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:
Inotuzumab ozogamicin (Besponsa)

Submitted Reimbursement Request:
For the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Submitted by:
Pfizer Canada Inc.

Manufactured by:
Pfizer Canada Inc.

NOC Date:
March 15, 2018

Submission Date:
November 13, 2017

Initial Recommendation Issued:
May 3, 2018

Approximate drug costs per patient per month (28 days) Submitted list price of $14,405.85 per 0.90 mg vial	Inotuzumab ozogamicin costs: • Cycle 1: $2,743.97 per day or $57,623.40 per 21-day course • Cycle 2 onward: $1,543.48 per day or $43,217.55 per 28-day course • Cycle 2 onward for patients who did not achieve complete response (CR): $2,057.98 per day or $57,623.40 per 28-day course Note: Costs are calculated based on an average body surface area of 1.7 m^2 and accounting for wastage.

pERC RECOMMENDATION	pERC conditionally recommends the reimbursement of inotuzumab ozogamicin (Besponsa) for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) only if the following condition is met: • cost-effectiveness being improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of inotuzumab ozogamicin. Eligible patients should have a good performance status. Treatment should be continued until unacceptable toxicity or disease progression, up to a maximum of three cycles, for those patients proceeding to hematopoietic stem cell transplant (HSCT). For patients not proceeding to HSCT who achieve a complete response or complete response with incomplete count recovery (CR/CRi) and minimal residual disease negativity, treatment may be continued for a maximum of six cycles. pERC made this recommendation because it was satisfied that, compared with chemotherapy, inotuzumab ozogamicin demonstrated an overall net clinical benefit based on a clinically meaningful improvement in progression-free survival (PFS), moderate but acceptable toxicity profile, and no detriment to overall quality of

	life (QoL). However, pERC acknowledged that there was not a statistically significant difference in overall survival (OS) between inotuzumab ozogamicin and chemotherapy. pERC was uncertain as to how inotuzumab ozogamicin compares with blinatumomab with regard to outcomes important to decision-making such as OS, PFS, and QoL due to a lack of robust direct or indirect efficacy data. pERC also concluded that inotuzumab ozogamicin aligns with patient values in that it offers an option for improvement in PFS and has no detriment in overall QoL. pERC concluded that, at the submitted price, inotuzumab ozogamicin could not be considered cost-effective compared with chemotherapy and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. pERC noted that there was considerable uncertainty in the cost-effectiveness estimates of inotuzumab ozogamicin compared with blinatumomab due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there was a net clinical benefit with inotuzumab ozogamicin in patients with relapsed/refractory ALL, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve cost-effectiveness to an acceptable level. **Wastage and Budget Impact Likely to Affect Adoption Feasibility** pERC noted that the number of vials needed per patient (which depends on the extractable amount per vial and the body surface area of a patient) is a key driver of the budget impact. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation. **Time-Limited Need for Inotuzumab Ozogamicin for Patients Who Are Currently Receiving Treatment With Combination Chemotherapy as Second or Later Salvage Therapy** At the time of implementing a reimbursement recommendation for inotuzumab ozogamicin, jurisdictions may consider addressing the time-limited need of inotuzumab ozogamicin for those patients who are currently receiving treatment with combination chemotherapy as second or later salvage therapy. pERC noted that this time-limited access should be for patients who would otherwise meet the reimbursement criteria. **Optimal Sequencing of Inotuzumab Ozogamicin and Other Available Therapies** pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of inotuzumab ozogamicin and other available treatments for relapsed/refractory B-cell precursor ALL, and therefore optimal sequencing is unknown. The Committee acknowledged that there is no direct evidence investigating the efficacy and safety nor the appropriate sequence for inotuzumab ozogamicin with other available therapies (e.g., blinatumomab) for treatment-relapsed/refractory ALL patients. Upon implementation of reimbursement of inotuzumab ozogamicin, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing and a collection of shared outcomes would be of value.

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

Approximately 15% of adult cases of acute leukemia involve ALL. Patients who present with an increased white blood cell count and those over age 34 are at higher risk of adverse outcomes. In contrast to upfront treatment, there is no standard treatment for patients with relapsed/refractory B-cell precursor ALL. The prognosis for these patients is poor, and prolonged survival is rare for those who fail to achieve remission with salvage chemotherapy. Treatment options for second-line relapsed or refractory treatment include combination chemotherapy not used in upfront treatment (e.g., hyper-CVAD, FLAG, cytarabine with mitoxantrone or HIDAC, among others) to achieve remission and, if possible, proceed to potentially curative HSCT in consolidation of remission. Patients who fail re-induction or for whom HSCT is not feasible due to comorbidities or lack of a donor have no curative options and are treated with palliative intent. Blinatumomab was recently recommended by pERC for reimbursement conditional on the cost-effectiveness being improved; however, at this time, no jurisdictions are currently reimbursing this therapy in the first relapsed or refractory setting. However, some jurisdictions are currently reimbursing blinatumomab in the third-line (for second relapse) and beyond setting. Survival of this small cohort of relapsed/refractory patients is limited. Therefore, there is a continued need for effective treatment options that prolong patients' survival.

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

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

pERC deliberated upon the results of one phase III, multi-centre, open-label randomized controlled trial, INO-VATE ALL. The trial assessed the efficacy and safety of inotuzumab ozogamicin compared with investigator's choice of chemotherapy (i.e., either FLAG or cytarabine with mitoxantrone or HIDAC) in patients with relapsed/refractory ALL. The Committee acknowledged that a multi-centre, international phase III randomized controlled trial was conducted despite the small number of relapsed/refractory ALL patients. pERC noted that there was a clinically meaningful and statistically significant improvement in CR/CRi and PFS for patients treated with inotuzumab ozogamicin compared with chemotherapy. pERC discussed that the difference in median OS of inotuzumab ozogamicin compared with chemotherapy was not statistically different after adjustments for multiple statistical tests of the trial outcomes. However, pERC acknowledged the profound difference in the Kaplan–Meier OS curves over time, noting that the curves separate at approximately month 14 and continue to separate beyond that time point, suggesting a favourable OS benefit later in treatment after month 14. However, pERC noted that the long-term benefit of inotuzumab ozogamicin is uncertain due to the short period of trial follow-up. pERC also noted that a greater proportion of patients in the inotuzumab ozogamicin group received therapy with HSCT compared with the chemotherapy group. The Committee discussed that this may be due to the fact that more patients in the inotuzumab ozogamicin group achieved CR/CRi and then subsequently proceeded to potentially curative HSCT. pERC agreed that there is uncertainty about whether the difference in HSCT rates between the groups explains the longer survival after 14 months observed in the inotuzumab ozogamicin group. Furthermore, the Committee considered that not all patients who received inotuzumab ozogamicin proceeded to potentially curative HSCT. Thus, pERC agreed that the long-term benefit of inotuzumab ozogamicin for transplant-ineligible patients is less certain.

pERC deliberated on the toxicity profile of inotuzumab ozogamicin. The most common grade 3 to 4 adverse events reported among patients receiving inotuzumab ozogamicin were thrombocytopenia and febrile neutropenia. The Committee noted that, overall, the toxicity profile was similar between the two groups. However, pERC discussed the fact that that hepatic venoocclusive disease was more common in patients treated with inotuzumab ozogamicin who had undergone HSCT previously or who went on to receive HSCT following treatment with inotuzumab ozogamicin. pERC concluded that the side effects of inotuzumab are moderate, but manageable through appropriate monitoring and dose adjustments.

pERC discussed the QoL data collected in the INO-VATE ALL trial. The Committee noted that QoL data were only collected when patients were receiving treatment in the trial. pERC considered that, overall, there were no differences observed in QoL in patients receiving inotuzumab ozogamicin compared with

chemotherapy. However, pERC noted that for some subcategories of QoL, patients in the inotuzumab ozogamicin group appeared to have improved physical, social, and role functioning compared with the chemotherapy group. Overall, pERC concluded that there is a net clinical benefit of inotuzumab compared with chemotherapy based on the statistically significant and clinically meaningful improvement of CR/CRi and PFS, the manageable but not insignificant toxicity profile, and the lack of detriment to overall QoL during treatment.

pERC considered the comparison with chemotherapy in the INO-VATE ALL trial to be reasonable in this setting, but also discussed the results of an indirect treatment comparison (ITC) provided by the submitter that compared inotuzumab ozogamicin with blinatumomab, a relevant therapy in the relapsed setting. The Committee discussed the pCODR Methods Team's critical appraisal of the ITC and agreed with the Methods Team that there are a number of methodological limitations including but not limited to substantial differences in patient populations and potential confounders that were not adjusted for in the analysis, making the results difficult to interpret. The Committee noted that the pCODR Methods Team and Clinical Guidance Panel (CGP) concluded that the analysis was considered only hypothesis-generating. pERC also considered input from the registered clinicians that inotuzumab ozogamicin has a higher response rate compared with blinatumomab, but pERC noted that this was based on an indirect comparison of clinical trials with different populations and potential confounders. The registered clinicians also noted that inotuzumab ozogamicin may be more favourable as it is easier to administer in the outpatient setting compared with blinatumomab, has no reported incidence of cytokine-release syndrome, and allows both Philadelphia chromosome (Ph)-positive and Ph-negative karyotypes to be treated. Overall, based on the lack of a direct head-to-head comparison of inotuzumab ozogamicin and blinatumomab and the limitations of the ITC submitted to pCODR, pERC concluded that while inotuzumab ozogamicin may be easier to administer, there is considerable uncertainty on how inotuzumab ozogamicin compares with blinatumomab with regard to outcomes important to decision-making such as OS, PFS and QoL.

pERC deliberated on patient input from one patient advocacy group. Patient input indicated that patients value new, effective treatment options that offer fewer side effects, symptom control, and improved QoL. The Committee discussed that toxicities associated with current treatments are difficult for both patients and caregivers. pERC considered the impact ALL has on both the patients and their caregivers and recognized that this disease affects younger adults and often significantly disrupts daily work activities and family duties. While patient input did not include patients who had direct experience with inotuzumab ozogamicin, the Committee noted that patients treated with inotuzumab ozogamicin in the INO-VATE ALL trial appeared to have no detriment to overall QoL and some observed improvement in physical, social and role functioning during treatment. Overall, pERC agreed that inotuzumab ozogamicin aligns with patient values in that it is an effective treatment option, has manageable toxicities, causes no detriment to overall QoL and some improvement in physical, social and role functioning during treatment.

pERC deliberated on the cost-effectiveness of inotuzumab ozogamicin compared with chemotherapy and compared with blinatumomab based on the submitted economic evaluation and the reanalysis estimate provided by the pCODR Economic Guidance Panel (EGP). pERC noted that the following factors had an impact on the incremental cost-effectiveness ratio (ICER): drug acquisition costs, time horizon, extractable amount of drug per vial, patient's body surface area (BSA), extrapolation of survival, utility values for adverse events and progression states, and attributing costs to every patient receiving treatment. The Committee noted that the factors that most influenced the incremental costs were drug cost, BSA, and extractable amount of drug per vial, while the incremental effect was most influenced by time horizon and survival extrapolation. pERC discussed the fact that the extrapolation of short-term trial data was a main source of uncertainty in the economic analysis and that the clinical assumptions in the submitted model may have overestimated the long-term benefit anticipated with the use of inotuzumab ozogamicin. pERC considered that the survival benefit of inotuzumab ozogamicin appears to be later on in treatment. However, the Committee was uncertain whether the survival benefit was due to treatment with inotuzumab ozogamicin alone or due to the fact that more patients received potentially curative HSCT. Furthermore, the Committee noted that not all patients who received inotuzumab ozogamicin proceeded to potentially curative HSCT. Thus, the long-term benefit of inotuzumab ozogamicin for transplant-ineligible patients is less certain. The Committee also agreed with the EGP and the CGP that a shorter time horizon was more clinically plausible in a relapsed/refractory patient population. Overall,

pERC agreed with the EGP's best estimate of the probabilistic ICER when compared with chemotherapy and blinatumomab. Therefore, pERC concluded that, compared with chemotherapy, inotuzumab ozogamicin at the submitted price is not cost-effective and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. pERC cautioned that there was considerable uncertainty in the cost-effectiveness estimates of inotuzumab ozogamicin and blinatumomab due to the lack of robust direct or indirect comparative effectiveness data in the submitted model. The Committee also noted the considerably high costs of both inotuzumab ozogamicin and blinatumomab. pERC noted that the considerable uncertainty in the model parameters, including the comparative effectiveness data, is demonstrated by the change in direction of the EGP's reanalysis of the probabilistic ICER compared with the submitter's base case. The Committee concluded that inotuzumab ozogamicin is not cost-effective and, to offset the considerable uncertainty in the clinical effect estimates, a substantial reduction in drug price would be required.

pERC considered the feasibility of implementing a reimbursement recommendation for inotuzumab ozogamicin. Overall, pERC noted that the EGP identified a number of key limitations in the budget impact analysis, which may underestimate the budget impact. The factors that most influence the budget impact include the number of vials needed per patient (which depends on the extractable amount per vial and the BSA of a patient) and the market share. pERC also discussed the potential need for more cycles of treatment with inotuzumab ozogamicin when a patient is waiting for HSCT. Given that the maximum number of cycles allowed for patients undergoing HSCT is three, the Committee noted that jurisdictions should consider resource availability and the potential need for additional cycles of inotuzumab ozogamicin after achieving a CR/CRi to ensure a patient remains in remission while awaiting transplant, which may affect the budget impact significantly.

The Committee discussed input from the Provincial Advisory Group (PAG) that requested guidance and clarification on clinical scenarios to assist with the implementation of inotuzumab ozogamicin. In summary, pERC discussed that the majority of the subgroups of patients in the INO-VATE ALL trial appeared to benefit from treatment with inotuzumab ozogamicin. Therefore, pERC agreed with the CGP that patients with high-risk features and those with more advanced disease — including but not limited to first relapse, second relapse, primary refractory, and relapse after a stem cell transplant — should be eligible for treatment with inotuzumab ozogamicin. pERC also recognized that there may be a time-limited need for inotuzumab ozogamicin for those patients who are currently receiving treatment with combination chemotherapy as second or later salvage therapy.

pERC also discussed that, compared with blinatumomab, the use of inotuzumab ozogamicin is more favourable because infusion time is shorter and it can be administered in the outpatient setting. pERC also noted that the time and hospital resources required to prepare and administer inotuzumab ozogamicin are significantly less compared with the preparation and administration of blinatumomab. Furthermore, pERC considered that inotuzumab ozogamicin has no reported incidence of cytokine-release syndrome. However, the Committee noted that there is the potential for venoocclusive disease, especially for patients who proceed to HSCT. The Committee discussed the high costs of both inotuzumab ozogamicin and blinatumomab and noted that, in the absence of more robust evidence, the choice between inotuzumab ozogamicin and blinatumomab will likely depend on the relative overall cost, treatment availability, patient values and preferences, and clinical factors, such as tolerability to adverse events. However, pERC noted that drug wastage is a significant concern because it is unlikely that vials can be shared due to the small number of relapsed/refractory ALL patients and because not all of the drug will be extractable from the vial.

Finally, pERC discussed PAG's request about the preferred sequencing of available treatments in the relapsed/refractory ALL setting. pERC noted that there is currently no clinical trial evidence to inform optimal sequencing of inotuzumab ozogamicin and other available treatments for relapsed/refractory ALL. pERC agreed that treatment with inotuzumab ozogamicin will likely be used as an option after first relapse on upfront chemotherapy or second relapse. The Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor on the appropriate sequence for inotuzumab ozogamicin with other available therapies (e.g., blinatumomab) for the treatment of relapsed/refractory ALL patients. Upon implementation of reimbursement of inotuzumab ozogamicin, pERC recognized that

collaboration among provinces to develop a national, uniform approach to optimal sequencing and shared outcomes would be of value.

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 manufacturer's economic model and budget impact analysis (BIA)
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of inotuzumab ozogamicin (Besponsa) for the treatment of adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL).

Studies included: Randomized phase III trial

The pCODR systematic review included one phase III randomized controlled trial, INO-VATE ALL. Patients (n = 326) were randomized to receive inotuzumab ozogamicin or the investigator's choice of chemotherapy. The primary end points of the trial were complete remission/incomplete hematologic recovery (CR/CRi), as assessed by the independent external Endpoint Adjudication Committee, and overall survival (OS). Patients who achieved a response to treatment and who had a suitable donor may have undergone stem cell transplantation at the discretion of the investigator and were followed for disease progression and survival.

The pCODR review also provided contextual information on a critical appraisal of an indirect treatment comparison of inotuzumab ozogamicin compared with blinatumomab.

Patient populations: Majority of patients were under 55 years and were in their first relapse

pERC noted that baseline characteristics were well balanced across treatment groups. Among all randomized patients, the median age was 47 years, with more than 60% of patients under the age of 55. More than 60% of patients were in their first relapse. Pre-study stem cell transplant was similar in both groups (17.7% in the inotuzumab ozogamicin group versus 18.2% in the chemotherapy group).

Key efficacy results: Statistically significant and clinically meaningful differences in complete response, progression-free survival; no difference in median overall survival

The key efficacy outcomes deliberated on by pERC were CR/CRi, progression-free survival (PFS), and OS.

Complete response was a co-primary end point in the trial. At the pre-specified final analysis, the rate of CR/CRi was higher in the inotuzumab ozogamicin group (80.7%) when compared with the chemotherapy group (29.4%), which was statistically significant (mean difference, 51.4%; $P < 0.001$). The median duration of remission was 4.6 months in the inotuzumab ozogamicin group and 3.1 months in the chemotherapy group.

PFS was a key secondary outcome. The trial reported PFS using two definitions. Using the definition of PFS in the trial (including treatment discontinuation due to global deterioration of health status and starting new induction therapy or post-therapy hematopoietic stem cell transplant [HSCT] without achieving CR/CRi), the stratified hazard ratio of PFS when comparing inotuzumab ozogamicin to chemotherapy was 0.45 (97.5% confidence interval [CI], 0.336 to 0.602; $P < 0.0001$). The median PFS was longer in the inotuzumab group than in the chemotherapy group (5 months versus 1.7 months). The common definition of PFS (without treatment discontinuation due to global deterioration of health status and starting new induction therapy or post-therapy HSCT without achieving CR/CRi) was also reported.

However, the effect size of PFS using the common definition was smaller compared with the PFS analysis using the protocol definition, stratified hazard ratio 0.568 (97.5% CI, 0.401 to 0.804; *P* = 0.0001).

OS was a co-primary end point. At the pre-specified final analysis, the median OS was 7.7 months in the inotuzumab ozogamicin group and 6.7 months in the chemotherapy group. The stratified hazard ratio of death was 0.77 (97.5% CI, 0.578 to 1.026; one-sided *P* = 0.0203, two-sided *P* = 0.04). pERC noted that the *P* value of the final analysis did not reach the pre-specified level of efficacy at one-sided *P* = 0.0111 or two-sided *P* = 0.02081. An updated analysis of OS was performed at a later data cut-off. The median survival at the updated OS analysis was 7.7 months in the inotuzumab ozogamicin group and 6.2 months in the chemotherapy group; stratified hazard ratio of death was 0.751 (97.5% CI, 0.568 to 0.993; one-sided *P* = 0.0105). pERC noted that this analysis was not included in the multiplicity adjustment, and therefore it was unclear whether the *P* value reached the efficacy boundary after multiplicity adjustment. However, pERC noted that the Kaplan–Meier curve showed a more profound difference between the treatment groups after month 14, suggesting a favourable long-term effect of inotuzumab ozogamicin. The Committee also noted that more patients in the inotuzumab ozogamicin group (47%) proceeded to HSCT after treatment compared with the chemotherapy group (20%).

Limitations: No direct comparison between inotuzumab and blinatumomab

pERC noted that the comparison with chemotherapy in the INO-VATE ALL trial was reasonable in this setting, but also discussed the results of an indirect treatment comparison (ITC) provided by the submitter that compared inotuzumab ozogamicin with blinatumomab, a relevant therapy in the relapsed setting. The ITC demonstrated that a greater number of patients receiving inotuzumab ozogamicin had CR/CRi and had proceeded to a stem cell transplant compared with blinatumomab. However, there were no significant differences in event free survival or OS. The Committee discussed the pCODR Methods Team's critical appraisal of the ITC and noted, in agreement with the pCODR Methods Team, that there are a number of methodological limitations, including but not limited to substantial differences in patient populations and potential confounders that were not adjusted for in the analysis, making the overall conclusions difficult to interpret. The Committee noted that the pCODR Methods Team and Clinical Guidance Panel (CGP) concluded that the analysis was considered only hypothesis-generating. Based on the lack of a direct head-to-head comparison of inotuzumab ozogamicin and blinatumomab and the limitations of the ITC submitted to pCODR, pERC concluded that there is considerable uncertainty on how inotuzumab compares with blinatumomab with regard to outcomes important to decision-making such as OS, PFS, and quality of life (QoL).

Patient-reported outcomes: No clinically meaningful differences in global health status score between the two treatment groups

Patient-reported outcomes were measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), v3.0, and the EuroQoL 5-Dimensions questionnaire three-level version (EQ-5D-3L). Patient-reported outcomes were collected from patients in each treatment arm during the treatment cycle period only. A change of 5 to 10 points in the EORTC QLQ-C30 and a change of more than 0.08 in the EQ-5D-3L were considered estimates of minimally important clinical differences in QoL.

The completion rates of at least one question in the EORTC QLQ-C30 and EQ-5D were higher in the inotuzumab ozogamicin group (85%) than in the chemotherapy group (65%). There was no difference in the EORTC QLQ-C30 overall global health status score in the inotuzumab ozogamicin group compared with the chemotherapy group (62.1 versus 57.8). Furthermore, there was no difference in the EQ-5D-3L index in the inotuzumab ozogamicin group compared with the chemotherapy group (0.80 versus 0.76). However, in three subcategories of the EORTC QLQ-C30, there were clinically meaningful differences (a change of more than 5 points) including physical functioning (75.0 versus 68.1), role functioning (64.7 versus 53.4), and social functioning (68.1 versus 59.8) in the inotuzumab ozogamicin group compared with the chemotherapy group.

Safety: Moderate but manageable toxicities, with increased risk of venoocclusive disease in patients treated with inotuzumab ozogamicin compared with chemotherapy

pERC noted that more patients in the chemotherapy group (96.5%) than in the inotuzumab ozogamicin group (89.6%) experienced a grade 3 or 4 all-cause adverse event (AE). The most common grade 3 and 4 hematological AEs in patients receiving inotuzumab ozogamicin were neutropenia (47%),

thrombocytopenia (40.9%), and febrile neutropenia (26.8%). The most common grade 3 and 4 hepatotoxicity AEs in patients receiving inotuzumab ozogamicin were venoocclusive liver disease (11%) and hyperbilirubinemia (6.1%). The most common grade 3 and 4 infection AEs in patients receiving inotuzumab ozogamicin were pneumonia (6.1%), bacteremia (3.7%), and neutropenic sepsis (3%). More patients died due to all-cause AEs in the inotuzumab ozogamicin group (15.9%) than in the chemotherapy group (11.2%).

Need and burden of illness: No standard of care; survival of relapsed/refractory ALL is limited

pERC noted that in contrast to initial treatment, where the standard approach is pediatric-inspired chemotherapy protocols, there is no standard treatment for patients with relapsed or refractory ALL. In general, patients receive an intensive chemotherapy regimen to induce a remission and, if possible, proceed to an allogeneic HSCT. Multi-drug chemotherapy regimens appropriate in the Canadian setting may include but are not limited to hyper-CVAD, FLAG-IDA, or Cy VP16. Patients who fail reinduction or for whom HSCT is not feasible due to comorbidities or lack of a donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited.

Registered clinician input: Need for effective treatments; more patients proceed to HSCT when treated with inotuzumab ozogamicin compared with chemotherapy

pERC noted that the registered clinician input acknowledged that the current treatment for relapsed ALL is retreatment with the multi-drug chemotherapy regimens used in the first line and that the regimens are quite toxic and often ineffective. Thus, there is a need for more effective treatments. The clinicians providing input noted that the benefits of inotuzumab ozogamicin include the high rate of response and complete response and the ability to deliver a better remission (less minimal residual disease) that is longer compared with multi-drug chemotherapy. They also noted that the toxicities associated with inotuzumab ozogamicin are toxic, but manageable. The registered clinicians acknowledged that, while there was no difference in median survival in the two treatment groups, there was a significant OS benefit with the appearance of a survival plateau approximately 15% higher when compared with standard chemotherapy. They noted that this may be due to the fact that more patients will go on to receive a potentially curative HSCT.

PATIENT-BASED VALUES

Experiences of patients with acute lymphoblastic leukemia: High symptom burden, current therapies have high toxicities

According to the Leukemia and Lymphoma Society of Canada (LLSC), common symptoms of ALL include fever, increased risk of infection, shortness of breath, chest pain, cough and vomiting, increased tendency to bleed, anemia, fatigue, and headache. Patient input noted that physical symptoms experienced by patients with ALL often disrupt daily routines and that everyday routines become more challenging. According to LLSC, ALL patients also experience anxiety, stress, depression, and feelings of being overwhelmed. As well, caregivers experience disruptions in daily routine and daily activities as a result of caring for a patients with ALL.

Patient values on treatment: New, effective treatment options, symptom and disease control, improvement in quality of life

Patient input indicated that patients value new, effective treatment options that offer fewer side effects, symptom control, and improved QoL. The patient group also noted that since the survival rate of ALL is low, management of symptoms such as fatigue and pain are valued. Treatment expectations for patients, as reported by LLSC, include treatments that control fatigue and pain. Furthermore, they noted that new treatments should not adversely impact QoL. pERC noted the impact of this disease on both the patients and their caregivers, acknowledging that this particular disease affects younger adults and can significantly disrupt daily work activities and family duties. According to survey data reported, none of the patients or caregivers surveyed had knowledge of or experience with inotuzumab ozogamicin. Overall, pERC noted that inotuzumab ozogamicin aligns with patient values in that it offers improvement in CR/CRi and PFS, has manageable toxicities, and has no detriment to overall QoL and may improve physical, social and role functioning during treatment.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis comparing inotuzumab ozogamicin (Besponsa) to standard of care (represented by chemotherapy with hyper-CVAD) for patients with ALL. An alternative scenario comparing inotuzumab ozogamicin to blinatumomab (Blincyto) was also submitted.

Basis of the economic model: State transition Markov model

The Pharmacoeconomic model used was a state transition Markov model. Patients enter the model in the health state "stable disease" and can either remain in that health state, experience disease progression, achieve CR/CRi, and proceed to HSCT or die. Patients who experience disease progression remain in that health state until they die.

Costs considered in the analysis were drug costs, drug administration costs, hospitalization costs, HSCT costs, and AE costs.

The Committee noted that the trial definition of PFS was different from the common definition of PFS, which was noted as a limitation to the model structure. This limitation may impact the decision to use different utility values for progression in the post-HSCT state.

Drug costs: High cost of inotuzumab ozogamicin

Inotuzumab ozogamicin costs $14,405.85 per 0.9 mg vial. At the recommended dose of 1.8 mg/m^2 for cycle 1, with a body surface area (BSA) of 1.7 m^2, the cost of inotuzumab ozogamicin is $2,743.97 per day or $57,623.40 per 21-day course. At the recommended dose of 1.5 mg/m^2 for cycle 2 onward for patients who achieved CR with a BSA of 1.7 m^2, the cost of inotuzumab ozogamicin is $1,543.48 per day or $43,217.55 per 28-day course. At the recommended dose of 1.8 mg/m^2 for cycle 2 onward for patients who did not achieve CR with a BSA of 1.7 m^2, the cost of inotuzumab ozogamicin is $2,057.98 per day or $57,623.40 per 28-day course. pERC noted that the costs presented account for drug and vial wastage.

Hyper-CVAD consists of multiple drugs. In the submitted model, the cost of hyper-CVAD is $2,049 per 28-day cycle (average of 1.23 cycles in the INO-VATE ALL trial.) The average cost per patient treated is $2,522.62.

At the list price, blinatumomab costs $2,978.26 per 38.5 mcg vial. Assuming two cycles, the recommended dose of 9 mcg/day for 7 days and then 28 mcg/day for 21 days for cycle 1, and 28 mcg/day for 28 days for cycle 2, the cost of blinatumomab is $1,978.38 per day or $55,394.59 per 28-day course or $83,091.89 per six-week cycle (accounting for drug wastage and administration costs), which is assumed in the submitted model.

Cost-effectiveness estimates: Inotuzumab ozogamicin is not cost-effective compared with chemotherapy at the submitted price; inotuzumab ozogamicin is likely not cost-effective compared with blinatumomab at the submitted price

pERC noted that the submitted base-case incremental cost-effectiveness ratio (ICER) of inotuzumab ozogamicin compared with chemotherapy was $91,840.63 per quality-adjusted life-year (QALY), and further noted that the pCODR EGP's best estimate ranged between $178,800.89 per QALY to $335,752.14 per QALY, with a best guess point estimate of $349,175.02 per QALY based on the probabilistic ICER. pERC noted that the submitted best case ICER of inotuzumab ozogamicin compared with blinatumomab was dominant (cost saving, −$7,642.65), and noted that the pCODR EGP's best estimate for the comparison of inotuzumab ozogamicin and blinatumomab ranged between being dominant (cost saving, −$61,195.10) to $112,898.91 per QALY, with a best guess point estimate of $126,625.47 per QALY based on the probabilistic ICER.

pERC also noted that the following factors had an impact on the ICER: drug acquisition costs, time horizon, extractable amount of drug per vial, patient's BSA, extrapolation of survival, utility values for adverse events and progression states, and attributing costs to every patient receiving treatment. The Committee noted that the factors that most influenced the incremental costs were drug cost, BSA, and extractable amount of drug per vial, while the incremental effect was most influenced by time horizon and survival extrapolation.

Sensitivity analyses (one way and multi-way) were performed on the following parameters to adjust for the limitations in the model, including but not limited to:

- actual number of vials used in the trial
- extractable amount of drug per vial
- extrapolations after trial period using pooled survival after HSCT (parametric Gen gamma) or relative risk (RR) of 10 compared with general population
- attributing costs to every patient entering the model (including those who died in the first cycle, when treatment costs incur in the model)
- adjusted utility values for venoocclusive disease
- unit-cost price reductions
- equal utility values for progression states.

pERC noted that the survival benefit of inotuzumab ozogamicin appears to be later on in treatment. However, the Committee was uncertain whether the survival benefit was due to treatment with inotuzumab ozogamicin or due to the fact that more patients received potentially curative HSCT. Furthermore, the Committee noted that not all patients who received inotuzumab ozogamicin proceeded to potentially curative HSCT. Thus, the long-term benefit of inotuzumab ozogamicin for transplant-ineligible patients is uncertain. pERC noted that the extrapolation of short-term trial data was a main source of uncertainty in the economic analysis. The Committee agreed with the EGP and the CGP that a shorter time horizon was more clinically plausible in a relapsed/refractory patient population. pERC noted that the best guess ICER was generated with the following assumptions: shortening the time horizon to 10 years, use of Kaplan–Meier data for the first 15 months plus pooled fitted curves for extrapolation up to 50 months plus pooled fitted curves for extrapolation after the trial period for HSCT survivors, an average extractable amount of drug of 0.90 mg per vial as per the Health Canada approved indication, an average BSA of 1.7 m^2, the actual average of vials used in the trial, and incurred treatment costs for every patient entering the model (including those who died in the first cycle).

Overall, pERC agreed with the EGP's best estimate of the probabilistic ICER when compared with chemotherapy and blinatumomab. Therefore, pERC noted that, compared with chemotherapy, inotuzumab ozogamicin at the submitted price is not cost-effective and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. pERC cautioned that there was considerable uncertainty in the cost-effectiveness estimates of inotuzumab ozogamicin and blinatumomab due to the use of indirect comparative effectiveness data in the submitted model. There were a number of methodological limitations in the ITC, limiting the overall conclusions on the comparative efficacy of inotuzumab ozogamicin and blinatumomab. pERC noted that the considerable uncertainty in the model parameters is demonstrated by the change in direction of the EGP's reanalysis of the probabilistic ICER compared with the submitted base case.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small population with relapsed/refractory ALL; favourable administration schedule compared with blinatumomab

pERC noted factors that would affect the feasibility of implementing a conditional reimbursement recommendation and that PAG considered important. Overall, pERC noted a number of key limitations in the budget impact analysis, which may underestimate the budget impact. pERC noted that the factors that most influence the budget impact include the number of vials necessary per patient (which depends on the extractable amount per vial and the BSA of the patient) and the market share. pERC also noted the potential need for more cycles of treatment with inotuzumab ozogamicin when a patient is waiting for HSCT. Given that the maximum number of cycles allowed for patients undergoing HSCT is three, the Committee noted that jurisdictions should consider resource availability and the potential need for additional cycles of inotuzumab ozogamicin after achieving a CR/CRi to ensure that a patient remains in remission while awaiting transplant, which may affect the budget impact significantly.

The Committee noted input from the PAG that requested guidance and clarification on clinical scenarios to assist with implementation of inotuzumab ozogamicin. In summary, pERC noted that the majority of the subgroups of patients in the INO-VATE ALL trial appeared to benefit from treatment with inotuzumab ozogamicin. Therefore, pERC agreed with the CGP that patients with high-risk features and those with

more advanced disease (e.g., first relapse, second relapse, primary refractory, and relapse after a stem cell transplant) should be eligible for treatment with inotuzumab ozogamicin. pERC also recognized that there may be a time-limited need for inotuzumab ozogamicin for those patients who are currently receiving treatment with combination chemotherapy as second or later salvage therapy.

pERC also noted that, compared with blinatumomab, the use of inotuzumab ozogamicin is favourable given the shorter infusion times and the fact that the drug can be administered in the outpatient setting. pERC also noted that the time and resources required to prepare and administer inotuzumab ozogamicin are significantly less than those for blinatumomab. However, pERC noted that drug wastage is a significant concern because it is unlikely that vials can be shared due to the small number of relapsed/refractory ALL patients and because of the amount of drug extractable from the vial.

pERC noted that there is currently no clinical trial evidence to inform optimal sequencing of inotuzumab ozogamicin and other available treatments for relapsed/refractory ALL. pERC agreed that treatment with inotuzumab ozogamicin will likely be used as an option after first relapse after upfront chemotherapy or second relapse. The Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor the appropriate sequence for inotuzumab ozogamicin with other available therapies (e.g., blinatumomab) for treatment relapsed/refractory ALL patients. Upon implementation of reimbursement of inotuzumab ozogamicin, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing and shared outcomes would be of value.

DRUG AND CONDITION INFORMATION

Drug Information	• Inotuzumab ozogamicin is available in a 0.90 mg vial. • Recommended dosage of 1.8 mg/m^2 for cycle 1 (day 1=, 0.8 mg/m^2; day 8 and day 15 =0.5 mg/m^2) and 1.5 mg/m^2 for cycle 2 onward, for a maximum of three cycles, to achieve complete response or complete response with incomplete count recovery (CR/Cri) for patients who are proceeding to HSCT. For patients who achieve a CR/CRi and minimal residual disease negativity and are not proceeding to HSCT, treatment may be continued for a maximum of six cycles.
Cancer Treated	• Philadelphia chromosome (Ph)-negative or Ph-positive relapsed/refractory B-cell precursor acute lymphoblastic leukemia
Burden of Illness	• 15% of adult cases of acute leukemia • Significant burden on patients and quality of life • Prognosis of patients is poor
Current Standard Treatment	• Combination chemotherapy (e.g., hyper-CVAD or any chemotherapy not used in upfront therapy) followed by allogeneic HSCT where possible
Limitations of Current Therapy	• Limited impact on long-term prognosis of patients as most patients eventually die of their disease

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)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Craig Earle, who was not present for the meeting
- Cameron Lane, who did not vote due to his role as the patient member alternate.

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 pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of inotuzumab ozogamicin for acute lymphoblastic leukemia, through their declarations, no member had a real, potential, or perceived

conflict. Based on application of the *pCODR Conflict of Interest Guidelines*, none of the members were excluded from voting.

Information sources used

To inform its deliberations, pERC was provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which included input from a patient advocacy group and the 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 pERC 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.

Disclaimer

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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
• Guidance on whether treatment is for patients with first relapse, second relapse, or either	pERC noted that the majority of the subgroups of patients in the INO-VATE ALL trial appeared to benefit from treatment with inotuzumab ozogamicin. Therefore, pERC agreed that patients with high-risk features and those with more advanced disease (e.g., first relapse, second relapse, primary refractory, and relapse after a stem cell transplant) should be eligible for treatment with inotuzumab ozogamicin.
• Guidance on use of inotuzumab ozogamicin in pediatric ALL	• The use of inotuzumab ozogamicin is for relapsed/refractory adult patients. The use of this drug in the pediatric population is out of scope for this review.
• Guidance on use of inotuzumab ozogamicin for patients with Philadelphia chromosome (Ph)-positive ALL	• As per the eligibility criteria of INO-VATE ALL, patients with Ph-positive ALL must have failed treatment with at least one second-generation or third-generation tyrosine kinase inhibitor and standard multi-drug induction chemotherapy before treatment with inotuzumab ozogamicin.
• Guidance on sequencing of therapies	• pERC noted that there is currently no clinical trial evidence to inform optimal sequencing of inotuzumab ozogamicin and other available treatments for relapsed/refractory ALL. pERC agreed that treatment with inotuzumab ozogamicin will likely be used as a second-line option (first relapse) after upfront chemotherapy or second relapse. The Committee acknowledged that there is no direct evidence investigating the efficacy and safety nor the appropriate sequence of inotuzumab ozogamicin with other available therapies (e.g., blinatumomab) for the treatment of relapsed/refractory ALL patients.

ALL = acute lymphoblastic leukemia; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.