) via 1-hour infusion in cycle 1 followed by oral decitabine and cedazuridine (35 mg and 100 mg, respectively) in cycle 2 (Sequence B). After completion of the first 2 treatment cycles, subjects continued to receive treatment with oral decitabine and cedazuridine in 28-day cycles until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study. A total of 133 subjects were randomized 1:1 to Sequence A (n = 66), or Sequence B (n = 67). Randomization was stratified by IPSS risk category.

The primary endpoint of the trial was the total 5-day (total cycle) AUC exposures of decitabine after treatment with decitabine and cedazuridine versus IV decitabine, calculated as the ratios of treatment least squares mean (LSM) for decitabine and cedazuridine relative to IV decitabine. The two treatments were to be considered equivalent if the two-sided 90% confidence interval (CI) of the 5-day decitabine AUC from time zero to 24 hours post-dose (AUC_{0-24}) ratio of LSM for decitabine and cedazuridine relative to IV decitabine was contained entirely within the range of 0.80 – 1.25. Secondary endpoints included safety as assessed by patient-reported and investigator-assessed AEs, clinical response (overall response rate [ORR], complete response [CR], partial response [PR], marrow complete response [mCR], and hematologic improvement [HI]) based on International Working Group (IWG) 2006 MDS response criteria, red blood cell (RBC) or platelet transfusion independence (TI), leukemia-free survival (LFS), defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause, and OS, defined as the number of days from the date of randomization to the date of death from any cause, as well as other pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

A total of 173 subjects were screened for eligibility, with 138 randomized, and 133 receiving treatment (66 to Sequence A, and 67 to Sequence B). The median age was 70.0 years (range = 44 to 85 years) in Sequence A and 72.0 years (range = 49 to 88 years) in Sequence B. In both groups, the majority of patients were Caucasian (90.9% and 91.0%) males (63.6% and 67.2%) and had an ECOG performance status of 1 (62.1% and 55.2%). Sequence A had a higher incidence of IPSS intermediate-2 and high-risk patients compared to Sequence B (21.2% and 21.2% vs 17.9% and 10.4%, respectively). The weight of the trial patients ranged from 45.0 kg to 157.9 kg. No exclusion criteria were applied to body weight or body-surface area (BSA). In line with the inclusion/exclusion criteria, the majority of patients did not have prior treatment with HMAs.

Efficacy Results

As of the March 2019 data cut off, the median duration of follow up was 155 days (5.1 months) and the median duration of study drug exposure was 4.0 cycles. At the [redacted], data cutoff ([redacted] follow up), patients received a median of [redacted] of treatment.[4] The ASCERTAIN trial is still ongoing for patient follow up. [redacted]

As of the March 2019 data cut off, the ASCERTAIN trial met its primary endpoint by demonstrating that the 5-day AUC_{0-24} ratio of geometric LSM for decitabine and cedazuridine relative to IV decitabine was 98.93% (90% CI: 92.66, 105.6). The two-sided 90% CI is contained entirely within the prespecified range of 0.80 to 1.25 for the primary analysis, indicating equivalent decitabine exposure

between oral decitabine and cedazuridine and IV decitabine. Secondary analyses of 5-day AUC at various time points confirmed the results of the primary analysis.

As of the first data cut off on March 19, 2019, clinical response outcomes were considered preliminary. Complete response was observed in 9.0% to 13.4% of subjects, however, response data was not available for 32 (24%) of subjects, with an additional 28.4% to 45.5% achieving mCR. The ORR (CR + PR + mCR + HI) ranged from 44.8% to 64.4%. [redacted]

Transfusion independence results were also considered preliminary due to the short follow up period of the March 19, 2019, data cut off. Of the 133 treated subjects, one-third (32.7%) who were RBC transfusion dependent at baseline were RBC TI for any consecutive greater than or equal to 56-day period post-baseline. Similarly, 30% of platelet transfusion dependent subjects became platelet TI for any greater than or equal to 56-day period post-baseline. [redacted]

[redacted]

[redacted]

ASTX727-01-B

ASTX727-01-B was a two-phased international, randomized, phase II, two-cycle, two-sequence crossover trial that evaluated the pharmacokinetics, pharmacodynamics, and safety of either sequence of oral decitabine and cedazuridine followed by IV decitabine or IV decitabine followed by decitabine and cedazuridine.

Eligible patients were age ≥18 years, intermediate-1, intermediate-2- or high-risk MDS, or CMML, ECOG performance status 0 to 2, adequate and renal function, and no evidence of active second malignancy. One prior cycle of either decitabine or azacitidine was allowed, but no other cytotoxic chemotherapy was permitted within 2 weeks of starting study treatment. Patients with prior allogeneic HSCT were eligible if they were free of graft-versus-host disease (GVHD) and off immunosuppressive therapy at the time of enrollment.

Patients were initially randomized 1:1 to receive 1 of 2 treatment sequences during the first two cycles: oral decitabine and cedazuridine daily for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 2 (sequence A); or IV decitabine in cycle 1, followed by the oral drug in cycle 2 (sequence B). The study was conducted in two stages; a dose-confirmation (DC) stage where oral decitabine and cedazuridine was received as two separate capsules, and following the preliminary PK analysis, a single tablet fixed-dose combination (FDC). All patients received oral treatment from cycle 3 onwards.

The primary endpoints of the ASTX727-01-B trial was oral/IV decitabine exposure over 5 days from time 0 to the time of last measurable concentration ($AUC_{0\text{-}t}$), DNA demethylation of oral decitabine and cedazuridine vs IV decitabine from the first 2 cycles, and ORR using IWG 2006 MDS criteria. Secondary end points included efficacy outcomes of duration of response, transfusion independence, time to AML (defined as the number of days from the date the subject received the first dose of study treatment to the date of MDS progression to AML as defined by ≥20% blasts in bone marrow or peripheral blood, or death from any cause), and overall survival (defined as the number of days from the date the subject received the first dose of study treatment to the date of death, regardless of cause), other PK measurements, and safety.

A total of 138 patients were screened, and 86 patients were randomized, including 52 into the DC cohort, and 34 into the FDC cohort. Of the 86 randomized, only 80 were treated, as two patients in the DC cohort, and four patients in the FDC cohorts did not receive any study treatment and were excluded from all analyses. Overall, 41 patients were randomized to receive treatment sequence A, and 39 were randomized to treatment sequence B. At data cutoff (June 5, 2018), 67 patients had discontinued treatment (n=41 [82%] in the DC cohort; n=26 [86.7%] in the FDC cohort), with a similar proportion remaining on treatment (n=13; 9 [18%] and 4 [13%] patients in the DC and FDC cohorts, respectively). The primary reason for treatment discontinuation in both groups was disease progression (14 [28%] and 7 [23.3%] in the DC, and FDC cohorts, respectively). Twelve patients (15%) overall discontinued treatment for stem cell transplant. Patients received a median of 7 treatment cycles (range = 1 to 29).

Baseline characteristics were generally balanced across the randomized treatment sequences in each cohort. The median age of all participants was 71 years, and the majority were male (76%), of Caucasian ethnicity (93%), and most subjects had an ECOG performance status score of 0 (44%) or 1 (48%); however, a greater proportion of subjects in Sequence A were ECOG performance status 0 (48.8% vs. 38.5%), while a greater proportion of patients in Sequence B were ECOG 1 (51.3% vs. 43.9%). A total of 7 (9%) patients overall had ECOG performance status of 2. Almost half (48%) of all patients were RBC transfusion dependent at baseline. The majority of patients were IPSS intermediate-1 risk (44%), while 24% were intermediate-2, and 11% and 21% were high-risk and CMML, respectively.

Efficacy Results

At the data cut off, the median follow-up was 24.3 months. In the primary paired analysis, the 5-day decitabine $AUC_{0\text{-}t}$ oral/IV geometric LSM ratios were 93.5 (80% CI, 82.1- 106.5) and 97.6 (80% CI, 80.5-118.3) in the DC and FDC cohorts, respectively, falling within the prespecified CI limits of 75 to 133, and 65-153.9. This demonstrates that both the DC and FDC administrations achieved decitabine AUC exposure equivalent to IV decitabine at 20 mg/m^2.

As of the June 5, 2018, data cut off, ORR was seen in 48 patients (60%), including 17 (21%) with CR, a PR rate of 0, and a mCR rate of 22%. A total of 16.3% of subjects showed HI in one or more lineage(s). Of the 17 patients with CR, 12 experienced disease progression, with a median duration of response (DOR) of 13.3 months (95% CI: 6.5, 13.8).

At the time of the analysis, of the 38 patients who were RBC transfusion dependent at baseline, 19 (50%) became TI, and of the 12 patients who were platelet transfusion dependent at baseline, 6 (50%) became TI.

Of the 80 subjects included in the ASTX727-01-B trial, 47 (58.8%) progressed to AML or death, and data were censored for the remaining 33 subjects (41.3%). The median time to AML or death for the overall population treated was 12.1 months (95% CI, 5.9, NE).

As of the June 5, 2018, data cutoff, 50% of subjects had died. Median overall survival for all patients treated was 18.3 months (95% CI, 9.1-not estimable).

ASCERTAIN and ASTX727-01-B Pooled Harms Outcomes

Pooled safety data from the Phase II ASTX727-01-B trial and the Phase III ASCERTAIN study were submitted in the original NDA based on the June 5, 2018, and March 19, 2019, data cuts. Overall, 205 (98.6%) patients included in the pooled analysis experienced at least one treatment emergent adverse event (TEAE). The most common TEAEs of any grade that occurred in all subjects were thrombocytopenia (52.4%), neutropenia (51.4%), anemia (39.4%), and fatigue (38.9%). The most frequent grade ≥ 3 AEs in the overall population included thrombocytopenia (50.0%), neutropenia (45.7%), anemia (33.7%), febrile neutropenia (27.9%), and leukopenia (22.6%). The most common non-fatal serious adverse events (SAEs) occurring in >5% of subjects in the overall decitabine and cedazuridine population across all cycles included febrile neutropenia (26%), pneumonia (10.6%), and sepsis (6.7%).

As of the safety update [redacted], a total of 147 patients had discontinued treatment. Of these, 11 (5.3%) patients discontinued treatment, and one patient withdrew from the study due to AEs. A total of 81 subjects in the pooled analysis had died as of the [redacted], with only four occurring during the treatment period, and five deaths were due to

AEs. The cause of death was unknown for the majority of patients who died (n = 40; 19.2%), followed by AEs (n = 23; 11.1%), and progressive disease (n = 13; 6.3%) across the ASTX727-01-B and ASCERTAIN trials.

Limitations

ASCERTAIN and ASTX727-01-B were randomized, open-label, 2-cycle crossover trials. The design of the trials was appropriate given the aim of the study to examine the equivalence between oral decitabine and cedazuridine and IV decitabine, however, the studies were not designed to demonstrate superiority or non-inferiority to relevant comparators, or to compare efficacy or safety of decitabine and cedazuridine to IV decitabine, or relevant agents used to treat MDS such as azacitidine. Health-related quality of life was not assessed in the trials, and therefore the impact of decitabine and cedazuridine on quality of life remains unknown.

Indirect Evidence

In the absence of direct evidence comparing decitabine and cedazuridine to relevant treatments, the sponsor provided an unpublished ITC/NMA comparing decitabine and cedazuridine to azacitidine, BSC, conventional care regimens (CCR), and LDAC for the treatment of intermediate-1, intermediate-2, and high-risk MDS, and CMML.

The analyses were conducted in a Bayesian framework and considered three possible evidence networks: 1) C-DEC Synthetic Trial; where OS outcome data was incorporated with historical IV decitabine data, 2) Limited Network; where the results of the AZA-001 trial were excluded on the assumption that the OS benefit from this trial has not been reproduced in real-world evidence studies, and 3) Full Network; where the complete evidence network of all available and eligible trials was considered. A key limitation to the NMA is that the Limited and Full network scenarios assumed equivalence of oral decitabine and cedazuridine to IV decitabine, and that data from the decitabine and cedazuridine trials was not included in these networks. Additionally, the ITC/NMA did not evaluate the Intermediate-1 and CMML populations and it was assumed that the results would hold across IPSS groups, however, this should be interpreted with caution and may not be generalizable in Canadian clinical practice. Results of the ITC/NMA suggested that decitabine and azacitidine were no different in any network scenario with regards to OS, with the exception of the full evidence network where azacitidine was favoured over decitabine and BSC. Both azacitidine and decitabine were favoured over BSC for all clinical response outcomes, and there was no difference between azacitidine and decitabine, however the results demonstrated significant imprecision evidenced by wide CIs.

Due to severe limitations identified in the sponsor provided ITC/NMA, including the small size and structure of the network, which had no closed loops, concerns of heterogeneity across study populations with regard to IPSS groups, and the clinical and methodological assumptions made including the assumption of equivalence between oral decitabine and cedazuridine and IV decitabine, as well as the omission of decitabine and cedazuridine in two of three network scenarios, and imprecision of results, caution must be taken when interpreting the comparative efficacy estimates.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with de novo or secondary MDS who are not considered candidates for hematopoietic stem cell transplantation. The base case population was split into three subgroups: • Intermediate 2 to high-risk MDS (INT-2 to high-risk MDS) • Intermediate 1 MDS (INT-1 MDS) • chronic myelomonocytic leukemia (CMML)
Treatment	Decitabine and cedazuridine[a] in addition to BSC (consisting of red blood cell and platelet transfusions, antibiotics, anti-bleeding, iron chelation, and vitamin supplementation).
Submitted price	Decitabine and cedazuridine, 35 mg / 100 mg: $879.20 per tablet

Component	Description
Treatment cost	At the recommended dosage of decitabine and cedazuridine is one tablet (35 mg decitabine and 100 mg cedazuridine) taken orally once daily on days one through five of each 28-day cycle, for a 28-day cycle cost of $4,396.
Comparators	Azacitidine[a] in addition to BSC BSC
Perspective	Canadian publicly funded health care payer
Outcome	Quality-adjusted life-years (QALYs)
Time horizon	Lifetime (50 years)
Key data sources	• The ASCERTAIN trial informed key efficacy and safety parameters of the trial period for decitabine and cedazuridine, with parametric survival analysis used to extrapolate the trial data for OS and acute myeloid leukemia free survival (AML-free survival) over the remainder of the entire model time horizon. • Data from Fenaux et al., and Silverman et al., informed OS and AML-free survival of the trial periods for azacitidine and BSC of the model, respectively, with parametric survival analysis used to extrapolate the trial data for OS and acute myeloid leukemia free survival (AML-free survival) over the remainder of the model time horizon.
Submitted results	• INT-2 to high-risk MDS: ICER = $65,906 per QALY versus BSC (incremental costs: $179,808; incremental QALYs: 2.73) • INT-1 MDS: ICER = $61,479 per QALY versus BSC (incremental costs: $231,578; incremental QALYs: 3.77) • CMML: ICER = $74,113 versus BSC (incremental costs: $186,563; incremental QALYs: 2.52) • In all populations azacitidine was subject to extended dominance through decitabine and cedazuridine and BSC.
Key limitations	• The comparative clinical efficacy and safety of decitabine and cedazuridine compared with azacitidine and BSC is highly uncertain. The key efficacy outcomes of the ASCERTAIN trial informing the submitted model (overall survival and AML-free survival) were exploratory, and the sponsor's NMA had several limitations. This included the structure of the networks and potential sources of heterogeneity across trials informing the networks that did not allow the CADTH clinical reviewers and clinical experts to make strong conclusions regarding the comparative efficacy of these treatments. Additionally, there was limited comparative safety information and no comparative information on achievement of transfusion independence. • The sponsor's piecewise modelling approach to estimating the OS and AML-free survival for all comparators constituted a naïve comparison (i.e., non-comparative in nature), leading to survival extrapolations that were associated with substantial uncertainty and did not align with clinical expectations which overestimated potential benefits with decitabine and cedazuridine in comparison with azacitidine and BSC. • The sponsor assumed treatment with azacitidine and decitabine and cedazuridine would be discontinued prior to disease progression, which does not align with its expected use in Canadian clinical practice, underestimating total drug costs. • The sponsor's model lacked transparency and face validity which was highlighted when certain inputs were altered probabilistically, making it difficult to critically appraise and explore areas of uncertainty. • Risk of developing AML and risk of dying (i.e., OS and AML-free survival) were assumed to be the same, regardless of the health state occupied, for each outcome, respectively. Feedback from the clinical experts consulted by CADTH indicated patients would have a different risk of developing AML and mortality depending on the health state. This adds to the uncertainty of the modelled results. • The majority of the data informing the sponsor's economic submission was for the INT-2 to high-risk subgroup, with limited clinical data including comparative efficacy data in the INT-1 and CMML subgroups.
CADTH reanalysis results	• Due to the limitations associated with the comparative clinical evidence and quality of the submitted model, CADTH could not produce a base case analysis.

Component	Description
	• CADTH undertook exploratory analyses using alternative efficacy and safety assumptions for decitabine and cedazuridine and azacitidine, and alternate wastage assumptions for azacitidine. • In an exploratory analysis where efficacy, safety and the rate of achieving transfusion independence were assumed to be equal for decitabine and cedazuridine and azacitidine, decitabine and cedazuridine was dominant due to a small QALY benefit (0.01 additional QALYs) due to the disutility associated with azacitidine administration and fewer costs due to assumed additional wastage and administration costs associated with azacitidine. • When no wastage was assumed with azacitidine in addition to equal efficacy, safety and rate of achieving transfusion independence for azacitidine and decitabine and cedazuridine, decitabine and cedazuridine was associated with an ICER above $4.8 million per QALY. A price reduction of over 15% is required for decitabine and cedazuridine to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY in this scenario in the INT-2 to high-risk subgroup. • Issues with the model mechanics and the lack of robust comparative efficacy data mean the cost-effectiveness of decitabine and cedazuridine in comparison with azacitidine and BSC is unknown.

BSC = best supportive care; CMML – chronic myelomonocytic leukemia; ICER = incremental cost-effectiveness ratio; INT-1 = intermediate-1 IPSS risk group; INT-2 = intermediate-2 IPSS risk group; LY = life-year; MDS = myelodysplastic syndrome; NMA = network meta-analysis; OS = overall survival; PSM = partitioned survival model; QALY= quality-adjusted life-year.

[a] No cost was attributed to BSC within the submission. BSC (as described by the sponsor) was not a component of the trials used to inform decitabine and cedazuridine or azacitidine.

Budget Impact

The sponsor estimated the budget impact of decitabine and cedazuridine with best supportive care (BSC) over three years. CADTH identified the following key limitations with the sponsor's analysis: Sponsor's market share assumptions did not align with the expectations of clinical experts consulted by CADTH; Clinical experts consulted by CADTH stated that some sub-groups of patients may receive comparator treatments not included in the BIA by the sponsor. CADTH reanalysis found the introduction of decitabine and cedazuridine to have an incremental cost of -$397 in Year 1, $953,072 in Year 2, and $2,290,933 in Year 3, and a cumulative 3-year budget increase of $3,243,608. The budgetary impact was driven entirely by the INT-1 patient group.

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

August 11, 2021 Meeting

Regrets

One expert committee member did not attend.

Conflicts of Interest

None

Appendix 1: CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) Responses to Drug Program Implementation Questions

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Response from Expert Committee**
Relevant Comparators	
PAG seeks an additional comparison of decitabine and cedazuridine with: • azacitidine in higher risk MDS subtypes • azacitidine and hydroxyurea for some patients with CMML. • lenalidomide in patients with deletion 5q chromosome change MDS • HSCT for MDS	• Decitabine and cedazuridine compared with azacitidine in higher risk MDS subtypes – pERC noted that the sponsor submitted NMA compared decitabine to azacitidine in intermediate-2 and high-risk MDS patients, however it was subject to a number of limitations resulting in significant uncertainty in the reported results. Thus, the magnitude of the clinical benefit, if any, of decitabine and cedazuridine compared to azacitidine remains unknown. • Decitabine and cedazuridine compared with azacitidine and hydroxyurea in CMML patients – The sponsor-submitted NMA attempted to include patients with CMML; however, subgroup analyses were not possible and thus, it was assumed the results of the NMA were similar across IPSS subgroups and CMML patients. Hydroxyurea was not included as a comparator. Thus, the comparative effectiveness of decitabine and cedazuridine to azacitidine and hydroxyurea in CMML patients remains unknown. • Decitabine and cedazuridine compared with lenalidomide in patients with deletion 5q chromosome change MDS – Comparison to lenalidomide was not possible in the sponsor submitted NMA due to its pre-specified population. Trials of lenalidomide were excluded from the NMA as they primarily included patients with low-risk MDS. As such, comparative effectiveness of decitabine and cedazuridine versus lenalidomide in patients with deletion 5q remains unknown. The clinical experts consulted by CADTH agree that, for patients with deletion 5q, lenalidomide would be the preferred regimen due to better available evidence. • Decitabine and cedazuridine compared with HSCT for MDS –The clinical experts consulted by CADTH noted that HSCT is the only curative option for patients with MDS and, as such, decitabine and cedazuridine would not replace HSCT for patients who are transplant-eligible. However, the decitabine and cedazuridine could be used as a bridge to transplant.
Considerations for Initiation of Therapy	
PAG is seeking clarity on whether the following patients would be eligible for treatment with decitabine and cedazuridine:	• Patients who have received prior HSCT – Patients with a history of HSCT were not excluded from eligibility from the decitabine and cedazuridine trials per protocol; however, none of the trial participants actually received prior HSCT; therefore, pERC was unable to comment on

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Response from Expert Committee**
• Patients who experienced prior HSCT • Candidates for intensive induction chemotherapy • Patients who are candidates for HSCT • Patients previously treated with a hypomethylating agent • Patients with ECOG PS ≥ 2	the effectiveness of decitabine and cedazuridine in this patient population. • Patients who are candidates for intensive induction chemotherapy – pERC agreed with the clinical experts consulted by CADTH that patients who are candidates for intensive induction chemotherapy could be eligible for decitabine and cedazuridine, based on patient preference. • Patients who are candidates for HSCT– pERC agreed that patients who are candidates for HSCT could use decitabine and cedazuridine as a bridge to transplant. • Patients previously treated with a hypomethylating agent (HMA) – pERC agreed that patients treated with a HMA who have had a response could switch to decitabine and cedazuridine; however, the committee noted that patients whose disease has progressed on a HMA are not eligible as there is no evidence to support the use of another HMA upon progression. • Patients with ECOG PS ≥2 – Clinical experts consulted by CADTH agreed that patients with ECOG PS 2 or higher would be eligible for treatment with decitabine and cedazuridine, at the treating clinician's discretion. .
If treatment with decitabine and cedazuridine were recommended for reimbursement, PAG noted a time-limited need and seeks confirmation from pERC that patients currently on azacitidine may switch for the convenience of an oral therapy and patients with deletion 5q MDS treated with lenalidomide would be able to access decitabine and cedazuridine.	• Patients receiving azacitidine (time-limited need) – pERC agreed that, upon implementation of this recommendation, patients who are currently receiving azacitidine and have not had a disease progression may switch to decitabine and cedazuridine, for the convenience of an oral therapy and based on patients' preference. • Patients with deletion 5q MDS who progress on lenalidomide – pERC agreed that these patients could be considered for treatment with decitabine and cedazuridine due to the limited treatment alternatives for these patients upon disease progression.
PAG noted potential indication creep in the following scenarios: use of decitabine and cedazuridine in second line after azacitidine, use of decitabine and cedazuridine for the treatment of AML where azacitidine is available and patients with low-risk MDS.	• Second line treatment after azacitidine – pERC noted that there was no evidence included in this review to support the use of decitabine and cedazuridine in second line after azacitidine. • Treatment of acute myeloid leukemia (AML) – pERC noted that patients with AML were excluded from the reviewed trials and, thus, there is no evidence to support the use of decitabine and cedazuridine over azacitidine in this patient population. • Low-risk MDS – pERC noted that there is no evidence to support the use of decitabine and cedazuridine in patients with low-risk MDS.

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Response from Expert Committee**
Considerations for continuation or renewal of therapy	
The sponsor indicated that best response may take longer than 4 cycles. Cycles are repeated every 28-days in the absence of hematologic toxicities not attributed to active disease and blood counts show absolute neutrophil count of at least 1.0×10^9/L and platelets are at least 50×10^9/L, or when they return to pre-treatment levels. The sponsor advised to delay or reduce the dose per cycle for hematologic toxicity. PAG is seeking a clear definition of "continuing treatment as long as the patient continues to benefit."	• pERC discussed the ideal treatment duration with decitabine and cedazuridine and agreed with the clinical experts consulted by CADTH that patients should be treated for at least 6 months in the absence of progressive disease or unacceptable toxicity. If the patient is stable or shows clinical improvement, then the treatment should continue. Treatment should be discontinued if there is progressive disease, unacceptable toxicity, or due to patient preference.
Considerations for prescribing of therapy	
PAG is seeking advice on dose reduction since it may not be possible with a single tablet strength unless skipping days is recommended.	• pERC discussed dose reductions using single tablet strength and noted that for patients who take decitabine and cedazuridine tablets as indicated in the product monograph (i.e., one tablet daily for 5 consecutive days in the beginning of each 28-day cycle), three dose reductions are possible: (1) one tablet daily through days 1 to 4; (2) one tablet once daily through days 1 to 3; and (3) one tablet daily on days 1, 3, and 5.
There is concern with possible drug wastage because dose reduction involves reducing the number of tablets per cycle (e.g., go from 5 days to 4 days to 3 days). The product monograph outlines a blister pack of 5 tablets with one blister card in a carton. PAG is seeking clarity on the packaging and whether this blister card can be cut to accommodate dose reduction and whether tablets can be used for another patient.	• pERC considered possible drug wastage due to dose reductions that involve reducing the number of tablets per cycle. pERC noted that decitabine and cedazuridine is packaged in a blister pack containing 5 tablets per box. The blister card can be cut by the pharmacy to dispense fewer tablets to accommodate dose reductions. Any remaining blistered tablets that have been cut can be subsequently used for other MDS patients if the tablets remain within the individual blister seal.
Funding algorithm	
PAG is seeking to confirm the place in therapy and sequencing with decitabine and cedazuridine including the scenarios below: • Options after treatment failure with decitabine and cedazuridine • Use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent) to achieve disease and symptom control and thus improve fitness • Sequencing with azacitidine (e.g., does failure of one hypomethylating agent precludes the use of another in subsequent lines)?	pERC discussed sequencing decitabine and cedazuridine with other treatments in the following scenarios requested by PAG: • Options after treatment failure with decitabine and cedazuridine – pERC agreed that, while there is no standard of care in this setting, options could include best supportive care, clinical trials, hydroxyurea, and induction chemotherapy. • Use of decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent) – The clinical experts consulted by CADTH noted that decitabine and cedazuridine could be used as a bridge

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Response from Expert Committee**
• For patients with deletion 5q- MDS who are currently on lenalidomide and progress, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression • For patients who have low risk MDS and are treated with EPO +/- G-CSF, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression?	to HSCT, and possibly intensive chemotherapy, however, the latter is not commonly done. • Sequencing decitabine and cedazuridine with azacitidine– The clinical experts consulted by CADTH indicated that decitabine and cedazuridine would not be sequenced with azacitidine; failure on one HMA precludes the use in subsequent line. • Use of decitabine and cedazuridine for patients with deletion 5q- MDS who are currently on lenalidomide and experience disease progression – the clinical experts consulted by CADTH agreed that decitabine and cedazuridine could be used in these patients. • Use of decitabine and cedazuridine for patients with low risk MDS and have progressed after treatment with EPO with or without G-CSF – pERC noted that it did not review any evidence that supported the use decitabine and cedazuridine in low-risk patients, unless the low-risk patients have progressed to higher risk MDS of intermediate-1 or higher.

CMML = chronic myelomonocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; EPO = erythropoietin; G-CSF = granulocyte-colony stimulating factor; HSCT = hematopoietic stem cell transplant; HMA = hypomethylating agent; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; NMA = network meta-analysis; PAG = Provincial Advisory Group

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