Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

ivosidenib (Tibsovo)

Indication: Ivosidenib in combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.

Sponsor: Servier Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The pCODR Expert Review Committee (pERC) recommends that ivosidenib in combination with azacitidine be reimbursed for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy, only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (AGILE; N = 146) demonstrated that ivosidenib in combination with azacitidine (ivosidenib + azacitidine) resulted in added clinical benefit in adult patients with newly diagnosed AML with an IDH1 R132 mutation who were not eligible to receive intensive induction chemotherapy. The AGILE trial demonstrated that ivosidenib + azacitidine, when compared with placebo + azacitidine, resulted in statistically significant and clinically meaningful improvements in event-free survival (EFS) (hazard ratio [HR] = 0.33; 95% confidence interval [CI]: 0.16 to 0.69; P = 0.0011) and overall survival (OS) (HR = 0.44; 95% CI: 0.27 to 0.73; P = 0.0005) at 15 months median follow-up time. 2-year OS rates with a 28.6-months median follow-up time were 53.1% (95% CI: [redacted]) and 17.4% (95% CI: [redacted]) for the ivosidenib + azacitidine and placebo + azacitidine groups, respectively. pERC considered the safety profile of ivosidenib + azacitidine to be manageable with similar incidence of treatment-emergent adverse events (TEAEs) and grade 3 TEAEs compared to placebo + azacitidine. pERC discussed the risk of QT prolongation and differentiation syndrome with ivosidenib treatment and noted that adequate monitoring and potential dose adjustments would be required.

Patients identified a need for treatment options that improve quality of life and disease control, prolong survival, and offer an additional treatment option. pERC concluded that ivosidenib + azacitidine met some of the patients' needs as it improves disease control, prolongs survival, and offers an additional treatment option. No definitive conclusion could be reached regarding the effects of ivosidenib + azacitidine on health-related quality of life (HRQoL) due to a significant decline in the number of patients available to provide assessments over time and the descriptive nature of the analyses.

pERC heard from the clinical experts that venetoclax + azacitidine is currently the most relevant available treatment option in the requested patient population. The evidence from sponsor-submitted indirect treatment comparisons (ITCs) was insufficient to conclude on the relative efficacy of ivosidenib + azacitidine compared to venetoclax + azacitidine.

At the sponsor submitted price for ivosidenib and publicly listed price for all other drugs, ivosidenib + azacitidine was more costly than venetoclax + azacitidine. As there is insufficient evidence to suggest that ivosidenib + azacitidine is more effective than venetoclax + azacitidine, the total drug cost of ivosidenib + azacitidine should not exceed that of venetoclax + azacitidine for the treatment of patients with newly diagnosed AML who have an IDH1 R132 mutation and are not eligible to receive intensive induction chemotherapy.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with ivosidenib + azacitidine should be reimbursed in adult patients with newly diagnosed AML with an IDH1 R132 mutation who are considered ineligible for standard intensive induction chemotherapy and meet at least 1 of the following criteria: 1.1. Age ≥ 75 years 1.2. ECOG PS = 2 1.3. Severe cardiac disorder 1.4. Severe pulmonary disorder 1.5. Creatinine clearance of < 45 ml/minute 1.6. Bilirubin level > 1.5 times ULN 1.7. Any other comorbidity judged to be incompatible with intensive induction chemotherapy	Evidence from the AGILE study demonstrated that treatment with ivosidenib + azacitidine resulted in clinical benefit in patients with these characteristics.	IDH1 mutation should be confirmed in patients with AML. IDH1 mutations can be detected by genetic testing using NGS or PCR. NGS is currently the standard of care testing for all AML-associated oncogenic driver mutation identification including IDH1, while PCR testing can be used to identify single nucleotide variants of the IDH1 R132 codon. In line with the implementation guidance for venetoclax + azacitidine, it may be reasonable to treat patients with ECOG status greater than 2 with ivosidenib + azacitidine at the discretion of the treating clinician.
2. Patients must not have any of the following: 2.1 Prior treatment for AML with the exception of treatments to stabilize disease such as hydroxyurea or leukapheresis.	There is no evidence to support a benefit of ivosidenib + azacitidine treatment in patients with prior therapy as they were excluded from the AGILE trial.	—
Discontinuation		
3. Treatment with the ivosidenib + azacitidine should be discontinued upon the occurrence of any of the following: 3.1. Progressive disease 3.2. Intolerable toxicity	These conditions correspond to the criteria used to determine whether treatment with ivosidenib + azacitidine should be discontinued in the AGILE trial. The clinical experts consulted for this review noted that disease progression was demonstrated by either increased number of blasts in the bone marrow according to the standard International Working Group criteria or, if a bone marrow aspiration is not performed, worsening of the blood counts and/or increased number of circulating blasts.	—
4. For patients without unacceptable toxicity, it is recommended that patients be treated for a minimum of 6 cycles.	In AGILE, patients received a minimum of 6 cycles of combination therapy with ivosidenib + azacitidine.	—
Prescribing		
5. Ivosidenib + azacitidine should only be prescribed by clinicians who have expertise in diagnosis and management of patients with AML in a	This condition will ensure that treatment with ivosidenib + azacitidine is prescribed only for appropriate patients	—

Reimbursement condition	Reason	Implementation guidance
specialized hematology or oncology clinic; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery.	and adverse effects are managed in an optimized and timely manner.	
6. Ivosidenib + azacitidine should only be reimbursed in combination.	There is no evidence from the AGILE trial supporting the efficacy and safety of ivosidenib when used alone.	—
Pricing		
7. Ivosidenib + azacitidine should be negotiated so that it does not exceed the drug program cost of treatment with venetoclax + azacitidine for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive intensive induction chemotherapy.	In the absence of direct head-to-head trials comparing ivosidenib + azacitidine with venetoclax + azacitidine and limitations in the sponsor's submitted indirect evidence, there is insufficient evidence to justify a cost premium for ivosidenib versus venetoclax when used in combination with azacitidine.	—
Feasibility of adoption		
8. The organizational feasibility of conducting testing for IDH1 R132 mutations must be addressed.	Testing for IDH1 R132 mutations is required to determine eligibility for ivosidenib + azacitidine. Clinical experts indicated that IDH1 mutation testing is not part of routine AML diagnostic testing for all jurisdictions across Canada, and implementation of IDH1 testing in jurisdictions that do not currently test for IDH1 mutations may have substantial health system impacts.	—

AML =acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; IDH1 = isocitrate dehydrogenase-1; NGS = next generation sequencing; PCR = polymerase chain reaction; ULN = upper limit of normal.

Discussion Points

- pERC deliberated on ivosidenib + azacitidine considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CDA-AMC Reimbursement Reviews. pERC considered that AML is an aggressive disease which is primarily affecting older adults with poor prognosis. Patients who are ineligible for induction chemotherapy regimens have limited treatment options and few patients survive 5 or more years. The incidence of IDH1-mutated AML is considered a rare condition with currently no access to IDH1-targeted treatment options. The available evidence demonstrated that ivosidenib + azacitidine resulted in clinically meaningful improvements in EFS and OS; at a 28.6-months median follow-up time median OS was 29.3 and 7.9 months with ivosidenib + azacitidine and placebo + azacitidine, respectively. The evidence was rated as moderate certainty using GRADE.
- pERC discussed available therapy options and heard from the clinical experts that venetoclax + azacitidine is currently the most relevant available treatment option in the requested patient population. pERC deliberated on the results of sponsor-submitted ITCs (1 network meta-analysis [NMA] and 3 matched-adjusted indirect comparisons [MAICs]) comparing ivosidenib + azacitidine to current treatment options (venetoclax + azacitidine, azacitidine, low-dose cytarabine [LDAC], venetoclax + LDAC). pERC acknowledged several limitations with the submitted ITCs, notably the small number of studies, heterogeneity across study designs and populations, and imprecision of study results from the wide credible or confidence intervals. Given the limitations, pERC could not draw definitive conclusions on the relative efficacy (i.e., OS, EFS, complete remission rates, and transfusion need) of ivosidenib + azacitidine compared with venetoclax + azacitidine.
- pERC discussed that transfusion independence and infections rates were deemed relevant endpoints by patient groups and clinicians with the potential to impact patients' quality of life. According to the GRADE assessment, ivosidenib + azacitidine may reduce the need for transfusions and likely results in fewer infections when compared with placebo + azacitidine. The committee noted that given wide CIs, the GRADE assessments for rates of transfusion independence and infections resulted in 'low' and 'moderate' certainty, respectively.
- pERC deliberated on the safety profile of ivosidenib + azacitidine. Evidence from the AGILE study suggested that the incidence of TEAEs, grade 3 TEAEs, and TEAEs leading to discontinuation of treatment, was similar between the study groups. TEAEs in the ivosidenib + azacitidine group were mostly driven by hematological and gastrointestinal toxicities. pERC discussed the risk of QT prolongation and differentiation syndrome with ivosidenib treatment and noted that adequate monitoring and potential dose adjustments would be required. Overall, pERC agreed with the clinical experts, that the safety profile of ivosidenib + azacitidine appeared manageable.
- The committee discussed that genetic testing for IDH1 R132 mutations may not be routinely performed for all people with AML in all jurisdictions within Canada. Should ivosidenib + azacitidine be reimbursed, testing frequency may increase in some jurisdictions, which would result in higher costs to the health care system.

Background

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy, and one of the most aggressive forms of leukemia. Typical symptoms of AML include fatigue, pale skin, dyspnea, infection, dizziness, headache, and coldness in hands and feet. Furthermore, leukopenia and neutropenia increase the risk of infections and fever, while thrombocytopenia increases the likelihood of bruising, bleeding, frequent or severe nosebleeds, bleeding gums, and heavy menstrual bleeding in women. Other symptoms include weight loss, night sweats, and loss of appetite. Prevalence of AML ranges from 0.6 to 11.0 per 100,000 persons for all age categories, genders, and ethnicities globally. The national age-standardized incidence rate (ASIR) for AML in Canada was reported to be 3.8 per 100,000 persons in 2018. Approximately 1,600 patients in Canada were diagnosed with AML in 2022. It is estimated that 6% to 10% of all patients with AML harbour an IDH1 mutation with an estimated incidence ranging from 0.24 to 0.40 per 100,000 persons. The incidence of IDH1-mutated AML is low and it is considered to be a rare disease. The age-standardized 1-year and 5-year survival rates for patients with AML are 42.1% and 19.9%, respectively. Approximately 40% to 50% of patients with newly diagnosed AML are ineligible for standard induction chemotherapy regimens because of older age, poor Karnofsky performance status (KPS)/Eastern Cooperative Oncology Group (ECOG) performance status and/or comorbid conditions.

Treatment options for patients with newly diagnosed AML who carry a mutation in the IDH1 enzyme and are ineligible for the standard intensive chemotherapy are limited. In Canada, active treatment options that are currently publicly funded for patients with AML who are ineligible for standard intensive chemotherapy but not specific for those carrying an IDH1 mutation include:

- venetoclax combined with azacitidine
- monotherapy with azacitidine or LDAC if the patients are not considered candidates for combination therapy

Ivosidenib is an inhibitor of the mutant IDH1 enzyme. On July 19, 2024, ivosidenib in combination with azacitidine was approved by Health Canada for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive intensive induction chemotherapy. The sponsor's reimbursement request is aligned with the Health Canada-approved indication. IDH1 R132 mutation must be confirmed before the combination regimen is initiated. The recommended dose for ivosidenib is 500 mg (2 x 250 mg tablets) taken orally once daily during the 28-day cycle. It should be started in combination with azacitidine at 75 mg/m^2 of body surface area, intravenously or subcutaneously, once daily during each 28-day cycle. It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a phase III, double-blind randomized controlled trial (AGILE) in adult patients with newly diagnosed AML with an IDH1 R132 mutation who were not eligible to receive intensive induction chemotherapy
- a review of 4 indirect treatment comparisons
- patients' perspectives gathered by 2 patient group(s): the Leukemia and Lymphoma Society of Canada (LLSC) and Heal Canada
- input from public drug plans and cancer agencies that participate in the CDA review process
- 2 clinical specialists with expertise diagnosing and treating patients with AML
- input from 2 clinician groups: the Leukemia and Lymphoma Society of Canada Clinician Network (LLSC) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committee)
- a review of testing procedure considerations for detecting IDH1 R132 mutations to determine eligibility for ivosidenib
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, LLSC and Heal Canada provided input to the review of ivosidenib. LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. Heal Canada is a registered not-for-profit organization that aims to empower patients, improve healthcare outcomes, and advocate for equitable access to quality healthcare across Canada. Data were gathered through online surveys or emails with patients diagnosed with AML. A total of 83 respondents participated in the survey from LLSC, and 7 respondents identified as having the IDH1 mutation. LLSC also conducted two 1 on 1 interviews with patients currently dealing with AML. Heal Canada launched an online survey to assess different aspects of patients living with blood cancer. Of a total of 22 respondents, 5 respondents were diagnosed with AML. Information was also gathered from semi-structured interviews with 2 patients and 2 caregivers. Patients or caregivers from Heal Canada did not have experience with ivosidenib, while LLSC interviewed one patient with previous experience with ivosidenib.

Most patients reported that mental, physical and financial effects of the AML experience have significant negative impact on the lives of patients and caregivers alike. The patient groups described the challenges linked to the currently available treatments, such as intolerable side effects, lack of treatment response, and limited options available to the patients. Both patient groups indicated that important patient outcomes included improved HRQoL (related to better control of anemia without transfusion or less transfusions, as well as a lower infection rate), improved disease control, and prolonged survival. The patient who had experience with ivosidenib was initially treated with induction chemotherapy after a diagnosis of IDH1-mutated AML. After relapse on chemotherapy, this patient started ivosidenib and reported great response and minimal side effects from the treatment.

Clinician Input

Input from Clinical Experts Consulted by the Review Team for this Submission

The clinical experts identified the following unmet needs associated with currently available treatments for patients with AML who are ineligible for intensive induction chemotherapy: 1) not all patients respond to available therapies, therefore, the outcomes of patients with AML (with or without IDH1 R132 mutation) who are not eligible for intensive chemotherapy are dismal, and 2) patients who respond to available therapy eventually relapse and succumb to their disease. Therefore, the clinical experts indicated that for patients in the target population, the most important treatment goals are to prolong remission and survival, reduce transfusion dependency, reduce the risk of infection and bleeding, and improve HRQoL.

The clinical experts indicated that ivosidenib would be reserved as first-line therapy for patients with AML who harbor the IDH1 R132 mutation and who are not eligible for intensive chemotherapy due to their age, comorbidities, or preference. Ivosidenib in combination with azacitidine could potentially replace the currently available combination therapy for these patients.

The clinical experts stated that only patients with a diagnosis of de novo AML with IDH1 R132 mutation and who are unfit for intensive induction chemotherapy would be eligible to receive treatment with ivosidenib.

According to the experts, important outcomes for patients with AML are survival, HRQoL, response rates (in particular complete remission), transfusion requirement, infection rates, and safety. The experts also noted that in clinical practice, patients' response to treatment are typically assessed every 28 days, corresponding to the length of treatment cycles for azacitidine.

The experts noted that treatment with the combination of ivosidenib and azacitidine will be discontinued if disease progression is detected, patients experience intolerable adverse effects (AEs), and/or based on patient preference.

The clinical experts noted that in general, patients should be treated by a hematologist and/or hematologist/oncologist with experience of AML management. Treatment with ivosidenib can be administered in both inpatient and outpatient settings.

Clinician Group Input

Two clinician groups provided input for the review of ivosidenib in combination with azacitidine: the LLSC and OH-CCO's Drug Advisory Committee.

In general, the clinician group inputs were consistent with the input provided by the clinical experts consulted by the review team. The treatment goals for this patient population would be to prolong life, improve quality of life, improve transfusion independence, and achieve remission. The clinician groups noted that the current publicly funded treatment options for patients with AML who are not eligible for intensive chemotherapy include venetoclax + azacitidine, single agent azacitidine, low dose cytarabine, and best supportive care. The clinician from OH-CCO's Drug Advisory Committee also mentioned venetoclax + low-dose cytarabine as available therapy. However, both clinician groups agreed that not all patients respond to these therapies. In addition, both clinician groups suggested that treatment with venetoclax + azacitidine is associated with increased risk of neutropenic fever and infections compared to azacitidine alone. According to the clinicians, infections may result in hospitalizations, which in many cases can be days to weeks depending on severity. The clinicians from LLSC added that no tumour lysis syndrome monitoring is required with ivosidenib + azacitidine. The clinician groups noted that specific inhibitors may offer a chance for increased treatment response and suggested ivosidenib + azacitidine be considered as first-line therapy and to become the new standard of care for adult patients with newly diagnosed IDH1-mutated AML who are not eligible for intensive induction chemotherapy or stem cell or bone marrow transplant. Both clinician groups indicated that remission rate, stabilization, and improvement in the frequency and severity of symptoms, such as improvement in blood counts, fewer transfusions, leukemia-free survival, and OS, using usual leukemia response timelines are the outcomes used to determine whether a patient is responding to ivosidenib + azacitidine. On the other hand, reasons for treatment discontinuation identified by the clinician groups included disease progression, intolerable side effects, and patient preference. Both clinician groups noted that ivosidenib + azacitidine can be given in the inpatient and outpatient settings, or even community centers that have experience in treating acute leukemias.

Both the LLSC and OH-CCO Drug Advisory Committee noted that timely results of testing for IDH1 mutation are required to identify patients who would benefit and be eligible for this treatment.

Drug Program Input

The clinical experts consulted for this review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In the AGILE study, ivosidenib + azacitidine was compared to placebo + azacitidine. Ivosidenib + azacitidine was not compared to other treatment options, such as azacitidine + venetoclax or LDAC in this study.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Eligibility criteria in the AGILE study were: > 18 years, confirmed IDH1-mutated AML, ECOG performance status of 0-2. Can patients with ECOG performance status > 2 receive treatment with ivosidenib + azacitidine?	The clinical experts indicated that patients with an ECOG performance status score of 3 or 4 are very frail, and these patients usually are excluded from the clinical trials. Even though a clinical benefit from treatment with ivosidenib + azacitidine may be derived for these patients, the extent of the benefit is unknown. The clinical experts noted that in clinical practice, some clinicians use a different scale to assess patient's performance status, such as KPS. This is a more detailed scale with the scores ranging from 0 (death) to 100 (normal) and provides more information when quantifying patient's general well-being, as compared to the ECOG performance status scale. The experts suggested that there may be patients whose performance status falls between

Implementation issues	Response
	ECOG score of 2 and 3 and who may benefit from treatment with ivosidenib + azacitidine. pERC agreed that it may be reasonable to treat patients with ECOG performance status of greater than 2 with ivosidenib + azacitidine at the discretion of the treating clinician.
Why would ivosidenib + azacitidine be considered for treatment versus venetoclax + azacitidine and vice versa? Is one preferred over the other?	The clinical experts noted that in the AGILE study (pivotal study of this submission), all patients had IDH1 mutation. In the VIALE-A study (venetoclax + azacitidine vs. placebo + azacitidine), approximately 25% of patients harbored an IDH1 or IDH2 mutation. Based on the mechanism of action of ivosidenib (inhibitor of the mutant IDH1 enzyme), the clinical experts anticipated that ivosidenib + azacitidine may be superior to venetoclax + azacitidine in patients with AML with IDH1 mutation. Patients without IDH1 mutation would not be suitable candidates for the treatment with ivosidenib + azacitidine. pERC agreed with the clinical experts that patients with newly diagnosed AML with an IDH1 R132 mutation should be considered for treatment with ivosidenib + azacitidine. pERC agreed that patients without IDH1 R132 mutation should not be offered ivosidenib + azacitidine.
Considerations for continuation or renewal of therapy	
ECG is required prior to treatment with ivosidenib + azacitidine, weekly for the first 3 weeks of therapy and monthly for the duration of therapy.	Comment from the drug programs to inform pERC deliberations.
Considerations for discontinuation of therapy	
In the AGILE study, treatment with the study drug was discontinued if disease progression or intolerable toxicities occurred. What is the definition of disease progression in patients with AML in clinical practice?	The clinical experts indicated that disease progression is observed if: 1) a patient obtained a response but thereafter lost the response, or 2) the patient did not have a response after treatment initiation and progressed. The clinical experts noted that disease progression is demonstrated if CR based on the bone marrow is lost and/or there is increased number of blasts in the bone marrow. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
In the AGILE study, ivosidenib was given as oral tablet 500mg (2x 250mg tablets) once daily until progression or no longer tolerated. Should ivosidenib be given with alternative dosing schedules of azacitidine (6-day or 5-2-2)? Azacitidine 5-2-2: azacitidine subcutaneously for 5 days, followed by 2 days of no treatment, then treatment for 2 days	The clinical experts indicated that in the AGILE study, patients received ivosidenib once daily from Day 1 through Day 28; azacitidine was given once daily on Days 1-7 of each 28-day cycle. The experts noted that in clinical practice, most clinicians would treat patients in line with the protocol of clinical trials. However, they felt it would be reasonable to generalize to an alternative schedule for azacitidine, i.e., 6-day or 5-2-2, as the 7-day schedule may pose logistic challenges in some centres. pERC agreed that some centres would likely not be able to accommodate a 7-day schedule for azacitidine and that currently azacitidine is administered on a 6-day or 5-2-2 schedule in some institutions. pERC felt that it would be reasonable to combine ivosidenib with azacitidine on a 6-day or 5-2-2 schedule at the discretion of the treating clinician.
Ivosidenib is administered with SC azacitidine. On Days 1-7 of each 28-day cycle, some jurisdictions will need to	Comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
coordinate injectable (SC) and oral therapy (managed separately).	
Generalizability	
For patients who are currently on the azacitidine therapy, can ivosidenib be added to azacitidine (time limited need)?	The clinical experts indicated that for patients with IDH1 mutation, it is reasonable to believe that patients who have received a limited number of cycles of azacitidine monotherapy could derive additional benefit if ivosidenib were to be added to azacitidine. The experts also suggested that the earlier the addition of ivosidenib (e.g., from Cycle 1), the greater the benefit to patients. pERC agreed that, on a time limited basis, it would be reasonable to offer ivosidenib to patients who have confirmed IDH1 mutation status and have started treatment with azacitidine monotherapy prior to ivosidenib + azacitidine becoming available.
In the AGILE study, patients who had received previous treatment with an HMA (e.g. azacitidine or decitabine) for MDS or an IDH1 inhibitor were ineligible. In clinical practice, can patients who experience intolerance or toxicity with venetoclax + azacitidine be switched to ivosidenib + azacitidine?	The clinical experts indicated that some patients with IDH1 mutation may be candidates to be switched to ivosidenib + azacitidine when experiencing intolerance or toxicity with venetoclax + azacitidine. However, the safety profile of venetoclax + azacitidine overlaps (except for differentiation syndrome) with that of ivosidenib + azacitidine, with the greatest toxicities for both combination regimens being related to cytopenia. Therefore, patients who do not tolerate treatment with venetoclax + azacitidine may not tolerate ivosidenib + azacitidine. pERC agreed with the clinical experts.
Funding algorithm	
The study drug may change the place in therapy of the comparator drugs.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Drug preparation, storage, administration or dispensing: During the treatment with ivosidenib + azacitidine, there is a need to monitor the interactions between study drug with CYP 3A4. Potential dose reduction will be required if the drug is given in combination of CYP3A4 inhibitors.	Comment from the drug programs to inform pERC deliberations.
Management of adverse effects: During the treatment with ivosidenib + azacitidine, monitoring for differentiation syndrome and QTC interval prolongations are required. Dose modifications may be required if adverse effects are observed.	Comment from the drug programs to inform pERC deliberations.
Companion diagnostics (e.g., access issues, timing of testing): IDH1 testing via PCR assay is required before ivosidenib + azacitidine is given. Is IDH1 testing part of routine testing (i.e. normally included in testing panel)? What is the turnaround time for IDH1 testing? If the treatment with venetoclax + azacitidine has to be started before IDH1 mutation status is confirmed, can	The clinical experts noted that most, but not all, leukemia-treating centres have routine access to NGS and PCR testing for IDH1 mutation. The experts noted that the turnaround time varies across regions, ranging from a few days to up to 2 weeks. The experts indicated that the majority of the patients are not IDH1-mutated, and usually will be treated with azacitidine or venetoclax + azacitidine initially. It is estimated that 6% to 10% of all patients with AML harbour an IDH1 mutation. It is reasonable to allow patients who are found to be IDH1-mutated to be

Implementation issues	Response
patients be switched to ivosidenib + azacitidine once the status is confirmed?	switched to ivosidenib + azacitidine once their IDH1 mutation status is confirmed. pERC agreed that it would be reasonable to allow patients on venetoclax + azacitidine to switch to ivosidenib + azacitidine upon IDH1 mutation status confirmation.
System and economic issues	
Involvement of additional payers: An inpatient component may be required. In some jurisdictions, systemic treatments administered in the inpatient setting are outside the scope of the drug plan budgets. Coverage of the inpatient treatment would need to be addressed.	Comment from the drug programs to inform pERC deliberations.
Presence of confidential negotiated prices for comparators: Confidential pricing for venetoclax (in combination with azacitidine) is in place. Confidential pricing for generic azacitidine is in place.	Comment from the drug programs to inform pERC deliberations.

R = complete remission; ECG = electronic cardiogram; ECOG = Eastern Cooperative Oncology Group; HMA = hypomethylating agent; LDAC = low-dose cytarabine; IDH1 = isocitrate dehydrogenase-1; KPS = Karnofsky Performance Status; MDS = myelodysplastic syndrome; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

One international, phase III, multicentre, double-blind randomized controlled trial (RCT) (AGILE, N = 146) evaluated the efficacy and safety of ivosidenib + azacitidine compared to placebo + azacitidine in adult patients with newly diagnosed AML with an IDH1 R132 mutation who were not eligible to receive intensive induction chemotherapy. Patients were recruited from 89 study sites across 20 countries. Eligible patients were randomized 1:1 to receive either 1) ivosidenib 500 mg orally once daily plus azacitidine 75 mg/m^2/day SC or IV for 7 days, in 28-day cycles or 2) placebo in combination with azacitidine. The primary efficacy endpoint in the AGILE study was EFS. Key secondary endpoints were complete remission (CR) rates, OS, complete remission and complete remission with partial hematologic recovery (CR + CRh), and objective response rate (ORR). Additional secondary endpoints in this study included HRQoL measured by the EORTC QLQ-C30 questionnaire, transfusion requirement, and harms. The majority (73.3% per Investigator [76% per Interactive Web Response System]) of patients had *de novo* AML at initial diagnosis. There were more male patients in the ivosidenib + azacitidine group (58.3%) compared to the placebo + azacitidine group (51.4%). Based on the WHO classification of AML, fewer patients in the ivosidenib + azacitidine group (22.2%) had AML with recurrent genetic abnormalities compared to those in the placebo + azacitidine group (32.4%); more patients in the ivosidenib + azacitidine group (38.9%) had AML with myelodysplasia-related changes compared to those in the placebo + azacitidine group (35.1%). R132C IDH1 was the most common (65.8%) polymorphism. In total, 63.8% of patients in the ivosidenib + azacitidine group and 67.6% of patients in the placebo + azacitidine group had ECOG performance status score of 0 to 1. Cytogenetic risk status as assessed by the investigators based on the 2017 NCCN guidelines was intermediate (63.0%: 66.7% in ivosidenib + azacitidine group versus 59.5% in placebo + azacitidine group) or poor (24.7%: 22.2% in ivosidenib + azacitidine group versus 27.0% in placebo + azacitidine group) for most patients at baseline. The median bone marrow blast at baseline was 52.5% (range, 17% to 100%).

Two data cut-offs (DCOs) were available for AGILE. The first DCO (March 18, 2021) represents an unplanned early interim analysis by the Independent Data Monitoring Committee (IDMC) which occurred prior to the protocol-specified number of events for the planned analysis. Due to a notable difference in the number of deaths which favoured ivosidenib, the IDMC recommended that trial recruitment should end early, treatment assignment should be unblinded, and crossover to ivosidenib should be allowed. Stopping boundaries were therefore adjusted and this became the final analysis. A later DCO (June 30, 2022) was available for OS, transfusion independence, and harms.

Efficacy Results

The AGILE study met its primary endpoint. As of DCO March 18, 2021, the between-group difference in EFS rate was 19.7% ([redacted]) at 6 months and 25.3% ([redacted]) at 12 months, favoring the ivosidenib + azacitidine group. [redacted]. The median EFS in the ivosidenib + azacitidine group was 0.03 months (95% CI 0.03 to 11.01 months) and 0.03 months (95% CI: not estimable [NE] to NE months) in the placebo + azacitidine group. The median did not appear different between groups due to the majority of events being treatment failure which were assigned the date of randomization. The corresponding hazard ratio (HR) was 0.33 (95% CI 0.16 to 0.69), p = 0.0011. Predefined sensitivity analyses supported the robustness of the primary analysis and suggested an event-free survival benefit associated with ivosidenib + azacitidine in a short term.

Treatment with ivosidenib + azacitidine was associated with prolonged OS, met the pre-specified efficacy boundary for a statistically significant OS benefit for ivosidenib + azacitidine at DCO of March 18, 2021. At the updated DCO of June 30, 2022, [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group had died. The median OS was 29.3 months (95% CI: 13.2 months to not estimable) in the ivosidenib + azacitidine group and 7.9 months (95% CI 4.1 to 11.3 months) in the placebo + azacitidine group, p < 0.0001. The corresponding HR was 0.42 (95% CI 0.27 to 0.65). The between-group differences in the Kaplan-Meier-estimated OS rate were 24.6% (95% CI [redacted]) at 12 months, and 35.7% (95% CI [redacted]) at 24 months.

Results of subgroup analyses for OS and EFS (pre-specified for EFS) based on various patient baseline characteristics were consistent with those in the overall population.

As of March 18, 2021, the CR rate was 47.2% (95% CI 35.3 to 59.3) in the ivosidenib + azacitidine group and 14.9% (95% CI 7.7 to 25.0) in the placebo + azacitidine group. However, these estimates were affected by high risk of bias due to missing data.

As of DCO of June 30, 2022, a higher proportion of patients in the ivosidenib + azacitidine group ([redacted]) were RBC and/or platelet transfusion independent compared to those receiving placebo + azacitidine ([redacted]). This was measured in a non-randomized subset of the population. According to the clinical experts, improved CR rates and reduced transfusion requirement are considered clinically meaningful changes. It was the clinical experts' opinion that improved CR and reduced transfusion rates could subsequently translate to improved HRQoL and potentially prolonged survival.

Harms Results

Overall, safety results from the two DCOs were consistent.

As of DCO of March 18, 2021, the proportion of patients who experienced at least one AE was 98.6% (70 patients) in the ivosidenib + azacitidine group and 100% (73 patients) in the placebo + azacitidine group. Patients treated with ivosidenib + azacitidine were more likely (5% or more) to report these AEs compared to those treated with placebo + azacitidine: vomiting (29 [40.8%] versus 19 [26.0%]), neutropenia (20 [28.2%] versus 12 [16.4%]), thrombocytopenia (20 [28.2%] vs. 15 [20.5%]), electrocardiogram QT prolonged (14 [19.7%] versus 5 [6.8%]), insomnia (13 [18.3%] versus 9 [12.3%]), differentiation syndrome (10 [14.1%] versus 6 [8.2%]), pain in extremity (10 [14.1%] versus 3 [4.1%]), hematoma (9 [12.7%] versus 1 [1.4%]), arthralgia (8 [11.3%] versus 3 [4.1%]), headache (8 [11.3%] versus 2 [2.7%]), leukocytosis (8 [11.3%] versus 1 [1.4%]), and leukopenia (6 [8.5%] versus 2 [2.7%]).

Grade 3 and higher AEs were reported in 66 patients (93.0%) in the ivosidenib + azacitidine group and 69 patients (94.5%) in the placebo + azacitidine group. In both groups, commonly reported Grade 3 and higher AEs were (ivosidenib + azacitidine versus placebo + azacitidine): anemia (25.4% versus 26.0%), febrile neutropenia (28.2% versus 34.2%), neutropenia (26.8% versus 16.4%), thrombocytopenia (23.9% versus 20.5%), and pneumonia (22.5% versus 28.8%).

The proportion of patients who experienced SAEs was 69.0% (49 patients) in the ivosidenib + azacitidine group and 82.2% (60 patients) in the placebo + azacitidine group. Commonly reported SAEs were febrile neutropenia (23.9% versus 27.4%) and pneumonia (19.7% versus 21.9%) in the two treatment groups.

The overall incidences of TEAEs which led to combination treatment discontinuation were similar between the treatment groups, and included 19 patients (26.8%) in the ivosidenib + azacitidine group and 19 patients (26.0%) in the placebo + azacitidine group.

Differentiation syndrome and infection were identified by the clinical experts as notable harms for the treatment with ivosidenib. As of June 30, 2022, differentiation syndrome was reported in 10 patients (13.9%) in the ivosidenib + azacitidine group and 6 patients (8.1%) in the placebo + azacitidine group. Infection was reported in 25 patients (34.7%) in the ivosidenib + azacitidine group and 38 patients (51.4%) in the placebo + azacitidine group.

Critical Appraisal

In the AGILE study, there were some imbalances in baseline patient characteristics between the two treatment groups, e.g. gender, WHO classification of AML, and cytogenetic risk status by investigator. These imbalances seem to likely be the result of the small sample size within which prognostic balance is not likely to be assured; as such there is some risk that the observed effects are over- or under-estimated. In addition, the post-baseline transfusion independence outcome seems to only be measured among approximately half the population who required transfusions at baseline. Randomization is not necessarily upheld in this population. However, results of transfusion requirement in patients who were dependent on transfusion at baseline did not differ significantly from that in the overall population. Therefore, the potential for bias is unlikely to have an impact on the study findings specific for this outcome.

The study originally had no planned interim analyses. Observations of a notable difference in the number of deaths (favouring the ivosidenib + azacitidine group) by the IDMC prompted an unplanned interim analysis prior to the protocol-defined number of events. To control multiplicity, new stopping boundaries were calculated based on the observed information fraction that were not outlined in the original Statistical Analysis Plan. Because the results are from an unplanned interim analysis (which became the final analysis), even though the new stopping boundaries are appropriate, there is a risk of overestimation of the true effects of the study drug.

HRQoL was assessed using the EORTC QLQ C-30, although this is not an AML-specific instrument. Even though a minimum important different (MID) for QLQ C-30 for patients with AML was not identified from the literature, a range of potential between-group MIDs (3 to 11 points for improvement and -5 to -13 for deterioration on the global QoL scale) were established based on clinical trials of 9 different cancer types and may provide some guidance when determining the clinical relevance of the study findings for HRQoL in the AGILE study. The completion rate of the EORTC QLQ C-30 questionnaire was low. The completion rates were [redacted] at 6 months, 12 months, and 18 months, respectively. The evidence for HRQoL was considered to be very uncertain due to large amounts of missing data and imprecision; the CIs included the potential for little-to-no clinically meaningful difference between groups. The approach of missing data imputation may not adequately address the issue. Therefore, there is a high risk of bias due to the large amount of missing HRQoL outcome data in this study; the direction of bias cannot be predicted.

EFS was the primary efficacy outcome in this study. It is a composite end point and the sample size of AGILE was small. In the AGILE study, almost all events occurred at baseline (i.e., one component of the composite). As such, there were few patients left at risk post-baseline, and as a result, the EFS could not robustly characterize the long-term efficacy of the study drug. The correlations between EFS and OS were modest in published research which provided trial-level information. However, one major limitation of these surrogacy studies was that they were not specific to the population nor drug class of interest and therefore the ability to generalize the study findings was not clear.

Based on feedback from the clinical experts, the eligibility criteria and baseline characteristics of patients randomized in the AGILE study generally reflected a patient population in Canadian clinical practice that would receive combination therapy of ivosidenib + azacitidine. The clinical experts noted that the study results from AGILE could be generalized to patients with IDH1-mutated AML in Canada who would be treated with ivosidenib + azacitidine. The clinical experts suggested applying some flexibility in terms of using ivosidenib + azacitidine in patients with slightly worse ECOG performance status than in the trial. Patients' IDH1 mutation status should be confirmed prior to the treatment. The experts indicated that the outcome measures in the AGILE study are generally appropriate and clinically relevant in clinical trials of AML.

The clinical experts consulted for this review indicated that azacitidine alone is not the most appropriate comparator for ivosidenib + azacitidine in the requested patient population. Instead, venetoclax + azacitidine is currently the most commonly used combination therapy in the target patient population, according to the clinical experts. In practice, monotherapy with azacitidine would typically be used for patients with increased frailty that would make treatment with the combination of venetoclax + azacitidine unreasonable. There is a lack of direct evidence within the AGILE study to examine the relative efficacy and safety of the study drug to the other combination regimens.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The threshold for a clinically important effect for OS and EFS in the study population was not obtained. Therefore, the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for survival rates. The threshold for a clinically important effect for the EORTC QLQ-C30 score was set according to the presence or absence of an important effect based on thresholds identified in the literature. In addition, the target of the certainty of evidence assessment was the presence or absence of any non-null effect for CR, CR + CRi, and transfusion requirements. For some harm events (e.g., differentiation syndrome) due to the unavailability of the absolute difference in effects, the certainty of evidence was summarized narratively.

Table 3 presents the GRADE summary of findings for ivosidenib + azacitidine versus placebo + azacitidine.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Overall survival
- Event-free survival
- Complete remission (CR)
- CR + CRi
- Change from baseline in EORTC QLQ C-30 scores
- Transfusion requirement
- Any serious adverse events
- Risk of adverse events of special interest (differentiation syndrome, infection)

Table 3: Summary of Findings for Ivosidenib plus Azacitidine Versus Placebo plus Azacitidine for Patients with IDH1-Mutated AML

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + azacitidine	Ivosidenib + azacitidine	Difference		
Efficacy (FAS)							
Overall survival [a]							
Probability of OS at 12 months Median follow-up: [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group as of DCO on June 30, 2022.	148 (1 RCT)	NR	383 per 1,000	629 per 1,000 [redacted]	246 more per 1,000 [redacted]	Moderate [b]	Ivosidenib + azacitidine likely results in a clinically important increase in the probability of overall survival at 12 months when compared with placebo + azacitidine.
Probability of OS at 24 months Median follow-up: [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group as of DCO on June 30, 2022.	148 (1 RCT)	NR	174 per 1,000	531 per 1,000 [redacted]	357 more per 1,000 [redacted]	Moderate [c]	Ivosidenib + azacitidine likely results in a clinically important increase in the probability of overall survival at 24 months when compared with placebo + azacitidine.
Event-free survival							
Probability of EFS at 6 months Median follow-up: approximately 15 months for both groups as of DCO on March 18, 2021.	146 (1 RCT)	NR	203 per 1,000	399 per 1,000 (286 to 510 per 1,000)	197 more per 1,000 [redacted]	Moderate [d]	Ivosidenib + azacitidine likely results in an increase in the probability of event-free survival at 6 months when compared with placebo plus azacitidine. The clinical importance of the increase is uncertain.
Probability of EFS at 12 months	146 (1 RCT)	NR	122 per 1,000	374 per 1,000 (259 to 489 per 1,000)	253 more per 1,000 [redacted]	Low [e]	Ivosidenib + azacitidine may result in an increase in the probability of event-free

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + azacitidine	Ivosidenib + azacitidine	Difference		
Median follow-up: approximately 15 months for both groups as of DCO on March 18, 2021.							survival at 12 months when compared with placebo + azacitidine. The clinical importance of the increase is uncertain.
Complete Remission							
CR rate Median follow-up: approximately 15 months for both groups as of DCO on March 18, 2021.	146 (1 RCT)	OR: [redacted]	149 per 1,000	472 per 1,000 (353 to 593 per 1,000)	310 more per 1,000 [redacted]	Low [f]	Ivosidenib + azacitidine may result in an increase in the probability of CR when compared with placebo + azacitidine.
CR+CRi rate Median follow-up: approximately 15 months for both groups as of DCO on March 18, 2021.	146 (1 RCT)	OR: [redacted]	162 per 1,000	542 per 1,000 (420 to 660 per 1,000)	370 more per 1,000 [redacted]	Low [g]	Ivosidenib + azacitidine may result in an increase in the probability of CR+CRi when compared with placebo + azacitidine.
Transfusion Requirement							
Rate of conversion to post-baseline transfusion independent (in a subset of patients who were transfusion dependent at baseline)	80 (1 RCT)	OR: [redacted]	[redacted]	[redacted]	[redacted]	Low [h]	Ivosidenib + azacitidine may result in an increase in the proportion of patients who became transfusion independent post-baseline when compared with placebo + azacitidine.
Health-related quality of life							
EORTC QLQ C-30 (Global health status score)							
LS Mean change from baseline (0 [severe impairment] to 100 [good health]), points At 6-months	146 (1 RCT)	NA	-2.0	10.6 (1.23, 19.97)	12.6 (1.51, 23.65)	Very low [i]	The effect of ivosidenib + azacitidine on Global Health Status score of EORTC QLQ-C-30 from baseline to 6-month when compared with placebo + azacitidine is very uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + azacitidine	Ivosidenib + azacitidine	Difference		
LS Mean change from baseline (0 [severe impairment] to 100 [good health]), points At 12-months	146 (1 RCT)	NA	4.2	19.1 (8.51, 29.72)	14.9 (-2.09, 31.97)	Very low [j]	The effect of ivosidenib + azacitidine on Global Health Status score of EORTC QLQ-C-30 from baseline to 12-month when compared with placebo + azacitidine is very uncertain.
Harms (safety analysis set)							
Any SAEs							
Proportion of patients with any SAEs Median follow-up: [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group as of DCO on June 30, 2022.	148 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate [k]	Ivosidenib + azacitidine likely results in a reduction in the proportion of patients who experience SAEs when compared with placebo + azacitidine.
Differentiation syndrome							
Proportion of patients with differentiation syndrome Median follow-up: [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group as of DCO on June 30, 2022	148 (1 RCT)	NR	81 per 1,000	139 per 1,000 (NR)	60 more per 1,000 [redacted]	Low [l]	Ivosidenib + azacitidine may result in an increase in the proportion of patients who experience differentiation syndrome when compared with placebo + azacitidine.
Infection							
Proportion of patients with infections	148 (1 RCT)	NR	514 per 1,000	347 per 1,000 [redacted]	170 less per 1,000 [redacted]	Moderate [m]	Ivosidenib + azacitidine likely results in fewer infections when compared with placebo + azacitidine.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + azacitidine	Ivosidenib + azacitidine	Difference		
Median follow-up: [redacted] in the ivosidenib + azacitidine group and [redacted] in the placebo + azacitidine group as of DCO on June 30, 2022.							

CI = confidence interval; DCO = data cutoff; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; NR = not reported; OS = overall survival; RCT = randomized controlled trial; SAE = serious adverse event.

Note: Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] The outcome of OS at DCO of June 30, 2022 was not multiplicity adjusted; however; significance was met at an earlier multiplicity-adjusted analysis at DCO of March 18, 2021.

[b-c] Rated down 1 level for serious imprecision. No threshold of clinical importance could be estimated, but it was considered that the effect estimate and entire confidence interval were consistent with important benefit. The sample size and number of events is small resulting in potential for overestimation of the true effect.

[d] Rated down 1 level for serious imprecision. A threshold of clinical importance could not be estimated, but it was judged that the lower bound of the 95% CI includes the potential for little-to-no important difference.

[e] Rated down 2 levels for very serious imprecision. The sample size is small for this composite endpoint; following the large majority of events assigned to the date of randomization due to treatment failure (first component of the composite), few patients remained at risk to robustly assess long-term effects on EFS.

[f-g] Rated down 1 level for serious imprecision (results were from interim analysis of study with small sample size and low number of events). Rated down 1 level for risk of bias due to what appears to be a large amount of missing outcome data due to no post-baseline assessment.

[h] Did not rate down for risk of bias; though only a subset of the population was represented in which randomization may not be upheld, results appeared similar when comparing to analysis of the full population. Rated down 2 levels for very serious imprecision. Using the null as the threshold, the point estimate suggests benefit while the lower bound of the confidence interval suggests harm.

[i-j] Rated down 2 levels for very serious study limitations due to risk of bias due to missing outcomes data (data were available for 9% to 33% of the study population). Rated down 1 level for serious imprecision; the between-group difference of EORTC QLQ-C30 subscales exceed the identified MID for the Global Health States subscale in this instrument, however the 95% CI included the possibility of little-to-no difference. Statistical testing for this outcome was not adjusted for multiplicity in the study and should be considered as supportive evidence.

[k] Rated down 1 level for serious imprecision. No threshold of clinical importance could be established, therefore the null was used. The point estimate suggests benefit but the 95% CI included the possibility of little-to-no difference.

[l] Rated down 2 levels for very serious imprecision. No threshold of clinical importance could be established, therefore the null was used. The point estimate suggests harm, but the 95% CI includes the possibility of little-to-no difference or benefit.

[m] Rated down 1 level for serious imprecision. No threshold of clinical importance could be established, therefore the null was used. The point estimate suggests benefit, but the 95% CI includes the potential for little-to-no difference.

Source: AGILE Clinical Study Report. Data should reflect the results reported in the Clinical Study Report(s) whenever possible. Details included in the table are from the sponsor's Summary of Clinical Evidence. The between-group differences of the efficacy and harm outcomes in this table were requested from the sponsor.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Studies

One report of 4 ITCs (including 1 NMA and 3 MAICs) was submitted by the sponsor to compare the treatment benefits and harms of ivosidenib + azacitidine with other active therapies for the treatment of IDH1-mutated AML. A feasibility assessment was conducted to determine the feasibility of conducting indirect comparisons in the study population for the outcome of interest, and to assess the heterogeneities across the included studies. The comparative efficacy of ivosidenib versus comparators (venetoclax + azacitidine, azacitidine, LDAC, decitabine, venetoclax + LDAC, and glasdegib + LDAC) on OS, EFS, CR rates, and transfusion requirement were evaluated, based on evidence from 6 RCTs.

Efficacy Results

For this submission, venetoclax + azacitidine was identified as the most relevant comparator. As per clinical experts consulted for this review, it is currently the most commonly used therapy in the present target patient population. Comparative evidence of ivosidenib + azacitidine to venetoclax + azacitidine was only available through a sponsor-submitted ITC. The rarity of the population of interest limits the size and number of clinical studies completed with potential comparators and adds to the practical challenges when indirectly comparing treatment options. Based on the results of NMA and MAICs, the evidence is insufficient to conclude whether ivosidenib + azacitidine differs from venetoclax + azacitidine in terms of OS, EFS, CR rates or transfusion requirement in patients with untreated AML. Limitations associated with the ITCs included limited evidence from 6 RCTs, existing heterogeneity in the included trials, and imprecision of study results from the wide credible or confidence intervals for these outcomes.

Harms Results

Harm outcomes were not assessed in the ITCs.

Critical Appraisal

There was no a-priori protocol for the ITCs, therefore, it cannot be known whether the analyses presented were selected from multiple analyses of the data. Although appropriate methods were used to reduce the risk of bias and error in data extraction, it was unknown if the risk of bias of the included trials was assessed by 2 independent reviewers. In addition, risk of bias was assessed at the level of the trial, rather than at the level of the reported results (i.e., per outcome), which ignores that risk of bias can vary by reported result within a trial. Some of the studies included within the NMA had some concerns for risk of bias.

Six RCTs were included in the NMA. Heterogeneities were identified in the analysis populations, which included IDH1 mutation status, gender, type of AML diagnosis, cytogenic risk, performance status, median bone marrow blast, differences in placebo arm rates across placebo-controlled studies, and differences in the definition of EFS. For the time-to-event comparisons, e.g., EFS, lengths of follow-up were different and with longer follow-up it may be expected that the HR would be attenuated, even when the PH assumption is not formally violated; the bias would likely favour the study drug. These differences would undermine the validity of the NMA which relies on the transitivity assumption being upheld. The use of fixed effect models was chosen based on the deviance information criterion. However, the use of fixed rather than random effects models means that the credible intervals are unlikely to adequately express the uncertainty arising from the heterogeneity. The limited number of included studies did not allow for meta-regression or other techniques to adjust for differences in effect modifiers across studies within the NMA. The rarity of the population of interest limits the size and number of clinical studies completed with potential comparators and adds to the practical challenges when indirectly comparing treatment options.

In the NMA, given the lack of closed loops in the networks, consistency in the ITC analyses could not be tested, which increases the level of uncertainty. When comparing ivosidenib + azacitidine with other combination regimens, the 95% credible intervals (CrIs) for the point estimates were wide for some efficacy outcomes and spanned the null, therefore, confidence in the relative effect estimates

for efficacy were limited due to imprecision indicated by the wide CrIs for these outcomes and precludes any conclusions as to which treatment may be favoured.

In the MAICs, the following potential effect modifier or prognostic factors were identified through the literature and a deliberating process by the sponsor: age, gender, ECOG performance status, type of AML, cytogenetic risk of AML, bone marrow blasts and IDH1 mutation. The clinical experts consulted for this review agreed that these are relevant effect modifiers/prognostic variables. However, it is unclear if identification of potential effect modifiers through literature would be sufficient to inform all relevant treatment effect modifiers. The population in the AGILE study and the other comparator studies were weighted and matched. Within the unanchored MAIC there was no reported estimate of the potential residual bias due to unadjusted confounders, as a result the magnitude of residual confounding remains uncertain.

Prior to adjustment the median OS and EFS for the placebo + azacitidine groups were substantially different, suggesting reduced comparability of the populations. The main differences for the 2 studies used (AGILE and VIALE-A) is that in AGILE, patients were younger, had better ECOG, and had a lower proportion of high-risk cytogenic status. In terms of ESS, the ESS for the anchored MAICs was substantially reduced by approximately one third, suggesting that results are heavily influenced by a subset of the sample in the trial who may not be representative of the full sample. Reduction in ESS and sample size in general resulted in wide CIs. Furthermore, there is uncertainty about comparing the IDH1-mutated population to the ITT population in VIALE-A. It was not possible to adjust for this factor.

The study population for this review includes patients with AML with IDH1 mutation who are ineligible for intensive chemotherapy. However, most of the selected trials were not specific for IDH1-mutated AML. No other studies included IDH1 mutated patients only, and it is not clear in other included trials, if there were separate results for this particular subgroup. The prognostic significance of IDH1 status in AML, or whether this may be a treatment effect modifier, remains uncertain. According to the clinical experts consulted for this review, the effect modifiers identified in patients with AML by the sponsor are also considered effect modifiers in patients with IDH1-mutated AML.

In this ITC, several efficacy outcomes were analyzed, such as OS, EFS and CR (not evaluated in the MAICs). However, other efficacy endpoints of interest to patients and clinicians, such as HRQoL, as well as harms were not investigated. Therefore, the relative treatment effect of ivosidenib + azacitidine versus relevant comparators on patients' HRQoL and harms remains unknown.

Studies Addressing Gaps in the Evidence from the Systematic Review

No relevant studies addressing gaps in the evidence from the systematic review were submitted by the sponsor.

Testing Procedure Considerations

In AML, mutations in the IDH1 gene occur at conserved arginine residues within the enzymatic active site, specifically at the R132 codon. As per the intended indication of ivosidenib, adult patients with IDH1 R123 mutation-positive AML who are not eligible to receive intensive induction chemotherapy represent <5% of the total AML population. AML is considered the most aggressive form of leukemia, and according to the National Comprehensive Cancer Network guidelines and Canadian Cancer Society, first-line treatment should be initiated promptly to improve patient outcomes. Thus, identifying people with AML who have an IDH1 R132 mutation in an efficient and timely manner has potentially significant health impacts for individuals who may benefit from IDH1 R132-targeted therapy.

The availability, funding, and testing procedure used for IDH1 R132 mutation testing vary across jurisdictions within Canada. There are 2 pathways for IDH1 R132 mutation identification for people with AML. Next generation sequencing (NGS) is currently the standard of care testing for all AML-associated oncogenic driver mutation identification which includes IDH1 mutations, while polymerase chain reaction (PCR) testing can be used to identify specific single nucleotide variants of the IDH1 R132 codon. To receive IDH1 R132-targeted therapy, such as ivosidenib, an IDH1 R132 mutation would need to be confirmed using NGS or a PCR test. Both methods of testing use blood or bone marrow samples collected for diagnosis.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts, and sources from the literature were validated by the review team and are summarized in Table 4.

Table 4: Considerations for NGS or PCR testing for IDH1 R132 mutation for establishing treatment eligibility for ivosidenib in adult patients with IDH1 R132 mutation-positive AML who are not eligible to receive intensive induction chemotherapy

Consideration	Criterion	Available Information
Health System	Availability of the testing procedure in jurisdictions across Canada	Information from Ontario, British Columbia, and Quebec indicated that IDH1 testing is included as part of NGS panel testing for routine AML diagnosis testing. IDH1 testing is currently reimbursed in Ontario and funded through the provincial government in British Columbia. IDH1 R132 testing is not currently in use, or funded, for routine AML diagnosis in Manitoba. There are no publicly funded or private genetic testing facilities in the territories. No additional information could be obtained regarding IDH1 R132 testing or funding for within other provinces.
	Number of individuals in Canada expected to require the test (e.g., per year)	According to the clinical experts, each suspected person with AML should be tested for IDH1 mutations as part of routine AML stratification efforts. The most recent Canadian estimates suggest that approximately 1,160 new cases of AML were diagnosed in 2019 and according to the clinical experts, approximately 6 to 10% of those with diagnosed AML have an IDH1 mutation and may be eligible for IDH1 R132-targeted therapy.
	Testing procedure as part of routine care	According to the clinical experts, NGS testing that includes IDH1 is performed to risk-stratify patients as part of routine diagnostic practice in AML treatment centres in Ontario. British Columbia uses an NGS myeloid panel test as part of routine AML diagnostic testing, which can be used to identify IDH1 R132 mutations. IDH1 gene testing is included within 2 approved NGS panel tests in Quebec.
	Repeat testing requirements	One clinical expert indicated that repeat testing is not necessary for people with confirmed or suspected IDH1 R132 mutation-positive AML.
	Impact on health care human resources by provision of the testing procedure	For jurisdictions that do not conduct routine IDH1 R132 testing for people with AML, its implementation may have impacts on health system infrastructure including personnel, lab equipment, and genetic counselling for patient-related clinical decision-making. One clinical expert indicated that incorporating PCR testing for diagnosing an IDH1 R132 mutation may not have significant health system impacts due to established accessibility of PCR testing and a relatively low number of PCR tests that would be needed to identify and diagnose AML patients with an IDH1 mutation.
Patient-oriented	Accessibility of the testing procedure in jurisdictions across Canada	One clinical expert indicated that people living in remote or rural areas may encounter additional barriers such as timely access to testing and the need to ensure appropriate collection, management, and possible shipment of patient testing samples to testing centres for accurate results.
	Expected wait times for the testing procedure	According to the clinical experts, the turnaround time for IDH1 R132 testing should be approximately 3 to 5 days to confirm the status of an IDH1 R132 mutation. Rapid testing response time is important specifically for people with AML suspected of an IDH1 R132 mutation because identifying patients that are likely to benefit from first line IDH1 R132-targeted therapy could improve overall survival outcomes and avoid unnecessary exposure to treatment that is not specific to their mutation status.

Consideration	Criterion	Available Information
	Burden associated with the testing procedure for patients, families, and/or caregivers	Due to the expedited testing requirements, the testing process may be emotionally burdensome for some patients where adequate time to process the testing procedures and their implications may be limited. Generally, older AML patients (i.e., over 60 years old) require more inpatient care and are likely to encounter longer hospital stays thus impacting both the patient and their caregivers. Additional patient-related considerations include informed clinical decision-making, possible psychological impact of AML related testing, adequate communications of testing procedures and possible outcomes, and access to testing.
Clinical	Clinical utility of the testing procedure	According to the clinical experts, testing for a specific IDH1 R132 mutation using NGS or PCR testing would provide guidance on treatment decision-making to identify and determine patients who are likely to be eligible for IDH1 R132-targeted therapy. One exploratory study provided by the sponsor indicated that NGS can also provide information related to potential co-mutations, which may impact a patient's clinical response to treatment. Additionally, specific single nucleotide variants of the IDH1 R132 mutation identified by PCR testing may provide insight into patient treatment responses; however, given the small proportion of patients analyzed between study subgroups, any slight or modest differences should be interpreted with caution.
	Risks of harm associated with the testing procedure	No direct risk of harm was identified related to testing for IDH1 R132 mutations in people with AML.
Cost	Projected cost of the testing procedure	A 2015 publication by INESSS regarding the prognostic stratification of AML by NGS panel testing showed that the cost of analyzing 9 genes was estimated to be between $810 and $2040, or approximately $1000 to $2525 adjusted to 2023 CAD. The current cost of PCR testing using the Abbott RealTime IDH1 in vitro PCR assay test in Canada is not publicly available. Based on one US Medicare reimbursement code for the Abbott Realtime IDH1 PCR test, the estimated cost of a PCR test is $193.25 USD, or $262.32 CAD.

AML = acute myeloid leukemia; CAD = Canadian dollars; IDH1 = isocitrate dehydrogenase 1; INESS = institut national d'excellence en santé et services sociaux; NGS = next generation sequencing; PCR = polymerase chain reaction; USD = US dollars.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Adults with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy
Treatment	Ivosidenib in combination with azacitidine (AZA)
Dose regimen	500 mg of ivosidenib taken orally once daily for a 28-day cycle in combination with AZA at 75 mg/m^2 intravenously or subcutaneously, once daily on days 1 to 7 of each 28-day cycle. Patients should receive ivosidenib for a minimum of 6 cycles.
Submitted price	Ivosidenib: $332.60 per tablet

Component	Description
Submitted treatment cost	Ivosidenib: $16,616 per 28-day cycle[a,b]
Comparators	• AZA alone • Low-dose cytarabine (LDAC) • Venetoclax plus AZA
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years (QALYs), life-years (LYs)
Time horizon	Lifetime (25 years)
Key data source	Efficacy of ivosidenib plus AZA and AZA alone informed by AGILE; efficacy of venetoclax plus AZA and LDAC informed by a sponsor-submitted network meta-analysis.
Key limitations	• The comparative efficacy of ivosidenib plus AZA to comparators other than AZA is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor was insufficient to conclude whether clinical outcomes (e.g., OS, EFS, complete remission [with or without complete hematologic recovery] [CR/CRi]) differ between ivosidenib plus AZA and venetoclax plus AZA, which is currently the most commonly used treatment in the indicated population according to clinical input received by CADTH. • The sponsor assumed that patients who received ivosidenib plus AZA or venetoclax plus AZA and remained event free for at least 5 years were cured and to no longer be at risk of disease progression or relapse. Clinical expert feedback received by CADTH indicated that it is highly uncertain whether and when patients with IDH1-positive AML who are not eligible to receive intensive induction chemotherapy can be considered cured. • It is uncertain whether ivosidenib plus AZA will improve long-term clinical outcomes (i.e., beyond the observed trial data), and clinical experts consulted by CADTH noted that EFS and OS predicted by the sponsor's model are likely overestimated. Approximately 84% of the QALYs predicted by the sponsor's model to be gained with ivosidenib plus AZA were accrued after the AGILE trial on the basis of extrapolation. The extent of QALYs that will be gained with ivosidenib plus AZA and the magnitude of any incremental gain in EFS or OS compared with venetoclax plus AZA are highly uncertain. • Health state utility values lacked face validity, in that the values used by the sponsor suggest that patients in the EFS health state without CR/CRi will have lower health-related quality of life compared to those in the progressed disease health state. Clinical expert feedback indicated that patients would be expected to have higher health-related quality of life prior to disease progression or relapse regardless of whether CR/CRi is reached, compared to after progression or relapse. • The sponsor incorporated costs related to health care resource use in the economic model, with differences depending on the treatment received. Clinical expert feedback obtained by CADTH indicated that resource use is expected to be correlated with a patient's health state (i.e., event free, post-progression or relapse) and differences in resource use would be captured based on how long a patient stays in each health state. • The sponsor assumed that all patients with AML currently undergo genetic testing and that the introduction of ivosidenib (the first drug targeted to the IDH1 R132 mutation) would not increase the rate of genetic testing. Clinical expert input indicated that not all jurisdictions in Canada routinely test for genetic mutations at AML diagnosis and that IDH1 mutation testing would likely be implemented for all AML patients if ivosidenib is reimbursed. If the rate of genetic testing increases in some jurisdictions, costs associated with the reimbursement of ivosidenib will be higher than estimated in the sponsor's analysis. • The impact of adverse events (AEs) was not adequately considered, owing to the use of naïve comparison and different incidence thresholds to inform the economic model.

Component	Description
	• Relative dose intensity (RDI) was used to reduce drug costs; however, this assumes a direct link between RDI and drug cost which may not hold in practice. • The model lacked transparency due to numerous IFERROR statements. The systematic use of IFERROR statements made a throughout auditing of the sponsor's model impractical and therefore it remains unclear if the model is running inappropriately by overriding errors.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted an alternative cure assumption, alternative survival curves for EFS and OS, alternative health state utility values, removed treatment-specific myelosuppression resource use, and assumed 100% RDI for drug acquisition costs. Additionally, due to limitations with the sponsor's implemented probabilistic analyses, the CADTH reanalysis results are presented deterministically. • Results of the CADTH base case suggest that ivosidenib is more costly (incremental costs: $577,580) and more effective (incremental QALYs: 0.48) compared to venetoclax plus AZA, resulting in an ICER of $1,206,919 per QALY gained. • There is insufficient clinical evidence to justify a price premium for ivosidenib over venetoclax when used in combination with AZA for adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive intensive induction chemotherapy.

AML = acute myeloid leukemia; AZA = azacitidine; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; EFS = event free survival; ICER = incremental cost-effectiveness ratio; IDH1 = isocitrate dehydrogenase-1; LY = life-year; PSM = partitioned survival model; QALY= quality-adjusted life-year.

[a] Ivosidenib + AZA: $23,827 per 28-day cycle.

[b] Assuming 98.2% relative dose intensity

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA, including the exclusion of relevant comparators, uncertainty in the proportion of patients with AML with an IDH1 R132 mutation, and an underestimation of the market uptake of ivosidenib + azacitidine. The CADTH reanalysis adopted alternative market share estimates for ivosidenib + azacitidine. In the CADTH base case, the 3-year budget impact of reimbursing ivosidenib + azacitidine for the treatment of adult patients with newly diagnosed AML with an IDH1 R132 mutation who are not eligible to receive intensive induction chemotherapy is expected to be $21,105,093 (Year 1: $1,399,495; Year 2: $6,778,829; Year 3: $12,926,769). In practice, the budgetary impact of reimbursing ivosidenib for use in combination with azacitidine will be influenced by the proportion of patients with an IDH1 mutation.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: August 14, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None