

CADTH Reimbursement Recommendation

Venetoclax (Venclexta)

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

Sponsor: AbbVie Corporation

Final recommendation: Do not reimburse

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What Is the CADTH Reimbursement Recommendation for Venclexta With Low-dose Cytarabine?

CADTH recommends that Venclexta in combination with low-dose cytarabine (LDAC) should not be reimbursed by public drug plans for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy.

Why did CADTH make this recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Venclexta plus LDAC did not improve overall survival compared to treatment with LDAC alone. No conclusions could be drawn for other important outcomes including remission rates, transfusion independence, event-free survival, quality of life, and symptoms.
- Patients identified a need for treatments that can maintain remission, improve quality of life and symptoms (fatigue), and that have fewer side effects. It is unclear whether Venclexta plus LDAC meets these needs.
- Economic evidence suggests that Venclexta plus LDAC is not cost-effective at a willingness-to-pay threshold of \$50,000 per quality-adjusted life-year (QALY), even at a 100% reduction in the price of Venclexta.
- Based on public list prices, the 3-year budget impact is \$70,006,541. This estimate is larger than the value identified by drug plans as feasible for adoption.

Additional Information

What is AML?

AML is a cancer of the blood and bone marrow which leads to a lower number of mature blood cells. AML is most common in older adults who are around 67 years of age and is typically associated with poor prognosis. Approximately 25% to 40% of patients over the age of 60 are expected to be alive after 3 years. In 2016, there were 1,090 Canadians diagnosed with AML.

Unmet needs in AML

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

How much does Venclexta cost?

Treatment with Venclexta combined with LDAC is expected to cost approximately \$11,759 for the first 28-day cycle, then \$12,529 per 28-day cycle thereafter.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) does not recommend reimbursement of venetoclax in combination with low-dose cytarabine (LDAC) for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy.

Rationale for the Recommendation

pERC could not recommend reimbursement of venetoclax plus LDAC due to several important limitations of the VIALE-C trial that resulted in a high degree of uncertainty regarding the magnitude of the treatment effect of venetoclax plus LDAC compared to placebo plus LDAC. The VIALE-C trial (N = 211) was a phase III, double-blind, multi-centre, randomized controlled trial (RCT) that evaluated the efficacy and safety of venetoclax plus LDAC compared to placebo plus LDAC in treatment-naïve patients with AML who were ineligible to receive intensive induction chemotherapy. The final analysis results for the primary outcome, overall survival (OS), were not statistically significant after a median follow-up of 12 months when the median OS was 7.2 months in the venetoclax plus LDAC group and 4.1 months in the placebo plus LDAC group (hazard ratio [HR] of 0.75; 95% confidence interval [CI], 0.52 to 1.27; P = 0.114). The failure of the trial to meet its primary outcome meant that the subsequent testing of outcomes pre-specified in the statistical testing hierarchy lacked control for multiple comparisons (i.e., at risk of type I error). Thus, statistical inferences could not be drawn with respect to complete remission (CR) rate, CR plus incomplete blood count recovery (CRi) rate (CR + CRi), CR plus complete remission with partial hematologic recovery (CRh) rate (CR + CRh), transfusion independence and event-free survival (EFS). Patients identified a need for treatments that can maintain remission, but pERC was uncertain whether venetoclax plus LDAC meets this need given the limitations of the evidence on remission outcomes. Improving health-related quality of life and addressing symptoms (fatigue) are also deemed important outcomes by patients. The analyses of these outcomes in the trial were also limited by the early failure of the statistical testing hierarchy and were confounded by the large amount of patient attrition that occurred in both treatment groups; therefore, no definitive conclusions could be drawn on the effects of venetoclax plus LDAC on patient quality of life. Finally, patients expressed a desire for treatments that have fewer side effects. While pERC considered the toxicity of venetoclax plus LDAC to be manageable, they noted that the overall incidence of adverse events (AEs) was higher with the combination treatment.

Discussion Points

- pERC discussed at length that the VIALE-C trial did not meet its primary outcome (OS). Based on the results of the pre-specified final analysis of OS, pERC concluded that when compared to placebo plus LDAC, the magnitude of the OS benefit associated with venetoclax plus LDAC was modest, not statistically significant, and uncertain. Further, since statistical inferences could not be drawn with respect to any of the secondary outcomes that were to be tested after OS, there was also uncertainty in the statistical and clinical significance of the results obtained for these outcomes.

- pERC considered that at the final analysis the VIALE-C trial showed numerical improvements in secondary outcomes including CR + CRi, CR + CRh, transfusion independence, and EFS in favour of venetoclax plus LDAC; however, pERC agreed that there was substantial uncertainty in the results obtained for these outcomes since they were not controlled for multiple comparison testing and their clinical significance was also uncertain since these improvements did not translate to a statistically significant gain in survival. A 6-month post hoc analysis of OS was performed after 17.5 months of follow-up and demonstrated a greater survival difference between the 2 treatment groups; the median OS was 8.4 months in the venetoclax plus LDAC group and remained at 4.1 months in the placebo plus LDAC group (HR of 0.70; 95% CI, 0.50 to 0.99). pERC discussed that this follow-up analysis was subject to the same limitation of uncontrolled testing due to the post hoc nature of the analysis.
- In the absence of head-to-head trials for all comparator treatments of interest, pERC considered indirect evidence from a network meta-analysis (NMA) that compared the efficacy of venetoclax plus LDAC to alternative treatments that included venetoclax plus azacitidine, LDAC, azacitidine, and best supportive care (BSC). The results of the NMA suggested that for OS, venetoclax plus LDAC was favoured over LDAC and BSC, with no treatment favoured between venetoclax plus LDAC and azacitidine, or venetoclax plus LDAC and venetoclax plus azacitidine. For CR + CRi, venetoclax plus LDAC was favoured over LDAC, azacitidine, and BSC, and no treatment was favoured between venetoclax plus LDAC and venetoclax plus azacitidine. In the NMA, there were important differences in variables that were potential treatment effect modifiers between the included studies. The small number of studies limited the method of analysis and did not permit adjustment for baseline differences; therefore, the comparative treatment effect estimates obtained were imprecise and at high risk of bias.
- The clinical experts consulted by CADTH indicated that some patients aged 75 years or older will be fit and eligible to receive intensive induction chemotherapy; thus, it is assumed that such patients would receive standard of care induction therapy with cytarabine and an anthracycline. However, a substantial portion of patients with AML are ineligible for intensive induction chemotherapy due to frailty associated with age or comorbidities. Patients who are ineligible for induction chemotherapy may be treated with LDAC or hypomethylating agents (HMA) such as azacitidine. pERC acknowledged that rates of CR with these regimens are low and remissions are not durable, and thus agreed with the clinical experts and patient groups providing input to this submission that there is a need for better treatment options for older patients with AML who are ineligible for intensive induction chemotherapy. However, based on the clinical evidence from the VIALE-C trial, pERC was uncertain that venetoclax plus LDAC fulfills this need.
- Patients expressed a desire for treatments that can be administered at home as outpatient treatment. pERC discussed that LDAC alone is administered at home and therefore addresses this patient value; whereas, venetoclax plus LDAC requires hospitalization during the initial phase of treatment.
- The pharmacoeconomic model submitted for venetoclax plus LDAC appeared to produce a bias in favour of venetoclax plus LDAC that could not be addressed in reanalysis, and as such the incremental cost-effectiveness ratio (ICER) was likely underestimated. The sponsor did not consider induction chemotherapy as a comparator in their pharmacoeconomic model, based on an assertion that patients 75 years of age and older would not be eligible to receive it. Feedback from the clinical experts consulted by CADTH suggested that fit patients 75 years of age and older would still be eligible for induction

chemotherapy. Consequently, the cost-effectiveness of venetoclax plus LDAC compared to induction chemotherapy is unknown in patients 75 years of age and older.

Background

Venetoclax in combination with LDAC has a Health Canada indication for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. Venetoclax is an orally administered selective inhibitor of the anti-apoptotic protein B cell lymphoma 2 (BCL2) and is available as 10 mg, 50 mg, and 100 mg oral tablets. The Health Canada–approved dose of venetoclax (after an initial dose ramp up of 4 days) is 600 mg once daily on days 1 to 28 in combination with LDAC at a dose of 20 mg/m² subcutaneously once daily on days 1 to 10 of each 28-day cycle.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 1 phase III RCT in adult patients ineligible for intensive 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
- two clinical specialists with expertise in diagnosing and treating patients with AML
- input from 2 clinician groups, including the Canadian Leukemia Study Group (CLSG) and the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO Hem-DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group, the LLSC, provided input for this submission. The LLSC used an online survey, conducted between December 7, 2020 and January 24, 2021 to gather input, and there were 29 patient respondents, ranging in age from 25 to 84 years of age.

Patients described the impact that symptoms such as fatigue, suddenness of symptom development, anxiety, and fear of relapse have on their quality of life. Many patients report symptoms that impact their social and family life, and some noted that they were unable to work due to their condition.

With respect to outcomes of importance to patients, respondents hoped that new treatment options could maintain remission and quality of life. Patients also hoped that a new therapy would have fewer side effects associated with it. Patients appear to value any treatment that can be administered on an outpatient basis, or that can be administered close to their home.

Clinician Input

Input from Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that current treatments have low rates of CR and not very durable responses when they do occur, and they noted that treatments that do have higher CR rates tend to have increased toxicity and are poorly tolerated in this population.

The clinical experts noted that venetoclax combinations will likely become first-line treatment for patients who are not fit for induction chemotherapy and this will likely change the standard of care for AML. The preferred combination will likely be venetoclax in combination with a HMA and venetoclax plus LDAC will likely be the treatment of choice in patients who have had prior HMA. The ability to administer venetoclax plus LDAC at home will be an advantage for a certain subset of patients. In patients who have not received prior treatment with a HMA, the clinical experts recommended venetoclax plus an HMA, and also suggested that venetoclax plus an HMA may even be suitable in patients with prior HMA use. One clinical expert also noted that ivosidenib plus azacitidine may be reasonable in patients with IDH1 mutations, if available.

With respect to venetoclax plus LDAC, the clinical experts believed this combination would be first-line standard of care in patients unfit for induction chemotherapy who had received prior treatment with a HMA, and they would not prescribe venetoclax plus LDAC in patients who were eligible for induction chemotherapy. It is currently not possible to identify which patients would and would not respond to treatment. The outcomes used to determine treatment response include complete blood count (CBC) and bone marrow blasts. A clinically meaningful response would be indicated by improved survival and CR rate, decreased hospitalizations and transfusion requirements, and a decreased rate of progression. Response should be assessed after cycle 1 and cycle 2 and a response would be expected after a maximum of 2 cycles.

The clinical experts agreed that disease progression and intolerable AEs are factors in the decision to discontinue treatment. Disease progression would be indicated by worsening CBC, increased marrow blasts, or loss of transfusion independence.

Clinician Group Input

Two clinician groups provided input on this submission, the CLSG and the OH-CCO Hem-DAC. Neither of the clinician groups held views that differed materially from the clinical experts consulted by CADTH for this submission. Both clinician groups viewed venetoclax plus LDAC as replacing LDAC monotherapy in this patient population.

Drug Program Input

The drug programs indicated that current treatment options for patients with newly diagnosed AML who are ineligible for intensive induction chemotherapy include azacitidine, LDAC, and BSC. It was noted that some patients 75 years of age and older may be fit to

tolerate induction chemotherapy. The ramp up dosing schedule for venetoclax plus LDAC 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. The drug programs indicated that this combination treatment may change the place in therapy of comparator drugs. They also identified the potential for indication creep for patients with a high risk of myelodysplastic syndrome (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 stem cell transplant and are then treated with LDAC. It was noted that venetoclax plus LDAC may require the need for increased health care resources (i.e., hospital admission, additional pharmacy and nursing resources for the potential management of tumour lysis syndrome [TLS] and monitoring for drug interactions, and home care resources and training if LDAC is administered at home). Affordability was also identified as an issue since venetoclax is an add on to existing treatment. The pCODR Provincial Advisory Group also raised questions on the implementation of venetoclax plus LDAC into current provincial drug plans, most of which related to the dosing schedule and administration, and the eligible patient population.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One study met the inclusion criteria of the CADTH review. The VIALE-C trial is an ongoing, sponsor-funded, phase III double-blind RCT that compared venetoclax plus LDAC (N = 143) to placebo plus LDAC (N = 68) in treatment-naïve patients with AML who were ineligible for intensive induction chemotherapy. The study was conducted at 76 sites in 21 countries including Canada (10 patients). The primary outcome was OS, and secondary outcomes included CR rate, CR + CRi rate, CR + CRh rate, duration of remission, transfusion independence, EFS, health-related quality of life, and fatigue.

Most patients in the study were male (55.5%) and white (70.6%) and the median age was 76 years (range 36 to 93 years). The majority of patients had de novo AML (61.6%) and intermediate cytogenetic risk (65.2%). Most patients were considered ineligible for intensive induction chemotherapy based on age (≥ 75 years) followed by Eastern Cooperative Oncology Group (ECOG) performance status in patients 18 to 74 years of age. Approximately 40% of patients were 75 years or older and had 1 comorbidity in addition to age.

Efficacy Results

The median OS at the final analysis (after a median follow up of 12 months) in the venetoclax plus LDAC group was 7.2 months versus 4.1 months in the placebo plus LDAC group, for a HR of 0.75 (95% CI, 0.52 to 1.27), $P = 0.114$. Thus, the VIALE-C trial failed to meet its primary outcome by not demonstrating a statistically significant difference in OS at the final analysis data cut-off date. Health Canada still granted venetoclax plus LDAC a Notice of Compliance (NOC) because of what it described as the “totality of the evidence,” namely, a clear consistent difference in favour of venetoclax plus LDAC when compared to placebo plus LDAC for other outcomes that included CR + CRi, CR + CRh, median duration of CR and transfusion independence. At a post hoc 6-month follow-up analysis (after a median follow-up of 17.5

months), the median OS was 8.4 months in the venetoclax plus LDAC group and remained at 4.1 months in the placebo plus LDAC group, for a HR of 0.70 (95% CI, 0.50 to 0.99). The results for OS remained the same at a 12-month post hoc follow-up analysis.

At the final analysis, per investigator assessment, the CR + CRi rate was 47.6% (95% CI, 39.1 to 56.1) in the venetoclax plus LDAC group and was 13.2% (95% CI, 6.2 to 23.6) in the placebo plus LDAC group. At the 6-month post hoc follow-up analysis, the CR + CRi rate was 48.3% (95% CI, 39.8 to 56.8) in the venetoclax plus LDAC group and was unchanged from the final analysis in the placebo plus LDAC group.

At the final analysis, the CR + CRh rate was 46.9% in the venetoclax plus LDAC group (95% CI, 38.5 to 55.4) versus 14.7% in the placebo plus LDAC group (95% CI, 7.3 to 25.4). At the 6-month post hoc follow-up analysis, the CR + CRh rate for patients in the venetoclax plus LDAC group was 48.3% (95% CI, 39.8 to 56.8) and was unchanged from the final analysis in the placebo plus LDAC group.

At the final analysis, the median duration of remission (CR + CRi) was 10.8 months in the venetoclax plus LDAC group and was 6.2 months in the placebo plus LDAC group. At the 6-month post hoc follow-up analysis, the median duration of remission (CR + CRi) was 11.7 months in the venetoclax plus LDAC group and was unchanged from the final analysis in the placebo plus LDAC group.

At the final analysis, transfusion independence (red blood cell and platelet) was achieved by 37.1% of patients in the venetoclax plus LDAC group and by 16.2% of patients in the placebo plus LDAC group. At the 6-month post hoc, follow-up analysis, transfusion independence was achieved by 39.2% of patients in the venetoclax plus LDAC group and 17.6% of patients in the placebo plus LDAC group.

At the final analysis, the median EFS was 4.7 months (95% CI, 3.7 to 6.4) in the venetoclax plus LDAC group and was 2.0 months (95% CI, 1.6 to 3.1) in the placebo plus LDAC group, for a HR of 0.58 (95% CI, 0.42 to 0.82). At the time of the 6-month post hoc follow-up analysis, the EFS in the venetoclax plus LDAC group was 4.9 months (95% CI, 3.7 to 6.4) and was 2.1 months (95% CI, 1.5 to 3.2) in the placebo plus LDAC group indicating a limited increase in EFS from the final analysis to the 6-month post hoc follow-up, for a HR of 0.61 (95% CI, 0.44 to 0.84).

Health-related Quality of Life and Fatigue

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – 30 items Global Health Status/Quality of Life Scale (QLQ-C30 GHS/QoL Scale) was assessed as a secondary outcome, and subscales were assessed as exploratory outcomes. For the QLQ-C30 GHS/QoL Scale and functioning subscales, an increase in score indicates improvement, whereas a decrease in score indicates improvement for symptom subscales or items. The minimal important difference (MID) is 10 points for this instrument. There were differences in baseline scores between the venetoclax plus LDAC and placebo plus LDAC groups, although there was no consistent pattern in the differences. There was a large amount of missing data with assessments missing for more than 50% of the intent to treat (ITT) population. A large portion of the missing data was due to attrition; however compliance with filling out the instrument was typically around 70% to 80% across time points. Data were reported every 2 cycles, starting with cycle 3. By cycle 3, data were only available for 69 out of 127 patients in the venetoclax plus LDAC group, and for 22 of 59 patients in the placebo plus LDAC group; and by cycle 9, data were available for 22 patients

in the venetoclax plus LDAC group and 7 patients in the placebo plus LDAC group. For the QLQ-C30 GHS/QoL Scale, the least squares mean (LSM) difference between the venetoclax plus LDAC and the placebo plus LDAC groups based on changes from baseline after 9 cycles was 6.381 (95% CI, -8.49 to 21.28). The results for individual subscales varied widely, with some reporting improvement for venetoclax plus LDAC from baseline and improvement over placebo plus LDAC (appetite loss); while for other scales there was a worsening (diarrhea and dyspnea) in the venetoclax plus LDAC group compared to the placebo plus LDAC group that exceeded the MID of 10.

Fatigue was assessed using the PROMIS Fatigue Score. Similar to the QLQ-C30 GHS/QoL Scale, there was a significant amount of missing data due mainly to attrition and also due to compliance of 70% to 80%. Fatigue scores decreased (improved) from baseline in the venetoclax plus LDAC group at the end of all cycles, and this exceeded the MID of 3 points for this instrument starting at cycle 5. Improvements from baseline were also seen in the placebo plus LDAC group beginning at cycle 7. The largest between-group difference occurred at cycle 5, with a LSM difference between venetoclax plus LDAC and placebo plus LDAC of -4.923 (95% CI, -10.03 to 0.19).

Harms Results

At the time of the 6-month post hoc follow-up analysis, 99.3% of patients in the venetoclax plus LDAC group and 98.5% of patients in the placebo plus LDAC group experienced at least 1 AE. The most common AEs (venetoclax plus LDAC versus placebo plus LDAC) were neutropenia (45.8% versus 17.6%), thrombocytopenia (45.8% versus 39.7%), nausea (43.0% versus 30.9%), diarrhea (33.1% versus 17.6%), and febrile neutropenia (32.4% versus 29.4%). Grade ≥ 3 AEs occurred in 97.2% of patients in the venetoclax plus LDAC group and 95.6% of patients in the placebo plus LDAC group, and the most common were neutropenia (48.6% versus 17.6%), thrombocytopenia (45.8% versus 38.2%) and febrile neutropenia (32.4% versus 29.4%).

Serious AEs (SAEs) occurred in 66.9% of patients in the venetoclax plus LDAC group and 61.8% of patients in the placebo plus LDAC group. The most common SAEs were febrile neutropenia (16.9% versus 17.6%) and pneumonia (14.1% versus 10.3%).

AEs leading to death occurred in 23.2% of patients in the venetoclax plus LDAC group versus 20.6% of patients in the placebo plus LDAC group. The most common AE that led to death in the venetoclax plus LDAC group was pneumonia, occurring in 4.9% of patients treated with venetoclax plus LDAC and no patients treated with placebo plus LDAC.

Notable harms included infections, and these were under the broad category of infections and infestations; 64.8% of patients in the venetoclax plus LDAC group and 60.3% of patients in the placebo plus LDAC group experienced an event. Pneumonia was the most common infection, occurring in 21.8% and 16.2% of patients in the venetoclax plus LDAC and placebo plus LDAC groups, respectively. The following notable harms occurred more frequently in the venetoclax plus LDAC group: second primary malignancy in 2.1% versus zero patients, TLS in 5.6% versus zero patients, hemorrhage in 41.5% versus 30.9% of patients, and any AE of neutropenia was reported in 68.3% and 45.6% patients, respectively.

Critical Appraisal

- VIALE-C failed to meet its primary outcome of OS. A statistical hierarchy was used to account for multiplicity; however, early failure of the hierarchy (at the level of the primary

outcome) meant that subsequent testing of outcomes lacked control for type I error. This limits any statistical inferences that can be drawn with respect to statistical significance for any of the subsequent outcomes that were to be tested in the hierarchy after OS.

- Interpretation of the patient-reported outcomes of health-related quality of life and fatigue is limited by the large amount of missing data. By cycle 5, for example, in assessment of the EORTC QLQ C30 GHS/QoL Scale there was approximately 30% of the original ITT population remaining in the venetoclax plus LDAC group and approximately 20% of the original ITT population in the placebo plus LDAC group. Even after cycle 3, which was the earliest time point assessed, nearly 50% of the ITT population was missing from the venetoclax plus LDAC group, and nearly two-thirds were missing from the placebo plus LDAC group. The large amount of missing data was not just due to attrition, as compliance with filling out these instruments was relatively low at about 78% at cycle 3, and lower at some other later time points.
- A large number of patients withdrew from the study, and there were numerically fewer withdrawals in the venetoclax plus LDAC group than in the placebo plus LDAC group (72.0% versus 82.4% of patients, respectively). Most of these withdrawals were due to deaths, and this also accounted for the difference between groups. This difference in withdrawals may have had an impact on the interpretation of patient-reported outcomes and harms, and the venetoclax plus LDAC group had longer exposure to study drug.
- The population included in the VIALE-C trial was consistent with the population that someone would expect to use venetoclax plus LDAC in Canada, according to the clinical experts consulted by CADTH. However, the dosing of LDAC may be different in VIALE-C, that used body surface area to determine dosing; whereas, in Canada a flat dose tends to be used.

Indirect Comparisons

Description of Studies

A systematic review and NMA were conducted by the sponsor of trials comparing venetoclax plus LDAC, venetoclax plus azacitidine, LDAC alone, azacitidine, and BSC in adults with AML who were not eligible for standard induction chemotherapy. Data were available for OS for 4 trials in a connected network and for CR + CRi for 3 trials.

Efficacy Results

For OS, venetoclax plus LDAC was favoured over LDAC (HR 0.70; 95% credible interval [CrI], 0.50 to 0.99) and BSC (HR 0.46; 95% CrI, 0.26 to 0.81), with no difference seen between venetoclax plus LDAC and azacitidine (HR 0.82; 95% CrI, 0.54 to 1.24), or venetoclax plus LDAC and venetoclax plus azacitidine (HR 1.23; 95% CrI, 0.76 to 2.01). For CR + CRi, venetoclax plus LDAC was favoured over LDAC (odds ratio [OR] 6.24; CrI, 2.98 to 14.42), azacitidine (OR 5.84; CrI, 2.39 to 15.22) and BSC (OR 73.35; 95% CrI, 8.05 to 2,370.88), with no difference seen between venetoclax plus LDAC and venetoclax plus azacitidine (OR 1.16; 95% CrI, 0.43 to 3.33).

Harms Results

No analysis of harms was included in the NMA.

Critical Appraisal

A key limitation of the NMA was the clinical heterogeneity between studies in important prognostic indicators and potential treatment effect modifiers of blast-count at baseline, prior

treatment with HMA, 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 highly imprecise due to low numbers of responses in some study arms.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model.
Target population	Patients who are 75 years or older with newly diagnosed AML who have comorbidities that preclude the use of intensive IC.
Treatment	Venetoclax in combination with low-dose cytarabine (Ven + LDAC)
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 + LDAC is \$11,759 (venetoclax: \$10,990 LDAC: \$769) and \$12,529 (venetoclax: \$11,760; azacitidine: \$769) 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	LDAC alone BSC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, Lys
Time horizon	Lifetime horizon (to 90 years of age)
Key data source	VIALE-C trial and NMA
Submitted results	<ul style="list-style-type: none"> Based on sequential analysis all treatments are on the frontier. The ICER for Ven + LDAC when compared to BSC was \$87,759 per QALY gained (1.07 incremental QALYs and \$78,294 incremental costs). The ICER for Ven + LDAC when compared to LDAC was \$122,766 per QALY gained (0.64 incremental QALYs and \$93,591 incremental costs).

Component	Description
Key limitations	<ul style="list-style-type: none"> • The sponsor excluded IC as a comparator even though clinical experts 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 + LDAC occurred after individuals exited the EFS state and no longer on first-line treatment. Clinical experts indicated that there was unlikely to be a substantive benefit for individuals who receive Ven + LDAC 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 + LDAC beyond the follow-up of the VIALE-C trial.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH reanalyses included: Estimates for OS curves limiting the benefit of Ven + LDAC post EFS; 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; varying estimates of effectiveness for Ven + LDAC and LDAC. CADTH was not able to address the exclusion of IC as a comparator. • In the sequential analysis, LDAC was associated with an ICER of \$46,333 per QALY compared to BSC. Ven + LDAC was associated with an ICER of \$337,964 per QALY compared to LDAC. • The probability that Ven + LDAC was cost-effective compared to LDAC at a WTP threshold of \$50,000 was 0%.

AML = acute myeloid leukemia; BSC = best supportive care; EFS = event-free-survival; IC = induction chemotherapy; CR/CRi = complete remission/complete remission with incomplete blood count recovery; IC = induction chemotherapy; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; PSM = partitioned survival model; QALY = quality-adjusted life-year; Ven + LDAC = venetoclax in combination with low-dose cytarabine; WTP = willingness to pay.

Budget Impact

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

- 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 azacitidine.

The CADTH reanalyses included revising market share estimates for venetoclax in the new drug scenario, revising the epidemiological inputs to derive the market size, updating the price of LDAC, and aligning drug cost inputs to those used in the pharmacoeconomic analysis.

Based on the CADTH reanalysis, the budget impact from the addition of venetoclax plus LDAC would result in an incremental budget impact of \$2,508,181 in year 1, \$4,751,405 in year 2, and \$5,865,333 in year 3, for a total budget impact of \$13,124,920. The results were primarily driven by the market share uptake of venetoclax plus LDAC.

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