

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

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

pERC Final Recommendation

This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Rituximab (Rituxan)

Submitted Funding Request:

In combination with standard-of-care chemotherapy for Philadelphia chromosome-negative, CD20 antigen-positive, B-cell precursor acute lymphoblastic leukemia in adults.

Submitted By:
Cancer Care Manitoba

Manufactured By:
Hoffmann-La Roche Limited

NOC Date:
N/A

Submission Date:
February 13, 2017

Initial Recommendation:
June 29, 2017

Final Recommendation:
August 31, 2017

pERC RECOMMENDATION

pERC does not recommend the reimbursement of rituximab in combination with standard-of-care chemotherapy for adult patients with Philadelphia chromosome-negative, CD20 antigen-positive, B-cell precursor acute lymphoblastic leukemia.

The Committee made this recommendation because, compared with chemotherapy (as defined in the pivotal clinical trial), there was uncertainty as to whether the addition of rituximab resulted in a net clinical benefit. While there was a statistically significant benefit in event-free survival (EFS), the Committee felt there was insufficient evidence to demonstrate that EFS is a validated surrogate for overall survival (OS). Toxicity was also increased with the addition of rituximab to chemotherapy, but manageable. The Committee agreed that rituximab partially aligned with patient values because it may offer some disease control, but there is some added toxicity, no demonstrated difference in OS, and no quality of life data available.

pERC considered rituximab to not be cost-effective compared with the Dana Farber or hyper-CVAD protocols as it resulted in an increase in the incremental cost with highly uncertain incremental benefit.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

Acute lymphoblastic leukemia (ALL) represents approximately 15% of adult cases of acute leukemia. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors for ALL. Patients who present with an increased white blood cell count and those over age 34 are at higher risk of adverse outcomes. Patients with both of these risk factors or who fail to achieve complete remission within four weeks of starting treatment are considered for allogeneic hematopoietic stem cell transplant (allo-HSCT) in first remission. The majority of young patients with ALL can expect favourable outcomes with modern chemotherapy protocols. Canadian standard practice include the Dana Farber protocol in younger patients and the modified Dana Farber or hyper-CVAD protocols in older patients. With the modified Dana Farber protocol complete remission is seen in 89% of patients and five-year relapse-free survival and overall survival is 71% and 63%, respectively. In general patients receive an intensive chemotherapy regimen to induce a remission and, if possible, proceed to potentially curative allo-HSCT. For patients who fail to achieve complete remission, hospitalization may last several months and the prolonged period of treatment has a significant impact on quality of life (QoL). pERC agreed that there is a continued need for more effective and tolerable treatment options in adult patients as they still have a significant risk for relapse and death.

[pERC's Deliberative Framework](#) for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The Committee deliberated on the results of one randomized controlled trial, GRAALL-2005-R, a sub-study of the GRAALL-2005, which evaluated the efficacy and safety of adding rituximab to chemotherapy or hyper-C chemotherapy (addition of hyper-fractionated cyclophosphamide during induction and late intensification). pERC noted that the comparators used in the trial are not the standard options in Canadian practice. The Committee noted statistically significant improvements with the addition of rituximab in the primary outcome of event-free survival (EFS), defined as a composite of failure of complete remission induction, relapse, and death. Improvements in EFS were attributed to a lower incidence of relapse in patients while failure of complete remission induction and death was the same between groups. Other key secondary outcomes such as overall survival (OS) did not demonstrate a statistically significant difference between treatment groups after a median follow up of 30 months. However, the trial was not powered to detect an OS benefit. Patient-reported outcomes were identified as a key outcome in this patient population but the trial did not include any QoL measurement. Thus, the Committee was unable to assess the impact of adding rituximab to chemotherapy on patient QoL. pERC discussed the toxicity profile of rituximab and noted that Grade 3 or 4 adverse events occurred more often in the rituximab group, most frequently in the induction phase. Infections also occurred more frequently in the rituximab group compared with the chemotherapy group. Given the toxicities associated with current chemotherapy protocols used, pERC noted that rituximab would result in added toxicity to patients. However, pERC agreed that the toxicity profile of rituximab, particularly infusion-related reactions, are well known and can be managed by treating oncologists/hematologists. The Committee discussed the totality of the available evidence and considered the clinical meaningfulness of EFS as an outcome in previously untreated ALL. pERC acknowledged that the benefit of rituximab appears to be in achieving a lower incidence of relapse in patients. pERC agreed this could be a meaningful outcome for patients and weighed the conclusions from the pCODR Clinical Guidance Panel (CGP), which indicated that the clinical importance of EFS is unclear when accompanied by uncertainty in OS. Given the absence of data to demonstrate the impact of rituximab on OS, pERC agreed that there is uncertainty in the conclusions that could be drawn from EFS alone. Furthermore, there is currently insufficient evidence to support using EFS as a surrogate for OS. pERC also noted that a greater proportion of patients in the control group experienced severe allergic reactions to L-asparaginase and/or received a reduced cumulative dose of L-asparaginase. Given that L-asparaginase is an effective component of the treatment protocol, pERC agreed that this could have contributed to the reduced EFS in the control group and consequently better outcomes in the rituximab group.

The Committee also noted that the chemotherapy backbones used in the GRAALL-2005-R trial are not representative of Canadian standards. According to the CGP's discussions, the protocols used in the study

were inspired by protocols used in the pediatric population. While the modified Dana Farber protocol is pediatric-inspired, it is considered a more intense protocol than those studied in GRAALL-2005-R, and hyper-CVAD is not pediatric-inspired. In the absence of head-to-head trials comparing these protocols, pERC agreed that there is considerable uncertainty in the generalizability of the GRAALL-2005-R trial results to the Canadian standard options. Overall, the Committee had a fulsome discussion on the available evidence and agreed that, due to the uncertainty in EFS benefit absence of OS benefit and inability to generalize the trial results into Canadian standard practice, there was considerable uncertainty as to whether or not rituximab conferred a net clinical benefit.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter and PAG regarding the relevance of EFS as an end point in front-line trials. pERC considered the CGP's response to the feedback that the prognosis of disease and relevance of outcomes among pediatric, adolescent, and young adult patients differ from those for older adults. With treatment, the survival of pediatric patients is typically very good; and in order to detect differences in OS between treatment groups in a randomized trial, a large sample size with a long follow-up time is required due to the small expected difference in OS. EFS is used as a relevant end point for trials in pediatric populations, as the composite outcome allows for a smaller sample size with more modest follow-up times required to detect statistically significant results. This, however, is not the case when considering older adults, who generally have a worse prognosis than younger patients with OS having more relevance as an outcome for these patients. pERC noted that the trials referenced by the submitter in support of using EFS as a primary end point in front-line trials were mostly in pediatric, adolescent, and young adults. One ongoing trial included patients aged 18 to 39; however, however, the rationale for using EFS as an endpoint in that trial was not explained. Other trials in older adults, albeit in relapsed refractory settings, have included OS as a primary end point. Therefore, pERC reiterated that conclusions drawn from EFS outcomes alone in trials of adult populations are less certain in the absence of OS benefit.

pERC also discussed feedback from the submitter and PAG related to the generalizability of the chemotherapy used in the GRAALL-2005-R trial to the Canadian setting. The CGP responded that adoption of one treatment over another has generally been due to familiarity with using treatments in clinical practice rather than in clinical trials. However, the leukemia community has adopted pediatric protocols to treat adolescents and young adults based on more favorable outcomes (i.e. OS [and not EFS]) observed when treating these patients with a pediatric protocol compared to an adult ALL protocols (despite a lack of a RCT comparing the 2 types of regimens). The CGP re-iterate that the GRAALL-2005-R protocol is different from Canadian protocols, and that older patients cannot tolerate pediatric protocols. pERC also noted feedback from the submitter discussing the anticipated QoL impact of adding rituximab to treatment protocols based on the EFS benefit gained. As the available evidence indicates that EFS is not a relevant end point with the population under consideration, pERC agreed with the CGP that it is difficult to assess the QoL impact of adding rituximab to chemotherapy backbones as there was no data collected in the trial to inform such a conclusion.

Lastly, pERC recognized that the current submission was from a provincially recognized tumour group which chose to make the submission based on an identified potential clinical benefit of adding rituximab to current chemotherapy backbones used in practice. Given the interpretation and conclusion provided by the pCODR CGP, pERC acknowledged that there are differences in opinion among experienced oncologists who treat this disease. In light of these differing opinions, pERC weighed all the available evidence and given the lack of confidence about the relevance of EFS benefit in the absence of OS, the inability to generalize the trial results into Canadian standard practice, pERC concluded that it is unclear whether rituximab confers a net clinical benefit.

The Committee acknowledged that patient advocacy groups did not provide input on the rituximab submission, which challenged the Committee's ability to understand the patient and caregiver experiences with this type of cancer. To provide insight for this essential component of pERC's deliberations, the Committee discussed a summary of grey literature compiled by pCODR staff that outlined information on patient experiences and perspectives regarding previously untreated ALL. Based on the reduced incidence of relapse, pERC agreed that rituximab aligned with the patient value of accessing effective treatment options. pERC further noted that patients find current treatments have various side effects that are difficult to manage and value new treatments that have fewer adverse effects. pERC noted that rituximab has an increased, albeit manageable toxicity profile. Finally, the summary of information on patient experiences identified that there is a considerable impact on patients' QoL due to disease symptoms and the psychological impact of illness. pERC noted that there was no QoL evaluation conducted for the GRAALL-2005-R study that could inform the impact of rituximab on QoL.

Therefore, pERC concluded that rituximab partially aligns with patient values because there was a lowered incidence of relapse. However, toxicity was increased and there are no QOL data available.

pERC deliberated on the cost-effectiveness of rituximab compared with the Canadian standard options (Dana Farber and Hyper-CVAD) and concluded that rituximab is not cost effective compared to Canadian standard options. pERC noted that a number of assumptions in the model, most notably the estimates of long-term benefit due to EFS, had a substantial impact on the incremental cost-effectiveness ratio (ICER). In the submitted economic model, patients were considered to be cured after 60 months in the EFS state and therefore a substantial amount of benefit was gained as patients transitioned from the EFS to the cured state. Given the uncertainty identified by pERC related to the treatment effect benefit accrued due to EFS and the absence of clinical evidence to support the presence of a survival advantage, pERC agreed with the pCODR Economic Guidance Panel (EGP) reanalysis, removing these assumptions from the model. When the EGP removed the modeled benefit due to EFS and OS, the ICER upper bound increased to more than \$4.1 million/quality-adjusted life year (QALY). pERC therefore concluded that rituximab is not cost-effective compared with the Dana Farber or hyper-CVAD protocols as it results in an increase in the incremental cost with very highly uncertain incremental benefit in overall survival.

The Committee discussed the feasibility of implementing a reimbursement recommendation for rituximab. pERC agreed that uncertainty remained in the conclusions that could be drawn from the GRAALL-2005-R trial results, which demonstrated an EFS benefit in the absence of an OS or QoL benefit. pERC further noted that the comparators used in the GRAALL-2005-R trial are different from Canadian standard options (Dana Farber or hyper-CVAD). Therefore, the Committee agreed that generalizability of the trial results to the Canadian setting was not appropriate. Overall, pERC agreed that the evidence presented to support the addition of rituximab to Canadian standard treatment options is not sufficient to make a reimbursement recommendation.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Patient advocacy group input was not received for this review; however, pERC used a summary provided by pCODR through a comprehensive search of published and grey literature on patient experiences and perspectives regarding acute lymphoblastic leukemia and rituximab to inform its deliberations.
- Input from one registered clinician
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- The PAG
- The submitter [Cancer Care Manitoba]

The pERC Initial Recommendation was to not recommend the reimbursement of rituximab in combination with standard-of-care chemotherapy for adult patients with Philadelphia chromosome-negative, CD20 antigen-positive, B-cell precursor acute lymphoblastic leukemia. Feedback on the pERC initial recommendation indicated that the manufacturer disagreed and PAG agreed in part with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of rituximab in combination with standard-of-care chemotherapy for adult patients with Philadelphia chromosome-negative, CD20 antigen-positive, B-cell precursor acute lymphoblastic leukemia (ALL).

Studies included: Comparator used in trial is inappropriate in Canadian setting

The pCODR systematic review included one randomized, open-label phase III clinical trial (GRAALL-2005-R, a sub-study of GRAALL-2005) comparing chemotherapy plus rituximab or hyper-C chemotherapy plus rituximab (rituximab group) to chemotherapy or hyper-C chemotherapy (control group). Hyper-C chemotherapy included the addition of hyper-fractionated cyclophosphamide during induction and late intensification. The goal of the treatment in GRAALL-2005-R (primary outcome) was to increase the two-year event-free survival (EFS) rate from 50% in the control group to 70% in the rituximab group. Rituximab was given during all treatment phases (induction, salvage re-induction when needed, consolidation, late intensification, late consolidation, and maintenance) for a total of 16 to 18 infusions at a dose of 375 mg/m².

The trial enrolled and randomized 220 patients. However, the results are based on a modified intent-to-treat analysis of only 209 patients. The missing 11 patients were excluded from the modified analysis because they no longer met the trial inclusion criteria or withdrew consent. During the first complete remission, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was offered to patients who were 55 years of age or younger if they had a suitable donor (a matched related donor or an unrelated donor with a 10/10 allele match) and were considered to be at high risk as defined in the trial protocol. Median follow-up of the trial was 30 months.

Patient populations: Patients are younger and have lower performance status

Baseline characteristics were well balanced between groups. The median age of patients was 40.2 years (range: 24.5 to 52.6). Most patients had a white-cell count below $30 \times 10^9/L$ (79%) and few patients had central nervous system involvement (6%). Compared with the control group, more patients in the rituximab group had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or less (91% versus 83%) and a minority had ECOG PS > 1 (9% versus 17%). The proportions of patients in the two treatment groups with high-risk ALL was similar. pERC noted that although baseline patient characteristics were balanced between groups and complete remission after first induction was similar,

more patients in the rituximab group compared with the control group underwent allo-HCST during the first remission (34 and 20, respectively). pERC also noted that adult patients with ALL typically present with a higher ECOG PS and are older. The patients in the GRAALL-2005-R trial may therefore not be representative of the clinical population, as patients between the ages of 18 and 59 with an ECOG PS of 1 or less (in most patients) were recruited. pERC noted this is particularly important because tolerability of agents varies in older patients.

Key efficacy results: Uncertainty in benefit due to event-free survival

The key efficacy outcome deliberated on by pERC included EFS, which was also the primary outcome of the trial. EFS was a composite end point defined as failure of complete remission induction, relapse, and death. A statistically significant improvement in EFS was reported at two years in favour of rituximab (65% and 52%; hazard ratio [HR] = 0.66; 95% CI, 0.45 to 0.98, $P = 0.04$). The benefit was noted to be due to a reduction in the incidence of relapse in the rituximab group ($n = 22$ and $n = 35$, respectively) while failures of complete remission induction ($n = 8$ and $n = 9$) and deaths during remission ($n = 14$ and $n = 13$) were similar in the rituximab and control groups, respectively. This benefit in EFS was maintained at four years. Key secondary end points included overall survival (OS) and hematological complete remission rate after one or two induction courses. Although the trial was not powered to detect a difference, OS was not statistically significantly different at two years in either the rituximab and control groups (71% and 64%, respectively; HR = 0.70; 95% CI, 0.46 to 1.07, $P = 0.10$). Complete remission rates were similar between groups for patients without salvage re-induction (90% versus 88%, $P = 0.52$) as well as for patients with or without salvage re-induction (92% versus 90%, $P = 0.63$) in the rituximab and control groups, respectively.

The Committee noted discussions by the pCODR Clinical Guidance Panel (CGP) indicating that most therapies introduced for use in this population are based on the demonstration of improvements in OS and/or quality of life (QoL) data. Based on this, pERC discussed the clinical relevance of improvement in EFS and its correlation to OS. pERC considered that EFS (notably, reduced incidence of relapse) could be a meaningful outcome for patients and weighted the CGP's conclusion indicating that, in this population, the clinical importance of EFS is uncertain when accompanied by uncertainty in OS. Given the absence of data to demonstrate the impact of rituximab on OS, pERC agreed that there is uncertainty in the conclusions that could be drawn from EFS alone. Furthermore, there is currently no evidence to support the validity of using EFS as a surrogate for OS. Post hoc analysis censoring patients who received a stem cell transplant demonstrated an OS advantage in favour of the rituximab group. pERC agreed that, with censoring of patients who had a transplant, randomization of the two treatment groups may have been compromised as more high-risk patients may have received a transplant resulting in a more favourable group of patients in the censored OS analysis. pERC also noted that a greater proportion of patients in the control group experienced severe allergic reactions to L-asparaginase and/or received a reduced cumulative dose of L-asparaginase. Given that L-asparaginase is an effective component of the treatment protocol, pERC agreed that this could have contributed to the reduced EFS in the control group. Furthermore, pERC discussed the relevance of the comparators used in the GRAALL-2005-R study in relation to Canadian standard practice. According to the CGP's discussions, the protocols used in the study were based on protocols used in the pediatric population and different from Canadian standards. Notably, the modified Dana Farber protocol is also pediatric-inspired, but it is generally a more intense protocol than those studied in GRAALL-2005-R. Hyper-CVAD is not pediatric-inspired. In the absence of head-to-head trials comparing these protocols, pERC agreed that there is considerable uncertainty in the generalizability of the GRAALL-2005-R trial results to the Canadian standard options. Overall, the Committee had a fulsome discussion on the available evidence and agreed that there was uncertainty as to whether or not rituximab conferred a net clinical benefit, due to the uncertainty in EFS benefit, absence of OS benefit, and inability to generalize the trial results into the Canadian standard practice.

Patient-reported outcomes: Not measured in trial

Patient-reported outcomes were not an end point in the GRAALL-2005-R trial. pERC noted that QoL is an important end point for patients. Based on the information gathered through the grey literature searches for patient and caregiver lived experiences with ALL, it was clear that patients have significant impacts on their QoL as a result of their disease symptoms and treatment. pERC also agreed that QoL is an important outcome for treatment decision-making in ALL.

Safety: Increased but manageable toxicity

Safety was evaluated on the basis of the incidences of Grade 3 or 4 adverse events and incidence rates of reported severe adverse events, according to 100 patient-years of treatment exposure. There were more

Grade 3 and 4 adverse events in all treatment phases except maintenance in the rituximab group compared with the control group (352 versus 282 events). The most common Grade 3 and -4 adverse events were increases in levels of alanine aminotransferase and aspartate aminotransferase; sepsis; pain; and nausea, vomiting and diarrhea for the rituximab and control groups. Grade 3 and 4 adverse events occurred most frequently during the induction phase (187 versus 176 events). Severe infections were experienced more often in the rituximab compared with control group (67.6% and 52.9%, respectively). pERC therefore agreed that rituximab will result in added toxicities to patients. pERC noted that data were not available on infusion-related reactions, which are typical with use of rituximab, occur most frequently in the first two infusions, and subside with later infusions. Overall, pERC agreed that the toxicity profile of rituximab is well known and can be managed.

Need and burden of illness: Effective options available, improvements needed in long-term outcome for patients

Approximately 15% of adult cases of acute leukemia are ALL, and adult treatment protocols are based largely on the principles that led to successful outcomes in children. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL. Patients who present with an increased white blood cell count (WBC > 30 x 10⁹/L for B-cells and > 100 x 10⁹/L for T-cells) and those over age 34 are at higher risk of adverse outcomes. Patients with both of these risk factors or who fail to achieve complete remission within four weeks of starting treatment are considered for allogeneic hematopoietic stem cell transplant (allo-HSCT) in first remission. The majority of young patients with ALL can expect favourable outcomes with modern chemotherapy protocols. Canadian standard practice include the Dana Farber protocol in younger patients and the modified Dana Farber or hyper-CVAD protocols in older patients. With the modified Dana Farber protocol complete remission is seen in 89% of patients and five-year relapse-free survival and overall survival is 71% and 63%, respectively. In general patients receive an intensive chemotherapy regimen to induce a remission and, if possible, proceed to potentially curative allo-HSCT. The choice between treatments is largely based on the age of patients and the jurisdiction. In patients that fail to achieve complete remission, hospitalization may last several months and the prolonged period of treatment has a significant impact on QoL. Population-based studies continue to show that the majority of adult patients with ALL will die from their disease, and there is a continued need for more effective and tolerable treatment options.

Registered clinician input: Improved event-free survival

The Committee deliberated on input received from one clinician. Based on this input, pERC noted that the incidence of ALL is low and current Canadian practice utilizes the modified Dana Farber chemotherapy protocol. The input indicated that the benefit of adding rituximab to treatment protocols is in providing patients with longer EFS with no increased adverse events. Based on the input, it is also anticipated that rituximab will improve the three-year relapse-free survival of patients. While pERC agreed that the benefit of rituximab is limited to EFS, the Committee reiterated that uncertainty remains in the ability to interpret EFS in the context of no OS benefit. pERC also noted that although the toxicity profile of rituximab is increased compared with the control group, rituximab is a well-known agent, and treating oncologists would be experienced in managing the added toxicity. However, pERC was unable to comment on the impact of rituximab on relapse-free survival. Although relapse-free survival was a secondary end point in the trial, data were not available for assessment.

PATIENT-BASED VALUES

Values of patients with acute lymphoblastic leukemia: Side effect and symptom control, quality of life improvements

pERC noted that no patient advocacy groups provided input on the review of rituximab. The Committee discussed a summary of grey literature results that illustrated patient experiences and perspectives on ALL. pERC noted that patients with ALL value treatments that can manage disease- and treatment-related side effects. Symptoms of ALL include tiredness, frequent minor infections, discomfort in bones or joints, neutropenia, bruising or bleeding, depression, anemia, enlarged spleen, liver or lymph nodes, mild fever, and thrombocytopenia. Common side effects of treatment include fatigue, nausea, and vomiting, upset stomach, hair loss, diarrhea or loose bowels, and infection. Patients indicated that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage with current therapies. Moreover, because treatments for this cancer are intensive, many elderly patients are deemed unfit for such therapies.

Input also indicates that acute leukemia may have a negative psychological effect on survivors at the time of diagnosis and throughout their illness. Increased distress scores for patients with acute leukemia were recorded. In addition, fatigue, depression, and anxiety interfere with the day-to-day life of patients and their ability to engage in social activities. These factors were the most common symptom concerns for patients and survivors. Fatigue had been described by patients as more difficult to deal with than pain, though it did improve over time from the start of the treatment to the end. Patients and caregivers also reported that their illness has had a significant impact on their relationship. For caregivers, QoL and the ability to enjoy life, especially those of young patients, is affected.

The Committee considered this information and agreed that patient's value effective treatment options that have a better toxicity profile, are able to manage their disease-related symptoms and improve QoL. pERC noted that uncertainty remained regarding the relevance of EFS in the absence of OS data, but agreed that a reduced incidence of relapse may be meaningful to patients. pERC further noted that rituximab would result in added but manageable toxicities. In the absence of data addressing the impact of rituximab on patient QoL, pERC was unable to comment on this patient value. Overall, pERC agreed the addition of rituximab partially aligned with patient values.

Patient values on treatment: Management of quality-of-life impact, symptom control

Intensive chemotherapy was the most common therapy used by newly diagnosed patients with ALL, resulting in short- and long-term physical and psychological effects on QoL. Most patients were also reported to be affected both physically and psychologically during the induction phase of the treatment, and in particular during week 3 of hospitalization. Depressive symptoms and anxiety were experienced by patients during treatment.

According to one patient providing input who had experience with rituximab, infusion-related reactions will be important to manage. This patient had a negative reaction to rituximab the first time it was used. The patient reported better experiences with subsequent infusions, for which the infusion time was adjusted to manage side effects. This is consistent with the known toxicity profile of rituximab, as infusion reactions occur most often with the first two infusions and become less pronounced and more uncommon with later cycles. Although data were not available on infusion-related reactions, pERC agreed that the toxicity profile of rituximab is well known and can be managed. No information was available on the effect of treatment on the patient's disease.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis and a cost-effectiveness analysis of rituximab plus chemotherapy backbone compared with chemotherapy backbone for patients with Philadelphia chromosome-negative (Ph-), CD20-positive (CD20+), B-cell precursor acute lymphoblastic leukemia (ALL).

The model was composed of four main health states: EFS, relapsed/resistant, cured, and dead. Patients were considered cured after spending 60 months in the EFS state.

Basis of the economic model: Clinical inputs based on non-standard comparators

Costs considered in the model included those associated with drug acquisition, drug administration, supportive care, adverse events, subsequent treatment, stem cell transplant and palliative care. The key clinical outcomes considered in the model were EFS, cure, relapsed/resistant, and utilities.

Drug costs: Additional cost to existing therapy

Rituximab costs \$4.71 per mg. When combined with hyper-CVAD, rituximab is dosed as two infusions during induction, two infusions during re-induction (if needed), six infusions during consolidation, two infusions during intensification, and six infusions during first-year maintenance at 375 mg/m² for a total of 16 to 18 infusions.

For 16 infusions, rituximab costs \$131.49 per day and \$3,681.62 per 28-day course. For 18 infusions, rituximab costs \$147.92 per day and \$4,141.82 per 28-day course. Based on the submitted economic

model, rituximab costs \$6,548.86 per cycle. It was reported that a 50 mL (10 mg/mL) vial of rituximab costs \$2,331.61, or approximately \$4.66 per mg.

Hyper-CVAD consists of multiple agents. Based on the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of hyper-CVAD is \$173.80 per day and \$6,316.72 per 28 days.

The Dana Farber protocol consists of multiple agents. Based on the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of the Dana Farber regimen is \$247.28 per day and \$6,923.92 per 28 days.

Cost-effectiveness estimates: Considerable uncertainty in clinical effect estimates

The Committee deliberated on the cost-effectiveness of rituximab compared with the Canadian standard options (Dana Farber and hyper-CVAD) and agreed that rituximab is not cost-effective. Uncertainty in the clinical effect estimates used in the model had the largest impact on the incremental cost-effectiveness ratio (ICER), namely, estimates of long-term benefit due to EFS. In the submitted analysis, it is assumed that patients were cured after 60 months in the EFS state. Generally, the assumption of cured after 60 months in the EFS state is accepted in clinical practice, as indicated by the CGP. However, uncertainty remained in the results of the GRAALL-2005-R trial, given the absence of evidence to support the presence of an OS benefit even after a median follow-up of 30 months. pERC therefore accepted the EGP reanalysis removing the assumptions related to clinical efficacy from the model. When the EGP removed the modeled treatment effect benefit due to EFS and cure, the ICER upper bound increased to more than \$4.1 million. pERC concluded that rituximab is not cost-effective compared with the Dana Farber or hyper-CVAD protocols as it results in an increase in the incremental cost with very minimal incremental benefit.

Furthermore, pERC concluded that the comparators used in the GRAALL-2005-R trial are not representative of Canadian standard practice. Additional uncertainty remained as to the relevance of the inputs used for efficacy in the model.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact:

Uncertainty in clinical data and generalizability of results to Canadian setting

The Committee discussed factors affecting the feasibility of implementing a funding recommendation for rituximab. Input from PAG indicated that ALL is relatively uncommon in adults and there would be a small number of younger (< 60 years) adult patients with Philadelphia chromosome negative, CD20 positive, B-cell precursor ALL. Currently, the Dana Farber Cancer Institute protocol is the standard of care for younger adult patients with ALL. Older patients may be treated with Hyper-CVAD or dose modified Dana Farber. pERC agreed that uncertainty remained in the conclusions that could be drawn from the GRAALL-2005-R trial results, which demonstrated an EFS benefit in the absence of OS and/or QoL benefit. pERC further noted that the comparators used in the GRAALL-2005-R trial are different from Canadian standard options (Dana Farber or hyper-CVAD). Therefore, the committee agreed that generalizability of the trial results to the Canadian setting was not appropriate, particularly in older patients for whom toxicity with treatment can be variable. Overall, pERC concluded that the evidence presented to support the addition of rituximab to Canadian standard treatment options is not sufficient to make a reimbursement recommendation. Therefore, it is not anticipated that implementation concerns will arise.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Chimeric anti-CD20 antibody • 100 mg and 500 mg single-use vials • 375 mg/m²
Cancer Treated	<ul style="list-style-type: none"> • Philadelphia chromosome-negative, CD20 antigen-positive, B-cell precursor acute lymphoblastic leukemia. • Previously untreated
Burden of Illness	<ul style="list-style-type: none"> • 15% of adult cases of acute leukemia • Significant symptom burden on patients and quality of life impact
Current Standard Treatment	<ul style="list-style-type: none"> • Dana Farber protocol (younger patients) • modified Dana Farber protocol (older patients) • Hyper-CVAD (older patients) •
Limitations of Current Therapy	<ul style="list-style-type: none"> • Majority of young patients with ALL can expect favourable outcomes with modern chemotherapy protocols • Prolonged period of treatment has a significant impact on patient's quality of life • Majority of adult patients with ALL will die from 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. Paul Hoskins, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Dr. Kelvin Chan, Oncologist
 Dr. Matthew Cheung, Oncologist
 Dr. Craig Earle, Oncologist
 Dr. Allan Grill, Family Physician
 Don Husereau, Health Economist

Dr. Anil Abraham Joy, Oncologist
 Karen MacCurdy Thompson, Pharmacist
 Valerie McDonald, Patient Member Alternate
 Carole McMahon, Patient Member
 Dr. Catherine Moltzan, Oncologist
 Jo Nanson, Patient Member
 Dr. Marianne Taylor, Oncologist
 Danica Wasney, Pharmacist

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

- Jo Nanson and Craig Earle, who were not present for the meeting
- Danica Wasney and Catherine Moltzan, who were excluded from the deliberations and voting due to a conflict of interest.

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

- Jo Nanson, Anil Abraham, Danica Wasney, and Kelvin Chan who were not present for the meeting.
- Catherine Moltzan, who was excluded from the deliberations and voting due to a conflict of interest.

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 rituximab (Rituxan) for acute lymphoblastic leukemia (ALL) through their declarations, five members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, two of these members was 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 based its recommendations 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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