CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

venetoclax (Venclexta)

AbbVie Corporation

Indication: Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.

January 29, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0238-000**
Generic Drug Name (Brand Name)	**Venetoclax and azacitidine**
Indication	**Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.**
Name of the Clinician Group	**Alberta Tumour Board Myeloid Physicians Group**
Author of the Submission	**Dr. Michelle Geddes**
Contact information	Name: Dr. Michelle Geddes Title: Clinical Associate Professor, Hematology, University of Calgary Email: [redacted] Phone: [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 regularly to discuss patient cases and upcoming and open clinical trials on a regular basis, and provincially we meet every 3 months and also annually to update treatment guidelines for Alberta for care of 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 literative 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:

Currently for patients with AML who are ineligible for induction chemotherapy, common clinical practice is to use azacitidine 75 mg/m2/d for 7 days every 28 days in the majority of patients, and some patients receive low dose cytarabine 20 mg bid daily for 10d. This is supported by our Alberta AML guidelines available at https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe006-aml.pdf as well as NCCN guidelines and common clinical practice. For patients with complex cytogenetics, a large proportion of our elderly patients, there was no survival benefit seen in AML with cytarabine, and azacitidine is preferred. Currently azacitidine is approved for patients with low blast count AML (20-30%) in Canada but it is commonly used and provides clinical benefit to patients unfit for induction chemotherapy with acute myeloid leukemia in common practice in Alberta and many other provinces with blast counts higher than 30%.

There is temporary compassionate access to an oral decitabine/cedazuridine compound which is available to patients with low blast count AML (20-30%). Ongoing access to this drug is not yet established.

Palliative basic supportive care options include hydroxyurea and blood transfusion support as well as antibiotics. Patients are also offered clinical trials when they are available.

In practical terms, patients are aware of the combination of venetoclax and azacitidine and some patients have been self-funding venetoclax with the use of CYP3A inhibitors to reduce the dose of venetoclax and therefore the cost. This has in effect been resulting in inequal access to care among patients in our province.

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, and improve health-related quality of life. In the care of AML patients, this includes reducing transfusion needs, hospital admissions, and severity of symptoms. Important goals include minimizing adverse events, 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:

Not all patients respond to available treatments, and all patients become refractory to current treatment options (azacitidine or cytarabine), with a limited life expectancy on these medications. There are few effective treatment options after relapse of up front AML therapy in patients unfit for intensive chemotherapy and transplant, and most patients will receive the alternative drug to what they received (azacitidine or cytarabine). The minority of patients who have flt3 mutations may then receive gilteritinib, and many patients are not well enough to tolerate further therapy and therefore receive best supportive care ie transfusions and symptoms management, with a very short life expectancy in the range of months.

Another important point is that average time to remission for azacitidine is around 4 months and maximal response can take >6 months; during this time many patients are transfusion dependent and may have admissions to hospital with infection, as well as significant burden of disease. Median time to response for the venetoclax and azacitidine combination is 1.2 months, with a much faster time to response and clinical improvement.

It is imperative that we provide our most effective treatment in the front life to provide survival benefit and the longest possible duration of response, with patients well and able to tolerate therapy, and often remaining active in the community.

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:

All patients who are unfit for induction chemotherapy with AML are in need of a better treatment option. At this time the treatment option with the best evidence is combination venetoclax and azacitidine.

Most of these patients are older, or have comorbidities that make them unable to tolerate intensive inpatient induction chemotherapy. A few patients decline intensive inpatient therapy for personal reasons.

This drug combination (azacitidine and venetoclax) is the treatment with the best evidence to improve survival and relapse-free surival in patients with AML unfit for induction. It is not a curative therapy, but has an excellent tolerance profile, is an oral outpatient drug, and provides clinically significant survival benefit and relapse-free survival benefit for these patients.

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:

This would become the standard of care for induction of remission in patients unfit for induction chemotherapy for AML due to strongest evidence for survival and relapse-free survival benefit, and a good tolerability profile. Some patients would benefit from venetoclax and cytarabine induction ie due to difficulty with travel or caregiver needs for daily subcutaneous azacitidine or intolerance to azacitidine, or possibly specific molecular profiles of disease, and this is also a good potential option for initial therapy in these patients.

This drug would be used as first line therapy for these patients.

For some patients who received induction chemotherapy and relapsed but are no longer eligible for transplantation, or relapsed after transplantation, and have never received hypomethylating agents such as azacitidine before, we commonly use azacitidine and the combination of azacitidine and venetoclax would be expected to be more effective. This population is not addressed in this CADTH application.

This drug is expected to cause a shift in the current treatment paradigm, as it is significantly more effective in survival and relapse-free survival, with a shorter time to maximal disease response, than current front line treatment options.

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:

The best evidence for this combination of drugs is in the front line setting, and especially in a disease where there are very limited options to treat relapsed disease, this should be recommended as first line therapy for patients unfit for induction chemotherapy. Response rates to adding venetoclax to azacitidine in patients who have progressed on azacitidine alone are consistently in the 20-30% range, and this drug is most effective when used as first line treatment.

Many patients who relapse leukemia and were unfit for intensive chemotherapy up front may not be medically fit for second line therapy at relapse, and available agents would be expected to provide short responses. These patients have a limited life expectancy.

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:

Front line:
venetoclax and azacitidine (or venetoclax and cytarabine)

Second line:
if flt3 positive AML - gilteritinib
if flt3 negative AML - cytarabine if initially treated with azacitidine, azacitidine if initial treatment with cytarabine

Third line:
hydroxyurea and transfusions, basic supportive care

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:

Patients with newly diagnosed AML unfit for intensive chemotherapy due to age, comorbidities, or patient decision not to undergo intensive treatment that is potentially curative.

All of these patients are in great need of more effective therapy than our current treatment options.

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 judgement, bone marrow biopsy results.
This is an objectively diagnosed disorder and testing is widely available.

Patients with the diagnosis of AML should be treated at the time of diagnosis; they would be expected to decline rapidly without diagnosis and may develop serious infections or other complications that preclude effective treatment if they are not treated at diagnosis.

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

Response:

Patients who may not tolerate treatment can include patients with severe comorbidities and poor functional status; this is a clinical judgement for patients who would not tolerate chemotherapy of any kind.

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:

Some patients with specific molecular mutations on next generation sequencing may be expected to respond better to this treatment combination, however this is on subgroup analysis and there is no patient group that would not be expected to benefit within the group of patients for which this application has been made.

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.

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 symptoms; ie infections, bleeding, improved functional status due to improved hemoglobin and less hospital admissions or outpatient visits for transfusion support.

6.10. How often should treatment response be assessed?

Response:

Patients undergoing initial therapy will likely have CBCs done weekly for transfusion needs and to assess for drug side effects. Marrow biopsy after 1-2 cycles is an early indicator of disease response as median time to maximal response is 1.2 months; some patients take longer to respond and may need repeat bone marrow biopsy after another 1-2 cycles. Once remission or maximal response is obtained repeat bone marrow biopsy would be indicated if there is clinical deterioration or significant cytopenias 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
Treatment intolerance ie cytopenias complicated by recurrent severe infections where the patient is unable to continue treatment - this is a 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 if pharmacy support for azacitidine, inpatient setting
This would be identical to the current processes in place for azacitidine alone

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	Jan 29, 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	29-01/2021
☒	**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	29 Jan 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	29 Jan 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	29/01/2021
☒	**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	29/01/2021
☒	**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 Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0238-000
Generic Drug Name (Brand Name)	Venetoclax (Venclexta)
Indication	in combination with a hypomethylating agent in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy
Name of the Clinician Group	Canadian Leukemia Study Group (CLSG) Groupe Canadien d'Étude Sur La Leucemie (GCEL)
Author of the Submission	Mary Lynn Savoie
Contact information	Name: Lynn Savoie Title: Clinical Associate Professor Email: Phone:

1. About Your Clinician Group

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

CLSG/GCEL is a cross-Canada collective of acute leukemia treating physician representing all major leukemia centres in all provinces. The CLSG incorporation documents of 23.10.2019 define the purpose of CLSG/GCEL:

'To improve the diagnosis and treatment of leukemia in Canada, by identifying diagnostic and management best practices, promoting Canada-wide standards-of-care, fostering clinical and basic leukemia research, and improving new drug access.'

The CLSG/GCEL website: https://www.clsg.ca/

2. Information Gathering

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

CLSG board members are all leukemia physicians working in an academic, university-based treatment setting. CLSG opinions are evidence- and literature-based, and are buttressed by extensive collective experience. CLSG opinions and positions are defined via ongoing group discussions and polling of members, with input requested from other international experts, as appropriate. Written opinions are reviewed, edited, and approved by the group.

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:

Approx. 40-50% of newly diagnosed AML patients are judged to be unfit for intensive induction chemotherapy. This includes most patients age 75 and over, and younger patients with severe co-morbidities. For these patients the treatment options include single agent azacitidine, low-dose cytarabine (LDAC) or best supportive care alone. Although azacitidine is only approved for AML patients with 20-30% blasts, it is widely used in Canada and worldwide for patients with >30% blasts.

For patients with poor risk cytogenetics or AML transformed from MDS, azacitidine is the current treatment of choice, while for patients with AML arising de novo with standard risk cytogenetics azacitidine or LDAC can be used. In real-world clinical practice many patients in Canada are not able to receive azacitidine-based therapy, as this drug needs to be administered in an oncology clinic setting because of its instability after reconstitution. Many patients who live in rural areas, and some in urban settings, are unable to travel to these clinics regularly to receive treatment due to the distances involved, their overall frailty and challenges in obtaining suitable transportation.

The use of these agents is supported by Canadian consensus guidelines (Am J Blood Res 7(4):30-40, 2017).

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:

Elderly or unfit patients with newly diagnosed AML can enjoy a significantly improved quality of life and increased survival if they receive an effective treatment.
Most of these patients require blood products at diagnosis and when a repsonse is acheived there is a decrease in health care utilization due to decreased transfusion of red cells and platelets. The better the response the longer the period on transfusion idependence lasts.

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:

The best available therapy - single agent azacitidine produces a complete remission in less than a quarter of patients with an overall survival typically less than an year. These remissions also usually require several monthly cycles of therapy, up to six, to achieve maximal effect translating in to an extended period of transfusion dependence.
Once a maximally achieved response is lost disease progression is quite rapid typically followed quickly by death due to poor salvaged therapies.

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:

Patients who are 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy are a subset of all patients diagnosed with acute myloid leukemia. The average age at diagnosis of AML is 68 so this is not an insignificant number.
The combination under review represents an important and valuable therpeutic advance in this underserved population.

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:

Approval of the combination of venetoclax and azacitidine for front line therapy will absolutely cause a shift in the current treatment paradigm as show in other jurisdictions.
It will replace current front line therapies, including azacitdine alone, with only modest effects and will lead to improved overall survival and quality of life in the population with an unmet medical need.

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:

This is the best available therapy for newly diagnosed AML in an elderly or unfit population. It stands to reason that the best treatment should be used first.
Also, the data under review is for first line therapy with little solid data in more advance disease.

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:

After failure of the combination of venetoclax and azacitidine possible therapeutic options would inlcude therapy targeted to a specific molecular lesion if present and available, an early phase clinical trial, low dose cytarabine, best supportive care or palliation. This is not a departure from current practice.

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:

The entire cohort of pateints over the age of 75 or unfit for intensive chemotherapy would be expeted to respond to the combination under review. They are all in an underserviced population and the treament has been shown to more efficacious than azacitidine alone in most studies subgroups, de novo as well as AML that is secondary to other conditions, and broadly across molecularly or cytogenetically defined leukemia subgroups.

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:

Acute myeloid leukemia is easily diagnosed. There are many ancillary studies that can be done to help with subclassification and prognosis or to establish targetable lesions however this combination of drugs shows an excellent response across many of these groups obviating the need for rapid turn-around expensive investigations at diagnosis.

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

Response:

Patients in very remote areas or with significant mobility issue due to the need to present to a medical insitution for seven consecutive days out of 28. This is true of azacitidine alone. The added Venetoclax is oral so does not add to that burdern.

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:

The data under review shows an improved response over standard of care azacitidine alone in most subgroups therefore there is no need to subclassify patients as most will respond.

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:

Repeated monitoring of complete blood counts and bone marrow aspirates/biopsies are standard in all active treatment of AML as well as in clincal trials including the one under review here.

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:

A minimal clinically meaningful response to treatment would be improved quality of life followed by transufsion independence then complete remission followed by an increase in overall survival.

6.10. How often should treatment response be assessed?

Response:

After 1 - 2 cycles of treatment (4-8 weeks) in order to adjust dosing appropriately.

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:

Adverse events such as severe nausea or neutropenic infections.
Failure of response or disease progression.

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

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

Response:

Outpatient clinics with expertise in chemotherapy preparation and administration.

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:

Similar patients are already treated in many jurisdictions with azacitidine alone so adding an oral medication that is well tolerated with a straightforward administration schedule dose not increase the complexity of the treatment regimen. Also, the benefits obtained with the combination are obtained much quicker than with single agent azacitidine.

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.**

   Please see Clinician Declarations on Following Pages:

Declaration for Clinician 1

Clinician Information	
Name	Yasser Abou Mourad
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	18-01-2021
☑	**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	☐	☒	☐	☐
Amgen	☐	☒	☐	☐
Paladin	☒	☐	☐	☐
Jazz	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	Julie Bergeron
Position	Vice-Chair, CLSG/GCEL
Date (DD-MM-YYYY)	23-01-2021
✔	**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
AbbVie	■			
Pfizer	■			
Amgen	■			
Astellas	■			
BMS	■			
Novartis	■			

Declaration for Clinician 3

Clinician Information	
Name	Joseph Brandwein
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	18-01-2021
✔	**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	■			
Astellas	■			
Amgen	■			
Celgene/BMS	■			
Taiho	■			
Abbvie	■			
Jazz	■			
Roche	■			
Teva	■			
Novartis	■			

Declaration for Clinician 4

Clinician Information	
Name	Brian Leber
Position	Treasurer, CLSG/GCEL
Date (DD-MM-YYYY)	18-01-2021
☑	**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		■		
Abbvie		■		
Novartis			■	
BMS/Celgene		■		
AMGEN	■			
Jazz	■			
Astellas	■			
Astex	■			
Paladin	■			
Alexion	■			
Roche	■			
Otsuka	■			
Janssen	■			
Treadwell	■			

Declaration for Clinician 5

Clinician Information	
Name	Kristjan Paulson
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	18-01-2021
✔	**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
Jazz Pharma	■			
Pfizer		■		
AMGEN	■			
Astellas	■			
Novartis	■			
BMS	■			

Declaration for Clinician 6

Clinician Information	
Name	Waleed Sabry
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	23-01-2021
☑	**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	☒			
BMS	☒			
Janssen	☒			

Declaration for Clinician 7

Clinician Information	
Name	Lalit Saini
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	19-01-2021
☑	**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	■			
Abbvie	■			
Tahio	■			
AMGEN	■			
Celgene/BMS	■			

Declaration for Clinician 8

Clinician Information	
Name	Mary Lynn Savoie
Position	Secretary, CLSG/GCEL
Date (DD-MM-YYYY)	20-01-2021
✔	**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
Amgen		■		
Novartis		■		
Pfizer			■	
Merck	■			
Astellas	■			
Jazz	■			
Celgene	■			
Abbvie	■			
BMS	■			

Declaration for Clinician [9]

Clinician Information	
Name	Andre Schuh
Position	Chairman of Board, CLSG/GCEL
Date (DD-MM-YYYY)	20-01-2021
✔	**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
AbbVie		■		
Agios	■			
Amgen	■			
Astellas		■		
BMS/Celgene		■		
GlycoMimetics	■			
Jazz	■			
Kite	■			
Novartis	■			
Paladin	■			
Phebra	■			
Pfizer		■		
Taiho	■			
Teva	■			

Declaration for Clinician 10

Clinician Information	
Name	John Storring
Position	Board Member, CLSG/GCEL
Date (DD-MM-YYYY)	18-01-2021
✔	**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

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Abbvie	■			
Amgen	■			
Astellas		■		
BMS/Celgene			■	
Jazz	■			
Novartis	■			
Paladin	■			
Pfizer	■			
Taiho	■			
Teva	■			

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0238-000
Generic Drug Name (Brand Name)	**Venetoclax**
Indication	**Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.**
Name of the Clinician Group	**Leukemia/Bone Marrow Transplant (L/BMT) Program of BC**
Author of the Submission	**David Sanford**
Contact information	Name: David Sanford Title: Hematologist Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

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

The L/BMT Program of BC is a joint program of BC Cancer and Vancouver Coastal Health with a primary mandate for the province to treat acute leukemia, perform stem cell transplantation and deliver cellular therapies for patients with hematologic malignancies. This submission was prepared by the members of the acute leukemia working group within the program. More information about the L/BMT Program of BC and treatment protocols used by the program can be found at the following sites:

http://www.leukemiabmtprogram.org/

http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/leukemia-bone-marrow-transplant

2. Information Gathering

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

For this submission, our group primarily reviewed the published data from the randomized phase 3 control trial (DiNardo CD, NEJM, 2020) as well the reported phase 1b trial (DiNardo CD, Blood 2019) of hypomethylating agents and venetoclax for newly diagnosed, older patients with AML. We also reviewed the most recent version of NCCN guidelines (Version 2.2021) for management of acute myeloid leukemia (AML). Our group has also previously reported provincial outcomes in BC for newly diagnosed older patients (age >/=60 years) treated with non-intensive and intensive therapies available here: https://ashpublications.org/blood/article/132/Supplement%201/3989/265378/Older-Adults-with-Acute-Myeloid-Leukemia-in-Rural.

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:

In BC, standard of care treatment options for older and unfit patients with newly diagnosed AML who are ineligible for intensive chemotherapy include: azacitidine, low-dose cytarabine (LDAC) and best-supportive care. Determination of eligibility for intensive chemotherapy is based on patient age, fitness, presence of comorbidities and patient preferences. In general, intensive chemotherapy is poorly tolerated in older patients and the majority of patients over age 70 years receive non-intensive therapy. In BC, azacitidine is given at many (although not all) BC Cancer sites as well as in other hospital outpatient settings depending on the geographic location and treating physician. The treatment is given as a subcutaneous injection usually in either a 7 day or 5+2 day schedule. Response to this treatment is often not evident before 3-4 cycles and is usually formally assessed around 6-7 cycles with a repeat bone marrow aspirate and biopsy. The treatment is continued indefinitely while patients are benefiting and tolerating the treatment. LDAC is given as a subcutaneous injection of 20 mg twice daily for 10 days every 4-6 weeks. This treatment can be given by the patient or a care-giver at home, and requires patient education by a chemotherapy trained nurse prior to initiation. This treatment is less frequently given than azacitidine, but is beneficial for patients that live a long distance from a centre that administers azacitidine or prefer to receive treatment at home. In the province of BC, we generally reserve LDAC for patients with an intermediate risk karyotype as previous studies have suggested it does not benefit AML patients with adverse karyotypes compared to supportive care alone. Older patients with AML also receive supportive treatments either in conjunction with azacitidine or LDAC or alone and this commonly includes: transfusion support, hydroxyurea, antibiotic treatment, pain control and palliative care. Currently, there are no relevant special access programs available for novel treatments for AML. Non-intensive treatments with LDAC and azacitidine can improve symptoms and result in clinical responses and a small proportion of patients achieve a complete remission. This treatment is associated with an improvement in overall survival, but is not considered curative and responding patients ultimately have disease progression.

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:

The most important goals for treatment in this group include:

-Prolongation of life

-Disease remission

-Time to remission

-Reduction in transfusion requirements

-prevention of infection

-improvement or maintenance of quality of life

-minimization of toxicity and adverse effects associated with treatment

Although treatment goals may differ for older patients, similar to younger patients with AML prolongation of life is an important goal for many.

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:

The primary unmet goals with current treatments for older and unfit patients not eligible for intensive chemotherapy are: low response rates and short overall survival. In the phase 3 RCT, the response rate (CR/CRi) for the azacitidine and placebo arm was only 28.3% and the median OS was 9.6 months. In comparison, the CR/CRi rate was 66.4% and the median OS was 14.7 months in patients that received azacitidine and venetoclax in the study. In a retrospective review of the BC population, the results with single agent azacitidine are consistent with the phase 3 RCT and the median OS in this group was only 7.1 months. In patients that received LDAC this was 4.7 months.

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:

The majority of patients who are diagnosed with AML are older and the median age at diagnosis is approximately 67 years. There is a pressing unmet need for more effective treatments in this large subset of patients. The combination of azacitidine and venetoclax represents a substantial improvement in efficacy over currently available standard of care treatments outlined above. There is increased myelosuppression with the combination of azacitidine and venetoclax compared to azacitidine, but this appears to be manageable and does not appear to be associated with a decrease in QoL.

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:

Venetoclax acts through inhibition of BCL-2 an anti-apoptotic molecule that is upregulated in many AML cases. The mechanism of venetoclax appears to complement azacitidine and clinical trial data supports a synergistic effect of these two agents. The combination is highly active in AML relative to other non-intensive therapies. There is a greater than doubling of response rates (CR/CRi) compared to azacitidine treatment alone (66 vs. 28%) and these response appear to be deep and relatively durable, with a duration of response of 17.5 months. Although many patients appear to ultimately progress on the combination, the longer term OS is still substantially better than treatment with azacitidine or LDAC alone. We anticipate that the combination of venetoclax and azacitidine would be used as a first-line treatment. We don't anticipate that this combination will be used as a later line of treatment in this patient group in the majority of patients. We believe that the introduction of this treatment will substantially shift the current treatment paradigm and anticipate that the majority of patients who would standardly receive single agent azacitidine or LDAC will be treated with the combination instead.

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:

We believe that the combination of azacitidine and venetoclax should be used as a front-line therapy and do not think there is evidence to support sequencing this after other treatments.

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:

At this time, there is no standard of care treatment for patients who do not respond to venetoclax and azacitidine or progress on this combination and we anticipate that the majority of patients would be treated with best-supportive care or possibly a clinical trial if available. This is similar to other currently available non-intensive treatments used in AML, where there is no standard 2nd line treatment. In patients receiving azacitidine and venetoclax frontline, we do not think currently there is evidence for re-treatment with the combination in a subsequent line of therapy.

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:

We agree with the recent Health Canada approval that the combination of azacitidine and venetoclax is best suited to treatment of patients with newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that precludes the use of intensive induction chemotherapy. The selection of age of 75 years or greater is based on the inclusion criteria for the phase 3 RCT, although this cut-off is somewhat arbitrary. Based on available registry data, we expect that in most centres in Canada only a relatively small number of AML patients over age 70 years are treated with intensive chemotherapy. There is some evidence that AML patients with mutations in genes IDH1 or IDH2 have a particularly good response to Azacitidine and Venetoclax, but other genetic subsets of AML as well as de novo and secondary AML also appear to benefit. We would not support limitation of the treatment beyond the Health Canada indication.

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:

AML is standardly diagnosed by the presence of greater than 20% myeloid blasts in the bone marrow or peripheral blood. Bone marrow examination is required for formal diagnosis and classification. In general, the diagnosis is relatively straight-forward and misdiagnosis is infrequent. The introduction of azacitidine and venetoclax would not require additional diagnostic tests. There is not a "pre-symptomatic" group of AML patients that would be considered for this treatment.

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

Response:

Younger, fit patients without significant comorbidities are less suitable for this treatment and generally should be treated with intensive chemotherapy. Patients that are not able to have regular blood-work monitoring for tumor-lysis syndrome during the initial ramp-up and regular monitoring of blood-work later on are also not good candidates for this treatment.

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:

As mentioned previously, patients with mutations in genes IDH1 or IDH2 appear to have a particularly good response to Azacitidine and Venetoclax, but other genetic subsets of AML as well as de novo and secondary AML also benefit. At this point, there is not a specific test or biomarker to indicate who will or won't respond or benefit from this treatment.

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:

Important outcomes in clinical practice are: remission status following treatment, tolerance of treatment, quality of life and transfusion requirements.

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:

A clinical meaningful response in most patients would a complete remission or complete remission with incomplete count recovery (CR/CRi) following 1-2 cycles of azacitidine and venetoclax. In patients without CR/CRi, a partial response (PR) or improvement in blood-counts may also be a meaningful improvement for some patients. In general, a sustained or durable remission in AML is usually

associated with several other important outcomes such as an improvement in quality of life and a reduction in transfusion requirements and hospital visits.

6.10. How often should treatment response be assessed?

Response:

We believe that response should be assessed with a bone marrow biopsy as well as evaluation of the blood counts following 1-2 cycles of azacitidine and venetoclax. In patients, achieving a CR/CRi we would suggest repeating the bone marrow aspirate biopsy as clinically indicated (e.g. repeated if there is concern a patient is losing response due to worsening blood-counts or the appearance of circulating blasts). In patients with less than a CR/CRi after 1-2 cycles who continue on treatment, we would generally repeat bone marrow biopsies every 3-4 month to evaluate response.

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:

In general, patients with disease progression following remission would likely discontinue treatment. There are few specific adverse events with this treatment that should automatically lead to discontinuation of treatment. Similar to other therapies in AML, some patients may experience severe adverse events during treatment (e.g. severe infection or severe cytopenias) that may lead to a decline in fitness or ability to safely administer this treatment. In this group, treatment would likely be interrupted or discontinued for some patients. Some patients may also express a preference to discontinue treatment after starting due to side-effects other considerations.

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

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

Response:

We believe this treatment could be delivered in the inpatient or outpatient setting depending on the characteristics of patient and available resources; this decision is most applicable to the first cycle of therapy. The treatment requires monitoring of blood counts, renal function and electrolytes more frequently early on during the first week, when there a small risk of tumor lysis syndrome. We believe that the treatment should be given in a setting where there is blood-bank support, physician/nursing/pharmacy expertise in chemotherapy, an ability to deliver IV fluids an antibiotics and an ability to admit patients to hospital for complications of treatment.

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:

Click here to enter response.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Based on our review of the available data and clinical experience, azacitidine and venetoclax treatment in the frontline setting in AML offers a large, clinically significant improvement in in overall survival and response over current standard of care options. The additional toxicities of this combination are largely related to increased myelosuppression and increased rates of febrile neutropenia early on during treatment, but this is manageable and does not offset the benefit of this combination. We strongly support the reimbursement of this treatment for older and unfit patients with AML due to the large, anticipated benefit for this group of patients, in which there is currently a large, unmet need for more effective treatments.

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	*David Sanford*
Position	*Clinical Assistant Professor, AML Lead, Division of Hematology, University of British Columbia*
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**
Astellas	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Jazz	☒	☐	☐	☐

Declaration for Clinician 2

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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Thomas John Nevill*
Position	*Clinical Director, Leukemia/BMT Program of BC*
Date	*25-01-2021 (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
Novartis	☒	☐	☐	☐
Celgene/BMS	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐
Taiho	X			

Declaration for Clinician 4

Clinician Information	
Name	*Sujaatha Narayanan*
Position	*Medical Director, Leukemia/BMT Program of BC*
Date	*27th January 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 5

Clinician Information	
Name	*Matthew Seftel, MD*
Position	*Clinical Professor, Division of Hematology, University of British Columbia*
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
Jazz	☒	☐	☐	☐

Novartis	☒	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Jennifer White*
Position	*Hematologist, Leukemia BMT Program of BC*
Date	*22-01-2021*
☒	**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 7

Clinician Information	
Name	*Carmen Mountford*
Position	*Clinical Pharmacist, L/BMT Program of BC, Vancouver General Hospital, Lower Mainland Pharmacy Services*
Date	*15-01-2021*
☒	**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 8

Clinician Information	
Name	*Shanee Chung*

Position	*Hematologist, The Leukemia/BMT Program of BC*
Date	*January 29, 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	☐	☐	☐	☐

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0238-000**
Generic Drug Name (Brand Name)	**Venetoclax (Brand: Venclexta); Manufacturer: AbbVie Corporation.**
Indication	**Indications:** Venclexta is indicated, in combination with a hypomethylating agent or in combination with low-dose cytarabine, in adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy. **Manufacturer Requested Reimbursement Criteria[1]:** In combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Name of the Clinician Group	Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee
Author of the Submission	Dr. Tom Kouroukis, Dr. Janet MacEachern, Dr. Jordan Herst, Dr. Pierre Villeneuve, Dr. Lee Mozessohn
Contact information	Name: Dr. Tom Kouroukis Title: Provincial Head – Complex Malignant Hematology (OH-CCO) Email: [redacted] Phone:

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.

Discussed jointly 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:

Azacitidine (Aza), LDAC, and supportive care

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:

Improve survival, improve QoL, improve hematopoiesis/transfusion independence

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:

Current available treatments offer short survival advantage and short transfusion independence

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:

Patients with AML who are not eligible for standard 7+3 induction therapy (older or with comorbidities)

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:

Would replace azacitidine monotherapy

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:

No. The submission is for 1L treatment

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:

Will substitute current 1L treatment

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 mentioned above.

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:

No companion diagnostics required.

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

Response:

- Aza-venetoclax is more difficult to give
- patients will need to travel to outpatient clinic to receive azacitidine
- this combination may not be suitable for very frail or very elderly patients

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:

IDH1/2 patients appeared to benefit more in the Aza-venetoclax trial

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:

Transfusion independence, remission status, hematopoietic improvement

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:

Improvement in hematopoiesis

6.10. How often should treatment response be assessed?

Response:

Frequent/regular CBC. Bone marrow as needed per clinician judgement.

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:

Overt disease progression (e.g., significant increase in bone marrow blasts), treatment-related toxicities, patient preference

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

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

Response:

Community setting and outpatient clinic

Patients may be admitted inpatient due to tumour lysis syndrome or AML complications while continuing with treatment.

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:

Venetoclax dose adjustment with co-administration of azole is sometimes required.

In patients presented with hyper leukocytosis, a longer ramp-up phase should be considered when initiating venetoclax.

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 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	*Dr. Tom Kouroukis*
Position	Provincial Head – Complex Malignant Hematology (OH-CCO)

Date	*21-Jan-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

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Janet MacEachern*
Position	*Hematologist/oncologist*
Date	*28-Jan-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

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AbbVie (advisory board)	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Jordan Herst*
Position	*Hematologist/oncologist*
Date	*21-Jan-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.

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Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Pierre Villeneuve*
Position	*Hematologist/oncologist*
Date	*21-Jan-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				
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Lee Mozessohn*
Position	*Hematologist/oncologist*
Date	*21-Jan-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				
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐