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Reimbursement Recommendation

Quizartinib (Vanflyta)

Indication: In combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib maintenance monotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia that is FMS-like tyrosine kinase 3 internal tandem duplication positive

Sponsor: Daiichi Sankyo Pharma Canada

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Vanflyta?

Canada's Drug Agency (CDA-AMC) recommends that Vanflyta should be reimbursed by public drug plans for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutation if certain conditions are met.

Which Patients Are Eligible for Coverage?

Vanflyta, in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy followed by maintenance monotherapy with Vanflyta, should only be covered to treat patients with newly diagnosed primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, and with good performance status. The presence of an *FLT3*-ITD–activating mutation in bone marrow should be identified using a validated test.

What Are the Conditions for Reimbursement?

Vanflyta should only be reimbursed if treatment is initiated by clinicians with expertise in managing AML in institutions with expertise in systemic therapy delivery. Vanflyta should be negotiated so that the total treatment cost does not exceed the drug program cost of treatment with midostaurin reimbursed for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial suggested that Vanflyta added to standard induction and consolidation chemotherapy then administered as maintenance monotherapy may prolong survival and improve relapse-free survival compared with placebo.
- Vanflyta meets some patient needs because it offers an additional treatment option that may prolong survival and delay disease relapse.
- Based on the CDA-AMC assessment of the health economic evidence, Vanflyta does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a higher total treatment cost for Vanflyta compared to the total treatment cost of midostuarin.
- Based on public list prices, Vanflyta is estimated to cost the public drug plans approximately $24 million over the next 3 years.

Summary

Additional Information

What Is AML?

AML is a type of cancer that affects bone marrow and blood that leads to fewer mature blood cells. AML causes weakness, infection, bleeding, anemia, and other symptoms and complications. Approximately 1,160 people in Canada were diagnosed with AML in 2022. The *FLT3*-ITD mutation is present in approximately 25% of individuals with AML. It is associated with a higher burden of disease at diagnosis as well as poorer relapse-free and overall survival.

Unmet Needs in AML

There is a need for effective therapies beyond transplant that can be used to increase durability of response beyond induction and consolidation therapy and improve longer-term survival, particularly in patients with *FLT3*-ITD–positive AML who have poorer survival outcomes.

How Much Does Vanflyta Cost?

Treatment with Vanflyta is expected to cost approximately $211,617 per patient in year 1 ($237,970 with chemotherapy) and $282,675 per patient per year thereafter.

Recommendation

The Canada's Drug Agency (CDA-AMC) pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that quizartinib be reimbursed in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib maintenance monotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) positive only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one phase III, randomized, double-blind trial (QuANTUM-First; N = 539) suggested that quizartinib when added to standard induction (for up to two 28-day cycles) and consolidation (for up to 4 cycles with or without allogeneic hematopoietic stem cell transplantation [HSCT]) chemotherapy then administered as maintenance monotherapy (for up to 36 cycles) likely results in a clinically important improvement in overall survival (OS) and may result in an increase in relapse-free survival (RFS) in adult patients with newly diagnosed AML that is *FLT3*-ITD positive compared to placebo. In the QuANTUM-First trial, the median OS was 31.9 months (95% confidence interval [CI], 21.0 months to not estimable [NE]) in the quizartinib group and 15.1 months (95% CI, 13.2 to 26.2 months) in the placebo group (hazard ratio [HR] = 0.776; 95% CI, 0.615 to 0.979; P = 0.0324). The median RFS was 39.3 months (95% CI, 22.6 months to NE) in the quizartinib group and 13.6 months (95% CI, 9.7 to 23.7 months) in the placebo group (HR = 0.613; 95% CI, 0.444 to 0.845; not tested statistically).

In the absence of direct evidence comparing quizartinib to midostaurin, which is the current standard of care in Canada for patients with newly diagnosed AML that is *FLT3*-ITD positive, pERC considered 2 sponsor-submitted indirect treatment comparisons (ITCs) that included an anchored matching-adjusted indirect comparison (MAIC) and a multilevel network meta-regression (ML-NMR). Outcomes evaluated in the MAIC and ML-NMR included OS, complete remission (CR), and cumulative incidence of relapse (CIR) for patients whose AML relapses after CR. The MAIC was restricted to data from patients younger than 60 years that demonstrated no difference between quizartinib and midostaurin, both in combination with chemotherapy, in terms of OS or CR. There were also favourable results for quizartinib over midostaurin in terms of CIR (HR = [redacted]; 95% CI, [redacted] to [redacted]). The ML-NMR generated effect estimates for quizartinib (from the QuANTUM-First trial) and midostaurin (from the phase III RATIFY trial) relative to placebo, including in patients older than 60 years. In both QuANTUM-First–like and RATIFY-like populations, point estimates of HR for OS favoured quizartinib and midostaurin over placebo, although the results were not statistically significant due to wide credible intervals (CrIs). pERC noted that due to important methodologic limitations and imprecision in the comparative effect estimates from the ITCs, the efficacy of quizartinib versus midostaurin remains uncertain.

Patients identified a need for effective and accessible treatment options with reduced side effects that can offer cure or prolonged remission, reduce the risk of relapse, and improve quality of life. pERC noted that

quizartinib meets some patient needs because it offers an additional treatment option that may prolong survival and delay disease relapse. In the QuANTUM-First trial, larger proportions of patients in the quizartinib group experienced 1 or more serious adverse events (AEs) or discontinued treatment due to AEs compared with the placebo group. However, pERC acknowledged that similar proportions of patients in both study groups had grade 3 or 4 AEs and agreed with the clinical experts that these harms were consistent with the safety profile of other AML-directed therapies and may be manageable in clinical practice. pERC also noted that although the results of the QuANTUM-First trial showed no clinically important difference in the change from baseline in health-related quality of life (HRQoL) compared with placebo, a conclusion regarding HRQoL could not be drawn due to the exploratory nature of patient-reported outcomes in the trial, absence of minimally important difference estimates in in the patient population under review, and substantial proportion of missing data.

At the sponsor-submitted price for quizartinib and publicly listed prices for all other treatments for AML, the total treatment cost of quizartinib (including induction, consolidation, and maintenance) was higher than the total treatment cost of midostaurin (including induction, consolidation, and a proportion of patients receiving azacitidine in maintenance). Because quizartinib is considered similarly effective as midostaurin, and no robust comparative information was provided for the maintenance phase, the total treatment cost of quizartinib should not exceed the total treatment cost of midostaurin.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy followed by maintenance monotherapy should be reimbursed in adult patients who have all the following criteria: 1.1. newly diagnosed primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm 1.2. presence of *FLT3*-ITD–activating mutation in bone marrow using a validated test 1.3. good performance status.	Evidence from the QuANTUM-First trial demonstrated that, in patients with these characteristics, treatment with quizartinib resulted in a clinical benefit over placebo when both administered in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy followed by quizartinib maintenance monotherapy. The QuANTUM-First trial included patients with an ECOG performance status of 0 to 2.	—
2. Quizartinib should not be initiated in patients who have a diagnosis of acute promyelocytic leukemia, French-American-British classification M3 or WHO classification of acute promyelocytic leukemia with translocation, t(15;17) (q22;q12), or *BCR-ABL*–positive leukemia.	The CDA-AMC review did not include any evidence to demonstrate the benefit of induction, consolidation, or maintenance therapy with quizartinib in patients with the listed conditions. Patients with these conditions were not included in the QuANTUM-First trial.	—

Reimbursement condition	Reason	Implementation guidance
Renewal		
3. To receive consolidation therapy with quizartinib in combination with standard chemotherapy, patients should have complete remission or complete remission with incomplete hematologic recovery during induction treatment.	In the QuANTUM-First trial, patients with complete remission or complete remission with incomplete neutrophil or platelet recovery received consolidation therapy with quizartinib in combination with standard cytarabine consolidation chemotherapy. No evidence was included in this review to show the efficacy and safety of consolidation therapy with quizartinib in patients who did not meet these criteria.	—
4. Continued reimbursement of quizartinib as maintenance monotherapy should be based on meeting all the following criteria: 4.1. completion of consolidation therapy 4.2. no active or grade 3 or higher GVHD in patients who undergo allogeneic hematopoietic stem cell transplantation 4.3. less than 5% of bone marrow blasts within 28 days before start of maintenance therapy.	In the QuANTUM-First trial, patients who met these criteria received maintenance therapy with quizartinib. No evidence was included in this review to show the efficacy and safety of maintenance therapy with quizartinib if these criteria were not met.	pERC agreed that patients who achieve complete remission or complete remission with incomplete hematologic recovery after induction but are unable to receive consolidation therapy may receive maintenance monotherapy with quizartinib at the discretion of the treating physician if they meet other criteria in this condition.
Discontinuation		
5. Treatment should be discontinued upon the occurrence of any of the following: 5.1. relapsed or refractory disease 5.2. unacceptable toxicity 5.3. completion of 36 cycles of maintenance therapy.	In the QuANTUM-First trial, maintenance therapy continued until refractory disease, relapse, start of non–protocol-specified treatment for AML, death, unacceptable toxicity, study closure, or completion of study treatment.	—
Prescribing		
6. Quizartinib should be initiated by clinicians with expertise in managing AML; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery.	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
7. Quizartinib should be negotiated so that the total treatment cost of quizartinib does not exceed the drug program cost of treatment with midostaurin reimbursed for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive.	The ITCs comparing quizartinib and midostaurin were associated with many limitations. As a result, the comparative efficacy was uncertain. Therefore, there is insufficient evidence to justify a cost premium for total treatment cost of quizartinib over that for midostaurin reimbursed for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive.	—

AML = acute myeloid leukemia; CDA-AMC = Canada's Drug Agency; ECOG = Eastern Cooperative Oncology Group; GVHD = graft-versus-host disease; ITC = indirect treatment comparison; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Discussion Points

- **Unmet needs:** Input from patient and clinician groups highlighted the need for effective non-transplant therapies that can be used to increase durability of response beyond induction and consolidation therapy and improve longer-term survival, particularly in patients with AML that is *FLT3*-ITD positive because these patients have worse survival outcomes. pERC discussed that the current standard of care (midostaurin) is only approved for the induction and consolidation phases and not for continuation into a maintenance phase. pERC noted that, currently, only oral azacitidine is available for maintenance therapy, and patients are only eligible to receive it if they are in first CR, have intermediate-risk or an adverse karyotype, and are not planned to receive or have not received allogeneic HSCT. The clinical experts also noted that azacitidine is associated with undesirable gastrointestinal effects. pERC agreed that there is an unmet need for effective therapies with tolerable side effects that can improve duration of response and reduce the risk of relapse in patients with newly diagnosed *FLT3*-mutated AML.
- **OS benefit:** Patient and clinician groups noted that prolonging OS is an important goal of treatment for patients with newly diagnosed *FLT3*-ITD–positive AML and, for patients who are eligible for intensive chemotherapy, the goal of treatment is to provide a cure. The QuANTUM-First trial demonstrated statistically significant results regarding its primary end point of OS with a median survival of 31.9 months in the quizartinib group and 15.1 months in the placebo group (HR = 0.776; 95% CI, 0.615 to 0.979; P = 0.0324). pERC noted that the interpretation of the HR for OS may be limited by the violation of the proportional hazard assumption (i.e., crossover of the curves occurred between 3 and 6 months due to an early detriment in the quizartinib arm); therefore, reliance on the HR alone to inform the effects of quizartinib versus placebo on this end point may be misleading. The committee further discussed that approximately 10% and 11% more patients in the quizartinib group than the placebo group were alive at 12 and 48 months of follow-up, respectively, suggesting a likely clinically important OS benefit. However, pERC noted that the extent to which this OS benefit can be attributed to a particular phase of treatment (i.e., induction, consolidation, or maintenance) is unclear. pERC discussed that despite the uncertainty regarding the specific benefit from maintenance quizartinib on OS, availability of quizartinib for maintenance treatment meets an unmet need for patients with AML that is *FLT3*-ITD mutation–positive by providing long-term durable treatment response after induction and consolidation therapy and improving survival benefit. The clinical experts noted that many physicians would choose quizartinib over midostaurin under the assumption that maintenance therapy could reduce the risk of relapses and prolong OS.
- **Adverse events**: pERC deliberated on the safety profile of quizartinib and noted that a larger proportion of patients in the quizartinib group than the placebo group experienced 1 or more serious AEs (54.0% versus 45.9%), discontinued treatment due to AEs (20.4% versus 8.6%), or reported to have notable harms, including an increase in the QT interval corrected using the Fridericia formula (QTcF) of more than 30 ms from baseline (55.1% versus 32.5%), and/or a prolonged QT interval (13.6% versus 4.1%). It was also noted that the results of the QuANTUM-First trial were suggestive of an increased risk of grade 3 or 4 graft-versus-host disease (GVHD) among patients in the quizartinib

group who underwent protocol-specified allogeneic HSCT compared with those in the placebo group (16.7% versus 6.6%). However, the magnitude and clinical relevance of this increase was uncertain due to the small number of events. pERC additionally discussed the observation that OS curves cross at 3 to 6 months. This suggested an apparent early OS detriment with quizartinib, with more deaths occurring within 60 days of starting induction therapy plus quizartinib compared with the placebo group. Most early deaths were attributed to infections. The clinical experts consulted noted that this apparent early OS detriment would not affect who would be treated with quizartinib but highlighted that patients should be closely monitored for infections and other AEs during induction therapy. pERC concluded that these AEs, although largely anticipated, need particular consideration regarding risk mitigation strategies and supportive care.

- **Uncertainty in relative efficacy to midostaurin from the ITCs:** pERC discussed that the current standard of care for patients with *FLT3*-mutated AML is the addition of midostaurin to induction and consolidation based on the RATIFY trial, which limited enrolment to patients younger than 60 years. The sponsor-submitted ITCs aimed to provide indirect evidence of the efficacy of quizartinib relative to midostaurin. The MAIC was insufficient to demonstrate superiority of quizartinib over midostaurin for either OS or CR among patients younger than 60 years. The ML-NMR aimed to address the limited generalizability of the MAIC by estimating the efficacy of quizartinib and midostaurin versus placebo in populations similar to those in the QuANTUM-First–like and RATIFY trials. The ML-NMR was subject to many of the same limitations as the MAIC and, although point estimates for between-group differences versus placebo for OS were suggestive of similar benefit of quizartinib and midostaurin, the absence of between-group effect estimates for the active treatments precluded any credible conclusions about their comparative efficacy for any outcome assessed. Overall, pERC concluded that the efficacy of quizartinib versus midostaurin is uncertain.
- **Testing considerations**: pERC discussed the need for *FLT3*-ITD mutation testing when determining eligibility for quizartinib. Overall, this is not anticipated to be an implementation issue because reflex testing for *FLT3*-ITD mutation status upon diagnosis of AML is currently part of routine care in Canada. Input from a patient group flagged that testing results are often not available before standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy. However, pERC agreed that quizartinib can be added to the treatment regimen once test results are available.
- **Cost-effectiveness:** pERC discussed the economic evidence and noted that although the results of cost-utility analysis reported a benefit associated with quizartinib plus chemotherapy compared with midostaurin plus chemotherapy, there was substantial uncertainty with this estimate. pERC discussed that the indirect evidence comparing quizartinib and midostaurin were from trials that considered the induction, consolidation, and maintenance phases and that there was no evidence to indicate a difference between quizartinib and midostaurin. There was no evidence presented comparing the 3 phases of quizartinib (i.e., induction, consolidation, and maintenance) with the first 2 phases of midostaurin (i.e., induction and consolidation). pERC noted that some patients initially treated with midostaurin may receive azacitidine as maintenance therapy. Although the committee acknowledged

the ability to use quizartinib in the maintenance phase may be associated with a benefit compared with no maintenance treatment or azacitidine maintenance, no evidence was presented to support this assumption because the relative efficacy of maintenance phase versus all phases of therapy was not distinguishable for both quizartinib and midostaurin.

Background

AML is a heterogeneous hematologic malignancy with a rapid disease onset due to proliferation of abnormal blast cells. AML is 1 of the most aggressive forms of leukemia, with an estimated 5-year survival rate of 31.9%. In 2019, approximately 1,160 people in Canada were diagnosed with AML and in 2022, 1,286 died from the disease. Symptoms of AML include those associated with anemia (e.g., fatigue, weakness, shortness of breath, light-headedness, dizziness, headaches), neutropenia (e.g., frequent infections, fever), and thrombocytopenia (e.g., easy bruising, petechiae, prolonged bleeding from minor cuts, frequent or severe nosebleeds, bleeding gums). Other symptoms may include loss of appetite, unexplained weight loss, discomfort in bones or joints, and fullness or swelling in the abdomen due to an enlarged spleen or liver.

The *FLT3* mutation can be found in approximately 30% of patients with newly diagnosed AML. The 2 main classes of *FLT3* mutations are the internal tandem duplication (ITD) mutations within the receptor's autoinhibitory juxtamembrane domain (approximately 25% of all AML diagnoses) and the point mutations that occur within the tyrosine kinase domain (TKD) activation loop (5% to 10% of all AML diagnoses). Patients with AML with the *FLT3*-TKD mutation and those without any *FLT3* mutation have a higher burden of disease at diagnosis and poorer OS and RFS compared with those with the *FLT3*-ITD mutation.

Among patients with newly diagnosed AML that is *FLT3*-ITD positive, the goal of treatment is to control the disease and, whenever possible, provide a cure. Patients who are eligible for intensive chemotherapy receive standard induction therapy with cytarabine and an anthracycline (either daunorubicin or idarubicin) in combination with the *FLT3* inhibitor midostaurin. For patients with CR after 1 or 2 cycles, induction therapy is followed by allogeneic HSCT and/or 1 to 4 cycles of consolidation therapy with either intermediate-dose or high-dose cytarabine plus midostaurin. This may be followed by maintenance treatment with oral azacitidine for patients not eligible for allogeneic HSCT.

Quizartinib is a small molecule inhibitor of *FLT3*. It is approved by Health Canada in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib maintenance monotherapy, for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive. The Health Canada–approved indication includes clarifying statements stating that "improvement in overall survival has not been demonstrated for maintenance monotherapy following allogeneic hematopoietic stem cell transplantation" and that "a validated test is required to confirm the *FLT3*-ITD status of AML." The product monograph includes a Serious Warnings and Precautions Box that states, "Do not initiate VANFLYTA therapy if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms or in patients with severe hypokalemia, hypomagnesemia, or long QT syndrome." The sponsor-requested reimbursement criteria align with the Health Canada indication.

Midostaurin is currently the only drug specifically indicated for the treatment of patients with newly diagnosed *FLT3*-mutated AML in Canada. Although the addition of midostaurin to standard induction and consolidation therapy improves outcomes among these patients, there remains an important risk of relapse after remission and long-term survival may be limited. Evidence suggests that the use of *FLT3* inhibitors as maintenance therapy presents an opportunity to prevent poor outcomes associated with relapse after allogeneic HSCT.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III randomized controlled trial (RCT) in adult patients with newly diagnosed AML that is *FLT3*-ITD positive and 2 sponsor-submitted ITCs
- patients' perspectives gathered by 2 patient groups: Health Canada and the Leukemia and Lymphoma Society of Canada (LLSC)
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with AML
- input from 3 clinician groups, the Ontario Health – Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee and a second joint input from the Canadian Leukemia Study Group/Groupe Canadien d'Étude sur la Leucémie (CLSG/GCEL) and Cell Transplant Therapy Canada (CTTC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Patients highlighted the profound impact of AML on their social lives, personal relationships, mental health, and independence. Nearly all patients reported needing caregiver support for daily tasks, which diminished their mental well-being by impeding independence and increasing the burden on caregivers. Patients also emphasized the impact of AML on their personal and home lives, reporting that symptoms, mental load, and frequent appointment travel limit their ability to participate in social activities and maintain relationships. For many patients, current treatments can have severe adverse effects and limited long-term efficacy.

When evaluating new treatment options for AML, patients and caregivers indicated that they would prioritize improvements in long-term adverse effects and the impact of adverse effects on daily life, and a reduced risk of relapse. High importance was also placed on quality of life (QoL), maintaining independence, the severity and frequency of adverse effects, and the duration of and potential for sustained remission. When asked to elaborate on the desired improvements to QoL they would like from new treatments, patients noted longer remission, decreased fear and risk of reoccurrence, complete remission and a cure, resumption of regular

daily activities, limited side effects, less time in hospital, reduced need for transfusions, and better access to care in smaller communities.

In the Health Canada input, 3 patients had experience with quizartinib and found the treatment to be well-tolerated. One patient reported improved response after switching from azacitidine-venetoclax-gilteritinib. Another patient had CR during the first induction, received allogeneic HSCT, reported no residual disease after transplantation, and continued with quizartinib maintenance therapy. In the LLSC input, 13 respondents to the first survey had experience with quizartinib. Respondents reported the most severe adverse effects were thrombocytopenia and anemia. Most respondents noted improved QoL, and all reported that they would choose quizartinib again and recommend it to others.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts identified the need for evidence to support decision-making, including studies to inform the efficacy and harms of *FLT3*-ITD inhibitors among patients older than 60 years; the comparative efficacy of midostaurin and more potent *FLT3*-ITD inhibitors, including quizartinib and gilteritinib; the role of minimal or measurable residual disease (MRD) assessment in determining which patients need more consolidative therapy and/or allogeneic HSCT; and the contribution of maintenance therapy to the efficacy of *FLT3*-ITD inhibitors, including among patients who have received allogeneic HSCT. The clinical experts also identified a need for an approved maintenance therapy for patients with newly diagnosed AML that is *FLT3*-ITD positive. Currently, only oral azacitidine is available, and patients are only eligible if they are in first CR, have an intermediate-risk or adverse karyotype, and are not planned to receive or have not received allogeneic HSCT. The clinical experts noted that azacitidine is associated with undesirable gastrointestinal effects.

According to the clinical experts, patients most likely to benefit from quizartinib are those with newly diagnosed AML that is *FLT3*-ITD positive and who are eligible for intensive induction and consolidation chemotherapy. These patients are currently treated with midostaurin. Midostaurin is also used in patients with *FLT3*-TKD mutations; however, these patients would not be treated with quizartinib. Although there is no direct evidence comparing quizartinib and midostaurin, the clinical experts indicated that most physicians would choose quizartinib over midostaurin, with the primary advantage being the option to administer it as maintenance therapy. According to the clinical experts, testing for *FLT3*-ITD mutations is currently performed as part of the standard of care for patients with newly diagnosed AML. Testing for *FLT3*-ITD mutations to determine treatment eligibility for quizartinib is not anticipated to pose any implementation issues.

According to the clinical experts, patients receiving quizartinib will be monitored for relapse based on clinical assessment and bloodwork at regular intervals, with a bone marrow assessment done when there is a concern about relapse. Patients will be discontinued from quizartinib upon disease relapse, the development of certain cardiac AEs, death, or the completion of 3 years of maintenance therapy (per the protocol for the pivotal trial). Quizartinib may also be discontinued due to patient preference.

The clinical experts noted that MRD is being evaluated routinely for an increasing number of AML subtypes as a potential marker of prognosis and to inform treatment decision-making. Testing for *FLT3*-ITD

MRD is being developed and validated at some Canadian centres but is not currently funded or used in clinical practice.

According to the clinical experts, patients receiving quizartinib should be treated by a hematologist with experience in treating patients with acute leukemia in a centre with the appropriate resources. Consolidation chemotherapy may be administered in the outpatient setting provided certain institutional criteria are met. Quizartinib maintenance therapy would be administered as an outpatient under the supervision of a hematologist with experience in administering lower intensity therapy in a centre with the appropriate resources.

Clinician Group Input

The clinician groups emphasized that there is currently no approved *FLT3*-ITD–specific maintenance therapy, highlighting this as a major cause of treatment failure and death in patients with this mutation. The clinician groups also noted that currently available treatments are highly toxic and that patients who receive them have poor outcomes, including high relapse rates and short OS. Because it is not possible to identify which patients with *FLT3*-ITD are most likely to respond to treatment, the clinician groups noted that all should receive it.

The clinician groups concurred that MRD response could be a surrogate; however, an appropriate *FLT3*-ITD MRD test is not available in Canada. The clinician groups suggested that, depending on the patient's disease phase, their treatment response could be reassessed weekly, every 2 weeks, monthly, or every 2 to 3 months. Postinduction bone marrow is used to confirm remission. The clinician groups indicated that discontinuation of quizartinib should be considered in the event of relapse or intolerable toxicity. They noted that the optimal duration of quizartinib maintenance therapy is currently unclear; however, at least 3 years of maintenance therapy would be recommended in the absence of disease relapse or intolerable toxicity per the design of the pivotal trial.

The clinician groups agreed that treatment would be initiated and monitored at a university-associated academic leukemia centre as an inpatient procedure for induction and as an outpatient procedure for consolidation. The groups noted that, during maintenance treatment, patients could be followed incrementally at a shared care site closer to home. Treatment would be initiated and monitored by specialists with expertise in leukemia, likely primarily hematologists, but also some oncologists.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The QuANTUM-First trial compared quizartinib to placebo in combination with chemotherapy for induction and consolidation and as a single agent for maintenance therapy. Midostaurin is currently funded, in combination with chemotherapy, for induction and consolidation of newly diagnosed *FLT3*-mutated AML. It is not currently indicated for maintenance therapy. Azacitidine is funded as maintenance for patients who are transplant-ineligible. There is limited access to other agents for maintenance across Canadian jurisdictions (e.g., sorafenib in combination with azacitidine is available in BC).	This was a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
FLT3 testing is standard across Canada. To be eligible, patients had to have a *FLT3*-ITD VAF of at least 3%. Should patients with a VAF < 3% be eligible for treatment?	Per the clinical experts, patients with VAF < 3% should be considered eligible for treatment with quizartinib. The clinical experts clarified that although *FLT3* testing is standard in Canada, the method will differ by centre (i.e., NGS for DNA or RT-PCR for RNA). The sensitivity, specificity, and limitations of the *FLT3*-ITD assay will depend on the methodology and the laboratory. As such, the presence of *FLT3*-ITD using a validated test should be used to inform eligibility, rather than a specific VAF threshold. pERC agreed with the clinical experts.
FLT3 testing results will be required in a timely manner to begin treatment on day 8.	This was a comment from the drug programs to inform pERC deliberations.
Considerations for continuation or renewal of therapy	
The response criteria used in the study were adapted from Cheson 2003 and Döhner 2017: CR required bone marrow blasts < 5%, neutrophils > 1,000/mm^3, and platelets > 100,000/mm^3. Is this congruent with Canadian practice?	In the QuANTUM-First trial, patients with CR or CR with incomplete hematologic recovery were eligible for consolidation therapy. Patients with CR with incomplete hematologic recovery were those who met the criteria for CR except for the platelet or neutrophil count. The clinical experts consulted for this review noted that this would align with clinical practice in Canada. However, per the clinical experts, achieving a strictly defined CR may not be required in clinical practice for patients to continue to consolidation therapy. pERC agreed that assessment of response criteria to select eligible patients to proceed to consolidation therapy should be left to the discretion of the treating physician.
To receive maintenance therapy, patients had to be able to start within 60 days of the first day of the last consolidation cycle or 30 to 180 days after allogeneic HSCT. Are there any reasons a patient might not be able to start treatment within these time frames and should remain eligible for maintenance with quizartinib?	Per the clinical experts, 60 days may be stringent for some patients; for example, some older patients may take longer to recover, particularly after multiple rounds of consolidation chemotherapy. Per the clinical experts, the time frame for starting maintenance therapy after allogeneic HSCT is very wide. The wide time range reflects the multiple factors that would need to be considered to determine when a patient may be ready to begin maintenance therapy with quizartinib (e.g., active GVHD, organ comorbidities). pERC agreed with the clinical experts.

Drug program implementation questions	Clinical expert response
Considerations for discontinuation of therapy	
Quizartinib and placebo were discontinued for unacceptable toxicity, refractory disease, relapse, or upon completion of 36 cycles of maintenance therapy. Are there specific or standard definitions that should be used for discontinuation?	Per the clinical experts, there are no standard definitions used for discontinuation. However, the criteria used in the pivotal trial are reflective of reasons for which patients would typically be discontinued from treatment. The clinical experts underscored the potential role of *FLT3*-ITD MRD testing in informing treatment decisions, including when to discontinue or prolong quizartinib maintenance therapy. pERC noted that *FLT3*-ITD MRD testing is not routinely available in clinical practice in Canada. The committee agreed that the discontinuation criteria in the QuANTUM-First trial should be used for discontinuation of quizartinib.
If a patient stops treatment with quizartinib for reasons other than progression, should they be able to resume quizartinib to complete 3 years total of maintenance therapy?	pERC agreed with the clinical experts who indicated patients should be allowed to resume treatment with quizartinib up to 36 cycles of maintenance therapy, if they needed to hold for a reason other than disease progression during maintenance therapy (e.g., to treat infections or other medical illnesses).
Considerations for prescribing of therapy	
In the trial, chemotherapy used for induction was 7 + 3 (cytarabine with daunorubicin or idarubicin) and chemotherapy used for consolidation was high-dose cytarabine. Should patients using other chemotherapy regimens in induction and/or consolidation be eligible for treatment with quizartinib?	The clinical experts did not believe that patients using other chemotherapy regimens during induction and/or consolidation should be eligible for treatment with quizartinib. No studies of quizartinib in combination with other chemotherapy regimens were included in this CDA-AMC review. Therefore, pERC was unable to comment on the safety and effectiveness of using quizartinib in combination with other chemotherapy regimens.
Generalizability	
Should any of the following groups be considered for treatment with quizartinib? • ECOG performance status > 2 • age < 18 • age > 75 • *BCR-ABL1*–positive leukemia • AML secondary to prior chemotherapy or radiotherapy for other neoplasms • history of known CNS leukemia, including CSF positive for AML blasts	pERC agreed with the clinical experts that patients younger than 18 and those with *BCR-ABL1*–positive leukemia should not be considered eligible for treatment with quizartinib as per indication in the current review. The clinical experts clarified that decisions to administer quizartinib in combination with chemotherapy should be based not only on a patient's performance status at the time of diagnosis of AML, but on their baseline performance status (i.e., before diagnosis of AML). pERC agreed that patients with an ECOG performance status of 2 or more and patients older than 75 years may be treated at the discretion of the treating physician. pERC noted there was insufficient evidence included in this review to support the use of quizartinib in combination with chemotherapy for induction and consolidation and as a single agent for maintenance therapy in patients with AML secondary to prior chemotherapy or radiotherapy for other neoplasms and in those with a known CNS leukemia, including CSF positive for AML blasts.
Should patients currently receiving treatment for newly diagnosed AML with midostaurin be eligible to switch to quizartinib? If yes, in which phases of treatment?	pERC agreed with the clinical experts who noted that, in the absence of intolerance or toxicity from midostaurin (e.g., significant nausea or vomiting), there is no reason to switch from midostaurin to quizartinib during induction or consolidation therapy.

Drug program implementation questions	Clinical expert response
Should patients who recently completed treatment with midostaurin be eligible for quizartinib maintenance therapy?	The clinical experts consulted for this review anticipated that, in clinical practice, physicians would likely be more willing to provide quizartinib maintenance therapy to patients who received midostaurin during induction and consolidation. pERC noted that, because the available evidence assessed the effects of quizartinib when used across induction, consolidation, and maintenance phases as a complete regimen, the benefit and safety attributable to its use in the maintenance phase alone remains unknown. There are no available data to support using quizartinib maintenance after a midostaurin-based induction and consolidation phase. For patients who have received midostaurin, oral azacitidine is currently available for maintenance therapy if certain conditions are met apply. pERC noted that, upon implementation of the reimbursement recommendation by jurisdictions, patients initiating treatment at induction should be informed of these limitations when considering treatment options (e.g., quizartinib maintenance is only available to patients initiating on quizartinib-based therapy at induction). However, there may be a legacy group of patients who have completed induction and/or consolidation therapy with midostaurin who did not have access to this option. Those patients may be considered for eligibility by jurisdictions on a case-by-case basis.
Funding algorithm	
Under what circumstances would quizartinib be preferred over midostaurin?	Per the clinical experts, the primary benefit of quizartinib would be that it can be used as a maintenance therapy after consolidation because midostaurin is not currently approved for use as maintenance therapy. The clinical experts clarified that there is no direct evidence of the efficacy of midostaurin vs. quizartinib; however, a perceived benefit of quizartinib during maintenance may result in most physicians choosing quizartinib over midostaurin. pERC acknowledged that this would likely be a scenario and emphasized that the maintenance therapy options should be discussed with patients to support informed decision-making aligned with their preferences and clinical needs.
Care provision issues	
There are 2 tablet strengths available, 17.7 mg and 26.5 mg (equivalent to 20 mg and 30 mg of quizartinib dihydrochloride respectively). Dose modifications were implemented for QTc prolongation, other non-hematological toxicities, and myelosuppression.	This was a comment from the drug programs to inform pERC deliberations.
Quizartinib metabolism is impacted by the CYP3A4 pathway. Concomitant use of strong or moderate CYP3A4 inducers should be avoided. Dose modifications are required for concomitant use of strong CYP3A4 inhibitors.	This was a comment from the drug programs to inform pERC deliberations.
In the maintenance phase, the dose of quizartinib was increased after ECG on cycle 1 day 15 or cycle 2 day 1 if the mean QTcF was ≤ 450 ms.	This was a comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
System and economic issues	
This will potentially add 3 years of maintenance treatment for newly diagnosed AML patients.	This was a comment from the drug programs to inform pERC deliberations.
Increased workload to be expected for required QTc monitoring.	This was a comment from the drug programs to inform pERC deliberations.
Confidential pricing exists for midostaurin.	This was a comment from the drug programs to inform pERC deliberations.

AML = acute myeloid leukemia; BC = British Columbia; CNS = central nervous system; CR = complete remission; CSF = cerebrospinal fluid; CYP = cytochrome P450; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; ITD = internal tandem duplication; NGS = next-generation sequencing; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QTc = corrected QT interval; QTcF = QT interval corrected by Fridericia formula; RT-PCR = reverse transcription polymerase chain reaction; VAF = variant allele frequency.

Clinical Evidence

Systematic Review

Description of Studies

The sponsor's systematic review identified 1 phase III, double-blind, multicentre RCT, QuANTUM-First. The QuANTUM-First study compared the effects of quizartinib (n = 268) versus placebo (n = 271) (administered with standard induction and consolidation chemotherapy [and/or allogeneic HSCT], then administered as maintenance therapy for up to 36 cycles) among adult patients with newly diagnosed AML that was *FLT3*-ITD positive (N = 539). The sponsor's systematic review did not identify any studies that directly compared the efficacy or harms of quizartinib and midostaurin.

The QuANTUM-First study was conducted in 193 sites in 26 countries, including 4 sites in Canada. The study consisted of 4 consecutive phases: induction, consolidation, continuation (hereafter termed *maintenance*), and long-term follow-up. The primary end point was OS. Secondary end points included event-free survival (EFS), CR rate, CR with *FLT3*-ITD MRD negativity rate, composite CR (CRc) rate (CR + CR with incomplete hematologic recovery), and CRc with *FLT3*-ITD MRD negativity rate after induction. Relevant exploratory end points included RFS, duration of CR and CRc, transplantation rate, and HRQoL, which was assessed via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). There were no interim analyses. The final data cut-off for efficacy analyses was August 13, 2021. At this time, the median duration of follow-up was 39.2 months in both groups. Updated safety data were provided up to a data cut-off of June 16, 2023.

Patients' demographic and disease characteristics were generally balanced across groups. The median age of patients was 56 years and 40% were aged 60 years or older. Overall, 54.5% of the trial population were female and 45.5% were male. Patients were primarily Asian (29.3%) or white (59.7%) and were recruited from Europe (60.5%), North America (6.3%) and Asia or other regions (33.2%). Most patients had de novo AML (92.4%), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (84.4%), and an intermediate cytogenetic risk status (72.4%). Approximately two-thirds of patients had a *FLT3*-ITD variant

allele frequency (VAF) of more than 25%, half had a *FLT3*-ITD VAF of more than 25% but less than 50%, and 10% had a *FLT3*-ITD VAF of 50% or more. Equal proportions of patients had a white blood cell count at diagnosis of less than 40 × 10^9/L and of 40 × 10^9/L or more. The mean bone marrow blast count at baseline was 66.91 to 67.60 across groups. The mean absolute neutrophil counts at baseline in the quizartinib and placebo groups were 0.60 (standard deviation [SD] = 1.83) and 0.44 (SD = 1.30), respectively; mean platelet counts were 28.76 (SD = 22.137) and 31.27 (SD = 33.942), respectively. Across groups, approximately one-half and one-quarter of patients, respectively, had*NPM1* and *CEBPA* mutations.

Of randomized patients, 265 of 268 (98.9%) in the quizartinib group and 268 of 271 (98.9%) in the placebo group were treated. Among these patients, all entered the induction phase. Sixty-five percent of patients in both groups entered the consolidation phase and 37.0% in the quizartinib group and 33.2% in the placebo group received allogeneic HSCT (with or without study drug plus chemotherapy). Forty-four percent of patients in the quizartinib group and 34.3% of patients in the placebo group entered the maintenance phase, including 70 of 98 (71.4%) patients in the quizartinib group and 49 of 89 (55.1%) patients in the placebo group who had received allogeneic HSCT during the consolidation phase. During the maintenance phase, an additional 4 (1.5%) patients in the quizartinib group and 2 (0.7%) in the placebo group received allogeneic HSCT. As of the time of the data cut-off, 84.9% of patients in the quizartinib group and 89.2% of patients in the placebo group had entered long-term follow-up.

Efficacy Results

Overall Survival

At the time of the data cut-off, 133 of 268 (49.6%) patients in the quizartinib group and 158 of 271 (58.3%) patients in the placebo group had died. The median OS was 31.9 months (95% CI, 21.0 months to NE) in the quizartinib group and 15.1 months (95% CI, 13.2 to 26.2 months) in the placebo group. The HR was 0.776 (95% CI, 0.615 to 0.979), in favour of quizartinib (P = 0.0324). The Kaplan-Meier (KM)–estimated probability of OS at 12 months was 67.4% (95% CI, 61.3% to 72.7%) in the quizartinib group and 57.7% (95% CI, 51.6% to 63.4%) in the placebo group (difference = 9.6%; 95% CI, 1.4% to 17.8%). The KM-estimated probability of OS at 48 months was 48.4% (95% CI, 41.9% to 54.5%) in the quizartinib group and 37.0% (95% CI, 29.8% to 44.2%) in the placebo group (difference = 11.4%; 95% CI, 1.8% to 21.0%). Sensitivity analyses censoring patients who received allogeneic HSCT and using restricted mean survival time to account for a possible plateau effect supported an OS benefit with quizartinib.

There was an apparent early OS detriment with quizartinib relative to placebo. In the quizartinib group, 15 (5.7%) and 20 (7.5%) patients died during the first 30 and 60 days, respectively, compared with 9 (3.4%) and 13 (4.9%) in the placebo group. Early deaths in the quizartinib versus placebo groups were attributed to AEs (6.4% versus 4.1%), AML disease progression (0.8% versus 0.7%), and other causes (0.4% versus 0%).

Results for OS among most prespecified subgroups were aligned with the main analysis; however, among patients aged from 60 years to less than 65 years, patients from North America, patients with a white blood cell count less than 40 × 10^9/L at diagnosis, and patients without an *NPM1* mutation, the point estimate for the HR of quizartinib versus placebo was near the null (i.e., no statistical difference). Among patients with a favourable AML cytogenetic risk score, the point estimate for the HR of quizartinib versus placebo favoured

placebo. Across categories within each subgroup, the 95% CIs for the comparative effect estimates were overlapping.

Among the subgroup of patients who entered the consolidation (65% of patients in each group) and maintenance (43.3% in the quizartinib group and 33.9% in the placebo group) phases of treatment, the results were consistent with the main analysis. Among patients who entered the consolidation phase, the median OS was NE (95% CI, 48.6 months to NE) in the quizartinib group and 42.5 months (95% CI, 21.9 months to NE) in the placebo group. The HR was 0.703 (95% CI, 0.509 to 0.971). The KM-estimated probability of OS at 48 months was 60.2% (95% CI, 52.0% to 67.5%) in the quizartinib group and 46.5% (95% CI, 36.5% to 56.0%) in the placebo group. Among patients who entered the maintenance phase, the median OS was NE in both groups. The HR was 0.683 (95% CI, 0.395 to 1.183). The KM-estimated probability of OS at 48 months was 76.3% (95% CI, 66.2% to 83.7%) in the quizartinib group and 67.9% (95% CI, 55.3% to 77.6%) in the placebo group.

In a post hoc analysis among patients who received allogeneic HSCT and continued to the maintenance phase, the median OS was not reached in either group. The HR for OS in this subpopulation was 1.622 (95% CI, 0.623 to 4.220).

Event-Free Survival

At the time of the data cut-off, 198 of 268 (73.9%) patients in the quizartinib group and 213 of 271 (78.6%) patients in the placebo group had an EFS event. The median EFS was 0.03 months (95% CI, 0.03 to 0.95 months) in the quizartinib group and 0.71 months (95% CI, 0.03 to 3.42 months) in the placebo group. The HR was 0.916 (95% CI, 0.754 to 1.114; P = 0.2371). The KM-estimated probability of EFS at 12 months was 34.2% (95% CI, 28.5% to 40.0%) in the quizartinib group and 25.0% (95% CI, 19.9% to 30.4%) in the placebo group (difference = 9.3%; 95% CI, 1.5% to 17.1%). The KM-estimated probability of EFS at 36 months was 24.1% (95% CI, 18.8% to 29.7%) in the quizartinib group and 19.2% (95% CI, 14.5% to 24.3%) in the placebo group (difference = 4.9%; 95% CI, −2.5% to 12.2%). Because no statistically significant difference between groups was observed, subsequent secondary end points were not tested statistically. Sensitivity analyses defining induction treatment failure as no CR or CRc by the end of induction (day 56, per the original protocol definition of EFS), and censoring patients at the start date of the conditioning regimen for allogeneic HSCT (with induction treatment failure defined as not achieving CRc) favoured quizartinib. A sensitivity analysis censoring patients at the start date of the conditioning regimen for allogeneic HSCT and defining induction treatment failure as not achieving CR was aligned with the main analysis.

Complete Remission and Composite Complete Remission, With or Without Minimal or Measurable Disease Negativity

At the end of the induction phase, 147 of 286 (54.9%; 95% CI, 48.7% to 60.9%) patients in the quizartinib group and 150 of 271 (55.4%; 95% CI, 49.2% to 61.4%) patients in the placebo group had CR (difference = −0.5%; 95% CI, −8.9% to 7.9%). Further, 71.6% (95% CI, 65.8% to 77.0%) and 64.9% (95% CI, 58.9% to 70.6%) of patients in the quizartinib and placebo groups, respectively, had CRc at the end of induction (difference = 6.7%; 95% CI, −1.1% to 14.5%).

Among patients in the quizartinib group and placebo groups, 20.1% (95% CI, 15.5% to 25.5%) and 18.8% (95% CI, 14.3% to 24.0%) had CR with *FLT3*-ITD MRD negativity (using a prespecified cut-off of 10^{-4} leukemic cells) at the end of induction, respectively; a respective 24.6% (95% CI, 19.6% to 30.2%) and 21.4% (95% CI, 16.7% to 26.8%) had CRc with *FLT3*-ITD MRD negativity at the end of induction.

Duration of Complete Remission and Composite Complete Remission

For patients with CR during induction, the median duration of CR was 38.6 months (95% CI, 21.9 months to NE) in the quizartinib group and 12.4 months (95% CI, 8.8 to 22.7 months) in the placebo group (HR = 0.621; 95% CI, 0.451 to 0.857). For patients with CRc during induction, the median duration of CRc was 27.2 months (95% CI, 17.7 months to NE) in the quizartinib group and 12.4 months (95% CI, 8.7 to 22.7 months) in the placebo group (HR = 0.742; 95% CI, 0.561 to 0.982).

Relapse-Free Survival

Among patients with CR during induction (147 of 268 [54.9%] in the quizartinib group and 150 of 271 [55.4%] in the placebo group), 44.2% in the quizartinib group and 58.7% in the placebo group had an RFS event at the time of the data cut-off. The median RFS was 39.3 months (95% CI, 22.6 months to NE) in the quizartinib group and 13.6 months (95% CI, 9.7 to 23.7 months) in the placebo group. The HR was 0.613 (95% CI, 0.444 to 0.845) in favour of quizartinib, although this end point was not tested statistically. The KM-estimated probability of RFS at 6 months was 88.1% (95% CI, 81.6% to 92.5%) in the quizartinib group and 71.8% (95% CI, 63.8% to 78.4%) in the placebo group (difference = 16.3%; 95% CI, 7.3% to 25.3%). The KM-estimated probability of RFS at 36 months was 51.7% (95% CI, 42.5% to 60.1%) in the quizartinib group and 38.2% (95% CI, 30.0% to 46.4%) in the placebo group (difference = 13.5%; 95% CI, 1.4% to 25.6%).

Transplantation Rate

At the time of the data cut-off, 102 of 268 (38.1%; 95% CI, 32.3% to 44.2%) patients in the quizartinib group and 91 of 271 (33.6%; 95% CI, 28.0% to 39.5%) patients in the placebo group underwent protocol-specified allogeneic HSCT (difference = 4.5%; 95% CI, −3.6% to 12.6%).

Health-Related Quality of Life

A total of 252 of 268 (94.0%) patients in the quizartinib group and 253 of 271 (93.4%) patients in the placebo group were included in the analysis of the global health status [GHS]/QoL scale of the EORTC QLQ-C30. Among these patients, all had baseline assessments. The proportion of patients available for assessment declined in both groups over time thereafter. In the quizartinib and placebo groups, respectively, 79.0% and 77.9% had assessments at day 28 of the first induction cycle, 40.9% and 42.3% had assessments at day 28 of the first consolidation cycle, and 39.7% and 33.2% had assessments at day 1 of the first maintenance cycle.

At baseline, the mean GHS/QoL scale score was similar across groups (45.9 [SD = 24.4] in the quizartinib group and 48.1 [SD = 24.9] in the placebo group). In the longitudinal (mixed-effects model of repeated measures) analysis summarizing the effect of quizartinib versus placebo over all time points, an improvement in GHS/QoL score was observed over time in both groups. The between-group difference in the least

squares mean change from baseline was −2.0 points (95% CI, −4.8 to 0.7 points). Results of a sensitivity analysis adjusting on additional covariates was aligned with the main analysis.

Harms Results

- AEs occurred among nearly all patients in the quizartinib and placebo groups (99.6% and 98.9%, respectively). The most common AEs that occurred among patients in the quizartinib and placebo groups, respectively, included febrile neutropenia (44.2% versus 42.2%), pyrexia (42.3% versus 40.7%), diarrhea (37.0% versus 35.1%), and hypokalemia (35.1% versus 35.8%).
- Grade 3 to 4 AEs occurred among 80.8% of patients in the quizartinib group and 79.9% of patients in the placebo group. The most common grade 3 to 4 AEs in the quizartinib and placebo groups, respectively, included febrile neutropenia (43.4% versus 41.0%), hypokalemia (18.9% versus 16.4%), neutropenia (18.1% versus 8.6%), and pneumonia (11.3% versus 11.2%).
- More patients in the quizartinib group (54.0%) than in the placebo group (45.9%) experienced 1 or more serious AEs. The most common serious AEs that occurred in the quizartinib and placebo groups, respectively, included febrile neutropenia (10.9% versus 8.2%), pneumonia (6.4% versus 5.6%), septic shock (4.2% versus 3.0%), and sepsis (3.8% versus 5.2%).
- More patients in the quizartinib group (20.4%) than in the placebo group (8.6%) stopped treatment due to AEs. The most common AEs leading to treatment discontinuation included septic shock (3.4% versus 0.4%), thrombocytopenia (1.1% versus 0%), and pneumonia (0.8% versus 1.1%) in the quizartinib and placebo groups, respectively.
- AEs leading to death occurred among 11.3% of patients in the quizartinib group and 9.7% of patients in the placebo group. The most common AEs leading to death were reported to be septic shock (3.0% versus 1.1%), sepsis (1.1% versus 0.7%), and general physical health deterioration (0% versus 1.5%) in the quizartinib and placebo groups, respectively.
- More patients in the quizartinib group than in the placebo group, respectively, had an increase in the QTcF more than 30 ms from baseline (55.1% versus 32.5%) and/or a prolonged QT interval (13.6% versus 4.1%). Among patients in the quizartinib and placebo groups, respectively, cardiac arrest with ventricular fibrillation (0.8% versus 0%) and ventricular tachycardia (0.4% versus 0.4%) were infrequent. Combined elevations of aspartate aminotransferase or alanine aminotransferase and total bilirubin occurred among 2.3% of patients in the quizartinib group and 3.4% of patients in the placebo group.
- Among patients who underwent protocol-specified allogeneic HSCT, 57 of 102 (55.9%) in the quizartinib group and 43 of 91 (47.3%) in the placebo group had GVHD. In the quizartinib and placebo groups, respectively, 45.1% and 38.5% had acute GVHD and 29.4% and 19.8% had chronic GVHD. More patients in the quizartinib group (16.7%) than the placebo group (6.6%) had grade 3 to 4 GVHD.

Critical Appraisal

- For all end points, there is low risk of bias arising from the randomization process. Due to the design of the QuANTUM-First study, the contribution of effects in each of the induction and consolidation phases, and maintenance phase to the overall efficacy of quizartinib cannot be isolated.
- The QuANTUM-First study was double-blind and there is a low risk of bias in the measurement of objective outcomes (OS and transplantation rate). Risk of bias in the measurement of CR, CRc, EFS, and RFS is low because they were assessed by an independent review committee. If patients became aware of their assigned treatment (e.g., due to known harms of quizartinib), there would be risk of bias in HRQoL and subjective harms, but the risk is likely low.
- Despite many major protocol violations, risk of bias due to deviations from the intended interventions is likely low because these deviations were generally balanced across groups and unlikely to seriously impact efficacy results.
- The QuANTUM-First study was powered to detect a statistically significant OS benefit. The family-wise type I error rate for the primary and secondary end points was adequate controlled for multiple testing. Because the result for EFS (tested second in the hierarchy after OS) was not statistically significant, no other end points were tested statistically.
- For the analyses of OS and EFS, there was a violation of the proportional hazards assumption; therefore, reliance on the HR alone to inform the effects of quizartinib versus placebo on these end points may be misleading. There was also a plateau in the KM curves for OS, so a comparison of median OS across groups may overestimate the benefit of quizartinib.
- The certainty of evidence for OS and EFS were affected by imprecision. Although the point estimates for the between-group differences in KM-estimated probabilities of OS at 12 and 48 months of follow-up suggested a clinically important benefit with quizartinib, the 95% CIs included small differences that may not be considered clinically important. For EFS, although the point estimates for between-group differences in KM-estimated probabilities at 12 and 36 months of follow-up suggested a little to no clinically important difference, the 95% CIs included the potential for a clinically important benefit with quizartinib.
- Some variation in between-group effects on OS were noted across subgroups. However, the 95% CIs were wide and overlapping across categories within each subgroup, there were no statistical tests for treatment by subgroup interactions, and there were no adjustments for multiple testing, limiting the ability to make credible conclusions about effect modification.
- Additional analyses of OS among patients who entered the consolidation and maintenance phases are at risk of bias because it is unlikely that prognostic balance was maintained across treatment groups among these subpopulations. The post hoc analysis of OS among patients who received allogeneic HSCT and continued to the maintenance phase was subject to the same limitation. Further, a small number of patients (n = 119) contributed to the analysis, the median was not reached in either group, and the effect estimate for the HR was affected by imprecision (the 95% CI included the potential that either group could be favoured).

- The validity of EFS and RFS as surrogates for OS among patients with newly diagnosed *FLT3*-ITD–positive AML who are treated with kinase inhibitors as an add-on to standard chemotherapy remains uncertain.
- RFS was evaluated only among patients with CR or CRc after induction; therefore, the results are at risk of bias because it is uncertain whether prognostic balance across treatment groups was maintained in this subpopulation of patients. The same limitation applies to the analysis of duration of CR and CRc.
- Although the point estimate for the between-group difference in transplantation rate suggested little to no clinically important difference between quizartinib and placebo, this estimate was affected by imprecision (i.e., the 95% CI included the potential for a clinically important increase).
- For HRQoL, there is a high risk of bias due to missing outcome data. The proportion of evaluable patients who provided assessments decreased substantially over time. In the longitudinal analysis (mixed-effects model of repeated measures), missing data were handled under a missing at random assumption, which is unlikely to be reasonable.
- The comparison group was not directly relevant to clinical practice. According to the clinical experts, up to 10% of patients with *FLT3*-ITD–positive AML and concomitant favourable risk core binding factor or adverse-risk karyotype may receive intensive chemotherapy with gemtuzumab ozogamicin or an alternative regimen, such as fludarabine, cytarabine, G-CSF, and idarubicin, also known as FLAG-IDA, rather than midostaurin. Of the remaining patients eligible for intensive induction and consolidation chemotherapy with midostaurin, less than 5% would not be treated with midostaurin, usually due to intolerance or gastrointestinal mucositis. Midostaurin was not yet approved at the start of the QuANTUM-First study.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal study (QuANTUM-First) identified in the sponsor's systematic review, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group (Table 3). Following the GRADE approach, evidence from the QuANTUM-First study started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. For OS, EFS, CR, CRc, transplantation rate, and HRQoL, the target of the certainty of evidence assessment was the presence or absence of a clinically important effect. For RFS and grade 3 to 5 AEs, the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: OS, EFS, CR rate, CRc rate, RFS, transplantation rate, HRQoL, and grade 3 to 5 AEs.

Table 3: Summary of Findings for Quizartinib Versus Placebo[a] for Patients With Newly Diagnosed *FLT3*-ITD–Positive AML

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Quizartinib	Difference		
Survival end points							
Probability of OS at 12 months Median follow-up: 39.2 months in both groups	539 (1 RCT)	NA	577 per 1,000	674 per 1,000 (613 per 1,000 to 727 per 1,000)	[redacted] more per 1,000 ([redacted] more per 1,000)	Moderate[b]	Quizartinib likely results in a clinically important increase in the probability of OS at 12 months compared with placebo.
Probability of OS at 48 months Median follow-up: 39.2 months in both groups	539 (1 RCT)	NA	370 per 1,000	484 per 1,000 (419 per 1,000 to 545 per 1,000)	[redacted] more per 1,000 ([redacted] more per 1,000)	Moderate[b]	Quizartinib likely results in a clinically important increase in the probability of OS at 48 months compared with placebo.
Probability of EFS at 12 months Median follow-up: 39.2 months in both groups	539 (1 RCT)	NA	250 per 1,000	342 per 1,000 (285 per 1,000 to 400 per 1,000)	[redacted] more per 1,000 ([redacted] more per 1,000)	Moderate[c]	Quizartinib likely results in little to no clinically important difference in the probability of EFS at 12 months compared with placebo.
Probability of EFS at 36 months Median follow-up: 39.2 months in both groups	539 (1 RCT)	NA	192 per 1,000	241 per 1,000 (188 per 1,000 to 297 per 1,000)	[redacted] more per 1,000 ([redacted] more per 1,000)	Moderate[c]	Quizartinib likely results in little to no clinically important difference in the probability of EFS at 36 months compared with placebo.
Probability of RFS (among patients with CR after induction) at 6 months Median follow-up: 39.2 months in both groups	297 (1 RCT)	NA	718 per 1,000	881 per 1,000 (816 per 1,000 to 925 per 1,000)	[redacted] more per 1,000 ([redacted] more per 1,000)	Low[d]	Quizartinib may result in an increase in the probability of RFS at 6 months. The clinical importance of the increase is uncertain.
Probability of RFS (among patients with CR after induction) at 36 months	297 (1 RCT)	NA	382 per 1,000	517 per 1,000 (425 per 1,000 to 601 per 1,000)	[redacted] more per 1,000 ([redacted]	Low[d]	Quizartinib may result in an increase in the probability of RFS at 36 months. The clinical

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Quizartinib	Difference		
Median follow-up: 39.2 months in both groups					more per 1,000)		importance of the increase is uncertain.
Remission end points							
CR rate Follow-up: after induction	539 (1 RCT)	NR	554 per 1,000	549 per 1,000 (487 per 1,000 to 609 per 1,000)	fewer per 1,000 (fewer to more per 1,000)	High[e]	Quizartinib results in little to no clinically important difference in CR rate compared with placebo.
CRc (CR + CR with incomplete hematologic recovery) rate Follow-up: after induction	539 (1 RCT)	NR	649 per 1,000	716 per 1,000 (658 per 1,000 to 770 per 1,000)	more per 1,000 (fewer to more per 1,000)	High[e]	Quizartinib results in little to no clinically important difference in CRc rate compared with placebo.
Transplantation Rate							
Patients undergoing allogeneic HSCT Median follow-up: 39.2 months in both groups	539 (1 RCT)	NR	336 per 1,000	381 per 1,000 (323 per 1,000 to 442 per 1,000)	more per 1,000 (fewer to more per 1,000)	Moderate[f]	Quizartinib likely results in little to no clinically important difference in transplantation rate compared with placebo.
HRQoL							
LS mean change from baseline EORTC QLQ-C30 GHS/QoL domain (0 [worse] to 100 [better]), summary effect, points Median follow-up: 39.2 months in both groups	505 (1 RCT)	NA	NR	NR	to)	Low[g]	Quizartinib may result in little to no clinically important difference in HRQoL compared with placebo.
Harms							
Patients with ≥ 1 grade 3 to 5 AE	533 (1 RCT)	NR	921 per 1,000	896 per 1,000 (853 per 1,000 to 929 per 1,000)	more per 1,000 (	Low[h]	Quizartinib may result in an increase in the proportion of patients with ≥ 1 grade 3 to 5

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Quizartinib	Difference		
Median follow-up: 39.2 months in both groups					fewer to [redacted] more per 1,000)		AEs compared with placebo. The clinical importance of the increase is uncertain.

AE = adverse event; CI = confidence interval; CR = complete remission; CRc = composite complete remission; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients; GHS = global health status; HRQoL = health-related quality of life; HSCT = hematopoietic stem cell transplantation; LS = least squares; NA = not applicable; NR = not reported; OS = overall survival; QoL = quality of life; RCT = randomized controlled trial; RFS = relapse-free survival.

Note: Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. Between-group differences for all but the HRQoL end point were not part of the statistical analysis plan. These were provided by the sponsor in response to an additional information request.

[a]In combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as maintenance monotherapy following consolidation.

[b]Rated down 1 level for serious imprecision. The 95% CI for the between-group difference includes the possibility of little to no clinically important difference based on a threshold of 5% to 10%, as informed by the clinical experts consulted.

[c]Rated down 1 level for serious imprecision. The 95% CI for the between-group difference includes the possibility of clinically important benefit with quizartinib based on a threshold of 10%, as informed by the clinical experts consulted.

[d]–Rated down 2 levels for very serious study limitations. RFS is measured only in the subpopulation of patients with CR after induction. It is uncertain whether prognostic balance across treatment groups is maintained in this subpopulation. The null was used as the threshold to inform the target of the certainty rating and the precision of the effect; hence, the clinical importance of the estimated effect is uncertain.

[e]A threshold of 10% to 15% for a clinically important between-group difference, as informed by the clinical experts consulted, was used to inform the target of the certainty rating and the precision of the effect estimate.

[f]Rated down 1 level for serious imprecision. The 95% CI for the between-group difference includes the possibility of clinically important benefit with quizartinib based on a threshold of 10%, as informed by the clinical experts consulted.

[g]Rated down 2 levels for very serious study limitations. The proportion of patients available for assessments diminished substantially over time. Missing data were handled under a missing at random assumption, which is unlikely reasonable. A threshold of 10 points for a clinically important between-group difference, as adopted by the sponsor in their analyses of within-group improvement and detriment, was used to inform the target of the certainty rating and the precision of the effect estimate. There is uncertainty in this threshold. To the knowledge of the review team, no minimally important difference has been estimated in the literature specific to patients with AML.

[h]Rated down 2 levels for very serious imprecision. The 95% CI for the between-group difference includes the possibility of benefit (i.e., reduced harms) and no difference. The null was used as the threshold to inform the target of the certainty rating and the precision of the effect; hence, the clinical importance of the estimated effect is uncertain. Results at the time of the updated safety addendum were identical.

Source: Clinical Study Report for QuANTUM-First; sponsor-submitted additional trial data.

Indirect Comparisons

Description of Indirect Treatment Comparisons

The QuANTUM-First study did not include a comparison to midostaurin plus chemotherapy, which is the current standard of care in Canada for patients with newly diagnosed AML that is *FLT3*-ITD positive. The sponsor submitted an anchored MAIC and ML-NMR to address this gap.

Two RCTs, QuANTUM-First and RATIFY, were identified by the sponsor for inclusion in the ITCs. RATIFY was a phase III, double-blind RCT comparing midostaurin and placebo as administered in combination with induction and consolidation chemotherapy in patients younger than 60 years with newly diagnosed AML with *FLT3* mutations. The common placebo group across the 2 RCTs created an anchored network for the MAIC and ML-NMR. The sponsor undertook a feasibility assessment and identified multiple sources of heterogeneity across the 2 RCTs, justifying the chosen ITC methods. The sponsor identified treatment effect modifiers (TEMs) by reviewing available RCT publications and subgroups data, conducting univariate analyses of QuANTUM-First data, and consulting with clinical experts.

The objective of the MAIC was to compare the efficacy of quizartinib and midostaurin in combination with chemotherapy for the treatment of patients with newly diagnosed AML that is *FLT3*-ITD positive younger than 60 years. Restriction of the MAIC population to those younger than 60 years was necessary because of the narrower age criteria for the RATIFY study. Due to limitations in the external validity of the MAIC results and to inform the economic evaluation, the ML-NMR was then used to generate effect estimates of quizartinib and midostaurin relative to placebo among a QuANTUM-First–like population and a RATIFY-like population. Outcomes evaluated in the MAIC and ML-NMR included OS, CR, and CIR for patients with AML that relapses after CR.

Efficacy Results

Matching-Adjusted Indirect Treatment Comparison

Among patients aged up to age 60 years with AML that is *FLT3*-ITD positive, the MAIC was insufficient to show a difference between quizartinib and midostaurin, in combination with chemotherapy, for OS (HR = [redacted] [95% CI, [redacted] to [redacted]]) and CR (odds ratio [OR] = [redacted] [95% CI, [redacted] to [redacted]]). Although the point estimates for the comparative effects favoured quizartinib for OS and midostaurin for CR, the 95% CIs were wide for both outcomes, including the possibility that either quizartinib or midostaurin could be favoured. Quizartinib was favoured over midostaurin for CIR (HR = [redacted] [95% CI, [redacted] to [redacted]]). Results of scenario analyses matching on alternative matching variables and defining CR as CR within 60 days were mostly aligned with the main analyses.

Multilevel Network Meta-Regression

In both QuANTUM-First–like and RATIFY-like populations, point estimates for the HR of OS favoured quizartinib and midostaurin compared with placebo, although the results were not statistically significant due to imprecision (i.e., the 95% CrI crossed the null). One exception was the comparison of midostaurin versus placebo in a RATIFY-like population, for which midostaurin was favoured (HR = [redacted] [95% CrI,

[redacted] to [redacted]). The predicted median OS with quizartinib was [redacted] months (95% CrI, [redacted] to [redacted]) in a QuANTUM-First–like population and [redacted] months (95% CrI, [redacted] to [redacted]) in a RATIFY-like population. In a scenario analysis using data from patients younger than 60 years from the QuANTUM-First study, the results generally aligned with those from the main analysis.

In both QuANTUM-First–like and RATIFY-like populations, the analysis was insufficient to show a difference between quizartinib or midostaurin and placebo in CR due to imprecision (i.e., wide 95% CrIs including the possibility that either the active treatments or placebo could be favoured). One exception was the comparison of midostaurin versus placebo in a RATIFY-like population, for which midostaurin was favoured (OR = [redacted] [95% CI, [redacted] to [redacted]]). In a scenario analysis using data from patients younger than 60 years from the QuANTUM-First study, the analysis was insufficient to show a difference between quizartinib and placebo in any population, owing to imprecision (i.e., wide 95% CrIs including the possibility that either quizartinib or placebo could be favoured). Midostaurin was favoured over placebo in the both QuANTUM-First–like and RATIFY-like populations.

In both QuANTUM-First–like and RATIFY-like populations, quizartinib was favoured over placebo for CIR. The analysis was insufficient to show a difference between midostaurin and placebo in either population, owing to imprecision (i.e., wide 95% CrIs including the possibility that either the midostaurin or placebo could be favoured). In a scenario analysis using data from patients younger than 60 years from the QuANTUM-First study, quizartinib was favoured over placebo in all populations. In this scenario, the analysis was insufficient to show a difference between midostaurin and placebo in any population due to imprecision.

Harms Results

No harms outcomes were evaluated in either of the ITCs.

Critical Appraisal

- The risk of bias for the QuANTUM-First and RATIFY studies was considered low or unclear across all domains assessed by the sponsor. These risk of bias assessments were undertaken at the study level, which does not account for differences in risk of bias that may occur across the different effect estimates (for OS, CR, and CIR) used in the analyses.
- Because the RATIFY study had narrower eligibility criteria than the QuANTUM-First study for age, the MAIC was restricted to patients up to 60 years. As such, the results cannot be generalized to patients older than 60 years who would be eligible for treatment with quizartinib. According to the clinical experts consulted, approximately 60% to 70% of patients in clinical practice are older than 60 years.
- Neither the QuANTUM-First nor RATIFY study were designed to inform on the contribution of the induction and consolidation and maintenance phases of treatment to overall efficacy; therefore, the MAIC and ML-NMR cannot inform on contributions of each of these distinct treatment phases. The maintenance regimen provided in RATIFY is not reflective of clinical practice in Canada, where midostaurin is not approved for this indication. The contribution of the maintenance phase in the

RATIFY study to the overall efficacy of midostaurin and the impact on comparative effect estimates from the MAIC cannot be determined.

- Unknown and known but unmeasured TEMs (e.g., race, ECOG performance status, demographic region, white blood cell count, modified European LeukemiaNet [ELN] class, cytogenetic risk, karyotype, and *CEBPA* mutation) could not be adjusted for in the analyses, which represents a source of residual confounding. To maintain at least [redacted] effective sample size, *FLT3*-ITD allele frequency was not adjusted for, and remained imbalanced across groups after adjustment for other TEMs.
- In the MAIC, patient characteristics before and after adjustment were provided only for the sponsor-identified TEMs. It is unknown whether additional patient characteristics were well balanced after adjustment. Imbalances in other baseline characteristics could represent an additional source of confounding.
- For age and platelet count, sponsor-identified TEMs that were adjusted for in the analyses. For this variable, only median values were reported in the RATIFY publications. These were used to impute the means required for analysis under the assumption that these were equivalent. This assumption is not verifiable and could be a source of bias if it is not valid.
- To confirm *FLT3*-ITD status among RATIFY patients, next-generation sequencing was used. Results were unavailable for [redacted] of patients, who were subsequently excluded from the MAIC analyses. It is unknown whether these results were missing completely at random and whether their exclusion may have biased the comparative effect estimates.
- In the MAIC, the effective sample size was [redacted] of the original sample size of QuANTUM-First. This reduction in effective sample size contributes to a loss of precision and indicates a greater influence of subsets of patients in the QuANTUM-First study. In both the MAIC and ML-NMR, effect estimates were frequently imprecise, precluding conclusions about which treatment was favoured (e.g., OS and CR in the MAIC, CR in the ML-NMR for comparisons of quizartinib and midostaurin versus placebo in a QuANTUM-First–like population).
- Because the definition of CIR was not reported in the RATIFY publications, the sponsor noted that heterogeneity in the definitions of this outcome across the 2 RCTs could not be assessed. It is unknown whether differences in the definition across the RCTs could have biased the results, challenging the ability to make credible conclusions about this outcome from the MAIC and ML-NMR.
- Between-group effects comparing quizartinib versus midostaurin with 95% CrIs from the ML-NMR were not reported, precluding credible conclusions of their comparative efficacy among QuANTUM-First–like and RATIFY-like populations.
- Although the outcomes assessed in the MAIC and ML-NMR were relevant according to inputs received from interest-holders, other relevant outcomes, such as HRQoL, were not investigated. No harms outcomes were investigated, precluding judgments regarding the balance of benefits and harms of quizartinib versus midostaurin.

Long-Term Extension Studies

No long-term extension studies were submitted for this review.

Economic Evidence

Note that the sponsor's application was filed on a pre–Notice of Compliance basis and the pharmacoeconomic submission is reflective of the indication and proposed dosage regimen that was initially submitted to Health Canada and CDA-AMC. The Health Canada–approved product monograph includes a Serious Warnings and Precautions Box which states "Do not initiate VANFLYTA therapy if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms or in patients with severe hypokalemia, hypomagnesemia, or long QT syndrome." The Dosing Considerations section of the product monograph also incorporated prescriptive language regarding monitoring for QTcF in each treatment phase. The changes to the product monograph may not be fully reflected in the pharmacoeconomic submission.

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Adult patients with newly diagnosed AML with the presence of *FLT3*-ITD–activating mutation
Treatments	Quizartinib plus chemotherapy[a]
Dose regimen	Induction (up to 2 cycles of 28 days) • Quizartinib: 35.4 mg (2 × 17.7 mg) once per day for 14 days, starting day 8 • Cytarabine: 200 mg/m^2 per day by continuous IV infusion from day 1 to day 7 • Anthracycline: IV infusion on days 1, 2, and 3 of 60 mg/m^2 per day of daunorubicin or 12 mg/m^2 per day of idarubicin Consolidation (up to 4 cycles of 28 days) • Quizartinib: 35.4 mg once per day for 14 days, starting day 6 • Cytarabine: IV infusion on days 1, 3, and 5 of 3,000 mg/m^2 every 12 hours for patients < 60 years and 1,500 mg/m^2 every 12 hours for patients ≥ 60 years Maintenance (up to 36 cycles of 28 days) • Quizartinib: 26.5 mg once per day for 14 days and 53 mg (2 × 26.5 mg) once daily thereafter if QTcF is ≤ 450 ms
Submitted price	Quizartinib: $388.29 per 17.7 mg tablet or 26.5 mg tablet
Submitted treatment cost	Year 1: $237,970 (quizartinib = $211,617; chemotherapy = $26,352) Year 2+: $282,675 (quizartinib = $282,675; chemotherapy = $0)
Comparator	Midostaurin plus chemotherapy[b]
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and life-years

Component	Description
Time horizon	Lifetime (53 years)
Key data sources	Sponsor-submitted MAIC in which the efficacy for quizartinib plus chemotherapy was determined from a subset of patients from the QuANTUM-First trial who were matched to patients from the RATIFY trial (midostaurin plus chemotherapy)
Submitted results	ICER = $33,415 per QALY gained (incremental costs = $133,317; incremental QALYs = 3.99)
Key limitations	• The clinical efficacy of quizartinib plus chemotherapy compared with midostaurin plus chemotherapy is highly uncertain. Due to a lack of head-to-head comparisons between quizartinib and midostaurin, the sponsor conducted 2 ITCs (MAIC and ML-NMR) to address the gap in the clinical evidence. CDA-AMC identified important limitations in the indirect comparisons that limit the interpretability of the results. As a result, the comparative efficacy and harms of quizartinib vs. midostaurin is uncertain. • The clinical experts consulted by CDA-AMC noted that quizartinib is expected to be similar to midostaurin in the induction and consolidation phase but suggested there may be benefit observed in the maintenance phase because midostaurin is not indicated for use in the maintenance phase in Canada. The CDA-AMC clinical review noted that quizartinib may be associated with a reduction in relapses and improved survival compared with placebo, but study design does not allow for isolation of the contribution of effects among the different phases of treatment. As such, effects of quizartinib in induction, consolidation, and maintenance cannot be estimated, nor can the efficacy of quizartinib as a maintenance therapy among patients who have received midostaurin during induction and consolidation. • The long-term efficacy of quizartinib is uncertain. The maximum follow-up for quizartinib in QuANTUM-First was 49 months based on the KM curves. Parametric survival functions were used to extrapolate KM curves over the model time horizon. The extrapolations chosen by the sponsor had poor visual fit and appeared to overpredict the long-term efficacy. The sponsor assumed patients in the “CR in first line” and “HSCT in first line” health states beyond 3 years were cured, which may overestimate long-term survival benefits. Clinical experts consulted by CDA-AMC indicated a 5-year threshold would be more appropriate. • Treatment costs are uncertain. The sponsor did not specify which treatment phase the drug costs were attributed to, making it difficult to assess the impact of each treatment phase. This is particularly important given the lack of robust comparative evidence, and potential differences in how quizartinib and midostaurin may be used in practice in Canada (midostaurin is not indicated for maintenance use, while the Health Canada indication for quizartinib includes use as maintenance treatment). The sponsor assumed alternate maintenance treatment for some patients who initially received midostaurin, although this impacted cost only, and not efficacy. Any assumed cost offsets due to the efficacy of quizartinib, particularly in the maintenance phase, are highly uncertain. • The sponsor’s modelling approach was associated with several limitations, and the output of the sponsor’s model lacked face validity. Furthermore, the model lacked the flexibility to explore the clinical benefit and costs by treatment phase.
CDA-AMC reanalysis results	• In the CDA-AMC base case, the following changes were made to address identified limitations: ML-NMR was used to inform the model inputs, post-HSCT survival assumption for midostaurin plus chemotherapy arm was assumed to be same as quizartinib, comparative efficacy for quizartinib plus chemotherapy compared with midostaurin plus chemotherapy in induction and consolidation phases was revised to be equal, and the definition of cured patients was modified. • In the CDA-AMC base case, in which quizartinib was used in all three phases and assumed to result in an incremental benefit, quizartinib plus chemotherapy was associated with an ICER of $104,121 per QALY gained (incremental costs: $112,992; incremental QALYs: 1.09) compared with midostaurin plus chemotherapy. • Although the clinical experts indicated that the ability to use quizartinib in the maintenance setting may assist in reducing the risk of relapse and prolonging OS, there is limited evidence to

Component	Description
	support this from the sponsor's submission. Due to the uncertainty identified with the comparative effectiveness evidence between quizartinib and midostaurin, CDA-AMC conducted a scenario analysis assuming equivalent effects. Assuming equivalent effects and use in the induction and consolidation phases only, quizartinib is more costly than midostaurin ($505,245 for quizartinib arm vs. $494,778 for midostaurin arm). If quizartinib is used in the maintenance phase, it would accrue greater costs.

AML = acute myeloid leukemia; CDA-AMC = Canada's Drug Agency; CR1 = complete remission in first line; HSCT 1L = allogeneic hematopoietic stem cell transplantation in first line; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; ML-NMR = multilevel network meta-regression; QALY = quality-adjusted life-year; QTcF = Fridericia heart rate correction formula.

[a]Chemotherapy consists of cytarabine and idarubicin or daunorubicin.

[b]Chemotherapy consists of cytarabine and daunorubicin. Midostaurin is not indicated for use in the maintenance phase. In the maintenance phase, 15% of patients are assumed to receive azacitidine; 85% of patients are assumed to receive no maintenance treatment.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the market share before and after quizartinib is publicly reimbursed for the indication under review is uncertain, the proportion of patients eligible to receive intensive chemotherapy is uncertain, the population modelled in budget impact analysis was inconsistent with that in economic evaluation, and treatment durations in induction and consolidation phases were uncertain. The CDA-AMC reanalysis adjusted the market share before and after public funding of quizartinib, adjusted the assumption for proportion of patients with *FLT*-ITD–mutated AML who are eligible for intensive chemotherapy, and changed the treatment durations for the induction and consolidation phases. In the CDA-AMC base case, the 3-year budget impact of reimbursing quizartinib is expected to be $24,393,381 (year 1 = $2,630,407; year 2 = $6,948,421; year 3 = $14,814,553). Because quizartinib is more costly than midostaurin and CDA-AMC could not address limitations that would increase the use of treatments (treatment duration and number of individuals treated in the outpatient setting), the budget impact of reimbursing quizartinib may be underestimated.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: May 13, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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