CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Rituximab (Rituxan) for Acute Lymphoblastic Leukemia

August 31, 2017

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding rituximab (Rituxan) for acute lymphoblastic leukemia (ALL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding rituximab (Rituxan) for acute lymphoblastic leukemia (ALL) conducted by the leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on rituximab (Rituxan) for acute lymphoblastic leukemia (ALL), a summary of submitted Provincial Advisory Group Input on rituximab (Rituxan) for acute lymphoblastic leukemia (ALL), and a summary of submitted Registered Clinician Input on rituximab (Rituxan) for acute lymphoblastic leukemia (ALL), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety 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 appropriate comparators for rituximab in this setting include hyper-CVAD (hyperfactionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose methotrexate and cytarabine) and the Dana Farber Cancer Institute Protocol (doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase) among others.

The recommended dose for rituximab is as follows:

- when combined with Hyper-CVAD: 2 infusions during induction, 2 infusions during reinduction (if needed), 6 infusions during consolidation, 2 infusions during intensification and 6 infusions during first-year maintenance at 375 mg/m^2 for a total of 16-18 infusions.
- when combined with Dana Farber ALL Consortium (DFCI) backbone: 2 infusions during induction, 2 infusions during reinduction (if needed), 6 infusions during intensification and 8 infusions during continuation at the 375 mg/m^2 for a total of 16-18 infusions.

Although there is no Health Canada regulatory approval for rituximab with this indication, rituximab in combination with standard of care chemotherapy was submitted to pCODR by Cancer Care Manitoba for review in adult patients with Philadelphia chromosome negative, CD20 positive, B-cell precursor acute lymphoblastic leukemia.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

GRAALL-2005-R (a sub-study of GRAALL-2005) is a randomized, controlled, open-label phase III clinical trial comparing standard dose chemotherapy plus rituximab or hyper-C chemotherapy (addition of hyperfractionated cyclophosphamide during induction and late intensification) plus

rituximab (rituximab group) to standard dose chemotherapy or hyper-C chemotherapy (control group). For the purposes of this report, only data relevant to GRAALL-2005-R are presented, unless otherwise specified.[1]

The study was sponsored by Regional Clinical Research Office, Paris and was independent of the manufacturer of rituximab: Roche.[1]

Only patients randomized from GRAALL-2005 with Philadelphia (Ph)-negative B-cell precursor (BCP)- acute lymphoblastic leukemia (ALL) expressing the CD20 antigen at the 20% threshold were randomized in the GRAALL-2005-R study. A total of 220 patients from 59 French and Swiss centers were enrolled and randomized in GRAALL-2005-R; there were no Canadian centres.[1]

Adults aged 18 to 59 years with CD20-positive, Ph–negative ALL were randomized to receive chemotherapy (either A or B) with or without rituximab. Rituximab was given during all treatment phases (during induction, salvage reinduction when needed, consolidation, late intensification, late consolidation, and maintenance) for a total of 16 to 18 infusions.[1]

The goal of the treatment in GRAALL-2005-R was to increase the 2-year event-free survival from 50% in the control group (chemotherapy—either standard dose chemotherapy [A] or hyper-C chemotherapy [B]—without rituximab) to 70% in the rituximab group (chemotherapy—either A or B—with rituximab). At a 5% level of significance, a recruitment of 110 patients per group was required to detect this difference with a power of 85%. It was therefore it was decided to include 220 patients in total.[1,2]

The primary endpoint for GRAALL-2005-R was event-free survival, a composite endpoint defined as failure of complete remission induction, relapse, and death. Secondary endpoints included:
- Hematological complete response (CR) rate after 1 or 2 induction courses
- Early mortality during induction
- Toxicity associated with induction, consolidation, late intensification or SCT, and maintenance
- Mortality in the first CR
- Cumulative incidence of hematological relapse
- Relapse-free survival
- Overall Survival[2]

Key limitations:
It is unclear how well the study was conducted to minimise bias. Details of the randomization method and allocation concealment were not reported in the study publication. The study was an open-label trial and outcomes were investigator-assessed rather than independently assessed. Given that primary endpoint was a composite endpoint (i.e. events were failure of complete remission induction, relapse, and death), which included an objective measure (i.e. death), bias due to investigator assessment may have been reduced. Notably, failure of complete remission and relapse are subjective endpoint and have a potentially greater risk of bias. Moreover, it is unclear if the assumption of no interaction between randomizations was validated, since no results to confirm this assumption were reported.

During the first complete remission, allogeneic hematopoietic stem-cell transplantation 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. More patients in the rituximab group than in the control group underwent allogeneic stem-cell transplantation during the first remission. The magnitude and direction of bias due to this imbalance is unknown. More patients in the control group also had less overall cumulative doses of L-asparaginase. Given that this is an active component of the treatment protocol, the removal of

this agent may have resulted in more favourable outcomes in the rituximab group but the magnitude of the impact is unknown.

Despite the limitations and risk of bias noted in Section 6 of this report and in Appendix B (SIGN50 Checklist for Randomized Controlled Trials), it may be reasonable to accept that the overall effect is due to the study intervention. However, greater information on the details of the trial would have strengthened the Methods Team's confidence in their overall conclusions. The Methods Team acknowledges that this was a tumour group submission therefore their access to more details information on trial, as the submitter was limited.

Below is a table highlighting the key efficacy outcomes (Refer to Table 1.1 Highlights of Key Efficacy Outcomes of GRAALL-2005-R)

Table 1.1: Highlights of Key Efficacy Outcomes GRAALL-2005-R[1]

Efficacy Outcomes	Rituximab (n=105)	Control (n=104)
Primary Endpoint - Event-Free Survival		
Hazard ratio	0.66 (95% CI, 0.45 to 0.98; *P* = 0.04)	
Rate at 2 years, %	65% (95% CI, 56 to 75)	52% (95% CI, 43 to 63)
Rate at 4 years, %	55% (95% CI, 46 to 66)	43% (95% CI, 34 to 55)
Secondary Endpoint - Rate of hematologic remission		
Complete remission without salvage reinduction	95 (90)	91 (88)
	P = 0.52	
Complete remission with or without salvage reinduction	97 (92)	94 (90)
	P = 0.63	
Secondary Endpoint - Cumulative incidences of relapse		
No. Relapse, %	22 (21)	35 (34)
Subdistribution hazard ratio	0.52 (95% CI, 0.31 to 0.89; *P* = 0.02)	
Rate at 2 years, %	18% (95% CI, 11 to 27)	32% (95% CI, 22 to 42)
Rate at 4 years, %	25% (95% CI, 16 to 35)	41% (95% CI, 30 to 51)
Secondary Endpoint - Death during the first remission		
No. deaths during remission, %	14 (13)	13 (13)
Subdistribution hazard ratio	0.98 (95% CI, 0.45 to 2.12; *P* = 0.96)	
Cumulative incidence at 2 years, %	12% (95% CI, 6 to 19)	12% (95% CI, 6 to 19)
Cumulative incidence at 4 years, %	16% (95 CI, 9 to 24)	12% (95% CI, 6 to 19)
Secondary Endpoint - Death during Induction		
No., %	7 (7)	9 (9)
Secondary Endpoint - Relapse-free survival	NR	NR
Secondary Endpoint - Overall survival		
Hazard ratio	0.70 (95% CI, 0.46 to 1.07; *P* = 0.10)	
Cumulative incidence at 2 years, %	71% (95% CI, 62 to 80)	64% (95% CI, 55 to 74)
Cumulative incidence at 4 years, %	61% (95% CI, 52 to 72)	50% (95% CI, 41 to 62)
Health Related Quality of Life	Not applicable	Not applicable

Abbreviations: CI = confidence interval; NR = not reported

Notes:
Data cut-off as of June 1, 2015
Median follow-up of 30 months
Submitter regards "rate of hematologic remission" as being synonymous with "hematologic remission"[3]
Submitter considered "mortality in the first complete response" as synonymous with "death during the first remission"[3]
Submitter believes that the terms "death during induction" and "early mortality during induction" are synonymous[3]

According to the Protocol, a secondary endpoint of GRAALL-2005-R was toxicity associated with induction, consolidation, late intensification or SCT, and maintenance.[2] According to Maury et al., 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 patient-years of treatment exposure.[1]

Overall (all treatment phases, except maintenance phase), there were more grade 3-4 adverse events reported in the rituximab group compared to the control group (352 versus 282 events). During all treatment phases (except maintenance phase), the most common grade 3-4 adverse events were ALT level increase, sepsis, AST level increase, pain, and nausea, vomiting and diarrhea for both groups. Grade 3-4 adverse events occurred most frequent during the induction phase (187 versus 176 events). [1,4]

Overall, 246 severe adverse events were reported in 124 patients: 67 patients with one event, 26 patients with two events, 13 patients with three events, and 18 patients with four or more events. According to Maury et al., the overall incidence of severe adverse events did not differ significantly between the groups and although infectious events were slightly more frequent in the rituximab group, the difference was not significant. There was however a difference between groups in the occurrence of severe allergic events. Among 16 severe allergic events that occurred, 15 were due to L-asparaginase administration. Among these, 2 of the severe allergic reactions to L-asparaginase were in the rituximab group. Overall, the cumulative dose of L-asparaginase received was less in the control compared to rituximab group. In terms of severe adverse events, infection and laboratory abnormalities were most commonly reported in both groups (71 versus 55 events, and 22 versus 23 events). [1,4]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) input, and registered clinician input, respectively.

Patient Advocacy Group Input

No patient advocacy group input was received by the pan-Canadian Oncology Drug Review (pCODR) on the submission for rituximab (Rituxan) in combination with standard of care chemotherapy for Philadelphia chromosome negative, CD20 antigen positive, B-cell precursor acute lymphoblastic leukemia (ALL). A literature search through MEDLINE (See Appendix A) was undertaken by CADTH to inform the pCODR Expert Review Committee's (pERC) deliberation on patient values as part of its deliberative framework.

From the information gathered, patients reported 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, thrombocytopenia. The current treatments for acute leukemia include chemotherapy, radiotherapy, bone marrow transplant, supportive care, and palliation. While some treatments, such as radiation and cyclophosphamide, have been successful at controlling common aspects of ALL for certain patients, there are a number of side effects. Common side effects of treatment include: fatigue, nausea and vomiting, upset stomach, hair loss, diarrhea or loose bowels and infection. Based on information reported by CCSN, patients indicated that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage with their current therapies. Moreover, because treatments for this cancer are intensive, reports have found that "many elderly patients are deemed unfit for such therapies".[5]

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Small number of adult patients with Philadelphia chromosome negative, CD20 positive, B-cell precursor ALL
- Requests for patients under 18 years of age and over 60 years of age

Economic factors:

- Use in hospital during induction phase
- Dose intensity of rituximab administration, up to 18 doses

See Section 4 for details

Registered Clinician Input

One registered clinician provided input on rituximab for ALL. According to the clinician who provided input, rituximab is an add-on to current therapy, improving relapse free survival.

See Section 5 for details

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for rituximab

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Pediatric ALL	PAG is seeking information on whether the results from the GRAALL-R study can be extrapolated to pediatric patients (under age of 18) GRAALL-2005-R included patients aged 18-59 years old.[1]	Are the trial results generalizable to pediatric patients (under age of 18)?	The CGP determined there is no net clinical benefit with the addition of rituximab to combination chemotherapy in untreated patients therefore questions related to generalizability are not relevant. In general, there was consensus among the CGP that pediatric ALL is different from the adult form. Therefore the results of this trial are not generalizable to pediatric patients. The CGP did however acknowledge that there may be a subgroup of pediatric ALL patients that behave the same as adults; these are the adolescent young adults aged 15 and up. These patients may be treated with adult protocols.
	Older Adults with ALL	PAG is seeking information on whether the results from the GRAALL-R study can be extrapolated to patients 60 years of age and over. GRAALL-2005-R included patients aged 18-59 years old.[1]	Are the trial results generalizable to patients age 60 and over?	The CGP determined there is no net clinical benefit with the addition of rituximab to combination chemotherapy in untreated patients therefore questions related to generalizability are not relevant. Additionally, the CGP agreed that it would be difficult to generalize trial results conducted in patients between the ages of 18-59 to older patients as the tolerability of the regimens may not be the same as is observed in younger adult patients.
	ECOG Performance Status	13% of patients in GRAALL-2005-R had an ECOG performance status greater than 1.	Is this representative of the Canadian setting?	The CGP determined there is no net clinical benefit with the addition of rituximab to combination chemotherapy in untreated patients therefore questions related to generalizability are not relevant. There was consensus among the CGP that generally patients in clinical practice present with worse ECOG performance status and are older, however, the CGP acknowledged that the eligibility criterion of 18-59 years may have resulted in a younger patient population with better PS.
Intervention	Feasibility of subcutaneous administration	PAG is seeking information on whether subcutaneous administration of rituximab would be reasonable in this setting, if and when subcutaneous rituximab is available. Rituximab was given as an intravenous infusion in GRAALL-2005-R [1]	Would subcutaneous administration of rituximab be reasonable in this setting?	The CGP determined there is no net clinical benefit with the addition of rituximab to combination chemotherapy in untreated patients therefore questions related to generalizability are not relevant. There was consensus among the CGP that in general, the subcutaneous rituximab would be interchangeable for the intravenous dose.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Time limited need	PAG is seeking guidance on whether it would be appropriate to add rituximab for patients who are currently undergoing induction or consolidation therapy. Rituximab was given as an intravenous infusion at a dose of 375 mg per square meter of body-surface area per day during induction (days 1 and 7), salvage reinduction when needed (days 1 and 7), consolidation blocks 1, 3, 4, and 6 (4 infusions), late intensification (days 1 and 7), late consolidation (blocks 7 and 9; 2 infusions), and maintenance (6 infusions), for a total of 16 infusions (18 in the case of salvage reinduction).[1]	Would it be appropriate to add rituximab for patients who are currently undergoing induction or consolidation therapy?	Given that the CGP do not agree there is a net clinical benefit with the addition of rituximab to combination chemotherapy in untreated patients, the CGP does not support the addition of rituximab to chemotherapy for patients currently undergoing induction or consolidation therapy.
Comparator	Relevant intervention	Standard chemotherapy for this patient population across Canada include: Dana Farber Protocol and Hyper-CVAD (depending on the age and province). The interventions in GRAALL-2005-R include: rituximab plus standard chemotherapy or HyperC (as per treatment refer to Table 6.5 GRAALL-2005-R Treatments)		There was consensus among the CGP that the accepted standard treatments used in Canada for this indication are the Dana Farber and Hyper-CVAD protocols. The CGP did not agree that the trial results could be generalized in the Canadian setting given the use of chemotherapy regimens that are not considered to be standard in Canada. The CGP agreed this was particularly true among older patients who would have variable tolerability for toxicities.
Outcomes	Appropriateness of primary outcome	Event-free survival was the primary outcome. Events were defined as failure of complete remission induction, relapse, and death.[1]	Was the primary outcome appropriate for the trial design?	There was consensus among the CGP that event free survival is not an endpoint that can be used to make decisions on treatment practice. Some improvement was seen, attributed to reduction in the incidence of relapse, however the CGP agreed that EFS is a soft endpoint and overall survival and or quality of life improvements are required in ALL. The CGP noted that most previous therapies introduced for use in this population have been based on the availability of OS and or quality of life data.
Setting	Countries participating in the Trial	220 patients were enrolled and randomized from 59 French and Swiss centers to one of the GRAALL-2005/R groups.[1] There were no Canadian centres.	Are the trial results generalizable to the Canadian setting?	The CGP agreed that the overall trial results are not generalizable to the Canadian setting mainly due to the comparators used in the trial which do not reflect standard Canadian treatment protocols.

Abbreviations: ALL = Acute lymphoblastic leukemia; CGP = clinical guidance panel; ECOG = Eastern Cooperative Oncology Group; PAG = Provincial Advisory Group

1.2.4 Interpretation

Burden of Illness and Need

Acute Lymphoblastic Leukemia (ALL) is a highly aggressive hematological malignancy characterized by bone marrow infiltration and marrow failure. With some modern treatment protocols 71% of young adults and 57% of older adults remain alive and in remission five years after starting treatment.[1, 2] Population-based studies, however, continue to show that a substantial proportion of adults with ALL die of their disease. [3, 4]

Rituximab is a humanized, monoclonal antibody directed against the B-cell antigen CD20. The addition of rituximab to standard chemotherapy has resulted in significant improvements in overall and progression-free survival in patients with B-cell non-Hodgkin lymphoma (REFS) and is now considered an essential part of treatment for patients with these diseases. It is estimated that CD20 is expressed by lymphoblasts in 30-50% of B-cell ALL. The current reimbursement request seeks endorsement for the use of rituximab in patients with B-cell ALL whose disease expresses CD20.

A diagnosis of ALL is life-changing. Initial therapy is administered in hospital and hospitalizations may last several months for patients who fail to achieve remission. Treatment for standard-risk patients includes several years of chemotherapy, making it difficult for patients to maintain employment, have productive family lives and participate fully in the life of their community. Patients with high-risk features face an uncertain future and are often left with high side-effect burdens as a result of intensive chemotherapy and allogeneic hematopoietic cell transplantation. Better treatment for ALL – treatment that improves overall survival and quality of life - would be expected to reduce the burden of this disease on the patient, family and healthcare system.

Effectiveness

The effectiveness of rituximab in patients with CD20+ B-cell ALL was evaluated in a randomized, open-label study performed by the French/Swiss GRAAL consortium.[1] Patients with newly-diagnosed ALL in whom CD20 was expressed by 20% or more blasts were randomly assigned to receive repeated infusions of rituximab during all phases of treatment. Study groups were not blinded due to the tendency for patients to develop fevers and hypotension during rituximab infusion. Eligible patients were between the ages of 18-59 and had $\geq$ 20% blasts in the bone marrow. Patients were eligible if they had testicular or central nervous system involvement, or if they had disease secondary to prior chemotherapy. Patients were excluded if they had reduced heart function (on the basis of scintigraphy or echocardiography), had a prior history of myeloproliferative neoplasm or CML, had Burkitt-type ALL or if they had poor liver or kidney function. Patients with uncontrolled infection or who were seropositive for HIV were excluded.

A total of 209 patients in the modified intent to treat analysis of this study, with 105 randomized to receive rituximab and 104 to the control group. After a median follow-up of 30 months patients randomized to rituximab experienced significantly better event-free survival than patients in the control group (HR 0.66 95% CI 0.45-0.98; P=0.04). The improved event free survival was attributed to a lower incidence of relapse in the rituximab-treated patients (HR 0.52, 95% CI 0.31-0.89, P=0.02). Non-relapse mortality and overall survival did not differ between groups (HR 0.98, 95% CI 0.45-2.12, P=0.96 and HR 0.70, 95% CI 0.46-1.01, P=0.10, respectively).

The addition of rituximab to standard chemotherapy for ALL was not associated with higher rates of complete remission or higher rates of remissions free of minimal residual

disease. Patients who received rituximab were more likely to undergo allogeneic hematopoietic cell transplantation as part of their initial therapy. The reduced incidence of relapse and improvement in event-free survival is not entirely explained by a potential benefit of transplantation. The improvement in EFS persisted when patients who underwent allo-SCT were censored, and when transplantation was added to the multivariate model as a time-dependent covariate.

Safety

The number of severe adverse events in patients who received rituximab did not differ from the number in control patients (128 vs. 118, p=0.72). Only the frequency of allergic reactions appeared to differ between the treatment groups, with two patients in the rituximab group experiencing such reactions compared with 14 control patients (2% vs. 11%, p=0.002). When examined across all treatment phases there were more grade 3 or 4 adverse events in patients who received rituximab (352 vs. 282); notably, the number of episodes of sepsis (40 vs. 28) and liver enzyme abnormalities (108 vs. 71) seem higher in the experimental group.

Important considerations

There was consensus among the CGP that event free survival is not an endpoint that can be used to make decisions on treatment practice. Some improvement was seen, attributed to reduction in the incidence of relapse, however the CGP agreed that EFS is a soft endpoint and overall survival and or quality of life improvements are required in ALL. The CGP noted that most previous therapies introduced for use in this population have been based on the demonstration of improvements in OS and/or quality of life data. The CGP noted several sources provided by the submitter to support the relevance of EFS as a meaningful endpoint in ALL. However, these sources did not speak to the merits of using EFS as an endpoint in clinical trials evaluating treatment in patients with ALL. Appropriate endpoints have been a subject of ongoing debate in pediatric and adult acute leukemia trials. Treatment failure, relapse after CR or death from any cause is important in all patients with acute leukemia; however, the goal of any therapy is improving OS and/or QoL. Using an endpoint of EFS would certainly increase the number of drugs available to treat acute leukemia, but without necessarily improving OS. EFS and OS do not always correlate as the rescue therapies may be effective.

In the GRAALL-R study, the authors indicate that the difference in EFS was mostly due to lower incidence of relapse in the rituximab group (induction failures and deaths during remission were comparable between both arms). The authors do not provide any information on what salvage therapy (including alloSCT) was administered and corresponding responses. They only indicate that a higher number of patients received alloSCT in first CR in the rituximab arm. It is not clear why more patients in the rituximab arm received an alloSCT in CR1 when there was no difference in the baseline characteristics between the 2 arms (specifically proportion of higher risk patients as defined by the authors), induction failures or the number of patients requiring a second induction to achieve a CR1. In post hoc sensitivity analysis, censoring for alloSCT, the EFS was still longer in the rituximab group (P=0.02) and now OS was improved (P=0.02). This may be due to the fact that the 2 groups are no longer comparable as more poorer risk patients received an alloSCT in the rituximab group, and hence a more favorable group of patients are now being evaluated for OS in the rituximab arm (e.g. were more patients > age 40 years sent for alloSCT resulting in a higher proportion of more favorable younger adults with ALL). Also, 15 out of 16 patients who had severe allergic events related to L'asparaginase administration. This is usually a marker of development of anti-asparaginase antibodies. Only 2 allergic events occurred in the rituximab arm. Patients

who had an allergic reaction were switched to Erwinia asparaginase. Therefore, as mentioned in the discussion, the rituximab group could have received higher cumulative doses of L'asparaginase and thus account for differences in EFS. Anti-asparaginase antibodies were not measured in the study.

Following the posting of the pERC initial recommendation and receipt of feedback from stakeholders on the initial clinical guidance report, the CGP provided further clarification on a number of concerns raised by the submitter and PAG.

The submitter highlighted that EFS is a clinically relevant and valuable endpoint in frontline trials and remains the standard and preferred outcome for frontline RCT's in ALL. The pCODR Provincial Advisory Group (PAG) feedback also comments on the relevance of EFS as an endpoint in this population. The CGP considered this feedback and noted that although EFS may be a valid endpoint in pediatric RCTs where OS is extremely good for pediatric patients, this does not hold true for adults with ALL where outcomes are significantly inferior to pediatric ALL patients.

In adolescents and young adults with ALL, outcomes are superior to older patients when using a pediatric regimen. This is seen when comparing to historical data with adult regimens. There has however never been an RCT solely targeting patients whose age range is anywhere from 15/16 years to 39 years. The median age for patients on the GRAALL-2005-R trial was 40.2 years (range 24.5 - 52.6 years).

With regards to the eight randomized controlled trial the submitter referred to within their feedback document in support of the use of EFS as an endpoint in the patient population under consideration, the CGP noted the following:

Trial	Rational by CGP
CCG-1882	Median age was not specified (just "children and adolescents" in the paper; age range, at least 1 year of age - upper age limit not specified), but a breakdown given as: • 1 to 9 years: 50 (32.1%) versus 54 (34.8%) • 10 to 15 years: 73 (46.8%) versus 68 (43.9%) • Over 16 years: 33 (21.2%) versus 33 (21.3%)
CCG1922	Median age was not specified (range, 1-10 years)
ALL97/99	Median age not specified (range, 1-18 years), with age breakdown as: • <2 years: 124 (8%) • 2–9 years: 1219 (76%) • >10 years: 260 (16%)
AIEOP-BFM ALL 2000	Median age is not specified (range, 1-17 years). No breakdown by age provided as the data is only presented as abstract at the 2008 ASH meeting.
CCG-1961	Median age not specified (range, 1-21 years), with age breakdown as: • 1 to 9 years: 249 (38.4%) versus 229 (35.2%) • 10 to 15 years: 324 (49.9%) versus 334 (51.4%) • Over 16 years: 76 (11.7%) versus 87 (13.4%)
CCG-1991	Median age not specified (range, 1-10 years)
COG AALL0232	Median age not specified (range, 1- 30 years). No breakdown provided as data is only presented as abstract at the 2011 ASCO meeting
AO41501	An RCT open for enrollment as of June 2017 in younger adults with ALL (age range 18-39 years) using EFS as primary outcome. In the opinion of the CGP, if there is a difference in favor of inotuzumab, it still does not speak to the efficacy of the drug under review (rituximab).

	The CGP note that the rational for using EFS in this trial would need to be explored further. It is difficult to make a conclusion on the appropriateness of EFS as an endpoint in ALL simply based on the fact that it is being used in a study that is current underway, with unknown results, and no peer-reviewed publication to assess.

Although the submitter makes reference to a number of pediatric, adolescent and young adult studies that have used EFS as a primary endpoint, RCTs in adult patients with ALL are available which use OS as an endpoint and led/will likely lead to drug approval (granted these are relapsed studies):

- Kantarjian et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017 Mar 2;376(9):836-847 - median age 40.8-41.1 years (range, 18-80 years)
- Kantarjian et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016 Aug 25;375(8):740-53. - median age 47 years (range, 18-79 years)

The submitter also commented on the CGP's concerns about the relevance of the comparator used in the GRAALL-2005-R trial to the Canadian setting, a comment that is also brought up by the PAG feedback. The CGP agree that that adoption of the one ALL protocol over another usually has been due to familiarity. However, the leukemia community has adopted a pediatric protocol 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.

Lastly, the submitter commented on the quality of life impact anticipated with the addition of rituximab to current treatment protocols. The CGP re-iterate that quality of life was not an endpoint in the GRAALL-2005-R trial. In the absence of evidence to demonstrate that EFS would translate to improved quality of life for patients, the CGP are unable to support such a claim.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is no net clinical benefit associated with the addition of rituximab to standard chemotherapy for patients with Philadelphia-negative CD20+ B-cell acute lymphoblastic leukemia. This was based the results of the GRALL-2005-R data which did not demonstrate OS and/or quality of life benefit, clinically important endpoints that are relevant for decision making in this setting.

In making this conclusion, the Clinical Guidance Panel also considered that:

- At the current time there is insufficient evidence to recommend routine incorporation of rituximab in intensive chemotherapy for patients with CD20+ ALL.
- While the study of Maury et al. demonstrated improved EFS and fewer relapses, an overall survival advantage was not shown. The Clinical Guidance Panel (CGP) acknowledged a non-significant difference in overall survival between treatment groups is difficult to interpret as the study was not designed to detect significant differences between groups in OS.
- Post hoc sensitivity analysis with censoring of data at the time of transplantation for patients who received an allogeneic transplant during the first remission demonstrated

significant improvement in EFS and OS. This analysis was not considered to be robust as it was a post hoc analysis. The CGP also considered that this observed effect may be due to the fact that the 2 treatment groups are no longer comparable as more poorer risk patients received an alloSCT in the rituximab group, and hence a more favorable group of patients are now being evaluated for OS in the rituximab arm, as well as potentially higher cumulative doses of L'asparaginase being administered in the rituximab arm.

- The addition of rituximab increases the burden of delivery for this treatment and increases toxicity. The impact of this on quality of life was not evaluated in this report.
- The added benefit of rituximab reported by Maury et al. was shown in association with a chemotherapy regimen that is not used in Canadian centers. The CGP was concerned that this same benefit could not be generalized to protocols such as Hyper-CVAD (which is not pediatric-inspired) or the modified Dana Farber protocol (which is generally more intense than the GRAAL-2005 protocol studied in combination with rituximab).
- Compliance with asparaginase dosing was better in the rituximab group which confounds the interpretation of these results.
- The upper limit of the 95% confidence interval for EFS is only just below unity (0.98), suggesting that benefit in EFS might be marginal. The CGP agreed that EFS is not an endpoint that can be used to make decisions on treatment practice.
- Approval in this context would be expected to increase the burden of treatment through prolonged infusions and increased toxicity without improving overall survival. It would also be expected to increase resource utilization in centers that treat patients with ALL.
- It is unclear whether the higher rate of allogeneic stem cell transplant improves outcomes.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma and Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Acute Lymphoblastic Leukemia (ALL) is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (lymph nodes or central nervous system (CNS)) and systemic complaints (chiefly fevers, fatigue and night sweats). Patients typically present to hospital acutely ill, often with infection in neutropenia, electrolyte disturbances related to tumour lysis syndrome or with neurological abnormalities. The majority of patients have circulating blast at presentation and the diagnosis is confirmed by bone marrow histology and ancillary tests like flow cytometry and immunohistochemistry.

2.2 Accepted Clinical Practice

ALL represents approximately 15% of adult cases of acute leukemia and adult treatment protocols are based largely on the principles that led to successful outcomes in children. These principles include the use of sequential multi-drug combinations for remission induction. Agents with activity in ALL induction include corticosteroids, cyclophosphamide, methotrexate, anthracyclines and L-asparaginase. Early application of CNS-directed therapy by direct intrathecal administration and whole-brain radiotherapy is intended to address occult CNS disease.[7] Intensification and maintenance phases may last up to 30 months with some protocols and impose significant personal and financial burdens on affected patients and their families.

A number of factors determine prognosis in ALL. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL.[8] Newer treatment protocols, however, have proven effective across the spectrum of cytogenetic abnormalities and seem to have abrogated some of the risk associated with high-risk cytogenetics in this disease.[9,10] The presence of the Philadelphia chromosome (which results from a balanced translocation between chromosomes 9 and 22) confers sensitivity to tyrosine kinase inhibitors (TKI) and while Philadelphia-positive ALL is not curable with conventional treatment the use of TKIs can be associated with durable remissions and good quality of life. In general, however, patients with Philadelphia-positive ALL are still considered for allogeneic hematopoietic cell transplantation (HCT) in first complete remission.[11] Patients who present with an increased white blood cell count (WBC > 30 x 109/L for B-Cell and > 100 x 109/L for T-Cell) and those over age 34 are at higher risk of adverse outcomes, and patients with both of these risk factors or who fail to achieve complete remission within four weeks of starting treatment are considered for allogeneic HCT in first remission.[10]

The majority of young patients with ALL can expect favourable outcomes with modern chemotherapy protocols. For instance, Storring et al.[12] reported the results of their experience using a modified version of the Dana Farber Cancer Institute protocol at the Princess Margaret Hospital. This pediatric-inspired protocol resulted in 89% of patients achieving a complete remission, five-year relapse free survival of 71% and 5 year OS of 63% was reported. [12] Population-based studies, however, continue to show that the majority of adult patients with ALL with die from their disease.[13]

In contrast to initial treatment, where the standard approach is pediatric-inspired 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 HCT.[14] Patients who fail reinduction or for whom HCT is not feasible due to comorbidities or lack of donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited.

2.3 Evidence-Based Considerations for a Funding Population

The management of B-Cell non-Hodgkin lymphoma was revolutionized by the introduction of monoclonal anti-CD20 antibodies into clinical practice. The addition of rituximab during initial treatment of patients with aggressive non-Hodgkin lymphoma[15-17], or as maintenance following successful induction chemotherapy[18] has led to improved overall and progression-free survival. Toxicity of rituximab is generally limited to infusion reactions, which range from flushing, sneezing and/or fever to urticaria, hypotension and angioedema. Reactions occur most often with the first two infusions and become less pronounced and more uncommon with later cycles. Adding rituximab to standard chemotherapy for ALL, another highly-aggressive CD20-positive B-cell neoplasm, has been shown to improve progression-free survival by decreasing the incidence of relapse in a randomized study carried out by the French GRAAL study group.[19]

2.4 Other Patient Populations in Whom the Drug May Be Used

Other patient groups that the current data could be applied to would be pediatric patients over the age of 15 that are treated with adult ALL treatment regimens. This would not include patients being treated with a pediatric regimen. The benefits of rituximab using pediatric protocols is unknown. Also, patients over the age of 60, able to tolerate intensive induction chemotherapy with curative intent would be candidates for the addition of rituximab if the data confirmed benefit. The addition of rituximab to Lmba protocol has also been studied in Burkitt's leukemia/lymphoma where a RCT has been presented in abstract form demonstrating that patients treated in the rituximab arm had a better EFS (3 year EFS 76%; 95% CI: 69–84 vs 64% in standard arm; 95%CI: 55–72; Logrank P value stratified on treatment group=0.046), and OS (3 year OS 82%; 95% CI: 77–90 vs 71% in standard arm; 95%CI: 63–79; Logrank P value, stratified on treatment group=0.016)[20] Notably, the available evidence in these population would need to be reviewed before a decision I made for use.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

By the deadline of February 28, 2017, no patient advocacy group input was received by the pan-Canadian Oncology Drug Review (pCODR) on the submission for rituximab (Rituxan) in combination with standard of care chemotherapy for Philadelphia chromosome negative, CD20 antigen positive, B-cell precursor acute lymphoblastic leukemia (ALL).

A literature search through MEDLINE (See Appendix A) was undertaken by CADTH to inform the pCODR Expert Review Committee's (pERC) deliberation on patient values as part of its deliberative framework. Of the 13 studies that were selected for full text review, none of the studies discussed the use of rituximab for acute leukemia. However, there was one study discussing lived experiences of adult patients with acute leukemia (including ALL)[5] and one systematic review of patient reported symptoms and quality of life in adults with acute leukemia[21] identified, and are included in the summary below. This search was also supplemented by a grey literature search of national and international patient group websites and cancer forums. Relevant information was compiled to help illustrate some of the patient experiences and perspectives for patients with ALL. pCODR also used the patient input summary from the most recent and relevant pCODR reviews for patients with ALL that were publicly available at the time of this review to inform patient values and experiences with ALL; this key information was gathered by the Canadian Cancer Survivor Network (CCSN), who provided patient input on blinatumomab (Blincyto). It is important to note that the review for blinatumomab was for patients with relapsed or refractory B cell precursor acute lymphoblastic leukemia, and the current review is for patients with untreated B cell precursor acute lymphoblastic leukemia.

Based on the grey literature search, pCODR found personal accounts from seven individual patients on their experiences with acute lymphoblastic leukemia, of which, one patient had experience with rituximab.

From the information gathered, patient reported 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, thrombocytopenia. The current treatments for acute leukemia include chemotherapy, radiotherapy, bone marrow transplant, supportive care, and palliation. While some treatments, such as radiation and cyclophosphamide, have been successful at controlling common aspects of ALL for certain patients, there are a number of side effects. Common side effects of treatment include: fatigue, nausea and vomiting, upset stomach, hair loss, diarrhea or loose bowels and infection. Based on information reported by CCSN, patients indicated that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage with their current therapies. Moreover, because treatments for this cancer are intensive, reports have found that "many elderly patients are deemed unfit for such therapies".[5]

Please see below for a detailed summary of patient experiences with diagnosis and treatment of acute lymphoblastic leukemia and experience with rituximab. Quotes are reproduced as they appeared on the website from personal accounts with no modifications made for spelling, punctuation or grammar.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with acute lymphoblastic leukemia

Based on the information reported from Canadian Cancer Survivor Network (CCSN) who provided input on blinatumomab (Blincyto) for the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia, patients are both physically and psychologically impacted by ALL. The key symptoms experienced by the respondents reported from the CCSN submission for ALL were the following:

Symptoms or Problems Experienced	No. of patients[†]
Tiredness	5 of 6 patients
Frequent minor infections	4 of 8 patients
Discomfort in bones or joints	4 of 8 patients
Neutropenia	4 of 8 patients
Bruising or bleeding	4 of 8 patients
Depression	4 of 8 patients
Anemia	1 of 3 patients
Enlarged spleen, liver or lymph nodes	1 of 3 patients
Mild fever	1 of 3 patients
Thrombocytopenia	1 of 5 patients

[†] not all 8 respondents responded to the question

Based on the systematic review conducted by Leak Bryant et al, "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 were the most common symptom concerns for patients and survivors as they interfere with day to day life and ability to carry out social roles. 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.[21]

Based on the information gathered by the pCODR program through a grey literature search, the following excerpt highlights some of the experiences with ALL:

- Patient: Female
  Age at interview: 55
  Age at diagnosis: 49

Brief outline: She is in remission from acute leukaemia.

The patient stated: "*I do believe that it is sometimes harder for the other person in a relationship to cope. The person with the disease has something to focus on, gets the help and support at the hospital but the partners do get forgotten in all this. There should be counselling readily available for people diagnosed with a cancer and their close relatives/partners. It is not something you may want to go to at first but along the way everyone would identify a time where this would be useful.*"

"Before my diagnosis I used to read articles about couples splitting up after one of them had been diagnosed with cancer and I couldn't understand how this could happen at such a time when they really should be together and helping each other …. now I can see what a devastating effect a cancer diagnosis can have on a couple and family and it really is not easy to deal with all this when you are trying to stay alive."
"We are several years down the line now and I would like to say that all was well but it is not, we have resumed a sort of 'status quo' but we will never be the people we were before I was diagnosed with leukaemia."

"This aspect of wrecking people's lives is really not recognised, people focus on the disease and the treatment but the psychological issues run deep and cracks in relationships become crevasses."

(Source: http://www.healthtalk.org/peoples-experiences/cancer/leukaemia/peoples-profiles/acute-leukaemias-aml-all-bal)

3.1.2 Patients' Experiences with Current Therapy for acute lymphoblastic leukemia

Based on the information gathered by CCSN, when asked what treatments patients had used or were using for ALL, respondents reported the following:

Type of Treatment	No. of patients†
Ara C	1 of 5 patients
Cyclophosphamide	2 of 5 patients
Doxorubicin	2 of 5 patients
Vincristine	2 of 5 patients
Dexamethasone	2 of 5 patients
Methotrexate	2 of 5 patients
Radiation	3 of 5 patients
CNS prophylaxis	0 of 5 patients
Hyper-CVAD	0 of 5 patients
Flag Ida	0 of 5 patients
Cy VP16	0 of 5 patients
Individualized treatment	0 of 5 patients

†not all 8 respondents responded to the question

According to CCSN, respondents to their survey reported that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage. One respondent noted: "*mouth ulcers, extreme pain in veins in arm when a port/Hickman's line was not used, headache from lumbar punctures.*"

Based on the systematic review conducted by Leak Bryant et al, the most common standard treatment for "de novo acute leukemia is intensive chemotherapy," resulting in short and long term physical and psychological effects on QoL. The authors also noted that most patients were both physically and psychologically affected during the induction phase of the treatment, and in particular during week 3 of hospitalization. Nausea was noted as improving over time. The authors also noted that depressive symptoms and anxiety was experienced by patients during treatment. This included intrusive thoughts and avoidance. Symptoms of acute leukemia significantly affects QoL and activities of daily living. This can intensify during chemotherapy. Patients at two years

post treatment for acute leukemia indicated improvement in QoL after entering remission. Experiences were categorized into one of two themes: "(a) believed in life, fought for it, and came through stronger or (b) life went on, adapted, and found a balance in the new life".[21]

Based on the information gathered by the pCODR program through a grey literature search, the following are excerpts of personal accounts on their experiences with current therapies. The information reported below is available on the healthtalk.org at: http://www.healthtalk.org/peoples-experiences/cancer/leukaemia/peoples-profiles/acute-leukaemias-aml-all-bal

- Patient #1: Male
  Age at interview: 43
  Age at diagnosis: 35

Brief outline: A period of stress and tiredness led to a diagnosis of acute lymphoblastic leukaemia. Treatment included chemotherapy, total body irradiation and autologous stem cell transplant. He is in remission.

The individual indicated that he was "*diagnosed with acute lymphoblastic leukaemia and told he would need 6 – 8 weeks in hospital for chemotherapy. During treatment he developed a deep vein thrombosis (DVT) in his left foot and needed heparin injections in his abdomen. [he] was eating poorly because he found the hospital food unappetising and the nurses told him to eat otherwise he would die. They gave him high energy drinks and he began to pick himself up physically. After about six weeks he broke down and begged to be let out of his hospital room and was allowed to be wheeled around the hospital grounds, which helped him to keep going. He was later allowed home for a visit and spent increasing amounts of time at home between treatments over a period of four months. He was then enrolled onto a clinical trial and received total body irradiation followed by an autologous stem cell transplant. It took three weeks for his immune system to recover. This put him into remission.*"

"*Chemotherapy was administered intravenously through a Hickman line and some intrathecally (in his spine). Treatment side effects included mouth ulcers, hair loss, diarrhoea, vomiting, rash, night sweats, and he has been left with numbness in his feet. He experienced complications including pneumonia, sight loss requiring cataract operations, and a second DVT that went from his leg to his lung. He takes warfarin daily to prevent further DVTs*."

- Patient #2: Female
  Age at interview: 39
  Age at diagnosis: 35

Brief outline: Diagnosed with acute lymphoblastic leukaemia after a persistent sore throat and various other symptoms. She had 4 courses of chemotherapy (intravenous and intrathecal) followed by radiotherapy and a bone marrow transplant. She reported that she is in remission.

Upon diagnosis, the patient stated that "*She would need to stay in hospital for at least a month to have chemotherapy and would be in isolation with limited access to her children*."

"*She was started on chemotherapy which made her feel sick, she gained weight from the steroids and started to lose her hair. After a month they allowed her home for a few days during which time she developed a blood clot in her leg and had to be given warfarin daily. During the next month she had intravenous chemotherapy daily as well as a weekly dose of chemotherapy into her spine (intrathecal) to prevent leukaemic cells entering her brain. Then she was allowed out*

again until her blood counts recovered sufficiently to start a further course of daily chemotherapy. She had four courses in all. After the fourth course she developed pneumonia. After three weeks at home with the family she went to a different hospital where she had a week of radiotherapy first to her brain then her whole body as preparation for a bone marrow transplant using her brother as a donor. The radiotherapy caused burns in her mouth and gullet and she developed thrush and she felt so ill that she was given morphine. She was allowed home a few weeks after the transplant and three months later was told she was in remission."

- Patient #3: Female
  Age at interview: 45
  Age at diagnosis: 42

Brief outline: Diagnosed with acute lymphoblastic leukaemia after a variety of symptoms. She spent a year in hospital having intensive chemotherapy followed by radiotherapy. Once in remission she took maintenance chemotherapy tablets for a year.

"*[She] found starting chemotherapy distressing because she didn't like the idea of having poison put into her body. She received chemotherapy intravenously through a Hickman line and intrathecally (in her spine via lumbar punctures). She disliked the Hickman line initially but got used to it. On one occasion the line became infected causing rigors (uncontrollable shaking), and on another there was a blood clot in it causing her head and shoulders to swell up. She became increasingly anxious about having lumbar punctures because the doctors had difficulty inserting the needle. Side effects included hair loss, sickness and a purple rash and [she] was disturbed by her changed appearance. She was prescribed the contraceptive pill to stop her menstrual bleeding and the chemotherapy forced her into an early menopause. After chemotherapy she was given radiotherapy. After a year in hospital she was declared to be in remission and sent home*."

"*She was subsequently put on maintenance chemotherapy consisting of tablets to take at home. While she appreciated getting her life back she felt insecure being away from the health professionals that had looked after her, and at this stage the shock of the whole experience hit her. [She] felt she had lost her identity through prolonged absence from work and was pleased to return to work, part time initially, gradually increasing to full time*."

- Patient #4: Male
  Age at interview: 24
  Age at diagnosis: 23

Brief outline: He was diagnosed with acute lymphoblastic leukaemia after feeling tired on exertion. He spent 35 days in hospital having intensive chemotherapy followed by outpatient chemotherapy. He is in remission but his treatment will continue for another 2.5 years.

"*In the specialist centre, he was told his precursor B cell acute lymphoblastic leukaemia required immediate chemotherapy*."

He had a "*PICC line inserted in his arm for administering chemotherapy, which remained in place for six months before the entry site became inflamed so the line was removed. He tolerated his first course of chemotherapy well but the steroids made him bloated and hungry. The choice of hospital food was limited but after speaking to the caterers he was given extra options, plus his mother and girlfriend, who stayed in the hospital with him, brought in food. [He] found that intrathecal (spinal) chemotherapy gave him severe headaches, which were not alleviated by painkillers, only by lying flat, until this was prevented by using a smaller needle*."

"*[He] found it took time to adjust to life at home again after such a long hospital stay, and also to being treated in the day care centre, where he has been treated ever since with a combination of intravenous, intrathecal and oral chemotherapy. [He] is in remission but his treatment will continue for another two and a half years*."

- Patient #5: Female
  Age at interview: 32
  Age at diagnosis: 28

Brief outline: Diagnosed with acute lymphoblastic leukaemia after finding a mass in her chest, losing weight and feeling breathless. Treatment included intensive chemotherapy, radiotherapy to her brain, and oral chemotherapy.

Upon diagnosis, the patient indicated that "*she was sent to another hospital for treatment, where she would stay for six months. This meant leaving her children with her mother, which was very hard for her. She had a Hickman line fitted and was started on intensive chemotherapy. Her blood cells recovered well after each treatment so she was able to spend many nights at home. Her treatment caused a blood clot on her brain for which she was given daily injections of Clexane to thin her blood. She also became jaundiced and refused to continue with the treatment that was damaging her liver."*

In addition to intravenous chemotherapy via her Hickman line, the patient reported that she had "*some intrathecally (in her spine) as well as oral chemotherapy for two years. After leaving hospital she had radiotherapy to her brain over a 4 week period, which caused her to lose what hair she had left after the chemotherapy. She is in remission*."

3.1.3 Impact of acute lymphoblastic leukemia and Current Therapy on Caregivers

CCSN indicated that ALL affect their quality-of-life and the ability to enjoy life, especially those of young patients and their caregivers. To help illustrate the caregivers' experiences, CCSN included the following quotations from these respondents:

1. *"Learning disabilities, sleep problems, low immune systems."*

2. *"Bone pain tummy pain, nausea."*

3. *"Emotional, fatigue, financial, splitting family up due to treatment (we have a younger child who we were separated from), managing side effects, being away from the world to protect her because of immune system."*

4. *"It's so hard to meet her needs especially when she's too little to express all of them. We have learned her 'language' for how she describes feeling awful, but it 'takes us to the mat'. Her hair loss was especially hard for me because it was her newborn hair, but she was OK with it. It is so gut-wrenching to know what could be her, could be her life, and cancer/cancer treatment takes so much of it away."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with rituximab

According to the drug monograph, the most common adverse effects are infusion-related symptoms, fatigue, headache, rash, neutropenia and infections. Adverse effects are more frequent in older patients, and in patients with high bulk disease. (source: CCO Formulary - August 2016, available at: https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&cad=rja&uact=8&ved=0ahUKEwjo2O611ffTAhVY3mMKHZYyDU8QFghJMAY&url=https%3A%2F%2Fwww.cancercareontario.ca%2Ffile%2F2491%2Fdownload%3Ftoken%3DyoqkwSUZ&usg=AFQjCNF3yVRTvcKUtBm_UfyN2jBqBzL5rQ)

Because there were no patient input submissions for this drug review, the following excerpt is a personal account that was obtained from the Leukemia & Lymphoma Society community forum to help illustrate a patient's lived experience with rituximab. (Source: http://community.lls.org/topic/13977-reactions-to-rituxan/)
Posted on January 1, 2014

The patient reported that "*The first time they tried to give it to me I had a very bad reaction. At first my heart rate went very high and I had extremely intense chills. I felt extremely cold and my teeth were chattering uncontrollably to the point that it was causing my teeth and jaw to hurt. My heart rate then dropped severely. I'm not completely sure but I thought I heard one of the nurses say my blood pressure was below 60 over 40 at one point and my family told me they were on the way down the hall with the crash cart. Fortunately for me the doctors and nurses were ready for my reaction and gave me the drugs I needed to stop the reaction. I don't know exactly what they gave me, but I know it included Dilaudid.*

The second time, I had another reaction, but it wasn't as bad . This time I started to react after about an hour or so into the infusion when they increased the dosage. I started having pain in my trapezius muscle on the right side and it quickly moved to both sides. Then I started feeling pressure in and behind my ears which quickly turned into a rash like hives. The rash seemed to move downward across my shoulders and back and then to my chest, eventually ending up on the inside of my calves. I did have some itching, but it wasn't too bad. I had a little bit of double vision too. The doctors gave me quite bit of intravenous hydrocortisone and oral Benadryl which stopped the reaction."

Posted on January 3, 2014

"*I'm happy to report that my most recent experience with Rituxan (1/3/14) was positive!. They gave it to me very slowly, over 8 hours. I did have a little itching, but no rash and no heart rate issues!!!. I'm really happy I'll be able to continue to get the infusions. My doctors tell me that I will really benefit from it.* "

Posted on January 9, 2014

"*I had another positive experience with Rituxan on 1/8/14. They gave it to me in just under 6 hour and no negative reaction. Much faster than last time (as fast as 300ml/hour at the end. I'm hoping I'll be able to get the infusion as an outpatient next time. Does anyone have any experience with this drug?* "]

3.3 Additional Information

No additional information was identified.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Small number of adult patients with Philadelphia chromosome negative, CD20 positive, B-cell precursor ALL
- Requests for patients under 18 years of age and over 60 years of age

Economic factors:

- Use in hospital during induction phase
- Dose intensity of rituximab administration, up to 18 doses

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that the Dana Farber Cancer Institute protocol is the standard of care for younger adult patients with ALL. PAG noted that older patients may be treated with Hyper-CVAD or dose modified Dana Farber.

4.2 Factors Related to Patient Population

PAG noted 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. PAG is seeking information on whether the results from the GRAALL-R study can be extrapolated to:

- Pediatric patients (under age of 18)
- Patients 60 years of age and over

PAG is seeking guidance on whether it would be appropriate to add rituximab for patients who are currently undergoing induction or consolidation therapy.

4.3 Factors Related to Dosing

Rituximab would be in addition to current chemotherapy. PAG noted that the 375mg/m^2 dose is standard for rituximab in other indications. However, for ALL, the administration schedule is intense during induction and reinduction, if necessary, and during intensification phase.

PAG is seeking information on whether subcutaneous administration of rituximab would be reasonable in this setting, if and when subcutaneous rituximab is available.

4.4 Factors Related to Implementation Costs

PAG noted that when rituximab is administered in outpatient chemotherapy clinics, vial sharing is possible and there would be minimal drug wastage as rituximab is widely used for other indications. However, when rituximab is used in hospital during the induction phase, vial sharing may not be possible as there is limited use of rituximab in hospital for other indications.

The number of patients with Philadelphia chromosome negative, CD20 positive, B-cell precursor ALL would be small. PAG also noted that patients who receive stem cell transplant as part of their treatment would not be eligible to receive rituximab in maintenance phase.

PAG identified there would be an incremental budget impact and a high per patient treatment costs as patients may receive a total of 16 to 18 doses of rituximab.

4.5 Factors Related to Health System

PAG identified that patients are treated in hospital during the induction, consolidation and intensification phases. Patients could be treated in outpatient chemotherapy clinics during the maintenance phase and coordination between the inpatient treatment and outpatient treatment centres would be required. PAG noted that there would be an increase in nursing and pharmacy resources for administration in both inpatient and outpatient settings and increased chemotherapy chair time requirements to administer rituximab and monitor for adverse events for outpatient administration.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One registered clinician provided input on rituximab for ALL. Rituximab is an add-on to current therapy, improving relapse free survival.

Please see below for a summary of specific input received from the registered clinician.

5.1 Current Treatment(s) for this Type of Cancer

The clinician providing input noted that the current treatment is a modified Dana Farber chemotherapy protocol. This is a multi-agent, 2 year pediatric type protocol. High risk patients may also proceed to allogeneic hematopoietic stem cell transplantation

5.2 Eligible Patient Population

The clinician providing input indicated that ALL is quite rare, seeing about 20 new cases per year in their particular jurisdiction.

5.3 Identify Key Benefits and Harms with New Drug Under Review

The benefits are longer event-free survival in patients receiving Rituximab versus those not when the same chemotherapy protocol is used. This comes with no increased adverse events. All patients whose leukemia cells express CD20 seem to benefit.

5.4 Advantages of New Drug Under Review Over Current Treatments

Rituximab is added to current therapy, rather than a substitute. The clinician providing input noted that the three year relapse free survival using the modified Dana Farber protocol is 71% and rituximab should improve this.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinician providing input noted that rituximab wound not be sequence but rather added to first line therapy. It would not replace any current therapies.

5.6 Companion Diagnostic Testing

Not applicable.

5.7 Additional Information

None provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety 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.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients based on input from patient advocacy groups are those in bold.

Table 6.1 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[A]	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of rituximab should be included	Adults with Philadelphia chromosome negative, CD20 antigen positive, B-cell precursor acute lymphoblastic leukemia	Rituximab in combination with standard of care chemotherapy	Acute lymphoblastic leukemia induction protocols This includes, but is not limited to: • Hyper-CVAD[B] • Dana Farber Cancer Institute Protocol[C] • CALGB 8811 Larson regimen[D] • Linker 4-drug regimen[E] • MRC UKALLXII/ECOG2993 regimen[F] • CALGB 10403 regimen[G] • COG AALL0232 regimen[H] • COG AALL0434 regimen with nelarabine[I] • USC ALL regimen based on CCG-1882 regimen[J] • GRAALL-2003 regimen[K] • PETHEMA ALL-96 regimen[L]	• **Overall Survival** • **Event Free Survival** • **Progression Free Survival** • **Relapse Free Survival** • **Relapse** • **Response Rate** • **Duration of Response** • **Time to Response** • **Health Related Quality of Life** • **Adverse Events** • **Serious Adverse Events** • **Withdrawal Due to Adverse Event**

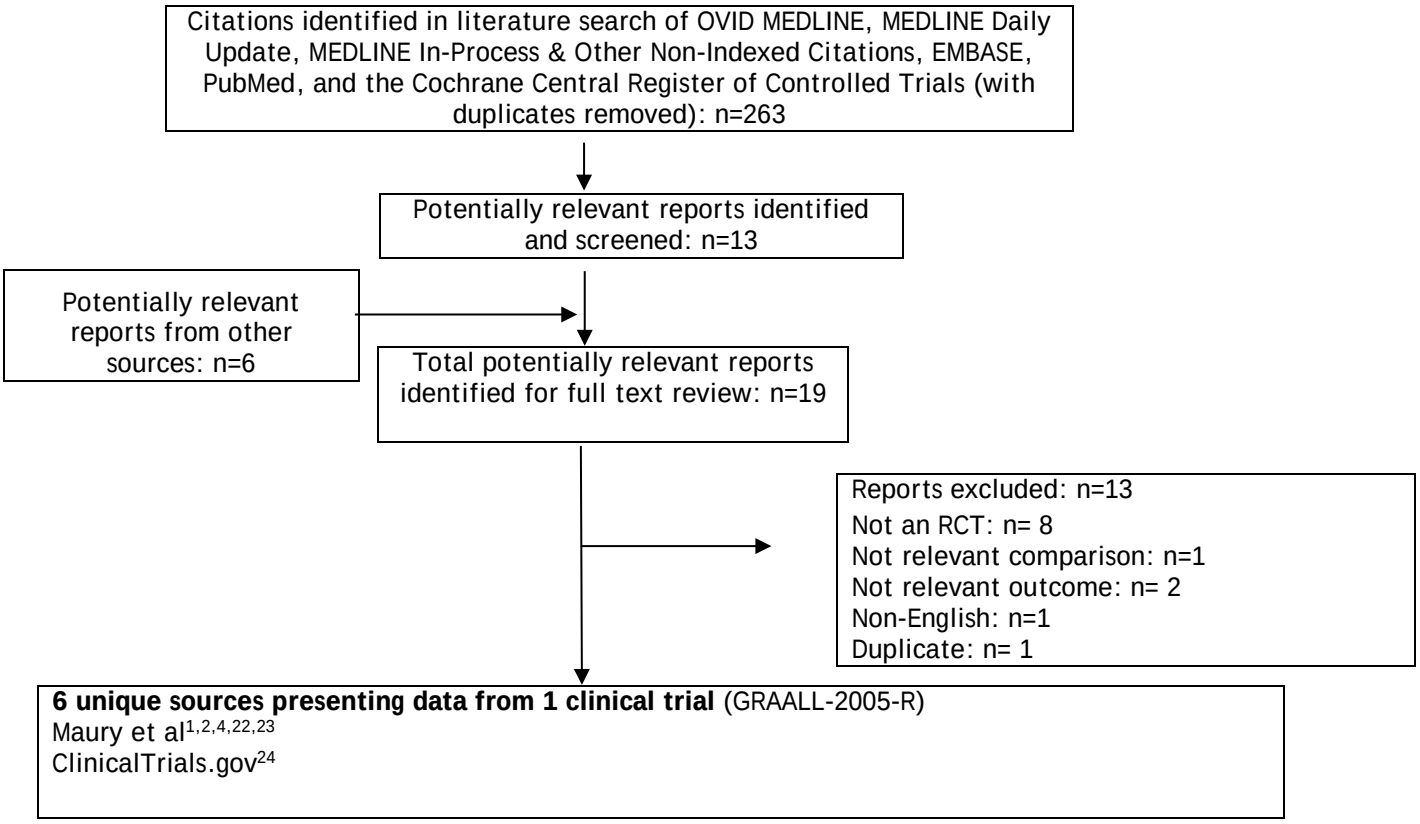
Abbreviations: RCT = randomized controlled trial
Notes:
[A] Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
[B] Hyper-CVAD = hyperfactionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose methotrexate and cytarabine
[C] Dana Farber Cancer Institute Protocol = doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase
[D] CALGB 8811 Larson regimen = daunorubicin, vincristine, prednisone, pegaspargase and cyclophosphamide; for patients aged ≥60 years, reduced doses for daunorubicin, prednisone, and cyclophosphamide
[E] Linker 4-drug regimen = daunorubicin, vincristine, prednisone, and pegaspargase
[F] MRC UKALLXII/ECOG2993 regimen = daunorubicin, vincristine, prednisone, and pegaspargase (induction phase I); cyclophosphamide cytarabine, and 6-MP (induction phase II)
[G] CALGB 10403 regimen = daunorubicin, vincristine, prednisone, and pegaspargase (ongoing study in patients aged <40 years)
[H] COG AALL0232 regimen = daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)
[I] COG AALL0434 regimen with nelarabine = daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen
[J] USC ALL regimen based on CCG-1882 regime = daunorubicin, vincristine, prednisone, methotrexate with augmented pegaspargase (patients 18-57 years)
[K] GRAALL-2003 regimen = daunorubicin, vincristine, prednisone, pegaspargase and cyclophosphamide (patients aged <60 years)
[L] PETHEMA ALL-96 regimen daunorubicin, vincristine, prednisone, pegaspargase and cyclophosphamide (patients aged <30 years)

Results

6.2.2 Literature Search Results

Of the 19 total potentially relevant reports identified, there were 6 unique sources presenting data from 1 clinical trial which were included in the pCODR systematic review[1,2,4,22-24] and 13 reports were excluded. Studies were excluded because they were not RCTs, did not include a relevant comparator, did not include a relevant outcome, were a non-English publication or were a duplicate.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to GRAALL-2005-R *were also obtained through requests to the Submitter by pCODR[25]*

6.2.3 Summary of Included Studies

One randomized open label phase III clinical trial met inclusion criteria, GRAALL-2005-R (a sub-study of GRAALL-2005). Trial details are summarized in the section below in Section 6.3.2.1 Detailed Trial Characteristics.

6.2.3.1 Detailed Trial Characteristics

a) Trials

GRAALL-2005-R (a sub-study of GRAALL-2005) is a randomized, controlled, open-label phase III clinical trial; it compares chemotherapy plus rituximab or hyper-C chemotherapy plus rituximab (rituximab group) to standard dose chemotherapy or hyper-C chemotherapy (control group). For the purposes of this report, data relevant to GRAALL-2005-R are presented in this report, unless otherwise specified.

The study was sponsored by Regional Clinical Research Office, Paris France; with grants from: Programme Hospitalier de Recherche Clinique, French Ministry of Health, Institut National du Cancer, and the Swiss State Secretariat for Education, Research, and Innovation. The study was independent of the manufacturer of rituximab; Roche. According to Maury et al., rituximab was donated by the manufacturer (Roche), which had no role in the study design, data collection, data analysis, or manuscript preparation.[1]

GRAALL-2005 (the main study)

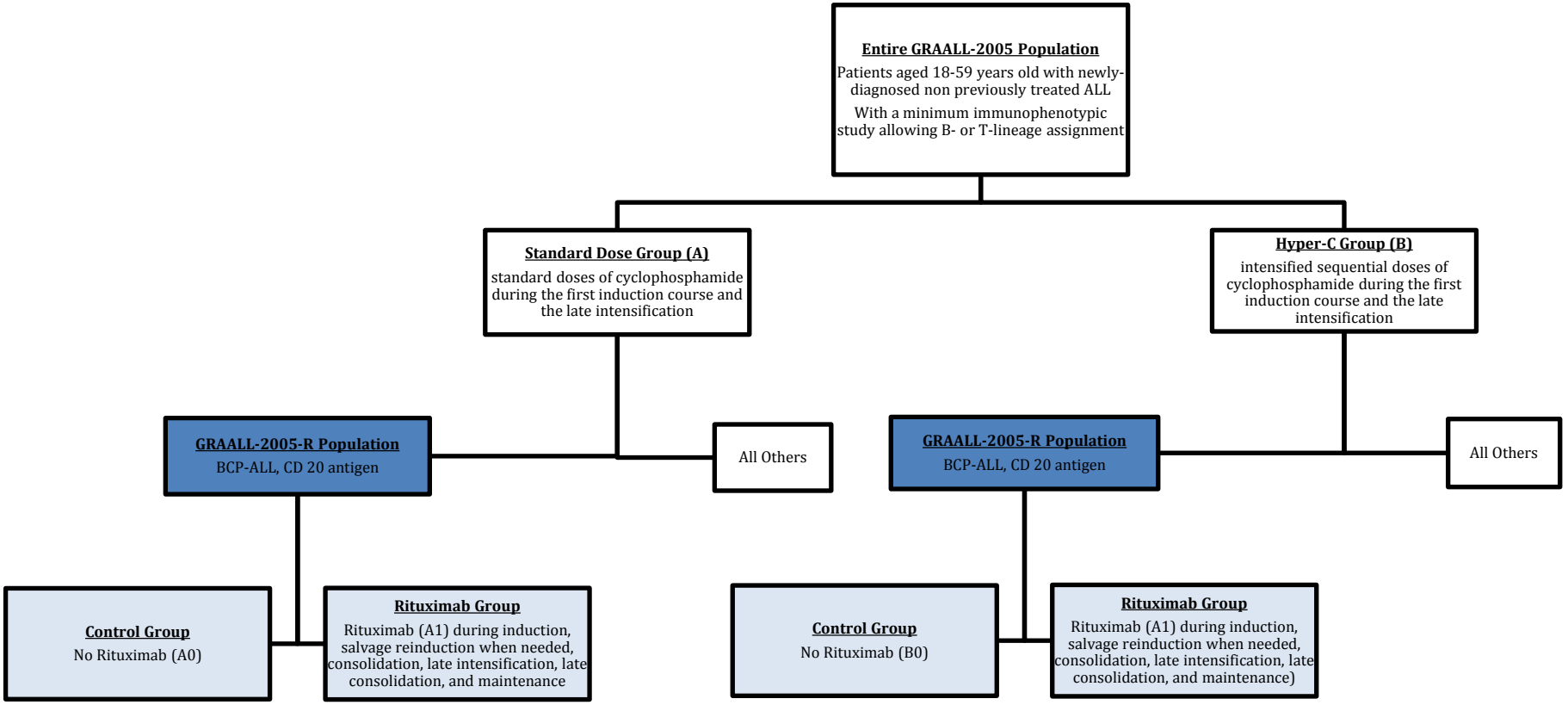
The main study, GRAALL-2005, is a randomized open label phase III clinical trial which included two randomizations aiming to evaluate:

1) intensified sequential cyclophosphamide administration during induction and late intensification (GRAALL-2005 study); and
2) addition of rituximab during induction, consolidation, late intensification and maintenance in CD20-positive Ph-negative B-cell precursor (BCP) ALL (GRAALL-2005-R study).[2]

In GRAALL-2005, all patients included in the trial (BCP-ALL and T-ALL patients) were randomized after the first 1-week prophase to receive either standard doses (arm A) or intensified sequential doses of cyclophosphamide (arm B) during the first induction course and the late intensification.[2] Refer to Figure 6.2 for a flow chart of GRAALL-2005 and GRAALL-2005-R.

According to the main publication [1], the goal of GRAALL-2005 was to increase the 2-year event-free survival from 35% in the standard dose group (arm A) to 45% in the Hyper-C group (arm B). At a 5% level of significance, a total of 405 patients per group were required to detect this difference with a power of 85%. It was therefore decided to include 810 patients in total.[1]

Figure 6.2 Flow Chart of GRAALL-2005 and GRAALL-2005-R[2]



The primary endpoint of GRAALL-2005 was event-free survival.[2] Secondary endpoints included:
- Hematological CR rate after 1 or 2 induction courses
- Early mortality during induction
- Toxicity associated with induction
- Mortality in the first CR
- Cumulative incidence of hematological relapse
- Relapse-free survival
- Overall Survival

Eligibility criteria for GRAALL-2005 are detailed in Table 6.2 Summary of Trial Characteristics of the Included Study.

GRAALL-2005 was conducted in 56 French and 9 Swiss centres; there were no Canadian centres.

GRAALL-2005-R (a sub-study of GRAALL-2005 and the focus of this report)

Only patients randomized from GRAALL-2005 with Ph-negative BCP-ALL expressing the CD20 antigen at the 20% threshold were randomized in the GRAALL-2005-R study. A total of 220 patients from 59 French and Swiss centers were enrolled and randomized in the GRAALL-2005-R study; there were no Canadian centres.[1]

Adults aged 18 to 59 years with CD20-positive, Philadelphia chromosome (Ph)–negative ALL were randomized to either chemotherapy (either A or B) with or without rituximab. Rituximab was given during all treatment phases (during induction, salvage reinduction when needed, consolidation, late intensification, late consolidation, and maintenance) for a total of 16 to 18 infusions.[1] Refer to Figure 6.2 for a flow chart of GRAALL-2005 and GRAALL-2005-R.

According to the Protocol[2], the lack of interaction between randomization studies GRAALL-2005 and GRAALL-2005-R is assumed and to check this, and if it was necessary to readjust the objectives according to the procedures of a flexible test, an interim analysis was planned after 100 patients randomized into the GRAALL 2005-R study were assessable. However, no interim analysis results were presented. It is therefore unclear if the assumption was validated.

Although there was some discrepancy in the reporting of the primary outcome, the submitter confirmed that the goal of the treatment in GRAALL-2005-R was to increase the 2-year event-free survival rate from 50% in the control group (chemotherapy either A or B without rituximab) to 70% in the rituximab group (chemotherapy either A or B with rituximab). At a 5% level of significance, 110 patients per group were expected to provide the required total of 88 events in order to detect this difference with a power of 85%. It was therefore decided to include 220 patients in total.[1]

The primary endpoint for GRAALL-2005-R was event-free survival. Secondary endpoints included:
- Hematological CR rate after 1 or 2 induction courses
- Early mortality during induction
- Toxicity associated with induction, consolidation, late intensification or SCT, and maintenance
- Mortality in the first CR
- Cumulative incidence of hematological relapse
- Relapse-free survival
- Overall Survival[2]

The results presented in this report are from the final analysis.

For trial characteristics of the included study refer to Table 6.2 Summary of Trial Characteristics of the Included Study.

Table 6.2 Summary of Trial Characteristics of the Included Study[1,2]

Trial Design	Eligibility Criteria Protocol[2],	Intervention and Comparator	Trial Outcomes Protocol[2]
GRAALL-2005-R (a sub-study of GRAALL-2005; NCT00327678) Randomized open label phase III clinical trial Randomization occurred no later than day 1 of induction chemotherapy (of the GRAALL-2005 trial). Only patients who were originally randomized in the GRAALL-2005 study and with Ph-negative BCP-ALL expressing CD20 antigen were randomized in the GRAALL-2005-R study. The first randomization occurred between the standard dose (arm A) and the HyperC (arm B) groups as part of the GRAALL-2005 study. This was then followed by a second randomization (GRAALL-2005-R) where arms A and B in the GRAALL-2005 study were further randomised to a control group (chemotherapy without rituximab) (0) versus rituximab (chemotherapy with rituximab) (1), leading to 4 treatment groups (A0 vs. A1 and B0 vs. B1). Please see Figure 6.2 for details on the two randomizations. Enrollment May 2006 - April 2014 220 patients enrolled and randomized from 59 French and Swiss centers to one of the GRAALL-2005-R groups 209 patients (105 in rituximab and 104 in control group) included in modified intention-to-treat analysis Data cut-off date: June 1, 2015 Sponsored by: Regional Clinical Research Office, Paris	<u>Inclusion Criteria for GRAALL-2005:</u> • Aged 18-59 years old with newly-diagnosed non previously treated ALL according to WHO definition. • With a percentage of marrow blasts ≥ 20%. • With or without testicular or CNS involvement. • With a minimum immunophenotypic study allowing B- or T-lineage assignment • Without other evolving cancer or its treatment should be finished at least since 6 months (amendment N°7). • Normal cardiac function (as determined by scintigraphy or echography). • Therapy-related ALL (history of chemotherapy and/or radiotherapy) may be included. <u>Exclusion Criteria for GRAALL-2005:</u> • Patients with lymphoblastic lymphoma with bone marrow blasts<20%. • Patients with a Burkitt-type ALL. • Patients with a history of CML or other myeloproliferative disease. • Not able to receive anthracycline, as well as any other general intensive treatment (amendment N°7). • Cardiomyopathy (NYHA grade 3 or 4). • Thrombophilic disease diagnosed before inclusion (amendment N°7). • Presence of severe comorbidity precluding intensive treatment. • Serum creatinine > 2 times UNL of the laboratory, total bilirubin> 2.5 UNL unless related to ALL, AST or ALT > 5 UNL, unless related to ALL • Progressive severe infection or seropositivity for HIV or HTLV-1, active HBC or HBC hepatitis. • Intolerance to treatment with monoclonal antibody. <u>Eligibility Criteria for GRAALL-2005-R:</u> Only patients randomized with Ph-negative BCP-ALL expressing the CD20 antigen at the usual 20% threshold may be randomized in the GRAALL-2005-R study.	<u>Intervention</u> Standard dose chemotherapy + Rituximab OR Hyper-C chemotherapy + Rituximab <u>Comparator</u> Standard dose chemotherapy OR Hyper-C chemotherapy	<u>Primary:</u> • event-free survival <u>Secondary:</u> • Hematological CR rate after 1 or 2 induction courses • Early mortality during induction • Toxicity associated with induction, consolidation, late intensification or SCT, and maintenance • Mortality in the first CR • Cumulative incidence of hematological relapse • Relapse-free survival • Overall Survival

Abbreviations: ALL = acute lymphoblastic leukemia; BCP = B-cell precursor; CML = chronic myeloid leukemia; CNS = central nervous system; UNL = upper normal limit: WHO = World Health Organization

Notes:

Events were failure of complete remission induction, relapse and death.

Rituximab was donated by Roche; Roche had no role in the study design, data collection, data analysis, or manuscript preparation.

CD20 is defined as baseline expression of the CD20 antigen in more than 20% of leukemic cells.

Table 6.3 Select quality characteristics of included studies of rituximab in patients with ALL[1-3]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
GRAALL-2005-R	Intervention Standard dose chemotherapy + Rituximab OR Hyper-C chemotherapy + Rituximab Comparator Standard dose chemotherapy OR Hyper-C chemotherapy	Event-free survival	220	220 209 in modified intent-to-treat analysis	2 phases of randomization: Phase 1 - randomized into standard dose or Hyper-C Phase 2 - randomized into chemotherapy + rituximab or chemotherapy + no rituximab	NR	No, open label	Modified intent-to-treat analysis	Yes	No	Yes

Abbreviation: ITT = intent-to-treat; NR = not reported

Notes:

During enrollment, 220 patients were randomly assigned to one of the GRAALL-2005/R study groups. Nine patients were not eligible (5 with Ph-positive ALL, 3 with CD20-negative ALL, and 1 with human immunodeficiency virus infection), and 2 patients withdrew consent. These 11 patients were excluded from the modified intention-to-treat analysis presented in this report.

At a 5% level of significance, 110 patients per group is required to detect a difference (an increase in the 2 year event-free survival from 50% in the control group 0 to 70% in the rituximab group 1) with a power of 85%. The lack of interaction between randomization studies GRAALL-2005 and GRAALL-2005-R is assumed.

Details on the method of randomization and concealment are limited, if any, and submitter was unable to provide additional details.

b) Populations

Details of baseline characteristics for GRAALL-2005-R are listed in Table 6.4 Baseline Characteristics of GRAALL-2005-R.

A total of 220 patients were enrolled and randomly assigned to one of the GRAALL-2005/R study groups. Among these, 11 patients were excluded from the modified intention-to-treat analysis presented in this report because patients no longer met the trial inclusion criteria or withdrew consent.

Baseline characteristics were well balanced between groups. The median age was 40.2 years. Most patients had an ECOG PS 1 or higher and a white-cell count less than 30×10^9/liter. Few patients had CNS involvement. Some patients had the following cytogenetic features (t(4;11)(q21;q23)/MLL-AFF1; t(1;19)(q23;p13)/TCF3-PBX1; low hypodiploidy or near triploidy; or complex).

According to the Clinical Guidance Panel (CGP), generally patients present with higher ECOG performance status and are older, however, the CGP acknowledged that the eligibility criterion of 18-59 years may have resulted in a younger patient population.

Table 6.4 Baseline Characteristics of GRAALL-2005-R[1]

Characteristic	All Patients (N=209)	Rituximab Group (N=105)	Control Group (N=104)
Age			
Median (IQR) — yr	40.2 (24.5–52.6)	39.9 (25.4–51.6)	41.5 (24.3–53.4)
≤30 yr — no. (%)	74 (35)	36 (34)	38 (37)
ECOG performance status >1 — no. (%)†	27 (13)	9 (9)	18 (17)
White-cell count ≥30×10^9/liter — no. (%)	44 (21)	21 (20)	23 (22)
CNS involvement — no. (%)‡	13 (6)	7 (7)	6 (6)
Cytogenetic features — no. (%)			
t(4;11)(q21;q23)/*MLL-AFF1*	2 (1)	1 (1)	1 (1)
t(1;19)(q23;p13)/*TCF3-PBX1*	5 (2)	3 (3)	2 (2)
Low hypodiploidy or near triploidy	20 (10)	11 (10)	9 (9)
Complex	21 (10)	10 (10)	11 (11)

* There were no significant between-group differences in the listed baseline characteristics. CNS denotes central nervous system, and IQR interquartile range.
† The Eastern Cooperative Oncology Group (ECOG) performance status is measured on a scale from 0 to 5, with higher numbers indicating increasing disability.
‡ Information about CNS involvement was missing for one patient in the rituximab group.
Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range.
Source: From The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

c) Interventions

According to the GRAALL[2], all patients randomized into the GRAALL-2005-R study will receive all chemotherapy as described for the standard arm A or HyperC arm B in the GRAALL-2005 study. See Table 6.5. Patients randomized in the rituximab arm 1 will receive rituximab infusions, at a dose of 375 mg/m² per infusion, according to the following schedule:

- Day 1 and 7 of the induction course; rituximab injections will be administered after steroids planned for these days.
- Day 1 and 7 of the salvage cycle, if applicable.

- Day 1 and 29 of consolidation 1 and 2. If the order of the blocks is changed according to protocol, the two injections of rituximab planned for blocks 1 and 3 remain assigned to these blocks.
- Day 1 and 7 of the late intensification cycle, rituximab injections will be administered after the corticosteroids planned for these days.
- Day 1 and 29 of consolidation 3.
- Day 1 of reinductions 1, 3, 5, 7, 9 and 11 of the maintenance phase (rituximab injection will be administered after the corticosteroids planned these days).

According to Maury et al[1], patients received acetaminophen and dexchlorpheniramine 30 to 60 minutes before the infusion was started. Of note, when the administration of prednisone or dexamethasone was planned for the same day, the glucocorticoid was also given before the rituximab infusion. No monitoring or replacement of the serum immunoglobulin level was planned.

During the first complete remission, allogeneic hematopoietic stem-cell transplantation was offered to patients who were 55 years of age or younger if they had a suitable donor and were considered to be at high risk. High-risk patients were those who met one or more of the following criteria:

- central nervous system involvement
- a white-cell count of 30×109 per liter or higher
- a CD10-negative immature immunophenotype
- *MLL* (mixed-lineage leukemia) gene rearrangement, defined as t(4;11) chromosomal translocation, *MLL-AFF1* fusion, or an another *MLL* rearrangement
- t(1;19) chromosomal translocation or *TCF3-PBX1* fusion
- low hypodiploidy or near triploidy on karyotype or DNA index analysis
- a complex karyotype, according to the criteria of Moorman and colleagues14
- poor early peripheral-blood blast clearance, defined as a blast count higher than 1×109 per liter at the end of the glucocorticoid prephase
- poor early bone marrow blast clearance, defined by morphologic evidence of more than 5% blasts at the end of the first week of induction chemotherapy
- late complete remission, defined by a need for salvage reinduction to achieve complete remission

Refer to Table 6.5 GRAALL-2005-R Treatments (taken directly from Maury et al. Appendix[4]) for details of the treatments for GRAALL-2005-R Treatments.

Compliance to rituximab during each treatment phase ranged from 76% to 94% (Refer to Table 6.6 Compliance to Rituximab Therapy), with the greatest compliance in induction (94%).[4] Compliance to rituximab at maintenance was not reported, nor were data on duration of response.

According to the Submitter, there were no dose adjustments to rituximab.[25]

Table 6.5 GRAALL-2005-R Treatments[4] [a]

	Drugs	Doses	Schedules
INDUCTION THERAPY:			
Prephase	**PDN**	60 mg/m²/d (PO)	Day -7 to -1
	MTX	15 mg (IT)	Between day -7 and -4
Induction course	**PDN**	60 mg/m²/d (PO)	Day 1 to 14
	VCR	2 mg/d (IV)	Day 1, 8, 15, and 22
	DNR	50 mg/m²/d (IV) 30 mg/m²/d (IV)	Day 1 to 3 Day 15 and 16
	L-ASPA	6,000 IU/m²/d (IV, 1h)	Day 8, 10 and 12 * Day 20, 22, 24, 26 and 28
	CPM	750 mg/m²/d (IV, 3h)	Day 1
		750 mg/m²/d (IV, 3h) or 300 mg/m²/12h (IV, 3h) **	Day 15 (1 infusion) Day 15 to 17 (6 infusions)
	Lenogastrim	263 µg/d (SC or IV)	Day 18 to neutrophil recovery
Salvage reinduction	**IDA**	12 mg/m²/d (IV, 1h)	Day 1 to 3
	Ara-C	2,000 mg/m²/12h (IV, 2h)	Day 1 to 4 (8 infusions)
	Lenogastrim	263 µg/d (SC or IV)	Day 9 to neutrophil recovery
INTERPHASE-1 ¶:			
	VCR	2 mg/d (IV)	Day 1
	DXM	40 mg/d (PO)	Day 1
FIRST CONSOLIDATION PHASE:			
Block 1	**Ara-C**	2,000 mg/m²/12h (IV, 2h)	Day 1 and 2 (4 infusions)
	DXM	10 mg/12h (PO)	Day 1 and 2
	L-ASPA	10,000 IU/m² (IV, 1h) ***	Day 3
	Lenogastrim	263 µg/d (SC or IV)	Day 9 to 13
Block 2	**VCR**	2 mg/d (IV)	Day 15
	MTX	3,000 mg/m²/d (CIV, 24h)	Day 15
	L-ASPA	10,000 IU/m²/d (IV, 1h) ***	Day 16
	6-MP	60 mg/m²/d (PO)	Day 15 to 21
	Lenogastrim	263 µg/d (SC or IV)	Day 23 to 27
Block 3	**MTX**	25 mg/m²/d (IV)	Day 29
	CPM	500 mg/m²/d (IV, 3h)	Day 29 and 30
	VP-16	75 mg/m²/d (IV, 1h)	Day 29 and 30
	Lenogastrim	263 µg/d (SC or IV)	Day 31 to neutrophil recovery
SECOND CONSOLIDATION PHASE:			

Block 4: identical to block 1			
Block 5: identical to block 2			
Block 6: identical to block 3			
LATE INTENSIFICATION (if CR after 1st course):			
	PDN	60 mg/m²/d (PO)	Day 1 to 14
	VCR	2 mg/d (IV)	Day 1, 8, 15, and 22
	DNR	30 mg/m²/d (IV)	Day 1 to 3 Day15 and 16
	L-ASPA	6,000 IU/m²/d (IV, 1h) ***	Day 8, 10, 12, 20, 22, 24, 26 and 28
	CPM	750 mg/m²/d (IV, 3h) 750 mg/m²/d (IV, 3h) or 300 mg/m²/12h (IV, 3h) **	Day 1 Day 15 (1 infusion) Day 15 to 17 (6 infusions)
	Lenogastrim	263µg/d (SC or IV)	Day 18 to neutrophil recovery
LATE INTENSIFICATION (if late CR):			
	IDA	9 mg/m²/d (IV, 1h)	Day 1 to 3
	AraC	2,000 mg/m²/12h (IV, 2h)	Day 1 to 4 (8 infusions)
	Lenogastrim	263 µg/d (SC or IV)	Day 9 to neutrophil recovery
THIRD CONSOLIDATION PHASE:			
Block 7: identical to block 1			
Block 8: identical to block 2			
Block 9: identical to block 3			
MAINTENANCE PHASE:			
	VCR	2 mg/d (IV)	Day 1, month 1 to 12
	PDN	40 mg/m²/d (PO)	Day 1 to 7, month 1 to 12
	6-MP	60 mg/m²/d (PO)	Month 1 to 24
	MTX	25 mg/m²/week (PO)	Month 1 to 24
INTERPHASE-2 [¶] **:**			
	MTX	1,500 mg/m²/d (IV, 30min)	Day 1
	L-ASPA	10,000 IU/m²/d (IV, 1h)	Day 2
CNS THERAPY (triple IT doses are indicated in footnotes):			
CNS prophylaxis	**Triple IT**	N=1	Day 1 and 8 of first induction course
	Triple IT	N=1	Day 29 of consolidation blocks 3 and 6
	Triple IT	N=1	Day 1 and 8 of late intensification if CR in one course Day 8 and 15 late intensification if late CR
	Cranial irradiation		18 Gy in non-SCT patients no irradiation if HSCT
	6-MP	60 mg/m²/d (PO)	During cranial irradiation

If CNS involvement	**Triple IT**	N=8	Between Day -7 and 18 of first induction course
	Triple IT	N=1	Day 12 of salvage reinduction (if needed)
	Triple IT	N=1	Day 8, 20, 24, 29 and 35 of first consolidation phase
	Cranial irradiation		15 Gy before HSCT or 24 Gy in non-HSCT patients
	6-MP	60 mg/m²/d (PO)	During cranial irradiation
RITUXIMAB (patients randomized to the rituximab arm):			
	Rituximab	375 mg/m²/d (IV) ****	Day 1 and 7 of first induction course Day 1 and 7 of salvage reinduction (if needed) Day 1 and 29 of consolidation phase 1, 2 and 3 Day 1 and 7 of late intensification Day 1 of month 1, 3, 5, 7, 9, and 11 of the maintenance therapy

PDN: prednisone; MTX: methotrexate; VCR: vincristine; DNR: daunorubicin; L-Aspa: *E. coli* L-asparaginase, CPM: cyclophosphamide; IDA: idarubicin; Ara-C: cytarabine; DXM: dexamethasone; 6-MP: 6-mercaptopurine; VP-16: etoposide; d: day; IT: intrathecal; PO: per os; SC: subcutaneously; IV: intravenous; CIV: continuous IV; triple IT: consisted of 15 mg MTX, 40 mg Ara-C, and 40 mg methylprednisolone IT.

*: not done if CNS involvement;
**: according to front-line GRAALL-2005 randomization;
***: a switch to the *Erwinia* form of asparaginase (12,000 UI/m²/infusion during late intensification or 20,000 UI/m²/infusion during consolidation) was planned in case of clinical allergic reaction to *E. coli* asparaginase.
****: it was recommended to administer the first dose of rituximab in 2 or 3 fractionated successive daily doses in case of persistent hyperleukocytosis after the steroid prephase, in order to prevent any tumor lysis syndrome.
†: up to 4 weekly interphase-1 cycles were allowed, if waiting for resolution of an induction-related adverse event was needed.
††: up to 2 interphase-2 cycles were allowed prior to HSCT in HSCT patients, if needed logistically.

Source: From supplementary appendix to: The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 6.6 Compliance to Rituximab Therapy[4] [a]

Treatment Phase	% (n/N)
Induction	94% (99/105)
Consolidation Block 1	83% (77/92)
Consolidation Block 3	77% (71/92)
Consolidation Block 4	88% (70/80)
Consolidation Block 6	80% (56/70)
Late intensification	85% (45/53)
Consolidation Block 7	76% (35/46)
Consolidation Block 9	79% (34/43)
Maintenance	NR
Abbreviations: NR = not reported	
Notes: Denominator is the number of patients who started the treatment phase of interest.	
Source: Maury et al [4]	

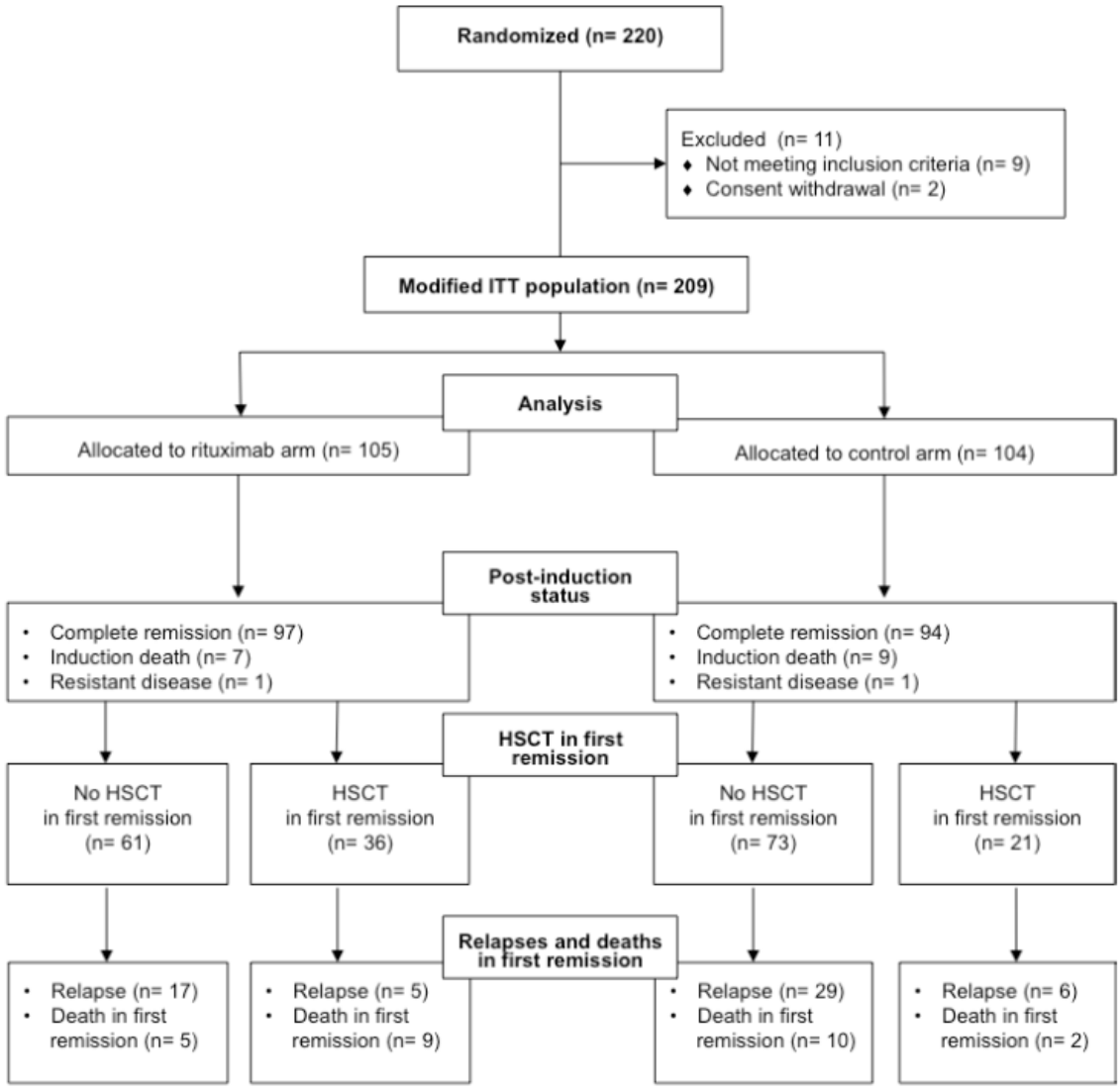
d) Patient Disposition

A total of 220 patients were enrolled, randomly assigned to one of the GRAALL-2005/R study groups. Nine patients were not eligible (5 with Ph-positive ALL, 3 with CD20-negative ALL, and 1 with human immunodeficiency virus infection), and 2 patients withdrew consent. These patients

(n=11) were excluded from the modified intention-to-treat analysis presented in this report (Figure 6.3 Patient Flow Chart).

Details related to the number of patients that were still on treatment at the time of the data cut off were not reported, nor were the number of patients that discontinued treatment, the most common reasons for discontinuing treatment, and subsequent treatment after progression, discontinued, or completion of rituximab.

Figure 6.3 Patient Flow Chart for GRAALL-2005-R Study[a,b,c 4 a]



ITT: intent-to-treat; HSCT: hematopoietic stem cell transplantation.

Notes:
[a] Database locked on June 1, 2015
[b] Reason for exclusion from modified ITT population: not meeting inclusion criteria (n=9; 5 patients with Ph-positive ALL, 3 patients with CD20-negative ALL, and 1 patient with human immunodeficiency virus infection) and consent withdrawal (n=2)
[c] Of note, two patients were lost to follow-up early (i.e., during the first two months of follow-up[1]
Source: From supplementary appendix to: The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053.

e) Limitations/Sources of Bias

- It is unclear how well the study was done to minimise bias. Details of the randomization method and allocation of concealment were unavailable. The study was an open label trial and outcomes were investigator assessed rather than independently assessed. However, the impact on the primary endpoint may have been minimal because it was a composite endpoint (i.e. events were failure of complete remission induction, relapse, and death), which included an objective measure (i.e. death), compared to subjective endpoints such as safety data which have a potentially greater risk of bias. Moreover, it is unclear if the assumption of no interaction between randomizations was validated, since no results to confirm this assumption were reported.
- Despite the limitations and risk of bias noted in the above sections, it may appear reasonable to believe that the overall effect is due to the study intervention. However, greater information on the details of the trial would have strengthened the Methods Team's confidence in their overall conclusions.
- **Major protocol deviations –** Major protocol deviations were not addressed in the publication. Therefore, it is unclear if any major protocol deviations occurred and had impacted the results of the study. This is a form of reporting bias.
- **Lack of trial design details –** Two abbreviated versions of the GRAALL-2005-R study protocol were publicly available[2,23] however, the full details of the trial (e.g. full protocol or Clinical Study Report) were not available. For example, details related to the randomization methods and concealment method were not reported. Therefore, making it difficult to appraise the quality of the trial.
- **Pooling of Data –** Patients in the GRAALL-2005-R study were randomized into 4 treatment groups, yet the results of the study are reported as if there were two groups (chemotherapy versus chemotherapy plus rituximab). This is a form of reporting bias. It is unclear if both chemotherapy treatments (standard dose chemotherapy or HyperC) contributed equally to the treatment effect. The Methods Team would have preferred separate results (standard dose chemotherapy versus standard dose chemotherapy plus rituximab, and HyperC versus HyperC plus rituximab), as there may be potential for a synergistic effect with rituximab in only of the chemotherapy treatments were used; however, this is unknown without the separate data. The Methods Team would have preferred, at the minimum, that the interim results to validate the lack of interaction between randomization were reported.
- **Investigator assessed outcome –** It appears that the outcomes were investigator assessed and no independent assessment was performed. Therefore, there is a potential for risk of bias in subjective outcomes such as quality of life and response.
- **Relapsed-Free Survival –** Relapse-free survival was a secondary outcome, however the results are not reported. This is a form of reporting bias.
- **Secondary endpoints** - The study was not powered to detect a difference in important secondary endpoints like PFS and OS. Notabley, it is possible that difference could exist in these outcomes, but the trial may not have been sufficiently large to demonstrate it.

6.2.3.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes[1]

Event-Free Survival

The primary endpoint for GRAALL-2005-R was event-free survival which was a composite endpoint of failure of complete remission induction, relapse, and death.[1]

After a median follow-up of 30 months (data cut-off June 1, 2015), 48% (101 patients) had had at least one event: 42% (44 patients) in the rituximab group and 55% (57 patients) in the control group. There were 17 failures of complete remission induction (8 in the rituximab group and 9 in the control group), 57 relapses (22 and 35, respectively), and 27 deaths during remission (14 and 13, respectively).[1]

There was a statistically significant difference in event-free survival in favour of the rituximab group (hazard ratio, 0.66 [95% CI, 0.45 to 0.98; *P* = 0.04]. According to Maury et al, patients in the rituximab group had longer event-free survival than patients in the control group (graph not shown here).

In a post hoc sensitivity analysis with censoring of data at the time of transplantation for patients who received an allogeneic transplant during the first remission, event-free survival was still longer in the rituximab group than in the control group (hazard ratio, 0.59; 95% CI, 0.37 to 0.93; P = 0.02).

Rate of Hematologic Remission / Hematological CR rate after 1 or 2 induction courses

There were similar complete remission without salvage reinduction rates (90% versus 88%, *P* = 0.52) as well as complete remission with or without salvage reinduction (92% versus 90%, P = 0.63).

Cumulative Incidences of Relapse

Overall, there were 57 patients that relapsed: 22 in the rituximab group and 35 in the control group. Among the 36 patients in the rituximab group who received a transplant, 5 had a relapse and among the 21 patients in the control group who received a transplant, 6 had a relapse.

At 2 years the cumulative incidence of relapse was estimated at 18% (95% CI, 11 to 27) in the rituximab group and 32% (95% CI, 22 to 42) in the control group. At 4 years, the cumulative incidence of relapse was estimated at 25% (95% CI, 16 to 35) and 41% (95% CI, 30 to 51) respectively. According to Maury et al., the difference in event-free survival was mostly due to a lower incidence of relapse in the rituximab group (subdistribution hazard ratio of 0.52 [95% CI, 0.31 to 0.89; *P* = 0.02]).

Death during the First Remission / Mortality in the first CR

Overall, there were 27 deaths during remission (14 versus 13). Among the 34% (36/105) patients in the rituximab group who received a transplant, 9 of the deaths occurred during remission and among the 20% (21/104) patients in the control group who received a transplant, 2 of the deaths occurred during remission.

At 2 years the cumulative incidence of death during first remission was estimated at 12% (95% CI, 6 to 19) in the rituximab group versus 12% (95% CI, 6 to 19) in the control group. At 4 years, the cumulative incidence of death during first remission was estimated at 16% (95 CI, 9 to 24) and 12% (95% CI, 6 to 19) respectively. The cumulative incidence of death during the first remission was similar in both groups (subdistribution hazard ratio of 0.98 [95% CI, 0.45 to 2.12; *P* = 0.96]).

Death during Induction / Early Mortality During Induction

Overall, there were 7 deaths during induction in the rituximab group and 9 deaths during induction in the control group.

Relapse-free survival

In the GRAALL-2005-R protocol, relapse-free survival is stated as a secondary endpoint. However, relapse-free survival does not appear to be reported in the Study Publication.

Overall Survival

No difference in overall survival was found (hazard ratio, 0.70; 95% CI, 0.46 to 1.07; *P* = 0.10). According to Maury et al, the benefit in event-free survival did not translate into significantly longer overall survival (graph not shown here). In a post hoc sensitivity analysis with censoring of data at the time of transplantation for patients who received an allogeneic transplant during the first remission, overall survival was longer in the rituximab group than in the control group (hazard ratio, 0.55; 95% CI, 0.34 to 0.91; P = 0.02).

Table 6.8 Summary of Efficacy Outcomes[1]

Efficacy Outcomes	Rituximab (n=105)	Control (n=104)
Primary Endpoint - Event-Free Survival		
Hazard ratio	0.66 (95% CI, 0.45 to 0.98; *P* = 0.04)	
Rate at 2 years, %	65% (95% CI, 56 to 75)	52% (95% CI, 43 to 63)
Rate at 4 years, %	55% (95% CI, 46 to 66)	43% (95% CI, 34 to 55)
Secondary Endpoint - Rate of hematologic remission		
Complete remission without salvage reinduction	95 (90)	91 (88)
	P = 0.52	
Complete remission with or without salvage reinduction	97 (92)	94 (90)
	P = 0.63	
Secondary Endpoint - Cumulative incidences of relapse		
No. Relapse, %	22 (21)	35 (34)
Subdistribution hazard ratio	0.52 (95% CI, 0.31 to 0.89; *P* = 0.02)	
Rate at 2 years, %	18% (95% CI, 11 to 27)	32% (95% CI, 22 to 42)
Rate at 4 years, %	25% (95% CI, 16 to 35)	41% (95% CI, 30 to 51)
Secondary Endpoint - Death during the first remission		
No. deaths during remission, %	14 (13)	13 (13)
Subdistribution hazard ratio	0.98 (95% CI, 0.45 to 2.12; *P* = 0.96)	
Cumulative incidence at 2 years, %	12% (95% CI, 6 to 19)	12% (95% CI, 6 to 19)
Cumulative incidence at 4 years, %	16% (95 CI, 9 to 24)	12% (95% CI, 6 to 19)
Secondary Endpoint - Death during Induction		
No., %	7 (7)	9 (9)
Secondary Endpoint - Relapse-free survival	NR	NR
Secondary Endpoint - Overall survival		
Hazard ratio	0.70 (95% CI, 0.46 to 1.07; *P* = 0.10)	
Rate at 2 years, %	71% (95% CI, 62 to 80)	64% (95% CI, 55 to 74)
Rate at 4 years, %	61% (95% CI, 52 to 72)	50% (95% CI, 41 to 62)
Health Related Quality of Life	Not applicable	Not applicable

Abbreviations: CI = confidence interval; NR = not reported

Notes:
Data cut-off as of June 1, 2015
Median follow-up of 30 months
Submitter regards "rate of hematologic remission" as being synonymous with "hematologic remission"[3]
Submitter considered "mortality in the first complete response" as synonymous with "death during the first remission"[3]
Submitter believes that the terms "death during induction" and "early mortality during induction" are synonymous[3]

Additional Outcomes of Interest

Response

Complete response rate, duration of response, time to response were outcomes identified as important by the Clinical Guidance Panel. In terms of response, Maury et al. reported the data on response to initial therapy: early response to therapy, response to induction, minimal residual disease $<10^{-4}$ bone marrow blasts, high-risk ALL, and allogeneic stem-cell transplant during first complete remission.

Table 6.9 Response to Initial Therapy[1,22]

Table 2. Response to Initial Therapy.*

Variable	All Patients (N=209)	Rituximab Group (N=105)	Control Group (N=104)	P Value
Early response to therapy — no. (%)				
Poor peripheral-blood blast clearance	34 (16)	20 (19)	14 (13)	0.35
Poor bone marrow blast clearance	87 (42)	46 (44)	41 (39)	0.58
Response to induction — no. (%)				
Complete remission				
Without salvage reinduction	186 (89)	95 (90)	91 (88)	0.52
With or without salvage reinduction	191 (91)	97 (92)	94 (90)	0.63
Resistant disease	2 (2)	1 (1)	1 (1)	
Death during induction	16 (8)	7 (7)	9 (9)	
MRD $<10^{-4}$ bone marrow blasts — no./total no. (%)				
After first induction course	54/85 (64)	32/49 (65)	22/36 (61)	0.82
After first consolidation phase	70/80 (88)	42/46 (91)	28/34 (82)	0.31
High-risk ALL — no. (%)†	140 (67)	73 (70)	67 (64)	
Allogeneic SCT during first complete remission — no. (%)	57 (27)	36 (34)	21 (20)	

* MRD denotes minimal residual disease, and SCT stem-cell transplantation.
† High-risk acute lymphoblastic leukemia (ALL) was determined according to protocol-specified criteria.

Notes: There is a significant difference in the proportion of patients receiving an allogeneic stem-cell transplant during first complete remission between groups (p=0.029).[22]
Source: From The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Health-Related Quality of Life

Health related quality of life data was not collected, as this was not an endpoint in GRAAL-2005-R. However, health related quality of life was an outcome of interest for the Clinical Guidance Panel.

Harms Outcomes[1,2]

According to the Protocol, a secondary endpoint of GRAALL-2005-R was toxicity associated with induction, consolidation, late intensification or SCT, and maintenance.[2] According to Maury et al., 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.[1] After a request, the submitter also provided some harm data based on the proportion of patients experiencing an severe adverse event as a percentage of the total number of patients in the treatment group.

Grade 3-4 adverse events

Overall (all treatment phases, except maintenance phase), there were more grade 3-4 adverse events reported in the rituximab group compared to the control group (352 versus 282 events). During all treatment phases (except maintenance phase), the most common grade 3-4 adverse events were ALT level increase, sepsis, AST level increase, pain, and nausea, vomiting and diarrhea for both groups. Grade 3-4 adverse events occurred most frequent during the induction phase (187 versus 176 events). Refer to Table 6.10 Reported grade 3-4 adverse events for a breakdown of grade 3-4 adverse events within each treatment phase and overall (all treatment

phases). It is unclear whether or not this data was reported as the number of events per 100 patient-years of treatment exposure.

Severe adverse events

Overall, 246 severe adverse events were reported in 124 patients: 67 patients with one event, 26 patients with two events, 13 patients with three events, and 18 patients with four or more events. According to Maury et al., the overall incidence of severe adverse events did not differ significantly between the groups and although infectious events were slightly more frequent in the rituximab group, the difference was not significant. There was however a difference between groups in severe allergic events. Among 16 severe allergic events that occurred, 15 were due to L-asparaginase administration. Among these, 2 of the severe allergic reactions to L-asparaginase were in the rituximab group. Overall, the cumulative dose of L-asparaginase received was less in the control compared to rituximab group. In terms of severe adverse events, infection and laboratory abnormalities were most commonly reported in both groups (71 versus 55 events, and 22 versus 23 events) Refer to Table 6.11 Severe adverse events for more details.

	Induction	Block 1	Block 2	Block 4	Block 5	Late intensification	Block 7	Block 8
Percentages of patients who received all planned infusions of asparaginase								
Rituximab	59% (62/105)	90% (81/90)	91% (82/90)	91% (73/80)	92% (68/74)	57% (31/54)	87% (39/45)	86% (37/43)
Control	48% (50/104)	81% (67/83)	87% (66/76)	80% (53/66)	84% (53/63)	54% (26/48)	57% (26/46)	50% (21/42)
p-value	0.13	0.09	0.46	0.09	0.19	0.84	0.002	0.001
Percentages of patients who switched from E. coli asparaginase to the Erwinia form								
Rituximab	0/62	0/81	0/82	5% (4/73)	6% (4/68)	3% (1/31)	3% (1/39)	3% (1/37)
Control	0/50	3 (2/67)	3% (2/66)	13% (7/53)	25% (13/53)	39% (10/26)	23% (6/26)	29% (6/21)
p-value	-	0.2	0.2	0.2	0.007	0.001	0.014	0.007

Source: From supplementary appendix to: The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Additional Harms Outcomes of Interest

The Clinical Guidance Panel considered the following harms outcomes important:

Infections

Severe infections were experienced by 67.6% of patients in the rituximab group compared to 52.9% in the control group.[3] As reported in the main publication, there were 126 infection events per 100 patient–years of exposure to treatment that were classified as severe adverse events. According to Maury et al, although infectious events were slightly more frequent in the rituximab group (71 versus 55 events), the difference was not significant.

Cardiovascular

Overall (in all treatment phases, except maintenance phase), grade 3-4 cardiac arrhythmia and other cardiac events were similar between groups (4 versus 4 and 3 versus 4). According to Maury et al., in terms of severe cardiac events, there was no significant difference between groups.

Other harms outcomes identified as important by the CGP included, withdrawal due to adverse event, treatment related death, infusion reactions, progressive multifocal leukoencephalopathy, tumor lysis syndrome, hepatitis b virus reactivation, and mucocutaneous reactions, however these data were not reported.

Table 6.10 Reported grade 3-4 adverse events[4]

Grade 3-4 Adverse event (AE)	Induction		Consolidation blocks 1 to 3		Consolidation blocks 4 to 6		Late intensification		Consolidation blocks 7 to 9		All treatment phases *	
	Rituximab (n=105 pts)	Control (n=104 pts)	Rituximab (n=92 pts)	Control (n=85 pts)	Rituximab (n=80 pts)	Control (n=66 pts)	Rituximab (n= 53 pts)	Control (n= 48 pts)	Rituximab (n=46 pts)	Control (n=46 pts)	Rituximab	Control
Pain	17	12	6	6	3	2	1	3	0	2	27	25
Cutaneous rash	6	3	2	2	1	1	1	1	1	0	11	7
Mucositis	6	10	2	4	1	0	1	0	1	0	11	14
Nausea, vomiting, diarrhea	10	4	6	5	1	3	2	1	2	1	21	14
Constipation	7	5	1	0	0	0	0	0	1	0	9	5
Hemorrhage	4	6	0	0	0	0	0	0	1	0	5	6
Sepsis **	39	35	19	13	9	5	6	7	6	3	40	28
Septic shock	11	17	1	2	1	1	1	1	2	1	5	5
Candidemia	6	10	1	2	0	0	0	0	0	0	1	2
Invasive aspergillosis	7	7	1	0	0	0	0	0	0	0	1	0
Pulmonary (other) ***	5	3	3	1	1	0	1	0	3	1	11	4
AST level increase	10	12	8	4	3	0	5	0	2	1	28	17
ALT level increase	27	25	14	9	8	4	10	1	6	3	65	42
Bilirubin level increase	11	11	2	1	0	0	2	0	0	0	15	12
Pancreatitis	9	7	1	2	0	0	0	0	0	0	10	9
Creatinine level increase	0	0	1	0	0	0	1	0	0	0	2	0
Cardiac arrhythmia	3	2	0	1	0	1	0	0	1	0	4	4
Other cardiac event	1	1	0	1	0	2	1	0	1	0	3	4
Peripheral neuropathy	4	3	6	3	2	1	0	1	0	1	12	9
CNS event	4	3	0	0	0	2	0	0	2	0	6	5
Total Events	**187**	**176**	**74**	**56**	**30**	**22**	**32**	**15**	**29**	**13**	**352**	**282**

Pts: patients; CNS: central nervous system; *: except maintenance; **: defined here as need for IV antibiotics with at least one positive blood culture for bacteria; ***: defined as Grade 3-4 pulmonary AE not related to invasive aspergillosis.

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Table 6.11 Number of severe adverse events occurring per 100 patient-years of exposure of treatment*, [a, b] [1]

Table 3. Severe Adverse Events.*

Event	All Patients (N=209)	Rituximab Group (N=105)	Control Group (N=104)	P Value†
	no. of events (incidence rate)			
No. of patient-yr	261	133	128	
Infection	126	71	55	
Laboratory abnormalities	45	22	23	
Allergy	16	2 (2)	14 (11)	0.002
Neurologic event	12	6	6	
Pulmonary event	8	5	3	
Coagulopathy	6	3	3	
Cardiac event	5	1	4	
Gastrointestinal event	5	3	2	
Other	23	15	8	
Total	246	128 (96)	118 (92)	0.72

* The incidence rate is the number of events per 100 patient-years of exposure to treatment. Incidence rates are shown for the total number of events and for allergy, which was the only adverse event for which there was a significant difference in rates between the rituximab group and the control group.
† P values are for the comparison of incidence rates (two-sided test).

Notes:
[a] Of the 246 patients, 67 patients with one event, 26 patients with two events, 13 patients with three events, and 18 patients with four or more events.
[b] P values only reported for allergy and total.
Source: From The New England Journal of Medicine, Maury S, Chevret S, Thomas X, et al, Rituximab in b-lineage adult acute lymphoblastic leukemia, 375(11), 1044-1053. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Table 6.12 Severe adverse events occurring in patients[3]

Event	All (%)	Rituximab	Control
Infection	60.2	67.6	52.9
Lab Abn	21.5	20.9	2.2
Allergy	7.6	2	11
Neuro	5.7	5.7	5.7
Pulm	3.8	4.7	2.9
Coag	2.8	2.8	2.9
Cardiac	2.4	1	3.8
Gastro	2.4	2.8	2
Other	11	14.2	7.7

6.3 Ongoing Trials

One randomized, phase III, open label trial (NCT01085617) whose recruitment status is unknown was identified as a potentially relevant study.[26] Of note, its unknown if the completion date has passed as the status has not been updated in more than two years. No results are reported in clinicaltrials.gov and it is unclear if subgroup results (relevant for this report: B cell precursor ALL, 20 antigen, Philadelphia negative) will be reported.

Nonetheless, the purpose of this study is to see how well standard chemotherapy works when given together with or without rituximab, and (for patients with T-cell precursor) with or without nelarabine in treating patients with newly diagnosed acute lymphoblastic leukemia. Newly diagnosed, previously untreated acute lymphoblastic leukemia adult patients age 25-65 years with Philadelphia chromosome-negative or -positive were eligible. The primary objectives are: 1) to determine if the addition of a monoclonal antibody (none vs. rituximab) improves event-free survival in patients with newly diagnosed precursor B-cell ALL; and 2) to determine if the addition of nelarabine improves outcome (mucositis score) for patients with T-cell ALL. It is important to note that only results pertaining to B cell precursor ALL, 20 antigen, Philadelphia negative is of interest.

Table 6.12: Ongoing trials of rituximab in ALL[26]

Trial Design	Eligibility Criteria	Interventions	Trial Outcomes

A Randomized Trial for Adults With Newly Diagnosed Acute Lymphoblastic Leukemia
NCT01085617
 	
Randomized, phase III, open label trial
 	
Estimated Enrollment n=720
Study Start Date: Jan 2010
Estimated Primary Completion Date: Jan 2016 (final data collection date for primary outcome measure)
 	
The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years
	• Adult age 25-65 years
	• Newly diagnosed, previously untreated acute lymphoblastic leukemia
	  ○ A pre-phase steroid treatment of 5-7 days is required and can be started prior to registration
	• Philadelphia chromosome-negative or -positive patients are eligible
	• No blast transformation of chronic myeloid leukemia
	• No mature B-cell leukemia [i.e., Burkitt disease t(8,14)(q24 ;q32)] or variant c-myc translocations [e.g., t(2;8)(p12;q24), t(8;22)(q24;q11)]
	• Patients who undergo study transplantation must have HLA-compatible sibling or unrelated donor
	  ○ 8/8 molecular match at -A, -B, -C, and -DR (DQ mismatch is permitted)
	• Patients meeting ≥ 1 the following criteria are considered high-risk:
	  ○ Over 40 years old
	  ○ WBC ≥ 30 x 10^9/L (precursor-B) OR ≥ 100 x 10^9/L (T-lineage)
	  ○ Any 1 or more of the following cytogenetic abnormalities:
	  ▪ t(4;11)(q21;q23)/MLL-AF4
	  ▪ Low hypodiploidy/near triploidy (30-39 chromosomes/60-78 chromosomes)
		Biological: palifermin
		Biological: rituximab
		Drug: cyclophosphamide
		Drug: cytarabine
		Drug: daunorubicin hydrochloride
		Drug: etoposide
		Drug: fludarabine phosphate
		Drug: imatinib mesylate
		Drug: melphalan
		Drug: mercaptopurine
		Drug: methotrexate
		Drug: nelarabine
		Drug: pegaspargase
		Drug: vincristine sulfate
		Procedure: allogeneic hematopoietic stem cell transplantation
		Procedure: assessment of therapy complications
			Primary:
			•Event-free survival
			•Toxicity related to pegaspargase
			•Mucositis score in patients treated with palifermin
			
			Secondary:
			•Anti-asparaginase antibodies in patients treated with monoclonal antibody therapy
			•Overall survival
			•Complete remission rate
			•Minimal-residual disease quantification after first phase of

Trial Design	Eligibility Criteria	Interventions	Trial Outcomes
Location: United Kingdom Sponsor: University College London Hospitals	▪ Complex karyotype (≥ 5 chromosomal abnormalities) ▪ Philadelphia chromosome t(9;22) (q34;q11)/BCR-ABL1 (detected by cytogenetic or molecular methods) o High-risk minimal-residual disease after completion of part 2 standard induction therapy • No known HIV infection • Not pregnant or nursing (no nursing during and for 12 months after completion of study therapy) • Negative pregnancy test • Fertile patients must use effective contraception during and for up to 12 months after completion of study therapy	**Radiation:** total-body irradiation	induction and post-transplantation •Relapse rate (including bone marrow and central nervous system relapse) •Death in Complete remission

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on rituximab for acute lymphoblastic leukemia (ALL). Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

Search Strategy for Patient Values

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

Line #	Searches	Results
1	Rituximab/	11134
2	(174722-31-7 or 4F4X42SYQ6).rn,nm.	11134
3	(rituximab* or rituxan* or rituxin* or mabthera* or mab thera or reditux* or HSDB7455 or HSDB 7455 or IDEC 102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or GP2013).ti,ab,ot,kf,hw,rn,nm,kw.	18134
4	or/1-3	18134
5	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/	25031
6	(acute adj3 (lymphocytic or lymphoblastic or lymphoid or lymphatic or lymphocyte or B-Cell or T-Cell) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	34197
7	((precursor cell lymphoblast* or precursor B-Cell or precursor B-cells or pre-B-cell or pre-B-cells or precursor T-cell or precursor T-cells or CALLA-positive or mixed-cell or null-cell) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	888
8	(acute adj (leukemia* or leukaemia*)).ti,ab,kf,kw.	20855
9	lymphoblastic lymphoma*.ti,ab,kf,kw.	1998
10	or/5-9	58152
11	exp patient acceptance of health care/ or caregivers/	232321

12	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ti.	353608
13	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab,kf.	340117

14	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2	267393
15	((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2	66911
16	(patient adj (reported or centered* or centred* or focused)).ti,ab,kf.	34954

17	(treatment* adj2 (satisf* or refus*)).ti,ab,kf.	9117
18	(lived experience* or shared decision making).ti,ab,kf.	8583
19	or/11-18	908089
20	4 and 19	952
21	10 and 19	2498
22	4 and 10 and 19	18
23	limit 20 to (english language and yr="2007 -Current")	795
24	exp patient acceptance of health care/ or exp patient participation/ or exp patient preference/ or exp patient satisfaction/ or caregivers/ or exp consumer participation/	247273
25	patient-reported outcome*.ti,ab.	8414
26	patient*.jw.	13178
27	((patient or patients or care giver* or caregiver* or carer or carers or family or families or consumer or consumers or public or layman or laymen or lay-man or lay-men or lay-person* or layperson* or user*) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or engage* or involvement)).ti.	62225
28	((patient or patients or care giver* or caregiver* or carer or carers or family or families or consumer or consumers or public or layman or laymen or lay-man or lay-men or lay-person* or layperson* or user*) adj3 (preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or engage* or involvement)).ab. /freq=2	75143

29	or/24-28	350459
30	4 and 29	188
31	limit 30 to (english language and yr="2007 -Current")	164
32	10 and 29	375
33	limit 32 to (english language and yr="2007 -Current")	169
34	limit 22 to (english language and yr="2007 -Current")	12
35	31 or 34	175

Search Strategy for Systematic Review

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2017, **Embase** 1974 to 2017 March 06, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	Rituximab/	70712
2	(174722-31-7 or 4F4X42SYQ6).rn,nm.	55489
3	(rituximab* or rituxan* or rituxin* or mabthera* or mab thera or reditux* or HSDB7455 or HSDB 7455 or IDEC 102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or GP2013).ti,ab,ot,kf,hw,rn,nm,kw.	80165
4	or/1-3	80165
5	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/	68836

6	(acute adj3 (lymphocytic or lymphoblastic or lymphoid or lymphatic or lymphocyte or B-Cell or T-Cell) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	81970
7	((Precursor cell lymphoblast* or precursor B-Cell or precursor B-cells or pre-B-cell or pre-B-cells or precursor T-cell or precursor T-cells or CALLA-positive or mixed-cell or null-cell) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	2046
8	(acute adj (leukemia* or leukaemia*)).ti,ab,kf,kw.	49931
9	Lymphoblastic lymphoma*.ti,ab,kf,kw.	4785
10	or/5-9	142035
11	4 and 10	1651
12	11 use ppez,cctr	229
13	*Rituximab/	16502
14	(rituximab* or rituxan* or rituxin* or mabthera* or mab thera or reditux* or HSDB7455 or HSDB 7455 or IDEC 102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or GP2013).ti,ab,kw.	50628
15	or/13-14	51564
16	exp Acute lymphoblastic leukemia/	68836
17	(acute adj3 (lymphocytic or lymphoblastic or lymphoid or lymphatic or lymphocyte or B-Cell or T-Cell) adj3 (leukemia* or leukaemia*)).ti,ab,kw.	81863
18	((precursor cell lymphoblast* or precursor B-Cell or precursor B-cells or pre-B-cell or pre-B-cells or precursor T-cell or precursor T-cells or CALLA-positive or mixed-cell or null-cell) adj3 (leukemia* or leukaemia*)).ti,ab,kw.	2014
19	(acute adj (leukemia* or leukaemia*)).ti,ab,kw.	49805
20	lymphoblastic lymphoma*.ti,ab,kw.	4776
21	or/16-20	141879

22	15 and 21	760
23	22 use oemezd	563
24	12 or 23	792
25	limit 24 to english language	741
26	remove duplicates from 25	585
27	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	1039026
28	Randomized Controlled Trial/	932216
29	exp Randomized Controlled Trials as Topic/	252697
30	"Randomized Controlled Trial (topic)"/	133715
31	Controlled Clinical Trial/	571305
32	exp Controlled Clinical Trials as Topic/	264245
33	"Controlled Clinical Trial (topic)"/	11122
34	Randomization/	195563
35	Random Allocation/	191697
36	Double-Blind Method/	380927
37	Double Blind Procedure/	141666
38	Double-Blind Studies/	244531
39	Single-Blind Method/	68314
40	Single Blind Procedure/	29989

41	Single-Blind Studies/	69764
42	Placebos/	331351
43	Placebo/	333868
44	Control Groups/	275609
45	Control Group/	275511
46	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3489837
47	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	697859
48	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2249
49	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	1283980
50	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	82957
51	allocated.ti,ab,hw.	150071
52	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	92603
53	or/27-52	4517096
54	26 and 53	74
55	conference abstract.pt.	2476668
56	54 not 55	38
57	26 and 55	283
58	limit 57 to yr="2012 -Current"	201
59	56 or 58	239

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#12	Search #10 AND #11	11
#11	Search publisher[sb] OR 2017/03/03:2017/03/07[edat]	517571
#10	Search #3 AND #9	328
#9	Search #4 OR #5 OR #6 OR #7 OR #8	100249
#8	Search Lymphoblastic lymphoma*[tiab]	1933
#7	Search Acute[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab])	93313
#6	Search (Precursor cell lymphoblast*[tiab] OR precursor B-Cell[tiab] OR precursor B-cells[tiab] OR pre-B-cell[tiab] OR pre-B-cells[tiab] OR precursor T-cell[tiab] OR precursor T-cells[tiab] OR CALLA-positive[tiab] OR mixed-cell[tiab] OR null-cell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab])	2023
#5	Search acute[tiab] AND (lymphocytic[tiab] OR lymphoblastic[tiab] OR lymphoid[tiab] OR lymphatic[tiab] OR lymphocyte[tiab] OR B-Cell[tiab] OR T-Cell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab])	39637
#4	Search Precursor Cell Lymphoblastic Leukemia-Lymphoma[mh]	24246
#3	Search #1 OR #2	17207
#2	Search rituximab*[tiab] OR rituxan*[tiab] OR rituxin*[tiab] OR mabthera*[tiab] OR mab thera[tiab] OR reditux*[tiab] OR HSDB7455[tiab] OR HSDB 7455[tiab] OR IDEC 102[tiab] OR IDEC102[tiab] OR IDEC-C2B8[tiab] OR IDECC2B8[tiab] OR GP2013[tiab]	15252
#1	Search Rituximab[mh] OR 174722-31-7[rn] OR 4F4X42SYQ6[rn]	10564

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Rituxan/rituximab, acute lymphoblastic leukemia

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Rituxan/rituximab, acute lymphoblastic leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

American Society of Hematology (ASH)
http://www.bloodjournal.org/page/ash-annual-meeting-abstracts

Search: Rituxan/rituximab, acute lymphoblastic leukemia – last 5 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Rituximab (rituxan) and acute lymphoblastic leukemia.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of June 1, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team. The SIGN-50 Checklist used in this review is included in Table X below.

Table 1. SIGN50 Checklist for Randomized Controlled Trials [19]

SECTION 1: INTERNAL VALIDITY		
In a well conducted RCT study...		Does this study do it?
1.1	The study addresses an appropriate and clearly focused question.	Yes. To confirm the potential benefit of adding rituximab to chemotherapy in patients with Ph-negative, B-lineage ALL expressing the CD20 antigen.
1.2	The assignment of subjects to treatment groups is randomised.	Unclear. Randomization is mentioned, but the method for randomization was not specified in the publication or the protocol. The Submitter was unable to provide additional details on the method of randomization as they did not conduct the trial and had no access to the trial data. Of note, patients were initially randomized to standard chemotherapy or HyperC prior to randomization of rituximab or no rituximab. According to the Protocol[2], the lack of interaction between randomization studies GRAALL-2005 and GRAALL-2005-R is assumed. To check this assumption and if it was necessary to readjust the objectives according to the procedures of a flexible test, an interim analysis was planned after 100 patients randomized into the GRAALL 2005-R study were assessable. However, no interim analysis results were presented. It is therefore unclear if the assumption was validated. It is unclear what bias may have been introduced due to the treatment patients were originally randomised to in GRALL-2005.
1.3	An adequate concealment method is used.	Unclear. Enrollment procedure briefly mentioned in protocol, but details of concealment are not reported. The Submitter was unable to provide additional details on the method of concealment as they did conduct the trial and had no access to trial data.
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	No. Open label study. The open label design has the potential to bias outcomes, including the primary endpoint, event free survival. According to the Clinical Guidance Panel, a blinded study would be difficult to conduct because of the premedication required for patients treated with rituximab. Although an open label study was reasonable, there is a risk for bias in subjective outcomes of quality of life. It is notable that the primary outcome is a composite endpoint which includes 2 subjective endpoints (relapse and failure of complete remission induction).
1.5	The treatment and control groups are similar at the start of the trial.	Yes. Baseline characteristics look reasonably similar.
1.6	The only difference between groups is the treatment under investigation.	No. Patients were initially randomized to standard chemotherapy or HyperC prior to randomization of rituximab or no rituximab. As well, during the first complete remission, allogeneic hematopoietic stem-cell transplantation 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. More patients in the rituximab group than in the control group underwent allogeneic stem-cell transplantation during the first remission. The magnitude and direction of bias due to imbalances of these baseline characteristics is unknown. More patients in the control group

		also had less overall cumulative doses of L-asparaginase. Given that this is an active component of the treatment protocol, the removal of this agent may have resulted in more favourable outcomes in the rituximab group but the magnitude of the impact is unknown.
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Primary outcome, event-free survival, is stated in the study and results are reported. Events are defined as failure of complete remission induction, relapse, and death. Secondary outcomes are stated and results are reported; however, definitions of the secondary outcomes were not available. Outcomes appear to be valid and reliable. The Submitter believes the outcomes for the trial subjects were investigator-assessed, and not independently-assessed. However, this conclusion could not be confirmed with the corresponding authors, as the trial was not conducted by the submitter.[25] Health related quality of life data was not collected, as this was not an endpoint in GRAALL-2005-R. However, health related quality of life was an outcome of interest for the Clinical Guidance Panel and patients.
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Two patients, both in the rituximab group, were lost to follow-up during the first 12 months of follow-up.[1] No further information regarding the number of patients that dropped out or the method for dealing with missing data was available. This is likely to have minimal impact on the overall trial results.
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	No. Modified intent-to-treat analysis was used in the first randomisation for the GRAALL-2005 study. Details on the method used to deal with missing data were not available. Intent to treat analysis not a modified intent to treat analysis should have been performed. It is preferred that the safety outcomes use the per protocol population (only patients who received treatment), rather than the modified intent-to-treat population. In the modified intent-to-treat analysis, a total of 11 patients were excluded from the analysis [9 patients were not eligible (5 with Ph-positive ALL, 3 with CD20-negative ALL, and 1 with human immunodeficiency virus infection), and 2 patients withdrew consent)]. Though this modified intent-to-treat analysis likely does not impact the study results given the small number of patients (n=11) excluded from the analysis.[1]
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Unclear. There were multiple sites but no site/centre specific data were given.
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias?	It is unclear how well the study was done to minimise bias. Details of the randomization method and allocation of concealment were unavailable. The study was an open label trial and outcomes were investigator assessed rather than independently assessed. However, the impact on the primary endpoint may have been minimal because it was a composite endpoint (i.e. events were failure of complete remission induction, relapse, and death), which included an objective measure (i.e. death), compared to subjective endpoints such as safety data which have a potentially greater risk of bias. Moreover, it is unclear if the assumption of no interaction

		between randomizations was validated, since no results to confirm this assumption were reported.
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Despite the limitations and risk of bias noted in the above sections, it may appear reasonable to believe that the overall effect is due to the study intervention. However, greater information on the details of the trial would have strengthened the Methods Team's confidence in their overall conclusions.
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Refer to Clinical Guidance Panel's Interpretation and Conclusion.
2.4	**Notes:** **Major protocol deviations –** Major protocol deviations were not addressed in the publication. Therefore, it is unclear if any major protocol deviations occurred and had impacted the results of the study. This is a form of reporting bias. **Lack of trial design details –** Two abbreviated versions of the GRAALL-2005-R study protocol were publicly available[2,23] however, the full details of the trial (e.g. full protocol or Clinical Study Report) were not available. For example, details related to the randomization methods and concealment method were not reported. Therefore, making it difficult to appraise the quality of the trial. **Pooling of Data –** Patients in the GRAALL-2005-R study were randomized into 4 treatment groups, yet the results of the study are reported as if there were two groups (chemotherapy versus chemotherapy plus rituximab). This is a form of reporting bias. It is unclear if both chemotherapy treatments (standard dose chemotherapy or HyperC) contributed equally to the treatment effect. The Methods Team would have preferred separate results (standard dose chemotherapy versus standard dose chemotherapy plus rituximab, and HyperC versus HyperC plus rituximab), as there may be potential for a synergistic effect with rituximab in only of the chemotherapy treatments were used; however, this is unknown without the separate data. The Methods Team would have preferred, at the minimum, that the interim results to validate the lack of interaction between randomization were reported. **Investigator assessed outcome –** It appears that the outcomes were investigator assessed and no independent assessment was performed. Therefore, there is a potential for risk of bias in subjective outcomes such as quality of life and response. **Relapsed-Free Survival –** Relapse-free survival was a secondary outcome, however the results are not reported. This is a form of reporting bias. **Secondary endpoints** - The study was not powered to detect a difference in important secondary endpoints like PFS and OS. Notably, it is possible that difference could exist in these outcomes, but the trial may not have been sufficiently large to demonstrate it.	
Abbreviations: ALL = acute lymphoblastic leukemia **Source:** [19]		

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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