pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Glasdegib (Daurismo) **Submitted Reimbursement Request:** In combination with low-dose cytarabine for the treatment of newly diagnosed and previously untreated acute myeloid leukemia in adult patients, who are age ≥ 75 years or who are not eligible to receive intensive induction chemotherapy	
Submitted By: Pfizer Canada ULC	**Manufactured By:** Pfizer Canada ULC
NOC Date: April 28, 2020	**Submission Date:** May 6, 2020
Initial Recommendation: October 29, 2020	**Final Recommendation:** January 8, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	Glasdegib costs $286.41 and $572.82 per 25 mg and 100 mg tablet, respectively. At the recommended dose of 100 mg administered orally once daily on days 1 to 28 of each 28-day cycle, glasdegib costs $16,039.00 per 28-day cycle. Glasdegib in combination with low-dose cytarabine costs $16,143.00 per 28-day cycle.

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 does not recommend reimbursement of glasdegib in combination with low-dose cytarabine (LDAC) for the treatment of adult patients with newly diagnosed and previously untreated acute myeloid leukemia (AML), who are 75 years or older or who are not eligible to receive intensive induction chemotherapy.

pERC made this recommendation because, based on the submitted evidence from the BRIGHT 1003 trial, the Committee was uncertain of the magnitude of clinical benefit of glasdegib in combination with LDAC compared with LDAC alone in adult patients with newly diagnosed and previously untreated AML, who are 75 years or older or who are not eligible to receive intensive induction chemotherapy. pERC acknowledged that glasdegib in combination with LDAC has anti-tumour activity; however, the Committee noted that there was uncertainty around the magnitude of the overall survival (OS) benefit with glasdegib in combination with LDAC compared with LDAC alone given the limitations in the evidence from the available phase II clinical trial. Although the trial showed manageable toxicities with glasdegib in combination with LDAC, pERC noted the lack of quality of life (QoL) data. Given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of glasdegib in combination with LDAC compared with azacitidine, another relevant treatment option. Given the availability of azacitidine and limitations with the submitted evidence, pERC was uncertain whether glasdegib in combination with LDAC addresses an unmet need, although the Committee acknowledged that it

	offers an additional and in-home treatment option especially for patients located in remote or rural areas. pERC also concluded that glasdegib in combination with LDAC aligns with the following patient values: offers an additional treatment option with anti-tumour activity, has manageable toxicities, offers the option of home-based care especially for patients located in remote or rural areas, and eligibility is not restricted by patient age. The Committee concluded that, based on the sponsor's economic analysis and at the submitted price, glasdegib in combination with LDAC is not considered cost-effective compared with LDAC alone. pERC noted that CADTH was unable to comment on the cost-effectiveness of glasdegib in combination with LDAC compared with azacitidine, a relevant comparator, given the limitations associated with the sponsor's submitted ITC. A reduction in the price of glasdegib would be required for glasdegib in combination with LDAC to be considered cost-effective when compared with LDAC. pERC noted that the budget impact was sensitive to the expected uptake of glasdegib in combination with LDAC and was likely overestimated in the sponsor's base case.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC considered that it is possible to conduct a phase III randomized controlled trial (RCT) in the requested reimbursement patient population. pERC noted that new clinical data comparing glasdegib in combination with LDAC with currently available treatments in Canada for adult patients with newly diagnosed and previously untreated AML who are not eligible to receive intensive induction chemotherapy, which may include patients aged 75 or older, could form the basis of a resubmission to CADTH if more robust comparative efficacy data that are important to decision-making, such as OS, progression-free survival (PFS), and QoL, were provided.

SUMMARY OF pERC DELIBERATIONS

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

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

AML is the most common form of acute leukemia in adults. In 2017, there were 1,509 new cases of AML and 1,184 deaths reported in Canada. AML incidence increases with age, with approximately one-quarter of diagnoses in those older than 75 years. The median age at diagnosis is 66 years. There is no consensus regarding the optimal management of older patients with AML who are not candidates for intensive therapy due to advanced age or frailty; therefore, there is inter-clinician variability in choosing the best treatment for each patient. Currently available treatment options in Canada include azacitidine, which is the most commonly used therapy, LDAC, best supportive care, and enrolment in clinical trials. With current treatment options, approximately 20% of patients older than 60 years are expected to survive two years. pERC agreed with the CADTH Clinical Guidance Panel (CGP) and the registered clinicians who provided input to this submission that there is a need for more effective therapies with manageable toxicities that offer longer remission, prevent relapse, and prolong survival. Upon reconsideration of the pERC Initial Recommendation, pERC agreed with feedback that although azacitidine is available, it is not fully accessible in rural or remote areas, it is not approved for all indications, and administration is challenging for this target population. Therefore, the Committee recognized the value of an effective, oral administration option in this setting. The Committee reiterated the significant unmet need in this patient population, particularly for older, frailer patients and those who may have financial or geographical difficulties in accessing current options.

pERC deliberated on the results of one randomized, multi-national, open-label, phase Ib/II trial (BRIGHT 1003) that investigated treatment with glasdegib in combination with LDAC in adult patients with newly diagnosed and previously untreated AML. The phase II portion evaluated the efficacy and safety of glasdegib in combination with LDAC compared with LDAC alone in patients who were not candidates for intensive chemotherapy (arm A) and glasdegib in combination with cytarabine and daunorubicin in patients who were candidates for intensive chemotherapy (arm C). pERC only considered the evidence base for arm A; the patient population in arm C was beyond the scope of this review because it was not part of the reimbursement request. Although the results for OS, the primary outcome of the trial, were statistically significantly in favour of glasdegib in combination with LDAC compared with LDAC alone, pERC noted several limitations with this phase II trial which resulted in considerable uncertainty around the magnitude of the OS benefit. Specifically, the Committee discussed that the magnitude of the treatment effect estimates observed in the small study sample of the BRIGHT 1003 trial may not be replicable in a larger study sample or generalizable to the target population in real-world clinical practice. pERC also noted that the application of subsequent therapies after progression, which was higher in the glasdegib in combination with LDAC group than in the LDAC group, may have confounded OS results. Furthermore, pERC discussed that the results of the key secondary outcome of complete remission (CR), subgroup analyses, and analyses at updated data cut-off dates were at risk of false-positive findings due to the effects of multiple testing, which had not been adjusted for. pERC also noted that based on a one-sided level of significance of 0.10 and use of pre-specified 80% confidence intervals (CIs), the trial investigators were willing to accept a relatively high false-positive rate for the test of the primary outcome of OS. In addition, pERC discussed that phase II trials are mainly hypothesis-generating and their intent is to determine whether there is sufficient promise to proceed to a phase III confirmatory trial. pERC noted that it is feasible to conduct a phase III RCT because there are ongoing phase III trials in this setting.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the sponsor, registered clinicians, and the patient advocacy group, noting that the overall magnitude of OS benefit demonstrated in the BRIGHT 1003 trial was clinically meaningful. Following a robust discussion, pERC considered that although the magnitude of OS observed with glasdegib compared with LDAC alone was important, the Committee was concerned about the strength of the evidence due to

the limitations with the phase II BRIGHT 1003 trial. The Committee also discussed feedback provided by the sponsor that the primary analysis results of the BRIGHT 1003 trial could have been the interim analysis results for a hypothetical phase III trial. pERC reiterated that the primary objective of phase II trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to warrant a confirmatory phase III trial. pERC noted that it is feasible to conduct a phase III RCT (e.g., VIALE-A) versus standard of care in the target population and that clinical data from RCTs are required to provide clarity on the comparative efficacy of glasdegib in combination with LDAC versus standard of care options based on outcomes important to decision-making, such as PFS, OS, and QoL.

Upon reconsideration of the pERC Initial Recommendation, pERC acknowledged that there is a need for additional treatment options for adult patients with newly diagnosed and previously untreated AML who are not candidates for intensive induction chemotherapy. However, given the limitations of the submitted evidence and the uncertainty around the magnitude of the clinical benefit in OS, pERC was uncertain whether glasdegib in combination with LDAC addresses the need for more effective therapies in this patient population.

pERC discussed the toxicity profile of glasdegib in combination with LDAC and noted that all patients in the trial experienced at least one all-grade treatment-emergent adverse event (TEAE), including anemia, nausea, febrile neutropenia, decreased appetite, and thrombocytopenia. Most TEAEs were of grade 3 and 4 and those occurring more frequently in the glasdegib in combination with LDAC group included anemia, febrile neutropenia, thrombocytopenia, and fatigue. Although adverse events (AEs) requiring treatment interruptions and dose reductions were higher in the glasdegib in combination with LDAC group, treatment discontinuation due to AEs occurred more frequently in the LDAC group. pERC noted a small number of electrocardiogram QT prolongation events and agreed that co-administration of medications that are known to potentially prolong the QT interval should be avoided. Overall, pERC agreed with the CGP and registered clinicians providing input to this submission that glasdegib in combination with LDAC has a manageable safety profile.

Additionally, pERC noted that QoL data were not collected in the BRIGHT 1003 trial and considered that the impact of glasdegib in combination with LDAC on a patient's quality of life is unknown. Patient input noted that impact on QoL is one of the most important factors they consider when deciding to take new treatments. However, pERC could not comment on how treatment with glasdegib in combination with LDAC impacts a patient's QoL for this predominantly elderly or frail population. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the sponsor that patients treated with glasdegib in combination with LDAC experienced longer quality-adjusted survival time and achieve higher rates of transfusion independence, resulting in improved QoL. pERC agreed with the CADTH Methods Team and reiterated that although the trial showed manageable toxicity with glasdegib in combination with LDAC, QoL data were not collected in the BRIGHT 1003 trial and quality-adjusted survival time is not an accepted measure of patient-reported QoL.

Furthermore, pERC discussed glasdegib in combination with LDAC in the context of other currently available treatment options in the requested patient population. pERC noted that there is no consensus regarding the optimal management of patients in this setting and inter-clinician variability exists in choosing the best treatment for each patient. Although the BRIGHT 1003 study included LDAC as the comparator treatment, pERC agreed with the CGP that azacitidine currently is the most commonly used therapy for these patients in Canada. pERC acknowledged that LDAC is primarily used in patient cases of intolerability or accessibility concerns with azacitidine (i.e., LDAC can be provided at home, whereas azacitidine requires travel to a cancer centre), or in patients who have received prior hypomethylating agents (azacitidine, decitabine) for an antecedent hematological disorder such as myelodysplastic syndrome (MDS).

In the absence of a direct comparison of glasdegib in combination with LDAC with other relevant treatment options, pERC considered the results of a submitted ITC that included a comparison of glasdegib in combination with LDAC against azacitidine. pERC acknowledged the limitations noted by the CADTH Methods Team and agreed with their key concerns regarding the violation of the assumption of within-study randomization and heterogeneity across the study designs and populations. pERC agreed with the CGP and the CADTH Methods Team and cautioned against drawing conclusions from the ITC on the magnitude of effect of glasdegib in combination with LDAC compared with azacitidine in the absence of more robust direct or indirect comparative evidence. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the registered clinicians that the BRIGHT 1003

study included higher-risk patients than other comparative studies in this setting. pERC agreed with the CGP to caution against drawing conclusions on level of cytogenetic risk given the different trial populations. pERC reiterated the lack of robust direct or indirect comparative evidence.

In summary, pERC was unable to conclude that there is a net clinical benefit of glasdegib in combination with LDAC compared to LDAC alone in adult patients with newly diagnosed and previously untreated AML, who are aged 75 years or older or who are not eligible to receive intensive induction chemotherapy. pERC acknowledged that glasdegib in combination with LDAC has antitumour activity; however, the Committee noted that there was uncertainty around the magnitude of the OS benefit given the limitations in the evidence from the available phase II clinical trial. Although the trial showed manageable toxicities with glasdegib in combination with LDAC, pERC noted the lack of QoL data. Given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of glasdegib in combination with LDAC compared with azacitidine, another relevant treatment option. Given the availability of azacitidine, pERC was uncertain whether glasdegib in combination with LDAC addresses an unmet need, although the Committee acknowledged that it offers an additional and in-home treatment option.

Also, upon reconsideration, pERC discussed feedback from the sponsor and registered clinicians noting that pERC has provided positive conditional recommendations with lower levels of evidence within the context of high unmet clinical need (e.g., phase II, non-comparative, no QoL). pERC reiterated that the Committee strives to make decisions that are equitable, transparent, timely, and accountable to patients, health care funders, and the public. However, pERC stressed that each submission is viewed independently and on its own merits.

pERC deliberated on the patient advocacy group input from the Leukemia & Lymphoma Society of Canada (LLSC). pERC noted that, according to patients, common symptoms with AML included fatigue, loss of appetite, and weight loss, which were reported to disrupt daily life. Fatigue was reported to have the most impact on daily life. Additionally, patients highlighted the disruptive effect of AML on their social life as a consequence of their fatigue and fear of catching infections. pERC noted that no patient had direct experience with glasdegib in combination with LDAC. pERC concluded that glasdegib in combination with LDAC aligns with the following patient values: offers an additional treatment option with anti-tumour activity, has manageable toxicities, offers the option of home-based care, and eligibility is not restricted by patient age. pERC noted that the impact of glasdegib in combination with LDAC on patients' QoL is unknown because it was not measured in the trial.

pERC deliberated on the cost-effectiveness of glasdegib in combination with LDAC compared with LDAC alone for patients with untreated AML who are not eligible for intensive induction chemotherapy. pERC noted the limitations associated with the sponsor's ITC and was unable to determine the comparative cost-effectiveness between glasdegib in combination with LDAC and azacitidine. pERC concluded that glasdegib in combination with LDAC was not cost-effective at the submitted price compared with LDAC alone and that a reduction in drug price would be required to improve cost-effectiveness to an acceptable level. Upon reconsideration of the Initial Recommendation, pERC reiterated that glasdegib in combination with LDAC was unlikely to be cost-effective at conventional willingness-to-pay thresholds, even with a substantial price reduction to glasdegib. pERC also noted that CADTH was unable to determine cost-effectiveness between glasdegib in combination with LDAC and azacitidine and additional data on clinical comparisons between these treatments are needed. pERC noted that the budget impact was sensitive to the expected uptake of glasdegib in combination with LDAC and was likely overestimated in the sponsor's base case.

EVIDENCE IN BRIEF

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

- A CADTH 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 CADTH clinical and economic review panels
- Input from one patient advocacy group: the Leukemia & Lymphoma Society of Canada (LLSC)
- Input from registered clinicians: one clinician provided input on behalf of Cancer Care Ontario (CCO) Hematology Drug Advisory Committee (DAC) and 10 clinicians provided input on behalf of the Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude sur la Leucémie (GCEL)
- Input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, LLSC
- One clinician on behalf of CCO Hematology DAC and 10 clinicians on behalf of the CLSG/GCEL
- The PAG
- The sponsor, Pfizer Canada ULC.

The pERC Initial Recommendation was to not recommend reimbursement of glasdegib in combination with LDAC for the treatment of adult patients with newly diagnosed and previously untreated AML, who are 75 years or older, or who are not eligible to receive intensive induction chemotherapy.

Feedback on the pERC Initial Recommendation indicated that the sponsor, the patient advocacy group, and registered clinicians disagreed with the Initial Recommendation. PAG agreed with the Initial Recommendation and supported conversion to Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the CADTH review was to evaluate the safety and efficacy of glasdegib in combination with LDAC compared with standard of care in Canada for the treatment of adult patients with newly diagnosed and previously untreated AML, who are age 75 years or older or who are not eligible to receive intensive induction chemotherapy.

Studies included: Multi-national, open-label, randomized phase Ib/II trial (BRIGHT 1003)

The CADTH systematic review included one randomized, multi-national, open-label, phase Ib/II RCT (BRIGHT 1003) that investigated treatment with glasdegib in combination with LDAC compared with LDAC alone for adult patients with newly diagnosed and previously untreated AML or high-risk myelodysplastic syndrome (MDS). The phase Ib portion evaluated the maximum tolerable dose of glasdegib in combination with LDAC. The phase II portion evaluated the efficacy and safety of glasdegib in combination with LDAC compared with LDAC alone in patients who were not candidates for intensive chemotherapy (arm A) and glasdegib in combination with cytarabine and daunorubicin in patients who were candidates for intensive chemotherapy (arm C). pERC only considered the evidence base for arm A; the patient population in arm C was beyond the scope of this review because it was not part of the reimbursement request.

A total of 132 patients were randomized in a 2:1 ratio to receive either glasdegib in combination with LDAC (glasdegib: 100 mg orally once daily continuously starting day 1 of a 28-day cycle; LDAC: 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle; n = 88) or LDAC (LDAC: 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle; n = 44). Randomization was stratified by cytogenetic risk (good or intermediate risk, poor risk). Treatment continued for up to one year (12 cycles) from start of therapy or until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever occurred first). Investigators could elect to continue treatment beyond 12 months if patients demonstrated clinical benefit with manageable toxicity.

The median duration of study treatments was 83 days and 47 days in the glasdegib in combination with LDAC and LDAC groups, respectively.

Eligible patients included newly diagnosed and previously untreated patients with AML or high-risk MDS, including those who may have had one prior regimen with a commercially available drug (e.g., azacitidine or decitabine) for their antecedent hematologic disease such as myelodysplastic syndrome (MDS). Patients were not permitted to have had any prior therapy for AML.

Patients with at least one of the following criteria were considered unfit for intensive chemotherapy and were eligible for participation in the phase II unfit or non-intensive population (arm A):

- Age 75 years or older
- Eastern Cooperative Oncology Group Performance Status (ECOG) = 2
- Serum creatinine greater than 1.3 mg/dL
- Severe cardiac disease (e.g., left ventricular ejection fraction less than 45% by multigated acquisition scan or echocardiography at screening).

Patient populations: Median age = 76 (unfit or non-intensive population), baseline characteristics balanced

Baseline demographics and characteristics in the unfit or non-intensive study group (arm A) were generally balanced between the two treatment groups. Overall, the median age of enrolled patients was 76 years; 97.7% were aged 65 or older. [redacted]. There were slightly more patients with good or intermediate cytogenetic risk in the glasdegib in combination with LDAC group compared with the LDAC group (59.1% versus 56.8%) and slightly less patients with poor cytogenetic risk in the glasdegib in combination with LDAC group compared with the LDAC group (40.9% versus 43.2%).

Most patients in the glasdegib in combination with LDAC group met one (29.5%) or two (43.2%) of the criteria used to qualify for the unfit or non-intensive inclusion category. Half of the patients in the LDAC group met one of the criteria (50%) and 36.4% met two criteria.

Key efficacy results: Uncertainty around the magnitude of OS benefit due to limitations of the phase II trial design

The primary outcome was OS and the key secondary outcome was CR. Other secondary efficacy outcomes included CR with incomplete blood count recovery, morphologic leukemia-free state, partial remission, partial remission with incomplete blood count recovery, minor response, stable disease, cytogenetic complete response, and molecular complete response. Quality of life was not measured in the trial. The exploratory PFS outcome was assessed in post-hoc analyses.

The planned sample size was 132 patients and a total of 92 OS events were to occur to achieve 80% power to detect a treatment effect with hazard ratio (HR) of 0.625 at a one-sided significance level of 0.10. The CADTH Methods Team noted that it is possible that the magnitude of the treatment effect estimates observed in this small study may not be replicable in a larger study sample or generalizable to the target population in real-world clinical practice. pERC also noted that based on a one-sided level of significance of 0.10 and the use of pre-specified 80% confidence intervals (CIs), the trial investigators were willing to accept a relatively high false-positive rate for the test of the primary outcome of OS. Data submitted to regulatory agencies and CADTH included post-hoc analyses using 95% confidence intervals, which showed consistent results with the 80% CI analyses. According to the statistical analyses plan, there was one pre-specified subgroup analysis for the primary end point of OS based on cytogenetic risk (poor versus good or intermediate). No multiplicity adjustments were made for either the secondary end points or the multiple analyses at various data cut-off dates. This increases the probability of type I error.

At the January 2017 data cut-off date (the primary study completion date), the median follow-up time for OS was 21.7 months in the glasdegib in combination with LDAC group and 20.1 months in the LDAC group. At an updated exploratory data cut-off date (April 2019), the median OS in the study groups was 47.6 months and 48.1 months in the glasdegib in combination with LDAC and the LDAC groups, respectively. The OS results at the April 2019 data cut-off date were consistent with the results observed at the January 2017 data cut-off date.

As of the data cut-off date (January 2017), there were 68 deaths (77.3%) in the glasdegib in combination with LDAC group and 41 deaths (93.2%) in the LDAC group. The median OS was longer in patients who

were randomized to receive glasdegib in combination with LDAC (8.8 months; 80% CI, 6.9 to 9.9) compared with patients who received LDAC (4.9 months, 80% CI, 3.5 to 6.0); this difference was statistically significant (HR = 0.513; 80% CI, 0.394 to 0.666; P = 0.0004). Additional analyses for the AML patients (n = 116) showed consistent results with the overall trial population. The OS results were consistent in additional post-hoc analyses using 95% CIs (HR = 0.513; 95% CI, 0.343 to 0.766; P = 0.0004). Pre-specified exploratory subgroup analyses for OS by cytogenetic risk showed that patients with good or intermediate cytogenetic risk taking glasdegib in combination with LDAC had a median OS of 12.1 months (80% CI, 8.3 to 14.4), and those taking LDAC had a median OS of 4.8 months (80% CI, 4.1 to 6.0). In patients with poor cytogenetic risk, median OS for patients taking glasdegib in combination with LDAC was 4.7 months (80% CI, 4.0 to 7.4) and for patients taking LDAC it was 4.9 months (80% CI, 2.3 to 6.4). For the comparison of glasdegib in combination with LDAC versus LDAC in the group with good or intermediate cytogenetic risk the HR was 0.427; and the HR was 0.633 for the group with poor cytogenetic risk. No 95% CIs were reported for these analyses of OS by cytogenetic risk.

In the full trial population (AML plus MDS patients), a higher rate of CR was observed in patients taking glasdegib in combination with LDAC (n = 15, 17.0%) compared to patients taking LDAC (n = 1, 2.3%) In the glasdegib in combination with LDAC group, the median duration of response was 9.9 (range = 0.03 to 28.8) months for patients with CR and 6.5 (range = 0.03 to 28.8) months for patients with either CR, CR with incomplete blood count recovery, or morphologic leukemia-free state.

Patients received subsequent therapies including chemotherapy (40% in the glasdegib in combination with LDAC and 34% in the LDAC group). One (1.3%) patient in the glasdegib in combination with LDAC group went on to receive a stem cell transplant and two (2.7%) patients in the glasdegib in combination with LDAC group received subsequent investigational treatments for AML. Chemotherapy treatments received by patients after study drug discontinuation included a variety of agents, notably cytarabine, decitabine, and azacitidine.

Patient-reported outcomes: Not measured

The BRIGHT 1003 trial did not collect patient-reported outcomes; therefore, the CADTH Methods Team noted that the impact of glasdegib in combination with LDAC on a patient's QoL is unknown.

Safety: Manageable toxicities

At the January 2017 data cut-off date, all patients in the trial experienced at least one all-grade TEAE. A slightly higher incidence of TEAEs occurring in 20% or more of patients were observed in the glasdegib in combination with LDAC group compared with the LDAC group, including anemia (45.2% versus 41.5%), nausea (35.7% versus 12.2%), febrile neutropenia (35.7% versus 24.4%), decreased appetite (33.3% versus 12.2%), and thrombocytopenia (31.0% versus 26.8%). Most TEAEs were of grade 3 and 4 severity, and those occurring more frequently in the glasdegib in combination with LDAC group included anemia (41.7% versus 36.6%), febrile neutropenia (35.7% versus 24.4%), thrombocytopenia (31.0% versus 24.4%), and fatigue (14.3% versus 4.9%). The incidence of serious AEs (occurring in 15% or more of patients) was broadly similar in both the glasdegib in combination with LDAC group and LDAC group, with febrile neutropenia (28.6% and 17.1%, respectively) and pneumonia (22.6% and 17.1%, respectively) being the most commonly reported events.

Fewer patients discontinued study treatments due to AEs in the glasdegib in combination with LDAC group (n = 30, 35.7%) compared with the LDAC group (n = 19, 46.3%). Forty-seven (56%) patients temporarily discontinued glasdegib and/or LDAC and 22 (26.2%) patients had their study treatment dose reduced due to AEs. In the LDAC group, 13 (31.7%) patients temporarily discontinued LDAC because of AEs, and no patient had dose reductions.

QT interval prolongation is an AE of interest for glasdegib; QT was prolonged in five (6%) patients taking glasdegib in combination with LDAC and two (11.8%) patients taking LDAC.

Incidence of AEs typically associated with hedgehog pathway inhibitors, which occurred within the first 90 days of study treatment in the AML and MDS populations, included (glasdegib in combination with LDAC versus LDAC) musculoskeletal pain (n = 30, 35% versus n = 17, 41%), muscle spasms (n = 15, 18% versus n = 5, 12%), dysgeusia (n = 21, 25% versus n = 2, 5%), fatigue (n = 36, 43% versus n = 32, 78%), weight decreased (n = 11, 13% versus n = 5, 12%), nausea (n = 29, 35% versus n = 12, 29%), vomiting (n = 18, 21% versus n = 10, 24%), diarrhea (n = 18, 21% versus n = 22, 54%), and renal insufficiency (n = 19, 23% versus n = 10, 24%).

Deaths occurred in 64 (76.2%) patients in the glasdegib in combination with LDAC group and 40 (97.6%) patients died in the LDAC group from the start of treatment through the follow-up period (i.e., occurring 28 days after the last dose). None of the deaths were due to treatment toxicity.

Limitations: No direct comparative data to azacitidine

The sponsor provided an ITC to provide estimates of comparative efficacy between glasdegib in combination with LDAC and azacitidine in the treatment of patients with AML who are ineligible for intensive chemotherapy. The results of the ITC suggested no statistically significant difference and wide CIs for the OS HRs of glasdegib in combination with LDAC compared to azacitidine in the base case using the Bucher method. For the sensitivity analyses using simulated treatment comparison methods, results for the 20% to 30% blasts subgroup showed no statistically significant differences for OS between glasdegib in combination with LDAC and azacitidine. Results for the more than 30% blasts subgroup demonstrated a statistically significant difference in favour of glasdegib in combination with LDAC; however, the CIs were wide and the upper bound of the CI interval was near or at 1.00. The CADTH Methods Team identified several limitations with the ITC. Most notably, the violation of the assumption of within-study randomization and concerns regarding heterogeneity across the study designs and populations. An absence of comparative safety and QoL data was also noted. The CADTH Methods Team concluded that given the aforementioned limitations and the high level of uncertainty reflected in the CIs, results of the ITC analyses should be interpreted with extreme caution.

Need and burden of illness: Need for treatments that offer longer remission and prolong survival

AML is the most common form of acute leukemia in adults. In 2017, there were 1,509 new cases of AML and 1,184 deaths reported in Canada. AML incidence increases with age, with approximately one-quarter of diagnoses in those older than 75 years. There is no consensus regarding the optimal management of older patients with AML who are not candidates for intensive therapy due to advanced age or frailty; therefore, there is inter-clinician variability in choosing the best treatment for each patient. Currently available treatment options in Canada include azacitidine, which is the most commonly used therapy, LDAC, best supportive care, and enrolment in clinical trials. With current treatment options, approximately 20% of patients older than 60 years are expected to survive two years. pERC agreed with the CADTH CGP and the registered clinicians providing input to this submission that there is a need for more effective therapies with manageable toxicities that offer longer remission, prevent relapse, and prolong survival.

Registered clinician input: Glasdegib in combination with LDAC well-tolerated; superior to LDAC alone; LDAC-based treatment option essential

A total of two registered clinician inputs were provided: one clinician provided input on behalf of CCO DAC and 10 clinicians provided input on behalf of the CCLSG/GCEL. Both inputs mentioned that patients with AML who are ineligible to receive intensive chemotherapy could receive best supportive care or less-intensive chemotherapy regimens; azacitidine and LDAC were noted in both inputs while the CCO clinician additionally specified azacitidine plus venetoclax, and the CCLSG/GCEL clinicians additionally specified decitabine. Compared to LDAC monotherapy, the CCLSG/GCEL clinicians highlighted that response rates (CR) and median OS were greater with glasdegib in combination with LDAC, as demonstrated in the pivotal trial. Further, they highlighted that glasdegib in combination with LDAC is safe and well-tolerated, and that contraindications to glasdegib in combination with LDAC are essentially the same as to LDAC alone, with the addition of known intolerance to glasdegib or another hedgehog pathway inhibitor. The CCLSG/GCEL clinicians specified that glasdegib in combination with LDAC would be a superior alternative to LDAC alone if the treatment under review becomes available for funding. The CCO clinician specified that the only patients who should not receive glasdegib align with the exclusions of the pivotal trial and there should be no age restriction. The CCLSG/GCEL clinicians stated that they would administer glasdegib in combination with LDAC in patients with one or more of the following: difficulty in attending hospital visits for geographic or distance reasons, standard risk cytogenetics, prior treatment failure with a hypomethylating agent, such as azacitidine or decitabine, and intolerance to a hypomethylating agent. For such patients, the CCLSG/GCEL clinicians stated that it is essential to have a LDAC-based treatment option in Canada. They specified that most patients receiving the treatment under review would be elderly; many elderly patients in Canada often live far from a cancer centre, and travel is difficult due to the distance and the requirement for an accompanying caregiver. The advantage of reducing the time needed to be in the hospital for the patient and caregiver is particularly favourable during the COVID-19 pandemic.

PATIENT-BASED VALUES

Experience of patients with AML: Fatigue key symptom; other symptoms include loss of appetite, weight loss, and lack of social life

One patient input was provided by LLSC on the glasdegib for AML review. Patient respondents noted common symptoms of AML, including fatigue, loss of appetite, and weight loss, which were reported to disrupt daily life. Fatigue was reported to have the most impact on daily life. Most patients (80%) noted that extreme fatigue had a "significant impact" on their daily lives. Additionally, the lack of a social life attributed to AML was highlighted; one patient noted experiencing social isolation due to a fear of catching an infection.

The most common side effects reported by patients included fatigue, infections (e.g., viral and fungal), hair loss, neutropenia (low number of white blood cells), reduced movement or inability to participate in physical activities, fever, and vomiting. The most serious side effect reported was a graft versus host reaction in which the donor's immune cells attack the patient's normal cells. Moreover, most patient respondents had some form of infection or disease other than cancer, which was attributed to the deficiency of white blood cells during treatment. In addition to the physical side effects, patients noted that treatments impacted their QoL through changes in physical activity (e.g., gardening, exercise), the ability to work, anxiety levels, and social life (e.g., visiting other people or attending social functions). Most patients reported easy access to treatment; however, for elderly patients, it was highlighted that patients should be able to receive treatment based on their general state of health and not their age. One patient reported having difficulty accessing treatment in the province of residence — but was able to receive first-line, high-dose chemotherapy by connecting with a hematologist in another province — and another patient noted having difficulty finding transportation to receive treatment.

Patient values, experience on, or expectations for treatment: Access to effective treatment options, better symptom management, reduced side effects, better QoL, and treatment based on patients' general state of health

None of the patient respondents had treatment experience with glasdegib; however, patients were asked if they would consider taking glasdegib and why they would be willing to tolerate the side effects. One patient would consider treatment with glasdegib if it meant choosing between life and death, and another patient would consider glasdegib if the positive results of glasdegib are as good or better than chemotherapy. Patients noted that doctor's recommendation, possible impact on the disease, and QoL were the most important factors for patients and caregivers when deciding on a new cancer treatment. Overall, patients with AML value having access to effective treatment options with better symptom management, reduced side effects, better QoL, and access to treatment based on patients' general state of health; specifically, access should not be limited by a patient's financial status or geographic location (province of residence).

ECONOMIC EVALUATION

Glasdegib is available as a 25 mg and 100 mg tablet, at a submitted price of $286.41 and $572.82 per tablet, respectively. The recommended starting dose is 100 mg daily in combination with LDAC. The 28-day cycle cost is $16,039 for glasdegib and $104 for LDAC, with a combined 28-day cycle cost of $16,143.

The sponsor submitted a three-state partitioned survival model that considered glasdegib in adult patients with newly diagnosed and untreated AML who were not eligible for intensive induction chemotherapy. The proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the five-year model time horizon was derived from non-mutually exclusive survival curves. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer. The sponsor explored the cost-effectiveness of glasdegib in combination with LDAC versus LDAC alone for the main population as part of its base-case analysis, with LDAC alone and azacitidine considered as part of scenario analyses according to bone marrow blast subgroups.

In the main population, Kaplan-Meier curves for glasdegib in combination with LDAC and LDAC alone were applied in the modelling of efficacy (i.e., OS and PFS-like) given the maturity of the data and that extrapolation was not required. Because PFS data were not collected as part of the BRIGHT AML 1003 trial, the sponsor estimated a PFS-like health state based on time-to-treatment discontinuation and OS data from the BRIGHT AML 1003 trial based on discontinuation criteria. Patients in the PFS-like health state were further stratified by their response status into remission or non-remission. Overall survival of glasdegib in

combination with LDAC and LDAC alone was also obtained from the BRIGHT AML 1003 trial. Relative azacitidine OS was derived using an unpublished ITC commissioned by the sponsor for bone marrow blast subgroups. Further, a simulated treatment comparison was included as part of scenario analyses to assess the impact of clinical trial differences on OS.

The following key limitations were identified:

- Given the limitations associated with the sponsor's ITC, CADTH was unable to determine the comparative efficacy or cost-effectiveness of glasdegib in combination with LDAC compared with azacitidine.
- There was uncertainty associated with the use of a PFS-like health state given that this end point was not included as part of the BRIGHT AML 1003 trial, and it is unknown to what extent the inclusion of partial responders in the non-remission health state biases cost-effectiveness results.
- The sponsor applied a general chemotherapy cost code for the administration of azacitidine; however, it was unclear which modes of administration for treatment were included and if this accurately reflects the administration costs for azacitidine. Treatment administration costs were likely overestimated and biased results in favour of glasdegib in combination with LDAC when compared with azacitidine.
- Given the lack of QoL data captured in the BRIGHT AML 1003 trial, the sponsor applied health state utility estimates from the published literature. CADTH considered these estimates to be associated with uncertainty given that the patient population (i.e., MDS patients) was not reflective of the patient population in the BRIGHT AML 1003 trial (i.e., AML patients). Further, the sponsor selected utilities that were based on the time spent in transfusion dependence as opposed to remission, the latter of which was only explored in the sponsor economic model using data from the BRIGHT AML 1003 trial. Given the uncertainty associated with health state utilities, conservative estimates (i.e., lower health state utility value for remission) were included in the CADTH base case.
- The sponsor adjusted glasdegib in combination with LDAC drug costs according to dose intensity (i.e., dose adjustments or drug interruption), which underestimated treatment costs. Further, the sponsor likely overestimated drug dose intensity for azacitidine, biasing results in favour of glasdegib in combination with LDAC.
- Due to the non-continuous nature of Kaplan-Meier curves, calculating point survival estimates was associated with challenges; specifically, long plateaus or sudden drops in survival could potentially bias results in favour of glasdegib in combination with LDAC.
- The CGP highlighted that subsequent treatments for glasdegib in combination with LDAC, LDAC alone, and azacitidine were not reflective of clinical practice because a subset of patients would receive gilteritinib and the proportion of patients receiving azacitidine was likely overestimated.

The CADTH base case reflected changes to the following parameters: using a parametric survival extrapolation for OS and PFS-like, using a more conservative health state utility value for remission, revising subsequent treatment distributions, adjusting treatment administration costs for azacitidine, and revising drug dose intensities for glasdegib in combination with LDAC and azacitidine. The latter two limitations primarily affected subsequent treatment costs in the CADTH base case and in exploratory analyses that included azacitidine as a comparator. Given the clinical review of evidence, there were multiple limitations associated with the sponsor's submitted ITC, meaning that CADTH was unable to determine the comparative efficacy between glasdegib in combination with LDAC and azacitidine. Therefore, CADTH was unable to determine the cost-effectiveness between these treatments and focused the base case results on the main population with azacitidine only being included as part of exploratory analyses. CADTH reanalyses indicated that glasdegib in combination with LDAC versus LDAC alone was not cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) gained with an incremental cost-effectiveness ratio of $229,622 per QALY gained at the submitted price. A reduction of 95% in the price of glasdegib would be required for glasdegib in combination with LDAC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact overestimated

The sponsor's assumed market share uptake of glasdegib in combination with LDAC was likely overestimated given feedback from clinical experts consulted by CADTH, suggesting that total budget impact was also overestimated. As part of its reanalysis, CADTH revised the market share for glasdegib in

combination with LDAC, drug dose intensity for glasdegib and azacitidine, azacitidine treatment duration, and the proportion of patients ineligible for chemotherapy. CADTH reanalyses suggest that the budget impact of introducing glasdegib to the market (based on a lower uptake of glasdegib in combination with LDAC over the three-year time horizon) was estimated to be $21,463,743 in the main population over the first three years. In scenario analyses, the use of the sponsor's submitted market share in CADTH reanalyses resulted in an estimated three-year budget impact of $63,084,041.

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. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
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. Maureen Trudeau, who did not vote due to her role as pERC Chair
- Dr. Michael Crump, who did not vote as he was not present for the discussion and deliberation for this review
- Dr. W. Dominika Wranik, who did not vote as she was absent from the meeting.

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

- Dr. Catherine Moltzan, who did not vote due to her role as pERC Chair for the reconsideration of glasdegib
- Drs. Maureen Trudeau, Kelvin Chan, and Avram Denburg who were not present for the reconsideration of glasdegib.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of glasdegib [Daurismo] in combination with LDAC 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*, none of these 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 CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.