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CADTH Reimbursement Recommendation

Azacitidine (Onureg)

Indication: Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete response with incomplete blood recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT).

Sponsor: Celgene Inc., a Bristol Myers Squibb Company

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Onureg?

CADTH recommends that Onureg be reimbursed by public drug plans as maintenance therapy for the treatment of adult patients with acute myeloid leukemia (AML) who have achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) after induction therapy with or without consolidation treatment, and are ineligible for hematopoietic stem cell transplantation (HSCT), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Onureg should only be covered to treat adult patients (at least 18 years of age) with newly diagnosed AML who have certain genetic changes that lead to greater risk of having unfavourable disease outcomes (i.e., intermediate- or poor-risk cytogenetics) and who are ineligible for HSCT. Patients eligible for reimbursement of Onureg must have achieved first remission (defined as CR or CRi) following induction with or without consolidation chemotherapy, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, and adequate organ function.

What Are the Conditions for Reimbursement?

Onureg should only be reimbursed if prescribed by clinicians with expertise managing patients with AML, familiarity with Onureg's toxicity profile exists, and its cost is reduced.

Why Did CADTH Make This Recommendation?

- Clinical trial evidence demonstrated that, compared with placebo, Onureg prolongs overall and relapse-free survival and has a manageable toxicity profile.
- Onureg met patient needs to maintains remission, offer convenient oral administration, and a manageable toxicity profile. No definitive conclusion could be reached regarding the effect of Onureg on patient quality of life and symptom severity (fatigue).
- Based on public list prices, Onureg is not considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to best supportive care (BSC). A price reduction of at least 85% is needed to ensure Onureg is cost effective at this threshold. Structural issues within the pharmacoeconomic model introduced a bias in the results, meaning that a greater price reduction is likely needed.
- Based on public list prices, the 3-year budget impact of funding oral azacitidine is $100,647,777.

Additional Information

What Is AML?

AML is a blood and bone marrow cancer that leads to fewer mature blood cells. AML causes weakness, infection, bleeding, and other symptoms and complications. There were 1,090 new cases of AML in Canada in 2016 and 1,184 deaths from AML in 2017.

Unmet Needs in AML

There are no publicly reimbursed maintenance regimens for patients with AML who are in first remission, have intermediate- or poor-risk cytogenetics, and are ineligible for HSCT.

How Much Does Onureg Cost?

Treatment with Onureg is expected to cost $19,992 per 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that oral azacitidine should be reimbursed as maintenance therapy for the treatment of adult patients with acute myeloid leukemia (AML) who have achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are ineligible for hematopoietic stem cell transplantation (HSCT) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, multi-centre, randomized controlled trial (RCT), (QUAZAR AML-001 trial, N = 472) in adult patients (≥ 55 years of age) with AML in first CR, demonstrated that oral azacitidine was associated with a statistically significant and clinically meaningful improvement in overall survival (OS). Median OS was 24.7 months (95% confidence interval [CI], 18.7 to 30.5) in the oral azacitidine group compared to 14.8 months (95% CI, 11.7 to 17.6) in the placebo group (hazard ratio [HR] = 0.69; 95% CI, 0.55 to 0.86; P = 0.0009). Oral azacitidine was also associated with a statistically significant and clinically meaningful longer relapse-free survival (RFS). Median RFS was 10.2 (95% CI, 7.9 to 12.9) months in the oral azacitidine group compared with 4.8 (95% CI, 4.6 to 6.4) months in the placebo group (HR = 0.65, 95% CI, 0.52 to 0.81; P = 0.0001). pERC concluded that oral azacitidine aligned with patients' expectations for new effective treatment options in that oral azacitidine maintains remission and is an oral drug that can be administered in a patient's home or as an outpatient treatment in a patient's local community. pERC acknowledged that patients also expressed an unmet need for treatments with fewer side effects and improved quality of life. pERC noted that patients treated with oral azacitidine had more gastrointestinal (GI) toxicities and myelosuppression events than those treated with placebo but agreed these toxicities and events can be adequately managed. While measures of fatigue and health-related quality of life (HRQoL) appeared similar between the oral azacitidine and placebo groups, no definitive conclusion could be reached regarding the effects of oral azacitidine on symptom severity (fatigue) and HRQoL due to a significant decline in the number of patients available to provide assessments over time and non-inferential analyses for patient-reported outcomes.

Using the sponsor-submitted price for oral azacitidine and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for oral azacitidine was $355,456 per quality-adjusted life-year (QALY) compared with best supportive care (BSC). At this ICER, oral azacitidine for AML patients who have achieved CR or CRi is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold. A reduction in price of at least 85% is required for oral azacitidine to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients must have newly diagnosed AML (de novo or secondary to prior MDS or CMML) with intermediate- or poor-risk cytogenetics[a]	Patients enrolled in the QUAZAR AML-001 trial must have had AML with intermediate- or poor-risk cytogenetics. The QUAZAR AML-001 trial excluded patients with AML and favourable-risk cytogenetics. There is no evidence to support the safety and efficacy of oral azacitidine in patients with favourable-risk cytogenetics.
2. Patients must have achieved first remission (CR or CRi) following induction with or without consolidation chemotherapy.	The HC indication specifies that oral azacitidine be used in patients who achieved CR or CRi following induction therapy with or without consolidation treatment. Patients enrolled in the QUAZAR AML-001 trial must have achieved CR or CRi following induction therapy with or without consolidation treatment within the last 4 months.
3. Patients must not be eligible for HSCT.	The HC indication specifies that oral azacitidine be used in patients who are ineligible for HSCT. The QUAZAR AML-001 trial excluded patients who were candidates for allogeneic bone marrow or stem cell transplantation at screening. There is no evidence to support the safety and efficacy of oral azacitidine in patients with AML who are eligible for HSCT.
4. Patients must have an ECOG performance status of 0 to 3 and adequate organ function.	Patients enrolled in the QUAZAR AML-001 trial had to have an ECOG performance status of 0 to 3 and adequate organ function.
5. Patients must be adults (≥ 18 years of age).	The approved HC indication is for adult patients (≥ 18 years of age).
Discontinuation	
6. Oral azacitidine should be discontinued upon the occurrence of any of the following: 6.1. Disease relapse (i.e., appearance of > 5% blasts in the bone marrow or peripheral blood). 6.2. Unacceptable toxicity. 6.3. Patient becomes eligible (at the discretion of the treating clinician) for allogeneic bone marrow or stem cell transplantation during the treatment period.	These conditions correspond with the criteria used in the QUAZAR AML-001 trial to determine whether treatment with oral azacitidine should be discontinued.
Prescribing	
7. Oral azacitidine should only be prescribed by clinicians who: 7.1. have expertise in the diagnosis and management of patients with AML 7.2. are familiar with the toxicity profile associated with the oral azacitidine regimen	This condition is required to ensure that oral azacitidine is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.
8. Patients should have access to a regional cancer clinic to ensure that treatment tolerance is confirmed, and that the disease has not relapsed.	Azacitidine is an oral drug that is self-administered, but monitoring of blood work is required to thereby monitor response to treatment.

Reimbursement condition	Reason
Pricing	
9. A reduction in price.	The ICER for oral azacitidine is $355,456 when compared with BSC. A price reduction of at least 85% would be required for oral azacitidine to be able to achieve an ICER of $50,000 per QALY compared to BSC.

AML = acute myeloid leukemia; BSC = best supportive care; CMML = chronic myelomonocytic leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; HC = Health Canada; HSCT = hematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; MDS = myelodysplastic syndrome; QALY = quality-adjusted life-year.

[a]Intermediate- or poor-risk cytogenetics defined according to the European LeukemiaNet (ELN) 2017 recommendations for risk stratification in AML.

Implementation Guidance

1. pERC agreed with the clinical experts consulted by CADTH that standard prior therapies currently received by patients in Canada are acceptable to be eligible for oral azacitidine maintenance therapy. The most commonly received induction therapies used in Canada are standard-dose cytarabine with an anthracycline (i.e., 7 + 3) or fludarabine plus high-dose cytarabine plus granulocyte colony-stimulating factors (G-CSF) (i.e., FLAG) with or without idarubicin in patients with high-risk disease. The most commonly received consolidation therapy is high-dose cytarabine (HiDAC).
2. pERC agreed that it would be reasonable to offer oral azacitidine maintenance to patients who received induction therapy with gemtuzumab ozogamicin, provided they meet the reimbursement conditions specified in Table 1. As well, pERC agreed with the clinical experts that it would be reasonable to offer oral azacitidine maintenance therapy to patients who are FMS-Like Tyrosine Kinase 3 gastrointestinal (FLT3) mutation positive and who received midostaurin in combination with induction and/or consolidation chemotherapy. This patient group in first complete remission is at high risk of relapse and there is no biologic rationale to assume that outcomes of oral azacitidine would be different in patients with FLT3 positive AML.
3. The QUAZAR AML-001 trial inclusion criteria specified that patients had to be at least 55 years of age. However, pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to generalize the QUAZAR AML-001 trial results to patients younger than 55 years given the acceptable safety profile of oral azacitidine and that there is no biologic rationale to assume that outcomes of oral azacitidine would be different in younger adult patients with AML who otherwise meet the trial's inclusion criteria.
4. In the QUAZAR AML-001 trial response assessment (according to the International Working Group (IWG) AML response criteria) for maintaining CR or CRi, was planned to occur every 3 cycles starting at cycle 3. pERC agreed with the clinical experts that patients should have regular clinical assessments and monitoring of blood work every 1 to 2 weeks in the beginning of treatment, moving to once a month at the start of every treatment cycle later on (i.e., the timing of moving assessments to once a month should be at the discretion of the treating clinician but will likely occur after 3 to 4 cycles).
5. In the QUAZAR AML-001 trial, a post-relapse dose escalation (300 mg once daily from 14 days to 21 days of the 28-day cycle) was allowed for patients with disease relapse with blasts of at least 5% and no more than 15% either in the peripheral blood or bone marrow.

This post-relapse dose escalation explored whether oral azacitidine could be used to reinitiate remission; however, this is not consistent with the Health Canada (HC) indication or the CADTH reimbursement request, which is for oral azacitidine as maintenance therapy. pERC agreed with the clinical experts that there is currently insufficient evidence to attempt dose escalation in Canadian clinical practice and felt that it is not reasonable to generalize the QUAZAR AML-001 trial results to oral azacitidine used to reinitiate remission.

6. In the QUAZAR AML-001 trial, some patients were eligible to undergo subsequent HSCT (6.3% of patients in the oral azacitidine group and 13.7% in the placebo group). The clinical experts consulted by CADTH noted that patients would be identified as possible candidates for oral azacitidine treatment if they are considered ineligible for transplantation. The transplantation ineligibility status may be known in patients at the time of diagnosis or may develop over the course of their treatment. pERC agreed with the clinical experts that a patient could be reconsidered as eligible for HSCT if their comorbidities improve or resolve while on maintenance oral azacitidine.
7. The 3-year total budget impact of funding oral azacitidine was estimated to be $100,647,777.

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

Discussion Points

- Patient groups and clinician input to CADTH highlighted that AML is an aggressive hematological malignancy with poor prognosis. There are currently no standard funded maintenance regimens for patients with AML who are in first remission and are ineligible for transplantation. pERC agreed with the patient groups and the clinician input to CADTH that there is a need for effective treatments in this setting that delay relapse, prolong life, maintain or improve patients' quality of life with an acceptable safety profile, and have a convenient oral route of administration.
- pERC discussed the results of the QUAZAR AML-001 trial that indicated that OS and RFS, which were clinical outcomes identified as of interest to patients and clinicians, were statistically significantly in favour of oral azacitidine. Given that most patients who are ineligible for HSCT relapse after a few months, the benefits observed with oral azacitidine over placebo were considered clinically meaningful in a setting where currently there is no standard maintenance treatment option.
- pERC discussed that the QUAZAR AML-001 trial enrolled patients with intermediate- or poor-risk cytogenetics. There is no evidence to support the safety and efficacy of oral azacitidine in patients with AML and favourable-risk cytogenetics. The clinical experts consulted by CADTH noted that patients with favourable cytogenetic risk are not generally considered for the present indication given their good outcomes and likely cure after consolidation therapy with standard chemotherapy treatment alone.
- The QUAZAR AML-001 trial inclusion criteria specified patients must have an ECOG performance status of 0 to 3. pERC noted that the trial enrolled a total of 3 patients with a performance status of 3. pERC discussed that patients should have adequate performance status and organ function to receive oral azacitidine, and that the decision to offer oral

azacitidine as maintenance therapy to patients with a performance status of 3 should be at the discretion of the treating clinician.

- pERC deliberated on the toxicity profile of oral azacitidine compared with placebo and noted that the safety profile of azacitidine was mainly driven by higher rates of GI toxicities and myelosuppression events in the oral azacitidine group, which could be adequately managed in clinical practice and were considered acceptable. pERC agreed with the clinical experts consulted by CADTH that most treatment-emergent adverse events (TEAE) associated with oral azacitidine could be managed with dose modifications and BSC and treatment discontinuation due to TEAEs was relatively uncommon.
- pERC deliberated on the cost-effectiveness of oral azacitidine and noted the existence of multiple structural and parameter assumptions that likely bias the ICER in favour of oral azacitidine. Accordingly, the ICER is likely underestimated, and further price reduction is likely needed to reach a WTP threshold of $50,000 per QALY.

Background

Azacitidine has a HC indication as maintenance therapy for the treatment of adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment, and who are ineligible for HSCT. Azacitidine is a cytidine nucleoside analogue administered orally and is available as 200 mg and 300 mg tablets. The HC-approved starting dose of oral azacitidine is 300 mg orally once daily on day 1 through day 14 of repeated 28-day treatment cycles. The product monograph states that if the absolute neutrophil count (ANC) is less than 500 mcL on day 1 of a cycle, oral azacitidine should not be administered and the start of the cycle should be delayed until the ANC is 500 mcL or more.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- A review of 1 phase III RCT in patients with AML who had achieved first remission (CR or CRi) following induction with or without consolidation chemotherapy
- 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
- Three clinical specialists with expertise diagnosing and treating patients with AML
- Input from 2 clinician groups, including the Ontario Health - Cancer Care Ontario (OH-CCO's) Hematological Cancer Drug Advisory Committee (H-DAC) and the Alberta Tumour Board Myeloid Physician Group (ATB-MPG)
- 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 group, the LLSC, provided input for this review. The input was based on an online survey created by LLSC to which a total of 29 patients with AML responded.

Respondents in the LLSC survey indicated that symptoms of AML affected their daily lives and social relationships and caused detrimental health effects. Patient respondents reported being easily fatigued, being unable to exercise or work, nausea, bruising, numbness or body aches, and being immunocompromized. They noted that many of these symptoms led to feelings of isolation and fear of relapse and negative effects on their psychological well-being.

Patients reported that they expect new treatments to maintain remission, have fewer side effects, be lower cost, and being accessible in their local communities. They also noted that they consider the following factors when choosing a new cancer treatment: physician recommendation, impact on disease, quality of life, closeness of home, and outpatient treatment. No survey respondents had experience taking oral azacitidine.

Clinician Input

Input from clinical experts consulted by CADTH

The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of AML.

The clinical experts consulted by CADTH indicated that there are currently no standard funded maintenance regimens although watch-and-wait approach or BSC are recommended for patients in the target population. The clinical experts identified an unmet need for effective therapies with acceptable toxicity profiles that delay relapse, prolong survival, maintain HRQoL, and potentially lead to cure in patients with AML who are in their first remission and ineligible for transplantation. The clinical experts highlighted that an oral treatment would lead to higher adherence and reduce the need for hospital-based resources. The clinical experts agreed that oral azacitidine would likely shift the current treatment paradigm; however, they also agreed that more experience with maintenance oral azacitidine therapy will be necessary to determine potential impacts on the current treatment paradigm (e.g., potentially fewer patients requiring transplant, a reduction in the number of cycles of consolidation chemotherapy, and refinement of the target population).

The clinical experts agreed that patients as selected per the inclusion/exclusion criteria of the QUAZAR AML-001 trial should be eligible for maintenance oral azacitidine therapy. While the clinical experts agreed that there is currently insufficient evidence to guide a recommendation on which patient subgroups would be best suited for or be most likely to show response to oral azacitidine, in their opinion, the following potential patient subgroups likely have the highest risk of relapse and therefore may be the most in need of maintenance therapy: patients aged 65 years or older, patients with minimal residual disease (MRD) positive status, patients who have not received consolidation chemotherapy, and patients with poor-risk karyotypes. In the opinion of the clinical experts, patient subgroups who would potentially

benefit the least from oral azacitidine may include patients with MRD negative status, patients with low-risk features for relapse, patients who develop unacceptable toxicities, and patients lacking the social or medical support necessary to be safely treated with oral azacitidine.

The clinical experts agreed that patients would be identified as possible candidates for oral azacitidine treatment if they are considered ineligible for transplantation. The transplantation ineligibility status may be known in patients at the time of diagnosis or may develop over the course of their treatment. Clinical assessments to evaluate the response to treatment with oral azacitidine would include regular monitoring of blood counts (every 1 to 2 weeks) to determine if a patient maintains CR or CRi. If changes in blood count signal potential relapse, a bone marrow examination may be required to determine if a patient is still in CR or CRi or has relapsed AML. The clinical experts indicated that the most clinically meaningful responses to treatment include prolonged OS and RFS while maintaining or improving HRQoL and reducing symptom burden. No increase of drug-related toxicities such as infections, neutropenia, and thrombocytopenia and a reduced risk of relapse were also noted as clinically meaningful outcomes.

In the opinion of the clinical experts, treatment with maintenance therapy with oral azacitidine should be discontinued if a patient experiences relapsed AML, has a markedly impaired performance status, or is intolerant to or experiences unacceptable toxicity from oral azacitidine. If AML recurs with at least 5% of blasts in the peripheral blood or bone marrow, then oral azacitidine should be discontinued. There is currently insufficient evidence from the QUAZAR AML-001 trial to recommend dose escalation when AML recurs with blasts of at least 5% and no more than 15% either in the peripheral blood or bone marrow.

Clinician group input

Two clinician group inputs were received, 1 from the OH-CCO's H-DAC and 1 from the ATB-MPG. The views of the clinician groups were overall consistent with the clinical experts consulted by CADTH indicating that the most important treatment goals are prolongation of life and remission as reflected by the pivotal trial's primary and key secondary end points, OS and RFS, respectively, as well as an improvement in quality of life. Similar to the clinical experts consulted by CADTH, the clinicians from OH-CCO's H-DAC reported that they would generalize the QUAZAR AML-001 trial results to patients younger than 55 years of age. In addition, the clinician group stated that patients with myelodysplastic syndrome (MDS) who have progressed on subcutaneous azacitidine and subsequently received induction chemotherapy with or without consolidation and achieve CR, if transplantation ineligible, may also benefit from oral azacitidine based on pharmacokinetic data. There was consensus among the clinical experts consulted by CADTH and the clinicians from both clinician groups that the place of therapy for oral azacitidine would be standard of care maintenance therapy for patients with AML who are in first CR and ineligible CR or HSCT.

Drug Program Input

The drug programs indicated that the standard approach for patients who have achieved CR or CRi after potential consolidation therapy is to "watch and wait" without any disease-targeting therapies. The drug programs noted that the HC product monograph for oral azacitidine indicates that oral azacitidine is not interchangeable with injectable azacitidine, which is available in generic form. As indicated by the product monograph, oral azacitidine is available as 200 mg and 300 mg tablets in a blister pack containing 7 tablets. The list price per tablet was noted as being extremely high. Furthermore, oral azacitidine would be supplied

in 7-day blister packs and dose adjustments or extending days of treatment (i.e., from days 1 to 14 to days 1 to 21) would have a significant effect on treatment costs or risk of wastage. The drug programs suggested that if partly filled prescriptions are mandated, jurisdictions may wish to limit the quantity dispensed (e.g., in 7-day increments versus the full 14 days of a 28-day cycle) and that dispensed quantities should align with the timing of clinical assessments and blood work. The drug programs highlighted that the most commonly reported serious adverse events of oral azacitidine is febrile neutropenia, and therefore patients may require granulocyte colony stimulating factor(s), which will be an added cost to patients' treatment.

Clinical Evidence

Clinical Trial

One ongoing, international, multi-centre, double-blind, placebo-controlled randomized phase III trial contributed evidence to this review (QUAZAR AML-001 trial). The QUAZAR AML-001 trial compared the efficacy and safety of maintenance therapy with oral azacitidine plus BSC versus placebo plus BSC in patients with AML in first CR. A total of 472 patients were randomized in a 1:1 ratio to receive maintenance oral azacitidine (300 mg tablets once daily for the first 14 days of each 28-day cycle) plus BSC or oral placebo (matching placebo tablets once daily for the first 14 days of each 28-day cycle) plus BSC. Randomization was stratified by age at time of induction therapy (55 to 64 years and ≥ 65 years), prior history of MDS or chronic myelomonocytic leukemia (CMML) (yes or no), cytogenetic risk category at time of induction therapy (intermediate-risk or poor-risk), and receipt of consolidation therapy following induction (yes or no). No crossover between the treatment groups was permitted. The primary outcome was OS, and the key secondary outcome was RFS. Other secondary end points included time to relapse and time to discontinuation from treatment. HRQoL measures, the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) and the Physical Impairment Numeric Rating (PINR) scale were included as secondary and exploratory outcomes, respectively. A symptom severity measure, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale was included as a secondary outcome.

The QUAZAR AML-001 trial enrolled adults, at least 55 years of age, diagnosed with AML or AML secondary to prior MDS or CMML, intermediate- or poor-risk cytogenetics, and who had achieved first remission (CR or CRi) following induction with or without consolidation chemotherapy. Patients were excluded if they were considered to be eligible for HSCT. Patients had to have an ECOG performance status of 0 to 3. The mean age of patients in the trial was 68.0 (standard deviation [SD]: 5.66) years of age. The oral azacitidine group had a lower proportion (oral azacitidine versus placebo) of male patients (49.6% versus 54.3%) and patients enrolled in trial sites in Asia (2.5% versus 7.3%); and a higher proportion of white patients (90.8% versus 84.2%) and patients enrolled in trial sites in Europe (70.2% versus 62.8%). The majority of patients had an ECOG performance status of 0 (48.7% versus 47.4%) or 1 (42.4% versus 45.3%) and intermediate cytogenetic risk (85.3% versus 86.8%). Most of the patients received 1 cycle (46.2% versus 43.6%) or 2 cycles (29.4% versus 32.9%) of consolidation therapy. The most common reason for transplantation ineligibility was age (64.7% versus 65.0%), followed by comorbidities (21.8% versus 21.4), and no available donor (15.5% versus 15.0%).

A post-relapse dose escalation (300 mg once daily from 14 days to 21 days of the 28-day cycle) was planned for patients with disease relapse with blasts of at least 5% and and less than 15% either in the peripheral blood or bone marrow. This dose escalation was used in the context of re-induction of remission, which is not consistent with the HC indication and the requested reimbursement criteria for oral azacitidine as maintenance therapy. The QUAZAR AML-001 trial was not designed to assess if dose escalation of oral azacitidine produces benefits for patients. Dose escalation has not been authorized by HC as per the product monograph.

Efficacy Results

At the final data cut-off date (July 15, 2019), the median duration of follow up for OS was [redacted] months in the oral azacitidine group and [redacted] months in the placebo group. Median OS was 24.7 (95% CI, 18.7 to 30.5) months in the oral azacitidine group compared with 14.8 (95% CI, 11.7 to 17.6) months in the placebo group, with a stratified HR of 0.69 (95% CI, 0.55 to 0.86; P = 0.0009) in favour of the oral azacitidine group. The OS results for the subgroups of interest, as pre-specified a priori in the protocol for this CADTH review, suggested that the treatment effect on OS for the subgroups was generally consistent with the primary analysis. The subgroup analysis by cycles of consolidation therapy suggested possible heterogeneity of treatment effect; however, a number of methodological issues limit the ability to interpret these results.

Median RFS was 10.2 (95% CI, 7.9 to 12.9) months in the oral azacitidine group and 4.8 (95% CI, 4.6 to 6.4) months in the placebo group with a stratified HR of 0.65 (95% CI, 0.52 to 0.81; P = 0.0001) in favour of the oral azacitidine group.

The percentage of patients that had relapsed was 64.7% in the oral azacitidine group compared with 76.5% in the placebo group. Median time to relapse was 10.2 (95% CI, 8.3 to 13.4) months in the oral azacitidine group and 4.9 (95% CI, 4.6 to 6.4) months in the placebo group.

Most patients in both treatment groups had discontinued study treatment (81.1% in the oral azacitidine group and 88.9% in the placebo group) at the time of the final analysis. The median time to treatment discontinuation was 11.4 (95% CI, 9.8 to 13.6) months in the oral azacitidine group and 6.1 (95% CI, 5.1 to 7.4) months in the placebo group.

Overall, there were no statistically significant or clinically meaningful differences between the oral azacitidine and the placebo groups in the observed mean changes from baseline at any post-baseline assessment for the EQ-5D-3L questionnaire (EQ-5D-3L health utility index and the EQ-5D visual analogue scale [VAS]), the PINR scale, and the FACIT-Fatigue scale. Furthermore, there were no statistically significant differences in the proportion of patients with clinically meaningful deterioration as well as a similar time to definitive deterioration between the treatment groups. Clinically meaningful deterioration and time to definitive deterioration were not reported for the PINR scale. All analyses performed on the HRQoL outcomes and symptom severity were non-inferential.

Harms Results

Nearly all patients in both study groups experienced at least 1 treatment-emergent AE (97.9% of patients in the oral azacitidine group and 96.6% in the placebo group). The most commonly reported AEs in the oral azacitidine and the placebo groups were nausea (64.8%

and 23.6%, respectively), vomiting (59.7% and 9.9%, respectively), diarrhea (50.4% and 21.5%, respectively), and neutropenia (44.5% and 26.2%, respectively). TEAEs led to discontinuation of study treatment in 13.1% of patients in the oral azacitidine group and 4.3% of patients in the placebo group. Grade 3 or 4 TEAEs occurred in 71.6% of patients in the oral azacitidine group and 63.1% of patients in the placebo group. The most commonly reported grade 3 or 4 AEs (oral azacitidine versus placebo) included neutropenia (41.1% versus 23.6%), thrombocytopenia (22.5% versus 21.5%), anemia (14.0% versus 12.9%), febrile neutropenia (11.4% versus 7.7%), and leukopenia (7.6% versus 6.0%). The percentage of patients experiencing serious TEAEs was 33.5% in the oral azacitidine group compared to 25.3% in the placebo group. The most common serious AEs reported in the oral azacitidine and the placebo groups were febrile neutropenia (6.8% and 3.9%, respectively), pneumonia (3.8% and 3.0%, respectively), and pyrexia (2.1% and 0.4%, respectively).

Notable harms included GI, myelosuppression, infections, fatigue, and hemorrhagic TEAEs. The percentage of patients experiencing GI AEs was 91.1% in the oral azacitidine group compared to 66.5% in the placebo group. The percentage of patients experiencing myelosuppression AEs was [redacted] in the oral azacitidine group compared to [redacted] in the placebo group. The percentage of patients experiencing infections was 62.3% in the oral azacitidine group and 52.8% in the placebo group. The percentage of patients experiencing fatigue was 29.7% in the oral azacitidine group and 19.3% in the placebo group. The most commonly reported hemorrhagic events (oral azacitidine versus placebo) included [redacted].

Critical Appraisal

Testing of treatment-by-time interactions in the overall Cox proportional hazards model suggested deviation from the proportional hazard assumption. Sensitivity analyses were performed to adjust for nonproportional hazards. Results of these analyses were consistent with the results of the proportional hazards analysis, which supported the results of the HR obtained in the primary analysis demonstrating that oral azacitidine improved OS for patients relative to placebo.

A higher proportion of patients in the placebo group compared with the oral azacitidine group received subsequent systemic therapy and subsequent transplantation after discontinuing study treatment. Results from planned sensitivity analyses, including censoring for the use of subsequent therapy or subsequent transplantation, were consistent with the primary OS results. Given the consistent results obtained in the sensitivity analyses and the fact that clinical experts consulted by CADTH anticipated limited impact of post-relapse therapy on survival, the potential of confounding effects on survival outcomes from subsequent treatment is expected to be low.

Only the primary end point, OS, and the key secondary end point, RFS, were included in the statistical hierarchy and adjusted for multiplicity. No adjustment for multiplicity was made for any other analyses of other outcomes in the trial, such as HRQoL and symptom severity.

Methodological issues limited the ability to interpret the results from subgroup analyses. The subgroup analyses were non-inferential, wide CIs reflected uncertainty in the effect estimates, and small sample sizes limited the generalizability to a broader population.

The interpretation of results for the EQ-5D-3L and FACIT-Fatigue scale is limited and results for the PINR scale are inconclusive, given several important limitations including the non-

inferential analyses, the significant decline in patients available to provide assessments over time, and the use of an unestablished method to derive a minimally important difference.

The standard dose of oral azacitidine in the trial would be the dose used in Canadian clinical practice and is in line with the HC–approved dosing. Post-relapse dose escalation, which was attempted in the QUAZAR AML-001 trial to reinitiate remission, is not generalizable to clinical practice in Canada according to the clinical experts consulted by CADTH and has not been approved by HC. The clinical experts noted that it is unlikely that dose escalation would significantly influence the clinical outcomes observed in the trial due to the small numbers of patients who received dose escalation relative to the study sample size.

Economic Evidence

Table 2: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population(s)	Adult patients with AML who achieved CR/CRi following induction therapy or without consolidation treatment and who were ineligible for HSCT. Reimbursement request aligns with HC-approved indication
Treatment(s)	Oral azacitidine 200 mg or 300 mg (Onureg) in combination with BSC
Submitted price	$952.00 per 200 mg tablet $1,428.00 per 300 mg tablet
Treatment cost	$19,992 per 28-day cycle
Comparator(s)	BSC (i.e., no active therapy), which includes red blood cell and platelet transfusions; use of an erythropoiesis-stimulating drug; antibiotic, antiviral, and/or antifungal therapy; nutritional support; and/or granulocyte colony-stimulating factor for patients experiencing neutropenic infections.
Perspective	Canadian publicly funded health care payer
Outcome(s)	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	RFS, OS, and treatment duration: QUAZAR AML-001 trial (data cut: July 15, 2019)
Key limitations	• The comparative clinical effectiveness (i.e., incremental QALYs) of oral azacitidine is uncertain. The sponsor's model results suggested that patients receiving oral azacitidine lived longer following relapse than those receiving no active therapy. This post-relapse survival benefit lacks face validity and was not supported by the clinical evidence. Additional uncertainty was contributed by several concerns about the goodness-of-fit of parametric survival models used to extrapolate RFS and OS data. Estimates of incremental effectiveness are likely biased in favour of azacitidine.

Component	Description
	• The sponsor excluded the dose extension from the calculation of oral azacitidine cost. This limitation is likely to overestimate the clinical benefits but underestimate the cost of oral azacitidine and the resulting ICER, because dose extension was considered in the evaluation of the RFS and OS end points. • The sponsor assumed that a smaller proportion of patients treated with oral azacitidine would receive HSCT than would those with no active therapy. This assumption did not align with feedback provided by clinical experts consulted by CADTH and was likely to underestimate the ICER.
CADTH re-analysis results	• CADTH revised the sponsor's model to consider dose extension in the calculation of oral azacitidine costs. • Based on the CADTH's base case, oral azacitidine + BSC is associated with an ICER of $355,456 per QALY compared with BSC alone. • A price reduction of at least 85% would be needed for oral azacitidine to be cost-effective at a WTP threshold of $50,000 per QALY. This price reduction value is likely an underestimate.

AML = acute myeloid leukemia; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete blood count recovery; HC = Health Canada; HSCT = hematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; RFS = relapse-free survival; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainty around the estimates used to derive the size of the eligible population; the use of median time on treatment to calculate total drug acquisition costs underestimated costs associated with oral azacitidine; dose extension was not considered; several relevant costs under the drug plan perspective were not considered.

The CADTH reanalyses included changing the total number of incident AML cases and the proportion of patients who achieved CR/CRi and were ineligible for stem cell transplant; incorporating all relevant drug costs under the drug plan perspective; updating the dose extension assumptions to align with expectations; estimating treatment duration based on the mean; and assuming the same proportion of patients are eligible to receive HSCT from the treatment and comparator groups.

Based on the CADTH reanalyses, the budget impact from the introduction of oral azacitidine would result in an incremental budget impact of $17,098,655 in year 1, $36,262,769 in year 2, $47,286,342 in year 3, for a total budget impact of $100,647,777 over the 3-year time horizon.

CADTH was unable to address limitations related to the uncertainty around the estimated proportion of patients eligible to receive full oral therapy coverage across all provinces, which has an affect on the estimated total population eligible for treatment. Changes in population size are associated with significant changes in the budget impact, as shown in scenario analyses varying the proportion of patients with oral therapy coverage.

CADTH

CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) Information

Members of the 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. 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: August 11, 2021

Regrets: One expert committee member did not attend

Conflicts of interest: None

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

Note that this appendix has not been copy-edited.

Table 3: pERC Responses to Drug Program Implementation Questions

Implementation issues	Responses from the expert committee
Considerations for initiation of therapy	
Which induction/consolidation therapies were used in the QUAZAR trial?	In the QUAZAR AML-001 trial, the most commonly received induction therapies included cytarabine, idarubicin, and daunorubicin. The most commonly received consolidation therapies included cytarabine, idarubicin, and daunorubicin.
Which induction/consolidation therapies are appropriate/acceptable to be eligible for azacitidine maintenance?	pERC agreed with the clinical experts consulted by CADTH that standard prior therapies currently received by patients in Canada are acceptable to be eligible for oral azacitidine maintenance therapy. The most commonly received induction therapies used in Canada are standard-dose cytarabine with an anthracycline (i.e., 7 + 3) or fludarabine plus high-dose cytarabine plus G-CSF (i.e., FLAG) with or without idarubicin in patients with high-risk disease. The most commonly received consolidating therapy is HiDAC.
Would patients with FLT3 mutation positive AML who received midostaurin in combination with induction and/or consolidation chemotherapy be eligible for oral azacitidine maintenance?	pERC agreed that it would be reasonable to offer oral azacitidine maintenance to patients who received induction therapy with gemtuzumab ozogamicin, provided they meet the reimbursement conditions specified in Table 1 of the CADTH Reimbursement Recommendation. As well, pERC agreed with the clinical experts that it would be reasonable to offer oral azacitidine maintenance therapy to patients who are FLT3 mutation positive and who received midostaurin in combination with induction and/ or consolidation chemotherapy. This patient group in first CR is at high risk of relapse and there is no biologic rationale to assume that outcomes of oral azacitidine would be different in patients with FLT3 positive AML.
Considerations for continuation or renewal of therapy	
How/when will patients be assessed for possible dose changes (including reductions and/or extending the number of treatment days based on clinical response)?	In the QUAZAR AML-001 trial, response assessment (according to IWG AML response criteria) for maintaining CR or CRi, was planned to occur every 3 cycles starting at cycle 3 and at the treatment discontinuation visit. pERC agreed with the clinical experts that patients should have regular clinical assessments and monitoring of blood work every 1 to 2 weeks in the beginning of treatment, moving to once a month at the start of every treatment cycle later on (i.e., the timing of moving assessments to once a month should be at the discretion of the treating clinician but will likely occur after 3 to 4 cycles).

Implementation issues	Responses from the expert committee
Considerations for prescribing of therapy	
The recommended starting dose is 300 mg orally daily on days 1 through 14 of a 28-day treatment cycle. In the clinical trial, QUAZAR AML-001, patients who had evidence of relapse with blasts ≥ 5% and ≤ 15% in either peripheral blood or bone marrow were eligible for an increase in the number of doses per cycle from 14 days to the first 21 days of each 28-day treatment cycle. • Are the increased number of doses recommended for patients losing response, as it is not reflected in the product monograph?	In the QUAZAR AML-001 trial, a post-relapse dose escalation (300 mg once daily from 14 days to 21 days of the 28-day cycle) was allowed for patients with disease relapse with blasts ≥ 5% and ≤ 15% either in the peripheral blood or bone marrow. This post-relapse dose escalation explored whether oral azacitidine could be used to reinitiate remission, however this is not consistent with the HC indication or the CADTH reimbursement request, which is for oral azacitidine as maintenance therapy. pERC agreed with the clinical experts that there is currently insufficient evidence to attempt dose escalation in Canadian clinical practice and felt that it is not reasonable to generalize the QUAZAR AML-001 trial results to oral azacitidine used to reinitiate remission.
Generalizability	
Patients were excluded from QUAZAR AML-001 if they were candidates for HSCT at the time of study. Should the following patients be eligible for azacitidine maintenance? • Patients who are transplant-ineligible immediately following completion of induction with or without consolidation, but where HSCT may be planned at some point in the future if the patient's eligibility status changes. • Patients < 55 years of age (who were excluded from the trial).	In the QUAZAR AML-001 trial, some patients were eligible to undergo subsequent HSCT (6.3% of patients in the oral azacitidine group and 13.7% in the placebo group). The clinical experts consulted by CADTH noted that patients would be identified as possible candidates for oral azacitidine treatment if they are considered ineligible for transplantation. The transplantation ineligibility status may be known in patients at the time of diagnosis or may develop over the course of their treatment. pERC agreed with the clinical experts that a patient could be reconsidered as eligible for HSCT if their comorbidities improve/resolve while on maintenance oral azacitidine and could undergo HSCT before or after disease relapse. The QUAZAR AML-001 trial inclusion criteria specified that patients had to be ≥ 55 years of age. However, pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to generalize the QUAZAR AML-001 trial results to patients aged less than 55 years given the acceptable safety profile of oral azacitidine and that there is no biologic rationale to assume that outcomes of oral azacitidine would be different in younger adult patients with AML who otherwise meet the trial's inclusion criteria.

AML = acute myeloid leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; FLAG = fludarabine + high-dose cytarabine + G-CSF; FLT3 = FMS-Like Tyrosine Kinase 3 gastrointestinal; G-CSF = granulocyte colony-stimulating factors; HC = Health Canada; HiDAC = high-dose cytarabine; HSCT = hematopoietic stem cell transplant; pERC = pCODR Expert Review Committee; 7 + 3 = standard-dose cytarabine with an anthracycline.