Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

ivosidenib (Tibsovo)

(Servier Canada Inc.)

Indication: Tibsovo (ivosidenib) in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.

April 2, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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Patient Input

Input from Heal Canada

About Heal Canada

Heal Canada is a registered not-for-profit organization that aims to empower patients, improve healthcare outcomes, and advocate for equitable access to quality healthcare across Canada. We are committed to fostering a patient-centred healthcare system that prioritizes every individual's well-being, dignity, and rights through:

- Patient Empowerment
- Patient Education and Awareness
- Advocacy for Equity
- Collaboration and Partnerships with the highest ethical standards.

Methodology:

On February 27 of this year, Heal Canada launched an online survey to assess different aspects of patients living with blood cancer. The survey includes questions regarding:

1) Diagnosis journey
2) Quality of treatment
3) Emotional and financial burdens
4) The effectiveness of existing patient resources
5) Demographic data impacting the clinical outcome

This report contains the survey sub-analysis of all individuals diagnosed with AML (5) as well as semi-structured interviews with AML patients and caregivers (4)

Survey sample size: Five of the twenty-two respondents were diagnosed with AML.

Responders' distribution:

- Regional distribution: 1 from Alberta and three from Ontario (n=4)
- Sexe Ratio: Male- Female 1:1 (n=4)
- Racial and ethnicity: 100% Caucasian (n=4)
- Age: 50% 55-64, 50% 65+ (n=4)
- Relationship status: 100% are married (n=4)
- Average family income: 25% between 50-100K, 25% between 100-200K, 25% more than 200K, 25% unknown (n=4)

Survey Limitations:

- The survey includes only white and married persons, limiting the racial and ethnic representativity as well as people with less support.
- The life expectancy for unfit AML patients is short and involves older patients. These factors probably contribute to the survey's representativeness. The survey captured AML survivors, who are typically younger patients and benefited from more aggressive front-line treatments.
- To overcome these limitations, we included caregiver feedback to give patients who had lost their battle against AML a voice.

Semi-structured interviews: 2 patients, two caregivers (an older patient who died from progression)

Colour code:

The blue text represents questions from CADTH.

The black text represents a summary of feedback from patients.

The purple text represents some elements from the scientific literature that corroborate with patients' experiences.

1) Information on the disease and its impact on daily activities and QoL

a. The diagnostic process and specialty are involved in their journey.

Survey Summary:

a. Diagnostic process can take more than a week. Only one patient (20%) received its diagnosis within a week, 40% within the 1st month and 40% within 1 to 3 months (n=5)
b. Most patients (80%) didn't fully understand why each test and procedure was done. (n=5)
c. One patient (25%) had the treatment delayed due to a diagnostic issue (n=4)

Patient Interview Summary:

- For some asymptomatic patients, a routine blood test allows the diagnosis.
- For some patients, receiving an accurate diagnosis can take several months (up to 6). Some clinical presentations, such as coughs, chest pain, recurrent infections, or lumps, can derail the diagnosis by referring to the wrong specialist. The role of the GP is crucial at that point, and blood tests are not always prescribed rapidly, favouring wrong specialist referral, wrong diagnostic, and unnecessary treatments.
- The second group of patients developed anxiety that does not disappear with the correct diagnosis because they understand that it is an acute and severe cancer, and all the time they lost on the wrong treatment increased their distress.
- Bone marrow biopsy is done at diagnosis to confirm blood test findings. It can also be done during follow-up, which is difficult for patients and can be a traumatic experience.

b. Disease management and any symptoms critical to control

Survey Summary:

a. Having a good quality of life has been identified as a significant challenge for 67% of patients (n=3)
b. High level of symptoms (n=3): i. Fatigue: 100%. ii. Sleep issues: 100%. iii. Emotional and mental health issues: 100%. iv. Reduced daily living and functional capabilities: 100%. v. Pain/Severe Pain: 67%. vi. Reduced social relationships and support: 67%. vii. Reduced sexuality and negative impact on body image: 67%. viii. Depression and Anxiety: 33%
c. 100% of patient sought mental health counselling, but only 25% received it through their Cancer Center (n=4).
d. All patients' engagement in social activities has been impacted to various extents by the disease: 50% less activities by 25%, 50% less activities by 75%. (n=4)
e. 75% of patients mentioned that their cancer had an impact financially, and 25% of patients have concerns about it. (n=4)
f. Their disease had an impact on their working situation (n=4):
    i. 50% retired prematurely.
    ii. 25% reduced work hours
    iii. 25% became disabled.

Patient Interview Summary:

- Patients from the interview experienced more depression and anxiety as well as more pain than what was observed in the survey.

- The most predominant symptoms are extreme fatigue, weakness, and tiredness, which make it difficult to accomplish basic daily tasks such as showering, washing dishes, cleaning the house, and shopping. People with this condition tend to be heavily dependent on their entourage.

    ▪ "I could walk up the stairs without sitting down."

- Coughs, mouth ulcers, breathlessness and recurrent infections are also predominant. Several patients received multiple rounds of antibiotics before being referred to a Hematologist/Oncologist.

- Bruising also came up during the conversation.

    o Chronic fatigue due to anemia and infection due to neutropenia are typical consequences of AML that lead to insufficient hematopoiesis.1

- After the diagnosis, blood transfusions are the most burdensome aspect of the disease and its treatment, impacting patients' lives.

    o Blood Transfusion is time-consuming for patients; it's a full day dedicated to this treatment.

        ▪ Planning to secure someone to accompany the patient if the principal caregivers cannot.

        ▪ Transportation to the hospital

        ▪ At the hospital: the procedure takes at least 3 hours in ideal conditions. It can take longer.

            • For example, if the patient's temperature exceeds usual, staff must test it before initiating the transfusion.

            • If the patient has a complication due to the transfusion (infections, allergic reaction), they must be admitted to the hospital for observation and treatment.

        ▪ After the transfusion, patients need to rest due to tiredness. This procedure takes a toll on the body.

    o Blood Transfusion is inefficient and must be repeated frequently.

        ▪ In AML, blood transfusion can be done as frequently as every two weeks. Blood transplantation has shortterm efficacy, and its clinical benefit wears off before the subsequent transfusion.

    o Frequent blood transfusions are toxic for patients and associated with side effects:

        ▪ AML patients can suffer rapidly from iron overload and experience restless legs syndrome; no iron chelator was offered to them.

            • People who received as little as ten transfusions are at risk of developing iron overload. 2

            • Iron overload contributes to increased morbidity, increases susceptibility to various infections, and participates in aggravating the symptoms of AML patients by contributing to bone marrow failure. 3,4,5

        ▪ Patients experienced complications that were associated with blood transfusions, like pulmonary hypertension, cardiovascular issues, and fluid retention.

    o Frequent blood transfusions can severely limit patients' future treatment options:

        • Developing antibodies against some pathogen due to transfusion can limit the patient's capabilities to receive immunotherapy or participate in clinical trials.

            o For example, a deceased patient couldn't participate in a clinical trial due to hepatitis antibodies found in his blood despite having never been exposed to the virus.

2) Treatments used:

a. Management – administration and follow-up required:

    a. Interviewed persons mentioned receiving Aza or the best supportive care (blood transfusion).

b. Aza:

i. Receiving Aza necessitated several hospital visits, which is problematic for patients and caregivers.

ii. Taking care of AML patients during the treatment is a full-time job.

iii. It is also associated with substantial side effects; cytopenia, infections, and diarrhea have been mentioned as frequent and significant.

c. Both treatments necessitate frequent blood transfusion, which, as discussed earlier, remains the most critical burden.

d. Hospitalisation because of blood transfusions can be frequent, too.

i. The patients' experiences depicted during the interviews are in line with the Canadian Real-World Treatment analysis conducted and published in 2022.6

b. Access: drug and testing

In the survey and during the interview, when we asked what improvements they would like to see in the healthcare system, they mentioned that having access to new treatment options and better mental health support was crucial. They feel trapped with no real options to treat their cancer and improve their QoL.

c. Treatment benefits, side effects, management, accessing treatment:

Current treatment options have limited efficacy and significant adverse events. Most patients do not receive active treatment and end up in the best supportive care.

d. Side effects: tolerability and management. What would patients and caregivers like to see in a new treatment option?

a. Reduced blood transfusion needs
b. Improve Symptoms
c. Improved QoL

e. Benefits—What improvements would patients and caregivers like to see in a new treatment not achieved in currently available treatments?

a. Remaining unmet needs: How might daily life and quality of life for patients, caregivers, and families differ if the new treatment provided those desired improvements?

i. Better control of anemia without transfusion or with less transfusion, which would drastically improve QoL.
    1. Less transfusion means less time dedicated to care.
    2. Better anemia control means more energy and vitality to do basic day-to-day activities: climbing the stairs, showering, sleeping less, and being physically active.
    3. Less co-morbidity and toxicity
ii. A lower rate of infections will improve QoL.
    1. Reduction of hospitalisation
    2. Improve social life: COVID-19 is another source of anxiety for patients with AML. Patients feel vulnerable and isolate themselves to avoid infections. Patients fear interacting with people who are against vaccination.
        a. Infections remain the second cause of mortality after disease progression. 6
iii. Improve disease control and live longer, e.g., progression-free, and overall survival.
    1. Patients have the impression that current treatments offer only a minimal benefit regarding survival and do not improve QoL.
    2. Patients have heard that the treatment is brutal, and there is no significant reduction of transfusion needs.

f. What should a new treatment offer? What trade-offs do patients, families, and caregivers consider when choosing therapy?

a. Avoiding transfusions or reducing their frequency will be a big plus.
b. Improving QoL and being functional by minimizing disease symptoms as much as possible (fatigue, pain, infections).
c. Improving QoL by accessing treatment with tolerable side effects.
d. Controlling the disease to survive as long as possible without being too sick.

3) If experience with a new or experimental treatment

a. Sadly, we couldn't connect with a patient or a caregiver who has experience with the new medication, ivosidenib. AML is a relatively rare blood cancer, and patients harbouring the mutation IDH1 represent only a tiny fraction of this patient population.
b. According to the Canadian RWT pattern analysis conducted in 2022, the current standard of care for unfit AML patients is Aza. 6

a. 59% of unfit AML patients received Aza as their first-line treatment, while 31% received the best supportive care.
b. In the portion of unfit AML patients who received systemic therapy, 85% of them received Aza.

c. Based on AGILE trials, combining ivosidenib and azacitidine vs. azacitidine alone improves critical clinical aspects for most patients.

a. Increase overall survival drastically vs Aza.
b. Fewer AEs vs Aza.
c. Many patients became transfusion-independent compared to Aza, and the fact that the ratio continued to improve over time is very encouraging for them.
d. Reduce infection rate vs Aza.
e. Improve QoL and functional capacities in many aspects impacted by the disease: Physical, Social, Role functioning and Emotional (Q1).
f. Improve several symptoms considered debilitating by patients: Fatigue, Pain, and Insomnia (Q1).

4) Companion Diagnostic testing:

a. Based on patient feedback, mutation testing doesn't represent a logistic issue.
a. A blood sample is taken when they are at their cancer centre, and it seems to be part of the routine already to assess patient risk. It is less stressful than the bone marrow biopsy.
b. One patient in Alberta said that the test was shipped to the USA, and it took her some time to get the results. It is increasing the stress level.
c. Some provinces seem more efficient than others in terms of turnaround time; Canada has inconsistency.
d. The test seems to be paid by the hospital, so no out-ofpocket fees are required.

5) Disclosure section:

- No help from outside the organization has been provided to support this submission.

- No help from outside the organization has been provided to collect or analyze data used in this submission.

- See the list of pharmaceutical companies that provide some funding to support Heal Canada digital magazine production below. However, none of these companies have a direct or indirect interest in the drug submission.

6) References

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7- Pau Montesinos et al. AGILE: A Global, Randomized, Double-Blind, Phase 3 Study of Ivosidenib + Azacitidine Versus Placebo + Azacitidine in Patients with Newly Diagnosed Acute Myeloid Leukemia with an IDH1 Mutation, Blood (2021) 138 (Supplement 1): 697

Input from LLSC

1. About Your Patient Group

The Leukemia & Lymphoma Society of Canada - bloodcancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- Funding research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

2. Information Gathering

One online survey was created through SurveyMonkey. Information was gathered in March 2024. The survey was developed and distributed by LLSC, in English only. The survey was distributed through various social media channels and directly by email.

To qualify to complete the survey:

Respondents must have been: An AML patient (past or present) - 68.88% or a caregiver of an AML patient (past or present) - 28.44%

Respondents also had to have identified that they or the person they cared for were ineligible for stem cell/bone marrow transplant.

83 respondents proceeded with the survey. 7 respondents identified as having the IDH1 mutation.

Respondents were asked to identify the age range of the person diagnosed with AML at the time of diagnosis. The age demographic breakdown is shown in the chart below.

ANSWER CHOICES	RESPONSES	
0-17	1.20%	1
18-39	13.25%	11
40-64	26.51%	22
65-74	36.14%	30
75+	22.89%	19
TOTAL		83

70 respondents identified their primary residence:
Ontario (36), British Columbia and Nova Scotia (9 in each province), Alberta (6), Quebec (4), Manitoba (2), Saskatchewan (1). 2 respondents were International, and 1 respondent was from the USA.

LLSC also conducted two 1 on 1 interviews with patients currently dealing with AML.

3. Disease Experience

Many AML patients require a high degree of caregiver support throughout their AML experience and need assistance with various day-to-day tasks. This creates an enormous burden on the caregivers as well.

This can be an enormous drain on the AML patient who struggles with not being able to do things independently and has to rely on their caregivers. The mental, physical and financial effects of the AML experience have significant impact on the lives of patients and caregivers alike.

Respondents were asked, do/did you require caregiver support to manage your AML symptoms?

43/67 (64.18%) -- Yes, I had/have caregiver support
22/67 (32.84%) -- No, I manage(d) fine on my own
2/67 (2.99%) -- Yes, but I was/am unable to access a caregiver (due to cost, no available family member etc.)

Caregivers expanded on their experiences caring for their loved ones with AML and detailed how stressed and overwhelmed they felt ensuring that the needs of their loved ones affected by AML were met, while also trying to manage their own regular routines, and keeping up with their responsibilities at work and in their personal lives:

- "Life completely changes. You worry about work, your own health and being there for the patient. There is no family life, or should I say a negative family life as it revolves around the patient. Taking care of their needs, talking about their illness and praying for recovery. That goes for social life as well. If anything there is guilt for going out and possibly enjoying yourself when a loved one is so restricted, ill and could be dying! Guilt for being alive and healthy! Romantic relationships are put on hold. Who can focus on someone else? There's already too much to deal with"

- "As a caregiver, the care for my dying mother is overwhelming and also trying to be supportive for my Father. All this and full time work, and my own three children and wife. Lots fell through the cracks during the last six months of life"

- "Not only was it my mother, the patient that was affected but also my father who did not do well with this at all. I had to take an extended period off work to spend with both of them in a strange city, staying in hotels, eating meals at restaurants (or not at all). The caretaking was for all 3 of us!"

The mental impacts of AML diagnosis can be unbearable for patients, as well as caregivers. Fear, anxiety, devastation, and worry can take over and add to fatigue and exhaustion already exacerbated by the disease.

47/70 (67.14%) of survey respondents stated that AML had a negative impact on their mental health status. This is significant, as decreased mental wellness impacts patients' and caregivers' overall health. Respondents mentioned that they developed serious mental health disorders as a result of their experience with AML, including depression, anxiety and PTSD.

Respondents reflected on their thoughts, feelings, and mental wellness through AML:

- "It was and is a very scary time for us. Too many unknown factors. We were away from our home and had many challenges to overcome"
- "Depression, feelings of losing hope"
- "Having survived AML (two years now), the biggest negative impact on my mental health is the impact from living with the threat of a recurrence"
- "I have PTSD, anxiety and trouble sleeping"
- "Dealing with major depressive disorder and PTSD since diagnosis but especially after treatment. Dealing with worrying every single day about my family and myself"

AML affects all aspects of the lives of patients and caregivers including home/family life, social life, and personal relationships. The physical impacts and risks of the disease can limit the ability to go outside of the home and participate in activities as one may have before diagnosis. Maintaining relationships and routines can be difficult, sometimes impossible for patients with fatigue, pain, and other symptoms and side effects.

Both patients and caregivers are forced to change how, if, and when they can interact with the people close to them which has both mental and physical impacts for those affected. The caregiver burden is significant, for older patients in particular. Especially for those living alone before AML. Some are no longer able to live alone, forcing caregivers to uproot their lives to be present for their loved ones.
43/70 (61.43%) of respondents stated that their family/home life was negatively affected by AML. Respondents commented in more detail on specific changes they had to make regarding their home and family life. These include **impacts on social activities, living arrangements, and the need for assistive devices in the home.**

- "We adapted to Steve's fatigue with chairs placed in certain places around the home, grab bars, use of a cane, wheelchair as necessary. He often felt cold so warm blankets, fireplace, higher room temperature helped. The day's timetable was what worked at the time, depending on how he was feeling"
- "I can't go to get togethers, dinners, missed out on Christmas! Feel alone a lot"
- "No sports activity"
- "My father lived alone, so I was his primary caregiver during his cancer journey. Spare time and work hours were spent trying to get clear information, coordinate

appointments, understand next steps and prognosis. My father would have never been able to navigate on his own"

The ability to participate in social activities is important for overall wellness.

This can be a form of relief for patients and caregivers and give them some respite time when they can talk to friends and loved ones and participate in activities that could take their mind off of their illness, if only for a brief time.

41/70 (58.57%) of respondents stated that AML had a negative impact on their social life.

Respondents gave examples of some of the changes they have had to make to their social activities due to AML:

- "Used to go to the gym, parties, friends. Not anymore"
- "Seeing less people due to physical changes"
- "Only focused on caregiving and work. No socializing, travel or fitness"
- "Hospital twice a week so no travel, home bound"

4. Experiences With Currently Available Treatments

This patient population is difficult to treat and currently have very few treatment options. Current treatments that are available cause various concerns for patients including toxicities and unstable blood counts, creating the need for blood product transfusions due to anemia, neutropenia, and thrombocytopenia.

Often, dosages must be decreased, or treatment has to be stopped completely because patients' side effects are intolerable, or patients just do not respond to treatment. If available treatments fail the patient, and stem cell/bone marrow transplant is not an option, the only alternative is often best supportive care until death.

The side effects of AML treatment can vary and be quite severe, causing significant patient burden and impacting various areas of patients' and caregivers' lives.

Stabilizing patient blood counts can be difficult throughout AML treatment and currently available treatments contribute to the patient's need for long and rigorous transfusions, which contribute to the already significant impact of fatigue. Some respondents listed varied serious side effects they experienced throughout AML treatment, including heart muscle damage, cerebellar damage, and aneurysm exacerbated by blood infection

Respondents were asked to identify the side effects of AML treatment that had the most affect on them. The top answers were as follows:

Fatigue – 50/69 (72.46%)
Thrombocytopenia – 37/69 (53.62%)
Neutropenia – 39/69 (56.52%)
Anemia – 30/69 (43.48%)

Respondents were asked, overall, how would you rate the side effects of your AML treatments? The top 2 answers were:

Bothersome -- 21/69 (30.43%) Severe -- 17/69 (24.64%)

Regardless of the impact of the side effects of treatment, many are willing to continue with treatment and tolerate whatever side effects come with it because they are holding onto the hope that the treatment will work.

We asked respondents what their personal reasons were for continuing with AML treatment despite the terrible side effects they described experiencing. Several respondents forthrightly answered that their driver was the desire to live, or the hope of survival. Others stated that they had no other choice, this was their only chance, and there were no other alternatives.

Below are more of their responses…

- "Promise of some remission, even if we knew it was not a cure"
- "Not ready to die yet. Still much to see and do with our lives"
- "I'm not that old, I would like to have more time with my family"
- "I thought it would work"
- "Can't give up"
- "Hopefully live until a cure is available"
- "My baby was 5 months old and I wanted to get home to him"
- "Only tolerated until death by suicide"

AML patients often have multiple serious side effects throughout treatment that negatively affect their ability to care for themselves without the assistance of a caregiver,

50/70 (71.43%) of respondents stated that AML treatment had a negative impact on their ability to care for themselves independently.

Respondents elaborated on the kind of care they needed or had to give to their loved ones to help them get through their day.

Many patients needed assistance with even the simplest day-to-day tasks such as walking, going to the bathroom, cooking, and completing household chores. Many activities were limited or made impossible due to the patient's inability to function at a pre-treatment level.

- "My husband has gained increased independence, but it is limited. He needs support and consistent supervision"

- “At the beginning of my disease I was unable to do anything such as cook, eat, walk any distance, difficult to go up and down stairs. I was unable to work as I had major fatigue. My caregiver did everything for me”

- “I needed to be driven to day appointments daily. In the early days I could not look after myself - going to the washroom, not being able to walk without help”

- “I needed help with household chores, cooking, laundry etc.”

Travel to treatment had a large impact and posed challenges including mental impact, financial impact, and impact on family and social life. It also led to increased risk of infections.

Patients have various challenges accessing available treatments for AML. These treatments are often not available in community cancer centres and require that patients attend specialized centres. This often means that patients and caregivers have to travel a far distance which creates a significant barrier. A lack of locally accessible treatment options can have various impacts on patients’ ability to access the care they need (including physical, mental and financial impacts). Patients are not feeling generally well and often require caregiver support to travel to these appointments, which may not always be an option for all patients. If patients are unable to travel, often their only recourse is an admittance to hospital which comes with its own set of problems including mental impact, financial impact, impact on family and social life, and increased risk of infections. Many patients have to leave their home communities, uproot their entire lives and relocate permanently, solely so that they can access treatment for their disease.

A meaningful 53/66 (80.3%) of respondents stated that if AML treatment was available to them within their home community, this would have a significant to extremely significant positive impact on their treatment experience.
Respondents expanded on potential impacts of treatment being available close to home:

- “Being close to home for the patient as well as family would ease the anxiety of not only the disease but being in a strange environment with nothing familiar. Also, if the patient would be able to stay home, in their own surroundings, much more reassuring and comfortable for them”

- “Instead of going to the hospital 11 times a month I would only have to go 3 times a month for blood work”

- “I was an in-patient for months and being home is the best!! I feel we heal quicker and are happier”

Many respondents relayed in detail the burden and stress of having to travel for treatment while already going through this difficult time and trying to manage their symptoms and feelings around their AML.

Having to travel for treatment and being away from home, loved ones and a sense of familiarity and community contributes to the mental and physical burdens that patients and caregivers are

already dealing with, and negatively affects various areas of their lives. Patients who live in rural communities are especially impacted.

- “Driving in rush hour traffic across town anywhere from daily to twice a week is a real drain, and will get worse when I can no longer drive, as will happen”
- “Victoria BC Cancer Clinic is unable to deal with AML patients. No choice but to go to Vancouver BC”
- “I received my chemo treatment 5 hours away from my hometown. The cost of being away from home was extreme and being away from my family was awful”
- “We live a distance from the hospital in which I spent a long time and my spouse had to travel back and forth for a year”
- Our home is 8 hrs away from treatment. It has been a tremendous burden for us”
- “Due to the isolated community my dad lives in, he had to travel 6 hours each way to receive treatments. The travel cost alone was substantial and minimal assistance was available to cover these costs”
- “My husband had to receive treatment in a different city (4 hours travel each way, including a ferry). Financial stress was extreme. We are classed as low/mid income. They told me to liquidate all our belongings. Give up my home. If it wasn't for donations from our co-workers, I would have been sleeping in our car”

Several respondents described that they had to pick up their lives and relocate to be closer to treatment centres in order to access treatment for their disease.

- “I was diagnosed in Iqaluit and had to move to Ottawa for treatment and lost my job and had to move permanently”
- “Travel distance from home. Had to relocate to the city for treatment”
- “Lived remote in Alberta, had to move to Ontario to have a caregiver so I could get blood regularly”

5. Improved Outcomes

More treatment options are needed in a space with limited options for these patients. If the limited available treatment options don’t work, if patients cannot tolerate them, or if patients relapse, and they are not eligible for transplant, patients and caregivers know that this the end of the road for them other than best supportive or palliative care until death.

The burden of the fear of not responding to treatment, or relapse, is immense when patients and loved ones are aware that there are no other options. Patients and caregivers feel helpless, afraid, and out of control. Having other options available to patients with this difficult to treat diagnosis is a necessity.

37/67 (55.22%) of respondents stated that they agree with the statement; “I am/was worried about running out of treatment options to effectively manage my AML”.
Respondents commented:

- “I know my options are limited so I just have to live with that. Worry won't help”
- “There did not appear to be more than one treatment path for my father - one round of chemo followed by injection therapies and blood transfusions. It worked until it didn't”
- “When she could not stand more than one treatment, it was awful. She began internal hemorrhaging and it was no longer possible to continue with treatment and she died within 24 hours after”
- “Daily worry”

Many patients are found to be ineligible for stem cell/bone marrow transplant as a potential long-term solution to treat their AML.

This can be for various reasons including, for example, the patients’ age, fitness level, or inability to find a donor match. Reasons for transplant ineligibility are often out of the patient’s control. These are unfortunate and unfair circumstances, as patients want access to treatment options that could offer them more time to complete life goals and dreams, or simply to spend more time with loved ones.

Respondents were asked, considering the ineligibility for a stem-cell or bone marrow transplant, what would it mean to have access to a treatment option that could offer an additional two years of life? Respondents explained in detail what they would do with that extra time and what having extra time would mean to the patient and their loved ones:

- “At our age it would have been wonderful! We would have gone on the fishing trip he planned for us.
- “My husband has no other illnesses. He is active, positive and loves life. It would mean the world to him to have another 2 years granted to him”
- “It would be a miracle to be able to have a few more years to see her grandchildren get married and become a great grandmother”
- “It would mean added years of living with hopes a better treatment comes along”
- “It would enable me to complete a research project that is important to me”
- “An additional two years would be a blessing to complete life goals/wishes”
- “It would have made a world of difference to give her time to prepare herself as well as my father, see other family members from afar, make her peace....”

- “It would mean more time with my family, and more time to watch my grandkids grow and mature”

- “Means everything to keep my soul mate alive”
- “Was never an option”

Many patients and caregivers relayed that they want more time, but that they want to be able to enjoy that time and not spend it suffering and having limited quality of life. These are factors that are important to patients and caregivers when they are considering new treatment options.

Respondents were asked to identify the top three factors that are most important to them when considering new therapies. 66 respondents answered this question. The top answers were:

Quality of life during treatment – 49/66 (74.24%)
Amount/Severity of side effects – 41/66 (62.12%)
Length of time in potential remission – 41/66 (62.12%)

The burden of having to receive blood product transfusions has significant implications on the quality of life of both patients and caregivers.

66/68 (97.06%) of respondents stated that they or their loved one required blood product transfusions due to AML.

People affected by AML know that their time is essentially limited, and they do not want to spend what time they do have in hospital. In many cases, rigorous transfusion schedules can take over their whole lives. Patients spend whole days, sometimes multiple days a week in hospital from 5-8 hours per day receiving transfusions. When they are finished with their transfusions, they are tired mentally and physically and it can take sometimes take days to fully recover, then they are back in hospital for more transfusions, and it is often an endless cycle. Patients are not able to do what they love and participate in activities that are meaningful to them because they are spending an overwhelming amount of time in hospital.

Respondents described the effects that transfusions had on their quality of life and their ability to participate in daily activities:

- “We would need to drop everything and run to the hospital at the drop of a hat. As a result, my father would not make plans just in case. My father was no longer comfortable driving himself, so I missed work or would have to call on friends to escort him. Transfusions often took most of the day”

- “Initially I would develop instant high fevers when receiving the transfusion. Doctors asked for the platelets to be irradiated before transfusion”

- “At first treatments gave a boost of energy. Later they become too hard for the body to cope”

- “Had to stay close to hospital due to visits twice weekly. Was extremely tired”
- “Waiting. Waiting. Waiting. Waiting. An 85 year old sitting in a chair waiting and slumped over”
- “Not having to spend two entire days going to the hospital for blood transfusions and blood count checks would have a huge impact on my energy level and mental health”

The number of hospital visits required during AML treatment is a significant hurdle for those affected by AML. Hospital visits and hospital stays are a burden and create strain on the physical, mental, social, and financial wellbeing of both patients and caregivers.

Respondents were asked to rate how the need for hospital visits impacted various aspects of their lives during AML treatment on a scale from 1(no impact) – 5(extremely large impact). Collective responses were measured by weighted average. 62 respondents answered this question.

Ability to participate in daily activities -- 3.7/5
Ability to socialize – 3.7/5
Physical health – 3.44/5
Fatigue – 3.42/5
Mental Health – 3.27/5
Recovery time – 3.22/5

The potential of less frequent hospital visits and less need for hospital stays with newly available treatments could offer a significant benefit to patients and caregivers over currently available treatment options.

57/64 (89.06%) of respondents stated that if they could take an AML treatment that could lessen the need for frequent hospital visits, this would have a positive to extremely positive impact on their physical heath.

Respondents expanded on how this could impact the patient and caregiver experience:

- “My partner would have been able to live a more normal life doing the things he loved while undergoing treatment”
- “Having to commute from rural SK for 2 hour drive is hard enough, never mind going thru a treatment, and having to return home. Other option is to be hospitalized and that is difficult for patient as well as family”
- “It took two people to get to/from hospital appointments. Parking, nightmare. Wheelchair, we had to buy our own. Avoiding winter weather conditions to keep Mom warm was a challenge”

58/64 (90.63%) of respondents stated that if they could take an AML treatment that could lessen the need for frequent hospital visits, this would have a positive to extremely positive impact on their mental health.

Respondents expanded on how this could impact the patient and caregiver experience:

- “The "to and fro" does have a negative impact on one's mental health”
- “It would lessen the ties that currently bind in my ongoing love-hate relationship with the hospital. Presumably, such new treatment would allow greater freedom in how I make use of my own time and space, the stuff that makes life a life. Hospital visits, however necessary, consume my time, waste my resources, and expose me to infections, and if I don’t need to go, I certainly won’t. Greta Thunberg would like that”
- “This would leave more time for other activities that are so important for feelings of well being”
- “When going to the hospital I always worry that I will get an infection”
- “Going to the hospital was always a nerve-wracking experience. We never know if we would be in hospital for two hours or eight hours. Sometimes due to treatments. Other times due to waiting for treatment and labs”

Infections are a significant risk for AML patients and contracting an infection can decrease their health and fitness status significantly.

Patients can spend days, weeks, even months in the hospital fighting these infections and there are many implications to their overall health being exposed to other things in the hospital as well, especially for older patients. The antibiotics needed to fight these infections also come with their own burden of side effects and complications and patients are often forced to isolate and miss out on living their lives to the fullest and spending the time they have with friends and loved ones due to the fear and risk of contracting a potentially life-threatening infection.

Respondents were asked to rate how frequent infections, or the fear of frequent infections impacted various aspects of their lives during AML treatment on a scale from 1(no impact) – 5(extremely large impact). Collective responses were measured by weighted average. 64 respondents answered this question.

Social life -- 3.66/5
Family life – 3.37/5
Work life – 3.24/5
Romantic relationships – 2.62/5
Daily routines – 3.5/5
Mental functioning – 3.36/5
Physical functioning – 3.17/5

Respondents expanded on the impact of infections and the fear of infection on the patient and loved ones:

- “My father was preoccupied by his compromised immune system and isolated himself quite a bit out of fear. The pandemic added to that fear and concern. Even while in remission, he was anxious and unable to go back to a normal life”
- “One specific round of infections was nearly fatal, so the impact of infections or fear of them is considerable”

- “My father lived in constant fear, and the isolation took a toll on him mentally”
- “Sex life was affected as we were advised not to have sexual relations during the week of and week after chemotherapy”
- “I would avoid large gatherings for fear I would catch germs or viruses. I would avoid physical romantic contact because of low energy and fear of germs”
- “We would have liked to still be travelling internationally, but are afraid to risk getting an infection away from home and not having familiar health care providers”
- “Not able to spend time with friends and family as my white blood cells are so low”

The risk of infection is significant throughout AML treatment and patients and their families are often forced to change their regular habits and take additional precautions to protect themselves against infection.

This can include isolating from friends and loved ones and not participating in their regular activities. This isolation, along with the fear of contracting a potentially life-threatening infection can weigh on patients and significantly affect their mental health.

Respondents were asked, how much of a factor was the risk of infection in your decision making regarding daily activities throughout AML treatment? 64 respondents answered this question.

31/64 (48.44%) -- Major factor	22/64 (34.38%) -- Somewhat a factor
6/64 (9.38%) – Neutral	5/64 (7.81%) – Not a factor

The possibility of reducing the risk of infection throughout AML treatment could make a significant difference for patients in various areas of their life and therefore improve their mental and physical wellness, as well as their social life, work life and family life/personal relationships. This improvement could also help to reduce caregiver burden and renew patients’ sense of independence.

Respondents were asked, if you could take an AML treatment that would decrease your risk of infections, how do you think that would impact the following things? 64 respondents answered this question. The results were noteworthy.

Reflected below, is the number of respondents who stated that a decreased risk of infections would have a positive impact on their:

Social life – 59/64 (92.19%)	Family life – 58/64 (90.63%)
Mental functioning – 57/64 (89.06%)	Daily routines – 55/64 (85.94%)

Physical functioning – 52/64 (81.25%) Romantic Relationships – 39/64 (60.94%)
Work life – 37/64 (57.81%)

Regarding infections, some respondents shared their thoughts:

- “Removing the fear of infection and/or actual infections would be a huge benefit”
- “Always a constant fear”

AML patients and their families have hope for the continued improvement in the efficacy, safety, and durability of responses of available AML treatments for themselves and for others. In the near future, they also hope to see AML treatments that will significantly improve health-related quality of life for people affected by AML.

Respondents relayed what desired improvements to quality of life they would like to see from new treatments. There were many common threads among their answers including emphases on;

- The need for less hospital visits and hospital stays, and for visits to be shorter in duration
- Treatments that eliminate/reduce the vulnerability of patients to infections, and treatments that allow patients to achieve an improved immune system
- Reduction/elimination of the need for blood transfusions, less neutropenia/thrombocytopenia/anemia, better maintained hemoglobin levels
- Less fatigue and increased energy
- No loss of appetite, ability to maintain regular diet, no nausea
- Ability to be home for treatments and have more time with family, ability to treat all AML patients at all cancer clinics, “Being able to be home as much as possible, especially if you live far from a hospital with leukemia expertise”, “Ability to have treatment options that can be available to isolated communities to allow patients to not be financially burdened”
- A reduction in pain (body, joint, injection site), less impacts on mobility
- More ability to socialize, participate in normal routines, and take part in all aspects of life
- Improved odds of remission, increased length of survival, better overall outcomes

Other answers included;

- “Greater freedom to plan activities. I guess that the best measure of ‘improvements’ is by how much of my old life can return: physical strength, mental acuity, lack of ‘side effects”

- “Pill instead of injection”
- “A cure for AML!!”

6. Experience With Drug Under Review

ivosidenib is a new treatment to Canada. As a result, there is very limited patient experience.

LLSC was able to conduct a 1:1 interview with one international patient, a Canadian living in Singapore at the moment, who is currently receiving treatment with ivosidenib. This patient shared with LLSC about her experiences with her disease and treatment, including treatment with the drug under review.

This patient had been living abroad temporarily for work, with her husband and 6-year-old son when she was diagnosed with AML.
The patient was initially diagnosed with AML (with IDH1 mutation present) in June 2021 and started induction chemotherapy treatments immediately. She would receive chemo treatments for 2 or 3 days in a row, then would stay in hospital for a few weeks until her counts would start increasing. She could then go home for 3-4 weeks, during which time she would attend hospital weekly for blood work. Then a new cycle of treatment would begin. This was continuous until the patient reached remission in September 2021, after 3 months of treatment.

When asked about her experience during treatment, the patient spoke about the effects of this on her home life and the fact that it was hard to be away from her family and young son, especially since she and her husband chose not to share her diagnosis with their 6-year-old son.

The patient also shared some of the **physical impacts** of AML she experienced. She had to go through several transfusions of red blood cells as well as platelets and that was a long and tiring process.
She struggled to eat as well, because she completely lost her senses of taste and smell for a few months during treatment. She also experienced significant joint and leg pain.

Fear of infection was a significant concern as well, especially with a child in her home. She relayed that she started eating more fresh foods but because of neutropenia she was unable to eat raw veggies and fruits had to be peeled. She could no longer participate in self-care activities like treating herself to a pedicure, in case they were to nick her skin and she were to contract an infection.

“After my last induction treatment, I got a fever and they were worried. They did a lot of tests and they put me on heavy doses of antibiotics. They felt there were some bacteria in the PICC line or somewhere, but after I was okay and had no fever for a few days they sent me home”

3 months into remission, right before Christmas in 2021, the patient relapsed. Her doctor informed her that there was nothing much that they could do for her in terms of treatment because due to the IDH1 mutation more chemo would not help. Her only treatment option would be bone marrow transplant.
The patient shared her reaction to finding out that she had relapsed:
“I didn't tell anybody at home because I wanted us to just enjoy Christmas. Part of me felt it might be my last Christmas, so I wanted us to remember it as a Christmas that we really

enjoyed if it were to be my last. I understood that chemo was not going to help anymore. I knew I had to find a donor, and that that's difficult.
When I had to go back to the hospital for blood tests, then I told my husband. I said, 'This is where we are. My doctor is doing her best. Let's see what comes."

A donor search was started. The patient's numbers kept dropping. Her brother was tested as a match but wasn't an appropriate donor. 4 donor matches were found in different countries, but all 4 declined donation.

"**Then my doctor told me she found this medication, ivosidenib**, but it wasn't available in Singapore, so my doctor wrote to the government, she got the clearance, found a vendor and got it imported from the US. I feel very blessed that my insurance plan covers it. Otherwise, there's no way I could afford it."

Many side effects come along with AML treatment. These side effects can vary in severity from mild to life threatening and can have a great impact to all areas of patient life including mental wellness, family, work and social life. Since starting treatment with ivosidenib, this patient states that she has experienced *absolutely no side effects* as a result of her treatment with ivosidenib.
"In February 2022, I started taking ivosidenib, 2 tablets daily, and luckily, I had no side effects. My numbers immediately started going up and if you were to just see me, you would never know that I'm in remission or that I have cancer. I basically do everything I did before. I go to work, clean, cook. I take care of a now 8-year-old boy, do all my activities with him, play games, exercise. I live a normal life thanks to ivosidenib. I do everything a normal, healthy person does. The medication has been working. I go for my blood tests every month and my results are great"

The patient described what each monthly hospital appointment looks like during ivosidenib treatment:
"I usually go in the mornings to give my blood and take a fasting blood count. When I started taking ivosidenib, every time I went in for blood tests, they would also do an ECG because they said sometimes it can impact your heart rate, but there were no issues, so after some time that wasn't needed. I still see the endocrinologist on those days. He checks my lipids because I had very low vitamin E and vitamin D previously. After I get my blood drawn it takes about 1.5-2 hours to get the results. Then I meet with my doctor. We're still looking for donors. I get my results from the endocrinologist and then I'm done. That's it."

When asked about how ivosidenib treatment has impacted the need for blood transfusions, the patient stated: "I've needed zero transfusions since starting ivosidenib. Nothing. From February 2022 to date"

When asked how long after ivosidenib treatment started, she started to feel better, the patient stated: "Immediately. I'm on the medication but if you look at me and the life I lead, its so normal. Nobody would know unless I told them. No more pain in my legs. I'm pretty much back to pre-diagnosis days"

When asked about mental health status on ivosidenib treatment, the patient stated:
"I didn't go through depression or anything. Anxiety and worry to a certain extent, yes, which is natural. I know that the fact that I can live life like I used to, is a big factor in that, and that I could return to work. The fact that there's a medication I can fall back on that keeps me healthy make a difference"

When asked what kind of lifestyle changes she had to make during ivosidenib treatment, the patient stated: “I eat more fresh food, I try to be healthier. I stopped drinking alcohol. I just don’t want anything to interfere with the ivosidenib. Less stress. Work related or home, I know stress inhibits recovery. There were times I worked until 3am but that has stopped. Of course, I’m very particular about making sure that I take my medication every day. I also just overall try to be more positive”

The patient shared that despite efforts, she is unable to return to Canada because she will not be able to continue treatment with ivosidenib. Stopping this treatment could cost her her life so she has no choice, other than remaining in Singapore with her family for the time being.
“After almost 6 years in Singapore, it’s time to come back to Canada. I reached out to doctors and others to figure out what the process would be. The moment I come back to Canada, my insurance won't be in place, and I didn't want anything to fall through the cracks.
They told me it isn't in Canada. I thought, no big deal, it wasn’t approved in Singapore either, but you just get approval from the government, and it comes in. They actually told me straight out - don't come back if you can help it. But Canada is our home! I want to come back. I have a child who's growing, and I want to bring him back. This has been like a nightmare. I was told that there's nothing that can be done because the medication just isn’t in Canada and it's just too expensive”

“So, what do people in my condition do? Do they just die?! I know they can do transplants, but I don’t have a donor! So, I can't come home. I reached that stage where I said we’re going back and I’m stopping the medication if that's what it takes. My doctor has tried too, she explained that my only management is this medication and that I don’t have a donor and that the treatment has worked perfectly for me for two years.
We asked about getting the treatment cost subsidized by the drug company, but they only do that in the US”

“I may be just one patient, but it has worked so well for me. Why wouldn't you make it affordable for Canadians?”

I'm so lucky to work for a company that understands my situation and why I haven’t returned to Canada.

I still haven't told my son about my illness. He’s too young. He knows I go to the hospital for checkups, but he doesn't know the gravity of it, and he doesn’t need to because as far as he's concerned, I'm fine. We have a normal life. And that’s because of ivosidenib.

There is concern for the future, what if I don’t find a donor? But I’m grateful because ivosidenib has kept me alive and fit with no side effects.

7. Companion Diagnostic Test

The treatment up for review is targeted to the IDH1 mutation. Laboratory test will be needed to confirm the presence of the IDH1 mutation to identify the appropriate patient population for a favourable response to this AML treatment.

Treatment with ivosidenib may be delayed in some treatment facilities if laboratory results are not made available with a short window of time.

This result is part of the NGS panel which is conducted on all AML patients. Identifying this mutation does not require an additional blood test for these patients.

8. Anything Else?

A significant theme throughout our survey and 1:1 interviews was that AML patients and caregivers suffer an overwhelming sense of loss throughout the AML experience. Whether it be loss of independence, loss of free time, loss of income, loss of their social life, loss of freedom, loss of hope, or loss of their loved one at the end of their AML journey, some sense of loss is experienced by all those affected by AML.

Treatment options that can minimize patients' risk of infection, as well as the need for blood product transfusions, and constant hospital visits, can help to alleviate these significant added burdens for patients and their caregivers.

Treatment options are needed that; are targeted to the genetic makeup of specific patients' disease, are effective in stabilizing disease, show durable patient responses, are more easily tolerated by patients, and that offer an additional line of treatment for a difficult to treat patient population with limited currently available options.

Oral combination treatments that may be able to be offered in community cancer centres could help to alleviate the physical, mental and financial burden that the need to travel for treatment creates. This can minimize the trauma of illness and treatment and make these unfortunate experiences more manageable for patients and their families, disturbing their home lives in a less invasive way than other treatments and allowing for continued support for patients from their loved ones and community.
ivosidenib, as not only an additional treatment option for newly diagnosed patients, but a targeted treatment for patients with the IDH1 mutation can offer an additional line of hope for patients with limited treatment options currently available as these patients are not eligible to receive intensive induction chemotherapy and are not able to receive a stem cell/bone marrow transplant.

The mental burden that comes along with AML is significant. One tragic case that amplifies the extreme impact of this burden was relayed to us by a caregiver.

This caregiver's loved one was between 65-74 years old when they were diagnosed with AML. The patient required caregiver support to manage their AML symptoms. This caregiver stated that AML had an extremely negative impact on their loved one's mental health and that this was difficult to manage throughout the AML experience.

The caregiver stated that AML had an extremely negative impact on the patient's personal life and home life, as this patient was forced to move away from their home community in Alberta, to Ontario in order to have access to a constant caregiver. This was a significant barrier to the ability of the patient to continue with their regular routines and future plans.

The caregiver also relayed that AML treatment had an extremely negative impact on the patient's social life because due to necessary hospital visits twice a week, this patient was unfortunately home bound.

Contributing factors to the extremely negative impact of AML on this patient were the burden of their AML symptoms, the need for frequent hospital visits, the patient's low energy, and the patient's struggles with depression and anxiety.

The caregiver relayed that they believed that if the AML patient had been able to receive treatment within their home community, that this would have had some positive impact on their treatment experience. The patient was unable to make the 6-hour commute required for treatment without caregiver support and they were forced to relocate from Alberta to Ontario to have the caregiver support needed for them to attend hospital for blood transfusion appointments twice/week which lasted 5 to 8 hours in duration, as the patient was severely anemic and thrombocytopenic.

The caregiver stated that this patient was extremely affected by fatigue, which was exemplified by their exhausting blood transfusions. The caregiver stated that all AML side effects experienced by this patient were classified as severe.

The caregiver believes that had the AML treatment for this patient required less frequent hospital visits, that this would have made an extremely positive impact for the patient. They stated that hospital visits severely limited the patient's social life and that hospital visits were "very long and depressing" and contributed greatly to the patient's extreme level of fatigue. The caregiver relayed that AML had an extremely large impact on various aspects of the patient's life including mental wellness, physical health, ability to socialize, and ability to participate in daily activities.

The caregiver detailed that this patient particularly struggled with knowing that this illness was terminal for them, and that they were ineligible for stem cell transplant. This patient ultimately committed suicide.

We would strongly advise CADTH to recommend reimbursement of ivosidenib treatment for adult patients with newly diagnosed acute myeloid leukemia (AML) with an (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy as there is a clear unmet need for additional treatment options that lessen the many burdens that come with currently available AML treatments.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it. No
2. Did you receive help from outside your patient group to collect or analyze data 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 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Servier	X			
AbbVie				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Colleen McMillan
Position: Advocacy Lead
Patient Group: The Leukemia and Lymphoma Society of Canada (LLSC)
Date: April 2, 2024

Clinician Input

CADTH Project Number: PC0349
Generic Drug Name (Brand Name): ivosidenib
Indication: in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.
Name of Clinician Group: Ontario Health (CCO) Hematology Cancer Drug Advisory Committee
Author of Submission: Dr. Tom Kouroukis, Dr. Pierre Villeneuve, Dr. Guillaume Richard-Carpentier

1. About Your Clinician Group

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

Information was gathered through videoconferencing and finalized by email.

3. Current Treatments and Treatment Goals

Current treatments available include azacitidine, low-dose cytarabine, low-dose cytarabine with venetoclax, azacitidine with venetoclax, and supportive care.

Treatment goals include to improve survival, improve quality of life, improve hematopoiesis/transfusion independence and attain remission.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond to available therapies, and specific inhibitors offer a chance for increased response.

Treatment with azacitidine + venetoclax is associated with increased risk of neutropenic fever and infections compared to azacitidine alone. Treatment that are better tolerated are needed.

5. Place in Therapy

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

First line therapy for *IDH1*-mutated AML with the above characteristics, not eligible for intensive induction.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As per the trial, patients best suited are those with AML, *IDH1* mutation, not eligible for intensive chemotherapy.

Patients least suited are those who are very fit and eligible for intensive induction chemotherapy.

Timely results of molecular testing for *IDH1* mutation is required to identify patients who would benefit and be eligible or this treatment. Funding of a targeted simple qPCR test for *IDH1* mutation (e.g. Abbott RealTime IDH1 or other) would help to timely identify patients suitable for Ivosidenib + Azacitidine without treatment delays.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Remission rate, improvement in blood counts, fewer transfusions, leukemia-free survival, and OS, using usual leukemia response timelines.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant toxicities, proceeding to allogeneic stem cell transplant, patient preference, or progression of disease.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Both inpatient and outpatient settings in centers that have experience treating acute leukemias.

6. Additional Information

This treatment requires IDH1 testing to be available in a timely fashion. Time-limited switch in therapy should be allowed for patients who have already started induction, or when IDH1 results become available.

7. 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.

4. 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 a secretariat function to the group.

5. 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.

6. 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 each clinician who 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

Name: Dr. Tom Kouroukis
Position: Lead, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Selay Lam
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Jordan Herst
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Lee Mozessohn
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Joanna Graczyk
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Pierre Villeneuve
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 56Company	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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Rami El-Sharkaway
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 15-02-2024

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 56Company	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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Guillaume Richard-Carpentier
Position: Member, OH (CCO) Hematology Drug Advisory Committee
Date: 22-02-2024

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 56Company	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				

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: PC0349-000
Generic Drug Name (Brand Name): ivosidenib (TBC)
Indication: Ivosidenib in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.
Name of Clinician Group: LLSC Clinician Network
Author of Submission: Colleen McMillan, LLSC

1. About Your Clinician Group

A group of Canadian clinicians including Hematologists and Nurse Practitioners who treat patients with acute leukemias

2. Information Gathering

LLSC gathered input via interviews and discussions with (6) clinicians from various Canadian cancer centres, who have experience treating patients in this patient population with acute leukemias

3. Current Treatments and Treatment Goals

This population of patients are newly diagnosed with AML and are not eligible to receive induction chemotherapy. The goal for this population is to achieve remission.

The current publicly funded treatment options are single agent azacitidine (aza), low dose cytarabine and azacitidine + venetoclax (aza-ven). Best supportive care is also an option. Current treatment options still result in a high mortality rate and as such, there is a need for more durable and effective treatment options.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Although treatment for AML has evolved and the current standard of care aza-ven has improved survival, physicians still experience challenges in effectively treating patients to remission. This is especially true in the older population. Data in Ontario indicate that the 5-year net survival is 44% between 44 – 54 years of age. This drops to 10 % between 65 – 74 years of age. At 75 + years of age the 5-year net survival is 3.0% (Cancer Quality Council of Ontario. Cancer Survival. https://www.csqi.on.ca/en/2020/indicators/cancer-survival). This is consistent with the clinical outcomes observed by the clinicians in clinic. Especially in the population who are ineligible for induction chemotherapy. There is a clear need for more effective treatment options that result in longer remissions and have a more tolerable toxicity profile.

Clinicians believe that aza-ivo is a new treatment that offers AML patients with IDH1 mutation, who are not eligible for induction chemo, a chance at improved overall survival with lower toxicities.

There is limited experience in Canada with this treatment.

Overall Survival (OS): Based on the data, clinicians feel that aza-ivo may have a more durable remission and OS benefit over aza-ven.

The AGILE study was a randomized phase 3 study, targeting the IDH1 population that compared aza-ivo to aza alone. This trial was not a head-to-head trial comparing aza-ivo to aza-ven. At the time of trial design, the standard of care was single agent aza. However, the study populations were very similar in both the VIALE-A (aza-ven) trial and AGILE (aza-ivo) trial. The main exception was that the AGILE trial targeted those with the IDH1 mutation. Currently there is no reimbursed treatment in Canada for AML patients that target the IDH1 mutation. AML patients who are not eligible for induction chemo regardless of their mutation status are treated with aza-ven. Based on this and the trial similarities, the clinicians are sharing insights on indirect comparisons based on their judgement and expertise.

Using an indirect comparison, the data indicates that aza-ivo appears to have a more durable remission and OS benefit over aza-ven. The VIALE-A trial demonstrated a 14.7-month median OS. The initial data readout in the AGILE trial indicated a median OS of 24.0 months and subsequent data indicated an even longer median OS of 29.3 months. 47.2% of patients achieved complete remission and the response was long lasting as the median duration of response was 22.1 months. Aza-ivo appears to work fast as the time to first response was 2.1 months. These numbers are significant to the population as it offers patients that have historically had poor prognosis two years.

One clinician in this submission who participated in the clinical trial stated:
"The first patient on the Agile study was a patient of mine and he achieved a complete remission in the first cycle. He was an older [gentleman] … and he was in remission for years."

Reduce severity of symptoms and lower rates of adverse effects compared to standard of care:

Clinicians noted that the time gained for patients on aza-ivo could be meaningful time. Clinicians note that the toxicity of aza-ven can be challenging to manage. This continues to be true for many patients on prolonged therapy with aza-ven, where the chance of cumulative toxicity to the normal marrow may be considerable and require frequent dose modifications that are difficult to predict.

In the aza-ivo combination, no tumour lysis syndrome monitoring is required. Incidence of febrile neutropenia was also lower in the aza-ivo arm vs the aza arm. This differed from the results of the VIALE-A trial where the incidence of febrile neutropenia is higher in the aza-ven arm vs the aza arm.

Reduced Infections: Patients with AML frequently experience myelosuppression. Infections are a big challenge and are a common reason for patient hospitalization, which in many cases can last

days to weeks depending on severity. This is a concern for older patients in particular. There are additional challenges for patients during hospitalisations – poor sleep, multiple blood draws, hospital acquired infections such as C.diff/pneumonias, blood clots, deconditioning, weight loss. It may take patients weeks to recover from even a short hospitalisation. This deconditioning can sometimes lead to patients stopping treatment – further compromising their survival. If patients run into trouble with 2-3 infections/hospitalizations, they can spend a significant period of the first few cycles in the hospital.

The risk of contracting infections alone severely impacts patients' quality of life. Many are forced to isolate due to their immunocompromised status.

> The AGILE trial noted that there was a fairly rapid recovery from AML-related myelosuppression. The percentage of patients with infections of any grade was 28% with aza-ivo compared to 49% with placebo and aza. This differs from the clinical experience of clinicians with aza-ven where infections remain one of the main risks. Less infections means less antibiotic treatment and in elderly people, antibiotics can cause other side effects like diarrhea and other general GI tract problems, as well as rashes that can affect patient QOL.

The manageable side effect incidence and profile, recovery from myelosuppression and lower rates of infections means that patients can have an increased and meaningful QOL. Infections also result in hospitalizations, which in many cases can be days to weeks depending on severity. Older patients face challenges with hospitalizations – poor sleep, multiple blood draws, hospital acquired infections such as C.diff/pneumonias, blood clots, deconditioning, weight loss.

It may take patients weeks to recover from even a short hospitalisation. This deconditioning can sometimes lead to patients stopping treatment – further compromising their survival. If patients run into trouble with 2-3 infections/hospitalizations, they can spend a significant period of the first few cycles in the hospital.

Decreased need for blood product transfusions: In trial, among patients who were dependent on transfusion of red cells, platelets, or both at baseline, a higher percentage of patients converted to transfusion independence with ivosidenib and azacitidine (46%) than with placebo and azacitidine (18%). Patients become very anemic and very thrombocytopenic and reduction in transfusions is significant to patient quality of life, particularly for a patient who is elderly and has a short amount of time and is having to attend hospital 3-5 times/week.

One clinician shared the following anecdote regarding the severity of the impact of this on patient quality of life:

"Often, patients attend hospital to get their blood counts checked, they need 2 or 3 units of red cells, so they'll come in for their units of red cells, but then they get thrombocytopenic the next day, so then they need to come in for their platelets. Then they're back the day after, and so on."

The burden of blood transfusions is extensive from the patient's perspective as well as the treating centre's perspective. Transfusions also come with their own side effects and toxicities. Patients can experience iron overload with multiple red blood cell transfusions, so there is a great need to reduce that burden.
Decreased transfusions and decreased infections mean decreased hospitalizations and decreased visits to the hospital. This is very significant for this patient population as the treatment and tests mean that there is already a baseline of frequent hospital visits. Aza-ivo offers these patients the ability to spend significantly less time at the hospital.

Additional options for a patient population with very limited options: Clinicians know that, unfortunately for a vast majority of the patients that start aza-ven or aza ivo, their disease is going to come back. This patient population is difficult to treat, so having another option for patients, a potentially better option for patients, that's less toxic is a necessity.

Aza-ivo specifically targets the IDH1 mutation. Clinicians have generally observed better outcomes when a treatment is able to target a specific molecular signature in the cancer. The subset of AML patients that have the IDH1 mutation and are ineligible for induction chemo will be small, approximately 5-10% of patients with AML.

Formulations are needed to improve convenience and accessibility for patients: Patients need treatment options that are more easily accessible. Differentiation syndrome is one of the side effects that require specialized care. However, based on anecdotal reports from clinicians who have used this treatment, and its use in combination with azacytidine that will predictably mitigate this effect, it appears that this side effect occurs early, tends to be mild and is treatable. Once the patient has become stable on treatment, it is possible for care to continue in the home community. This allows patients to be treated closer to home. This would help in maintaining patient quality of life and limit financial toxicities of having to travel for treatment

5. Place in Therapy

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

This treatment would become the new standard of care for newly diagnosed adult patients with AML with the IDH1 mutation who are not eligible to receive intensive induction chemotherapy and are also not eligible for stem cell or bone marrow transplant.

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

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy would be best suited for this treatment. At this time, this treatment would not be recommended for use for patients without the IDH1 mutation.

A companion diagnostic test for IDH1 is required to identify those that qualify for aza-ivo. Currently IDH1 is part of a NGS panel that all AML patients receive upon diagnosis. Turnaround times vary across the country and generally range from about 4–6 weeks. This turnaround time is a barrier to treatment. The situation for AML is acute and patients do not have this time to wait. Improvements would need to be made in order to have the test result back in time to inform treatment decisions. A stand-alone PCR test for IDH1 is readily available that allows for the results to be returned in a few days. This test is not currently funded. Improvements can also be made to the NGS panel process. One clinician noted that his centre made system improvements and investments that reduced their NGS results turnaround time to about 10 days. Improvements to the current testing turnaround time or the addition of a standalone test would be required for the purpose of identifying the correct patients for this treatment in a timely manner. However, it should be noted that testing for FLt-3 mutations in AML was also not widely available in a rapid fashion; when midostaurin, which improves survival when added to standard chemotherapy became publicly funded, all leukemia genetics laboratories in the country were able to adapt to the changed clinical requirements with shorter turn-around times.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Clinicians agree that stabilization and improvement in the frequency and severity of symptoms, composite complete remission (complete remission or complete remission with incomplete hematologic recovery), red-cell and platelet transfusion reduction or independence are measures that contribute to the determination of success.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Reasons for discontinuing treatment identified by the clinicians (based on signs, symptoms, examination, laboratory tests) included disease progression, patient not responding to treatment, patient no longer tolerating treatment, severe adverse events, intolerable side effects that are not able to be treated, and patient preference.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Hospital (outpatient clinic) or potentially a community setting

6. Additional Information

While AZA + Ven is an improvement in the treatment of patients with AML – it is only an improvement. All patients treated with this regimen will eventually relapse. New treatments are urgently needed both in the front line setting and for patients that have relapsed following AZA+VEN treatment. AZA+IVO provides a more tolerable option for patients and may improve survival in the subset of patients with IDH1 mutations.

7. 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

2. 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 each clinician who 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

Name: Dr. Florian Kuchenbauer
Position: Associate Professor, Department of Medicine, University of British Columbia
Clinician Scientist, Leukemia/Bone Marrow Transplant Program of BC, Vancouver General Hospital
Date: 29-03-2024

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Brian Leber
Position: Professor of Medicine (Hematology) McMaster University
Date: 27-03-2024

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Servier		X		
Abbvie		X		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Cindy Murray
Position: NP, Malignant Hematology - Princess Margaret Cancer Centre
Date: 29-03-2024

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
LLSC	X			
AbbVie	X			
Astellas	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Lalit Saini
Position: Hematologist, London Health Sciences Centre.
Date: 26-03-2024

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Servier	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Jane Li
Position: Nurse Practitioner, Complex Malignant Hematology - Princess Margaret Cancer Centre
Date: 27-03-2024

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company