CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

AZACITIDINE (Onureg)

(Celgene Inc., a Bristol Myers Squibb Company)

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

March 26, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0245-000
Generic Drug Name (Brand Name)	**Azacitidine (Onureg)**
Indication	**Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT).**
Name of the Clinician Group	**Alberta Tumour Board Myeloid Physicians Group**
Author of the Submission	**Dr Adam Bryant**
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are a group of physicians who treat myeloid malignancies and acute leukemias (myelodysplastic syndromes, myeloproliferative neoplasms, acute myeloid leukemia and acute lymphoblastic leukemia) within Alberta and function as a group within the Alberta Hematology Tumour Group. We meet as Edmonton and Calgary groups weekly to discuss patient cases and upcoming and open clinical trials. Provincially we meet quarterly to discuss clinical trials, streamlining of patient care across the province, and improving diagnostics, management, and follow-up of patients with myeloid disease. We also meet annually at a provincial level to update Alberta provincial treatment guidelines for these diseases.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Members of the Alberta myeloid tumour group are hematologists who work in academic and community based settings to treat patients with hematologic disease. We review data for new drugs as publications come out and review evidence for optimal patient treatment in an Alberta context as we develop guidelines for patient care in a formal setting every year. We review literature and have group discussions around care. Written guidelines are reviewed in a group setting, modified based on written and oral discussion and edits, and approved by the group before publication on the website.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

A majority new AML cases are diagnosed in patients that are elderly and/or comorbid. Most patients (80%) are diagnosed with intermediate or high risk AML, which often achieves remission with induction chemotherapy, but will invariably relapse without further chemotherapy to consolidate and maintain remission. In patients who are fit and younger than 70, allogeneic stem cell transplantation is the post-remission standard of care and offers the potential for cure. Many patients are not eligible for allotransplant given the serious and prohibitive morbidity and mortality this procedure poses for older or comorbid patients. In the current treatment landscape there is unfortunately no available post-remission therapy for AML patients who are not transplant candidates, and prognosis in their cases is guarded and generally measured in months.

Results recently reported from the Quazar AML-001 study (Wei et al NEJM 2020) provided a promising option for these patients, potentially addressing a large unmet need in the AML treatment landscape. In a group of transplant-ineligible AML patients in remission, oral Azacitidine, administered at 300 mg for 14 days out of a 28 day cycle, was associated both with a significant prolongation of remission (relapse free 45 vs 27% at 12 months, $p<0.001$), and a significant improvement in overall survival (73 vs 56% at 12 months, $p <0.001$) when compared to placebo. Oral Azacitidine was generally well tolerated and carries important quality of life and feasibility advantages in that it is oral, obviating the need for frequent visits to treatment centres for therapy.

Given the promising results reported with its use, and the convenience of administration, we believe oral Azacitidine, if readily available, would become the standard of care post-remission therapy for this large group of transplant-ineligible patients. This has the potential to change the treatment landscape in that there is no comparable alternative therapy for this sizeable group of patients.

On 1 September 2020 the Food and Drug Administration approved oral Azacitidine for post-remission treatment of transplant-ineligible AML patients. Health Canada subsequently approved of its use in this same population on 12 January 2021. In Alberta oral Azacitidine is currently accessed only through compassionate access from the drug manufacturer, a program whose accessibility is expected to be temporary, can be cumbersome to navigate, and may not be available for all candidate patients.

There are currently no available treatment options that offer prolonged survival for these patients. Remaining options involve a palliative approach focused on transfusion support, hydroxyurea, treatment of infections, and general symptom based care.

In practical terms, the current treatment landscape this group of AML patients is bleak. Oral Azacitidine has the potential to change this landscape, and to offer improved survival and quality of life for a large group of AML patients who otherwise have no other options available to them.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Prolong life, prolong disease-free state, and improve health-related quality of life. In the care of AML patients, this includes reducing transfusion needs, hospital admissions, and severity of symptoms. Other important quality of life goals include minimizing adverse events, decreasing hospital visits to receive therapy (particularly important for patients who live far from treatment centres and/or are not independent), and reduction of burden on caregivers.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Treatment goals in this population involve extending life and improving quality of life, and the available options do not address these needs. Given the non-curative nature of non-transplant approaches, and the elderly and/or comorbid nature of this target population, treatments are urgently needed that not only prolong remission and survival but that also do so without adversely affecting quality of life - meaning they are easy to administer, and are convenient and well tolerated. This is particularly important for patients who are not independent and for their caregivers, who together may struggle to manage the demands more intensive therapies.

Oral Azacitidine addresses many of these important unmet needs for this substantial population of AML patients, for whom no better alternatives exist.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

This therapy would be targeted for all transplant-ineligible patients with intermediate or high risk AML who achieve remission after induction chemotherapy. Patients may have received additional cycles of chemotherapy to consolidate their remission. Given that the large majority newly diagnosed AML have intermediate or high risk disease, and that a sizeable portion of these patients are not candidates for allogeneic stem cell transplant, this group of patients represents a substantial cohort of AML patients. Without additional therapy this large group of will patients invariably relapse, with a prognosis that is measured in months.

Oral Azacitidine has potential to have landscape-changing impact given the size of the candidate population and the lack of realistic alternatives. This remains a large therapeutic hole in the treatment landscape and oral Azacitidine has potential to address a huge unmet need.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Oral Azacitidine would become the standard of care and first line post-remission* maintenance therapy for patients who are not candidates for allogeneic stem cell transplant.

Oral Azacitidine offers the prospect of prolonged remission and prolonged survival, and with decreased disease-related complications, an acceptable safety profile, and convenient oral administration, oral Azacitidine also offers real potential for improved quality of life. These qualities would also be expected to result in substantial reduction in healthcare burden to patients, their caregivers, and to the healthcare system as a whole. Oral Azacitidine could be expected to cause a shit in the current treatment paradigm for this group of patients for whom few other therapeutic options exist.

**Prior to starting oral Azacitidine, patients may have received additional cycles of chemotherapy to consolidate their remission, emulating eligibility criteria for the Quazar AML-001 study.*

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Given the limited treatment landscape, there are no other treatment options available for this select group of patients that we would recommend trialing before oral Azacitidine. Oral Azacitidine would be offered as a first line post-remission therapy for all candidate patients. Prior to starting oral Azacitidine, patients may have received

additional cycles of chemotherapy to consolidate their remission, emulating eligibility criteria for the Quazar AML-001 study.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Sequencing of post-remission* therapy for all AML patients who are not candidates for allogeneic stem cell transplant

Front Line
- Oral Azacitidine (oral Azacitidine)

Second Line
- Clinical Trial if available
- Palliative supportive therapy (transfusion, hydroxyurea, symptom-driven care)

**Prior to starting oral Azacitidine, patients may have received additional cycles of chemotherapy to consolidate their remission, emulating eligibility criteria for the Quazar AML-001 study.*

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Oral Azacitidine would be offered as a first line post-remission* therapy for all AML patients with intermediate or high risk disease who are not candidates for allogeneic stem cell transplant. This would be offered to all patients who meet these broad criteria. To date no subpopulation of these patients has been identified with a higher potential for favorable outcomes.

**Prior to starting oral Azacitidine, patients may have received additional cycles of chemotherapy to consolidate their remission, emulating eligibility criteria for the Quazar AML-001 study.*

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Clinician examination and assessment. This is an objectively diagnosed disorder and testing is widely available. Candidacy (or non-candidacy) for allogeneic stem cell transplant involves complex multifactorial clinical assessment and judgement, and may additionally require formal allogeneic stem cell transplant consultation and assessment to confirm non-candidacy.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients who would otherwise be a candidate for allogeneic stem cell transplant.

Patients included in clinical trials with Oral Azacitidine were as elderly as 86. As this is a non-intensive therapy intended to be tolerable to a wide range of patients, identification of patients who are too elderly or comorbid to trial oral Azacitidine would fall to a multifaceted clinical judgement on the part of the treating physician. Patients who choose against Oral Azacitidine therapy for personal or other reasons would not be suitable.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Not at this time. Available data from the Quazar AML-001 trial suggested that the benefit seen with oral Azacitidine was consistent across all subgroups analyzed. Potential identification of particular subpopulations that may experience greater benefit would require further long term analysis complimented by additional patient and clinical experience with oral Azacitidine use.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

1) Bone marrow biopsy to assess disease response
2) Improvement in cytopenias and transfusion needs, decrease in blast counts in peripheral blood
3) Quality of life, measured subjectively by patient described experiences and objectively through quality of life scores.

These are aligned with outcomes used in the clinical trials, although bone marrow biopsy to assess for relapse is done more frequently in a clinical trial setting.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

1) Remission status on bone marrow biopsy
2) Reduced or eliminated transfusion requirements for red cells and platelets
3) Improvement in disease related symptoms including infections, bleeding, and fatigue, amongst others
4) Improvement in functional status owning to improvements in cytopenias, decreased disease related complications, and decreased need for hospital admission and outpatient visits to for therapy administration, transfusion or other support, or for management of disease-related complications fewer hospital admissions or outpatient visits for transfusion support.
4) Improvement or maintenance of quality of life, as measured subjectively by patient described experiences and objectively through quality of life scores

6.10. How often should treatment response be assessed?

Response:

Patients undergoing initial therapy will have labwork done weekly for to assess for transfusion needs and to assess for drug side effects. This monitoring will steadily decrease in frequency to monthly depending on individual transfusion needs, cytopenias, drug tolerability, and stability of treatment response.

Improvement in cytopenias and transfusion requirements will be monitored as patients proceed through each cycle. Marrow biopsy after 4-6 cycles will be a definitive indicator of disease response. Once remission or maximal response is obtained, repeat bone marrow biopsy would be indicated if there is clinical deterioration, significant cytopenias, or other clinical findings requiring reassessment of disease status.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression as measured by peripheral blood indices, transfusion needs, and definitively by bone marrow biopsy

Treatment intolerance which could include: cytopenias complicated by recurrent severe infections, transfusion needs that do not improve after 4-6 cycles of therapy, intolerable adverse effects (i.e. gastrointestinal intolerance), or patient preference. Therapy cessation for these factors will amount to physician clinical judgement.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Outpatient cancer clinic, community setting where regular lab and transfusion support is available.
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** Not applicable
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: No

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information

Name	Michelle Geddes
Position	Hematologist, Foothills Medical Centre and Tom Baker Cancer Centre
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	☒	☐	☐	☐
Jazz	☒	☐	☐	☐
Celgene/BMS	☐	☒	☐	☐
Taiho	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Astellas	☒	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	Kareem Jamani
Position	Hematologist, Tom Baker Cancer Centre & Clinical Assistant Professor, University of Calgary
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	☒	☐	☐	☐
Jazz	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

Paladin	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	Dr. Aniket Bankar
Position	Hematologist and Assistant Professor, University of Alberta Hospital, Edmonton, AB
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
AbbVie	☒	☐	☐	☐
Pfizer	☒			

Declaration for Clinician 4

Clinician Information	
Name	Adam Bryant
Position	Clinical Assistant Professor
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
No conflicts of interest to disclose	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	Deirdre Jenkins
Position	Clinical Associate Professor
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
No conflicts of interest to disclose	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	Sonia Cerquozzi
Position	Clinical Assistant Professor
Date	26 March 2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☐	☒	☐	☐
Celgene/BMS	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0245-000
Generic Drug Name (Brand Name)	oral azacitidine (Onureg) – Celgene-BMS
Indication	**Indications:** Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT). **Manufacturer Requested Reimbursement Criteria1**: Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT).
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Hematological Cancer Drug Advisory Committee (DAC)**
Author of the Submission	Dr. Tom Kouroukis, Dr. Janet MacEachern, Dr. Jordan Herst, Dr. Lee Mozessohn
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

This input was jointly discussed at a DAC meeting

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Currently there is no funded maintenance therapy for these patients. Patients will be treated with induction chemo +/- consolidation and followed by surveillance.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

Prolong life – as reflected by the primary endpoint overall survival; improve quality of life

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Currently there is no other maintenance treatment for these AML patients.

Maintenance azacitidine demonstrated overall survival benefit in a patient population that had not seen a benefit of new therapies dating back to 1973 when 7+3 became the standard of care.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

For patients who are not transplant eligible (including those who don't have an available donor), AML remains a highly lethal cancer with poor outcomes.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Maintenance therapy for AML patients in CR1 and ineligible for HSCT.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Not applicable.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

No effect.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

As per study inclusion, including patients who do not have any available donor.

Although not included in the pivotal trial:

- Maintenance oral azacitidine would also be appropriate for patients < 55 y.o.
- MDS patients who progressed on sc azacitidine, and subsequently received induction chemo +/- consolidation and achieve CR, if transplant ineligible, they may benefit from oral azacitidine based on pharmacokinetic data

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Diagnosis of AML treated with induction therapy +/- consolidation in complete remission who are ineligible for transplant

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

All transplant ineligible patients in CR1 would be equally suitable for oral azacitidine.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

There are no subgroup of patients who did not benefit.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

As per usual clinical practice and continue drug until clinical overt relapse. Bone marrow is not necessarily required.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Absence of relapse

6.10. How often should treatment response be assessed?

Response:

CBC and bone marrow surveillance as per clinician judgment

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression or treatment intolerance

6.12. What settings are appropriate for treatment with the drug under review?
Examples: Community setting, hospital (outpatient clinic), specialty clinic ***Response:*** Community setting – oral azacitidine is a take home cancer drug
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** NA
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: None

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the DAC in completing this input.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each</u>**

clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Tom Kouroukis*
Position	*Provincial Head – Complex Malignant Hematology (OH-CCO)* *Chair – Hematology Cancer DAC*
Date	*11-Mar-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Janet MacEachern*
Position	*Hematologist/Oncologist*
Date	*11-Mar-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Lee Mozessohn*

Position	*Hematologist/oncologist*
Date	*11-March-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Jordan Herst*
Position	*Hematologist/oncologist*
Date	*11-Mar-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐