CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

venetoclax (Venclexta)

Indication: In combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: July 2021
Report Length: 13 Pages

Single Technology

VENETOCLAX (VENCLEXTA— AbbVie Corporation)

Therapeutic Area: Acute Myeloid Leukemia

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that venetoclax in combination with azacitidine should be reimbursed for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One double-blind, randomized, placebo-controlled Phase 3 trial (VIALE-A, N= 431) of venetoclax plus azacitidine demonstrated prolonged survival and improved response rates in adult patients with newly diagnosed AML who were ineligible for standard induction chemotherapy due to age or comorbidities. After a median follow-up of 20.5 months, patients randomized to receive venetoclax (400 mg daily) plus azacitidine (75 mg/m2 azacitidine on days 1 through 7 of a 28-day cycle) showed a greater overall survival (OS) benefit compared to those who received azacitidine plus placebo (14.7 months versus 9.6 months), with a hazard ratio (HR) of 0.66 (95% confidence interval [CI] 0.52 to 0.85; p-value<0.001). The composite complete remission rate (complete remission with incomplete blood count recovery; CR+CRi) was 66.4% (95% CI 57.0 to 73.0%) in the venetoclax plus azacitidine group and 28.3% (95% CI 16.2% to 36.4%) in the placebo plus azacitidine group. Statistically significant treatment differences were also reported for event-free survival (EFS), transfusion independence rate, and secondary measures of disease response including complete remission (CR) and complete remission with incomplete hematological recovery (CR+CRh).

Patients identified a need for treatment options that could maintain remission, have fewer side effects, improve quality of life, and can be accessed closer to home or as an outpatient treatment in their geographic regions. Overall, pERC concluded that venetoclax plus azacitidine provides a treatment option for older patients and patients with comorbidities that has an impact on the disease and improves survival. However, it does not offer fewer side effects and must be initiated as inpatient therapy in medical facilities with experience and expertise in delivery of this type of treatment. While clinically meaningful differences in health-related quality of life were observed at individual time points in the trial, no definitive conclusion could be reached regarding the effects of venetoclax plus azacitidine on quality of life due to high rate of attrition over treatment cycles and the lack of a statistical testing for patient-reported outcomes.

In the absence of direct comparative evidence for all comparisons of interest, pERC considered indirect evidence from a network meta-analysis (NMA) comparing venetoclax plus azacitidine and venetoclax plus low-dose cytarabine (LDAC) with alternative treatments, and two propensity-score weighting comparisons of venetoclax plus azacitidine with LDAC. The results of NMA suggested that treatment with venetoclax plus azacitidine may be associated with improvements in OS and CR+CRi when compared with azacitidine, LDAC, and best supportive care (BSC), but did not detect a difference between venetoclax plus azacitidine and venetoclax plus LDAC on these same outcomes. pERC noted that the NMA results must be considered within the context of methodological limitations including heterogeneity between studies in potential treatment effect modifiers, sparse network, and the lack of adjustment for baseline covariates. Estimates from propensity score analyses were also considered to be at high risk of bias due to the small number of available patients and imbalances in unmeasured confounders.

Using the sponsor submitted price for venetoclax plus azacitidine and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for venetoclax plus azacitidine was $125,580 per quality-adjusted life-year (QALY) compared with low-dose cytarabine LDAC.

At this ICER, venetoclax plus azacitidine is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for patients with newly diagnosed AML for whom intensive chemotherapy is unsuitable or those who are age 75 years or older. The combination of venetoclax and azacitidine does not achieve a $50,000 per QALY threshold with a 100% reduction in the price of venetoclax. Venetoclax plus azacitidine is therefore not cost-effective at that threshold at any price.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Patients with AML who are considered ineligible for standard intensive induction chemotherapy are defined as either of the following: 1.1. Age 75 years or older and an ECOG performance status of 0 to 2 1.2. Age 18 to 74 years and fulfil at least one of the following: 1.2.1. ECOG performance status of 2 to 3 1.2.2. History of congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina 1.2.3. DLCO ≤65% or FEV1 ≤65% 1.2.4. Creatinine clearance ≥30 mL/min to 45 mL/min 1.2.5. Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 ULN	These conditions reflect the patient population enrolled in the VIALE-A trial. There is no evidence to support the safety and efficacy of venetoclax plus azacitidine in patients without any of these criteria.
2. Venetoclax plus azacitidine should be initiated in patients with no prior history of receiving a hypomethylating agent, venetoclax, or chemotherapy for MDS	No evidence was available to support the efficacy of venetoclax plus azacitidine in patients who previously received a hypomethylating agent (e.g., azacitidine) for treatment of MDS as such patients were excluded from the VIALE-A trial.
Renewal	
1. Venetoclax plus azacitidine should be reimbursed in patients who continue to receive clinical benefit from the treatment and do not have intolerable toxicity.	In the VIALE-A trial, treatment could continue as long as the patient derived clinical benefit and did not have documented disease progression or develop unacceptable toxicity.
2. For patients without unacceptable toxicity, it is recommended that patients be treated for a minimum of 6 cycles.	In the VIALE-A trial, the study treatments were planned for a minimum of six cycles.
Discontinuation	
1. Treatment with the venetoclax plus azacitidine should be discontinued upon the occurrence of any of the following: 1.1. Progressive disease (per ELN criteria) 1.2. Intolerable toxicity	These conditions correspond to the criteria used to determine whether treatment with venetoclax plus azacitidine should be discontinued in the VIALE-A trial.
2. If a patient stops treatment with the azacitidine component for reasons other than disease progression (e.g., toxicity or intolerance), venetoclax should also be discontinued.	The VIALE-A trial did not have a provision for patients to stop azacitidine and continue venetoclax or placebo. Therefore, the safety and efficacy of continuing on venetoclax monotherapy in patients who discontinue the azacitidine component of the treatment have not been established in the population under review.
Prescribing	
1. Venetoclax plus azacitidine should only be prescribed by clinicians who: 1.1. have expertise in diagnosis and management of patients with AML 1.2. are familiar with the toxicity profile associated with the venetoclax and azacitidine regimen.	This condition is required to ensure that venetoclax plus azacitidine is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.

Reimbursement Condition	Reason
Pricing	
1. Reduction in price	The ICER for venetoclax plus azacitidine is $125,580 per QALY gained when compared to LDAC. A 100% reduction in the price of venetoclax would still not achieve an ICER of $50,000 per QALY compared to LDAC. Azacitidine is more costly than LDAC and would also need to be reduced in price to reach this threshold.

AML = acute myeloid leukemia; DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; ELN criteria = European LeukemiaNet criteria; FEV1 = forced expiratory volume in one second; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; QALY = quality-adjusted life year; TLS = tumour lysis syndrome; ULN = upper limit of normal

Implementation Guidance

- The VIALE-A trial excluded patients with favourable cytogenetic risk (defined according to AML National Comprehensive Cancer Network [NCCN] guidelines). However, pERC agreed that all patients who are considered ineligible for treatment with intensive induction chemotherapy should be eligible for treatment with venetoclax plus azacitidine regardless of their cytogenetic risk.
- Patients ≥ 75 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status greater than 2 may be eligible for venetoclax plus azacitidine depending on whether their performance status is judged to be related to their AML; therefore, eligibility for venetoclax plus azacitidine should be determined for these patients on an individual basis.
- The clinical experts consulted by CADTH indicated that, in the clinical practice, a proportion of patients aged 75 years or older will be fit and eligible to receive intensive induction chemotherapy. PERC agreed that these patients could be treated with intensive induction chemotherapy as standard of care.
- Venetoclax plus azacitidine needs to be administered in hospitals and centres with expertise in the delivery of this type of treatment and patients may need to travel to receive care. pERC suggested that the jurisdictions may need to consider developing intra- and inter-provincial agreements and to ensure equitable access for eligible patients, including considerations for logistic support for required travel and short-term relocation.
- Intensive monitoring and prophylactic measures are required to minimize the risk of tumour lysis syndrome (TLS) with the use of venetoclax. TLS prophylaxis with anti-hyperuricemia agents (such as allopurinol, or hydroxyurea in patients with a high white blood cell count) should be administered prior to starting treatment and during the ramp up phase of treatment. Patients may periodically require hospitalization during the first month of treatment. Therefore, patients may need to remain within close proximity of a hospital for the first month of therapy to appropriately manage potential toxicities.
- Clinical experts indicated that, in clinical practice, azacitidine is usually administered on a 5-2-2 dosing schedule. There is evidence demonstrating that there is no difference in clinical outcome of the treatment based on the dosing scheduled used (i.e., 5-2-2, 6 and 7 consecutive days). Therefore, pERC agreed that reimbursement of venetoclax would be appropriate with alternative azacitidine dosing schedules.
- There is no evidence to inform on the appropriate time frame to consider adding venetoclax to the treatment regimen of patients who are currently on azacitidine receiving single agent azacitidine. The clinical experts consulted by CADTH noted that clinicians typically give up to 6 cycles (i.e., 6 months) of single agent azacitidine to determine a patient's response to therapy. Therefore, pERC agreed that it would be reasonable to add venetoclax to azacitidine if the patient is within the 6-month timeframe of initiating azacitidine and has not progressed.

Discussion Points

- The clinical experts consulted by CADTH indicated that intensive induction therapy with cytarabine and an anthracycline is the standard treatment for patients with newly diagnosed AML, who are medically fit. However, a substantial proportion of patients with AML are ineligible for induction chemotherapy due to frailty associated with age or comorbidities. Patients who are ineligible for induction chemotherapy may be treated with hypomethylating agents, such as azacitidine, or low dose cytarabine, but rates of complete remission are low, and duration of remission tends to be short. pERC agreed with the

clinical experts and patient groups providing input to this submission that there is an unmet need for better treatment options for older patients with AML that are ineligible for induction chemotherapy.

- pERC deliberated the results of the VIALE-A trial that indicated venetoclax plus azacitidine improved most outcome measures that were identified as of interest to clinicians and patients. Statistically significant treatment differences were reported in the VIALE-A trial for OS, EFS, measures of disease response (CR+CRi, CR+CRh, CR), and post-baseline transfusion independence. Improvements in OS and CR+CRi were also reported in the subgroup of patients with IDH1 or IDH2 mutation, and improvement in CR+CRi was reported for patients with FLT3 mutations.
- pERC deliberated the toxicity profile of venetoclax plus azacitidine and noted that, compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, dose interruptions, or AEs leading to death. However, pERC agreed with the clinical experts that common harms in all categories were generally predictable from the known mechanism of action for venetoclax and/or azacitidine and the underlying disease.
- In the absence of direct comparative evidence for all comparator treatments of interest, pERC considered indirect evidence from a NMA that demonstrated favorable OS and CR+CRi results for venetoclax plus azacitidine over azacitidine, LDAC, and BSC, but did not detect a statistically significant difference between venetoclax plus azacitidine and venetoclax plus LDAC on these same outcomes. Results from two propensity score weighting analyses were also included in the review which used OS, EFS, and CR+CRi data from the VIALE-A and VIALE-C trials to compare venetoclax plus azacitidine to LDAC and azacitidine. The propensity score analyses suggested that venetoclax plus azacitidine could improve OS, EFS and CR+CRI when compared to LDAC, and improve OS when compared with azacitidine alone. pERC noted that small study sizes and potential for bias limit the interpretation of these indirect treatment comparison results.
- The patient input submitted for this review indicated that AML has a significant impact on quality of life of patients, their social life as well as the quality of life of their families, and that the current standard therapies for newly diagnosed AML are associated with toxicities and significant impact on quality of life. Patients desired treatment options with fewer side effects that can delay disease progression, improve quality of life, and can be accessed closer to home or as an outpatient treatment in their geographic regions. Overall, pERC concluded that venetoclax plus azacitidine provides a treatment option that has an impact on disease and improves survival. However, it does not offer fewer side effects and it must be initiated as an inpatient therapy in a medical centre with experience and expertise in the prevention and management of TLS. In patients who do not have any side effects after initiation of venetoclax, it may be possible for subsequent cycles to be initiated at a community cancer site that is able to deliver treatment with azacitidine. pERC considered that clinically meaningful differences were observed in the VIALE-A trial for patient-reported outcomes of global health status and fatigue at individual assessment points. However, the committee agreed with the CADTH review team that differences between treatment groups were uncertain due to methodological limitations.
- pERC discussed the use of venetoclax plus azacitidine as a bridge to allogeneic stem cell transplant (SCT) in patients with AML who have a contraindication to chemotherapy but are otherwise candidates for an allogeneic SCT. Clinical experts consulted by CADTH indicated that patients with a contraindication to chemotherapy rarely proceed to allogeneic SCT, but it may happen in some circumstances (e.g., for patients who have an ejection fraction of less than 50% and hence have a comorbidity that renders them ineligible for intensive chemotherapy). Allogeneic SCT could be considered as an option in these patients if they achieve a response to venetoclax plus azacitidine. pERC noted that further evidence is required to better understand the efficacy and safety of venetoclax plus azacitidine as a bridge to allogeneic SCT.
- Patients who previously received azacitidine for treatment of myelodysplastic syndrome (MDS) were excluded from the VIALE-A trial but were included in the VIALE-C trial that evaluated the efficacy and safety of venetoclax plus LDAC in adult patients with newly diagnosed AML who were ineligible for standard induction chemotherapy. Clinical experts noted that there is non-comparative clinical trial evidence that suggests patients previously treated with azacitidine for MDS may benefit from venetoclax plus azacitidine; the response rate, although lower than what has been observed in patients without prior exposure to azacitidine, is comparable to the response rate observed in the VIALE-C trial among patients who had prior exposure to a hypomethylating agents (HMA) and were treated with venetoclax plus LDAC. Based on these data, it would be reasonable to consider the use of venetoclax plus azacitidine in patients with a history of treatment with a HMA for MDS.
- pERC noted that the presence of TP53 gene mutations is regarded as a factor for poor prognosis in AML patients, and that response to the standard induction chemotherapy is low in these patients. pERC discussed that venetoclax plus azacitidine combination has been used to improve response rates patients with TP53-mutated AML. Therefore, pERC suggested that venetoclax plus azacitidine could be considered as a treatment option in patients with TP53 mutations.

- In exploratory analysis, a 72% reduction in the price of venetoclax plus azacitidine as a combination therapy achieved a threshold of $50,000 per QALY. The pharmacoeconomic model for venetoclax plus azacitidine appeared to produce a bias in favour of venetoclax plus azacitidine that could not be addressed in reanalysis. As such, the ICER and exploratory price reduction are likely underestimated.
- The pharmacoeconomic analysis, including the estimate of price reduction, are based on publicly available list prices for all drugs including azacitidine. This may be larger than the price paid by participating drug plans. As a result, CADTH's estimates of the ICER and price reduction associated with venetoclax plus azacitidine compared to LDAC are likely overestimated.
- The sponsor did not consider induction chemotherapy as a comparator in their pharmacoeconomic model, based on an assertion that patients over 75 years would not be eligible to receive it. Feedback from clinical experts suggested that age is not a necessary component of IC eligibility. Consequently, the cost-effectiveness of venetoclax plus azacitidine compared to induction chemotherapy is unknown in patients over 75 years of age.

Background

Venetoclax in combination with azacitidine (a hypomethylating agent) has a Health Canada indication for adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Venetoclax is an orally-administered highly selective inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (BCL2) and is available as 10 mg, 50 mg, 100 mg tablets. The Health Canada approved dose of venetoclax in combination with azacitidine is 400 mg/day for each day of a 28 day cycle, following a three-day ramp up; azacitidine is to be administered at 75 mg/m2 for days 1 to 7 of the cycle. Dose adjustments are required in patients treated with strong and moderate inhibitors of CYP3A enzymes.

Sources of Information Used by the Committee

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

- A review of one Phase 3 randomized controlled trial in adult patients ineligible for standard induction chemotherapy due to age or comorbidities
- Patients' perspectives gathered by one patient group, the Leukemia and Lymphoma Society of Canada (LLSC)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise diagnosing and treating patients with AML
- Input from four clinician groups, including the Canadian Leukemia Study Group (CLSG), the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO Hem-DAC), the Leukemia/Bone Marrow Transplant (L/BMT) Program of BC, and the Alberta Tumour Board Myeloid Physicians Group
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by Canadian patient and clinician groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient advocacy group (LLSC) provided input on venetoclax in combination with azacitidine for the treatment of AML. The LLSC used an online survey for its submission, which was conducted between December 7, 2020 and January 24, 2021. Twenty-nine patients responded, all from Canada, five of whom had experience with venetoclax in combination with azacitidine.

Many patients did not provide information on specific symptoms but described being diagnosed with AML as a life-changing event that affected not only themselves but their caregivers. Some patients needed to relocate to access treatment. Side effects of treatment, transfusion dependence and hospital admissions had a large impact on patients' quality of life, as did isolation due to their vulnerability to infection. Patients reported the desired characteristics of treatment options as those that could maintain remission, were targeted with fewer side effects, covered by public plans, and accessible in their geographic regions.

Clinician input

Input from clinical experts consulted by CADTH

The experts indicted that currently available lower intensity treatments have low rates of complete remission; and complete remissions that are produced are not durable. They indicated that venetoclax plus azacitidine (or other hypomethylating agent) would change the current treatment paradigm, becoming the new standard of care for patients with treatment naive AML who were ineligible for standard induction therapy, and an option for patients aged 75 years or older who were eligible for intensive chemotherapy, following discussion about risks and benefits.

The experts indicated that at this time there is insufficient information to make treatment decisions based on disease characteristics, and that while certain subgroups had been excluded from clinical trials, such as patients with CNS involvement, they might reasonably be expected to benefit. The experts indicated that current evidence does not fully support the use of venetoclax plus azacitidine in fit patients eligible for standard induction treatment or patients aged ≥ 75 years with good cytogenetic risk (core binding factor) AML who were fit for intensive induction chemotherapy, and their opinions differed in its suitability for patients with relapsed or refractory disease.

The experts indicated that response to treatment would be determined by achievement of complete remission with or without complete hematological recovery as measured by CBC and bone marrow biopsy and/or transfusion independence or stable disease. Overall survival and hospital visits, transfusion needs, and quality of life were the most important endpoints. Assessment of response could be carried out after the first or second cycle.

The experts indicated that discontinuation of treatment might be determined by disease progression or intolerable adverse events but could not comment whether single agent venetoclax could be continued after azacitidine discontinuation. One respondent indicated bone marrow biopsy should be performed after the first and second cycles of treatment, as response would be expected after a maximum of two cycles. Another indicated that response should be assessed at minimum after four to six cycles, but that most practitioners assess after the first cycle given cost and to guide dosing of venetoclax for subsequent cycles.

The experts indicated that treatment should be given in a hospital or outpatient setting, by a physician with experience in looking after acute leukemia patients. Pharmacist involvement would be needed for management of drug interactions (e.g., azoles). Hospitalization might be required for venetoclax dose ramping up, with prophylaxis for tumour lysis syndrome, and the need for admission to manage neutropenic fever and other complications during therapy should be anticipated.

Clinician group input

Four clinician groups provided input: CLSG, OH-CCO's Hem-DAC, L/BMT Program of BC, and the Alberta Tumour Board Myeloid Physicians Group.

There were no substantive differences in opinions between the clinical experts consulted by CADTH and the clinical groups. The groups noted that patients are aware of venetoclax and azacitidine, and some patients have been "self-funding" venetoclax with the use of CYP3A inhibitors to reduce the dose, and thereby cost of venetoclax.

Drug program input

The drug programs indicated that current treatment options for patients with newly diagnosed AML who are ineligible for intensive chemotherapy include azacitidine, LDAC, and best supportive care. The reimbursement of venetoclax plus azacitidine would likely replace single agent azacitidine in this treatment setting. Azacitidine is funded in most jurisdictions for patients with AML who are ineligible for intensive chemotherapy, and some jurisdictions fund alternate dosing schedules for azacitidine (i.e., 5-2-2, and 6 consecutive days) in addition to the 7 consecutive day schedule. However, it was noted that some patients 75 years of age and older may be fit to tolerate intensive chemotherapy. The ramp up dosing schedule for venetoclax with azacitidine differs significantly from the ramp up dosing schedule already in use for chronic lymphocytic leukemia (CLL) indications and the current packaging for venetoclax is designed for the CLL ramp up dosing schedule. Venetoclax plus azacitidine includes an oral and an intravenous/subcutaneous drug and therefore would be reimbursed through different programs in some jurisdictions. The drug programs identified the potential for indication extension for patients with a high-risk of MDS, those who have progressed or have

had an inadequate response on low dose chemotherapy for AML, and patients who have relapsed after induction chemotherapy and are not eligible for SCT and are then treated with azacitidine. It was noted that treatment combination may require the need for increased health care resources (i.e., hospital admission and additional pharmacy and nursing resources for the potential management TLS and monitoring for drug interactions). Affordability was also identified as an issue since the combination is expected to replace azacitidine monotherapy.

Clinical experts were consulted by CADTH for questions related to the implementation of venetoclax plus azacitidine into current provincial drug plans. Overall, most implementation questions related to the dosing schedule and administration and the eligible patient population.

Clinical Evidence

Clinical Trials

One double-blind, placebo-controlled Phase 3 randomized controlled trial (VIALE-A) contributed evidence to this review. The trial objective was to evaluate the efficacy and safety of venetoclax plus azacitidine compared with placebo plus azacitidine in adults with newly diagnosed AML who were 18 years or older and ineligible for standard induction therapy due to age or comorbidities. The trial was restricted to patients who had not previously been treated with a hypomethylating agent and who had intermediate or poor risk cytogenetics. The primary outcomes were OS and composite complete remission rate (complete remission with incomplete blood count recovery CR+CRi). Secondary outcomes were complete remission (CR), Complete remission with incomplete hematological recovery (CR+CRh), rate of CR+CRi by the initiation of Cycle 2, transfusion independence rate, minimal/measurable disease (MRD) response rate, response rates and OS in molecular subgroups, fatigue and global health status/QoL, and EFS.

A total of 431 patients were randomized in a 2:1 ratio, 286 to venetoclax (400 mg daily) plus azacitidine (75 mg/m^2 on days 1 through 7 of a 28-day cycle) and 144 to placebo plus azacitidine. The most common reasons given for patients to be considered ineligible for standard induction therapy were age and ECOG performance status. Patients were elderly, with poor performance, and markers of severe disease. The mean age was 75.4 years, with 60.6% aged 75 years or older. Almost all patients were White or Asian, and the majority of patients were male (60.1%). Most (75.2%) had de novo rather than secondary AML. Nearly two-thirds had intermediate risk cytogenetics and one third had poor risk, and half had bone marrow blasts ≥50% at baseline.

Efficacy Results

Venetoclax plus azacitidine improved most outcome measures that were identified as of interest to clinicians and patients. Statistically significant treatment differences were seen for OS, EFS, measures of disease response (CR+CRi, CR+CRh, CR), and post-baseline transfusion independence. After a median follow-up of 20.5 months, patients randomized to receive venetoclax (400 mg daily) plus azacitidine (75 mg/m2 azacitidine on days 1 through 7 of a 28-day cycle) showed a greater overall survival (OS) benefit compared to those who received azacitidine plus placebo (14.7 months versus 9.6 months), with a hazard ratio (HR) of 0.66 (95% confidence interval [CI] 0.52 to 0.85; p-value<0.001). The composite complete remission rate (CR + CRi) was 66.4% (95% CI 57.0 to 73.0%) in the venetoclax plus azacitidine group and 28.3% (95% CI 16.2% to 36.4%) in the placebo plus azacitidine group. Venetoclax plus azacitidine improved EFS over placebo plus azacitidine, with a median EFS of 9.8 months versus 7.0 months (HR 0.632, 95% CI 0.502 to 0.796; p-value<0.001).

Improvements also seen for OS and CR+CRi in the subgroup of patients with IDH1 or IDH2 mutation, and for CR+CRi for patients with FLT3 mutations. No statistically significant difference was detected in OS for patients with FLT3 mutations, however, the subgroup was small, making it difficult to detect a difference. While clinically meaningful differences in patient-reported outcomes of global health status and fatigue were observed at individual endpoints, differences between treatment groups cannot be interpreted because the sequential testing strategy failed prior to this level.

Harms Results

All patients in both groups experienced at least one adverse event, and almost all experienced at least one adverse event of grade ≥3. Compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced one or more SAEs, one or more AEs leading to discontinuation or dose interruption for venetoclax or

placebo or azacitidine, or one or more AEs leading to death. Common harms in all categories are generally predictable from the known mechanism of action for venetoclax and/or azacitidine and the underlying disease. Cytopenias were common, with neutropenia, febrile neutropenia, thrombocytopenia, and anemia represented across all categories, as were gastrointestinal adverse effects. Febrile neutropenia and infections contributed substantially to most common serious adverse events and were the most frequent adverse events leading to death.

The notable harms as identified for the protocol were neutropenia, febrile neutropenia, infections, tumour lysis syndrome, hemorrhage, and secondary malignancies. Neutropenia, febrile neutropenia, infections and infestations, and secondary primary malignancies all occurred in a greater proportion of patients who received venetoclax plus azacitidine than patients who received placebo plus azacitidine. Hemorrhage and tumour lysis syndrome occurred in similar proportions, and the proportion of patients with tumour lysis syndrome was low (≤2.5%). The most common secondary malignancies were basal cell carcinoma and squamous cell carcinoma of skin.

Critical Appraisal

The study was well-conducted, with no clinically meaningful imbalance in baseline characteristics, minimal loss to follow-up and collection of endpoints that were standardized and meaningful to patients. Multiplicity was controlled throughout testing of primary and secondary efficacy endpoints, with prespecified strategies for testing of endpoints. The overall rate of discontinuations from the study were low and assumptions surrounding missing data were conservative for most endpoints. Interpretation of patient reported outcome data is limited due to attrition of numbers over cycles.

Generalizability concerns that were identified included the assumption that patients ≥75 years would not be eligible for standard induction therapy and the limitation in the use of venetoclax or azacitidine to settings that could provide monitoring and supportive care. In the Canadian setting patients aged ≥75 years would be considered for treatment if they were medically fit, especially if they had good or intermediate risk cytogenetics. Patients from rural and remote Canadian settings would have to travel for care, or would be limited to other treatment options.

Indirect Comparisons

Description of studies

A systematic review was conducted of trials comparing venetoclax plus azacitidine, venetoclax plus low-dose cytarabine, azacitidine, low-dose cytarabine and best supportive care in adults with AML who were not eligible for standard induction chemotherapy. Three indirect treatment comparison analysis were conducted, NMA and two propensity score weighting analyses which compared venetoclax plus azacitidine to low-dose cytarabine and azacitidine to low-dose cytarabine. For the NMA, HR data were available for OS for four trials in a connected network and proportions of patients responding for CR+CRi for three trials. For the propensity score weighting analysis, data were available for OS, EFS, and CR+CRi from VIALE-A and the low-dose cytarabine group form VIALE-C.

Efficacy Results

In the NMA, the results favoured lower hazard of death for patients assigned to venetoclax plus azacitidine compared with azacitidine (HR 0.66, 95% credible interval [CrI] 0.52 to 0.85), low-dose cytarabine (HR 0.57, 95% CrI 0.40 to 0.81), and best supportive care (HR 0.37, 95% CrI 0.24 to 0.58), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus low-dose cytarabine (HR 0.81, 95% CrI 0.50 to 1.31). For CR+CRi, venetoclax plus azacitidine was favoured over azacitidine (odds ratio [OR] 5.05, 95% CrI 3.30 to 7.87), low-dose cytarabine (OR 5.42, 95% CrI 2.80 to 10.50), and best supportive care (OR 61.55, 95% CrI 8.23 to 1881.53), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus low-dose cytarabine (OR 0.86, 95% CrI 0.30 to 2.35).

In the first propensity score analysis, venetoclax plus azacitidine was favoured over low-dose cytarabine, for OS (HR 0.50, 95% CI 0.35 to 0.73), EFS (HR 0.40, 95% CI 0.28 to 0.58), and CR+CRi (OR 10.17, 95% CI 4.55 to 22.73). In the second propensity score analysis for OS, venetoclax plus azacitidine was favoured over low-dose cytarabine (HR 0.52, 95% CrI 0.36, 0.77) and azacitidine (HR 0.64, 95% CrI 0.50, 0.82), and no statistically significant difference was seen between azacitidine and low-dose cytarabine (HR 0.78, 95 CrI 0.52 to 1.17). For EFS, venetoclax plus azacitidine was favoured over azacitidine (HR 0.62, 95% CrI 0.49 to 0.77) and

low-dose cytarabine (HR 0.41, 95% CrI 0.29 to 0.59), and azacitidine was favoured over low-dose cytarabine (HR 0.63, 95% CrI 0.43, 0.92). For CR+CRi, venetoclax plus azacitidine was favoured over azacitidine (OR 5.02, 95% CrI 3.24 to 7.77) and low-dose cytarabine (OR 9.69, 95% CrI 4.30 to 21.85), and no statistically significant difference was seen between azacitidine and low-dose cytarabine (OR 1.93, 95% CrI 0.82 to 4.54).

Harms Results

No analysis of harms was included in the indirect comparisons.

Critical Appraisal of Indirect Comparisons

A key limitation of the NMA was the clinical heterogeneity between studies in potential treatment effect modifiers of blast-count at baseline, prior treatment of HMAs, and cytogenetic risk. As the network was sparse, fixed-effects models had to be used, and there was no opportunity for baseline covariate adjustments. Due to the above limitations the comparative efficacy estimates may be biased, and it is not possible to quantify or identify the direction of the bias. Certain estimates, particularly for CR+CRi, were imprecise due to sparse data. In the propensity score analyses, weighting was generally good, but the relatively small numbers of patients in the LDAC comparator group limited the number of covariates that could be included in the model. The comparisons were not randomized and the results were highly susceptible to bias due to imbalances in unmeasured confounders.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost utility analysis Partitioned survival model.
Target population	Patients with newly diagnosed AML for whom intensive chemotherapy (IC) is unsuitable or who are 75+ year or older.
Treatment	Venetoclax in combination with azacitidine (Ven + Aza)
Submitted drug price	Venetoclax, 100 mg tablet: $70
Cost per course	The total drug acquisition cost per patient for the first 28-day cycle of Ven + Aza is $15,890 (venetoclax: $7,490 azacitidine: $8,400 and $16,240 (venetoclax: $7,840; azacitidine: $8,400) for subsequent 28-day cycles, based on a venetoclax unit price of $70 per 100 mg tablet. The total drug acquisition cost per patient for each 28-day cycle of LDAC was $769. The total drug acquisition cost per patient for each 28-day cycle of azacitidine monotherapy was $8,400.
Comparators	Azacitidine (Aza) alone Low-dose cytarabine (LDAC) Best supportive care (BSC)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime horizon (to 90 years of age)
Key data source	VIALE-C, VIALE-A trial and a network meta analysis (NMA)
Submitted results	• Based on the sequential analyses, the optimal treatments (i.e., on the cost effectiveness frontier) are BSC, LDAC, and Ven + Aza. • ICER for Ven + Aza when compared to LDAC was $105,286 per QALY gained (1.59 incr. QALYs and $167,432 incr. costs).

Component	Description
Key limitations	• The sponsor excluded IC as a comparator. Clinical experts consulted for this review indicated that individuals older than 75 would be eligible to receive IC. • The sponsor incorporated a cure assumption for individuals who remain in the CR/CRi health state for more than 5 years. Clinical experts indicated that this assumption was unlikely to be correct. • A substantial portion of the QALY benefits of Ven + Aza occurred after individuals exited the event-free state (EFS) state and were no longer on first line treatment. Clinical experts indicated that there was unlikely to be a substantive benefit for individuals who receive Ven + Aza after exiting the EFS health state. • In the sponsor's model, EFS and the duration of first-line treatment were estimated independently. It is likely that EFS and treatment duration are highly correlated. • There exists substantial uncertainty surrounding the effectiveness of Ven + Aza beyond the follow-up of the VIALE-A trial.
CADTH reanalysis results	• CADTH reanalyses included: estimates for OS curves limiting the benefit of Ven + Aza post EFS; and, a cure assumption for those who remain in the CR/CRi health state for more than 10 years. In addition to the above modifications, CADTH conducted several scenario analyses to quantify the uncertainty surrounding the CADTH base case. These scenario analyses included: all individuals in the EFS health state being on treatment; and, varying estimates of OS for Ven + Aza. CADTH was not able to address the exclusion of IC as a comparator. • In the sequential analysis, Ven + Aza was associated with an ICER of $125,580 per QALY compared to LDAC; LDAC was associated with an ICER of $72,232 per QALY compared to BSC. Aza was dominated by other options in the sequential analysis. • The probability that Ven + Aza was cost-effective at a $50,000 WTP threshold compared to LDAC was 0%.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- There was uncertainty with several epidemiological inputs used to derive the market size.
- The sponsor's market share uptake assumptions of venetoclax in the new drug scenario does not reflect the expectations of the clinical experts consulted for this review. The estimated market shares remain uncertain with the potential availability of venetoclax in combination with low dose cytarabine.

The CADTH reanalyses included revising market share estimates for venetoclax in the new drug scenario, revising the epidemiological inputs to derive the market size, allowing for drug wastage; removing patient co-payments, and aligning BIA model inputs to those applied in the pharmacoeconomic analysis.

Based on the CADTH reanalysis, the budget impact from the venetoclax in combination with azacitidine would result in an incremental budget impact of $16,784,064 in Year 1, $21,182,961 in Year 2, and $32,039,516 in Year 3, for a total budget impact of $70,006,541. The results were primarily driven by the market share uptake of venetoclax plus azacitidine, number of patients eligible for treatment, and proportion of patients ineligible for induction chemotherapy.

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. Avram Denburg, 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.

June 10, 2021 Meeting

Regrets

None

Conflicts of Interest

None

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.