

CADTH Reimbursement Recommendation

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

Sponsor: AbbVie Corporation

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Venclexta in Combination With Azacitidine?

CADTH recommends that Venclexta 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 certain conditions are met.

What Are the Conditions for Reimbursement?

Venclexta plus azacitidine should only be reimbursed if prescribed by clinicians who have expertise in managing patients with AML and are familiar with the toxicity profile of this regimen, and if the costs of Venclexta and azacitidine are reduced.

Which Patients Are Eligible for Coverage?

Venclexta plus azacitidine should only be covered to treat adult patients who are considered ineligible for standard intensive induction chemotherapy and have not been treated with venetoclax or chemotherapy for myelodysplastic syndrome.

Why Did CADTH Make This Recommendation?

- One clinical study showed Venclexta plus azacitidine prolonged life (a need important to patients) and improved treatment response rates compared to placebo plus azacitidine.
- Based on public list prices, Venclexta plus azacitidine is not considered cost-effective versus low-dose cytarabine at a willingness to pay (WTP) of \$50,000 per quality-adjusted life-year (QALY).
- Economic evidence suggests Venclexta plus azacitidine would not reach this WTP threshold even with a 100% price reduction in Venclexta. A price reduction of 72% in both Venclexta and azacitidine would be required to reach this threshold.
- Based on public list prices, the 3-year budget impact is \$70,006,541.

Additional Information

What Is AML?

AML, a cancer of the blood and bone marrow, leads to decreased mature blood cells. AML is most common in older adults (average 67 years) and typically has a poor prognosis; 25% to 40% of patients over age 60 are expected to be alive after 3 years. In 2016, 1,090 Canadians were diagnosed with AML.

Unmet Needs in AML

Current treatments may have several side effects and limited effectiveness. There is a need for treatments that prolong survival, maintain remission, and have an acceptable side effect profile and favourable impact on quality of life.

How Much Does Venclexta Cost?

Treatment with Venclexta plus azacitidine is expected to cost \$15,890 for the first 28-day cycle and \$16,240 per 28-day cycle thereafter.

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 III 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 with 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 < 0.001). The composite complete remission rate (complete remission [CR] plus 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 CR plus 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 be accessed closer to home or as an outpatient treatment in their geographic regions. Overall, pERC concluded that venetoclax plus azacitidine provides older patients and patients with comorbidities with a treatment option 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. Although 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 a 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 2 propensity score-weighting comparisons of venetoclax plus azacitidine with LDAC. The results of the 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 no difference between venetoclax plus azacitidine and venetoclax plus LDAC was detected for 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, a 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 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. Therefore, venetoclax plus azacitidine is not cost-effective at that QALY threshold at any price.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
<p>1. Patients with AML who are considered ineligible for standard intensive induction chemotherapy are defined as either of the following:</p> <p>1.1. Age 75 years or older with an ECOG performance status of 0 to 2</p> <p>1.2. Age 18 to 74 years and fulfill at least 1 of the following:</p> <p>1.2.1. ECOG performance status of 2 to 3</p> <p>1.2.2. history of congestive heart failure requiring treatment, ejection fraction $\leq 50\%$, or chronic stable angina</p> <p>1.2.3. DLCO $\leq 65\%$ or FEV₁ $\leq 65\%$</p> <p>1.2.4. creatinine clearance ≥ 30 mL/min to 45 mL/min</p> <p>1.2.5. moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 ULN</p>	<p>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.</p>
<p>2. Venetoclax plus azacitidine should be initiated in patients with no prior history of receiving a hypomethylating agent, venetoclax, or chemotherapy for MDS</p>	<p>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 because these patients were excluded from the VIALE-A trial.</p>
Renewal	
<p>3. Venetoclax plus azacitidine should be reimbursed in patients who continue to receive clinical benefit from the treatment and do not have intolerable toxicity.</p>	<p>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.</p>
<p>4. For patients without unacceptable toxicity, it is recommended that patients be treated for a minimum of 6 cycles.</p>	<p>In the VIALE-A trial, the study treatments were planned for a minimum of 6 cycles.</p>

Reimbursement condition	Reason
Discontinuation	
5. Treatment with the venetoclax plus azacitidine should be discontinued upon the occurrence of any of the following: 5.1. progressive disease (per ELN criteria) 5.2. 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.
6. 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	
7. Venetoclax plus azacitidine should only be prescribed by clinicians who: 7.1. have expertise in diagnosis and management of patients with AML 7.2. are familiar with the toxicity profile associated with the venetoclax plus 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.
Pricing	
8. 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 = European LeukemiaNet; FEV₁ = forced expiratory volume in 1 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 a favourable cytogenetic risk (as defined according to AML National Comprehensive Cancer Network 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 aged 75 years or older 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 clinical practice, a proportion of patients aged 75 years or older would 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; therefore, 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 (e.g., allopurinol; hydroxyurea for patients with a high white blood cell count) should be administered before 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 to a hospital for the first month of therapy to appropriately manage potential toxicities.
- The clinical experts consulted by CADTH indicated that, in clinical practice, azacitidine is also 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 about the appropriate time frame to consider adding venetoclax to the treatment regimen of patients who are currently 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 within the 6-month time frame of initiating azacitidine if the patient's disease has not progressed.
- pERC discussed the public drug plans' request for clarity on the eligibility of patients with high-risk myelodysplastic syndrome (MDS), who are not fit for intensive induction chemotherapy, to receive venetoclax plus azacitidine as part of upfront treatment. pERC did not review any evidence for the use of venetoclax plus azacitidine in patients with high-risk MDS because this was out of the scope of this review.
- Patients who previously received azacitidine for treatment of MDS were excluded from the VIALE-A trial but were included in the VIALE-C trial which evaluated the efficacy and safety of venetoclax plus LDAC in adult patients with newly diagnosed AML who were ineligible for standard induction chemotherapy. The clinical experts consulted by CADTH 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 that 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 (HMAs) and were treated with venetoclax plus LDAC. Based on these data, the use of venetoclax plus azacitidine could be considered 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 standard induction chemotherapy is low in these patients. pERC discussed that the venetoclax plus azacitidine combination has been used to improve response rates in patients with *TP53*-mutated AML. Therefore, pERC suggested that venetoclax plus azacitidine could be considered as a treatment option in patients with *TP53* mutations.

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 HMAs, such as azacitidine, or LDAC, but CR rates 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 who are ineligible for induction chemotherapy.
- pERC deliberated the results of the VIALE-A trial which 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* mutations, 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 an NMA that demonstrated favourable 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 2 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, and 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 desire 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.
- 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. A reduction greater than 60% in the price of venetoclax would be needed for venetoclax plus azacitidine to be cost-effective compared to azacitidine monotherapy at that threshold. 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 higher 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 older than 75 years would not be eligible to receive it. Feedback from the clinical experts suggested that age is not a necessary component of eligibility for induction chemotherapy. Consequently, the cost-effectiveness of venetoclax plus azacitidine compared with induction chemotherapy is unknown in patients older than 75 years of age.

Background

Venetoclax in combination with azacitidine (an HMA) 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 and is available as 10 mg, 50 mg, and 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 3-day ramp-up; azacitidine is to be administered at 75 mg/m² for days 1 to 7 of the cycle. Dose adjustments of venetoclax are required for patients receiving medications that are 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 1 phase III randomized controlled trial in adult patients ineligible for standard induction chemotherapy due to age or comorbidities
- patients' perspectives gathered by 1 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
- 2 clinical specialists with expertise diagnosing and treating patients with AML
- input from 4 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 British Columbia, 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, 5 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, had fewer side effects, were covered by public plans, and were accessible in their geographic regions.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The experts indicated that currently available lower-intensity treatments have low rates of CR, and the CRs that are produced are not durable. They indicated that venetoclax plus azacitidine (or another HMA) would change the current treatment paradigm, and become the new standard of care for patients with treatment-naive AML who were ineligible for standard

induction therapy, and be 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 although 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 or older with AML with good cytogenetic risk (core binding factor) 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 CR 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 end points. 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 AEs, but they could not comment on whether single-agent venetoclax could be continued after azacitidine discontinuation. One expert indicated bone marrow biopsy should be performed after the first and second cycles of treatment because response would be expected after a maximum of 2 cycles. Another indicated that response should be assessed after a minimum 4 to 6 cycles, but that most practitioners assess after the first cycle given costs and to guide the dosing of venetoclax in subsequent cycles.

The experts indicated that treatment should be given in a hospital or outpatient setting, by a physician with experience treating acute leukemia patients. Pharmacist involvement would be needed for management of drug interactions (e.g., azoles). Hospitalization might be required during venetoclax dose ramp-up and prophylaxis for TLS; 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 Hem-DAC, L/BMT Program of British Columbia, 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 BSC. 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 plus azacitidine differs significantly from the ramp-up dosing schedule already in use for chronic lymphocytic leukemia indications and the current packaging for venetoclax is designed for the chronic lymphocytic leukemia ramp-up dosing schedule. Venetoclax plus azacitidine includes an oral and an IV and/or 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 need increased health care resources (i.e., hospital admission and additional pharmacy and nursing resources for the potential management of TLS and monitoring for drug interactions). Affordability was also identified as an issue because 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 III randomized controlled trial (VIALE-A) contributed evidence to this review. The objective of the trial 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 an HMA and who had intermediate- or poor-risk cytogenetics. The primary outcomes were OS and composite complete remission rate (CR + CRi). Secondary outcomes were CR, CR + CRh, rate of CR + CRi by the initiation of cycle 2, transfusion independence rate, minimal or measurable disease response rate, response rates and OS in molecular subgroups, fatigue and global health status and/or 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/m² on days 1 through 7 of a 28-day cycle) and 144 to placebo plus azacitidine. The most common reasons for patients to be considered ineligible for standard induction therapy were age and ECOG performance status. Patients were elderly, with poor performance, and had 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; half had bone marrow blasts of 50% or greater 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 OS benefit compared with those who received azacitidine plus placebo (14.7 months versus 9.6 months), with an HR of 0.66 (95% confidence interval, 0.52 to 0.85; $P < 0.001$). 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 more than 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; $P < 0.001$).

Improvements were also seen for OS and CR + CRi in the subgroup of patients with *IDH1* or *IDH2* mutations, 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. Although clinically meaningful differences in patient-reported outcomes of global health status and fatigue were observed at individual end points, differences between treatment groups cannot be interpreted because the sequential testing strategy failed before this level.

Harms Results

All patients in both groups experienced at least 1 AE, and almost all experienced at least 1 AE of grade 3 or higher. Compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced 1 or more SAEs; 1 or more AEs leading to discontinuation or dose interruption for venetoclax, placebo, or azacitidine; or 1 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 were the most common SAEs and were the most frequent AEs leading to death.

The notable harms as identified for the protocol were neutropenia, febrile neutropenia, infections, TLS, 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 TLS occurred in similar proportions, and the proportion of patients with TLS was low ($\leq 2.5\%$). The most common secondary malignancies were basal cell carcinoma and squamous cell carcinoma of the skin.

Critical Appraisal

The study was well-conducted, with no clinically meaningful imbalance in baseline characteristics, minimal loss to follow-up, and collection of end points that were standardized and meaningful to patients. Multiplicity was controlled throughout testing of primary and secondary efficacy end points, with pre-specified strategies for testing of end points. The overall rate of discontinuations from the study were low, and assumptions surrounding missing data were conservative for most end points. 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 or older 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 or older 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 LDAC, azacitidine, LDAC, and BSC in adults with AML who were not eligible for standard induction chemotherapy. Three indirect treatment comparison analyses were conducted: NMA and 2 propensity score–weighting analyses that compared venetoclax plus azacitidine to LDAC and azacitidine to LDAC. For the NMA, HR data were available for OS from 4 trials in a connected network; proportions of patients with CR + CRi were available from 3 trials. For the propensity score–weighting analysis, data were available for OS, EFS, and CR + CRi from the VIALE-A trial and the LDAC group from the VIALE-C trial.

Efficacy Results

In the NMA, the results showed a lower hazard of death for patients assigned to the venetoclax plus azacitidine group compared with the azacitidine (HR = 0.66; 95% credible interval, 0.52 to 0.85), LDAC (HR = 0.57; 95% credible interval, 0.40 to 0.81), and BSC (HR = 0.37; 95% credible interval, 0.24 to 0.58) groups, and no difference between venetoclax plus azacitidine and venetoclax plus LDAC (HR = 0.81; 95% credible interval, 0.50 to 1.31). For CR + CRi, venetoclax plus azacitidine was shown to be superior to azacitidine (odds ratio [OR] = 5.05; 95% credible interval, 3.30 to 7.87), LDAC (OR = 5.42; 95% credible interval, 2.80 to 10.50), and BSC (OR = 61.55; 95% credible interval, 8.23 to 1,881.53), with no difference between venetoclax plus azacitidine and venetoclax plus LDAC (OR = 0.86; 95% credible interval, 0.30 to 2.35).

In the first propensity score analysis, venetoclax plus azacitidine was shown to be superior to LDAC, 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 shown to be superior to LDAC (HR = 0.52; 95% credible interval, 0.36, 0.77) and azacitidine (HR = 0.64; 95% credible interval, 0.50, 0.82), and no statistically significant difference was seen between azacitidine and LDAC (HR = 0.78, 95% credible interval, 0.52 to 1.17). For EFS, venetoclax plus azacitidine was favoured over azacitidine (HR = 0.62; 95% credible interval, 0.49 to 0.77) and LDAC (HR = 0.41; 95% credible interval, 0.29 to 0.59), and azacitidine was shown to be superior to LDAC (HR = 0.63; 95% credible interval, 0.43, 0.92). For CR + CRi, venetoclax plus azacitidine was superior to azacitidine (OR = 5.02; 95% credible interval, 3.24 to 7.77) and LDAC (OR = 9.69; 95% credible interval, 4.30 to 21.85), and no statistically significant difference was seen between azacitidine and LDAC (OR = 1.93; 95% credible interval, 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 these 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

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Patients with newly diagnosed AML for whom intensive chemotherapy is unsuitable or who are 75 years or older
Treatment	Venetoclax in combination with azacitidine
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 venetoclax plus azacitidine 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	<ul style="list-style-type: none"> • Azacitidine alone • LDAC • 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 trial, VIALE-A trial, and a network meta-analysis
Submitted results	<ul style="list-style-type: none"> • Based on the sequential analyses, the optimal treatments (i.e., on the cost-effectiveness frontier) are BSC, LDAC, and venetoclax plus azacitidine • ICER for venetoclax plus azacitidine when compared to LDAC was \$105,286 per QALY gained (1.59 incremental QALYs and \$167,432 incremental costs).

Component	Description
Key limitations	<ul style="list-style-type: none"> • The sponsor excluded intensive chemotherapy as a comparator. Clinical experts consulted for this review indicated that individuals older than 75 would be eligible to receive intensive chemotherapy. • 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 venetoclax plus azacitidine occurred after individuals exited the EFS state and were no longer on first-line treatment. The clinical experts indicated that there was unlikely to be a substantive benefit for individuals who receive venetoclax plus azacitidine 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 is substantial uncertainty about the effectiveness of venetoclax plus azacitidine beyond the follow-up of the VIALE-A trial.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH reanalyses included estimates for OS curves limiting the benefit of venetoclax plus azacitidine after EFS and a cure assumption for those who remain in the CR + CRi health state for more than 10 years. CADTH also conducted several scenario analyses to quantify the uncertainty surrounding the CADTH base case. These scenario analyses included all individuals in the EFS health state on treatment and varying estimates of OS for venetoclax plus azacitidine. CADTH was not able to address the exclusion of intensive chemotherapy as a comparator. • In the sequential analysis, venetoclax plus azacitidine 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. Azacitidine was dominated by other options in the sequential analysis. • The probability that venetoclax plus azacitidine is cost-effective at a \$50,000 WTP threshold compared to LDAC was 0%.

AML = acute myeloid leukemia; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete blood count recovery; EFS = event-free state; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; WTP = willingness to pay.

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 did 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 LDAC.

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 the budget impact analysis model inputs to those applied in the pharmacoeconomic analysis.

Based on the CADTH reanalysis, 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 the proportion of patients ineligible for induction chemotherapy.

Members of the pCODR Expert Review Committee

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.

Meeting date: June 10, 2021

Regrets: None

Conflicts of interest: None