pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Gilteritinib (Xospata)

Submitted Reimbursement Request:
For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by a validated test.

Submitted by: Astellas Pharma Canada Inc.

Manufactured by: Astellas Pharma Canada Inc.

NOC Date: December 23, 2019

Submission Date: October 28, 2019

Initial Recommendation Issued: April 30, 2020

Approximate per patient drug costs, per month (28 days)	Price: $325 per tablet Daily cost: $975 Cycle cost (28-day cycle): $27,300

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of gilteritinib for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation, if the following conditions are met:

- cost-effectiveness improved to an acceptable level
- feasibility of adoption (budget impact) addressed.

Eligible patients include adults with relapsed or refractory AML whose FLT3 mutation status is confirmed by a validated test and who have good performance status. Treatment with gilteritinib should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. In the absence of disease progression or unacceptable toxicity, treatment may be given for a minimum of six months to determine clinical benefit as a delay in clinical response can occur.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of gilteritinib based on clinically and statistically significant benefit in overall survival (OS) for gilteritinib compared with salvage chemotherapy, and a manageable toxicity profile.

pERC members agreed that gilteritinib aligns with patient values in that it offers a higher chance of success (improves survival compared to salvage chemotherapy), and it offers an additional treatment option. Patients value an oral treatment option, although in some jurisdictions there may be concerns about cost to individual patients and to institutions that might need to navigate alternative funding sources. pERC acknowledged that the impact of gilteritinib on quality of life (QoL) is uncertain.

	pERC concluded that, at the submitted price, gilteritinib was not cost-effective compared to best supportive care or salvage chemotherapy (azacitidine, fludarabine plus cytarabine plus granulocyte colony-stimulating factor plus idarubicin [FLAG-IDA], mitoxantrone plus etoposide plus cytarabine (MEC), and low-dose cytarabine [LoDAC]). pERC also highlighted that the potential budget impact of gilteritinib may be underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of gilteritinib compared with salvage chemotherapy for the treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability. **Accessibility and Feasibility of Companion Diagnostic Test** A validated test is required to confirm the FLT3 mutation status of AML prior to initiating treatment with gilteritinib. pERC noted that FLT3 mutation testing is done in most provinces; however, in provinces where FLT3 mutation testing is not currently available, its implementation would be required. **Time-Limited Need for Patients Currently Receiving Treatment (Salvage Chemotherapy) for Relapsed or Refractory AML** Given that pERC was satisfied that there is a net clinical benefit of gilteritinib compared with salvage chemotherapy for the treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation, jurisdictions may consider addressing short-term, time-limited need at the time of implementing a reimbursement recommendation for gilteritinib for patients who are currently receiving salvage chemotherapy for relapsed or refractory AML. **Time-Limited Need for Patients in Second Hematologic Relapse or Later** pERC noted that very few patients in second or later hematologic relapse were included in the trial; however, agreed that it was reasonable to extend the use of gilteritinib to patients in second or later hematologic relapse on a time limited basis for those who did not have a prior tyrosine kinase inhibitor (TKI). Jurisdictions may consider addressing short-term, time-limited need at the time of implementing a reimbursement recommendation for gilteritinib for patients who are in second or later relapse and have not previously been treated with a TKI. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC noted that in Canada, the age-adjusted incidence of AML is approximately 3.75 per 10,000 people and that in 2017, there were 1,509 new cases of AML reported. pERC noted the five-year survival rate for adults with AML is approximately 21%. pERC acknowledged that treatment selection and outcomes are strongly influenced by cytogenetic abnormalities at diagnosis, and that FLT3 mutations (specifically, internal tandem duplication [ITD] or tyrosine kinase domain [TKD] mutations) are considered driver mutations and occur in 25% to 30% of patients. pERC noted patients with such FLT3 mutations have a lower remission rate, shorter remission duration, and shorter survival (median survival is approximately 12 to 24 months).

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC discussed that currently available treatment options for patients with newly diagnosed FLT3-mutated AML include primary induction therapy with daunorubicin and cytarabine (7 + 3) with FLT3-inhibitor, midostaurin. Consolidation for younger patients typically includes high-dose cytarabine; whereas for patients over 60 years old, standard dose cytarabine is used. pERC noted that for patients with unfavourable-risk cytogenetics and no (or few) comorbidities, consolidation with allogeneic stem cell transplant is preferred. For patients with relapsed or refractory FLT3-mutated AML, pERC noted that current treatment options include intensive induction with MEC or FLAG-IDA. pERC also noted that additional treatment options include azacitidine, azacitidine plus sorafenib, and LoDAC. Overall, pERC recognized that there is no standard of care in this setting with a continued need for effective treatment options that offer a survival advantage; gilteritinib represents a new treatment alternative for those with relapsed or refractory FLT3-mutated AML.

pERC deliberated on one multi-centre, randomized, open-label, phase III, superiority trial (ADMIRAL) that assessed the efficacy and safety of gilteritinib compared to salvage chemotherapy in adult patients with FLT3-mutated AML who were refractory to or relapsed after complete remission (CR) to first-line therapy. Patients were randomized in a 2:1 ratio to gilteritinib or salvage chemotherapy; and salvage chemotherapy included high-intensity (MEC or FLAG-IDA) and low-intensity regimens (LoDAC or azacitidine). pERC discussed the co-primary end points, OS, and CR with full or partial hematological recovery (CR/CRh) rate. Due to the short duration of treatment in the salvage chemotherapy arm, pERC noted that most patients entered long-term follow-up and did not have systematic protocol-defined assessments, while patients in the gilteritinib arm continued on the study for a longer duration, and thus interpretation of most secondary end points (for example, event-free survival [EFS]) was limited due to high censoring. pERC further discussed that in the ADMIRAL trial a higher proportion of patients in the gilteritinib arm proceeded to hematopoietic stem cell transplant (HSCT) compared to the salvage chemotherapy arm. pERC noted that only patients in the gilteritinib arm could proceed to allogeneic HSCT and resume maintenance with gilteritinib, whereas in the salvage chemotherapy arm HSCT was considered an off-study therapy, which may have underestimated transplant rates in the salvage chemotherapy arm and introduced bias through unequal comparison. pERC also discussed that a higher proportion of patients achieved CR; thus, were eligible for transplant in the gilteritinib arm, whereas patients do not typically have durable remission following chemotherapy, which may have contributed to lower transplant rates in the salvage chemotherapy arm. pERC concluded that while there may be uncertainty in the magnitude of the treatment effect due to subsequent HSCT, a survival improvement with gilteritinib was demonstrated.

pERC noted that approximately 6% of patients in the ADMIRAL trial had prior midostaurin, which was not widely available at the time the trial was conducted. pERC discussed that, in current clinical practice, a much larger proportion of patients would have prior exposure to midostaurin and would be considered for gilteritinib in the relapsed or refractory setting. pERC noted that patients with therapy-related AML (t-AML) were excluded, and a small proportion of patients would have FLT3-mutated t-AML. pERC discussed a significant unmet need for treatment options in this patient population. Ultimately, pERC did not support extending the use of gilteritinib to t-AML patients, noting the lack of evidence to support gilteritinib use in patients with t-AML and the uncertainty expressed in the clinician input.

pERC also deliberated the safety of gilteritinib and noted that main side effects included myelosuppression, febrile neutropenia, anemia, and thrombocytopenia, with a small number of patients that experienced drug-related severe adverse events (AEs) of febrile neutropenia, elevated aspartate aminotransferase or alanine aminotransferase, and QT prolongation. pERC noted that only a small proportion of patients discontinued treatment due to drug-related AEs. There was a discussion on the overall higher proportion of deaths due to AEs in the gilteritinib arm compared to the salvage chemotherapy; however, fatal AEs that were considered drug-related were comparable between treatment arms. pERC noted there were some signals of cardiotoxicities related to gilteritinib that were not seen in the salvage chemotherapy arm, which may have contributed to fatal AEs in the gilteritinib arm. However, cardiotoxicity affected a small number of patients and was not reported by the investigators to be drug-related. Overall, pERC considered gilteritinib to be well tolerated with a manageable toxicity profile.

pERC therefore concluded that there is a net clinical benefit of gilteritinib in relapsed or refractory FLT-3 mutated AML based on a statistically significant and clinically meaningful improvement in OS and manageable toxicity profile.

Input from one patient group, the Leukemia and Lymphoma Society of Canada, was deliberated by pERC. pERC noted that patients value having additional treatment options, maintaining QoL, and treatment options that offer a higher chance of success and a reduced possibility of relapse. pERC also noted that older patients valued having access to treatment options in the relapsed setting, and that the ADMIRAL trial included patients up to 85 years old. In addition, subgroup analyses demonstrated the efficacy of gilteritinib relative to salvage chemotherapy in patients who were aged 65 years or older and in patients who were preselected for low-dose salvage chemotherapy. Patient input also noted that treatment options administered in the outpatient setting and those that can be administered close to home were valued and gilteritinib is an oral treatment option. pERC discussed that while health-related quality of life (HRQoL) and fatigue scores were collected in the trial, meaningful conclusions could not be drawn due to the short duration of treatment in the salvage chemotherapy arm and lack of systematic collection of HRQoL data when patients entered long-term follow-up. Overall, pERC agreed that gilteritinib aligns with patient values in that it offers a higher chance of success (improves survival) and an additional treatment option, although the impact on QoL is uncertain. pERC agreed that patients value an oral treatment option, although in some jurisdictions there may be concerns about cost to individual patients and to institutions that may need to navigate alternative funding sources.

pERC deliberated on the cost-effectiveness of gilteritinib compared with salvage chemotherapy and best supportive care (BSC). The Committee discussed the limitations of the economic model described by the Economic Guidance Panel (EGP). pERC highlighted the uncertainty regarding OS in patients undergoing HSCT, which might have resulted in an overestimation of the OS by the sponsor. pERC also noted there was no evidence to support the assumption that treatment with gilteritinib results in any additional OS benefit post-HSCT. Finally, pERC discussed the implications of gilteritinib dose modifications on the incremental cost-effectiveness ratio (ICER) but was reassured by the way this was managed in CADTH reanalysis. pERC concluded that gilteritinib was not cost-effective at the submitted price. pERC considered that a reduction in drug price would be required to improve cost-effectiveness to an acceptable level.

pERC deliberated on the feasibility of implementing a reimbursement recommendation for gilteritinib in adult patients with relapsed or refractory FLT3-mutated AML. pERC discussed the budget impact and noted that the factors that most influence the budget impact include increasing the prevalence of eligible patients with AML, increasing the speed of uptake and the market share between therapies, mutation testing access rates and costs, uncertainty of OS benefits, and the cost per treatment course. pERC discussed that irrespective of treatment arm, OS benefit in patients who had received HSCT was similar for gilteritinib and salvage chemotherapy, and thus, there was uncertainty of additional OS benefits in the gilteritinib arm despite higher transplantation rates. pERC noted the EGP considered the market share of year 1 to year 3 to be underestimated and that an alternative market share was used by the EGP, which yielded a higher budget impact over a three-year period compared with the sponsor's estimate. pERC also noted that treatments being used off-label, not yet reimbursed, or having not yet obtained marketing authorization were included in the sponsor's base case, which may not be reflective of treatment use in Canada and may have led to an underestimation of the budget impact analysis. Therefore, pERC agreed with the EGP's reanalysis in that the budget impact was underestimated and suggested that jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Finally, the Committee deliberated on the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group: Leukemia and Lymphoma Society of Canada
- input from registered clinicians: three from individual oncologists, and one group input on behalf of eight oncologists from the Leukemia and Bone Marrow Transplant Program of BC Canada; a total of eleven oncologists provided input from Ontario, British Columbia, and Alberta
- input from PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of gilteritinib compared to standard of care for the treatment of adult patients with relapsed or refractory AML with an FLT3 mutation.

Studies included: Phase III superiority trial (ADMIRAL)

The pCODR systematic review included one international, open-label, phase III, superiority, randomized controlled trial (ADMIRAL). Patients were randomized 2:1 to gilteritinib or salvage chemotherapy (patients randomized to 1 of 4 options: FLAG-IDA, MEC, LoDAC, or azacitidine). Patients in the gilteritinib arm were permitted to have HSCT while on the study and could resume gilteritinib as maintenance therapy.

Patient populations: Adults with relapsed or refractory AML with an FLT3 mutation

Key eligibility criteria included adult patients 18 years of age and older, and the ADMIRAL trial included patients that ranged in age up to 85 years old. Patients were required to have an FLT3 mutation, either an ITD, or a TKD/D835 or TKD/I836 mutation, which are subtypes that comprise the majority of FLT3 mutations. Patients with AML from antecedent myelodysplastic syndrome were eligible for inclusion in the trial; however, patients with t-AML were excluded.

Included patients were relapsed or refractory to at least one prior line of therapy, and very few patients were in second relapse or later (< 2% of the total population). A total of 40% of patients were considered refractory and 60% of patients were considered relapsed to prior therapy. Patients were considered refractory after a minimum of one induction cycle of prior therapy; very few patients included in the trial had two cycles of induction therapy prior to being considered refractory. Approximately 20% of patients had prior transplant, and patients with a prior FLT3 inhibitor were excluded except for patients who received prior midostaurin or sorafenib. Approximately 6% of the trial population had exposure to prior midostaurin.

Key efficacy results: Clinically and statistically significant improvement in OS

The key efficacy outcome deliberated by pERC was the co-primary end point of OS. pERC noted that the median OS was 9.3 months in the gilteritinib arm, and 5.6 months in the salvage chemotherapy arm, and the net improvement in median OS of 3.7 months was considered clinically meaningful. pERC discussed the role of HSCT in improving survival outcomes and agreed that, irrespective of HSCT, there was a statistically and clinically significant survival advantage demonstrated with gilteritinib relative to salvage chemotherapy (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.49 to 0.83; P < 0.001).

pERC also noted the co-primary end point of the CR/CRh rate was met at the time of interim analysis, and at the time of final analysis; the CR/CRh rate in the gilteritinib arm was double that of the salvage chemotherapy arm (34% versus 15%; risk difference: 18.6%; 95% CI: 9.8 to 27.4). pERC discussed that the higher proportion of patients who achieved CR contributed to the higher proportion of patients who underwent HSCT in the gilteritinib arm compared to the salvage chemotherapy arm (transplant rates: 25.5% versus 15.3%, respectively). This 10% difference was considered clinically meaningful and an important part of the AML treatment strategy; although pERC acknowledged that the HSCT rates may have been underestimated due to HSCT being an on-study treatment in the gilteritinib arm and an off-study treatment in the salvage chemotherapy arm, and noted uncertainty around the survival benefit

despite higher transplant rates. pERC acknowledged that 60% of patients in the salvage chemotherapy had high-intensity chemotherapy, most of whom had only one cycle of induction therapy; thus, these patients completed treatment and entered long-term follow-up within two months. As such, pERC agreed the key secondary end point of EFS was not statistically significant and that the interpretation was limited due to high censoring.

Patient-reported outcomes: Impact on QoL uncertain

Patient-reported outcomes were measured with the Brief Fatigue Inventory questionnaire, EuroQoL 5-Dimensions 5-Level questionnaire, Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Forms, Functional Assessment of Cancer Therapy-Leukemia, and dizziness and mouth sore questionnaires. As mentioned in the key efficacy results section, a large proportion of patients entered long-term follow-up in the salvage chemotherapy arm where HRQoL was not assessed (fewer than 12% of patients had completed questionnaires beyond cycle 2, day 1 in the salvage chemotherapy arm). There were minimal changes reported from baseline to cycle 2, day 1, for most summary scores on scales and subscales measured by each of these respective questionnaires; however, pERC acknowledged that meaningful comparisons and conclusions on long-term QoL could not be drawn from the available data. Thus, pERC concluded that the impact of gilteritinib on QoL remains uncertain.

Limitations: Unequal comparison of treatment arms may have influenced the magnitude of efficacy

The main limitation outlined by the Methods team and discussed by pERC was the unequal comparison of treatment groups. Patients in the gilteritinib treatment arm were able to undergo HSCT while on the study, whereas in the salvage chemotherapy arm this was considered an off-study treatment. Patients in the gilteritinib arm were additionally able to resume treatment with gilteritinib after HSCT. pERC debated whether this introduced bias and influenced the primary efficacy results of the trial, ultimately agreeing that any patient who is able to undergo HSCT, regardless of treatment arm, may have potential survival benefit. pERC concluded that, irrespective of subsequent HSCT, a survival advantage with gilteritinib was demonstrated. However, uncertainty around the magnitude of the benefit remains due to the unequal comparison limitation. pERC additionally noted that most patients in the salvage chemotherapy received high-intensity chemotherapy (approximately 60%), and after completing one to two cycles, most of these patients entered long-term follow-up where systematic evaluations comparable to the patients that remained on the study were not conducted. As a result, a large proportion of patients were censored for secondary outcomes such as EFS and for HRQoL outcomes; and therefore, meaningful conclusions cannot be drawn on these end points due to the unequal comparison.

pERC additionally noted and agreed with the Methods team and the Clinical Guidance Panel (CGP) that the proportion of patients receiving the high-intensity versus low-intensity salvage chemotherapy regimens may not have been reflective of Canadian clinical practice. However, pERC did not believe this would have impacted the primary efficacy results (i.e., OS) of the ADMIRAL trial or the degree of benefit to Canadian patients offered gilteritinib in this clinical setting.

Safety: Manageable toxicities

In the ADMIRAL trial, gilteritinib was associated with higher hematological toxicities. Specifically, a higher proportion of patients in the gilteritinib arm compared to the salvage chemotherapy arm experienced grade 3 or higher febrile neutropenia (45.9% versus 36.7%), anemia (40.7% versus 30.3%), and thrombocytopenia (22.8% versus 16.5%). Severe AEs that occurred in a higher proportion of patients in the gilteritinib arm, compared to the salvage chemotherapy arm, included febrile neutropenia (30.9% versus 8.9%), elevated alanine aminotransferase (5.3% versus 0%), elevated aspartate aminotransferase (4.1% versus 0%). pERC noted these are typical side AEs observed in this patient population and are considered manageable toxicities.

pERC discussed AEs of special interest, which included cardiac toxicities. pERC noted a higher proportion of patients experienced any-grade QT prolongation in the gilteritinib arm (6.9%) compared to the salvage chemotherapy arm (0.0%); however, it was considered unlikely to affect the ability of patients to continue therapy or patient outcomes due to the small number of affected patients. As well, a higher proportion of patients experienced any-grade cardiac failure (7.7% versus 2.8%) and pericarditis or pericardial effusion (6.1% versus 0.0%) in the gilteritinib arm compared to the salvage chemotherapy arm, respectively. pERC discussed that a higher proportion of patients discontinued due to AEs in the gilteritinib arm (23.6%) compared to the salvage chemotherapy arm (11.9%); however, only 11.0% in the gilteritinib arm and 4.6% in the salvage chemotherapy arm were considered related to the study

treatment. pERC also noted the higher proportion of fatalities due to AEs in the gilteritinib arm (28.9%) compared to 14.7% in the salvage chemotherapy arm, but noted only 4.1% in the gilteritinib arm and 4.6% in the salvage chemotherapy arm were considered to be drug-related. pERC acknowledged that toxicities attributable to study treatment in the gilteritinib arm may have been underestimated due to the open-label study design and safety signals that suggest higher cardiac toxicities associated with gilteritinib. However, pERC concluded that, overall, the reported AEs of gilteritinib were manageable.

Need and burden of illness: Continued need for effective treatment options that offer a survival advantage

The age-adjusted incidence of AML is approximately 3.75 per 10,000 Canadians. In 2017, there were 1,509 new cases of AML reported. The five-year survival rate for adults with AML is approximately 21%. FLT3 mutations (specifically ITD or TKD mutations) are considered driver mutations, and occur in approximately 30% of patients. Patients with FLT3 mutations have a lower remission rate, shorter remission duration, and shorter survival (median survival is approximately12 to 24 months). Patients who have relapsed after or are refractory to induction chemotherapy have a poor prognosis with standard chemotherapy.

Currently available treatment options for patients with relapsed or refractory FLT3-mutated AML include intensive induction with MEC or FLAG-IDA. Azacitidine, azacitidine with sorafenib, LoDAC, and BSC are also used for patients who are unsuitable for high-intensity regimens. Overall, pERC recognized that there is no standard of care in this setting with a continued need for effective treatment options that offer a survival advantage. Gilteritinib represents a new treatment alternative for patients with relapsed or refractory FLT3-mutated AML.

Registered clinician input: Clinicians endorse the reimbursement of gilteritinib

Overall, clinicians generally endorse the reimbursement of gilteritinib as it highlights an unmet need for effective treatment options among this patient group.

Clinicians were divided on extending the use of gilteritinib to patients with t-AML; some reported lack of evidence while others indicated patients with t-AML would also benefit. Some clinicians supported the use of gilteritinib with more advanced disease than those included in the ADMIRAL trial. Gilteritinib was suggested as a second-line option following midostaurin; however, all clinicians commented on the lack of subsequent treatment options. Gilteritinib used in combination with another drug outside of a clinical trial was not supported. Repeat FLT3 testing may be required as FLT3 mutation status can change over time; thus, clinicians noted that greater lab resources to support widespread testing of patients may be required.

PATIENT-BASED VALUES

Experience of patients with AML: AML and side effects of treatments impact physical and emotional QoL, and current treatment options are manageable with some challenges

Patients with AML who participated in patient advocacy group surveys reported fatigue, loss of appetite and/or weight loss, feeling dizzy or lightheaded, bruising and/or bleeding, and rashes and/or skin changes as the most impactful symptoms of AML. Fever, night sweats, headaches, nausea and/or vomiting, vision changes, and pain were also symptoms that were concerning to patients. Patients commented that AML added stress on family, and they felt like a burden to family and friends. They were also continually stressed about relapse and/or recurrence.

Current treatment options and related side effects were reported to be more manageable than expected, with neutropenia having the most impact, followed by reduced movement, nausea, hair loss, eyesight issues, pain, vomiting, organ damage, neuropathic pain, and constipation, which had the least impact. Patients noted going through treatment had ups and downs and that they appreciated how well their health care teams communicated and prepared them for treatment. Challenges with current treatment options included length of treatment time and being away from family, pain associated with bone marrow biopsies, and concerns about access to treatment options. One patient reported being denied treatment because of age and having to relocate to another province for treatment.

Patient values, experience on or expectations for treatment: Additional treatment options, maintaining QoL, and treatment options with a higher chance of success and reduced possibility of relapse.

While no patients who participated in the patient advocacy group survey had experience with the drug under review, they reported that when deciding to take a new treatment, important considerations included: QoL, impact on disease, physician recommendation, outpatient treatment, and closeness to home. Patients expressed a need for treatments to help maintain remission and for older patients facing relapse. Overall, patients with AML value additional treatment options, maintaining QoL, and treatment options that have a higher chance of success, and reduced possibility of relapse.

ECONOMIC EVALUATION

Gilteritinib is available as 40 mg tablets. The recommended dose of gilteritinib is 120 mg per day, given as three 40 mg tablets once daily. At the recommended dose of gilteritinib, and at the sponsor's submitted price of $325.00 per tablet, the drug cost per 28-day dosing cycle is $27,300.

The sponsor submitted a cost-utility analysis assessing gilteritinib compared with salvage chemotherapy in adult patients with relapsed or refractory AML with an FLT3 mutation. The sponsor undertook scenario analyses that considered the following individual comparators: azacitidine, FLAG-IDA, MEC, LoDAC, and BSC. The economic analysis was undertaken over a lifetime (41 years) time horizon from the perspective of the public health care payer. Patients who underwent HSCT or not were modelled separately with a partitioned survival model and could transition to progression-free survival, post-progression, or death at the end of each monthly cycle. The proportion of patients who were progression-free, who experienced progressive disease, or who were dead at any time over the model horizon was derived from non-mutually exclusive survival curves.

For patients without HSCT, the clinical efficacy of gilteritinib and salvage chemotherapy were sourced from the ADMIRAL trial in the subset of patients that did not undergo HSCT. Given that survival data from the ADMIRAL trial for the HSCT population have short follow-up, and are based on a small sample, these were not deemed reliable to inform long-term efficacy. Therefore, OS inputs for patients undergoing HSCT were sourced from the literature regardless of initial treatment. Parametric survival models and hazard ratios informed OS and progression-free survival for patients with and without HSCT until year 3, after which their survival was assumed to follow a constant standardized mortality ratio–adjusted mortality risk regardless of initial treatment.

The sponsor reported a probabilistic ICER of $114,800 per quality-adjusted life-year (QALY) gained for gilteritinib versus salvage chemotherapy.

CADTH identified the following key limitations of the sponsor's submitted economic analysis:

- The sponsor used a mixture of salvage therapy regimens to represent salvage chemotherapy in the base case; however, the proportion of patients receiving each individual salvage regimen were based on the ADMIRAL trial and were not reflective of the clinical practice in Canada. Individual salvage regimen comparators were considered in scenario analyses, based on the inappropriate assumption that treatment efficacy of each individual regimen was the same as the salvage chemotherapy arm observed in the ADMIRAL trial. BSC was excluded from the base-case analysis even though it was a relevant comparator; however, it was included in a scenario analysis.
- The sponsor assumed that long-term survival was associated with mortality rates twice as high as those of the general population but provided no evidence for this assumption. Values from the literature suggest a four- to nine-fold increase in mortality (compared to the general population). This suggests an overestimation in OS in the sponsor's analysis. Furthermore, the sponsor assumed that patients on gilteritinib maintenance post-HSCT would receive OS benefits, which was based on immature data with short follow-up. This assumption was deemed to be unrealistic and leads to further overestimation of OS favouring gilteritinib.
- Adjustment of treatment costs according to dose intensity underestimated costs of oral treatments, possibly favouring gilteritinib.
- Only grade 3 and 4 AEs that affected 5% or more of the patients were included in the sponsor's analyses. Some AEs considered clinically meaningful (such as cardiac toxicities, fatigue, and vomiting) according to clinical experts and patient groups consulted by CADTH were excluded, possibly overestimating the benefits of gilteritinib.

To account for these limitations, CADTH considered adding BSC as comparator, alternative salvage chemotherapy treatment distributions based on clinical expert feedback, alternative standardized mortality ratio for long-term survivors based on the literature, exclusion of post-HSCT gilteritinib benefit, and revised dose intensity for oral treatments. Based on probabilistic analysis of CADTH's base-case analysis, BSC had the lowest cost and fewest QALYs followed by salvage chemotherapy and then by gilteritinib. At a willingness-to-pay threshold of less than $98,720 per QALY, BSC is the optimal therapy. Salvage chemotherapy is the optimal therapy if the willingness-to-pay threshold is at least $98,720 but less than $168,451 per QALY gained; and gilteritinib is the optimal therapy at a willingness-to-pay threshold of at least $168,451. When using the CADTH base case, approximately 40% and 90% price reductions of gilteritinib would be required to bring the ICER down to around $100,000 and $50,000 per QALY, respectively.

Some identified limitations could not be addressed by CADTH such as missing relevant comparators, the use of a fixed (rather than variable) time point where patients undergo HSCT, the impact of different sequences of subsequent treatment, and the impact of grade 1 and 2 AEs relevant to patients. CADTH was also unable to perform analyses comparing each individual salvage chemotherapy regimen due to lack of data.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Prevalence of eligible patients with AML, market share, and use of off-label therapies

The factors that most influence the budget impact include increasing the prevalence of eligible patients with AML, increasing the speed of uptake and the market share between therapies, mutation testing access rates and costs, uncertainty of OS accrual benefits, and the cost per treatment course. pERC noted that the EGP considered the market share of year 1 to year 3 to be underestimated and that an alternative market share was used by the EGP that yielded a higher budget impact over a three-year period compared with the sponsor's estimate. pERC also noted that treatments being used off-label, not yet reimbursed, or having not yet obtained marketing authorization were included in the sponsor's base case, which may have not been reflective of treatments used in Canadian clinical practice and may have underestimated the budget impact analysis. pERC agreed with the CGP that there may be some off-label use of therapies such as sorafenib; however, it would not be considered extensive. Therefore, pERC agreed with the EGP's reanalysis in that the budget impact was underestimated for these reasons and suggested that jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Christopher Longo, who was not present for the meeting
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of gilteritinib for AML, through their declarations, no members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and no members were excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Astellas Pharma Canada Inc., as the primary data owner, did not agree to the disclosure of certain clinical and economic information; therefore, this information has been redacted in the publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • PAG identified that there is no one standard of care for patients with relapsed or refractory AML with an FLT3 mutation. Treatments include FLAG-IDA, azacitidine, azacitidine plus sorafenib, MEC, low-dose ARA-C, allogeneic stem cell transplant, and best supportive care. • In some jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated AML.	• pERC acknowledged that there is no standard of care for patients with relapsed or refractory AML with an FLT3 mutation and that currently funded treatment options include FLAG-IDA, azacitidine, azacitidine plus sorafenib, MEC, low-dose ARA-C, allogeneic stem cell transplant, and best supportive care. Overall, pERC recognized that even though there are treatment options available for these patients, there is a continued need for effective treatment options that offer a potential survival advantage. • pERC noted that midostaurin is currently funded in some jurisdictions for the treatment of adult patients with newly diagnosed FLT3-mutated AML and as a result, recognized that most Canadians would have prior exposure to midostaurin. pERC noted that a small proportion of patients in the ADMIRAL trial had prior exposure to midostaurin because at the time of the ADMIRAL trial, midostaurin was not widely available.

Eligible Patient Population
• PAG is seeking guidance on whether gilteritinib is appropriate for the following:
  ○ Patients with t-AML
  ○ Patients treated with midostaurin and sorafenib
  ○ Patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3- TKD/I836
  ○ Patients in second or later hematologic relapse or who have received salvage therapy for refractory disease.
• If recommended for reimbursement, PAG noted that patients currently receiving treatment (e.g., salvage chemotherapy) for relapsed or refractory AML would need to be addressed on a time-limited basis.
• There is a potential for indication creep to AML without an FLT3 mutation or earlier lines of treatment prior to refractory or relapsed disease (e.g., in addition to chemotherapy for patients who require re-induction or salvage chemotherapy).
	• pERC noted that the ADMIRAL trial excluded patients with t-AML. pERC acknowledged there is an unmet need for patients with t-AML, and that only a small proportion would be FLT3-mutated. pERC did not support extending the use of gilteritinib to t-AML patients due to lack of evidence and uncertainty in clinician support.
	• pERC noted that patients with prior midostaurin and sorafenib were included in the ADMIRAL trial, and a small proportion of patients were previously treated with midostaurin (5.7%) and sorafenib (6.5%); however, specific data on these patient populations are limited. pERC agreed with the CGP that these patients would be eligible for gilteritinib.
	• pERC noted that the majority of patients harbouring an FLT3 mutation are FLT3-ITD, FLT3-TKD/D835, or FLT3- TKD/I836, and that the ADMIRAL trial did not include patients with other FLT3 mutations. pERC also noted that other FLT3 mutations are not routinely tested. Moreover, the CGP stated that it is not clear whether gilteritinib would be appropriate in settings other than those examined in the ADMIRAL trial. Therefore, pERC concluded that there was insufficient evidence to support the use of gilteritinib in FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835, or FLT3- TKD/I836.
	• pERC noted that the Health Canada indication and funding request included patients with second or later hematological relapse; and very few patients (< 2%) included in ADMIRAL were in second or later relapse. pERC agreed with the CGP that patients who have not received a TKI as a component of previous salvage therapy and are in second or later hematologic relapse would be reasonable candidates for treatment with gilteritinib and would need to be addressed on a time-limited basis.
	• Given that pERC was satisfied that there is a net clinical benefit of gilteritinib compared with salvage chemotherapy for the treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation, pERC agreed with the CGP that it would be reasonable to switch patients from salvage chemotherapy to gilteritinib in a time-limited basis.

	• pERC noted that treatment of gilteritinib in patients without an FLT3 mutation or earlier lines of treatment prior to refractory or relapsed disease is out of scope.
Implementation Factors • Gilteritinib is an oral therapy available as 40 mg tablets with a dose of 120 mg (three 40 mg tablets) once daily. In the absence of a response after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily. The once daily administration is an enabler to implementation. Dose adjustments are made by adjusting the number of tablets so there would be minimal wastage. However, the potential five tablets daily are a high tablet burden and may be difficult for some patients. • PAG is seeking guidance on treatment duration as treatment "should continue as long as clinical benefit is observed"; such as clarity on whether treatment is until progression or treatment should be stopped for patients who achieve complete remission. • Additional pharmacy resources would be required for dispensing the medication. Increased nursing resources and clinic visits are required to monitor and treat adverse events (e.g., QT interval monitoring, side effects such as pancreatitis and myalgias). • However, in some jurisdictions, oral medications are not funded in the same mechanism as IV cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions that fund oral and IV cancer medications differently are private insurance coverage or full out-of-pocket expenses.	• pERC acknowledged that for dose adjustment, if required, wastage would be minimal given that dose adjustments are made by adjusting the number of tablets. • pERC noted that the Health Canada Product monograph recommends that treatment with gilteritinib be continued as long as clinical benefit is observed or until unacceptable toxicity occurs; and that in the absence of disease progression or unacceptable toxicity, treatment may be given for a minimum of six months as a delay in clinical response can occur.
Sequencing and Priority of Treatments • PAG is seeking guidance on: ○ Optimal sequencing with available treatments (e.g., midostaurin)	• pERC noted that midostaurin is currently funded in some jurisdictions for the treatment of adult patients with newly diagnosed FLT3-mutated AML. pERC agreed that patients with prior midostaurin exposure would be eligible for gilteritinib in the relapsed or refractory setting.

○ Resumption of gilteritinib following HSCT ○ What treatment options would be available to patients upon progression on gilteritinib ○ Whether there are clinical scenarios in which gilteritinib would be used in combination (with azacitidine or low-dose cytarabine or FLAG-IDA or MEC).	• pERC agreed with the CGP that per the treatment criteria in the ADMIRAL trial, patients who initiate treatment with gilteritinib would be able to resume gilteritinib following HSCT. • Treatment options that would currently be available upon progression on gilteritinib would include salvage chemotherapy, best supportive care, or clinical trials. • The ADMIRAL trial does not provide specific information regarding combination therapy; as a result, there is insufficient evidence to support the use of gilteritinib combination in this setting.
Companion Diagnostic Testing • PAG recognized that FLT3 testing would be required to determine the subset of patients with the FLT3 positive mutation. PAG noted that FLT3 testing is done in most provinces. In provinces where FLT3 testing is not currently available, implementation of FLT3 testing would be required.	• A validated test is required to confirm the FLT3 mutation status of AML prior to initiation with gilteritinib. pERC noted that FLT3 testing is done in most provinces; however, in provinces where FLT3 testing is not currently available, implementation of FLT3 testing would be required. pERC acknowledged that in the ADMIRAL trial, central or local FLT3 mutation testing was performed after the completion of the patient's last treatment (i.e., at relapse or in the refractory setting); however, in current Canadian clinical practice, FLT3 mutation testing generally occurs at diagnosis, and in select circumstances, at relapse. pERC agreed that jurisdictions may want to consider if re-testing for FLT3 mutation should be implemented.

AML = acute myeloid leukemia; ARA-C = cytarabine; CGP = Clinical Guidance Panel; FLAG-IDA = fludarabine, idarubicin, granulocyte colony-stimulating factor, and high-dose cytarabine; FLT3 = FMS-like tyrosine kinase; MEC = mitoxantrone, etoposide, cytarabine; HSCT = hematopoietic stem cell transplant; ITD = internal tandem duplication; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; t-AML = therapy-related acute myeloid leukemia; TKD = tyrosine kinase domain; TKI = tyrosine kinase inhibitor.