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: Gemtuzumab Ozogamicin (Mylotarg)

Submitted Reimbursement Request: In combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia

Submitted by: Pfizer Canada ULC

Manufactured by: Pfizer Canada ULC

NOC Date: November 28, 2019

Submission Date: August 9, 2019

Initial Recommendation Issued: January 30, 2020

Approximate per Patient Drug Costs	$20,000.00 per 4.5 mg vial

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 recommends the reimbursement of gemtuzumab ozogamicin in combination with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia (APL).

Eligible patients include adults with previously untreated, de novo CD33-positive AML, except APL, who have good performance status and favourable, intermediate, or unknown cytogenetics (using the European LeukemiaNet (ELN) 2017 risk classification). Should a patient's unknown cytogenetic status become known as adverse, pERC recommends that gemtuzumab ozogamicin be discontinued.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of adding gemtuzumab ozogamicin to daunorubicin and cytarabine based on statistically significant and clinically meaningful improvement in event-free survival (EFS) and survival advantage seen in an individual patient data meta-analysis. pERC made this recommendation even though it acknowledged that there were no data on quality of life and that treatment with gemtuzumab ozogamicin is associated with manageable but not insignificant toxicities.

pERC agreed that gemtuzumab ozogamicin aligns with patient values of having additional and effective treatment options. However, pERC noted that the impact on patients' quality of life compared with other treatment options is unknown.

	The Committee concluded that, based on the sponsor's economic analysis and at the submitted price, gemtuzumab ozogamicin in combination with daunorubicin and cytarabine may be considered cost-effective compared with daunorubicin and cytarabine in this patient population. pERC also concluded that the market share may be greater than estimated; therefore, the submitted budget impact of the addition of gemtuzumab ozogamicin to daunorubicin and cytarabine may be underestimated and the actual budget impact may be substantially greater.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Timing of Cytogenetic Testing and Eligibility of Patients With Unknown Cytogenetics** pERC agreed that cytogenic testing status is required to determine status prior to initiating treatment with gemtuzumab ozogamicin. The Committee noted that cytogenetics testing is available in all jurisdictions; however, it was also noted that there are variations in the turnaround timing of the results. As a result, pERC noted that it would be ideal for jurisdictions to require timely cytogenetic testing and should a patient's unknown cytogenetic status become known as adverse, it recommends gemtuzumab ozogamicin be discontinued. pERC does not recommend the use of gemtuzumab ozogamicin for patients with adverse cytogenetics. **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 4.1 out of 100,000 and that in 2019, approximately 1,675 new cases of AML were projected to occur in Canada. pERC acknowledged that AML is diagnosed predominantly in adults, with a slight predominance in men, and with a median age at diagnosis of 66 years. pERC also noted a five-year overall survival rate of 21% for patients with AML.

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

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

pERC discussed available treatment options such as daunorubicin (or idarubicin) and cytarabine (3+7), which are used for remission induction, while high-dose cytarabine (HiDAC) is used for consolidation in Canada. pERC noted that fludarabine, idarubicin, granulocyte-colony stimulating factor, and high-dose cytarabine (FLAG-IDA) is a regimen available in some jurisdictions as a remission induction regimen. pERC also noted that in most Canadian jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and with cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FMS-like tyrosine kinase 3 (FLT3)-mutated AML. pERC also acknowledged that although allogeneic hematopoietic stem cell transplantation (HSCT) offers the potential of cure, HSCT is a medically risky, resource-intensive procedure that is only available to a small proportion of AML patients. 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 deliberated on one randomized open-label phase III, superiority trial (Acute Leukemia French Association [ALFA]-0701) that assessed the efficacy and safety of a daunorubicin and cytarabine induction regimen with or without gemtuzumab ozogamicin in previously untreated patients 50 to 70 years old with AML regardless of their expression of the CD33 antigen on leukemic blast cells (i.e., CD33 status of positive, negative, or unknown). The Committee noted that CD33 status was not a requirement in ALFA-0701, and that the reimbursement request was for CD33-positive patients only. pERC noted that fewer than 1% of patients with known CD33 status were known to be CD33 negative in ALFA-0701 and that CD33 status was not available (unknown) for more than a quarter of the patients. As well, pERC noted that the Clinical Guidance Panel (CGP) stated that, at diagnosis, CD33 is expressed in the majority (more than 90%) of cases of AML and that patients who are proven to be CD33 negative at time of diagnosis are unlikely to derive clinically meaningful benefit from the addition of gemtuzumab ozogamicin. Therefore, pERC agreed with the CGP to recommend against the use of gemtuzumab ozogamicin in patients whose AML is CD33 negative.

pERC discussed that there was a statistically significant and clinically meaningful improvement in EFS. pERC acknowledged that complete remission or complete remission with incomplete platelet recovery (CR/CRp) rates were not statistically different between the gemtuzumab ozogamicin group and the control group, and that there was no statistical improvement in overall survival. However, pERC noted that a survival advantage was demonstrated in patients with favourable and intermediate cytogenetics in an individual patient data meta-analysis of ALFA-0701 that was combined with four other randomized clinical trials. Taking the results of subgroup analyses from the meta-analysis into account, pERC agreed that the clinical benefit associated with gemtuzumab ozogamicin appears to be isolated to those patients whose AML cytogenetic risk group is either favourable or intermediate in nature and not for patients with adverse cytogenetics. Moreover, pERC noted that registered clinicians agreed that the benefit of gemtuzumab ozogamicin was suggested to be greatest for patients with favourable-risk AML; however, it was reported that overall, all patients benefited from the treatment. In addition, pERC acknowledged that in pre-specified subgroup analyses in ALFA-0701 (at two years with the modified intention-to-treat population), for patients with favourable or intermediate cytogenetics, EFS was longer in the gemtuzumab ozogamicin group but not for patients with adverse cytogenetics. pERC acknowledged that although the trial was not sufficiently powered to detect a subgroup treatment effect, pERC felt it was reasonable to limit reimbursement of gemtuzumab ozogamicin to patients with favourable, intermediate, or unknown cytogenetics because of the consistency of these subgroup results with the overall primary analysis results, and given the fact that the survival advantage was demonstrated in patients with

favourable and intermediate cytogenetics in the individual patient data meta-analysis. As well, pERC agreed with the CGP recommendation that it was reasonable to limit to patients with favourable, intermediate, or unknown cytogenetics.

pERC deliberated on the safety profile of gemtuzumab ozogamicin and noted gemtuzumab was associated with excess rates of clinically significant hematological toxicity (delayed platelet recovery and persistent thrombocytopenia) and a higher incidence of grade three or more hemorrhage and hepatotoxicity in the gemtuzumab ozogamicin group compared with the control group. pERC also noted the numerically higher hepatic veno-occlusive disease (VOD) rate experienced in patients in the gemtuzumab ozogamicin group compared with the control group; however, the difference was not statistically significant. Overall, pERC concluded that treatment with gemtuzumab ozogamicin was associated with manageable but not insignificant toxicities.

pERC therefore concluded that there is a net clinical benefit of adding gemtuzumab ozogamicin to daunorubicin and cytarabine based on statistically significant and clinically meaningful improvement in EFS and survival advantage seen in an individual patient data meta-analysis. pERC made this recommendation even though it acknowledged that there were no data on quality of life and that treatment with gemtuzumab ozogamicin is associated with manageable but not insignificant toxicities.

pERC deliberated on input from one patient group, the Leukemia and Lymphoma Society of Canada. pERC noted that patients with AML value having additional and effective treatment options, reduced side effects, improved quality of life. pERC also noted that one patient with AML had experience with gemtuzumab ozogamicin through a clinical trial. Although the patient described the treatment process as convenient (i.e., able to receive treatment at their local hospital), the patient was removed from the trial due to side effects (thrombocytopenia), which pERC believed accurately reflects the adverse event seen in ALFA-0701. Overall, pERC agreed that gemtuzumab ozogamicin aligns with patient values of having additional and effective treatment options. However, pERC noted that the impact on patients' quality of life compared with other treatment options is unknown.

pERC also deliberated on the cost-effectiveness of the addition of gemtuzumab to daunorubicin and cytarabine compared with daunorubicin and cytarabine in this patient population. The Committee considered the estimates provided by the sponsor and the pCODR Economic Guidance Panel (EGP), and in particular considered the sponsor's and the EGP's scenario analysis, which considered patients with favourable, intermediate, and unknown cytogenetics (i.e., excluding patients with adverse cytogenetics). pERC discussed the limitations of the economic model described by the EGP, which included the complexity of the model and lack of transparency; uncertainty as a result of population heterogeneity (inclusion of CD33-negative patients), long-term extrapolation of overall survival, excessive time horizon, and utility accrual (affected by the toxicity of the treatments); and the omission of some costs related to monitoring and management of adverse events. pERC noted that the percentage of patients receiving HSCT after relapse was the main factor that affected the incremental cost, while time horizon was the main factor that affected the incremental effectiveness. pERC also noted that the EGP's best estimate considered a 15-year time horizon and that the probabilities of HSCT for patients having relapsed were considered the same in both groups. In addition to the EGP's best-case estimate, the EGP conducted a scenario analysis that excluded patients with adverse cytogenetics and applied this scenario to the EGP's best-case estimate. pERC noted that doing so led to a decrease in the EGP's best-case estimate by approximately half. Given the limitations of the submitted economic model, pERC concluded that, based on the sponsor's economic analysis and at the submitted price, gemtuzumab ozogamicin combined with daunorubicin and cytarabine may be considered cost-effective compared with daunorubicin and cytarabine in adult patients with previously untreated, de novo CD33-positive AML, except APL, who have good performance status and favourable, intermediate or unknown cytogenetics (using the ELN 2017 risk classification).

pERC deliberated on the feasibility of implementing a reimbursement recommendation for gemtuzumab ozogamicin in combination with daunorubicin and cytarabine for adult patients with previously untreated, de novo CD33-positive AML, except APL, who have good performance status and favourable, intermediate or unknown cytogenetics (using the ELN 2017 risk classification). pERC discussed the budget impact and noted that the factors that most influence the budget impact include the number of patients eligible to be treated with gemtuzumab ozogamicin and the extent of market expansion. pERC noted that both the CGP and 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 noted that the budget impact included all patients

regardless of cytogenetic risk and that no scenario analysis excluding patients with adverse cytogenetics was requested or performed by the EGP (nine per cent of patients in ALFA-0701 had adverse cytogenetics); nonetheless, pERC believed the market share of year 1 to year 3 to be underestimated; therefore, the submitted budget impact of the addition of gemtuzumab ozogamicin to daunorubicin and cytarabine may be underestimated and the actual budget impact may be substantially greater.

As well, pERC agreed that cytogenetic testing to determine status is required prior to initiating treatment with gemtuzumab ozogamicin. The Committee noted that cytogenetics testing is available in all jurisdictions; however, there are variations in the turnaround timing of the results. As a result, pERC noted that it would be ideal for jurisdictions to require timely cytogenetic testing. pERC also discussed that patients are eligible to start induction therapy with gemtuzumab ozogamicin when either the cytogenetic test confirms that the cytogenetic status is favourable, intermediate, or unknown (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available ; and patients are eligible to start consolidation therapy when their cytogenetic tests confirm that the cytogenetic status is favourable, intermediate, or unknown (because the test was unsuccessful). pERC recommends that should a patient's unknown cytogenetic status become known as adverse, gemtuzumab ozogamicin should be discontinued.

pERC discussed that a treatment course including gemtuzumab ozogamicin in combination therapy consists of 1 induction cycle and 2 consolidation cycles; and if second induction cycle is required, gemtuzumab ozogamicin should not be administered during the second induction cycle. Also, according to CGP, gemtuzumab ozogamicin in combination with single agent HIDAC consolidation therapy for 2 cycles would offer comparable outcomes. However, pERC agreed with CGP in that if a third cycle of HIDAC consolidation were to be given, gemtuzumab ozogamicin should not be included in this third consolidation cycle, given the absence of data supporting the addition of gemtuzumab ozogamicin beyond 1 cycle of induction and 2 cycles of consolidation chemotherapy.

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 upon:

- 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 group: Leukemia and Lymphoma Society of Canada
- input from registered clinicians: one joint clinician input on behalf of six oncologists and two pharmacists from the Pediatric Oncology Group of Ontario, and three inputs from individual clinicians; a total of nine oncologists and two clinical pharmacists provided input on behalf of the provinces of 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 gemtuzumab ozogamicin in combination therapy with daunorubicin and cytarabine compared with daunorubicin and cytarabine for the treatment of adult patients with previously untreated CD33-positive acute AML, except APL.

Studies included: Phase III superiority trial — ALFA-0701
The pCODR systematic review included one randomized open-label phase III, superiority trial (ALFA-0701).

The pCODR review also provided contextual information on gemtuzumab ozogamicin in patients younger than 18 or older than 70 years of age, gemtuzumab ozogamicin in combination with other treatments, gemtuzumab ozogamicin in combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML, and a meta-analysis of five randomized control trials to determine whether patients experience benefit from treatment with gemtuzumab ozogamicin.

Patient populations: Previously untreated patients 50 to 70 years old
Key eligibility criteria included previously untreated patients 50 to 70 years old with AML if they had normal cardiac function. Expression of the CD33 antigen on leukemic blast cells was not required for study entry.

Key efficacy results: Clinically and statistically significant improvement in EFS
The key efficacy outcome deliberated on by pERC included the primary end point (EFS) and secondary end points including CR, overall survival, and safety. pERC noted that ALFA-0701 showed that gemtuzumab ozogamicin was associated with superior EFS (hazard ratio of 0.66; 95% confidence interval (CI), 0.49 to 0.89) compared with control (13.6 months versus 8.5 months). However, CR/CRp rates were not statistically different between the gemtuzumab ozogamicin and control groups (81.5% and 73.6%, respectively). As well, there was no statistical improvement in overall survival (hazard ratio of 0.81; 95% CI, 0.6 to 1.09).

In a subgroup analysis, the EFS benefit of gemtuzumab ozogamicin was isolated to the patients with favourable or intermediate cytogenetic risk (hazard ratio of 0.46; 95% CI, 0.31 to 0.68; $P < 0.0001$), as defined by the International System for Human Cytogenetic Nomenclature criteria. In contrast, the EFS of gemtuzumab ozogamicin in patients with adverse cytogenetic risk was not apparent (hazard ratio 1.11; 95% CI, 0.63 to 1.95; $P = 0.72$). This effect modification was similarly noted when two different AML genetic risk classification systems were applied (National Comprehensive Cancer Network and the ELN systems). In another exploratory subgroup analysis, the EFS benefit of gemtuzumab ozogamicin was noted even in FLT3 internal tandem duplication–mutated patients.

As well, a survival advantage was demonstrated in an individual patient data meta-analysis of ALFA-0701 combined with four other randomized clinical trials. According to the CGP, the clinical benefit associated with gemtuzumab ozogamicin appears to be isolated to those patients whose AML genetic risk group is of either favourable or intermediate in nature and not for patients with adverse cytogenetics.

Patient-reported outcomes: Not measured
Patient-reported outcomes, including quality of life, were not measured in the ALFA-0701 trial; therefore, pERC was unable to comment on the impact of gemtuzumab on quality of life.

Limitations: Open label, but knowledge of treatment is unlikely to influence the efficacy outcomes
The Methods team stated that overall the study was well conducted and that the study was open label, but knowledge of treatment is unlikely to influence the efficacy outcomes given that the primary outcome is objective, and an independent blinded review of the EFS end point was conducted.

In terms of limitations, the Methods team stated that the possibility of reporting bias (e.g., for subjective adverse events) should be noted. Quality of life was not reported. Some patients in the gemtuzumab ozogamicin group did not receive gemtuzumab ozogamicin as planned, but there was no crossover. A total of six patients in the control group received gemtuzumab ozogamicin after induction failure and 24 received it after relapse. Any potential crossover effects would bias the results against gemtuzumab ozogamicin. The analysis of secondary outcomes did not account for multiple testing; therefore, these analyses are considered exploratory. As well, multiple testing can increase the probability of type I error and lead to false-positive conclusions. Finally, ALFA-0701 was funded by manufacturer Wyeth (Pfizer).

Safety: Manageable but not insignificant toxicities
In the ALFA-0701 trial, gemtuzumab ozogamicin was associated with excess rates of clinically significant hematological toxicity (delayed platelet recovery and persistent thrombocytopenia). Grade 3 or higher hemorrhage was reported in 30 (22.9%) patients in the gemtuzumab ozogamicin group and 13 (9.5%) patients in the control group. The median time to recovery of platelets was longer for patients in the gemtuzumab ozogamicin group than in the control group for each treatment course.

Additional analyses conducted to identify severe (grade 3 and 4) and persistent thrombocytopenia (i.e., platelet count lower than 50×10^9/L at 45 days after day 1 of the previous treatment phase in which a patient experienced CRp) showed that more patients had severe persistent thrombocytopenia in the gemtuzumab ozogamicin group (20.4%) than in the control group (2.0%).

Grade 3 or higher hepatotoxicity was more frequently associated with gemtuzumab ozogamicin (13% gemtuzumab ozogamicin versus 6% controls). A total of six (4.6%) patients in the gemtuzumab ozogamicin group and two (1.5%) patients in the control group experienced hepatic VOD ($P = 0.165$).

The number of patients who died during the period from the time of the first dose of chemotherapy to 28 days after the last dose of study treatment was six (4.6%) in the gemtuzumab ozogamicin group and five (3.6%) in the control group.

Need and burden of illness: Continued need for effective treatment options with potential to offer a survival advantage
The age-adjusted incidence of AML is 4.1 out of 100,000. In 2019, approximately 1,675 new cases of AML were projected to occur in Canada. AML is diagnosed predominantly in adults, with a slight predominance in men, with a median age at diagnosis of 66 years old. The five-year overall survival rate for patients with AML is estimated at 21%.

Available treatment options include daunorubicin (or idarubicin) and cytarabine (3+7), which is used for remission induction; HiDAC, which is used for consolidation in Canada. FLAG-IDA is a regimen available in some jurisdictions as a remission induction regimen. In most Canadian jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and with cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated AML. Allogeneic hematopoietic cell transplantation is only available for a small proportion of patients with AML.

Registered clinician input: Clinicians endorse the reimbursement of gemtuzumab ozogamicin
Overall, clinicians generally endorse the reimbursement of gemtuzumab ozogamicin, as patients with AML have poor outcomes and current treatments are associated with potentially life-threatening toxicities.

In general, the clinicians did not support using age as an eligibility criterion for gemtuzumab ozogamicin. Clinicians expressed uncertainty about extending the use of gemtuzumab ozogamicin to patients with therapy-related AML. All clinicians providing input agreed that there are no data to support using

gemtuzumab ozogamicin in combination with midostaurin and chemotherapy for patients with newly diagnosed FLT3-mutated AML. One clinician suggested that the use of gemtuzumab ozogamicin be extended to patients with relapsed or refractory AML.

PATIENT-BASED VALUES

Experiences of patients with AML: Pathway to diagnosis not straightforward, challenges experienced during front-line treatment, and need to provide support for both physical and emotional symptoms and side effects
Patients reported fatigue, fever, night sweats, dizziness and light-headedness, bruising and/or bleeding, rashes and skin changes as symptoms of AML. Many respondents described the pathway to diagnosis as one that was not straightforward, and in a few cases it took multiple visits to a physician before the diagnosis was made. Respondents reported mistaking their symptoms for a prolonged flu or cold or other ailments until receiving a diagnosis of AML. There were also comments regarding the difficulty of finally receiving a diagnosis, as patients had to go through multiple appointments and interactions with different physicians before receiving a diagnosis.

Patients experienced many challenges during front-line treatment such as hospitalization, developing side effects, impact on family, and loss of independence. Loss of independence impacted respondents' ability to care for themselves, engage in activities, and conduct basic motor functions.

Respondents commented on the need to obtain support for both physical and emotional symptoms and side effects due to treatment.

Patient values on treatment: Having additional and effective treatment options, reduced side effects, improved quality of life
Patients' main considerations for new treatments include fewer side effects, maintaining quality of life, and controlling disease.

One patient with AML had experience with gemtuzumab ozogamicin and had accessed the treatment through a clinical trial. The treatment process was described as convenient as they were able to receive treatment at their local hospital. However, the patient was removed from the trial due to side effects; specifically, the patient experienced thrombocytopenia that "slowed platelet recovery after each chemo session."

Overall, patients with AML value having additional and effective treatment options, reduced side effects, and improved quality of life.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis
The EGP assessed the sponsor's cost-effectiveness and cost-utility analysis of gemtuzumab ozogamicin in combination therapy with daunorubicin and cytarabine compared with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive AML, except APL.

Basis of the economic model: Markov cohort state-transition
A cohort state-transition model was developed by the sponsor to capture health states and events that occur throughout the entire disease course and that impact costs and outcomes. The model included several health states: induction therapy, CR/CRp (includes two sub-states: consolidation therapy and off treatment), relapse (includes two sub-states: salvage therapy and noncurative therapy), refractory (includes two sub-states: salvage therapy and noncurative therapy), HSCT, post-HSCT CR/CRp (includes two sub-states: with and without GVHD), functionally cured (off treatment), and death.

The model had a cycle length of one month and a 40-year time horizon. Response rates and survival data from the ALFA-0701 study were used to inform health state transitions. Adverse event rates were also obtained from this study. Utility values were obtained from the published literature.

Drug costs: Gemtuzumab ozogamicin is an add-on to daunorubicin and cytarabine; cost of gemtuzumab ozogamicin is $20,000.00 per 4.5 mg vial
The recommended dose of gemtuzumab ozogamicin is 3 mg/m^2 per dose (up to a maximum of one 4.5 mg vial) infused over a two-hour period on days 1, 4, and 7 in combination with daunorubicin 60 mg/m^2 per day infused over 30 minutes on days 1 to 3 and cytarabine 200 mg/m^2 per day by continuous infusion on days 1 to 7.

Gemtuzumab ozogamicin should not be administered during the second induction therapy.

Up to two consolidation courses of intravenous daunorubicin (60 mg/m^2 for one day [first course] or two days [second course]) in combination with intravenous cytarabine (1,000 mg/m^2 every 12 hours, infused over two hours on days 1 to 4) with intravenous gemtuzumab ozogamicin (3 mg/m^2 per dose infused over two hours up to a maximum dose of one 4.5 mg vial on day 1) are recommended.

The cost of gemtuzumab ozogamicin is $20,000.00 per 4.5 mg vial.

The cost of daunorubicin is $91.00 per 20 mg vial.

The cost of cytarabine is:
- $5.09 per 100 mg vial
- $76.85 per 500 mg vial
- $153.25 per 1,000 mg vial
- $306.50 per 2,000 mg vial.

Cost-effectiveness estimates: May be cost-effective
The sponsor's base case was $56,255 per quality-adjusted life-year (QALY). The EGP's best estimate of incremental cost-effectiveness ratio (ICER) for gemtuzumab ozogamicin in combination with daunorubicin and cytarabine when compared with daunorubicin and cytarabine was $102,938 per QALY.

- Two assumptions made about the overall survival after HSCT might affect the ICER, yet, their magnitude is unknown. These were:
  1) The overall survival after HSCT was considered to be similar for all patients, regardless of whether the HSCT followed first- or second-line CR or CRp and the chemotherapies received or whether the patients were refractory to induction therapy or relapsed.
  2) Adjustments are included in the model to increase the predicted survival for patients after HSCT and reduce the predicted survival for patients who do not receive HSCT, proportionally.
- An extra cost might be required for additional monitoring and supportive care for hepatotoxicity and hematological toxicities, or for additional resources, in terms of chemotherapy chair time, pharmacy preparation, and nursing in the gemtuzumab ozogamicin group not accounted for in the submitted model. The EGP believed that the ICER is underestimated.
- The extra cost of gemtuzumab ozogamicin is $75,302 (incremental cost). The percentage of patients receiving HSCT after relapse is the main factor that affected the incremental cost.
- The extra clinical effect of gemtuzumab ozogamicin is 0.73 QALYs (incremental effectiveness). The time horizon is the main factor that affected the incremental effectiveness.

The limitations of the economic model described by the EGP included the complexity of the model and lack of transparency; uncertainty as a result of population heterogeneity (inclusion of CD33 negative patients) and long-term extrapolation of overall survival, excessive time horizon, and utility accrual (affected by the toxicity of the treatments); and the omission of costs related to monitoring and management of adverse events. The EGP's best estimate considered a 15-year time horizon and that the probabilities of HSCT for patients having relapsed were considered the same in both groups. In addition to the EGP's best-case estimate, the EGP conducted a scenario analysis which considered patients with favourable, intermediate, and unknown cytogenetics [i.e., excluding patients with adverse cytogenetics] and applied this scenario to the EGP's best-case estimate. This exclusion of patients with adverse cytogenetics AML led to a decrease in the EGP's best-case estimate by approximately half ($54,440 per QALY versus $102,938 per QALY).

The review team requested that the sponsor provide a subgroup economic analysis specific to the reimbursement request population (i.e., CD33-positive patients) and the sponsor responded that the test

was absent in 28% of the patients; as such, no sensitivity analysis was performed for patients with CD33 positive only, and the EGP was unable to explore this parameter.

Given the limitations of the submitted economic model, pERC concluded that, based on the sponsor's economic analysis and at the submitted price, gemtuzumab ozogamicin in combination with daunorubicin and cytarabine may be considered cost-effective compared with daunorubicin and cytarabine in adult patients with previously untreated, de novo CD33-positive AML, except APL, who have good performance status and favourable, intermediate, and unknown cytogenetics (using the ELN 2017 risk classification).

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Number of patients eligible to be treated with gemtuzumab ozogamicin and the extent of market expansion most influence the budget impact

The factors that most influence the budget impact include the number of patients eligible to be treated with gemtuzumab ozogamicin and the extent of market expansion. Both the CGP and the EGP considered the market share of year 1 to year 3 to be underestimated. As a result, an alternative market share was used by the EGP and this yielded a higher budget impact over a three-year period compared with the sponsor's estimate. The budget impact included all patients regardless of cytogenetic risk and no scenario analysis excluding patients with adverse cytogenetics was requested or performed by the EGP (nine per cent of patients in ALFA-0701 had adverse cytogenetics).

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 CADTH's 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. Catherine Moltzan and Dr. Michael Crump, who were not present for the meeting
- Dr. Maureen Trudeau, who was excluded from voting due to her position as 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 gemtuzumab ozogamicin for AML, through their declarations, one member had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, this member was not 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*.

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.

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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 daunorubicin (or idarubicin) and cytarabine are used for induction and high-dose cytarabine is used for consolidation for AML. The comparator in the ALFA-0701 trial was anthracycline and cytarabine in both the induction and consolidation phases. As cytarabine consolidation is the current standard of care, PAG is seeking information on gemtuzumab ozogamicin in combination with and comparing with high-dose cytarabine (HiDAC) consolidation. • FLAG-IDA is also available in some jurisdictions. 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. As some patients in the ALFA-0701 trial were FLT3-ITD status positive, for patients with FLT3-mutated AML, PAG is seeking comparative information on gemtuzumab ozogamicin versus midostaurin (both with combination chemotherapy).	• According to the CGP, there is no strong evidence that daunorubicin is required in any consolidation cycles. As a result, the CGP believe that it is unlikely that Canadian leukemia centres will follow the exact consolidation chemotherapy template followed in the ALFA-0701 trial. pERC noted that in Canada, HiDAC is commonly given as an outpatient regimen (as a single drug) in consolidation cycles and that the CGP does not see this practice difference as an impediment to adopting gemtuzumab ozogamicin into regular practice. The CGP foresees that gemtuzumab ozogamicin in combination with single-agent HiDAC consolidation therapy for two cycles would offer comparable outcomes. However, if a third cycle of HiDAC consolidation were to be given, the CGP recommends that gemtuzumab ozogamicin not be included in this third consolidation cycle, given the absence of data supporting the addition of gemtuzumab ozogamicin beyond one cycle of induction and two cycles of consolidation chemotherapy. As a result, pERC believe it would be reasonable to allow for HiDAC consolidation therapy for two cycles. • The safety and efficacy of gemtuzumab ozogamicin in combination with midostaurin is unknown. Registered clinicians noted that there is no data to support using gemtuzumab ozogamicin in combination with midostaurin and chemotherapy for patients with newly diagnosed FLT3-mutated AML. Therefore, pERC agreed with the CGP to recommend against the addition of gemtuzumab ozogamicin to midostaurin for the management of untreated FLT3-mutated AML.

Patient Eligibility
• PAG is seeking guidance on whether the addition of gemtuzumab ozogamicin is appropriate for the following:
  • Patients < 15 or > 70 years of age
  • Patients with t-AML
  • In combination with other treatments (e.g., FLAG-IDA, idarubicin, high-dose cytarabine, or azacitidine)
  • In combination with midostaurin along with combination chemotherapy for patients with newly diagnosed FLT3-mutated AML
	• pERC noted that the eligibility criteria in the ALFA-0701 was patients who were 50 to 70 years old; however, that the approved Health Canada indication is for adult patients. pERC agreed with the CGP that for patients aged 70 years and older with an absence of adverse cytogenetics, they should be eligible for gemtuzumab ozogamicin. Given the Health Canada–approved indication is for adult patients, pERC did not recommend gemtuzumab ozogamicin for patients under 18 years of age. pERC considered this out of scope but acknowledged the COG AML 0531 trial, which examined the safety and efficacy of gemtuzumab ozogamicin in children and young adults using a different chemotherapy regimen.
	• pERC noted that t-AML patients were not included in ALFA-0701. The CGP believed that in patients who have received previous systemic chemotherapy, it would seem plausible that there is a heightened risk of hepatic VOD after gemtuzumab ozogamicin exposure. Registered clinicians expressed uncertainty in extending the use of gemtuzumab ozogamicin to patients with t-AML.
	• pERc noted that the CGP sees daunorubicin and idarubicin as interchangeable as the anthracycline drug that is used in

• Patients with CD33-negative AML • If recommended for reimbursement, PAG noted that the following groups of patients would need to be addressed on a time-limited basis: • Patients who have already initiated or completed induction chemotherapy • Patients who have already initiated consolidation • There is a potential for indication creep to patients who are not receiving induction chemotherapy. PAG is seeking information on the use of gemtuzumab ozogamicin in patients who are undergoing re-induction and consolidation, recognizing this may be out of scope of the current review of gemtuzumab ozogamicin for previously untreated, de novo CD33-positive AML. There is also a potential for indication creep of gemtuzumab ozogamicin, particularly for older patients in the relapsed setting as a single agent for CD33-positive AML.	remission induction regimens; as a result, the CGP recommends that cytarabine in combination with either daunorubicin or idarubicin be used. In contrast, the CGP noted that the safety and efficacy of gemtuzumab ozogamicin in combination with other induction regimens (e.g., FLAG-IDA, anthracycline combined with HiDAC, or azacitidine) is very limited. As a result, the CGP does not recommend that gemtuzumab ozogamicin be added to other treatments for the management of untreated AML. pERC agreed that cytarabine in combination with either daunorubicin or idarubicin may be used, and that gemtuzumab ozogamicin in combination with other treatments (e.g., FLAG-IDA, anthracycline combined with HiDAC, or azacitidine) is not recommended. • pERC noted that less than one per cent of patients were known be CD33 negative in ALFA-0701 and that CD33 status was not available (unknown) for more than a quarter of patients. As well, pERC noted that CGP stated that at diagnosis, CD33 is expressed in the majority (more than 90%) of cases of AML and that patients who are proven to be CD33 negative at time of diagnosis are unlikely to derive clinically meaningful benefit from the addition of gemtuzumab ozogamicin. Therefore, pERC agreed with the CGP to recommend against the use of gemtuzumab ozogamicin in this setting. • Regarding patients who have already initiated or completed induction chemotherapy or patients who have already initiated consolidation, pERC noted that the CGP recognize that this is a rare situation and that an individualized discussion and decision would need to take place. • pERC agreed with the CGP that re-challenge (undergoing re-induction and consolidation) with a gemtuzumab ozogamicin-based regimen would not be recommended based on the lack of data of the benefit of gemtuzumab ozogamicin in the setting of patients with relapsed or refractory AML. According to registered clinicians, in general, clinicians also did not support the use of single-agent gemtuzumab ozogamicin in the front-line setting; therefore, pERC does not recommend the use of single-agent gemtuzumab ozogamicin in this setting.
Implementation Factors • The recommended dose of gemtuzumab ozogamicin is 3 mg/m^2 (up to a maximum dose of one 4.5 mg vial), the maximum of one vial is an enabler to implementation and there would be minimal wastage. • Gemtuzumab ozogamicin is an intravenous drug that is an add-on to current induction and consolidation treatment with intravenous chemotherapy. • PAG noted that gemtuzumab ozogamicin is administered by intravenous infusion over two hours and would be administered in hospital and in the clinic setting as induction is administered as an in-patient and consolidation chemotherapy may be administered as an in-patient for older patients. Consolidation chemotherapy, for	• pERC noted that the maximum of one vial is an enabler to implementation and there would be minimal wastage. • pERC agreed with PAG that gemtuzumab ozogamicin is an add-on to current induction and consolidation treatment with intravenous chemotherapy. • pERC acknowledged that there would be additional chemotherapy chair utilization time, increased pharmacy preparation time, and increased nursing resources, as well as a need for monitoring and supportive care resources for hepatotoxicity and hematological toxicities. • pERC agreed with PAG that given the complexity of AML, gemtuzumab ozogamicin will likely only be administered in treatment centres where clinicians have experience with AML practice.

most adults, is administered as an outpatient. This would be a barrier as there would be additional chemotherapy chair utilization time, increased pharmacy preparation time, and increased nursing resources. Additional chair time for infusion and monitoring may be an issue, especially when given the same day as high-dose cytarabine, which is a three-hour infusion. PAG also noted that light exposure must be minimized during drug preparation. Monitoring and supportive care resources would be required for hepatotoxicity and hematological toxicities. Defibrotide is not available in all jurisdictions in the event of VOD. • PAG noted that given the complexity of AML, gemtuzumab ozogamicin will likely only be administered in treatment centres where clinicians have experience with AML practice.	

Sequencing and Priority of Treatments
• PAG is seeking guidance on:
  • For patients with FLT3-positive mutation AML, whether there is a preference for gemtuzumab ozogamicin or midostaurin, or if patients should receive both?
  • What clinical scenarios would gemtuzumab ozogamicin or chemotherapy alone be the preferred treatment option?
  • What treatment options would be available to patients upon progression on gemtuzumab ozogamicin?
	• pERC agreed with the CGP recommendation that the decision to use one of either gemtuzumab ozogamicin or midostaurin should be individualized.
	• pERC noted that chemotherapy alone may be preferred treatment option for patients with adverse cytogenetics, as acknowledged in the registered clinician input.
	• pERC agreed with registered clinicians that upon progression on gemtuzumab ozogamicin, treatment options available to patients would include those that are already currently available, such as salvage chemotherapy and allogeneic stem cell transplant.

Companion Diagnostic Test • CD33 positivity and cytogenetics testing is completed in all jurisdictions.	• pERC agreed that cytogenetic testing status is required prior to initiating treatment with gemtuzumab ozogamicin. The Committee noted that cytogenetics testing is available in all jurisdictions; however, it was also noted that variation in the timing of the results of the testing exists. As a result, pERC noted that it would be ideal for jurisdictions to have cytogenetic testing done in a timely fashion.

ALFA = Acute Leukemia French Association; AML = acute myeloid leukemia; CGP = Clinical Guidance Panel; FLAG-IDA = fludarabine, idarubicin, granulocyte-colony stimulating factor, and high-dose cytarabine; FLT3 = FMS-like tyrosine kinase 3; HiDAC= high-dose cytarabine; ITD = internal tandem duplications; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; t-AML = therapy-related acute myeloid leukemia; VOD = veno-occlusive disease.