NHS England

Evidence review: Addition of Rituximab to standard chemotherapy for newly diagnosed CD20 positive B-cell precursor Acute Lymphoblastic Leukaemia

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Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Introduction

- Acute lymphoblastic leukaemia (ALL) is a heterogeneous haematological disorder that is characterised primarily by an overproduction of immature lymphocytes in the bone marrow; however, it is not uncommon for ALL to be present in extramedullary sites such as the CNS, testes, lymph nodes (Jabbour et al 2005).
- ALL is broadly classified by the cell lineage that is affected: B-cell versus T-cell. B-cell ALL (B-ALL) represents 75% of all adult ALLs (Pui et al 2006).
- Precursor B-lymphoblastic leukaemia, also known as B-cell acute lymphoblastic leukaemia and B-cell acute lymphocytic leukaemia, is the most common type of ALL. In precursor B-lymphoblastic leukaemia, B cells are at an early stage of maturation.
- B-ALL can be further categorised as Philadelphia chromosome[1] (Ph) positive, Ph-negative, or Ph-like. Depending on the stage of developmental arrest, B-cells will have a distinct immunophenotype (Zhou et al 2012).
- The clinical signs and symptoms associated with ALL are either a consequence of bone marrow failure (infections, bruising, petechiae, pallor and tiredness) or consequence of the uncontrolled proliferation of the blasts (lymphadenopathy, hepatosplenomegaly, cranial nerve palsies) (Jabbour et al 2005).
- While being a lethal disease in the 1960s, now over 80% of children are being cured. In contrast, treatment of ALL in adults has proven to be more challenging as the leukaemias are more resistant to chemotherapy and there is a reduced treatment tolerance particularly in elderly patients (Linker et al 2002, Rowe 2005).
- The majority of adult patients with ALL will have a response to multiagent induction chemotherapy, with complete remission (CR) rates as high as 93%, however, the majority of these patients will relapse and ultimately succumb to their disease. Those most likely to relapse include older patients and those with high risk cytogenetics, unfavourable molecular mutations, and the presence of minimal residual disease (MRD)[2] following induction chemotherapy (Linker et al 2002, Rowe 2005).
- Rituximab is a chimeric monoclonal antibody that targets CD20[3] on the surface of B-cells. Although the majority of B cells express the CD20 antigen, it is only present on 30 to 50% of B-cell precursor ALL blasts. However, CD20 expression in adults with B-cell precursor ALL has been associated with poor prognosis; this has prompted the incorporation of rituximab into chemotherapy regimens (Zhou et al 2012, Maury 2016).

Existing national policies and guidance

- No relevant published guidance from the National Institute of Health and Care Excellence (NICE) regarding first line treatment of ALL was found.

1 The Philadelphia chromosome or Philadelphia translocation (Ph) is a specific genetic abnormality in chromosome 22 of leukaemia cancer cells

2 Minimal residual disease (MRD) is the name given to small numbers of leukaemic cells (cancer cells from the bone marrow) that remain in the patient during treatment or after treatment when the patient is in remission (no symptoms or signs of **disease**). It is the major cause of relapse in cancer and leukaemia.

3 CD20 is a protein (antigen) expressed on normal and malignant B cells during nearly all stages of differentiation. It may be found in higher than normal amounts in certain types of B-cell lymphomas and leukaemias

The indication and epidemiology

- ALL is a rare cancer. It occurs at all ages but is more prevalent among children than adults and, importantly, accounts for a much higher proportion of cancers in that age group. In the UK based on Cancer Research UK incidence statistics in 2015, there were 832 reported new cases of ALL. Of these approximately 300 were adults (Cancer Research UK 2018).
- Worldwide, the incidence of ALL among younger children aged between 1 and 4 years is high at 3-5 per 100,000 per year and this is often referred to as the "childhood peak". The incidence in infants, older children and adults is ~1/100,000/year (Abbasi et al 2013).
- ALL can be B or T cell but in adults B cell ALL subtypes are more predominant with approximately 17% being the T cell subtype. In the UK this equates to about 250 cases of the B cell ALL subtype per year. Of these 30-50 % will be CD20 positive (defined as ≥20% leukaemic cells expressing CD20 as measured by immunohistochemistry). Clinically, expression of CD20 has been shown to be an independent predictor of relapse in adult patients with B-ALL (Zhou et al 2012, Maury et al 2016).
- Although the cure rate in children is over 80%, the 5-year overall survival (OS) is about 29% to 41% in adults with ALL, with most of the deaths attributed to disease relapse and significant treatment related complications (Horvat et al 2018).

Standard treatment and pathway of care

- ALL treatment protocols take around two to three years. Standard chemotherapy for ALL consists of several months of intensive multidrug induction, consolidation and intensification chemotherapy (including steroids, vincristine, asparaginase, daunorubicin or doxorubicin, cytarabine, cyclophosphamide, etoposide, intrathecal methotrexate to target blasts in the central nervous system) and low intensity maintenance therapy (with oral 6-Mercaptopurine and Methotrexate) for up to three years (Yorkshire and The Humber Clinical Networks 2016).
- Treatment is stratified according to the response to treatment and other prognostic biomarkers (including genetics). Allogeneic haematopoietic stem cell transplantation is used predominantly in the relapse setting for children but in front-line therapy for adult patients to consolidate chemotherapy (Yorkshire and The Humber Clinical Networks 2016).
- In the UK, adult patients between the ages of 25 and 65 with Ph-negative de-novo B-ALL are treated according to the standard arm of the UKALL14 protocol. In brief, patients receive two induction blocks followed by an intensification block, followed by allogeneic stem cell transplantation if they have any high-risk features or are still MRD positive after the two induction blocks. Patients with no additional risk factors will continue to receive four courses of consolidation chemotherapy followed by two years of maintenance therapy (Yorkshire and The Humber Clinical Networks 2016).
- Patients under 25 years of age are treated according to the standard arm of the UKALL 2011 protocol. Patients are risk stratified as in adults but there is an additional intermediate risk group. The duration of the different treatment phases are tailored according to risk (Yorkshire and The Humber Clinical Networks 2016).
- In the UK older patients are treated according to the UKALL60+ protocol. Patients receive two courses of induction chemotherapy followed by a block of intensification chemotherapy, three blocks of consolidation therapy and subsequent 2-year maintenance therapy (Yorkshire and The Humber Clinical Networks 2016).

The intervention (and licensed indication)

- Rituximab is a chimeric monoclonal antibody (MoAb) that modulates the CD20 receptor, thereby inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDCC), and apoptosis. It is licensed for the following cancers:

Non-Hodgkin's lymphoma (NHL)

- The treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
- Maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy.
- Monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- The treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy (Medicines.org.uk 2018).

Chronic lymphocytic leukaemia (CLL)

- In combination with chemotherapy Rituximab is licensed for the treatment of patients with previously untreated and relapsed/refractory CLL (Medicines.org.uk 2018).

Rationale for use

- Rituximab is a chimeric monoclonal antibody that targets CD20 on the surface of B-cells (Horvat et al 2018). The adverse prognostic significance of CD20 expression in adults with B-cell precursor ALL has therefore prompted the incorporation of Rituximab into chemotherapy regimens (Maury et al 2016).

2. Summary of results

- We found four papers fulfilling the PICO criteria: one systematic review, one randomised controlled open-label phase III trial (GRAALL-2005R; n = 209), one non-randomised open-label phase II trial (n = 282) and one economic evaluation study. The systematic review reported data from the phase III trial only; the findings from the systematic review are therefore presented under the data for this study.

What is the evidence of clinical and cost effectiveness for the addition of Rituximab to first line chemotherapy for Philadelphia negative and positive CD20 positive B-cell precursor ALL?

- Addition of Rituximab to first line chemotherapy for Ph-negative CD20 positive B-cell precursor ALL, after a median follow up of 30 months, resulted in a significant improvement in event free survival (EFS) in the GRAALL-2005R study (hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.45 to 0.98; p = 0.04). At 2 years EFS rates were: rituximab 65% (95% CI, 56 to 74) v control 52% (95% CI, 43 to 63). At 4 years EFS rates were: rituximab 55% (95% CI, 46 to 66) v control 43% (95% CI, 34 to 55). It also resulted in an increase in 3-year complete remission duration (CRD) in the phase II study (67% v control 40%; p = 0.002). These results were due to a significant reduction in relapse rates (sub distribution HR; this was not defined in the

study, 0.52; 95% CI, 0.31 to 0.89; p = 0.02).

- The improvements in EFS and CRD did not result in any significant improvement in overall survival (OS) in either of the studies. Maury et al (2016) reported overall survival: Rituximab 61% vs. control 50%; HR, 0.70; 95% CI, 0.46 to 1.07; p = 0.10). At 2 years OS rates were: rituximab 71% (95% CI, 62 to 80) v control 64% (95% CI, 55 to 74). At 4 years OS rates were: rituximab 61% (95% CI, 52 to 72) v control 50% (95% CI, 41 to 62). However in a post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission, overall survival was longer in the Rituximab group than in the control group (HR 0.55; 95% CI, 0.34 to 0.91; p = 0.02). Thomas et al reported no significant difference in overall survival rates: (Rituximab 61% v control 45%; p = not significant (NS)). However, in a subset analysis in younger patients (age ≤ 60 years) overall survival was significantly improved in the Rituximab group (Rituximab 70% v control 38%; p < 0.001). However, due to flaws in the methodology applied, the reliability of the results from these post hoc subset and sensitivity analyses is uncertain.
- The overall incidence of severe adverse events did not differ significantly between the groups (Rituximab 96% vs. control; 92%; p = 0.72). Although infection was slightly more frequent in the Rituximab group, the difference was not significant; Rituximab 71% vs. control 55%; p = NS. Allergic reactions to asparaginase were less common in the Rituximab group (2% vs. 11%; p = 0.002). It is not clear why this was the case and hence how it might affect the interpretation of the results.
- These results should be treated with caution because of the design and methodological flaws in the studies. The study by Maury et al (2016) was randomised, but the details of randomisation and concealment were not reported. It was an open label study and patients were assessed by the investigators, not by an independent assessor. This could have created some bias in the results. The study by Thomas et al (2010) was prospective, but the patients were not randomised into groups. The control patients were all treated under a different chemotherapy protocol from the Rituximab group and there were a number of protocol changes over the course of the study.
- The incremental cost-effectiveness ratio of addition of Rituximab to standard chemotherapy was calculated at Canadian $21,828 (~£12,308) per quality adjusted life year (QALY) with a 98% probability of being cost effective. The effectiveness was based on GRAALL-2005R, and costs were based on expert opinion and the perspective of a publicly funded Canadian health system. The accuracy of the effectiveness assessment could therefore have been impaired by the limitations in this study. Furthermore, the costs collected from a Canadian health system are unlikely to apply to the UK health service.

What is the most effective treatment schedule using Rituximab, including the total number of doses, in first line treatment of Philadelphia negative and positive CD20 positive B-cell precursor ALL?

- We did not identify any studies comparing different Rituximab schedules using Rituximab as first line treatment in Ph-negative or positive CD20 positive B-ALL.

Does the proportion (%) of antigen expressed in CD20 positive B-cell precursor ALL predict the response to Rituximab immunotherapy?

- We did not find any studies that evaluated how the proportion of antigen expressed in CD20 positive B-ALL predicts response to Rituximab immunotherapy. All the studies included patients based on CD20 expression of 20% or more, but results were not reported by different

degrees of CD20 expression.

Does the clinical and cost effectiveness of treatment of CD20 positive B-cell precursor ALL vary by subgroup?

- Thomas et al carried out a subset analysis to assess the influence of Rituximab in younger CD20 positive patients by excluding the older patients (≥60 years). Significant improvements in 3-year CRD rates (70% v 38%; p< 0.001) and OS (75% v 47%; p = 0.003) favouring Rituximab were observed.
- We did not identify any studies that evaluated the relative cost-effectiveness in different subgroups.

3. Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Embase, MEDLINE, Cochrane library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 30th January 2008 and 29th January 2018.The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4. Results

A total of four papers fulfilling the PICO criteria were identified. Three papers fulfilled the criteria for clinical effectiveness and safety: one systematic review (CADTH 2017), one randomised controlled open-label phase III trial – the GRAALL-2005R study (Maury et al 2016) and one non-randomised prospective open-label phase II trial (Thomas et al 2010). The systematic review was based only on data from the GRAALL-2005R study; therefore, for the purpose of this report, results from the systematic review are presented under the GRAALL-2005R study. The fourth paper was an economic analysis that fulfilled the PICO criteria for cost-effectiveness. No studies involving patients with Ph-positive B-ALL were identified. Only patients with Ph-negative CD20 positive B-ALL were included in the papers identified.

What is the evidence of clinical and cost effectiveness for the addition of Rituximab to first line chemotherapy for Philadelphia negative and positive CD20 positive B-cell precursor ALL?

Clinical effectiveness outcomes reported include event-free survival (EFS), overall survival (OS), remission after induction courses, early mortality during induction, relapse rates and death during first remission. Safety was also evaluated in one study (Maury et al 2016). Incremental cost-effectiveness was reported in the economic analysis (Nam et al 2018) in Canadian dollars/QALY (C$/QALY).

Event-free survival

EFS was the primary endpoint for GRAALL-2005R. This was a composite endpoint of failure of complete remission induction, relapse, and death. At 2 years EFS rates were: rituximab 65% (95% CI, 56 to 74) v control 52% (95% CI, 43 to 63). At 4 years EFS rates were: rituximab 55% (95% CI, 46 to 66) v control 43% (95% CI, 34 to 55). After a median follow-up of 30 months, there was a statistically significant difference in EFS in favour of the Rituximab group (HR 0.66; 95% CI 0.45 to 0.98; p = 0.04; absolute numbers not reported). In their post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission, EFS was still improved in the Rituximab group compared with the control group (HR, 0.59; 95% CI 0.37 to 0.93; p = 0.02).

Overall survival

OS was a secondary endpoint for GRAALL-2005R, and was also reported in the open-label study by Thomas et al (2010). No difference in overall survival was observed in either study. According to Maury et al (2016) the benefit in EFS did not translate into significantly longer overall survival. At 2 years OS rates were: rituximab 71% (95% CI, 62 to 80) v control 64% (95% CI, 55 to 74). At 4 years OS rates were: rituximab 61% (95% CI, 52 to 72) v control 50% (95% CI, 41 to 62). HR 0.70; 95% CI, 0.46 to 1.07; p = 0.10). In their post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission, overall survival was higher in the Rituximab group than in the control group (HR 0.55; 95% CI, 0.34 to 0.91; p = 0.02). Thomas et al reported no significant difference in overall survival rates: (Rituximab 61% v control 45%; p = NS). However, in their subset analysis in younger patients (age ≤ 60 years) overall survival was significantly improved in the Rituximab group (Rituximab 70% v control 38%; p < 0.001).

Rate of haematological remission

Rate of haematological remission was reported in both GRAALL-2005R and the open label study (Thomas et al 2010). In GRAALL-2005R, there were similar rates of complete remission in the two study arms following one or two induction courses (Rituximab 92% v control 90%; p = 0.63) (Maury et al 2016). Thomas et al (2010) also found similar complete remission rates in the two groups (94% v 94% p=NS).

Complete remission duration

Thomas et al (2010) in analysing the entire CD20-positive group reported a 3-year complete remission duration (CRD) that was significantly higher in the Rituximab group compared to the control group 67% versus 40%; (p = 0.002). A subset analysis of the younger patients (age ≤ 60 years) also showed significant improvements (Rituximab 70% v control 38%; p < 0.001).

Cumulative incidence of relapse

According to Maury et al (2016), the difference in EFS was mostly due to a lower incidence of relapse in the Rituximab group (Rituximab 21% vs. control 34%; sub-distribution HR 0.52; 95% CI,

0.31 to 0.89; p = 0.02). Thomas et al reported a relapse rate of 60% in the Rituximab group compared with 37% in the control group (p = 0.003).

Time to complete remission
Thomas et al reported a time to complete remission, in median days, of 23 days for Rituximab and 21 days for the control group (p = NS).

Death during induction
In the Maury et al (2016) study, there were 7 deaths during induction in the rituximab group compared with 9 in the control group. The significance of this difference was not reported.

Death during the first remission
Maury et al (2016) reported no significant difference in rates of death during the first remission (Rituximab 13% v control 13%; subdistribution HR 0.98 (95% CI, 0.45 to 2.12; p = 0.96). The results were similar in their post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission; subdistribution HR 0.79; 95% CI, 0.43 to 1.47; p = 0.96.

Severe adverse events associated with induction, consolidation, late intensification or stem cell transplantation (SCT), and maintenance
Maury et al observed 246 severe adverse events reported in 124 patients. The overall incidence of severe adverse events did not differ significantly between the groups (Rituximab 96% vs control 92%; p = 0.72)

INFECTION
Although infectious events were slightly more frequent in the Rituximab group, the difference was not significant; Rituximab 71% vs. control 55%; p = NS

LABORATORY ABNORMALITIES
Laboratory abnormalities were reported to a similar extent in both groups; Rituximab 22% vs control; 23% (p = NS)

ALLERGIC REACTION TO L-ASPARAGINASE
There were differences between the two groups in terms of severe allergic reactions. (Rituximab 2% vs control 11%; p = 0.002). Among 16 severe allergic events that occurred, 15 were due to L-asparaginase administration. Among these, two of the severe reactions were in the Rituximab group. Overall the cumulative dose of L-asparaginase received was less in the control group compared to the Rituximab group.

Incremental cost-effectiveness ratio
The economic evaluation by Nam et al (2018) evaluated the cost effectiveness of adding Rituximab to standard chemotherapy in de novo Ph-negative B-ALL compared with standard chemotherapy only. Data on efficacy was based on GRAALL-2005R, costs were based on the Canadian healthcare system and quality of life measures from a separate study. Nam et al estimated the incremental cost-effectiveness ratio at Canadian $21,828 (~£12,308) per QALY, with a 98% probability of being cost-effective at a willingness to pay (WTP) of Canadian$100,000/QALY. Costs were calculated from the perspective of the Canadian publicly funded healthcare payer, and included all direct drug and administration costs as well as costs of all treatment related resource for all cycles of treatment.

What is the most effective treatment schedule using Rituximab, including the total number of doses, in first line treatment of Philadelphia negative and positive CD20 positive B-cell precursor ALL?

We did not identify any studies, comparing different Rituximab dosing schedules using Rituximab as first line treatment in Ph-negative or positive CD20 positive B-ALL.

Does the proportion (%) of antigen expressed in CD20 positive B-cell precursor ALL predict the response to Rituximab immunotherapy?

We did not identify any studies evaluating how the proportion of antigen expressed in CD20 positive B-ALL predicts response to Rituximab immunotherapy. All the studies selected patients for Rituximab based on CD20 expression of 20% or more.

Does the clinical and cost effectiveness of treatment of CD20 positive B-cell precursor ALL vary by subgroup?
Thomas et al (2010) carried out a subset analysis to assess the influence of Rituximab in younger CD20 positive patients by excluding the older patients (≥60 years). Significant improvements in 3-year CRD rates (70% v 38%; p< 0.001) and OS (75% v 47%; p = 0.003) favouring Rituximab were observed. Older patients (age ≥ 60 years) in the CD20-positive subset had no improvement in CRD or OS. However, no data on actual rates were provided.

5. Discussion

The research evidence identified reported that adding Rituximab to standard chemotherapy in de novo Ph-negative CD20 positive B-ALL is safe, improves certain outcomes and is potentially cost-effective. However there were limitations in the quality of the studies, methodologies applied and meaningfulness of the clinical effectiveness outcomes that showed improvements. These cast uncertainties on the usefulness of the results.

The clinical effectiveness evidence identified was based upon patients with Ph-negative B-ALL, and Rituximab treated patients were all CD20 positive. Positive CD20 was defined as baseline expression of the CD20 antigen in more than 20% of leukaemic cells. The choice of chromosome type was based on the known success of tyrosine inhibitors in Ph-positive B-ALL; the choice of CD20 expression status was based on published data on the adverse prognostic significance of CD20 expression in adults with B-ALL.

The control arms in both of the primary studies received standard chemotherapy as hyper-CVAD with or without intensification. Rituximab was administered as an intravenous (IV) infusion during induction, consolidation, late intensification and maintenance (12 to 16 infusions in total).

Addition of Rituximab to standard chemotherapy showed significant improvements in event-free survival and complete remission duration mostly due to an improved relapse rate. However, these improvements did not result in a significant improvement in overall survival. Without an improvement of overall survival, the clinical benefit of these outcomes is uncertain. Post hoc sensitivity and subgroup analyses showed overall survival improved in younger patients and after censoring data on patients who received an allogeneic transplant. However the reliability of these post hoc analyses is uncertain especially because of the limitations of the study methods applied. Furthermore, there was no indication that the study was powered to identify a difference in overall

survival.

The results from these studies must be treated with caution. In GRAALL-2005R (Maury et al 2016), details of the randomisation method and allocation concealment were not reported in the study publication. The study was an open-label trial and outcomes were investigator-assessed. The composite endpoint included objective measures (e.g. death) which could have reduced investigator assessment bias. However, it also included potentially subjective endpoints (e.g. failure of complete remission and relapse which may be relatively subjective as the criteria for these outcomes were not clearly defined in the report). There were important differences in patient exposure to control therapy; for example, more patients in the Rituximab group than in the control group underwent allogeneic stem cell transplantation during the first remission (36 vs. 21 patients), and patients in the control group had fewer overall cumulative doses of L-asparaginase. The improvement in EFS was statistically significant, but the upper limit of the 95% CI was just below unity (0.98); therefore it was only just significant. No absolute numbers were reported and hence the number of avoided events (the size of the effect on EFS) is not clear.

Although the study by Thomas et al (2010) was prospective, patients were not randomised into groups and there was no evidence of an attempt to ensure that the comparison groups were well balanced for factors known to affect outcomes and response to therapy; for example age and performance status. According to the protocol, only CD20 positive patients were eligible to receive Rituximab. The Rituximab patients, in this study, received a different form of standard chemotherapy (modified hyper-CVAD) from the control group (hyper-CVAD), which could have biased the results of the study.

The safety profile of Rituximab in this setting was good, with no significant difference in severe adverse events compared with control groups.

Nam et al evaluated the cost-effectiveness of Rituximab in de novo Ph-negative CD20 positive B-ALL. They reported the incremental cost-effectiveness to be Canadian$21,828 (~£12,308) per QALY (98% probability of being cost-effective at a willingness to pay of Canadian$100,000/QALY). The decision-analytic model used was appropriate and all relevant parameters were sensitivity-tested. The efficacy estimates were based on GRAALL-2005R. Although Maury et al (2016) showed significant improvements in EFS, the upper limit of the confidence interval of the EFS outcome measure was just below unity, and the study did not show any benefits in terms of overall survival, which is a more clinically meaningful outcome. Costs were calculated from the perspective of the Canadian publicly funded healthcare payer and included all treatment-related resources for all cycles of treatment; including hospitalisation, physician time and other hospital resources. However, these costs may not necessarily apply in the UK Health Service. Additionally, management strategies for the condition may be different in the UK compared to Canada. Quality of life assessments were not based on utility data collected in the trial, but based on data collected in a separate study in a relapsed/refractory ALL population. The reliability and relevance of the results of this economic analysis to the UK health setting is therefore uncertain.

6. Conclusion

Addition of Rituximab to standard chemotherapy (with or without intensification) significantly increases event-free survival and 3-year complete remission duration in Ph-negative CD20 positive B-ALL. These benefits are mostly due to a significant reduction in relapse rates; however, improvement in overall survival was not seen. Post hoc subgroup analysis suggests that overall survival might be improved in younger patients. However these results were based on

open-label studies with no proper concealment from investigators; therefore the lower reliability of such analyses makes interpretation uncertain.

The administration of Rituximab in this setting is well tolerated with no increase in risk of adverse events seen in the one study that reported this.

Limited economic study data show that the treatment is potentially cost-effective. However, there are uncertainties regarding the applicability of the quality of life data employed in this analysis and the relevance to the UK. Costs were calculated from the perspective of a Canadian publicly funded healthcare payer, which is not necessarily applicable to the UK health service.

7. Evidence Summary Table

Addition of Rituximab to standard chemotherapy Vs. Standard Chemotherapy as first line therapy of CD20 positive B-ALL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
CADTH 2017 Maury et al (GRAALL-2005R study) 2016	S2 Systematic review of Maury 2016 P1 Randomised controlled open label phase III trial Multicentre: 56 French and 9 Swiss centres. Median follow-up 30 months	209 adults with newly diagnosed Ph-negative, B-cell precursor ALL expressing CD20 (CD20 antigen in more than 20% of leukemic cells). Median age (range): 40.2 years (18 to 59)	Study compared standard dose or hyper-C chemotherapy + Rituximab (Rituximab group; n = 105); vs. standard dose or hyper-C chemotherapy alone (control group; n = 104). Rituximab was given as an IV infusion dose of 375 mg/m^2. BSA per day during induction (days 1 and 7), salvage re-induction 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. Total of 16-18 infusions of Rituximab	Primary Clinical effectiveness	Event-free survival (EFS). Events defined as composite of failure of complete remission induction, relapse and death	Absolute numbers NR; HR 0.66 (95% CI 0.45 to 0.98; p = 0.04)	7/10	Direct	Details of the randomisation method and allocation concealment were not reported in the Maury et al study publication. This study was an open-label trial and patients were investigator-assessed, rather than independently assessed. There is a potential for risk of bias in subjective outcomes such as quality of life and response. However, the composite endpoint included objective measures (e.g. death) which could have reduced investigator assessment bias. There were important differences in patient exposure to control therapy; for example, more patients in the Rituximab group than in the control group underwent allogeneic stem cell transplantation during the first remission (36 versus 21 patients), and patients in the control group had fewer overall cumulative doses of L-asparaginase. It is not clear why this was the case and hence how it might affect the interpretation of the results. The upper limit of the 95% CI was just below unity (0.98) for the primary study outcome measure (EFS) therefore it was only just significant. The study was not powered to detect a difference in important secondary endpoints like OS. It is possible that a difference existed, but the trial may not have been sufficiently large to detect it. Generally patients present with higher ECOG performance status and are older than the population in this study. The eligibility criteria (age 18 to 59 years) may have recruited a younger population than those who present with this condition in the general population.
				Primary Clinical effectiveness	EFS at 2 years	Rituximab 65% (95% CI, 56 to 75) v control 52% (95% CI, 43 to 63			
				Primary Clinical effectiveness	EFS at 4 years	Rituximab 55% (95% CI, 46 to 66) v control 43 (95% CI, 34 to 55)			
				Primary Clinical effectiveness	EFS ***Post hoc sensitivity analysis*	Absolute numbers NR; HR 0.59 (95% CI 0.37 to 0.93; p = 0.02)			
				Secondary Clinical effectiveness	Haematological remissions after one or two induction courses	Rituximab 92% vs. control 90% (p = 0.63)			
				Secondary Clinical effectiveness	Early mortality during induction	Rituximab 7 patients vs. control 9 patients (p = NR)			
				Secondary Clinical effectiveness	Cumulative incidences of relapse	Rituximab 21% vs. control 34% Subdistribution HR 0.52 (95% CI, 0.31 to 0.89; p = 0.02)			
				Secondary Clinical effectiveness	Cumulative incidences of relapse ***Post hoc sensitivity analysis*	Absolute numbers NR; HR 0.49 (95% CI, 0.27 to 0.89; p = 0.02)			

Addition of Rituximab to standard chemotherapy Vs. Standard Chemotherapy as first line therapy of CD20 positive B-ALL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Clinical effectiveness	Cumulative relapse rate at 2 years	Rituximab 18% (95% CI, 11 to 27) vs. control 32% (95% CI, 22 to 42)			
				Secondary Clinical effectiveness	Cumulative relapse rate at 4 years	Rituximab 25% (95% CI, 16 to 35) vs. control 41% (95% CI, 30 to 51)			
				Secondary Clinical effectiveness	Death during the first remission	Rituximab 13% vs. control 13%; Subdistribution HR 0.98 (95% CI, 0.45 to 2.12; p = 0.96)			
				Secondary Clinical effectiveness	Death during the first remission ***Post hoc sensitivity analysis*	Absolute numbers NR Subdistribution HR 0.79 (95% CI, 0.43 to 1.47; p = 0.96)			
				Secondary Clinical effectiveness	Cumulative incidence of death at 2 years	Rituximab 12% (95% CI, 6 to 19) vs. control 12% (95% CI, 6 to 19)			
				Secondary Clinical effectiveness	Cumulative incidence of death at 4 years	Rituximab 16% (95% CI, 9 to 24) vs. control 12% (95% CI, 6 to 19)			
				Secondary Clinical effectiveness	Overall survival (OS)	Absolute numbers NR; HR 0.70 (95% CI, 0.46 to 1.07; p = 0.10)			
				Secondary Clinical effectiveness	OS at 2 years	Rituximab 71% (95% CI, 62 to 80) vs. control 64% (95% CI, 55 to 74)			
				Secondary Clinical effectiveness	OS at 4 years	Rituximab 61% (95% CI, 52 to 72) vs. control 50% (95% CI, 41 to 62)			
				Secondary Clinical effectiveness	Overall survival (OS) ***Post hoc sensitivity analysis*	Absolute numbers NR; HR 0.55 (95% CI, 0.34 to 0.91; p = 0.10)			

Addition of Rituximab to standard chemotherapy Vs. Standard Chemotherapy as first line therapy of CD20 positive B-ALL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Clinical effectiveness	Cumulative overall survival at 2 years	Rituximab 71% (95% CI, 62 to 80) vs. control 64% (95% CI, 75 to 84)			
				Secondary Clinical effectiveness	Cumulative overall survival at 4 years	Rituximab 61% (95% CI, 52 to 72) vs. control 50% (95% CI, 41 to 62)			
				Secondary Safety	Severe adverse events associated with induction, consolidation, late intensification of SCT, and maintenance	Incidence rate; Rituximab 96% vs. control; 92% (p = 0.72)			
				Secondary Safety	Infection	Incidence rate; Rituximab 71% vs. control; 55% (p = NS)			
				Secondary Safety	Laboratory abnormalities	Incidence rate; Rituximab 22% vs. control; 23% (p = NS)			
				Secondary Safety	Allergic reaction to L-asparaginase	Rituximab 2% vs. control 11% (p = 0.002)			
Thomas et al 2010	P1-sequential prospective, open label, single-centre, phase II trial	282 adolescents and adults with de novo Ph-negative B-ALL Median age: 41 years (range, 13 to 83) Median follow-up 64 months,	Rituximab group (n = 101) received hyper-CVAD (with or without anthracycline intensification) plus rituximab if CD20 expression ≥ 20%. Rituximab was administered, as an IV infusion dose of 375 mg/m2 BSA, on days 1 and 11 of hyper-CVAD	Primary Clinical effectiveness	Complete Remission defined as ≤ 5% blasts in normocellular or hypercellular marrow with ANC ≥ 1 x 10^9/L and resolution of extramedullary disease.	CR rates: 94% v 94%; (p = NS) Median follow-up 64 months (range 4 to 200)	5/10	Direct	Although the study was prospective, patients were not randomised into groups and there were insufficient attempts to ensure that the comparison groups were balanced in terms of factors known to affect outcomes and response to therapy; for example age and performance status. There were significant differences in the study protocols employed during the treatment of the Rituximab and the control patients. All the control patients were treated between 1992 and 1999 with standard hyper-CVAD. The Rituximab patients were treated after a protocol change (2000 – 2001), and all received modified hyper-CVAD standard chemotherapy with or without anthracycline intensification. Significant differences in CRD (but not OS) were recorded between hyper-CVAD and modified hyper-CVAD without
				Secondary Clinical effectiveness	% 3-year Complete Remission Duration (CRD)	Rituximab 67% v control 40%; (p = 0.002) Median follow-up 64 months (range 4 to 200)			

Addition of Rituximab to standard chemotherapy Vs. Standard Chemotherapy as first line therapy of CD20 positive B-ALL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		range 4 to 200	cycles and on days 1 and 8 of intensification cycles for eight total doses over the first four courses. Rituximab was given with early and late hyper-CVAD intensifications during months 6 and 18 of maintenance therapy. Control group (*n = 53) received standard hyper-CVAD.	Secondary Clinical effectiveness	Over Survival (OS)	OS rates: Rituximab 61% v control 45% (p = NS)			intensification, but it was not clear whether or how much of this varied by CD20 status or whether it was influenced by Rituximab treatment. A parallel control group of CD20 positive patients treated under the same protocol, or separate comparisons of rituximab patients receiving and not receiving intensification therapy would have permitted a more reliable evaluation.
				Secondary Clinical effectiveness	Relapse rate	Rituximab 60% v control 37% (p = 0.003)			
				Secondary Clinical effectiveness	Time to CR	Median days; Rituximab 23 days v control 21 days (p = NS)			
				Secondary Clinical effectiveness	% 3-year CRD *Subset analysis in younger patients; age ≤ 60 years (n = 114)*	Rituximab 70% v control 38%; (p < 0.001) Median follow-up 64 months (range 4 to 200)			
				Secondary Clinical effectiveness	OS *Subset analysis in younger patients; age ≤ 60 years (n = 114)*	Rituximab 75% v control 47% (p = 0.003) Median follow-up 64 months (range 4 to 200)			
Nam et al 2018	S2 – Economic analysis based on a decision-analytic model.	Efficacy based on 209 adults patients in the Maury et al (2016) study. Costs for the comparator were based on Hyper-CVAD or DFCI ALL consortium	The treatment effects of adding Rituximab to hyper-CVAD protocols were based on data from the Maury et al (2016) study. Costs were taken from the perspective of a Canadian publicly funded healthcare payer, and included all drug	Secondary Cost-effectiveness	Mean incremental cost-effectiveness ratio (ICER) The analysis used a lifetime horizon (max ~ 60 years)	Canadian $21,828 (~£12,308) per QALY (98% probability of being cost-effective)	7/10	Indirect	Efficacy estimates used in the model were based on EFS data from the best available clinical trial (Maury et al 2016). Although Maury et al showed significant improvements in EFS, they did not show any benefits in terms of overall survival, which is a more clinically meaningful outcome. The upper limit of the confidence interval of the EFS was just below one. The LY and QALY gains estimates used may therefore have been exaggerated however all relevant parameters were sensitivity-tested. Costs were calculated from the perspective of the Canadian publicly funded healthcare payer and included all treatment-related resources for all cycles of treatment; including hospitalisation, physician time and other hospital resources. However, these costs may not necessarily apply in the UK Health Service.
				Secondary Cost-effectiveness	Incremental costs	Canadian$48,108			
				Secondary Cost-effectiveness	Life years (LY) gained	2.63 life years			
				Secondary Cost-	QALY gained	2.2 QALYs			

Addition of Rituximab to standard chemotherapy Vs. Standard Chemotherapy as first line therapy of CD20 positive B-ALL									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		regimen for adults, which is used more in the younger population in Canada.	and non-drug medical costs associated with all cycles of treatment. Quality of life assessment was based on health state utilities extrapolated from other studies.	effectiveness					Quality of life assessments, were not based on utility data collected in the trial, but based on data collected in a separate study in a relapsed/refractory ALL population. Three of the authors (including the main author) were employed by the manufacturer.

Hyper-CVAD - First line chemotherapy usually includes the use of steroids and antineoplastic agents such as, vincristine, asparaginase, daunorubicin or doxorubicin, cytarabine, cyclophosphamide, etoposide, intrathecal methotrexate, oral 6-Mercaptopurine and Methotrexate; and Imatinib in PH+ve ALL. This protocol was used in the studies by Maury et al (2016) and Thomas et al (2010). ** Post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission Maury et al (2016)

ALL –acute lymphoblastic leukaemia; ANC-absolute neutrophil count; B-ALL – B-cell acute lymphoblastic leukaemia; BSA – body surface area; CI-confidence interval; CR – complete remission; CRD – complete remission duration; CVAD– cyclophosphamide, vincristine, doxorubicin (also known by its trade name, Adriamycin), and dexamethasone; DFCI - Dana Faber Cancer Institute; EFS – event free survival; HR – Hazard Ratio, relating to hazard or risk of death, relapse, other event depending on outcome measure; ICER-incremental cost-effectiveness ratio; NR – not reported; NS – not significant; OS – overall survival; Ph–Philadelphia; QALY – quality-adjusted life years; SCT – stem cell transplantation

8. Grade of Evidence Table

For abbreviations see list after each table

Addition of Rituximab to Standard Chemotherapy Vs. Standard Chemotherapy as first line therapy of Ph-negative CD20 positive B-ALL					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Event free survival (EFS).	Maury et al 2016	7/10	Direct	B	The event-free survival (EFS) is defined by Maury et al (2016) as a composite endpoint of failure of complete remission induction, relapse, and death. It refers not just to the patient being alive, but alive and free from relapses or treatment failure. Maury et al (2016) reported that patients who received Rituximab in addition to standard chemotherapy as first line therapy, for Ph-negative CD20 positive B-ALL, had longer EFS than those assigned to the control group. After a median follow up of 30 months, 58% of patients on Rituximab had not experienced an event compared with only 45% in the control group. The ratio of Rituximab treated patients experiencing any of these events compared with those who received standard chemotherapy (the hazard ratio) was 0.66 (95% CI, 0.45 to 0.98; p = 0.04). Although no significant effect was observed of Rituximab on overall survival, it is possible that the statistically significantly higher EFS reported in this study may be meaningful to patients. However the meaningfulness of this to patients is not clear. This result must be treated with caution because no absolute numbers were reported and hence the number of avoided events (the size of the effect on EFS) is not clear. It is also not clear how meaningful an increase in EFS is to patients compared to the reported lack of effect on overall survival, which may be more important to patients with a potentially fatal condition. Also, the 95% confidence interval for the hazard ratio is wide (95% confidence interval 0.45 to 0.98) and the upper limit of the confidence interval is close to 1, which indicates that it was only just statistically significant. The multiple sources of bias in the methodology employed in this study, for example higher rates of allogeneic stem cell transplantation in the Rituximab group and the lack of blinding of assessors, suggest further need for caution in interpretation of these results. This study was non-blinded, and patients were assessed by the investigator not an independent assessor.
Overall survival (OS)	Maury et al 2016	7/10	Direct	B	Overall survival is the proportion surviving for the duration that patients were followed up in the study or for a particular time period. Maury et al (2016) is the more reliable study because patients were randomised to the two treatment groups. The study reported no significant difference in overall survival between those patients that had Rituximab and those who had standard chemotherapy alone. 71% of patients in the Rituximab group survived 2 years compared with just 64% of patients in the control group. 61% of Rituximab patients survived 4 years compared with 50% in the control group. The difference was not statistically significant: HR 0.70 (95% CI, 0.46 to 1.07; p = 0.10). This means that the evidence does not show that Rituximab improves overall survival when added to first line therapy for B-ALL.
	Thomas et al 2010	5/10	Direct		

Addition of Rituximab to Standard Chemotherapy Vs. Standard Chemotherapy as first line therapy of Ph-negative CD20 positive B-ALL					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					However the results have to be treated with caution because this was an open-label study. In addition, there was not assessment of the statistical power of this study to measure significant differences in overall survival.
Haematological remissions after one or two induction courses	Maury et al 2016	7/10	Direct	B	Patients are considered to be in haematological remission if they have: ≤ 5% blasts in normocellular or hypercellular marrow with ANC ≥ 1 x 10^9/L and resolution of extramedullary disease. Maury et al reported on the rate of haematological remission after one or two courses or treatment and did not find any significant benefit of Rituximab compared with standard chemotherapy in terms of remission after one or two induction courses. Maury reported complete remission rates of: Rituximab 92% versus control 90% (p = 0.63). These results suggest that most patients will respond to the initial induction chemotherapy and that the initial response does not appear to be improved or worsened by adding in Rituximab to the chemotherapy. This result is from a randomised controlled open-label study. It is not clear whether it was sufficiently powered to assess differences in this outcome measure.
	Thomas et al 2010	5/10	Direct		
Early mortality during induction	Maury et al 2016	7/10	Direct	B	Maury et al reported rates of early death during induction. This outcome was not defined and the statistical significance was not reported. Overall there were 7 deaths during induction in the rituximab group and 9 deaths during induction in the control group (p = NR). This result does not clarify whether the addition of Rituximab to standard chemotherapy results in any benefit or harm over standard chemotherapy alone in terms of early mortality during induction. A definition of the time period covered and statistical tests may help understand this result better, but it is also not clear whether the study was adequately powered to detect a difference in this outcome.
Cumulative incidences of relapse	Maury et al 2016	7/10	Direct	B	Maury et al reported the cumulative number of relapses experienced by these patients during the follow up period. There was a significantly lower cumulative incidence of relapse in the Rituximab group; Rituximab 21% v control 34%; HR 0.52 (95% CI, 0.31 to 0.89; p = 0.02). This means the patients are likely to experience fewer relapses if they had Rituximab added to their chemotherapy. This result should be treated with caution because it was reported by the investigators assessment, not by any objective parameters and not by an independent assessor. In addition, it did not translate into significantly longer overall survival and there were no

Addition of Rituximab to Standard Chemotherapy Vs. Standard Chemotherapy as first line therapy of Ph-negative CD20 positive B-ALL					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					data on quality of life changes during survival or during relapse. This means that patients are likely to have fewer relapses during their follow up period, but without any improvement in overall survival or measure of the effect of the relapse on the patients' quality of life, the clinical benefit of this reduction is relapse rate is uncertain.
Cumulative incidences of death during the first remission	Maury et al 2016	7/10	Direct	B	Maury et al reported the cumulative number of deaths in each study group during the first remission. Addition of Rituximab to standard chemotherapy did not confer any benefit over standard chemotherapy in terms of the cumulative incidences of death during the first remission; Rituximab 13% versus control 13%; HR 0.98 (95% CI, 0.45 to 2.12; p = 0.96) This means a similar proportion of patients died in each treatment group during the first remission, and addition of Rituximab did not reduce the incidence of death at this stage. However, it is not clear from the report whether the study was sufficiently powered to measure a difference in this specific outcome.
Severe adverse events associated with induction, consolidation, late intensification of SCT, and maintenance	Maury et al 2016	7/10	Direct	B	Severe adverse events associated with induction, consolidation, late intensification of chemotherapy, and maintenance were reported. According to Maury et al, the overall incidence of severe events did not differ significantly between the two groups; Rituximab 96% versus control; 92% (p = 0.72). Infectious events were slightly more frequent in the Rituximab group, but the difference was not significant; Rituximab 71% versus control; 55% (p = NS). Laboratory abnormalities were also not significantly different between groups; Rituximab 22% versus control; 23% (p = NS), Severe allergic events to L-asparaginase were more common in the control group than in the Rituximab group; Rituximab 2% versus control 11% (p = 0.002) These results found no increase in severe adverse events associated with the addition of Rituximab to standard chemotherapy and found a reduction in severe allergic reactions to L-asparaginase. It is not clear what the effect of this is on the reliability or interpretation of the results. This result should be treated with some caution as it was an open-label trial which means that there was no blinding regarding which treatment the patient had and there could therefore have been bias in the reporting of adverse events.

Addition of Rituximab to Standard Chemotherapy Vs. Standard Chemotherapy as first line therapy of Ph-negative CD20 positive B-ALL					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Complete Remission Duration (CRD)	Thomas et al 2010	5/10	Direct	C	Thomas et al reported on Complete Remission Duration (CRD), which was measured from CR to relapse with a median follow-up of 64 months (range 4 to 200). When analysing the CD20-positive group, incorporation of Rituximab into the modified hyper-CVAD regimens was associated with significant improvements in 3-year CRD rates; 67% v 40% ($p = 0.002$). Thomas et al also carried out a subset analysis in patients aged ≤ 60 years. ($n = 114$). 70% of Rituximab treated patients had a 3-year CRD, with just 38% in the control group ($p < 0.001$). This result suggests that adding Rituximab to standard chemotherapy prolongs the period during which the patients remain in remission, and younger patients might benefit more from this treatment approach. The importance of this finding is not certain because, apart from younger patients, no improvement in overall survival was observed. In addition there were several other design flaws that could have biased the result. Importantly, there were several changes to the standard chemotherapy protocol used during the course of the study and all the Rituximab treated patients were treated under a different protocol from the control patients.
Mean incremental cost-effectiveness ratio (ICER)	Nam et al 2018	7/10	Indirect	C	The incremental cost-effectiveness ratio (ICER) is used to assess the economic benefit of different health interventions. It is a ratio of the total cost of the treatment and other associated costs to the health utility benefit it is believed to provide. The latter is usually measure in life-years gained (LY). This is usually adjusted by a factor to account for changes in quality of life: quality-adjusted life years (QALY). Nam et al evaluated the cost/QALY of adding rituximab to standard chemotherapy for de novo treatment of Ph-negative CD20 positive B-ALL. Data from the Maury et al (2016) study was used for estimation of the effectiveness of the therapy. Costs were based on the Canadian healthcare systems and expert opinion. Rituximab added to standard chemotherapy led to greater total cost versus standard chemotherapy alone; difference = Canadian $48,108, 2.63 life years and 2.2 QALYs. This led to an ICER of Canadian $18,327/LY and $21,828/QALY (~£12,308 per QALY). This means that adding Rituximab to standard chemotherapy will cost approximately £12,308 for ever quality adjusted life year gained. However this result should be treated with caution because the efficacy data is based on the Maury et al (2016) study which showed no gain in overall survival rate, so the LY and QALY gains might have been overestimated. The costs were calculated from the perspective of the Canadian publicly funded healthcare payer which does not necessarily apply in the UK Health Service where both costs and management strategies may differ. Three of the authors (including the main author) were employed

Addition of Rituximab to Standard Chemotherapy Vs. Standard Chemotherapy as first line therapy of Ph-negative CD20 positive B-ALL					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					by the manufacturer.

ALL –acute lymphoblastic leukaemia; ANC-absolute neutrophil count; B-ALL – B-cell acute lymphoblastic leukaemia; BSA – body surface area; CI-confidence interval; CR – complete remission; CRD – complete remission duration; CVAD– cyclophosphamide, vincristine, doxorubicin (also known by its trade name, Adriamycin), and dexamethasone; DFCI - Dana Faber Cancer Institute; EFS – event free survival; HR – Hazard Ratio, relating to hazard or risk of death, relapse, other event depending on outcome measure; ICER-incremental cost-effectiveness ratio; NR – not reported; NS – not significant; OS – overall survival; Ph–Philadelphia; QALY – quality-adjusted life years; SCT – stem cell transplantation

9. Literature Search Terms

Search Strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients of all ages newly diagnosed with Philadelphia chromosome negative and positive B-cell precursor ALL expressing CD20 antigen in at least 20% of leukaemic cells. Potential sub-groups: 1. Patients 60 and over, as this cohort of patients may be less fit and so require a less intensive treatment regime 2. Children, as this cohort have been shown to have a higher rate of CR 3. Philadelphia status
I – Intervention Which intervention, treatment or approach should be used?	Rituximab in combination with first line chemotherapy[4] for Philadelphia negative and positive CD20 positive B-cell precursor ALL
C- Comparison What is /are the main alternatives to compare with the intervention being considered?	First line chemotherapy for Philadelphia negative and positive CD20 positive B-cell precursor ALL
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Any and including ○ Complete Remission (CR) ○ Progression Free Survival (PFS) ○ Event Free Survival (EFS) ○ Overall Survival (OS) ○ Minimal Residual Disease (MRD) ○ Safety/incidence rate of adverse events ○ Mortality ○ Relapse Rate *Important to decision-making:* Cost effectiveness
Assumptions / limits applied to search	
Inclusion Criteria	English Peer reviewed, published in the last 10 years, case series, case reports, cohort studies, randomised controlled trials, comparator studies, systematic reviews, meta-analyses
Exclusion Criteria	Conference papers, abstracts, posters, letters, unpublished literature

4

10. Search Strategy

We searched Embase, MEDLINE, Cochrane library, TRIP and NICE Evidence limiting the search to papers published in England from **30th January 2008 to 29th January 2018**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 29th January 2018

Embase search:

▲	earches
1	*Rituximab/
2	(Rituximab or mabthera).ti,ab.
3	1 or 2
4	*acute lymphoblastic leukemia/
5	((acute lymphoblastic or precursor cell lymphoblastic or b cell lymphoblastic or b cell precursor) adj2 leuk?emia?).ti,ab.
6	((precursor cell or b cell) adj2 (leukaemia? or all)).ti,ab.
7	(philadelphia adj5 (leukaemia? or all)).ti,ab.
8	(cd20 adj2 positive adj5 (leukaemia? or all)).ti,ab.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	limit 10 to (english language and yr="2008 -Current")
12	conference*.pt.

11. Evidence Selection

- Total number of publications reviewed: 31
- Total number of publications considered potentially relevant: 11
- Total number of publications selected for inclusion in this briefing: 4

12. References

Abbasi S, Maleha F, and Shobaki M. 2013. Acute Lymphoblastic Leukemia Experience: Epidemiology and Outcome of Two Different Regimens. *Mediterranean Journal of Hematology and Infectious Diseases*, *5*(1), e2013024.

CADTH pan-Canadian Oncology Drug Review. 2017. Final Clinical Guidance Report- Rituximab (Rituxan) for Acute Lymphoblastic Leukemia

Cancer Research UK. 2018. *Acute lymphoblastic leukaemia (ALL) statistics*. [online] Available at:

http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all [Accessed 17 Mar. 2018].

Horvat T, Seddon A, Ogunniyi A, King A, Buie L, and Daley R. 2017.The ABCs Of Immunotherapy For Adult Patients With B-Cell Acute Lymphoblastic Leukemia. *Annals Of Pharmacotherapy* 52 (3): 268-276.

Jabbour E, Faderl S, and Kantarjian H. 2005. Adult Acute Lymphoblastic Leukemia. *Mayo Clinic Proceedings* 80 (11): 1517-1527.

Linker C, Damon L, Ries C, and Navarro W. 2002. Intensified And Shortened Cyclical Chemotherapy For Adult Acute Lymphoblastic Leukemia. *Journal Of Clinical Oncology* 20 (10): 2464-2471.

Londoncanceralliance.nhs.uk. 2015. *LCA Haemato-Oncology Clinical Guidelines. Acute Leukaemias and Myeloid Neoplasms Part 1: Acute Lymphoblastic Leukaemia*. [online] Available at:

http://www.londoncanceralliance.nhs.uk/media/111203/lca-acute-lymphoblastic-leukaemia-clinical-guidelines-april-2015.pdf [Accessed 17 Mar. 2018].

Maury S, Chevret S, Thomas X, Heim D, Leguay T, Huguet F, and Chevallier P, Hunault M, Boissel N, Escoffre-Barbe M, Hess U, Vey N, Pignon JM, Braun T, Marolleau JP, Cahn JY, Chalandon Y, Lhéritier V, Beldjord K, Béné MC, Ifrah N, Dombret H. 2016. Rituximab In B-Lineage Adult Acute Lymphoblastic Leukemia. *New England Journal Of Medicine* 375 (11): 1044-1053.

Medicines.org.uk. 2018. *Mabthera 100mg Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC) - (eMC)*. [online] Available at:

https://www.medicines.org.uk/emc/product/3801/smpc [Accessed 17 Mar. 2018].

Nam, J., Milenkovski, R., Yunger, S., Geirnaert, M., Paulson, K. and Seftel, M. 2018. Economic evaluation of Rituximab in addition to standard chemotherapy for adult patients with acute lymphoblastic leukemia. *Journal of Medical Economics;* 21(1): 47-59.

Pui C, and Evans W. 2006. Treatment Of Acute Lymphoblastic Leukemia. *New England Journal Of Medicine* 354 (2): 166-178.

Rowe J. 2005. Induction Therapy For Adults With Acute Lymphoblastic Leukemia: Results Of More Than 1500 Patients From The International ALL Trial: MRC UKALL XII/ECOG E2993. *Blood* 106 (12): 3760-3767.

Roche Products Limited. 2018. Summary of Product Characteristics.https://www.medicines.org.uk/emc/product/3801/smpc Last accessed 12 March 2018

Thomas D., O'Brien S, Faderl S, Garcia-Manero G, Ferrajoli A, Wierda W, and Ravandi F, Verstovsek S, Jorgensen J, Bueso-Ramos C, Andreeff M, Pierce S, Garris R, Keating M, Cortes J, and Kantarjian H. 2010. Chemoimmunotherapy With A Modified Hyper-CVAD And Rituximab Regimen Improves Outcome In De Novo Philadelphia Chromosome–Negative Precursor B-Lineage Acute Lymphoblastic Leukemia. *Journal Of Clinical Oncology* 28 (24): 3880-3889.

Yorkshire and The Humber Clinical Networks Yhscn.nhs.uk. 2016. *Clinical Guidelines for Lymphoid Diseases – Acute Lymphoblastic Leukaemia (ALL)*. [online] Available at:

http://www.yhscn.nhs.uk/media/PDFs/cancer/Haem%20docs/SYR%20Network%20Guidelines%20ALL%20May%202016.pdf [Accessed 17 Mar. 2018].

Zhou Y. You J, Young K, Lin P, Lu P, Medeiros J, and Bueso-Ramos C. 2012. Advances In The Molecular Pathobiology Of B-Lymphoblastic Leukemia. *Human Pathology* 43 (9): 1347-1362.