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Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia (Review)

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Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia.
Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008079.
DOI: 10.1002/14651858.CD008079.pub2.

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[Intervention Review]

Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

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Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 11, 2012.

Citation: Bauer K, Rancea M, Roloff V, Elter T, Hallek M, Engert A, Skoetz N. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD008079. DOI: 10.1002/14651858.CD008079.pub2.

ABSTRACT

Background

Chronic lymphocytic leukaemia (CLL) accounts for 25% of all leukaemias and is the most common lymphoid malignancy in western countries. Standard treatments include mono- or polychemotherapies, usually combined with monoclonal antibodies such as rituximab or alemtuzumab. However, the impact of these agents remains unclear, as there are hints for increased risk of severe infections.

Objectives

The objectives of this review are to provide an evidence-based answer regarding the clinical benefits and harms of monoclonal anti-CD20 antibodies (such as rituximab, ofatumumab, GA101) compared to no further therapy or to other anti-leukaemic therapies in patients with CLL, irrespective of disease status.

Search methods

We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 12, 2011), MEDLINE (from January 1990 to 4 January 2012), and EMBASE (from 1990 to 20 March 2009) as well as conference proceedings (American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and European Society of Medical Oncology) for randomised controlled trials (RCTs).

Selection criteria

We included RCTs examining monoclonal anti-CD20 antibodies compared to no further therapy or to anti-leukaemic therapy such as chemotherapy or monoclonal antibodies in patients with newly diagnosed or relapsed CLL.

Data collection and analysis

We used hazard ratios (HR) as effect measures for overall survival (OS), progression-free survival (PFS) and time to next treatment, and risk ratios (RR) for response rates, treatment-related mortality (TRM) and adverse events (AEs). Two review authors independently extracted data and assessed quality of trials.

Main results

We screened a total of 1150 records. Seven RCTs involving 1763 patients were identified, but only five could be included in the two separate meta-analyses we performed. We judged the overall the quality of these trials as moderate to high. All trials were randomised and open-label studies. However, two trials were published as abstracts only, therefore we were unable to assess the potential risk of bias for these trials in detail.

Three RCTs (N = 1421) assessed the efficacy of monoclonal anti-CD20 antibodies (i.e. rituximab) plus chemotherapy compared to chemotherapy alone. The meta-analyses showed a statistically significant OS (HR 0.78, 95% confidence interval (CI) 0.62 to 0.98, P = 0.03, the number needed to treat for an additional beneficial effect (NNTB) was 12) and PFS (HR 0.64, 95% CI 0.55 to 0.74, P < 0.00001) advantage for patients receiving rituximab. In the rituximab-arm occurred more AEs, World Health Organization (WHO) grade 3 or 4 (3 trials, N = 1398, RR 1.15, 95% CI 1.08 to 1.23, P < 0.0001; the number needed to harm for an additional harmful outcome (NNTH) was 9), but that did not lead to a statistically significant difference regarding TRM (3 trials, N = 1415, RR 1.19, 95% CI 0.70 to 2.01, P = 0.52).

Two trials (N = 177) evaluated rituximab versus alemtuzumab. Neither study reported OS or PFS. There was no statistically significant difference between arms regarding complete response rate (CRR) (RR 1.21, 95% CI 0.94 to 1.58, P = 0.14) or TRM (RR 0.31, 95% CI 0.06 to 1.51, P = 0.15). However, the CLL2007FMP trial was stopped early owing to an increase in mortality in the alemtuzumab arm. More serious AEs occurred in this arm (43% with alemtuzumab versus 22% with rituximab; P = 0.006).

Two trials assessed different dosages or time schedules of monoclonal anti-CD20 antibodies. One trial (N = 104) evaluated two different rituximab schedules (concurrent arm: fludarabine plus rituximab (Flu-R) plus rituximab consolidation versus sequential arm: fludarabine alone plus rituximab consolidation). The comparison of the concurrent versus sequential regimen of rituximab showed a statistically significant difference of the CRR with 33% in the concurrent-arm and 15% in the sequential-arm (P = 0.04), that did not lead to statistically significant differences regarding OS (HR 1.14, 95% CI 0.20 to 6.65, P = 0.30) or PFS (HR 0.96, 95% CI 0.43 to 2.15, P = 0.11). Furthermore results showed no differences in occurring AEs, except for neutropenia, which was more often observed in patients of the concurrent arm. The other trial (N = 61) investigated two different dosages (500 mg and 1000 mg) of ofatumumab in addition to FluC. The arm investigating ofatumumab did not assess OS and a median PFS had not been reached owing to the short median follow-up of eight months. It showed no statistically significant differences between arms regarding CRR (32% in the FCO500 arm versus 50% in the FCO1000 arm; P = 0.10) or AEs (anaemia, neutropenia, thrombocytopenia).

Authors' conclusions

This meta-analysis showed that patients receiving chemotherapy plus rituximab benefit in terms of OS as well as PFS compared to those with chemotherapy alone. Therefore, it supports the recommendation of rituximab in combination with FluC as an option for the first-line treatment as well as for the people with relapsed or refractory CLL. The available evidence regarding the other assessed comparisons was not sufficient to deduct final conclusions.

PLAIN LANGUAGE SUMMARY

The role of the monoclonal anti-CD20 antibodies for treatment of patients with chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a malignant disease and accounts for 25% of all leukaemias. The disease is the most common lymphoid malignancy in western countries, and is characterised by a highly variable clinical course and prognosis. Some patients may have minimal or no symptoms for many years with a normal life expectancy, without requiring treatment. Other people are symptomatic at diagnosis or soon thereafter and can experience infectious and autoimmune complications, leading to a reduced lifespan. Standard treatment includes chemotherapy with one or more agents. Presently monoclonal antibodies are added, especially alemtuzumab and rituximab. However, the impact of these agents remains unclear, as there have been hints for increased overall survival, but also for an increased risk of severe infections in non-randomised trials. In this systematic review we summarised and analysed the evidence from randomised controlled trials on efficacy and safety of monoclonal anti-CD20 antibodies (such as rituximab and ofatumumab) in the treatment of CLL. We searched medical databases, such as EMBASE, MEDLINE and CENTRAL, and found seven randomised controlled trials fulfilling our inclusion criteria. Included trials compared anti-CD20 antibodies, particularly rituximab, to no further therapy or compared to anti-cancer therapy in CLL, irrespective of whether the patients were newly diagnosed or relapsed patients. Only five of the seven identified trials could be included in one of the two performed meta-analyses.

Three trials (N = 1421) were included in the meta-analysis assessing the efficacy of chemotherapy plus rituximab compared to chemotherapy without further therapy. The meta-analysis showed for patients receiving additional rituximab a statistically significant improvement of overall survival and a longer time without progression of the disease. Treatment with rituximab caused more adverse events, but this did not lead to a statistically significant difference regarding death caused by treatment. However, patients who were treated within these trials did not suffer from other severe health problems aside from CLL; therefore, it remains unclear whether patients with severe co-morbidities will benefit from this treatment option.

In summary, this meta-analysis showed that patients receiving chemotherapy plus rituximab benefited in terms of survival compared to those with chemotherapy alone. Therefore, it supports the recommendation of rituximab in combination with fludarabine and cyclophosphamide as an option for the first-line treatment as well as for people with relapsed or refractory CLL. Further research should focus on the evaluation of benefits of adding rituximab to other chemotherapy regimens than fludarabine with cyclophosphamide in the therapy of previously untreated, relapsed or refractory patients. It should also assess whether patients with serious co-morbidities will benefit from the addition of rituximab to chemotherapy.

The available evidence regarding assessed comparisons from four other trials was not sufficient to deduct final conclusions.Two trials evaluated polychemotherapy in combination with rituximab versus alemtuzumab respectively. One trial evaluated two different rituximab schedules: rituximab given concurrently with primary treatment plus rituximab therapy given subsequently to the primary treatment versus primary treatment alone with subsequent administration of rituximab. One trial investigated two different dosages (500 mg and 1000 mg) of ofatumumab in addition to fludarabine with cyclophosphamide.

Randomised Controlled Trials (RCTs) are needed to determine the clinical effects of novel anti-CD20 antibodies, such as ofatumumab or GA101, compared to rituximab. We are aware of 16 ongoing studies, including three trials comparing ofatumumab with or without additional chemotherapy versus no treatment. The findings of these trials will be included in an update of this review and could lead to different conclusions and may allow a judgement on general efficacy and safety of monoclonal anti-CD20 antibody in the treatment of CLL.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Anti-leukaemic therapy plus monoclonal anti-CD20 antibody compared with anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups) for newly diagnosed or relapsed patients with CLL

Patient or population: newly diagnosed or relapsed patients with CLL
Intervention: anti-leukaemic therapy plus monoclonal anti-CD20 antibody
Comparison: anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-leukaemic therapy alone	Anti-leukaemic therapy plus monoclonal anti-CD20 antibody				
OS (at 3 years)	Study population		**HR 0.78** (0.62 to 0.98)	1421 (3)	⊕⊕⊕⊕ **high**	
	830 per 1000	749 per 1000 (667 to 824)				
PFS (at 3 years)	Study population		**HR 0.64** (0.55 to 0.74)	1421 (3)	⊕⊕⊕◯ **moderate**[1]	
	450 per 1000	318 per 1000 (280 to 358)				
TRM	Study population		**RR 1.19** (0.70 to 2.01)	1415 (3)	⊕⊕⊕◯ **moderate**[1]	
	35 per 1000	**42 per 1000** (25 to 71)				
SAEs - overall analysis	Study population		**RR 1.05** (0.89 to 1.23)	598 (2)	⊕⊕◯◯ **low**[1,2]	
	480 per 1000	**504 per 1000** (427 to 590)				

Grade 3/4 AEs - overall analysis	**Study population**		**RR 1.15** (1.08 to 1.23)	1398 (3)	⊕⊕⊕○ **moderate**[1]
	680 per 1000	**782 per 1000** (735 to 837)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AE: adverse effect; CI: confidence interval; OS: overall survival; PFS: progression-free survival; RR: risk ratio; SAE: serious adverse effect

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgrading owing to lack of blinding (subjective outcomes are highly susceptible to biased assessment)
[2] GCLLSG CLL8 trial assessed serious adverse events, but did not report this outcome (quote: "adverse events and serious adverse events were documented according to the Common Toxicity Criteria.")

BACKGROUND

Description of the condition

Chronic lymphocytic leukaemia (CLL) accounts for 25% of all leukaemias and is the most common lymphoid malignancy in western countries (Chiorazzi 2005). The disease is characterised by a highly variable clinical course and prognosis. Some patients may have no or minimal symptoms for many years with a normal life expectancy, without requiring treatment. Other people are symptomatic at diagnosis or soon thereafter. They experience infectious or autoimmune complications and may die of drug-resistant disease long before reaching the normal life expectancy.

The extent of the disease is reflected by enlargement of lymph nodes, liver and spleen; raised lymphocyte count in blood and the degree of impairment of normal haematopoiesis. These variables can be used to define the different stages of the disease. The two most widely used staging systems, proposed by Rai et al. and Binet and co-workers, discriminate between early (Rai 0; Binet A), intermediate (Rai I, II; Binet B) and advanced (Rai III/IV; Binet C) disease with substantial differences in clinical course and long-term survival. However, these clinical staging systems are often of limited prognostic value at the time of diagnosis, when most patients are in the early stages of the disease (Binet 1981; Hallek 2008; Rai 1975). Other prognostic factors have been identified that distinguish better between more and less active forms of the disease. In particular, patients with a 17p-deletion have an aggressive form of the disease with a median survival time of less than one year (Dohner 2000).

Most patients with CLL are treated when they have an advanced stage of the disease with haematopoietic insufficiency or symptoms. Standard treatment options include monotherapy with chlorambucil (Clb), bendamustine, or purine analogues (fludarabine, pentostatine); polychemotherapies with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP); cyclophosphamide, vincristine, and prednisolone (COP); or fludarabine with cyclophosphamide (FluC). During the last few years, antibody monotherapy and the addition of monoclonal antibodies to chemotherapy have moved into the focus of interest.

While fludarabine leads to higher response rates and longer progression-free survival (PFS) compared to other monotherapies, CHOP and COP do not improve overall survival (OS), as shown in a Cochrane Review (Steurer 2006). The same is true for the combination of FluC when compared to fludarabine alone in randomised trials (Eichhorst 2006; Flinn 2007). So far, there are no randomised data showing an impact on OS for any of the various treatment options. However, patients with CLL are at increased risk of infection and infectious complications, including death. This may be related to the disease itself, the consequences of therapy, or both. Indeed, infections are more pronounced with treatments leading to longer PFS (e.g. fludarabine alone or FluC) (Hallek 2008).

Monoclonal antibodies against surface proteins expressed in CLL cells may allow a more targeted therapy of CLL. Examples are alemtuzumab (directed against CD52), rituximab (anti-CD20), ofatumumab (anti-CD20) and lumiliximab (anti-CD23). Both alemtuzumab and rituximab have shown improved PFS compared to treatment without the antibodies (Hallek 2010; Hillmen 2007b). In a retrospective analysis comparing FluC with FluC-rituximab (FluC-R), Wierda et al. showed a possible benefit for OS (Wierda 2006).

This review is part of a series of reviews examining the role of monoclonal antibodies in CLL (Skoetz 2012).

Description of the intervention

Currently, three monoclonal anti-CD20 antibodies, rituximab, ofatumumab and GA101 (synonym: obinutuzumab, RO5072759), are being investigated in clinical trials.

The most evaluated anti-CD20 antibody, rituximab, showed efficacy in patients with CLL, both as a single agent (Huhn 2001) and in combination with chemotherapies (Schulz 2002). The early studies demonstrated that rituximab alone in relapsed CLL had only a moderate activity (seven of 28 patients showed a partial remission) (Huhn 2001). The effects of rituximab have been shown to be improved when it is given combined with chemotherapy (27 of 31 fludarabine- and anthracycline-naive patients achieved complete remission or partial remission) (Schulz 2002). This led to further studies evaluating rituximab in combination with a variety of chemotherapeutic regimens (CALBG 9712; CLL2007FMP; GCLLSG CLL 8; Iannitto 2011; Kay 2010). The clinical effect of rituximab treatment is limited by the often occurring resistance or reduced response to re-treatment with rituximab. Therefore, novel anti-CD20 antibodies are in development, including ofatumumab and GA101 (Czuczman 2010).

How the intervention might work

The CD20 antigen is present on more than 90% of B-cell lymphoma cells and is neither shed nor internalised after antibody binding (Tedder 1994). These characteristics make it an effective target for immunotherapeutic removal of malignant B cells by monoclonal anti-CD20 antibodies. Preclinical studies of monoclonal anti-CD20 antibodies have shown that several mechanisms are involved in providing therapeutic efficacy, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and the induction of cell growth arrest and apoptosis (Li 2008; Li 2009; Teeling 2004; Teeling 2006).

Rituximab is less active in CLL than in follicular lymphoma unless very high doses are used, because CLL cells have a lower density of CD20 than most other B-cell malignancies (Huhn 2001; Jacobs 2005). In non-randomised comparisons the combination of rituximab with chemotherapy showed promising results (Byrd 2003b;

Schulz 2002). Similar observations were made for the combination of rituximab with FluC (FluC-R) (Byrd 2005; Keating 2005; Wierda 2005), bendamustine (Robinson 2008), or mitoxantrone (FluCM) (Bosch 2008). In a historical comparison of FluC-R versus FluC, FluCM, or fludarabine monotherapy, in both first-line and relapse therapy, survival benefits for rituximab combinations have been reported (Tam 2008; Wierda 2006). However, increased adverse haematological effects caused by rituximab, particularly in terms of neutropenia and leukocytopenia have also been observed (Hallek 2010; Robak 2008a).

Ofatumumab, the second-generation anti-CD20 antibody, showed higher in vitro efficacy on CLL cells than rituximab (Teeling 2004). A Phase I/II clinical trial has been completed in patients with relapsed or refractory CLL, showing promising clinical efficacy in this difficult-to-treat patient population (Coiffier 2008).

Why it is important to do this review

Based on the published trials, targeting CD20 with monoclonal antibodies in addition to chemotherapy may be an effective treatment and well-tolerated option for CLL patients (Coiffier 2008; Hallek 2010; Robak 2008a).

So far, there is no systematic review assessing the efficacy and safety of monoclonal anti-CD20 antibodies in the treatment of CLL. This Cochrane review will identify and summarise the available evidence regarding the impact of these monoclonal anti-CD20 antibodies on the treatment of patients with CLL. It will also examine differences of treatment effectiveness caused by different types of monoclonal anti-CD20 antibodies.

OBJECTIVES

The objective of this review is to assess and summarise the evidence for the treatment of patients with CLL with monoclonal anti-CD20 antibodies.

METHODS

Criteria for considering studies for this review

Types of studies

We only considered randomised controlled trials (RCTs). We included both full-text and abstract publications, if sufficient information was available on study design, characteristics of participants, interventions and outcomes.

Types of participants

We included trials on patients with histologically confirmed B-cell CLL. Both pre-treated and chemotherapy-naive patients were included. If trial populations would have been mixed (i.e. patient groups with different haematological malignancies), data from the CLL subgroups would have been used. If subgroup data for CLL patients would not have been provided (after contacting the authors of the trial), the trial would have been excluded if less than 80% of patients had CLL.

Types of interventions

We included all randomised trials of anti-CD20 antibody given alone or in combination with chemotherapy as primary treatment or maintenance treatment in untreated as well as refractory or relapsed patients.

We considered different treatment approaches for the control group including 'watchful waiting' and conventional therapies such as fludarabine or Clb monotherapy, fludarabine in combination with other chemotherapeutic agents, or other antibody therapy.

We included trials comparing different dosages or time schedules of anti-CD20 antibodies.

We examined the following comparisons.

1. Anti-leukaemic therapy plus anti-CD20 antibody versus anti-leukaemic therapy alone; anti-leukaemic therapy identical in both groups.
2. Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups).
3. Different dosages or times of anti-CD20 antibody (with or without identical chemotherapy in both arms).

We did not identify any trial regarding the comparison of anti-CD20 antibody versus anti-leukaemic therapy.

Types of outcome measures

Primary outcomes

OS; defined as the time interval from random treatment assignment/entry onto study to death from any cause or to last follow-up.

Secondary outcomes

We analysed the following outcomes as secondary outcomes:

- PFS;
- time to next treatment;
- treatment-related mortality (TRM);
- complete response rate (CRR);
- overall response rate (ORR);
- minimal residual disease (MRD);

- adverse events (AE);
- number of patients discontinuing the study because of drug-related AEs.

Search methods for identification of studies

Electronic searches

We adapted the search strategies suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). No language restriction was applied to reduce the language bias.

Bibliographic databases

Ovid MEDLINE (1990 to 4 January 2012) (Appendix 1).
Ovid EMBASE (1990 to 20 March 2009) (Appendix 2).
The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 12) (Appendix 3).

Conference proceedings

We searched the conference proceedings of relevant conferences of the following societies for the years that were not included in CENTRAL:

- American Society of Clinical Oncology (ASCO) (2011);
- American Society of Hematology (ASH) (2011);
- European Hematology Association (EHA) (2011);
- European Society of Medical Oncology (ESMO).

Electronic search in databases of ongoing trials

We searched the metaRegister of Controlled Trials (mRCT) to identify ongoing trials (www.clinicaltrials.gov).

Searching other resources

We handsearched:

- references of all identified trials, relevant review articles;
- current treatment guidelines (www.g-i-n.net; Cheung 2009; NICE 2009; NICE 2010; NICE 2010a).

Data collection and analysis

Selection of studies

Two review authors (KB, MR) independently screened the results of the search strategies for eligibility for this review by reading the abstracts. In case of disagreement the full-text publication was obtained (Higgins 2011a). If no consensus had been reached, we would have asked a third review author's opinion, although this procedure was not necessary.

The study selection process was documented in a flow chart as recommended in the PRISMA statement (Moher 2009) showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and management

Two review authors (KB, MR) independently extracted the data according to the guidelines proposed by the Cochrane Collaboration (Higgins 2011a). Authors of individual studies would have been contacted for additional information, but it was not required. We used a standardised data extraction form containing the following items:

- general information: study ID; author; title; journal; publication date; citation and contact details of primary or corresponding authors; sources of funding;
- study characteristics: design; objectives and duration of the study; source of participants; number of participating centres; inclusion and exclusion criteria; sample size; treatment allocation; comparability of groups; subgroup analysis; statistical methods; power calculations; compliance with assigned treatment; length of follow-up;
- participant characteristics: age; sex; ethnicity; setting; number of participants recruited/randomised/evaluated; additional diagnoses; stage of the disease; numbers of participants lost to follow-up; drop-outs (percentage in each arm) with reasons; protocol violations; previous treatments; prognostic factors;
- interventions: setting; dose and duration of anti-CD20 antibody; type, dosage and duration of chemotherapy (number of cycles); administration route; supportive treatment; compliance to interventions; additional interventions given; any difference between interventions;
- outcomes: OS; PFS; response rate; time to next treatment; TRM; MRD rate; AEs; number of patients discontinuing the study because of drug-related AEs; number of patients evaluated for primary outcomes, number of patients evaluated for secondary outcomes; length of follow-up for survival endpoints; definitions for the outcomes.

We used both full-text versions and abstracts including additional information (e.g. slides) of eligible studies to retrieve the data. We extracted trials reported in more than one publication on one form only.

Assessment of risk of bias in included studies

To assess quality and risk of bias, we used a questionnaire (validity assessment form) containing the items as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);

- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

For every criterion a judgement was made using one of three categories:

- 'low risk': if the criterion was adequately fulfilled in the study (i.e. the study was at a low risk of bias for the given criterion);
- 'high risk': if the criterion was not fulfilled in the study (i.e. the study is at high risk of bias for the given criterion);
- 'unclear': if the study report did not provide sufficient information to allow for a judgement of 'high risk' or 'low risk' or if the risk of bias is unknown for one of the criteria listed above.

Measures of treatment effect

We estimated treatment effect measures of individual studies as the relative effect measures (risk ratio (RR)) with 95% confidence intervals (CI) for dichotomous data. For survival data we estimated treatment effects of individual studies as hazard ratios (HR) using the methods described by Parmar (Parmar 1998) and Tierney (Tierney 2007).

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) there are many potential sources of missing data that have to be taken into account: at study level, at outcome level and at summary data level. It was important to distinguish between 'missing at random' and 'not missing at random'. We judged all missing data as 'missing at random'. Therefore, we analysed only the available data (i.e. ignored the missing data).
In case we assumed data not to be missing at random, we would have imputed the missing data with replacement values, and treated these as if they were observed (e.g. last observation carried forward, imputing an assumed outcome such as assuming all were poor outcomes, imputing the mean, imputing based on predicted values from a regression analysis).

Assessment of heterogeneity

Because of the small number of studies in each analysis (two), the quantification of heterogeneity was not reliable, since the CIs were very wide. In meta-analyses with more trials, we would have assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. In that case, we would have used the I^2 statistic to quantify possible heterogeneity ($I^2 >$ 30% moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2011). We explored potential causes of heterogeneity by sensitivity and subgroup analyses.

Assessment of reporting biases

In a meta-analysis with more than 10 trials, we would have explored potential reporting bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2011). A P value less than 0.1 would have been considered significant for this test. However, we only included five trials so this test was not done.

Data synthesis

We performed analyses according to the recommendations of Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into the Cochrane statistical package Review Manager (RevMan) 5.1 (RevMan 2011). One review author (KB) entered data into the software and a second review author (MR) checked it for accuracy. We performed meta-analyses using a fixed-effect model (for example the generic inverse variance method for survival data outcomes and Mantel-Haenszel method for dichotomous data outcomes). We used the random-effects model in terms of sensitivity analyses.
We calculated the number needed to treat for an additional beneficial effect (NNTB) for the primary outcome OS and the number needed to treat for an additional harmful effect (NNTH) for the total number of AEs WHO grade 3 or 4.
The GRADE profiler was used to create Summary of Finding tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Subgroup analysis and investigation of heterogeneity

We took the following parameters into consideration for subgroup analyses as there is some evidence that these parameters cause heterogeneity:

- age (e.g. adults < 50 years versus adults ≥ 50 years);
- stage of disease (Rai and Binet);
- influence of prognostic factors (e.g. 11q- or 17p-deletion);
- different treatment regimens (e.g. combination with chemotherapy or not);
- different anti-CD20 antibody treatment regimens (e.g. primary therapy or maintenance);
- different types of anti-CD20 antibodies (e.g. rituximab, ofatumumab).

Sensitivity analysis

We assessed robustness of the overall results by sensitivity analysis with respect to the quality and design of the trials.

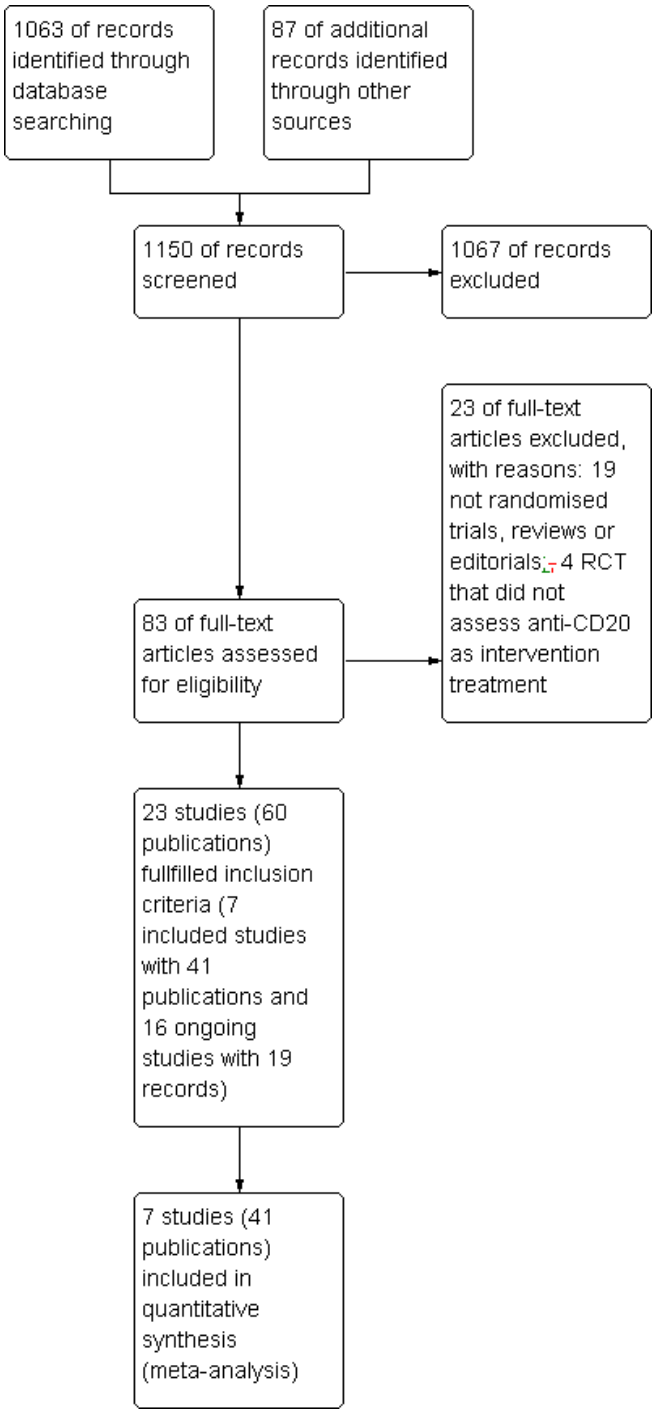
RESULTS

Description of studies

Results of the search

We identified 1150 potentially relevant references by database searches and handsearching. Of these, 1067 were excluded at the initial stage of screening because they did not fulfil our pre-defined inclusion criteria. The remaining 83 publications were retrieved as full-text publications or abstract publications for detailed evaluation. Of these 87 publications, we excluded 23 publications and identified seven included trials (41 publications) and 16 ongoing trials (19 publications) that fulfil the pre-defined inclusion criteria. Zagoskina et al. and Foa et al. published abstracts with preliminary results. These abstracts reported only cumulative results about included patients, which did not provide enough information to be analysed in the meta-analysis (Foa 2010; Zagoskina 2011). Therefore, we decided to include these trials in the group of ongoing studies. The overall numbers of references screened, identified, selected, excluded and included are documented according to the PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.



We performed two main analyses. The first main analysis (anti-leukaemic therapy plus monoclonal anti-CD20 antibody versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)) included three trials with 1421 patients in the main meta-analyses of this review (GCLLSG CLL 8; NCRI-CLL 201; REACH). The second main analysis (anti-leukaemic therapy with monoclonal anti-CD20 antibody versus anti-leukaemic therapy without monoclonal anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)) included two trials with 177 participants (CLL2007FMP; Gribben 2005).
Two trials assessed different doses or time schedules. The CALBG 9712 with 104 participants compared two different time schedules for the administration of rituximab. The other trial included 61 participants and assessed two different dosages of ofatumumab (Wierda 2011).

Included studies

We included seven trials (CALBG 9712; CLL2007FMP; GCLLSG CLL 8; Gribben 2005; NCRI-CLL 201; REACH; Wierda 2011) in the review. We extracted data from full-text publications for five trials (CALBG 9712; GCLLSG CLL 8; NCRI-CLL 201; REACH; Wierda 2011). For the other two trials, we extracted data from abstract publications (CLL2007FMP; Gribben 2005). See also the table Characteristics of included studies.

Design

Seven included trials were two-armed RCTs.
The CALBG 9712 recruited patients from 1998 to 2000; GCLLSG CLL 8, NCRI-CLL 201 and REACH from 2003 to 2007; and CLL2007FMP from 2007 to 2009. The two other trials did not provide dates on trial recruitment (Gribben 2005; Wierda 2011).

Sample size

The smallest trial randomised 12 patients (Gribben 2005) and the largest trial 817 patients (GCLLSG CLL 8).

Location

Three included trials were conducted in Europe and the US (CALBG 9712; GCLLSG CLL 8; Wierda 2011). Three trials did not report the countries of recruitment (CLL2007FMP; Gribben 2005; NCRI-CLL 201). The REACH trial recruited patients in Australia, Canada, Europe, New Zealand and the US.

Participants

The trials included a total of 1763 male and female randomised patients with histologically confirmed CLL. Four trials evaluated the anti-CD20 antibody in patients receiving first-line therapy (CALBG 9712; CLL2007FMP; GCLLSG CLL 8; Wierda 2011). Three trials included relapsed or refractory patients (Gribben 2005; NCRI-CLL 201; REACH).

Interventions

Three trials evaluated rituximab versus no further therapy and observation (GCLLSG CLL 8; NCRI-CLL 201; REACH). Two trials (CLL2007FMP; Gribben 2005) assessed the role of rituximab versus alemtuzumab. One trial compared the effects of rituximab 500 mg with rituximab 1000 mg (Wierda 2011). The other trial assessed two schedules: rituximab and fludarabine plus rituximab (Flu-R) maintenance compared to fludarabine alone plus rituximab maintenance (CALBG 9712).

Primary outcome measure

Four trials analysed OS (CALBG 9712; GCLLSG CLL 8; NCRI-CLL 201; REACH). Wierda 2011, CLL2007FMP and Gribben 2005 did not assess OS.

Secondary outcome measures

Five trials reported data regarding PFS (CALBG 9712; GCLLSG CLL 8; NCRI-CLL 201; REACH; Wierda 2011). CLL2007FMP and Gribben 2005 did not report PFS. Response rate was analysed in all seven trials, MRD was evaluated in three trials (CLL2007FMP; NCRI-CLL 201; REACH). Six trials mentioned TRM (CLL2007FMP; GCLLSG CLL 8; Gribben 2005; NCRI-CLL 201; REACH; Wierda 2011). All trials reported AEs. None of the trials reported results regarding number of patients discontinuing the study because of drug-related AEs.

Conflict of interest

Gribben 2005 did not provide a conflict of interest statement (abstract publication). In one trial, the authors indicated no potential conflict of interest (CLL2007FMP). The research for CALBG 9712 was supported, in part, by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B. The other trials were granted by the pharmaceutical industry:

- GCLLSG CLL 8: the trial was funded by F Hoff mann-La Roche;

- NCRI-CLL 201: Roche Pharmaceuticals provided rituximab for the trial as well as an unrestricted grant to support the running of the trial;

- REACH: 13 of 20 authors were employees, consultants or stock owners, or received research funding or honoraria from Roche, Bayer Schering Pharma, Mundipharma, Genzyme, Genentech, Novartis or Biogen Idec;

- Wierda 2011: 13 of 18 authors were employees, consultants or stock owners, or received research funding or honoraria from Genmab, GlaxoSmithKline, Abbott Industries, Celgene, Biogen Idec, Cephalon, Sanofi-Aventis, Medimmune, Memgem, Lundbeck or Novo Nordisk.

Excluded studies

A total of 23 articles were excluded after detailed evaluation of full-text publications. The main reasons for exclusion were:

- 19 non-randomised comparisons or reviews;
- four RCTs but either patients in all arms received anti-CD20 antibodies or anti-CD20 antibodies were not administrated to any patient.

These publications are described under Characteristics of excluded studies.

Risk of bias in included studies

Overall the quality of included trials was moderate to high. Two included trials were published as abstracts only (CLL2007FMP; Gribben 2005), therefore we were unable to assess the potential risk of bias for these trials in detail. For more information see 'Risk of bias' tables of included trials and for an overview of the results see Figure 2 and Figure 3.

Figure 2.

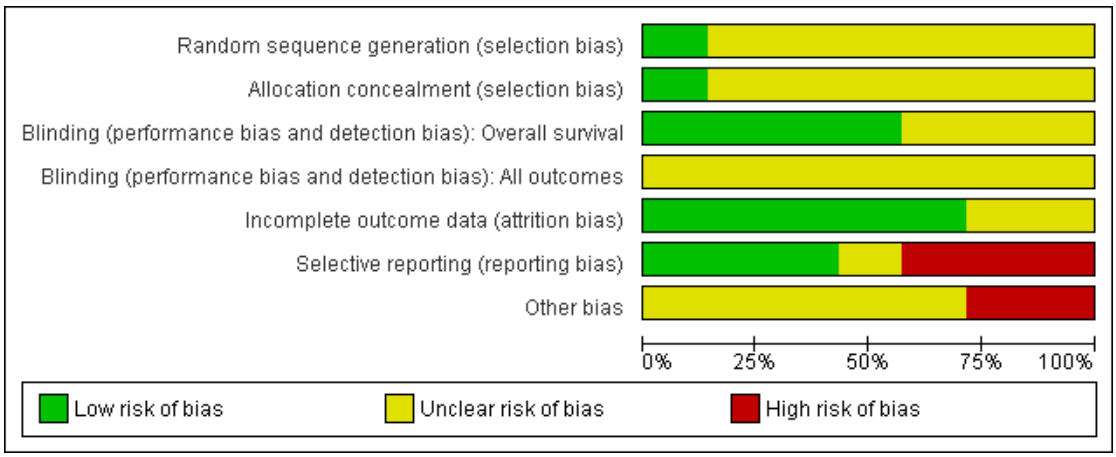
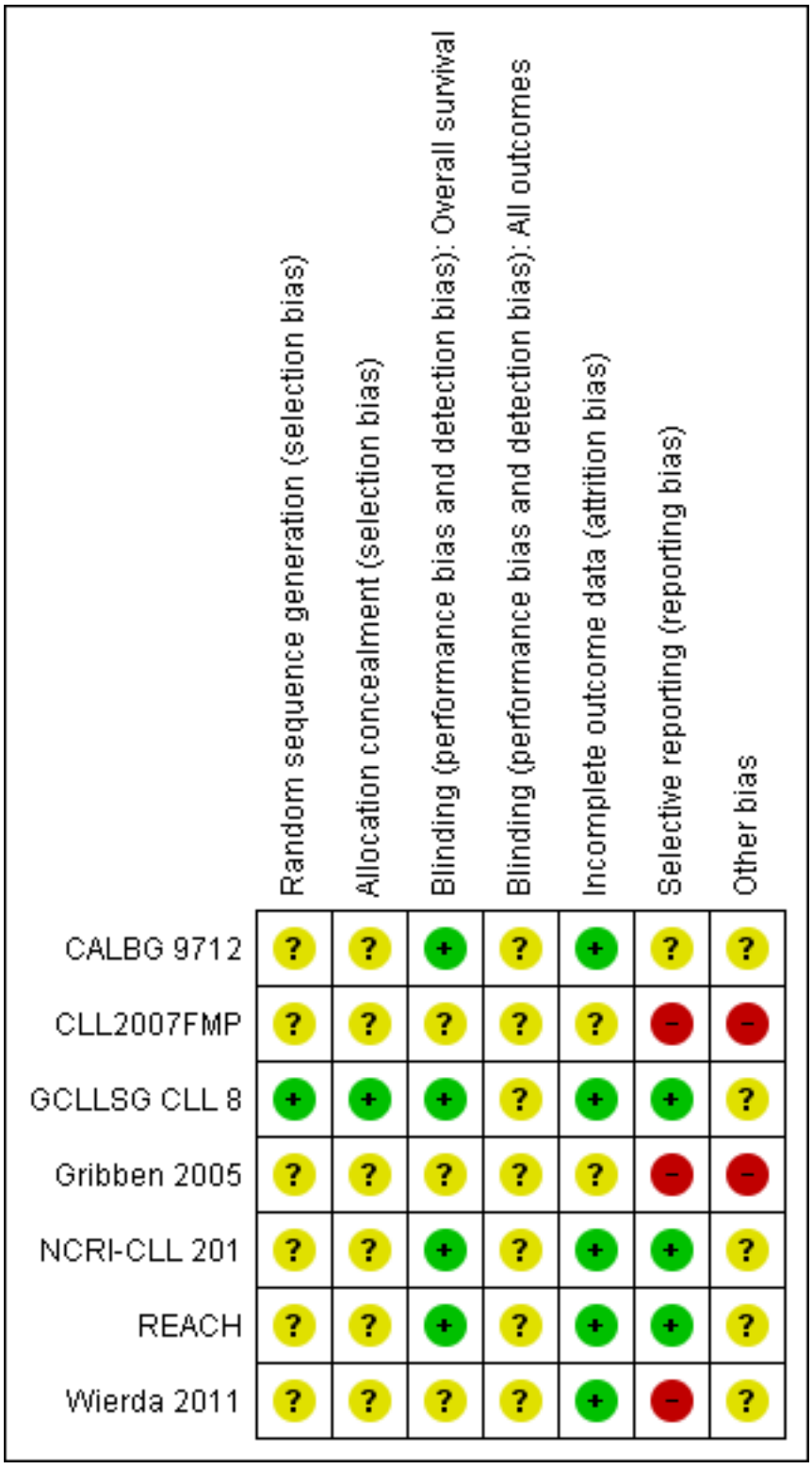


Figure 3.



Allocation

All trials stated that they were 'randomised'. In one trial the random sequence generation was adequate (computer generated; assignment to treatment was done centrally at the Institute for Medical Statistics and Epidemiology, Technical University of Munich) (GCLLSG CLL 8). No information was available for the other trials. Therefore we judged GCLLSG CLL 8 as 'low' and the other trials as 'unclear' for random sequence generation as well as allocation concealment.

Blinding

Results with respect to OS were judged not to be influenced by this source of bias, because to define the status of a patient as dead or alive is not a question of individual judgement. Wierda 2011 did assess but not report results regarding OS. CLL2007FMP and Gribben 2005 did not assess OS. Therefore we left the judgment of these three trials as 'unclear'.

None of the trials provided information regarding the blinding of the outcome assessor. As blinding of the outcome assessors is considered important for all outcomes aside from OS in this review. Therefore all trials were judged 'unclear' for the question of blinding regarding these other outcomes.

Incomplete outcome data

The five trials published as full texts described missing outcome data in detail and included all randomised patients in the analysis (CALBG 9712; GCLLSG CLL 8; NCRI-CLL 201; REACH; Wierda 2011). These trials stated that they performed analyses according to the intention-to-treat-principle; we judged risk of attrition bias for these studies as 'low'.

The two trials published as abstracts only provided no information regarding missing data, therefore we judged the risk of attrition bias for these trials as 'unclear' (CLL2007FMP; Gribben 2005).

Selective reporting

For all seven studies there was a study protocol at www.controlled-trials.com/mrct/ available. With the exception of CALBG 9712 all protocols reported the pre-planned outcomes. Therefore, we left the risk of reporting bias of CALBG 9712 as 'unclear'. GCLLSG CLL 8, NCRI-CLL 201 and REACH reported all pre-planned outcomes and we judged the risk of reporting bias as 'low'. The other three studies, Wierda 2011, CLL2007FMP and Gribben 2005, reported only a few outcomes of the pre-planned outcomes. We judge the risk of reporting bias as 'high' for these trials.

Other potential sources of bias

One trial was stopped prematurely owing to an increased incidence of severe infections or an excess of mortality in the alemtuzumab arm (CLL2007FMP). In the Phase II trial by Gribben 2005 only 12 patients were randomised instead of the 150 patients pre-planned as described in the protocol (ClinicalTrials.gov: NCT00086775; Gribben 2005). A total of 150 patients (75 per treatment arm) were needed for this study. The small number of 12 patients instead of 150 indicates that these are very preliminary results and we judge the risk of other sources of bias as 'high'.

No other potential sources of bias were identified for the other trials. We judge their risks of other sources of bias as 'unclear'.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Anti-leukaemic therapy plus monoclonal anti-CD20 antibody versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Three RCTs (N = 1421) evaluated the efficacy and safety of the monoclonal anti-CD20 antibody rituximab plus anti-leukaemic therapy versus anti-leukaemic therapy alone (GCLLSG CLL 8; NCRI-CLL 201; REACH).

Subgroup analysis regarding 'different types of anti-CD20 antibodies' was not performed since rituximab was administered in all identified studies included in the meta-analysis. Furthermore, we did not perform any sensitivity analysis, because all these trials showed no differences regarding publication form (full-text publications/abstracts), type of results (preliminary results/mature results) or quality issues (see Figure 3).

Primary outcome: overall survival (OS)

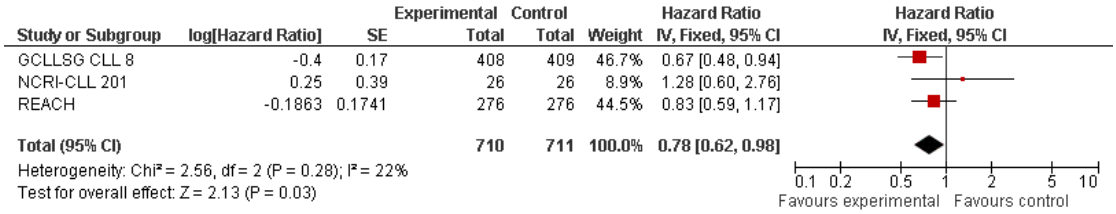
Participants

Three trials with 1421 participants provided information regarding this outcome (GCLLSG CLL 8; NCRI-CLL 201; REACH).

Results

In the main analysis OS was statistically significantly longer with rituximab than with chemotherapy alone: HR was 0.78 (95% CI 0.62 to 0.98, P = 0.03; Summary of findings for the main comparison). There was low heterogeneity between the trials, with an I^2 of 22% (see Figure 4). The NNTB was 12 (95% CI 6 to 166).

Figure 4. Forest plot of comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), outcome: 1.1 OS - overall analysis.



Subgroup analyses

No statistically significant heterogeneity was apparent. We conducted subgroup analysis to explore the underlying clinical heterogeneity in order to assess the influence of clinical differences between the studies.

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistical differences between the following subgroups:

- different anti-CD20 antibody treatment regimens (P = 0.22; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 604);
- different treatment regimens (P = 0.18; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52).

Subgroup analyses in terms of 'age', 'stage' and 'prognostic factors' were not performed, because GCLLSG CLL 8 was the only study that provided data of subgroup analyses regarding OS (see Table 1) and the identified studies did not systematically differ owing to these study characteristics (see Subgroup analysis and investigation of heterogeneity).

Secondary outcome: progression-free survival (PFS)

Three trials provided information regarding PFS (GCLLSG CLL 8; NCRI-CLL 201; REACH). These included 1421 participants.

Results

The main analysis of PFS showed a statistically significantly improved outcome for patients with rituximab: HR was 0.64 (95% CI 0.55 to 0.74; P < 0.00001).

Subgroup analysis

We conducted subgroup analysis to explore the potential underlying clinical heterogeneity between the studies.

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistically significant differences between the following subgroups:

- age (P = 0.05; < 65 years: 2 trials, N = 889; ≥ 65 years: 1 trial, N = 245; ≥ 65 to < 70 years: 1 trial, N = 142; ≥ 70 years: 1 trial, N = 93);
- stage (P = 0.60; Binet A: 2 trials, N = 95; Binet B: 2 trials, N = 848; Binet C: 2 trials, N = 423);
- prognostic factors (P = 0.25; del17p: 2 trials, N = 93; del11q: 2 trials, N = 705; trisomy 12: 2 trials, N = 143, del13q: 2 trials, N = 659);
- different anti-CD20 antibody treatment regimens (P = 0.05; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 604);
- different treatment regimens (P = 0.70; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52).

Secondary outcome: time to next treatment

Participants

Data for the outcome the time to next treatment were available from the GCLLSG CLL 8 and REACH trials with 1369 participants.

Results

There was a statistically significant difference favouring the treatment with rituximab regarding time to next treatment: HR was 0.61 (95% CI 0.51 to 0.73; P < 0.00001).

Subgroup analysis

Subgroup analyses in terms of 'age', 'stage' and 'prognostic factors' were not performed since the identified studies differ only with regard to 'anti-CD20 antibody treatment regimens'. The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistically significant differences between the following subgroup:

- different anti-CD20 antibody treatment regimens (P = 0.60; first-line treatment: 1 trial, N = 817; previously treated: 1 trial, N = 552).

Secondary outcome: overall response rate (ORR)

Participants

ORR data were available from three trials (GCLLSG CLL 8; NCRI-CLL 201; REACH). We included in this meta-analysis three trials with 1421 participants.

Results

The overall estimate of ORR showed an RR of 1.16 (95% CI 1.09 to 1.23, P < 0.00001, I^2 = 0%) in favour of treatment with rituximab.

Subgroup analysis

We did not find any statistically significant differences between the following subgroups:

- age (P = 0.48; < 65 years: 2 trials, N = 889; ≥ 65 years: 1 trial, N = 245; ≥ 65 to < 70 years: 1 trial, N = 142; ≥ 70 years: 1 trial, N = 93);
- stage (P = 0.25; Binet A: 2 trials, N = 95; Binet B: 2 trials, N = 848; Binet C: 2 trials, N = 423);
- prognostic factors (P = 0.07; del17p: 2 trials, N = 93; del11q: 2 trials, N = 694; trisomy 12: 2 trials, N = 130, del13q: 2 trials, N = 533);
- different anti-CD20 antibody treatment regimens (P = 0.26; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 604);
- different treatment regimens (P = 0.91; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52).

Secondary outcome: complete response rate (CRR)

Participants

Three trials with 1421 participants provided information of the CRR (GCLLSG CLL 8; NCRI-CLL 201; REACH).

Results

The main analysis of CRR showed a statistically significantly improved outcome for patients receiving rituximab (RR 2.11, 95% CI 1.72 to 2.59, P < 0.00001, I^2 = 0%).

Subgroup analysis

Data of subgroup analyses of 'age', 'stage ' and 'prognostic factors' with regard to CRR was only provided by GCLLSG CLL 8 (see Table 2).

We did not find any statistically significant differences between the following subgroups:

- different anti-CD20 antibody treatment regimens (P = 0.35; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 604);
- different treatment regimens (P = 0.93; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52).

Secondary outcome: minimal residual disease (MRD) negativity

Participants

Data regarding MRD negativity were provided by two trials (NCRI-CLL 201; REACH). In this meta-analysis we included 121 participants.

Results

The meta-analyses of MRD showed no statistically significant difference between treatment with chemotherapy plus rituximab or chemotherapy alone: RR of 1.43 (95% CI 0.81 to 2.54, P = 0.22).

Subgroup analysis

Since the two studies differ only with regard to 'different treatment regimens', we performed this subgroup analysis.

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistically significant differences between the following subgroup:

- different treatment regimens (P = 0.80; FluC-R versus FluC: 1 trial, N = 69; FluCM-R versus FluCM: 1 trial, N = 52).

Secondary outcome: treatment-related mortality (TRM)

Participants

Data of the TRM were available from the GCLLSG CLL 8, NCRI-CLL 201 and REACH trials with 1415 participants.

Results

There were no statistically significant differences between treatment with chemotherapy plus rituximab or chemotherapy alone regarding TRM (3 trials, N = 1415, RR 1.19, 95% CI 0.70 to 2.01, P = 0.52).

Subgroup analysis

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistically significant differences between the following subgroups:

- different anti-CD20 antibody treatment regimens (P = 0.30; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 598);
- different treatment regimens (P = 0.58; FluC-R versus FluC: 2 trials, N = 869; FluCM-R versus FluCM: 1 trial, N = 546).

Secondary outcome: adverse events (AE)

Participants

We included the following AEs, World Health Organization (WHO) grade 3/4 in the meta-analyses, because they were provided by more than one trial: serious adverse events (SAEs) (NCRI-CLL 201; REACH), total of AEs WHO grade 3/4 (GCLLSG CLL 8; NCRI-CLL 201; REACH), anaemia (GCLLSG CLL 8; REACH), neutropenia (GCLLSG CLL 8; NCRI-CLL 201; REACH) and thrombocytopenia (GCLLSG CLL 8; REACH). Further AEs WHO grade 3/4 that are only reported by one trial are listed in a tabular form (see Table 3).

Results

The addition of rituximab caused statistically significantly more acute AEs WHO grade 3/4 in terms of:

- total AEs WHO grade 3/4 (3 trials, N = 1398, RR 1.15, 95% CI 1.08 to 1.23, P < 0.0001, NNTH 9);
- neutropenia (3 trials, N = 1398, RR 1.28, 95% CI 1.11 to 1.48, P = 0.001).

No statistically significant differences between treatment with chemotherapy plus rituximab or chemotherapy alone were found for:

- SAEs (2 trials, N = 598, RR 1.05 95% CI 0.89 to 1.23, P = 0.57);
- anaemia (2 trials, N = 1346, RR 0.88, 95% CI 0.62 to 1.24, P = 0.45);
- thrombocytopenia (2 trials, N = 1346, RR 0.86, 95% CI 0.61 to 1.19, P = 0.36).

Subgroup analyses

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed no statistically significant differences between the following subgroups:

- SAE - different treatment regimens (P = 0.92; FluC-R versus FluC: 1 trial, N = 546; FluCM-R versus FluCM: 1 trial, N = 52);
- grade 3/4 AEs - different anti-CD20 antibody treatment regimens (P = 0.07; first-line treatment: 1 trial, N = 800; previously treated: 2 trials, N = 598);
- grade 3/4 AEs - different treatment regimens (P = 0.28; FluC-R versus FluC: 2 trials, N = 1346; FluCM-R versus FluCM: 1 trial, N = 52);
- anaemia 3/4 AEs - different anti-CD20 antibody treatment regimens (P = 0.66; first-line treatment: 1 trial, N = 800; previously treated: 1 trial, N = 546);
- neutropenia 3/4 AEs - different treatment regimens (P = 0.33; FluC-R versus FluC: 2 trials, N = 1346; FluCM-R versus FluCM: 1 trial, N = 52);
- thrombocytopenia 3/4 AEs - different anti-CD20 antibody treatment regimens (P = 0.09; first-line treatment: 1 trial, N = 800; previously treated: 1 trial, N = 546).

The 'test for subgroup differences' implemented in RevMan 5.1 (RevMan 2011) showed statistically significant differences between the following subgroups:

- neutropenia 3/4 AEs - different anti-CD20 antibody treatment regimens (P = 0.007; first-line treatment: 1 trial, N = 800; previously treated: 1 trial, N = 598).

In addition the GCLLSG CLL 8 reported statistically significantly more infections in the rituximab-receiving group (rituximab 103 of 404 patients, control 85 of 396 patients) and grade 3/4 haematological toxicity (rituximab 225 of 404 patients, control 157 of 396 patients). We listed further reported AEs in Table 3.

Secondary outcome: number of patients discontinuing the study because of drug-related adverse events

GCLLSG CLL 8 reported that 138 (17%) of 800 patients discontinued treatment as a result of AEs. In the REACH trial 72 patients (26%) of the FC-R arm and 69 patients (25%) in the FluC arm discontinued treatment because of AEs. The NCRI-CLL 201 trial did not provide data with regard to this outcome.

Anti-leukaemic therapy with monoclonal anti-CD20 antibody versus anti-leukaemic therapy without monoclonal anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Two RCTs (N = 177) evaluated the role of additional rituximab versus additional alemtuzumab in CLL patients (CLL2007FMP; Gribben 2005).

Primary outcome: overall survival (OS)

Neither studyprovided data on OS.

Secondary outcome: progression-free survival (PFS)

Neither study reported PFS data.

Secondary outcome: time to next treatment

Neither study provided data for time to next treatment.

Secondary outcome: overall response rate (ORR)

Participants

Both trials report on ORR (N = 176).

Results

There was no statistically significant difference between groups regarding the ORR (RR 1.01, 95% CI 0.89 to 1.14, P = 0.91).

Subgroup analysis

We found no statistically significant differences between treatment with chemotherapy plus rituximab or chemotherapy plus alemtuzumab for:

- different anti-CD20 antibody treatment regimens (P = 0.26; first-line treatment: 1 trial, N = 165; previously treated: 1 trial, N = 11).

Secondary outcome: complete response rate (CRR)

Participants

Both trials report on ORR (N = 176 patients).

Results

There was no statistically significant difference in terms of CRR between the patients receiving additional rituximab and those receiving additional alemtuzumab (RR 1.21, 95% CI 0.94 to 1.58, P = 0.14).

Subgroup analysis

We found no statistically significant differences between treatment with chemotherapy plus rituximab or chemotherapy plus alemtuzumab for:

- different anti-CD20 antibody treatment regimens (P = 0.16; first-line treatment: 1 trial, N = 165; previously treated: 1 trial, N = 11)

Secondary outcome: minimal residual disease (MRD) negativity

In the CLL2007FMP trial MRD negativity was assessed both in blood and bone marrow nine months after therapy. At this time point 35 of 83 patients (42%) receiving additional rituximab were MRD negative compared to 20 of 82 patients (25%) that received alemtuzumab.
Gribben 2005 did not report data regarding this outcome.

Secondary outcome: treatment-related mortality (TRM)

Participants

Both trials reported on TRM (N = 177 patients)

Results

No statistically significant difference was found between patients receiving additional rituximab compared to those receiving additional alemtuzumab (RR 0.31, 95% CI 0.06 to 1.51, P = 0.15). However, the CLL2007FMP trial was stopped prematurely owing to an excess of mortality in the alemtuzumab arm.

Subgroup analysis

We found no statistically significant differences between treatment with chemotherapy plus rituximab or chemotherapy plus alemtuzumab for:

- different anti-CD20 antibody treatment regimens (P = 0.23; first-line treatment: 1 trial, N = 165; previously treated: 1 trial, N = 12)

Secondary outcome: adverse events (AE)

In the Gribben 2005 trial two cytomegalovirus (CMV) re-activations (50%) were reported in the additional alemtuzumab arm. The number of CMV reactivations for patients receiving additional rituximab is not reported.
CLL2007FMP provided data for all grade 3/4 AEs (75 patients (90%) in the rituximab arm versus 72 patients (87%) in the alemtuzumab arm, P = 0.76). There was no statistically significant difference for grade 3/4 neutropenia (62 patients (75%) in the rituximab arm versus 65 patients (79%) in the alemtuzumab arm, P = 0.49). However, SAEs occurred statistically significantly more frequently in the alemtuzumab arm (18 patients (22%) in the rituximab arm versus 35 patients (43%) in the alemtuzumab arm, P = 0.006). Additionally, serious febrile neutropenia was statistically significantly more frequent in the alemtuzumab arm (13 patients (16%) in the rituximab arm versus 27 patients (33%) in the alemtuzumab arm, P = 0.01).

Secondary outcome: number of patients discontinuing the study because of drug-related adverse events

In the Gribben 2005 study, six patients (75%) in the rituximab arm discontinued treatment because of AEs, while in the alemtuzumab arm, there was one patient (24%) (P = 0.22).
The CLL2007FMP trial was stopped prematurely because of an increase in mortality in the alemtuzumab arm (seven patients; 8.5%). In the rituximab arm 63 patients (76.5%) received all six cycles and, in the alemtuzumab arm, 59 patients (71.4%) received all six cycles.

Monoclonal anti-CD20 antibody versus anti-leukaemic therapy

We did not identify any RCTs comparing monoclonal anti-CD20 antibody versus anti-leukaemic therapy.

Different dosages or time schedules of monoclonal anti-CD20 antibody

CALBG 9712 included 104 previously untreated participants and assessed two different schedules for the administration of rituximab, the concurrent (Flu-R and rituximab consolidation for patients with stable disease) and sequential (fludarabine plus observation and rituximab consolidation for patients with stable disease) regimens.
Wierda 2011 was the only trial investigating two different dosages of ofatumumab in addition to FluC: 500 mg (FCO500) and 1000 mg (FCO1000). The trial included 61 previously untreated participants.

Primary outcome: overall survival (OS)

CALBG 9712 showed no statistically significant difference between the concurrent and sequential regimen regarding OS (HR 1.14, 95% CI 0.20 to 6.65, P = 0.30).
Wierda 2011 did not assess OS.

Secondary outcome: progression-free survival (PFS)

CALBG 9712 indicated no statistically significant difference regarding PFS between the concurrent and sequential regimen (HR 0.96, 95% CI 0.43 to 2.15, P = 0.11).
Wierda 2011 stated that median PFS has not been reached with the short median follow-up of eight months.

Secondary outcome: time to next treatment

Neither trialassessed time to next treatment.

Secondary outcome: overall response rate (ORR)

CALBG 9712: the ORR was not statistically significant (90% of the patients receiving rituximab concurrent with chemotherapy compared to 77% in the sequential arm, P = 0.08).
Wierda 2011: there was no statistically significant difference of ORR between the FCO500 arm (77%) and FCO1000 arm (73%) (P = 0.71).

Secondary outcome: complete response rate (CRR)

CALBG 9712: the difference regarding CRR was statistically significant with 33% in the concurrent arm and 15% in the sequential arm (P = 0.04).
Wierda 2011: the difference regarding CRR was not statistically significant (32% patients of the FCO500 arm compared to 50% of the FCO1000 arm, P = 0.10).

Secondary outcome: minimal residual disease (MRD) negativity

Neither trial assessed MRD negativity.

Secondary outcome: treatment-related mortality (TRM)

CALBG 9712: the trial did not report results regarding TRM.
Wierda 2011: during treatment and up to 30 days following the last dose one patient in the FCO1000 arm died.

Secondary outcome: adverse events (AE)

Table 4 presents a list of reported AEs.
CALBG 9712 showed a statistically significant difference in neutropenia (39 of 51 patients in the concurrent arm versus 21 of 53 patients in the sequential arm, P = 0.0004). However, there were no statistically significant differences regarding infections (10 of 51 patients in the concurrent arm versus 12 of 53 patients in the sequential arm, P = 0.71) or grade 3/4 anaemia (2 of 51 patients (4%) in the concurrent arm versus 0 of 53 patients (0%) in the sequential arm, P = 0.28) and thrombocytopenia (10 of 51 patients (20%) in the concurrent arm versus 5 of 53 patients (9%) in the sequential arm, P = 0.15).
Wierda 2011 showed no statistically significant difference of anaemia (2 of 31 patients in the FCO500 arm versus 6 of 30 patients in the FCO1000 arm, P = 0.14), neutropenia (11 of 31 patients in the FCO500 arm versus 18 of 30 patients in the FCO1000 arm, P = 0.06) and thrombocytopenia (2 of 31 patients in the FCO500 arm versus 7 of 30 patients in the FCO1000 arm, P = 0.09).

Secondary outcome: number of patients discontinuing the study because of drug-related adverse events

CALBG 9712 reported that four patients in the concurrent arm and two patients in the sequential arm required cessation of fludarabine therapy because of drug-related AEs.

Wierda 2011 stated that FluC dose reductions or withholding occurred in 14 patients, primarily because of cytopenia (N = 12). Furthermore, six patients withdrew from treatment despite dose reductions.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Anti-leukaemic therapy with monoclonal anti-CD20 compared with anti-leukaemic therapy without monoclonal anti-CD20 antibody (anti-leukaemic therapy not identical in both groups) for newly diagnosed or relapsed patients with CLL

Patient or population: newly diagnosed or relapsed patients with CLL
Intervention: anti-leukaemic therapy plus monoclonal anti-CD20 antibody
Comparison: anti-leukaemic therapy alone (anti-leukaemic therapy not identical in both groups)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-leukaemic therapy alone	Anti-leukaemic therapy plus monoclonal anti-CD20 antibody				
OS not reported	**Study population**					
	See comment	See comment	Not estimable	0	See comment	Neither study provided data on OS
PFS not reported	See comment	See comment	Not estimable	0	See comment	Neither study provided data on PFS
Time to next treatment	See comment	See comment	Not estimable	0	See comment	Neither study provided data on time to next treatment
CRR	**Study population**		**RR 1.18** (0.93 to 1.49)	170 (2)	⊕⊕⊕◯ **moderate**[1]	
	566 per 1000	668 per 1000 (527 to 844)				
TRM	**Study population**		**RR 0.31** (0.06 to 1.51)	177 (2)	⊕⊕◯◯ **low**[1,2]	

	58 per 1000	18 per 1000 (3 to 88)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; CRR: complete response rate; OS: overall survival; PFS: progression-free survival; RR: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One trial stopped prematurely owing to an excess of mortality in the alemtuzumab arm.
[2] The trials included a few events for this outcome and thus have wide confidence intervals.

DISCUSSION

Summary of main results

In this systematic review, we analysed the efficacy and safety of anti-CD20 antibodies for the treatment of patients with primary untreated and relapsed CLL. The findings that emerged from these meta-analyses were as follows:

- In trials assessing anti-leukaemic therapy plus monoclonal anti-CD20 antibody versus identical anti-leukaemic therapy alone the results are as follows (3 trials, N = 1421 patients, Summary of findings for the main comparison):
    - to date, the identified interventional trials assessed only the efficacy and safety of rituximab;
    - OS, PFS, time to next treatment, ORR and CRR were statistically significantly improved in patients receiving rituximab compared to those not receiving rituximab;
    - the present meta-analysis showed no statistically significant difference in TRM and SAEs for newly diagnosed or relapsed patients with CLL;
    - the total amount of WHO grade 3 or 4 AEs, especially neutropenia, was statistically significantly higher in patients receiving rituximab.

For the interpretation, particularly of the following comparisons, it is very important to consider that results that are not statistically significant do not necessarily mean that there is no difference.

- In trials evaluating anti-leukaemic therapy with monoclonal anti-CD20 versus anti-leukaemic therapy without monoclonal anti-CD20 (in both studies patients were randomised to additional rituximab or to additional alemtuzumab) the results were as follows (2 trials; N = 177 patients, Summary of findings 2):
    - Neither study provided data regarding OS, PFS and time to next treatment;
    - the present meta-analysis did not show statistically significant differences in TRM, ORR and CRR. There was a trend favouring treatment with rituximab but the small number of included patients, as well as observed events, limited the certainty of the results;
    - one of the two included trials had to be stopped early because of an excess of mortality in the alemtuzumab arm. Furthermore, statistically significantly more serious AEs and serious febrile neutropenia occurred in patients receiving alemtuzumab compared to those receiving rituximab.

- The following results emerge from the two trials that assessed different dosages or time schedules of monoclonal anti-CD20 antibodies:
    - one trial (N = 104) evaluated two different rituximab schedules (concurrent arm: Flu-R plus rituximab consolidation versus sequential arm: fludarabine alone plus rituximab consolidation):
        - there were no statistically significant differences between arms in OS, PFS or AEs (except for neutropenia, which was more often observed in patients of the concurrent arm);
        - the study showed a statistically significant difference of the CRR favouring concurrent treatment.
    - the other trial (N = 61) investigated two different dosages (500 mg and 1000 mg) of ofatumumab in addition to FluC:
        - there were no data for OS, PFS and time to next treatment;
        - there were no statistically significant differences between the administration of FluC plus ofatumumab 500 mg or FluC plus ofatumumab 1000 mg regarding the following outcomes, which were assessed during treatment and up to 30 days: ORR, CRR, TRM and AEs (such grade 3/4 AEs were infections, febrile neutropenia, neutropenia, anaemia, thrombocytopenia and haemolytic anaemia).

Overall completeness and applicability of evidence

To date, seven published studies have addressed the use of monoclonal anti-CD20 antibodies in CLL patients. All are included in this systematic review. Six of these assessed the efficacy and safety of rituximab (only one study evaluated different doses of ofatumumab). Therefore, results of this review cannot be interpreted as general effects of monoclonal anti-CD20 antibodies in the treatment of CLL.

The six trials of rituximab are clinical heterogeneous and are therefore not pooled in one meta-analysis. Five were included in two main analyses. The other trial assessed two different time schedules for the administration of rituximab. Particularly the second main analysis (anti-leukaemic therapy with monoclonal anti-CD20 versus anti-leukaemic therapy without monoclonal anti-CD20) is only based on data provided by abstracts. The full-text publications are likely to provide more data on relevant outcomes such as OS, PFS and time to next treatment.

Moreover, we are aware of 16 ongoing studies, including three trials comparing ofatumumab with or without additional chemotherapy versus no treatment. The findings of these trials will be included in an update of this review and could lead to different conclusions and may allow a judgement on general efficacy and safety of monoclonal anti-CD20 antibody in the treatment of CLL.

OS was the primary endpoint of this review, because it has the greatest clinical relevance and is most important for patients. Furthermore, death is an endpoint not susceptible to be biased by the outcome assessor. Unfortunately only four of the seven included trials assessed this outcome, since it is a universally accepted direct measure of benefit of cancer treatment. The most accurate outcome to assess stable disease or more precise the absence of treatment-requiring symptoms of disease is time to next treatment. Therefore, this outcome might be more useful than OS to compare

the quality of life caused by the different treatment approaches. However, only two of the seven trials reported this outcome.

Quality of the evidence

Overall, the quality of the seven included trials (1763 patients) was moderate to high. Two included trials were published as abstracts only; therefore we were unable to assess the potential risk of bias for these trials in detail. All the included trials were reported as randomised studies. None of the studies were placebo-controlled or reported any information regarding the blinding of the outcome assessor. Aside from GCLLSG CLL 8, none of the included trials reported allocation concealment. The open-label design and unclear allocation concealment could lead to selection, performance or detection biases. In the CLL2007FMP and Gribben 2005 trials, both published only as abstracts, a number of outcomes that were pre-defined in the protocol were not reported. The protocol of CALBG 9712 does not provide information about the outcomes that will be assessed. Therefore, we judged selective reporting as unclear in these three trials. The prematurely closure of one trial (CLL2007FMP) owing to an increased incidence of severe infections or excess of mortality in the alemtuzumab arm, as well as the unexplained decrease of included patients (12 instead of 150 patients in the Gribben 2005 trial), could lead to other sources of bias.

The robustness of all results was tested by subgroup analysis based on prospectively defined parameters. However, because of the small number of trials included in each analysis, obtaining reliable information from subgroup analyses is unlikely.

Potential biases in the review process

To prevent bias within the review, only RCTs were considered. In addition, all important conference proceedings were searched up to 2011. We tried to avoid bias by doing all relevant processes (searching, data collection, analysis) in duplicate. In summary, there is maximum likelihood that all relevant studies were identified and we are not aware of any obvious deficiencies in our review process.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first comprehensive systematic review with meta-analysis focusing on the treatment of CLL patients with the monoclonal anti-CD 20 antibodies. We searched for guidelines or health technology reports with systematic searches of databases and identified the following publications: reports and guidelines with respect of the treatment of rituximab used data from the GCLLSG CLL 8 trial (NICE 2009), the REACH trial (NICE 2010a) or abstracts of the GCLLSG CLL 8; and NCRI-CLL 201 and REACH trials (Cheung 2009), which were the only available publications at the time of search. The guidelines recommend the administration of rituximab in combination with FluC as an option for first-line treatment as well as for the people with relapsed or refractory CLL (NICE 2009, NICE 2010a). NICE 2010 discussed a non-randomised trial, Wierda 2010, regarding the efficacy of ofatumumab in refractory CLL patients.

We have shown in this meta-analysis that the addition of rituximab to fludarabine-based chemotherapy is effective and we judged the quality of evidence regarding the statistically significant improvement in terms of OS as high and of PFS as moderate (Summary of findings for the main comparison). However, additional rituximab in total caused more AEs than FluC or FluCM. But there was no statistically significant difference of the treatment arms regarding infections or SAEs. The administration of rituximab also does not statistically significantly increase the risk of TRM. These findings are in line with other systematic reviews focusing on side effect of patients treated with rituximab (Lanini 2011; Singh 2011). Relatively rare AEs such as rituximab-associated hepatitis B have not been reported in the analysed trials of our review (Evens 2011). However, for the interpretation of the results of studies as well as of the meta-analysis we have to keep in mind that the inclusion criteria of the trials restrict the involved patients to a population without severe co-morbidities. This raises the question of whether patients with limited physical condition can be safely treated with chemoimmunotherapy. A meta-analysis of co-morbid patients showed that co-morbid patients had significantly shorter PFS and OS than those without additional health problems. Nevertheless, these co-morbid patients did benefit from the administration of more intense chemotherapy-regimen (median OS: FluC: not reached, F: 38.29 and Clb: 33.72 months, P = 0.0248; median PFS: FluC: not reached, F: 18.8 and Clb: 14.1 months, P = 0.00001) (Cramer 2006). Therefore, more intensive chemo(immuno)therapy regimens are reasonable new treatment approaches that should be evaluated in patients with co-morbidities. Furthermore, there are other chemotherapy regimens, besides the fludarabine-based chemotherapy, that have been successfully combined with rituximab for treatment of untreated or relapsed patients with CLL (e.g. pentostatin and cyclophosphamide (PCR) (Lamanna 2006; Lamanna 2007; Shanafelt 2007), pentostatin, cyclophosphamide and mitoyantrone (PCMR) (Lamanna 2007a), high-dose methylprednisolone (Castro 2009), Clb (Hillmen 2009) or bendamustine (Fischer 2008; Fischer 2009)), but these regimens still have to be evaluated in RCTs.

In accordance with our review, the Cochrane review assessing "Alemtuzumab for patients with chronic lymphocytic leukaemia" summarises the available evidence regarding the comparison of rituximab versus alemtuzumab as not sufficient to deduct final conclusions (Skoetz 2012). However, the authors of the review pointed out that alemtuzumab compared to no further treatment increased risk of infections in general, CMV infections and CMV

re-activations (Skoetz 2012). Other non-randomised studies also showed an increased rate of CMV re-activation and other opportunistic infections (Byrd 2009; Hainsworth 2008), which led to the suggestions of a close monitoring for CMV infections and pre-emptive therapy with intravenous ganciclovir in CLL patients receiving alemtuzumab (Byrd 2009; Elter 2009).

To date, the optimal dose of ofatumumab remains unclear. In addition to the assessed doses of 500 mg and 1000 mg, non-randomised studies have shown that doses up to 2000 mg are well tolerated by pre-treated or refractory CLL patients (Coiffier 2008; Wierda 2010).

Finally, non-randomised trials have shown that other anti-CD20 antibodies, ofatumumab (Badoux 2010; Castro 2010; Wierda 2011a) and GA101 (Goede 2010; Morschhauser 2009), also had anti-leukaemic activity and were well tolerated in CLL patients. Results of RCTs to determine their role in the treatment of CLL are urgently awaited.

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis showed that patients receiving chemotherapy plus rituximab benefited in terms of OS as well as PFS compared to those with chemotherapy alone. Therefore, it supports the recommendation of rituximab in combination with FluC as an option for the first-line treatment as well as for the people with relapsed or refractory CLL. The available evidence regarding the other assessed comparisons was not sufficient to deduct final conclusions.

Implications for research

Further research should focus on the evaluation of benefits of adding rituximab to other therapeutic regimens than FluC in the therapy of previously untreated as well as relapsed or refractory patients. Furthermore, open questions regarding the use of rituximab maintenance should be addressed. It should also assess whether patients with serious co-morbidities will benefit from the addition of rituximab to chemotherapy. Finally, RCTs are needed to determine the clinical effects of novel anti-CD20 antibodies, such as ofatumumab or GA101, compared to rituximab.

ACKNOWLEDGEMENTS

We are grateful to the following people for their comments and improving the review: Lena Specht and Keith Wheatley (Editors), Céline Fournier (Consumer Editor), as well as Andrea Will and Sabine Kluge (Managing Editors).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CALBG 9712

Methods	Randomisation: • RCT with 2 arms: arm 1 (sequential): 6 monthly courses of fludarabine alone followed 2 months later by rituximab consolidation therapy versus arm 2 (concurrent): 6 monthly courses of Flu-R followed 2 months later by 4 weekly doses of rituximab for consolidation therapy Recruitment period: • from January 1998 to January 2000 Median follow-up time: • 23 months (range not provided)
Participants	Eligibility: Inclusion criteria: • histologically and immunophenotypically documented CLL • either Rai stage III/IV disease or required therapy for Rai stage I/II disease • no prior therapy for CLL • age: older than 17 years • CALGB performance status of ≤ 3 Exclusion criteria: • patients with bright expression of surface immunoglobulin Patients recruited (N = 104): • sequential (N = 53): all patients were analysed • concurrent (N = 51): all patients were analysed Mean age: • sequential: 63 years (range: 36-79 years) • concurrent: 63 years (range 36-86 years) Gender (male, female): • sequential: 34%, 19% • concurrent: 24%, 27% Stage of disease (Rai stage group): • stage I-II (intermediate risk): sequential: 58%; concurrent: 61% • stage III-IV (high risk): sequential: 42%; concurrent: 39% Country: • US, multicentre trial with 26 principal investigators
Interventions	Arm 1: sequential, 6 cycles, every 28 days: • fludarabine (25 mg/m^2 IV daily, 1 to 5 cycles) • after 2 months of observation patients with stable disease or better were then treated with 4 weekly doses of rituximab (375 mg/m^2) Arm 2: concurrent, 6 cycles, every 28 days: • fludarabine (25 mg/m^2 IV daily, 1 to 5 cycles) • rituximab (375 mg/m^2, on days 1 and 4 of cycle 1 of fludarabine therapy - 2 doses of rituximab were administered to the first 44 patients with the first cycle to ensure adequate saturation of CD20-binding sites; a single dose of rituximab was then administered on day 1 of cycles 2, 3, 4, 5 and 6. Modification: the stepped-up dosing

CALBG 9712 (*Continued*)

	improved tolerability of rituximab, so the schedule of administration was modified for the last 7 patients: day 1 of the first cycle rituximab (50 mg/m^2) IV without rate escalation, day 3: rituximab (325 mg/m^2) IV at 50 mg/h, and then infusion rate was escalated in 50 mg/h to a maximum of 400 mg/h; day 5 and during all subsequent cycles of fludarabine: rituximab (375 mg/m^2) started at 100 mg/h and the rate was increased to entire dose, rituximab with this same 1-hour dosing on day 1 of cycles 2 to 6) • after 2 months of observation patients with stable disease or better were then treated with 4 weekly doses of rituximab (375 mg/m^2) Additional therapy: • all patients received allopurinol (300 mg orally) for the rst 14 days and antiemetics (not specified, but could not include corticosteroids) • at 30 minutes prior to all rituximab doses, paracetamol (acetaminophen) (650 mg) and diphenhydramine (50 mg IV) were administered
Outcomes	Outcomes and time points from the study that are considered in the review: • reported: ○ OS ○ PFS ○ CRR ○ ORR ○ AEs • not reported: ○ time to next treatment ○ TRM ○ MRD ○ Number of patients discontinuing the study because of drug-related AEs
Notes	The research for CALGB 9712 was supported, in part, by grants from the NCI (CA31946) to the CALGB. A table of these grants is provided in the article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Low risk	Comment: the review authors judge that the outcome OS in this unblinded trial is unlikely to be influenced by lack of blinding

CALBG 9712 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were assessed for analyses
Selective reporting (reporting bias)	Unclear risk	Comment: protocol is registered (ClinicalTrials.gov: NCT00003248), but outcomes for assessment were not stated
Other bias	Unclear risk	Not reported

CLL2007FMP

Methods	Randomisation: • 2 arms: 6 courses of FluC--R versus 6 courses of FluC-Cam Recruitment period: • November 2007 to January 2009 Median follow-up time: • not stated
Participants	Eligibility criteria: • previously untreated B-cell CLL • Binet classification stages B or C • younger than 65 years • medically fit patients (CIRS score $\leq$ 6); creatinine clearance at least 60 mL/min • no 17p-deletion Patients randomised (N = 165): • FluC-R (N = 83): withdrawals or exclusions not stated • FluC-Cam (N = 82): withdrawals or exclusions not stated The trial was stopped early owing to unacceptable toxicity in the FluC-Cam arm (6 deaths in FluC-Cam arm versus 0 in FluC-R arm) Mean age: • not stated Gender (male, female): • not stated Stage of disease (Rai stage group): • not stated Countries: • French and Belgium
Interventions	FluC-R: • patients received fludarabine 40 mg/m^2 days 1 to 3 and cyclophosphamide 250 mg/m^2 days 1 to 3 plus 375 mg/m^2 rituximab IV day 0 at first cycle and 500 mg/m^2 day 1 all subsequent cycles FluC-Cam (every 28 days; up to 6 cycles): • patients received fludarabine 40 mg/m^2 days 1 to 3 and cyclophosphamide 250

CLL2007FMP (*Continued*)

	mg/m^2 days 1 to 3 plus alemtuzumab 30 mg SC days 1 to 3 Anti-infective prophylaxis included trimethoprim-sulfamethoxazole and valacyclovir during immunochemotherapy and until the CD4-positive lymphocyte count reached 0.2 × 10^9/L
Outcomes	Outcomes and time points from the study that were considered in the review: • reported: ○ CRR ○ ORR ○ TRM ○ MRD ○ AEs • not reported: ○ OS ○ PFS ○ time to next treatment ○ number of patients discontinuing the study because of drug-related AEs
Notes	The trial was discontinued after randomisation of 165 patients for unacceptable toxicity in the FluC-Cam arm (6 deaths in FluC-Cam arm versus 0 in FluC-R arm). The last 13 patients enrolled were not randomised The authors stated that they had no relevant conflict of interest to declare

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Unclear risk	The study did not assess this outcome
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "165 patients were randomized to (...) R (N = 83 (...)) or Cam (N = 82)"; "Clinical responses were as follows: CRR (FCR [FluC-R]: 56/80 = 70%, FCCam: 45/79 = 59%, ns)" Reasons of exclusions are not provided

CLL2007FMP (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: the trial is published as abstracts Comment: protocol is registered (ClinicalTrials.gov: NCT00564512) Pre-planned outcomes (relevant for the review) that were reported: • CRR • ORR • TRM • MRD • AEs Pre-planned outcomes (relevant for the review) that were not reported: • OS • PFS • time to next treatment • number of patients discontinuing the study because of drug-related AEs
Other bias	High risk	Quote: "the trial recruitment was discontinued because of an excess of mortality in the FCCam arm (6 deaths versus 0 in FluC-R arm), and the last 13 patients enrolled were not randomized" Comment: the trial was stopped early owing to data-dependent process

GCLLSG CLL 8

Methods	Randomisation: • RCT with 2 arms: FluC-R versus FluC Recruitment period: • from July 2003 to March 2006. Median follow-up time: • not provided (assessment at 3 years after randomisation)
Participants	Eligibility criteria: • ≥ 18 years • diagnosed B-cell CLL defined by the NCI Working Group criteria • ECOG performance status 0 to 1 • CIRS score > 6 • life expectancy > 6 months • Binet stage C disease or Binet stage B disease (plus symptoms) Patients recruited (N = 817): • FluC-R: N = 408 (4 did not receive study drugs, 20 without response assessment, 7 lost to follow-up) • FluC: N = 409 (13 did not receive study drugs, 38 without response assessment, 20 lost to follow-up) Mean age:

GCLLSG CLL 8 (*Continued*)

	• FluC-R: 61 years (range: 30 to 80 years) • FluC: 61 years (range: 36 to 81 years) Gender (male, female): • FluC-R: N = 303, N = 105 • FluC: N = 304, N = 105 Stages of disease: • FluC-R: Binet A 4%, Binet B 64%, Binet C 31% • FluC: Binet A 5%, Binet B 63%, Binet C 31% Country: 190 centres in 11 countries
Interventions	Arm 1: FluC-R, 6 cycles, every 28 days: • fludarabine (25 mg/m^2 IV daily, 1 to 5 cycles) • cyclophosphamide (250 mg/m^2 per day, for the first 3 days) • rituximab (375 mg/m^2 on day 0 of the first course, and 500 mg/m^2 on day 1 of the second to sixth courses) Arm 2: FluC, 6 cycles, every 28 days: • fludarabine (25 mg/m^2 IV daily, 1 to 5 cycles) • cyclophosphamide (250 mg/m^2 per day, for the first 3 days) Additional therapy: • prophylaxis of pneumonia caused by *Pneumocystis* was recommended for severe leukocytopenia that lasted for more than 7 days • prophylaxis with antiviral drugs or granulocyte-colony stimulating factor were not recommended in this study
Outcomes	Outcomes and time points from the study that are considered in the review: • reported: ○ OS ○ PFS ○ time to next treatment ○ CRR ○ ORR ○ TRM ○ AEs ○ number of patients discontinuing the study because of drug-related AEs • not reported: ○ MRD
Notes	The trial was funded by Hoff mann-La Roche

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned" Quote: "using a randomisation list that was computer generated"

GCLLSG CLL 8 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "assignment to treatment was done centrally at the Institute for Medical Statistics and Epidemiology, Technical University of Munich"
Blinding (performance bias and detection bias) Overall survival	Low risk	Comment: the review authors judge that the outcome OS in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "investigators and patients were not masked to the treatment assignment" Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were assessed in the analyses. The small number of missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups (i.e. FluC-R, 4 did not receive study drugs, 20 without response assessment, 7 lost to follow-up; FluC: 13 did not receive study drugs, 38 without response assessment, 20 lost to follow-up)
Selective reporting (reporting bias)	Low risk	Comment: protocol is registered (ClinicalTrials.gov: NCT00281918) Pre-planned outcomes (relevant for the review) that were reported: • OS • PFS • time to next treatment • CRR • ORR Pre-planned outcomes (relevant for the review) that were not reported: • none Reported outcomes that were not predefined in the protocol: • TRM • AEs • number of patients discontinuing the study because of drug-related AEs
Other bias	Unclear risk	No information provided

Gribben 2005

Methods	Randomisation: • 2 arms: up to 6 cycles Flu-R versus up to 6 cycles Flu-Cam Recruitment period: • not stated Median follow-up time: • not stated
Participants	Eligibility criteria: • relapsed B-cell CLL patients after failure to first-line treatment Patients recruited (N = 12): • Flu-R (N = 8): withdraws or exclusions not stated • Flu-Cam (N = 4): withdraws or exclusions not stated Mean age: • 67 years, no data for each arm Gender: • 7 male, 5 female no data for each arm Stage of disease (Rai stage group): • stage I-II: Flu-R: 1 patients (12.5%); Flu-Cam: 2 patients (50.0%) • stage III-IV: Flu-R: 7 patients (87.5%); Flu-Cam: 2 patients (50.0%) Country: • not stated
Interventions	Patients were assessed monthly for response while on therapy, and interim restaging occurred at cycle 4. Those who achieved a complete response received no further therapy, whereas those who achieved a partial response or stable disease received 2 additional cycles Flu-R: • patients received fludarabine 25 mg/m^2 IV on days 1 to 5 and rituximab 375 mg/m^2 IV on days 1 and 4 of the first cycle. In the subsequent cycles they received additional rituximab 375 mg/m^2 IV on day 1 Flu-Cam: • patients received fludarabine 25 mg/m^2 IV and alemtuzumab 30 mg SC, on days 1 to 5 of each cycle
Outcomes	Outcomes relevant for this review: • reported: ◦ CRR ◦ ORR ◦ AEs ◦ number of patients discontinuing the study because of drug-related AEs • not reported: ◦ OS ◦ PFS ◦ time to next treatment ◦ TRM ◦ MRD
Notes	No conflict of interest statement in the abstract

Risk of bias

Gribben 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Unclear risk	The study did not assess this outcome
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the information about completeness of outcome data is insufficient to permit judgement
Selective reporting (reporting bias)	High risk	Comment: the trial is published as abstracts Comment: protocol is registered (ClinicalTrials.gov: NCT00086775) Pre-planned outcomes (relevant for the review) that were reported: • CRR • ORR • AEs • number of patients discontinuing the study because of drug-related AEs Pre-planned outcomes (relevant for the review) that were not reported: • OS • PFS • MRD
Other bias	High risk	According to the protocol a total of 150 patients (75 per treatment arm) were needed for this study. The abstract reported the results of only 12 recruited patients Comment: the small number of 12 patients instead of 150 indicate that this are very preliminary results

NCRI-CLL 201

Methods	Randomisation: • RCT with 2 arms: arm 1 FluCM-R versus arm 2 FluCM Recruitment period: • from July 2005 to January 2007 Median follow-up time: • median follow-up of 29 months (range 24 to 46 months)
Participants	Eligibility criteria: • diagnosis of CLL requiring therapy • previously treated with ≥ 1 chemotherapeutic regimen • WHO performance status 0 to 2 • life expectancy ≥ 12 weeks Patients recruited (N = 52): • FluCM-R: N = 26 (1 withdrew consent to participate, 0 withdrew consent for follow-up, 12 stopped treatment early) • FluCM: N = 26 (2 withdrew consent to participate, 1 withdrew consent for follow-up, 14 stopped treatment early) Mean age: • FluCM-R: 66 years (range 44 to 79 years) • FluCM: 68 years (range 32 to 79 years) Gender (male, female): • FluCM-R: 85%, 15% • FluCM: 73%, 27% Stage: • FluCM-R: Binet A 15.4%, Binet B 42.3%, Binet C 38.5% • FluCM: Binet A 19.2%, Binet B 15.4%, Binet C 61.5% Country: • participating centres not stated
Interventions	Arm 1: FluCM-R, 6 cycles, every 28 days: • fludarabine (24 mg/m^2 PO, days 1 to 5) • cyclophosphamide (150 mg/m^2 PO, days 1 to 5) • mitoxantrone (6 mg/m^2 IV on day 1) • rituximab (375 mg/m^2 on day 0 of the first course, and 500 mg/m^2 on day 1 of the second to sixth courses. NOTE: dose of rituximab was originally 375 mg/m^2 for all cycles, but the protocol was amended to increase the dose of rituximab to 500 mg/m^2 for cycles 2 to 6. Three patients were treated prior to this amendment and received all cycles at 375 mg/m^2) Arm 2: FluCM, 6 cycles, every 28 days: • fludarabine (24 mg/m^2 PO, day 1 to 5) • cyclophosphamide (150 mg/m^2 PO, day 1 to 5) • mitoxantrone (6 mg/m^2 IV on day 1) Additional therapy: • no recommended additional treatment was stated

Outcomes	Outcomes and time points from the study that are considered in the review:
	• reported:
	  ○ OS
	  ○ PFS
	  ○ CRR

	○ ORR ○ MRD ○ TRM ○ AEs ○ number of patients discontinuing the study because of drug-related AEs • not reported: ○ time to next treatment
Notes	Roche Pharmaceuticals provided rituximab for the trial as well as an unrestricted grant to support the running of the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Low risk	Comment: the review authors judge that the outcome OS in this unblinded trial is unlikely to be influenced by lack of blinding
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "multi-centre, randomized, controlled, open, two-stage, parallel group, Phase II trial" Quote: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were assessed in the analyses. The small number of missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups (i.e. FluCM-R: 1 withdrew consent to participate, 0 withdrew consent for follow-up, 12 stopped treatment early; FluCM: 2 withdrew consent to participate, 1 withdrew consent for follow-up, 14 stopped treatment early)
Selective reporting (reporting bias)	Low risk	Comment: protocol is registered (ClinicalTrials.gov: NCT00337246) Pre-planned outcomes (relevant for the re-

NCRI-CLL 201 (*Continued*)

		view) that were reported: • OS • PFS • CRR • ORR • MRD • AEs • TRM • number of patients discontinuing the study because of drug-related AEs Pre-planned outcomes (relevant for the review) that were not reported: • none
Other bias	Unclear risk	No information provided

REACH

Methods	Randomisation: • RCT with 2 arms: arm 1: FluC-R versus arm 2 FluCM Recruitment period: • from July 2003 to August 2007 Median follow-up time: • 25 month (range: not reported)
Participants	Eligibility criteria: • B-CLL confirmed according to NCI Working Group criteria • minimum 1 lone treatment of the CLL • age ≥ 18 • expected survival > 6 months Patients recruited (N = 571 screened, N = 552 assigned): • FluC-R: 276 patients (2 did not receive treatment, 87 discontinued treatment, 6 did not enter follow-up phase, 131 withdrew from follow-up) • FluCM: 276 patients (4 did not receive treatment, 91 discontinued treatment, 14 did not enter follow up phase, 162 withdrew from follow up) Mean age: • FluC-R: 63 years (range: 35 to 83 years) • FluCM: 62 years (range: 36 to 81 years) Gender (male, female): • FluC-R: 68%, 32% • FluCM: 66%, 34% Stage: • Binet A: FluC-R 24 (9%); FluCM 31 (11%) • Binet B: FluC-R 166 (60%); FluCM 160 (58%) • Binet C: FluC-R 86 (31%); FluCM 85 (31%) Country • 87 centres in Australia, Canada, Europe , New Zealand and US

REACH (*Continued*)

Interventions	Arm 1: FluC-R, 6 cycles, every 28 days: • fludarabine (25 mg/m^2 PO, days 1 to 3) • cyclophosphamide (250 mg/m^2 PO, days 1 to 3) • rituximab (375 mg/m^2 on day 1 of the first course, and 500 mg/m^2 on day 1 of the second to sixth courses) Arm 2: FluCM, 6 cycles, every 28 days: • fludarabine (24 mg/m^2 PO, days 1 to 5) • cyclophosphamide (150 mg/m^2 PO, days 1 to 5) • mitoxantrone (6 mg/m^2 IV on day 1) Additional therapy: • pre-medication (oral paracetamol (acetaminophen) and an antihistamine) • supportive care as needed, including antibiotics, blood transfusions and haematopoietic growth factors • prophylaxis for tumour lysis syndrome (including allopurinol or rasburicase) • prophylactic antimicrobials (cotrimoxazole and acyclovir/valacyclovir)
Outcomes	Outcomes and time points from the study that are considered in the review: • reported: ◦ OS ◦ PFS ◦ time to next treatment ◦ CRR ◦ ORR ◦ MRD ◦ TRM ◦ AEs ◦ number of patients discontinuing the study because of drug-related AEs
Notes	The trial was funded by Hoffmann-La Roche, Genentech, and Biogen Idec

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "phase III trial randomly assigned patients" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Low risk	Comment: the review authors judge that the outcome OS in this unblinded trial is unlikely to be influenced by lack of blinding

REACH (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "multicenter, open-label, phase III trial" Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were assessed in the analyses. The small number of missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups (i.e. FluCR: 2 did not receive treatment, 87 discontinued treatment, 6 did not enter follow-up phase, 131 withdrew from follow-up; FluCM: 4 did not receive treatment, 91 discontinued treatment, 14 did not enter follow-up phase, 162 withdrew from follow-up)
Selective reporting (reporting bias)	Low risk	Comment: protocol is registered (ClinicalTrials.gov: NCT00090051) Pre-planned outcomes (relevant for the review) that were reported: • OS • PFS • CRR • ORR • AEs • number of patients discontinuing the study because of drug-related AEs Pre-planned outcomes (relevant for the review) that were not reported: • none Not pre-planned outcomes (relevant for the review) that were reported: • MRD • time to next treatment
Other bias	Unclear risk	No information provided

Wierda 2011

Methods	Randomisation: • RCT with 2 arms: arm 1 FCO500: (fludarabine plus cyclophosphamide plus ofatumumab) (500 mg) versus arm 2 FCO1000 (fludarabine plus cyclophosphamide plus ofatumumab) (1000 mg) Recruitment period: • not provided Median follow-up time: • 8 months (range: not reported)
Participants	Eligibility criteria: • previously untreated patients • active CLL Patients recruited (N = 67 screened, N = 61 assigned): • FCO500: 31 patients (9 discontinued treatment: cytopenias (N = 3), autoimmune haemolytic anaemia requiring treatment (N = 2), myocardial infarction (N = 1), non-response (N = 2) or patient request (N = 1)) • FCO1000: 30 patients (13 discontinued treatment: cytopenias (N = 7), autoimmune haemolytic anaemia requiring treatment (N = 1), non-response (N = 1), chest discomfort (N = 1), patient request (N = 1), death (N = 1) or investigator's decision (N = 1)) Mean age: • FCO500: 56 years (range: 38 to 73 years) • FCO1000: 56 years (range: 38 to 72 years) Gender (male, female): • FCO500: gender not provided • FCO1000: gender not provided Stage: • FCO500: Binet A or B 74%, Binet C 26% • FCO1000: Binet A or B 60%, Binet C 40% Country: • Czech Republic, Germany, Lithuania, UK, US
Interventions	Arm 1: FCO500, 6 cycles, every 4 weeks: • fludarabine (25 mg/m^2 PO, days 1 to 3) • cyclophosphamide (250 mg/m^2 PO, days 1 to 3) • ofatumumab (300 mg/m^2 on day 1 of the first course, and 500 mg/m^2 on day 1 of the second to sixth courses) Arm 2: FCO1000, 6 cycles, every 28 days: • fludarabine (24 mg/m^2 PO, days 1 to 5) • cyclophosphamide (150 mg/m^2 PO, days 1 to 5) • ofatumumab (300 mg/m^2 on day 1 of the first course, and 1000 mg/m^2 on day 1 of the second to sixth courses) Additional therapy: • pre-medication was paracetamol (acetaminophen) 1000 mg and cetirizine 10 mg prior to each infusion • glucocorticoid (prednisolone 100 mg) prior to infusions 1 and 2 • allopurinol, neutrophil growth factor and anti-infective prophylaxis were permitted at the discretion of the investigator

Outcomes	Outcomes and time points from the study that are considered in the review: • reported: ○ OS ○ time to next treatment ○ PFS ○ CRR ○ ORR ○ TRM ○ AEs • not reported: ○ MRD ○ number of patients discontinuing the study because of drug-related AEs
Notes	The trial was funded by GlaxoSmithKline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients (...) were randomized to" Comment: the authors did not describe the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Overall survival	Unclear risk	The study did report results regarding this outcome owing to the short time period of median follow-up
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: patient and physician unblinded. No information about blinding of outcome assessor provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were assessed in the analyses. The small number of missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups (i.e. FCO500: 9 discontinued treatment; FCO1000: 13 discontinued treatment)
Selective reporting (reporting bias)	High risk	Comment: protocol is registered (ClinicalTrials.gov: NCT00410163) Pre-planned outcomes (relevant for the review) that were reported: • PFS • CRR

Wierda 2011 (*Continued*)

		• ORR • AEs • time to next treatment Pre-planned outcomes (relevant for the review) that were not reported: • OS • MRD
Other bias	Unclear risk	No information provided

CALGB: Cancer and Leukemia Group B; Cam: alemtuzumab; CIRS: cumulative illness rating scale; CLL; chronic lymphocytic leukaemia: CRR: complete response rate; ECOG: Eastern Cooperative Oncology Group; FluC: fludarabine plus cyclophosphamide; FluCM: fludarabine plus cyclophosphamide plus mitoxantrone; FluCM-R: fludarabine plus cyclophosphamide plus mitoxantrone plus rituximab; FluC-R: fludarabine plus cyclophosphamide plus rituximab; Flu-Cam: fludarabine plus alemtuzumab; FluC-Cam: fludarabine plus cyclophosphamide plus alemtuzumab; FluC-R: fludarabine plus cyclophosphamide plus rituximab; Flu-R: fludarabine plus rituximab; IV: intravenous; MRD: minimal residual disease; NCI: National Cancer Institute; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PO: per os; RCT: randomised controlled trial; SC: subcutaneous; TRM: treatment-related mortality; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmadi 2009	Review
Bazargan 2010	Not an RCT
Byrd 2003	Not an RCT
Byrd 2003a	Review
Castagna 2003	Editorial
Castillo 2009	Review
Decker 2009	Not an RCT
Drapkin 2000	Not an RCT
Faderl 2010	Not an RCT
Han 1990	Review
Hillmen 2007	RCT: comparison arms not treated with rituximab

(*Continued*)

Janssens 2009	Review
Keating 2009	Review
Keating 2010	Editorial
Mulligan 2010	RCT: all arms receive equal doses of rituximab
Negrea 2009	Not an RCT
Pitini 2009	Not an RCT
Quinn 2008	Not an RCT
Reynolds 2008	RCT: both arms treated with rituximab
Rigacci 2009	Not an RCT
Rosen 1999	Editorial
Schweighofer 2009	RCT: comparison arms not treated with rituximab
Tonino 2010	Case report

RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

2006-0767

Trial name or title	Alemtuzumab and rituximab for consolidation in CLL (NCT00771602)
Methods	Consolidation therapy for patients with CLL with evidence of residual disease following prior chemo(immuno) therapy Randomisation: • 3 arms: rituximab versus alemtuzumab versus alemtuzumab plus rituximab
Participants	Inclusion criteria: • patients with CLL, CLL/PLL, or SLL who have achieved an NCI-WG nPR or CR with documentation of residual disease by MRD flow cytometry following chemotherapy or chemoimmunotherapy • patients with CLL, CLL/PLL or SLL who have achieved an NCI-WG PR following prior chemotherapy or chemoimmunotherapy • age $\geq$ 18 years • ECOG performance status $\leq$ 2 • without previous treatment with alemtuzumab plus rituximab in combination

2006-0767 (*Continued*)

Interventions	Arm 1: 375 mg/m^2 IV rituximab alone Arm 2: 30 mg SC alemtuzumab alone Arm 3: 375 mg/m^2 IV rituximab plus 30 mg SC alemtuzumab

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ PFS
	  ○ CRR
	  ○ ORR
	  ○ AEs
	• will not report:
	  ○ OS
	  ○ time to next treatment
	  ○ TRM
	  ○ MRD
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	August 2008
Contact information	Stefan Faderl, M.D. at The University of Texas M.D. Anderson Cancer Center
Notes	Estimated enrolment: 100 Estimated primary completion date: December 2010 Study status according to ClinicalTrials.gov: this study is terminated - 1 patient enrolled

BO25341

Trial name or title	A study to compare subcutaneous versus intravenous MabThera (rituximab) in combination with chemotherapy in patients with CLL (NCT01292603)
Methods	SC rituximab versus IV rituximab both in combination with chemotherapy (FluC), in patients with previously untreated CLL Randomisation: • 2 arms: FluC plus rituximab SC versus FluC plus rituximab IV
Participants	Inclusion criteria: • adult patients, ≥ 18 years of age • patients with treatment-requiring CLL • ECOG performance status of 0-1 • life expectancy > 6 months additional inclusion criteria for patients enrolled in Part 1 only • patients having received 4 cycles of rituximab in combination with chemotherapy without experiencing a grade 3 or 4 infusion-related reaction • patients have not received prior treatment for CLL
Interventions	Arm 1: FluC, 1 additional cycle of IV rituximab (MabThera) and 1 cycle of SC rituximab, after already received IV rituximab without experiencing grade 3 or 4 infusion-related reactions Arm 2: FluC, 6 cycles of IV rituximab Arm 3: FluC, 1 cycle of IV rituximab, followed by 5 cycles of SC rituximab

BO25341 (*Continued*)

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ AEs
	• will not report:
	  ○ OS
	  ○ PFS
	  ○ time to next treatment
	  ○ TRM
	  ○ CRR
	  ○ ORR
	  ○ MRD
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	February 2011
Contact information	Hoffmann-La Roche
Notes	Estimated enrolment: 200 Estimated primary completion date: November 2018 Study status according to ClinicalTrials.gov: this study is not yet open for participant recruitment

CHRUT-LLC-2007-SA

Trial name or title	Fludarabine, cyclophosphamide, and rituximab followed by rituximab or observation in treating older patients with previously untreated CLL (NCT00645606)
Methods	Maintenance after combined induction immunochemotherapy with FluC-R in patients older than 65 years with previously untreated B-CLL Randomisation: • 2 arms: rituximab versus observation
Participants	Inclusion criteria: • diagnosis of B-CLL, Binet stage B or C (Rai stage III or IV) • no 17p-deletion by FISH (> 10% positive cores) • life expectancy > 6 months • ECOG performance status 0 or 1 • no severe co-morbidities • CIRS < 6 • no previous treatment for CLL by chemotherapy, radiotherapy or immunotherapy
Interventions	Arm 1: rituximab Arm 2: observation

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS

CHRUT-LLC-2007-SA (*Continued*)

	○ time to next treatment ○ CRR ○ ORR ○ AEs • will not report: ○ TRM ○ MRD ○ number of patients discontinuing the study because of drug-related AEs
Starting date	November 2007
Contact information	Caroline Dartigeas, MD Centre Hospitalier Universitaire Bretonneau de Tours
Notes	Estimated enrolment: 304 Estimated primary completion date: August 2012 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

CLL 2010 FMP

Trial name or title	Intensified rituximab pre-phase before FluC-R in untreated CLL (NCT01370772)
Methods	Pre-phase monotherapy before standard FC-R regimen in previously untreated symptomatic CLL Randomisation: • 2 arms: standard rituximab versus Dens rituximab
Participants	Inclusion criteria: • age 18 to 65 years • confirmed B-CLL Matutes score 4 or 5 • Binet stage C or Binet stage A and B with active disease could be considered for inclusion. For stage A with active disease an agreement of investigator coordinator is required • no 17p-deletion as assessed by FISH < 10 % positive nuclei • performance status ECOG < 2 • CIRS < 6 • life expectancy > 6 months • any severe co-morbid conditions such as Class III or IV heart failure, myocardial infarction within 6 months, unstable angina, ventricular tachyarrhythmias requiring ongoing treatment, severe chronic obstructive pulmonary disease with hypoxaemia, uncontrolled diabetes mellitus, or uncontrolled hypertension
Interventions	Arm 1: standard rituximab • Cycle 1 rituximab: 375 mg/m^2 IV on day 1 • Cycle 2-6 rituximab: 500 mg/m^2 IV on day 1, repeated every 28 days • Cycle 1-6: cyclophosphamide: 250 mg/m^2 PO, days 2-4, repeated every 28 days • Cycle 1-6: fludarabine: 40 mg/m^2 PO, days 2-4, repeated every 28 days Arm 2: dense rituximab • Pre-phase: rituximab: 500 mg on day 0, 2000 mg on days 1, 8 and 15 • Cycle 1-6 cycle 1 beginning at day 22: rituximab: 500 mg/m^2 IV on day 1, repeated every 28 days • Cycle 1-6: cyclophosphamide: 250 mg/m^2 PO, days 2-4, repeated every 28 days

CLL 2010 FMP (*Continued*)

	• Cycle 1-6: fludarabine: 40 mg/m^2 PO, days 2-4, repeated every 28 days

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS
	  ○ time to next treatment
	  ○ CRR
	  ○ ORR
	  ○ MRD
	• will not report:
	  ○ TRM
	  ○ AEs
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	May 2011
Contact information	Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang GOELAMS (Guillaume CARTRON)
Notes	Estimated enrolment: 140 Estimated primary completion date: December 2017 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

ECOG-E1908

Trial name or title	Rituximab and alemtuzumab in treating older patients with progressive CLL (NCT01013961)
Methods	Phase II comparing standard and low-dose rituximab for initial treatment of progressive CLL in older patients using alemtuzumab and rituximab Randomisation: • 2 arms: alemtuzumab plus standard rituximab versus alemtuzumab plus low-dose rituximab
Participants	Inclusion criteria: • diagnosis of CLL • has progressive, symptomatic CLL • no massive splenomegaly > 6 cm below left costal margin, at rest, on clinical examination • no lymphadenopathy > 5 cm in any diameter • ECOG performance status 0 to 3 • no prior treatment for CLL
Interventions	1. Arm I: course 1: alemtuzumab SC and standard-dose rituximab IV on days 8, 15, 22 and 29; courses 2 and 3: alemtuzumab SC on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26 and standard-dose rituximab IV on days 3, 10, 17 and 24 2. Arm II: course 1: alemtuzumab as in arm 1 and also low-dose rituximab IV on days 6, 8, 10, 13, 15, 17, 20, 22, 24, 27, 29 and 31 courses 2 and 3: alemtuzumab as in arm I and low-dose rituximab IV on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26

ECOG-E1908 (*Continued*)

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ CRR
	  ○ ORR
	  ○ MRD
	  ○ AEs
	• will not report:
	  ○ OS
	  ○ PFS
	  ○ TRM
	  ○ time to next treatment
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	October 2010
Contact information	Clive S. Zent, MD Mayo Clinic
Notes	Estimated enrolment: 90 Estimated primary completion date: February 2012 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

Foa 2010

Trial name or title	A phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukaemia
Methods	Randomisation: • RCT with 2 arms: arm 1: maintenance therapy rituximab, arm 2: observation Median follow-up time: • not reported
Participants	Eligibility criteria: • Older patients • CD20+ CLL requiring therapy according to the IWCLL criteria • no previous treatment for CLL Patients recruited (N = 97; presented data based on interim analysis with first 54 patients): • recruitment stratified by treatment arm not provided (6 patients were not available for response: 1 investigator's decision, 2 because of AEs, 3 because of SAEs) Mean age (interim analysis of the first 54 patients): • median age: 70.5 years (range 61-84 years) Gender (male, female - interim analysis of the first 54 patients): • N = 38, N = 16 Stage of disease (interim analysis of the first 54 patients): • stage stratified by treatment arm not provided • stage for recruited population (Binet A 25.9%, Binet B 57.4%, Binet C 16.7%) Country: • 19 Italian centres

Foa 2010 (*Continued*)

Interventions	All patients received: Clb (up to 8 courses, every 28 days) of 8 mg/m^2/day PO on days 1 to 7 combined with 375 mg/m^2 rituximab for cycle 3 and 500 mg/m^2 for cycles 4 to 8 Responsive patients were randomised to: • Arm 1 (2 years' maintenance): rituximab (375 mg/m^2 every 2 months) • Arm 2: observation
Outcomes	Outcomes and time points from the study that are considered in the review: • reported: ○ OS ○ PFS ○ CRR ○ ORR ○ AEs ○ number of patients discontinuing the study because of drug-related AEs • not reported: ○ TRM ○ time to next treatment ○ MRD
Starting date	Recruitment period: • October 2008 and January 2010
Contact information	Robin Foa, Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy
Notes	The authors stated the following disclosures: • Foa: Roche - Consultancy, Speakers Bureau • Montillo: Roche - Membership on an entity's Board of Directors or advisory committees, Speakers Bureau • Runggaldier: Roche employment • Gamba: Roche employment

GAO4768g

Trial name or title	A study comparing RO5072759 (GA101) 1000 mg versus 2000 mg in patients with previously untreated chronic lymphocytic leukaemia (NCT01414205)
Methods	An open-label, randomised Phase II trial comparing the efficacy, safety and pharmacokinetics of GA101 1000 mg versus 2000 mg in patients with previously untreated CLL Randomisation: • 2 arms: RO5072759 1000 mg versus RO5072759 2000 mg
Participants	Inclusion criteria: • CD20-positive B-CLL (per IWCLL guidelines) • Rai stage III/IV or Binet stage C disease, or Rai stage I/II or Binet stage B disease that requires treatment according to IWCLL guidelines • No previous treatment for CLL chemotherapy, radiotherapy or immunotherapy; no previous rituximab treatment for AIHA or ITP; prior use of steroids for AIHA or ITP is allowed • ECOG performance status of 0, 1 or 2

GAO4768g (*Continued*)

Interventions	Arm 1: RO5072759 1000 mg IV dose Arm 2: RO5072759 2000 mg IV dose

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS
	  ○ ORR
	  ○ CRR
	  ○ time to next treatment
	• will not report:
	  ○ MRD
	  ○ AEs
	  ○ TRM
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	September 2011
Contact information	Contact: Genentech Trial Information Support Line (global.rochegenentechtrials@roche.com)
Notes	Estimated enrolment: 80 Estimated primary completion date: January 2017 Study status according to ClinicalTrials.gov: this study is not yet open for participant recruitment

GCLLSG-CLL11

Trial name or title	A study of RO5072759 with chlorambucil in patients with previously untreated CLL (NCT01010061)
Methods	3-arm randomised study to investigate the safety and efficacy on PFS of GClb compared to RClb or Clb alone in previously untreated CLL patients with co-morbidities Randomisation: • 3 arms: GClb versus RClb versus Clb
Participants	Inclusion criteria: • adults ≥ 18 years • documented CD20 + B-CLL • previously untreated CLL requiring treatment according to the NCI criteria
Interventions	Arm 1: GClb Arm 2: RClb Arm 3: Clb

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ PFS
	  ○ ORR
	  ○ CRR

GCLLSG-CLL11 (*Continued*)

	○ MRD ○ AEs • will not report: ○ OS ○ time to next treatment ○ TRM ○ number of patients discontinuing the study because of drug-related AEs
Starting date	November 2009
Contact information	Study Director: Hoffmann-La Roche (genentechclinicaltrials@druginfo.com)
Notes	Estimated enrolment: 786 Estimated primary completion date: March 2022 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

GCLLSG-CLL7

Trial name or title	Rituximab, fludarabine, and cyclophosphamide or observation alone in treating patients with stage 0, I, or II CLL (NCT00275054)
Methods	Randomised Phase III trial comparing early treatment with FluC-R versus deferred treatment in untreated Binet stage a patients with CLL and high risk of progression Randomisation: • 2 arms: FluC-R versus deferred treatment ('watch and wait')
Participants	Inclusion criteria: • established diagnosis of B-CLL, first diagnosis within 12 months before inclusion in study, previously untreated disease • Binet stage A disease (Rai stage 0, I or II) • life expectancy > 6 months • ECOG performance status 0 to 2 • all parameters for risk stratification (lymphocyte doubling time, cytogenetics, unmutated IgVH, and serum thymidine kinase level > 10 U/L) present • no prior chemotherapy, radiotherapy or antibody treatment
Interventions	Arm 1: patients receive rituximab IV on day 1, fludarabine IV on days 1-3, and cyclophosphamide IV on days 1-3. Treatment repeats every 28 days for up to 6 courses Arm 2: patients undergo observation only until disease progression
Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review: • will report: ○ OS ○ PFS ○ time to next treatment ○ CRR ○ OR ○ MRD

GCLLSG-CLL7 (*Continued*)

	○ AEs • will not report: ○ TRM ○ number of patients discontinuing the study because of drug-related AEs
Starting date	October 2005
Contact information	Michael Hallek, MD Medizinische Universitaetsklinik I at the University of Cologne
Notes	Estimated enrolment: 600 Estimated primary completion date: not reported Study status according to ClinicalTrials.gov: this study is currently recruiting participants

GSKStudy ID 110913

Trial name or title	Ofatumumab added to FC versus FC in relapsed subjects with CLL (NCT00824265)
Methods	A Phase III, open-labee, randomised trial of ofatumumab added to FluC versus FluC alone in subjects with relapsed CLL Randomisation: • 2 arms: FCO versus FluC
Participants	Inclusion criteria: • confirmed and active CLL requiring treatment • at least 1 previous treatment for CLL and having achieved a complete or partial remission/response but after a period of ≥ 6 months, shows evidence of disease progression • Age ≥ 18 years
Interventions	Arm 1: FCO Arm 2: FluC
Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review: • will report: ○ PFS • will not report: ○ OS ○ time to next treatment ○ TRM ○ CRR ○ ORR ○ MRD ○ AEs ○ number of patients discontinuing the study because of drug-related AEs
Starting date	March 2009
Contact information	GSK Clinical Trials GlaxoSmithKline

GSKStudy ID 110913 (*Continued*)

Notes	Estimated enrolment: 352 Estimated primary completion date: December 2012 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

GSKStudy ID 112517

Trial name or title	Ofatumumab maintenance treatment versus no further treatment in relapsed CLL responding to induction therapy (PROLONG) (NCT01039376)
Methods	A Phase III, open label, randomised trial of ofatumumab maintenance treatment versus no treatment in subjects with relapsed CLL who have responded to induction therapy Randomisation: • 2 arms: ofatumumab versus no treatment
Participants	Inclusion criteria: • adults with documented diagnosis of CLL based on the modified IWCLL updated NCI-WG guidelines • CR or PR according to the revised 2008 NCI-WG CLL criteria, confirmed by CT scan, after second- or third-line treatment • the anti-leukaemic treatment before study entry should have been at least 4 months of monotherapy with alkylating agents with or without at least 4 consecutive cycles of polychemotherapy (e.g. CVP), fludarabine-containing chemotherapy or immunochemotherapy • ECOG performance status of 0 to 2 • no primary or secondary fludarabine-refractory subjects, defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months of last anti-leukaemic therapy. Note: subjects refractory to rituximab therapy as last therapy are permitted
Interventions	Arm 1: ofatumumab for maintenance therapy as IV infusions every 8 weeks. The first dose will be 300 mg followed 1 week later by 1000 mg and 1000 mg every 8 weeks thereafter for up to 2 years Arm 2: no treatment

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS
	  ○ AEs
	• will not report:
	  ○ time to next treatment
	  ○ TRM
	  ○ ORR
	  ○ CRR
	  ○ MRD
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	May 2010
Contact information	US GlaxoSmithKline Clinical Trials Call Center (GSKClinicalSupportHD@gsk.com)

GSKStudy ID 112517 (*Continued*)

Notes	Estimated enrolment: 532 Estimated primary completion date: May 2017 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

GSKStudy ID 114242

Trial name or title	Ofatumumab versus physicians' choice in subjects with bulky fludarabine-refractory chronic lymphocytic leukaemia
Methods	An open-label study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine-refractory CLL Randomisation: • 2 arms: ofatumumab versus physicians' choice
Participants	Inclusion criteria: • Adults with documented diagnosis of active CLL requiring treatment • Bulky lymphadenopathy, defined as at least 1 lymph node > 5 cm • Must be refractory to fludarabine treatment • Age ≥ 18 years • At least 2 prior therapies for CLL • ECOG performance status 0 to 2
Interventions	Arm 1: ofatumumab Arm 2: physicians' choice (non-ofatumumab-containing regimen as per physicians' choice for up to 6 months. Permitted therapies include treatments approved for CLL, and well established standards of care for CLL)

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS
	  ○ ORR
	  ○ CRR
	  ○ AEs
	• will not report:
	  ○ time to next treatment
	  ○ TRM
	  ○ MRD
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	April 2011
Contact information	US GlaxoSmithKline Clinical Trials Call Center (GSKClinicalSupportHD@gsk.com)
Notes	Estimated enrolment: 120 Estimated primary completion date: April 2019 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

Mabtenance

Trial name or title	Rituximab versus observation as maintenance therapy in CLL (NCT01118234)
Methods	Randomised Phase III study comparing rituximab as maintenance treatment with observation alone in patients with CLL Randomisation: • 2 arms: rituximab versus observation
Participants	Inclusion criteria: • B-CLL • Age > 18 years • ECOG performance status 0 to 2 • Previous rituximab containing induction treatment of the CLL in first or second line • Patient must be in complete remission or partial remission after an induction treatment containing rituximab • Life expectancy > 6 months
Interventions	Arm 1: rituximab Arm 2: observation
Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review: • will report: ○ OS ○ PFS ○ time to next treatment ○ TRM ○ CRR ○ MRD ○ AEs • will not report: ○ ORR ○ Number of patients discontinuing the study because of drug-related AEs
Starting date	December 2009
Contact information	Richard Greil, Prof. Dr. Arbeitsgemeinschaft medikamentöse Tumortherapie
Notes	Estimated enrolment: 256 Estimated primary completion date: December 2015 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

ML21283

Trial name or title	A study of maintenance treatment with rituximab in patients with progressive CLL (NCT00718549)
Methods	A randomised, open-label study to assess the effect of maintenance treatment with rituximab versus no treatment, after induction with rituximab, cladribine and cyclophosphamide on PFS in previously untreated patients with progressive B-CLL Randomisation: • 2 arms: rituximab versus no treatment

ML21283 (*Continued*)

Participants	Inclusion criteria: • adult patients, 18-75 years of age • confirmed diagnosis of B-CLL • stage I to IV disease with evidence of progression • no previous chemotherapy, radiotherapy or immunotherapy for B-CLL • ECOG performance status 0 to 2
Interventions	Arm 1: • induction: rituximab, cladribine, cyclophosphamide • maintenance: rituximab Arm 2: • induction: rituximab, cladribine, cyclophosphamide

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ PFS
	  ○ CRR
	• will not report:
	  ○ OS
	  ○ time to next treatment
	  ○ TRM
	  ○ ORR
	  ○ MRD
	  ○ AEs
	  ○ number of patients discontinuing the study because of drug-related AEs
	Primary outcome measures: PFS in the maintenance phase
	Secondary outcome measures: CR and PR in induction phase

Starting date	July 2009
Contact information	Clinical Trials Hoffmann La Roche
Notes	Estimated enrolment: 200 Estimated primary completion date: July 2017 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

OMB110911

Trial name or title	Ofatumumab + chlorambucil versus chlorambucil monotherapy in previously untreated patients with CLL (NCT00748189)
Methods	A Phase III, open-label, randomised trial of ofatumumab added to Clb versus Clb alone in previously untreated patients with CLL Randomisation: • 2 arms: ofatumumab plus Clb versus Clb

OMB110911 (*Continued*)

Participants	Inclusion criteria: • Confirmed CLL diagnosis and active CLL requiring treatment • Considered inappropriate for fludarabine-based therapy • Not been treated for CLL before • Age ≥ 18 years
Interventions	Arm 1: ofatumumab + Clb Arm 2: Clb

Outcomes	Outcomes and time points from the registered protocol of the study that are considered in the review:
	• will report:
	  ○ OS
	  ○ PFS
	  ○ ORR
	• will not report:
	  ○ time to next treatment
	  ○ TRM
	  ○ CRR
	  ○ MRD
	  ○ AEs
	  ○ number of patients discontinuing the study because of drug-related AEs

Starting date	December 2008
Contact information	US GlaxoSmithKline Clinical Trials Call Center (GSKClinicalSupportHD@gsk.com)
Notes	Estimated enrolment: 444 Estimated primary completion date: January 2013 Study status according to ClinicalTrials.gov: this study is currently recruiting participants

Zagoskina 2011

Trial name or title	Rituximab therapy of chronic lymphocytic leukaemia patients in remission
Methods	Randomisation: • RCT with 2 arms: arm 1: maintenance therapy rituximab, arm 2: observation Median follow-up time: • not reported
Participants	Eligibility criteria: • Patients in remission after FluC-R (N = 117) or FluC (N = 96) (no further information provided) Patients included 213 patients in remission: • observation (N = 133) • rituximab (N = 60) Mean age: • 59 years (range: 34 to 76 years) Gender (male, female - interim analysis of the first 54 patients):

Zagoskina 2011 (*Continued*)

	• not reported Stage of disease: • not reported Country: • Russian (number of centres not reported)
Interventions	All patients received either FluC-R or FluC alone to introduce remission Arm 1: observation Arm 2: rituximab therapy in the form of 4 weekly injections (375 mg/m^2) every 6 months over 2 years
Outcomes	Outcomes and time points from the study that are considered in the review: • will report: ○ PFS ○ AEs • not reported: ○ OS ○ TRM ○ time to next treatment ○ MRD ○ CRR ○ ORR ○ number of patients discontinuing the study because of drug-related AEs
Starting date	Recruitment period: • not reported
Contact information	P Zagoskina, Kirov Scientific Research Institute of Hematology and Blood Transfusion of FMBA, Kirov, Russian Federation
Notes	The abstract provided no declaration on authors' conflicts of interest

AIHA: autoimmune haemolytic anaemia; B-CLL: B-cell chronic lymphocytic leukaemia; CIRS: cumulative illness rating scale; Clb: chlorambucil; CLL: chronic lymphocytic leukaemia; CR: complete response; CRR: complete response rate; CT: computerised tomography; CVP: cyclophosphamide plus vincristine plus prednisolone; ECOG: Eastern Cooperative Oncology Group; FluC: fludarabine plus cyclophosphamide; FCO: fludarabine plus cyclophosphamide plus ofatumumab; FluC-R: fludarabine plus cyclophosphamide plus rituximab; FISH: fluorescence in situ hybridisation; GCib: RO5072759 plus chlorambucil; ITP: immune thrombocytopenic purpura; IV: intravenous; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; MRD: minimal residual disease; NCI-WG: National Cancer Institute-Working Group; nPR: nodular partial response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PLL: prolymphocytic leukaemia; PO: per os; PR: partial response; RClb: rituximab plus chlorambucil; RCT: randomised controlled trial; SAE: serious adverse event; SC: subcutaneous; SLL: small lymphocytic lymphoma; TRM: treatment-related mortality.

DATA AND ANALYSES

Comparison 1. Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 OS - overall analysis	3	1421	Hazard Ratio (Fixed, 95% CI)	0.78 [0.62, 0.98]
2 OS - subgrouped by different anti-CD20 antibody treatment regimens	3		Hazard Ratio (Fixed, 95% CI)	Subtotals only
2.1 first-line treatment	1	817	Hazard Ratio (Fixed, 95% CI)	0.67 [0.48, 0.94]
2.2 previously treated	2	604	Hazard Ratio (Fixed, 95% CI)	0.89 [0.65, 1.22]
3 OS - subgrouped by different treatment regimens	3		Hazard Ratio (Fixed, 95% CI)	Subtotals only
3.1 FluC-R versus FluC	2	1369	Hazard Ratio (Fixed, 95% CI)	0.74 [0.59, 0.94]
3.2 FluCM-R versus FluCM	1	52	Hazard Ratio (Fixed, 95% CI)	1.28 [0.60, 2.76]
4 PFS - overall analysis	3	1421	Hazard Ratio (Fixed, 95% CI)	0.64 [0.55, 0.74]
5 PFS - subgrouped by age	2		Hazard Ratio (Random, 95% CI)	Subtotals only
5.1 < 65 years	2	889	Hazard Ratio (Random, 95% CI)	0.53 [0.44, 0.65]
5.2 ≥ 65 years	1	245	Hazard Ratio (Random, 95% CI)	0.55 [0.38, 0.80]
5.3 ≥ 65 years to < 70 years	1	142	Hazard Ratio (Random, 95% CI)	0.87 [0.56, 1.35]
5.4 ≥ 70 years	1	93	Hazard Ratio (Random, 95% CI)	0.99 [0.58, 1.69]
6 PFS - subgrouped by stage	2		Hazard Ratio (Random, 95% CI)	Subtotals only
6.1 Binet A	2	95	Hazard Ratio (Random, 95% CI)	0.59 [0.31, 1.10]
6.2 Binet B	2	848	Hazard Ratio (Random, 95% CI)	0.56 [0.43, 0.72]
6.3 Binet C	2	423	Hazard Ratio (Random, 95% CI)	0.67 [0.52, 0.88]
7 PFS - subgrouped by prognostic factor	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
7.1 del17p	2	93	Hazard Ratio (Fixed, 95% CI)	0.59 [0.37, 0.95]
7.2 del 11q	2	705	Hazard Ratio (Fixed, 95% CI)	0.38 [0.29, 0.51]
7.3 trisomy 12	2	143	Hazard Ratio (Fixed, 95% CI)	0.60 [0.35, 1.03]
7.4 del13q	2	659	Hazard Ratio (Fixed, 95% CI)	0.52 [0.41, 0.66]
8 PFS - subgrouped by different anti-CD20 antibody treatment regimens	3		Hazard Ratio (Fixed, 95% CI)	Subtotals only
8.1 first-line treatment	1	817	Hazard Ratio (Fixed, 95% CI)	0.56 [0.46, 0.68]
8.2 previously treated	2	604	Hazard Ratio (Fixed, 95% CI)	0.75 [0.61, 0.94]
9 PFS - subgrouped by different treatment regimens	3		Hazard Ratio (Fixed, 95% CI)	Subtotals only
9.1 FluC-R versus FluC	2	1369	Hazard Ratio (Fixed, 95% CI)	0.63 [0.55, 0.74]
9.2 FluCM-R versus FluCM	1	52	Hazard Ratio (Fixed, 95% CI)	0.72 [0.39, 1.32]
10 Time to next treatment - overall analysis	2	1369	Hazard Ratio (Fixed, 95% CI)	0.61 [0.51, 0.73]
11 Time to next treatment - subgrouped by different anti-CD20 antibody treatment regimens	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
11.1 first-line treatment	1	817	Hazard Ratio (Fixed, 95% CI)	0.59 [0.47, 0.74]

11.2 previously treated	1	552	Hazard Ratio (Fixed, 95% CI)	0.65 [0.49, 0.86]
12 ORR - overall analysis	3	1421	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.09, 1.23]
13 ORR - subgrouped by age	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 < 65 years	2	889	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.10, 1.29]
13.2 ≥ 65 years	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.02, 1.23]
13.3 ≥ 65 years to < 70 years	1	142	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.72, 2.81]
13.4 ≥ 70 years	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.80, 4.14]
14 ORR - subgrouped by stage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Binet A	2	95	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.10, 2.17]
14.2 Binet B	2	848	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.07, 1.24]
14.3 Binet C	2	423	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.05, 1.39]
15 ORR - subgrouped by prognostic factor	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 del17p	2	93	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.20, 3.64]
15.2 del11q	2	694	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.97, 1.34]
15.3 trisomy 12	2	130	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]
15.4 del13q	2	533	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.22, 1.59]
16 ORR - subgrouped by different anti-CD20 antibody treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 first-line treatment	1	817	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.06, 1.19]
16.2 previously treated	2	604	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.07, 1.43]
17 ORR - subgrouped by different treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 FluC-R versus FluC	2	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.09, 1.24]
17.2 FluCM-R versus FluCM	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.74, 1.75]
18 CRR - overall analysis	3	1421	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.72, 2.59]
19 CRR - subgrouped by different anti-CD20 antibody treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 first-line treatment	1	817	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.65, 2.54]
19.2 previously treated	2	604	Risk Ratio (M-H, Fixed, 95% CI)	2.9 [1.44, 5.84]
20 CRR - subgrouped by different treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 FluC versus FluC-R	2	1369	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.74, 2.64]
20.2 FluCM versus FluCM-R	1	52	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.40, 9.99]
21 MRD negativity - overall analysis	2	121	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.81, 2.54]
22 MRD negativity - subgrouped by different treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 FluC versus FluC-R	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.73, 2.61]
22.2 FluCM versus FluCM-R	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.44, 6.26]
23 Treatment-related mortality - overall analysis	3	1415	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.70, 2.01]
24 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 first-line treatment	1	817	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.01]
24.2 previously treated	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.77, 2.75]

25 Treatment-related mortality - subgrouped by different treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 FluC-R versus FluC	2	869	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.44, 2.28]
25.2 FluCM-R versus FluCM	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.63]
26 SAEs - overall analysis	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.23]
27 SAEs - subgrouped by different treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 FluC versus FluC-R	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.24]
27.2 FluCM versus FluCM-R	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.64, 1.82]
28 Grade 3/4 AEs - overall analysis	3	1398	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.23]
29 Grade 3/4 AEs - subgrouped by different anti-CD20 antibody treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 first-line treatment	1	800	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.11, 1.33]
29.2 previously treated	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.99, 1.18]
30 Grade 3/4 AEs - subgrouped by different treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 FluC versus FluC-R	2	1346	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.08, 1.24]
30.2 FluCM versus FluCM-R	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.87, 1.25]
31 Anaemia grade 3/4 - overall analysis	2	1346	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.62, 1.24]
32 Anaemia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 first-line treatment	1	800	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.46, 1.38]
32.2 previously treated	1	546	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.46]
33 Neutropenia grade 3/4 - overall analysis	3	1398	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.11, 1.48]
34 Neutropenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 first-line treatment	1	800	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.27, 2.03]
34.2 previously treated	2	598	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.28]
35 Neutropenia grade 3/4 - subgrouped by different treatment regimens	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 FluC versus FluC-R	2	1346	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.12, 1.52]
35.2 FluCM versus FluCM-R	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.60, 1.65]
36 Thrombocytopenia grade 3/4 - overall analysis	2	1346	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.19]
37 Thrombocytopenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 first-line treatment	1	800	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.04]
37.2 previously treated	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.72, 2.01]

Comparison 2. Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ORR - overall analysis	2	176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.14]
2 ORR - subgrouped by different anti-CD20 antibody treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 first-line therapy	1	165	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.16]
2.2 relapse therapy	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.20, 1.59]
3 CRR - overall analysis	2	176	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.94, 1.58]
4 CRR - subgrouped by different anti-CD20 antibody treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 first-line therapy	1	165	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.98, 1.65]
4.2 relapse therapy	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.04, 2.25]
5 Treatment-related mortality	2	177	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.06, 1.51]
6 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 first-line therapy	1	165	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.01]
6.2 relapse therapy	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 8.00]

Analysis 1.1. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 1 OS - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 1 OS - overall analysis

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
GCLLSG CLL 8	408	409	-0.4 (0.17)		46.7 %	0.67 [0.48, 0.94]
NCRI-CLL 201	26	26	0.25 (0.39)		8.9 %	1.28 [0.60, 2.76]
REACH	276	276	-0.1863 (0.1741)		44.5 %	0.83 [0.59, 1.17]
Total (95% CI)	**710**	**711**			**100.0 %**	**0.78 [0.62, 0.98]**

Heterogeneity: Chi^2 = 2.56, df = 2 (P = 0.28); I^2 =22%

Test for overall effect: Z = 2.13 (P = 0.033)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 2 OS - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 2 OS - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 first-line treatment						
GCLLSG CLL 8	408	409	-0.4 (0.17)		100.0 %	0.67 [0.48, 0.94]
Subtotal (95% CI)	**408**	**409**			**100.0 %**	**0.67 [0.48, 0.94]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.35 (P = 0.019)						
2 previously treated						
NCRI-CLL 201	26	26	0.25 (0.39)		16.6 %	1.28 [0.60, 2.76]
REACH	276	276	-0.1863 (0.1741)		83.4 %	0.83 [0.59, 1.17]
Subtotal (95% CI)	**302**	**302**			**100.0 %**	**0.89 [0.65, 1.22]**
Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Chi^2 = 1.51, df = 1 (P = 0.22), I^2 =34%						

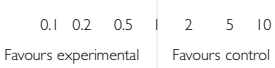
Analysis 1.3. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 3 OS - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 3 OS - subgrouped by different treatment regimens

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 FluC-R versus FluC						
GCLLSG CLL 8	408	409	-0.4 (0.17)		51.2 %	0.67 [0.48, 0.94]
REACH	276	276	-0.1863 (0.1741)		48.8 %	0.83 [0.59, 1.17]
Subtotal (95% CI)	**684**	**685**			**100.0 %**	**0.74 [0.59, 0.94]**
Heterogeneity: Chi^2 = 0.77, df = 1 (P = 0.38); I^2 =0.0%						
Test for overall effect: Z = 2.43 (P = 0.015)						
2 FluCM-R versus FluCM						
NCRI-CLL 201	26	26	0.25 (0.39)		100.0 %	1.28 [0.60, 2.76]
Subtotal (95% CI)	**26**	**26**			**100.0 %**	**1.28 [0.60, 2.76]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi^2 = 1.78, df = 1 (P = 0.18), I^2 =44%						



Analysis 1.4. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 4 PFS - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 4 PFS - overall analysis

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
GCLLSG CLL 8	408	409	-0.5798 (0.1004)		55.6 %	0.56 [0.46, 0.68]
NCRI-CLL 201	26	26	-0.33 (0.31)		5.8 %	0.72 [0.39, 1.32]
REACH	276	276	-0.2744 (0.1206)		38.5 %	0.76 [0.60, 0.96]
Total (95% CI)	**710**	**711**			**100.0 %**	**0.64 [0.55, 0.74]**

Heterogeneity: $Chi^2 = 3.94$, df = 2 (P = 0.14); $I^2 = 49\%$

Test for overall effect: Z = 5.98 (P < 0.00001)

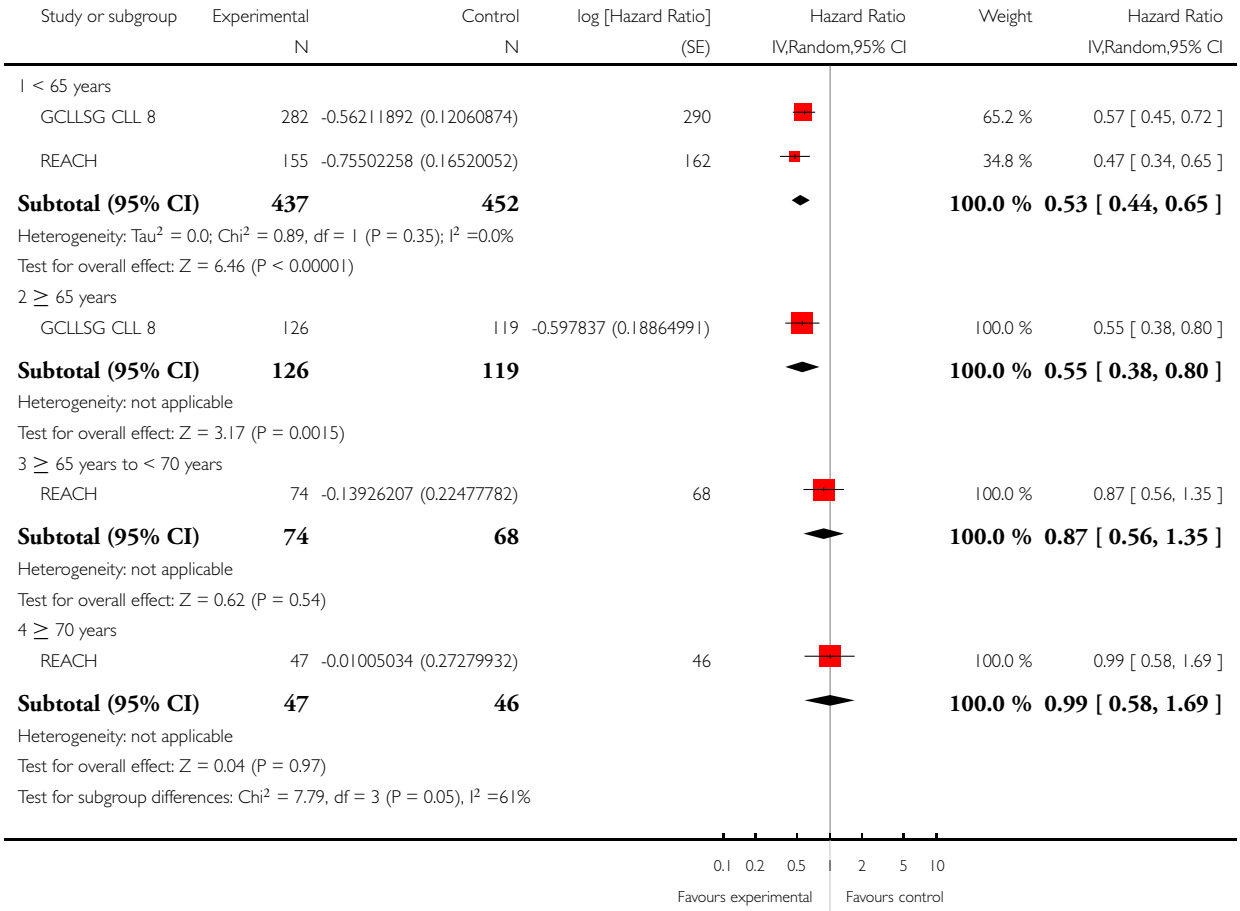
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 5 PFS - subgrouped by age.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 5 PFS - subgrouped by age

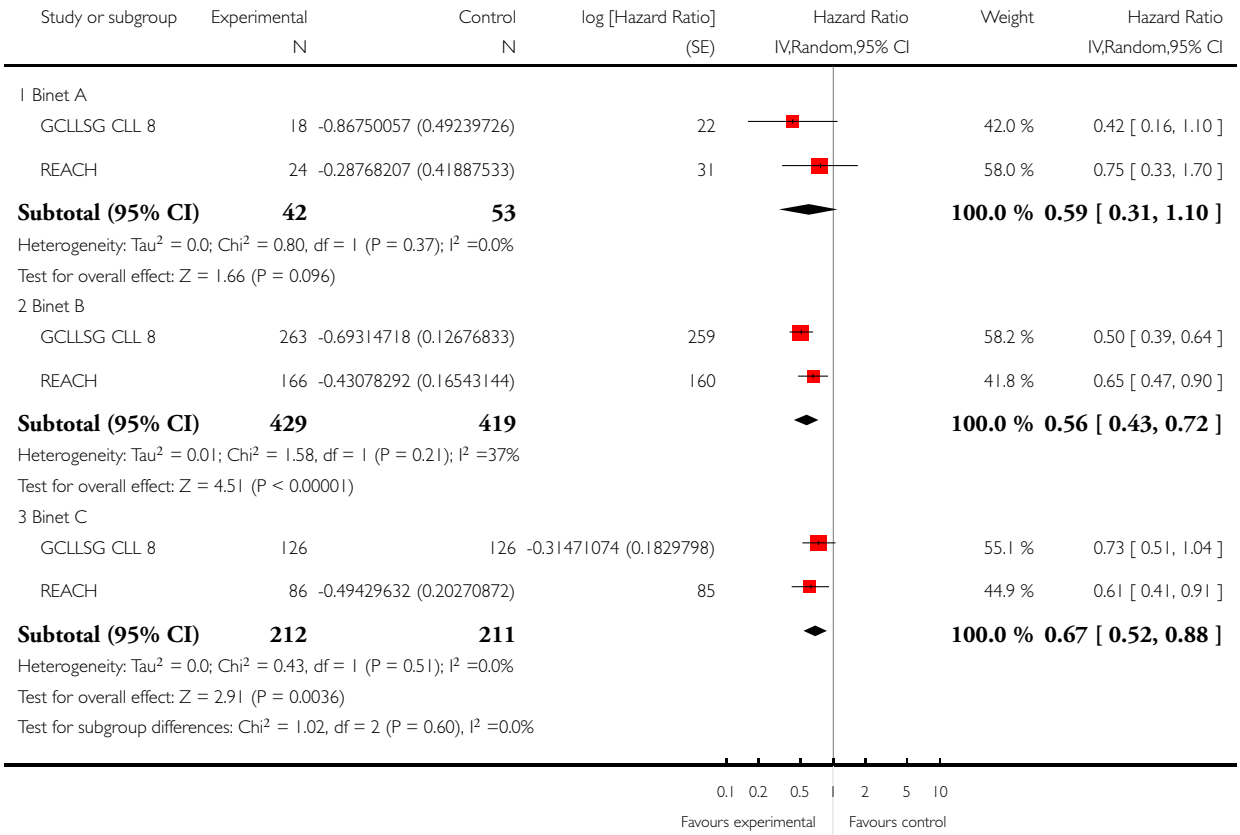


Analysis 1.6. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 6 PFS - subgrouped by stage.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 6 PFS - subgrouped by stage



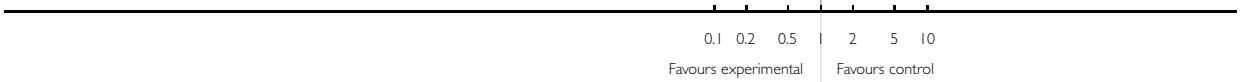
Analysis 1.7. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 7 PFS - subgrouped by prognostic factor.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 7 PFS - subgrouped by prognostic factor

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 del17p						
GCLLSG CLL 8	22	-0.75502258 (0.34291129)	29		50.6 %	0.47 [0.24, 0.92]
REACH	18	-0.28768207 (0.34689513)	24		49.4 %	0.75 [0.38, 1.48]
Subtotal (95% CI)	**40**	**53**			**100.0 %**	**0.59 [0.37, 0.95]**
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² =0.0%						
Test for overall effect: Z = 2.15 (P = 0.032)						
2 del 11q						
GCLLSG CLL 8	84	-1.07880966 (0.17771076)	69		64.5 %	0.34 [0.24, 0.48]
REACH	276	-0.73396918 (0.23980218)	276		35.5 %	0.48 [0.30, 0.77]
Subtotal (95% CI)	**360**	**345**			**100.0 %**	**0.38 [0.29, 0.51]**
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² =25%						
Test for overall effect: Z = 6.70 (P < 0.00001)						
3 trisomy 12						
GCLLSG CLL 8	30	-1.13943428 (0.45959342)	44		36.4 %	0.32 [0.13, 0.79]
REACH	29	-0.16251893 (0.34768554)	40		63.6 %	0.85 [0.43, 1.68]
Subtotal (95% CI)	**59**	**84**			**100.0 %**	**0.60 [0.35, 1.03]**
Heterogeneity: Chi² = 2.87, df = 1 (P = 0.09); I² =65%						
Test for overall effect: Z = 1.87 (P = 0.062)						
4 del13q						
GCLLSG CLL 8	168	-0.84397007 (0.21887933)	182		31.0 %	0.43 [0.28, 0.66]
REACH	150	159	-0.5798185 (0.1468)		69.0 %	0.56 [0.42, 0.75]
Subtotal (95% CI)	**318**	**341**			**100.0 %**	**0.52 [0.41, 0.66]**
Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² =0%						
Test for overall effect: Z = 5.43 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.13, df = 3 (P = 0.25), I² =27%						



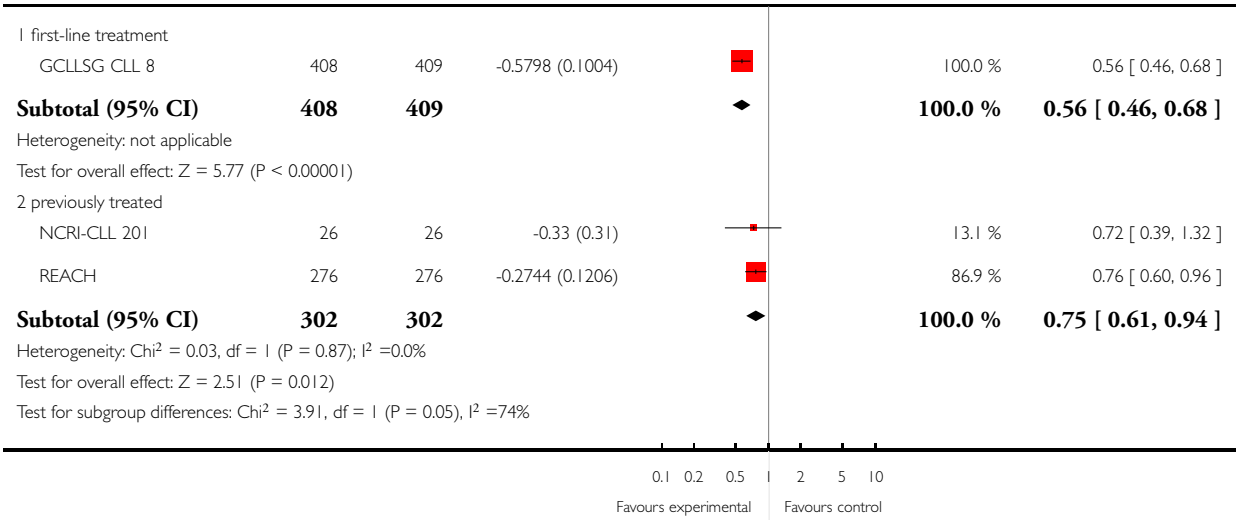
Analysis 1.8. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 8 PFS - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 8 PFS - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 first-line treatment						
GCLLSG CLL 8	408	409	-0.5798 (0.1004)		100.0 %	0.56 [0.46, 0.68]
Subtotal (95% CI)	**408**	**409**			**100.0 %**	**0.56 [0.46, 0.68]**
Heterogeneity: not applicable						
Test for overall effect: Z = 5.77 (P < 0.00001)						
2 previously treated						
NCRI-CLL 201	26	26	-0.33 (0.31)		13.1 %	0.72 [0.39, 1.32]
REACH	276	276	-0.2744 (0.1206)		86.9 %	0.76 [0.60, 0.96]
Subtotal (95% CI)	**302**	**302**			**100.0 %**	**0.75 [0.61, 0.94]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%						
Test for overall effect: Z = 2.51 (P = 0.012)						
Test for subgroup differences: Chi^2 = 3.91, df = 1 (P = 0.05), I^2 =74%						



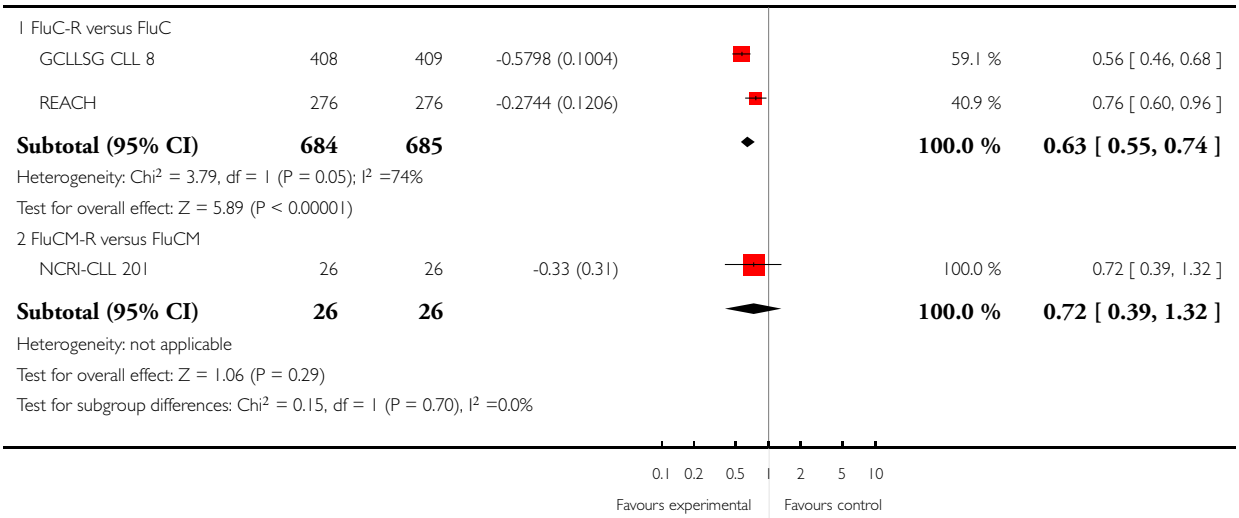
Analysis 1.9. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 9 PFS - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 9 PFS - subgrouped by different treatment regimens

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 FluC-R versus FluC						
GCLLSG CLL 8	408	409	-0.5798 (0.1004)		59.1 %	0.56 [0.46, 0.68]
REACH	276	276	-0.2744 (0.1206)		40.9 %	0.76 [0.60, 0.96]
Subtotal (95% CI)	**684**	**685**			**100.0 %**	**0.63 [0.55, 0.74]**
Heterogeneity: Chi^2 = 3.79, df = 1 (P = 0.05); I^2 =74%						
Test for overall effect: Z = 5.89 (P < 0.00001)						
2 FluCM-R versus FluCM						
NCRI-CLL 201	26	26	-0.33 (0.31)		100.0 %	0.72 [0.39, 1.32]
Subtotal (95% CI)	**26**	**26**			**100.0 %**	**0.72 [0.39, 1.32]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%						



Analysis 1.10. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 10 Time to next treatment - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 10 Time to next treatment - overall analysis

Study or subgroup	Experimental N		Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
GCLLSG CLL 8	408	-0.52763274 (0.11493295)	409			61.1 %	0.59 [0.47, 0.74]
REACH	276	-0.43078292 (0.14416947)	276			38.9 %	0.65 [0.49, 0.86]
Total (95% CI)	**684**		**685**			**100.0 %**	**0.61 [0.51, 0.73]**

Heterogeneity: $Chi^2 = 0.28$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 5.45 (P < 0.00001)

Test for subgroup differences: Not applicable

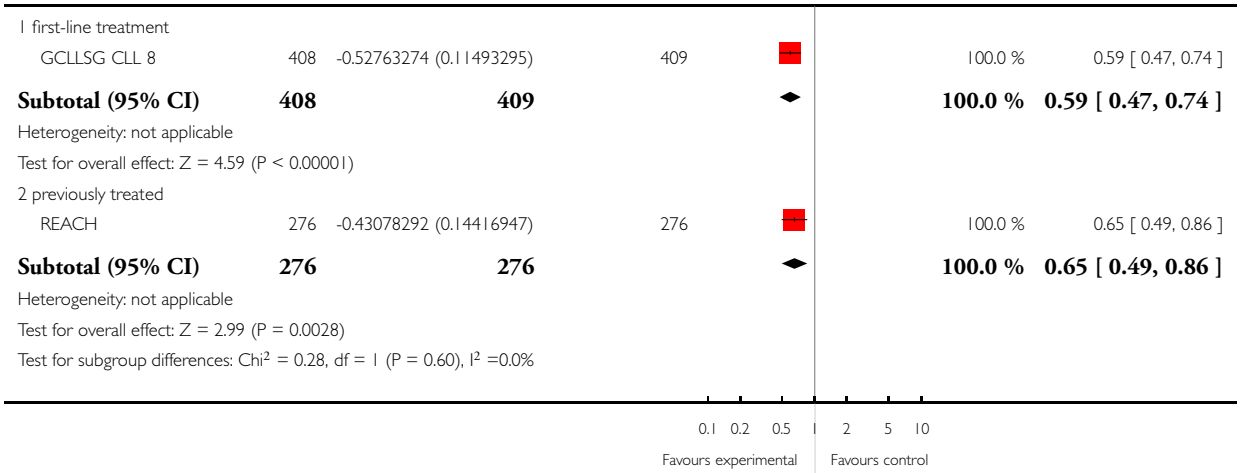
Analysis 1.11. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 11 Time to next treatment - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 11 Time to next treatment - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 first-line treatment						
GCLLSG CLL 8	408	-0.52763274 (0.11493295)	409		100.0 %	0.59 [0.47, 0.74]
Subtotal (95% CI)	**408**	**409**			**100.0 %**	**0.59 [0.47, 0.74]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.59 (P < 0.00001)						
2 previously treated						
REACH	276	-0.43078292 (0.14416947)	276		100.0 %	0.65 [0.49, 0.86]
Subtotal (95% CI)	**276**	**276**			**100.0 %**	**0.65 [0.49, 0.86]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.99 (P = 0.0028)						
Test for subgroup differences: Chi^2 = 0.28, df = 1 (P = 0.60), I^2 =0.0%						



Analysis 1.12. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 12 ORR - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 12 ORR - overall analysis

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GCLLSG CLL 8	369/408	328/409		68.6 %	1.13 [1.06, 1.19]
NCRI-CLL 201	17/26	15/26		3.1 %	1.13 [0.74, 1.75]
REACH	168/276	135/276		28.3 %	1.24 [1.07, 1.45]
Total (95% CI)	**710**	**711**		**100.0 %**	**1.16 [1.09, 1.23]**

Total events: 554 (Experimental), 478 (Control)

Heterogeneity: $Chi^2 = 1.77$, df = 2 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 4.80 (P < 0.00001)

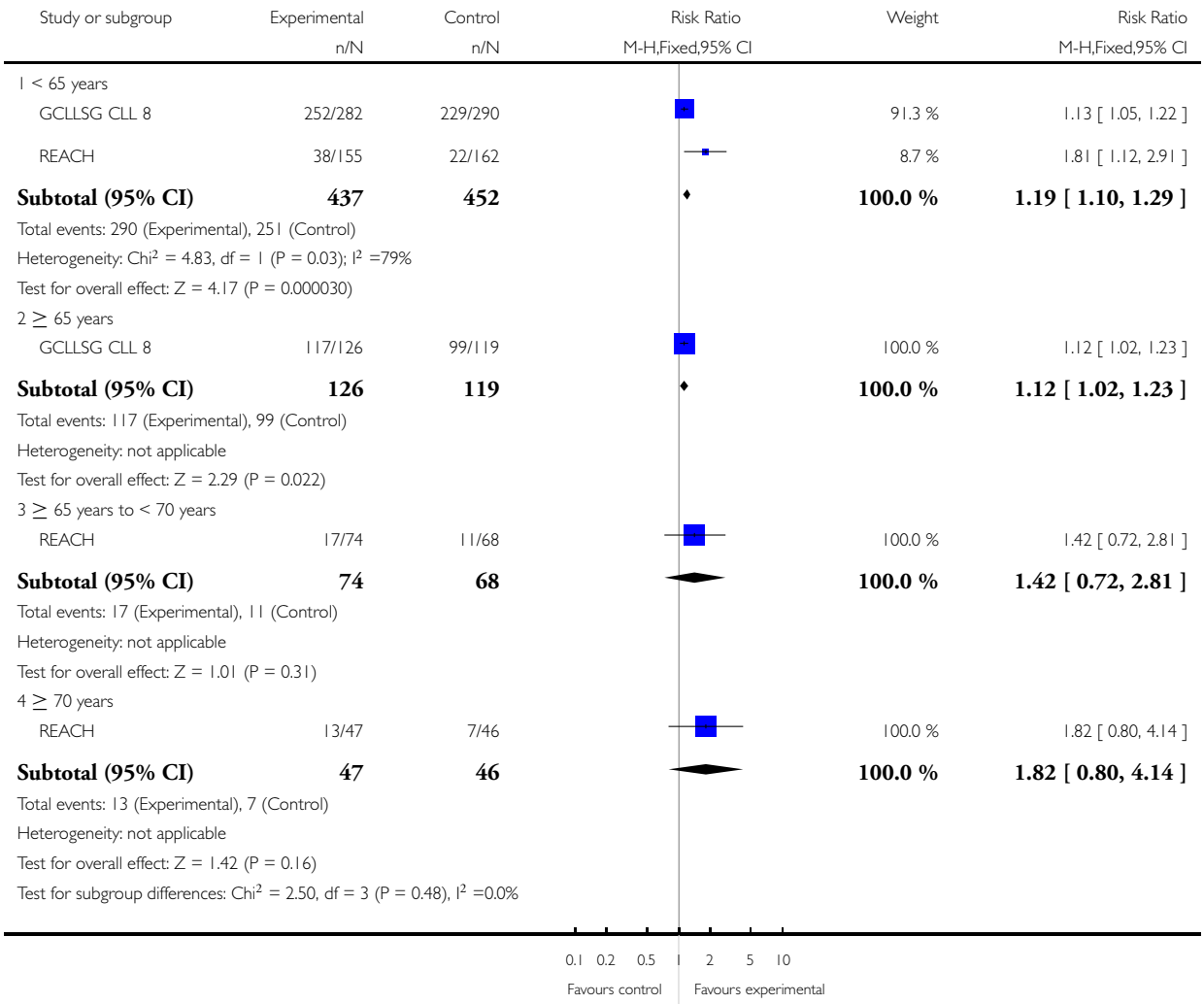
Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 13 ORR - subgrouped by age.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 13 ORR - subgrouped by age

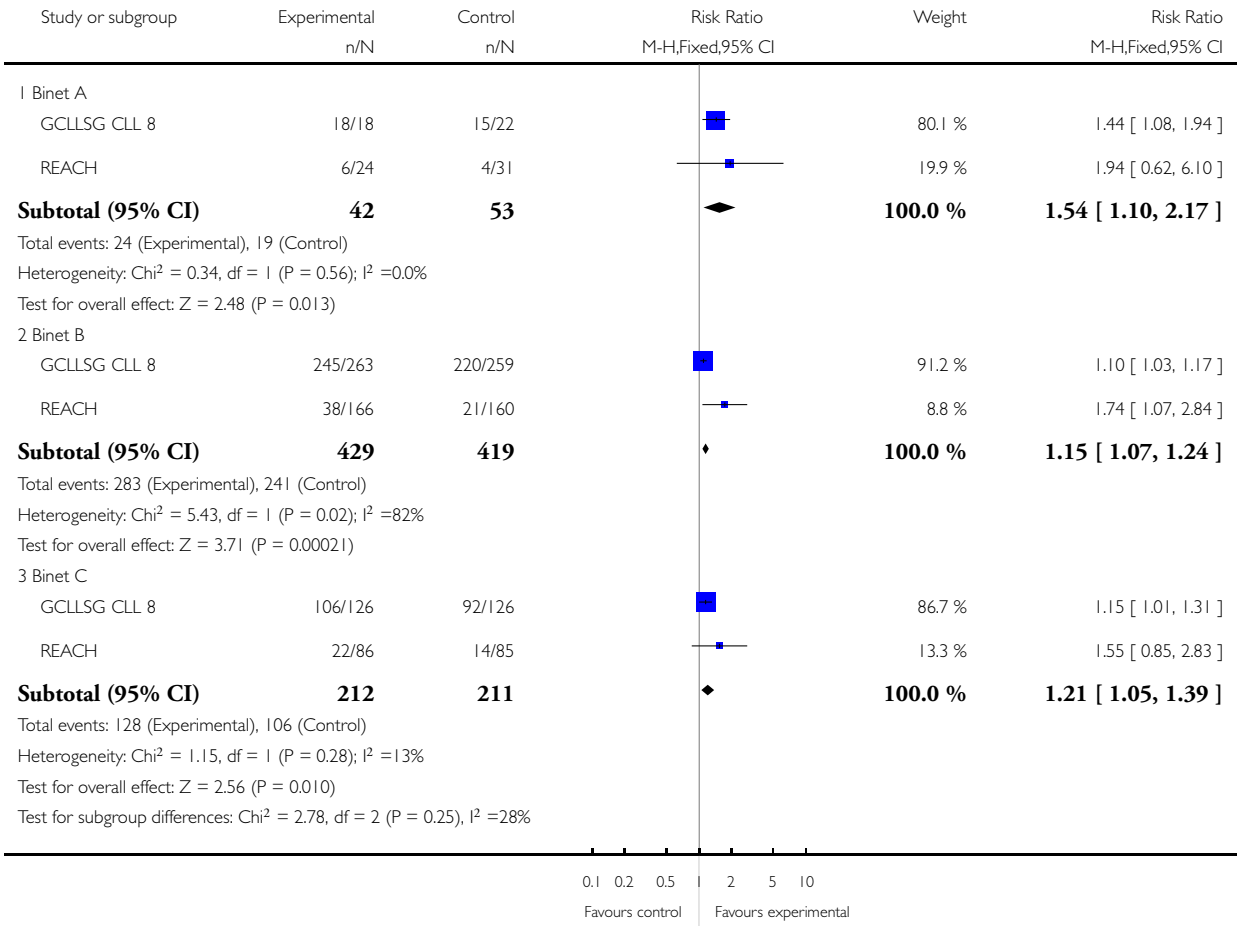


Analysis 1.14. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 14 ORR - subgrouped by stage.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 14 ORR - subgrouped by stage

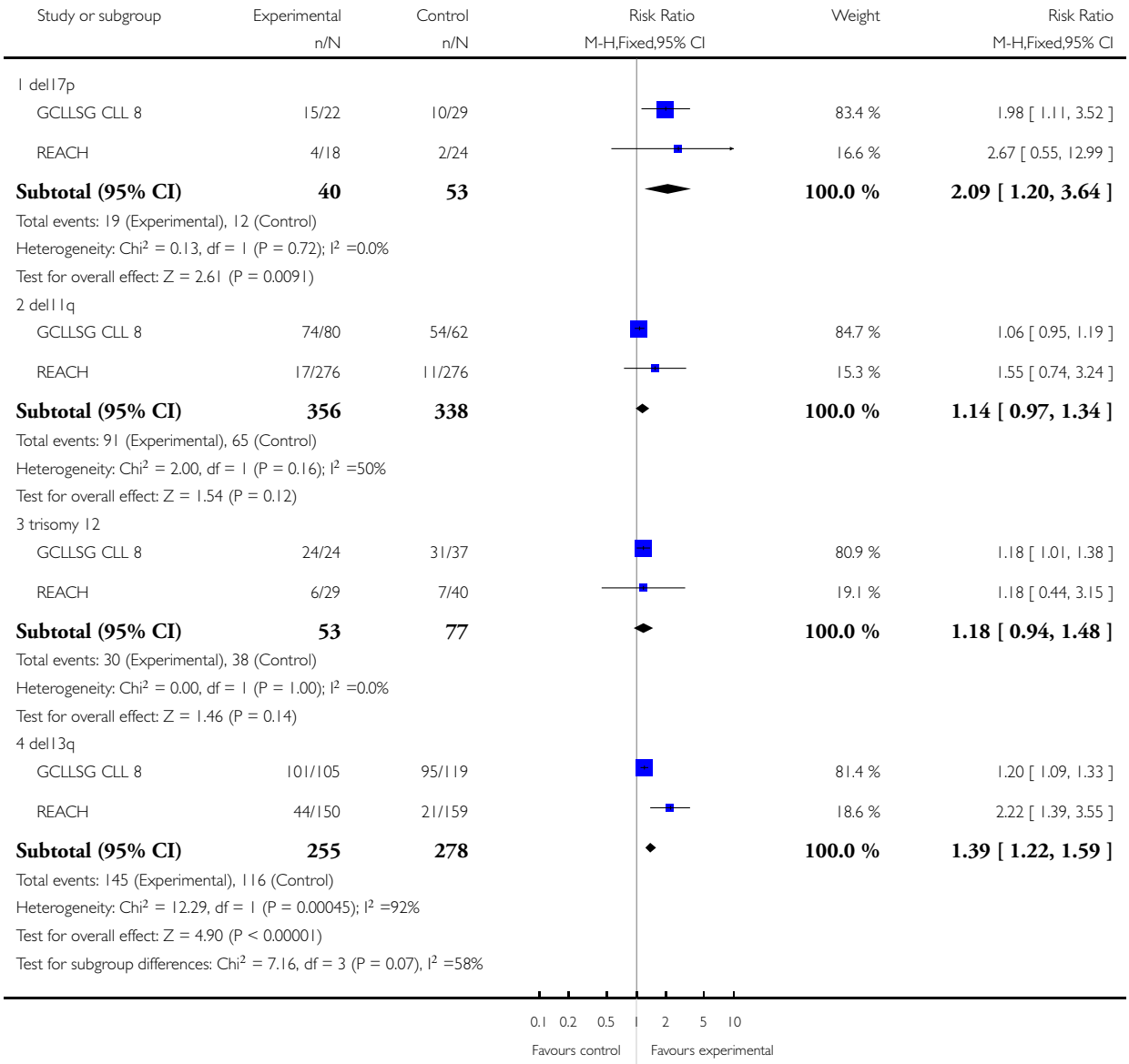


Analysis 1.15. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 15 ORR - subgrouped by prognostic factor.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 15 ORR - subgrouped by prognostic factor



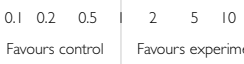
Analysis 1.16. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 16 ORR - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 16 ORR - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line treatment					
GCLLSG CLL 8	369/408	328/409		100.0 %	1.13 [1.06, 1.19]
Subtotal (95% CI)	**408**	**409**		**100.0 %**	**1.13 [1.06, 1.19]**
Total events: 369 (Experimental), 328 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.09 (P = 0.000043)					
2 previously treated					
NCRI-CLL 201	17/26	15/26		10.0 %	1.13 [0.74, 1.75]
REACH	168/276	135/276		90.0 %	1.24 [1.07, 1.45]
Subtotal (95% CI)	**302**	**302**		**100.0 %**	**1.23 [1.07, 1.43]**
Total events: 185 (Experimental), 150 (Control)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 2.84 (P = 0.0045)					
Test for subgroup differences: Chi^2 = 1.27, df = 1 (P = 0.26), I^2 =21%					



Analysis 1.17. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 17 ORR - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 17 ORR - subgrouped by different treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FluC-R versus FluC					
GCLLSG CLL 8	369/408	328/409		70.8 %	1.13 [1.06, 1.19]
REACH	168/276	135/276		29.2 %	1.24 [1.07, 1.45]
Subtotal (95% CI)	**684**	**685**		**100.0 %**	**1.16 [1.09, 1.24]**
Total events: 537 (Experimental), 463 (Control)					
Heterogeneity: Chi^2 = 1.80, df = 1 (P = 0.18); I^2 =44%					
Test for overall effect: Z = 4.80 (P < 0.00001)					
2 FluCM-R versus FluCM					
NCRI-CLL 201	17/26	15/26		100.0 %	1.13 [0.74, 1.75]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**1.13 [0.74, 1.75]**
Total events: 17 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 =0.0%					

Analysis 1.18. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 18 CRR - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 18 CRR - overall analysis

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
GCLLSG CLL 8	180/408	88/409		91.4 %	2.05 [1.65, 2.54]
NCRI-CLL 201	4/26	2/26		1.6 %	2.00 [0.40, 9.99]
REACH	25/276	8/276		7.0 %	3.13 [1.43, 6.81]
Total (95% CI)	**710**	**711**		**100.0 %**	**2.11 [1.72, 2.59]**

Total events: 209 (Experimental), 98 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.06$, df = 2 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 7.13 (P < 0.00001)

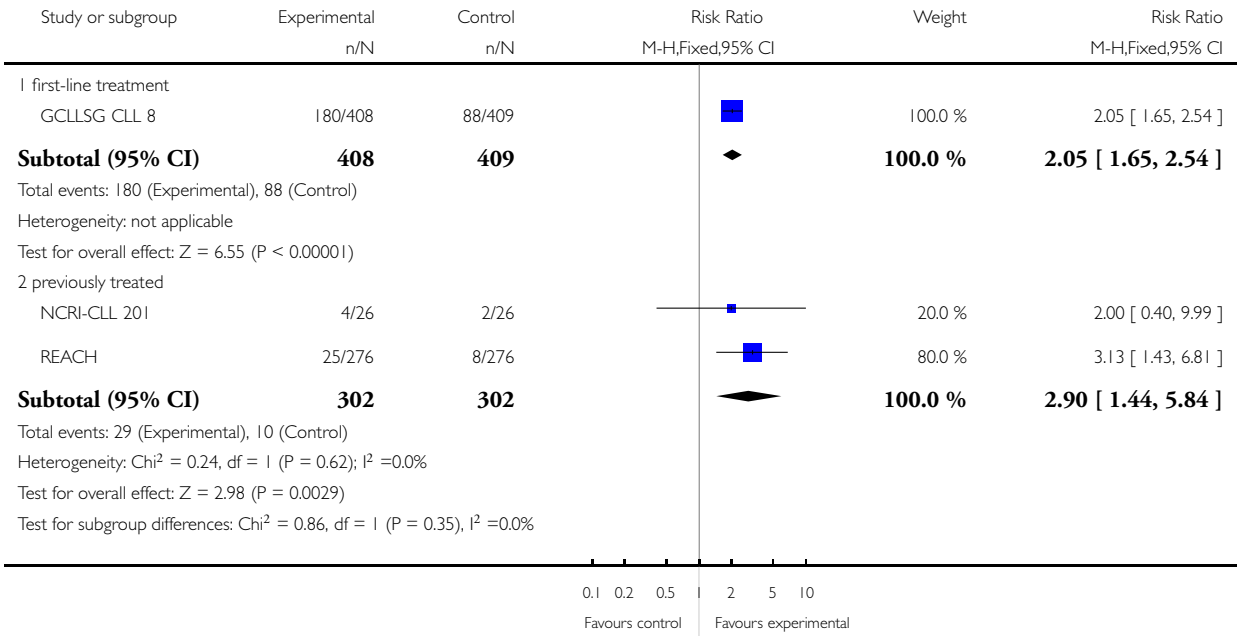
Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 19 CRR - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 19 CRR - subgrouped by different anti-CD20 antibody treatment regimens

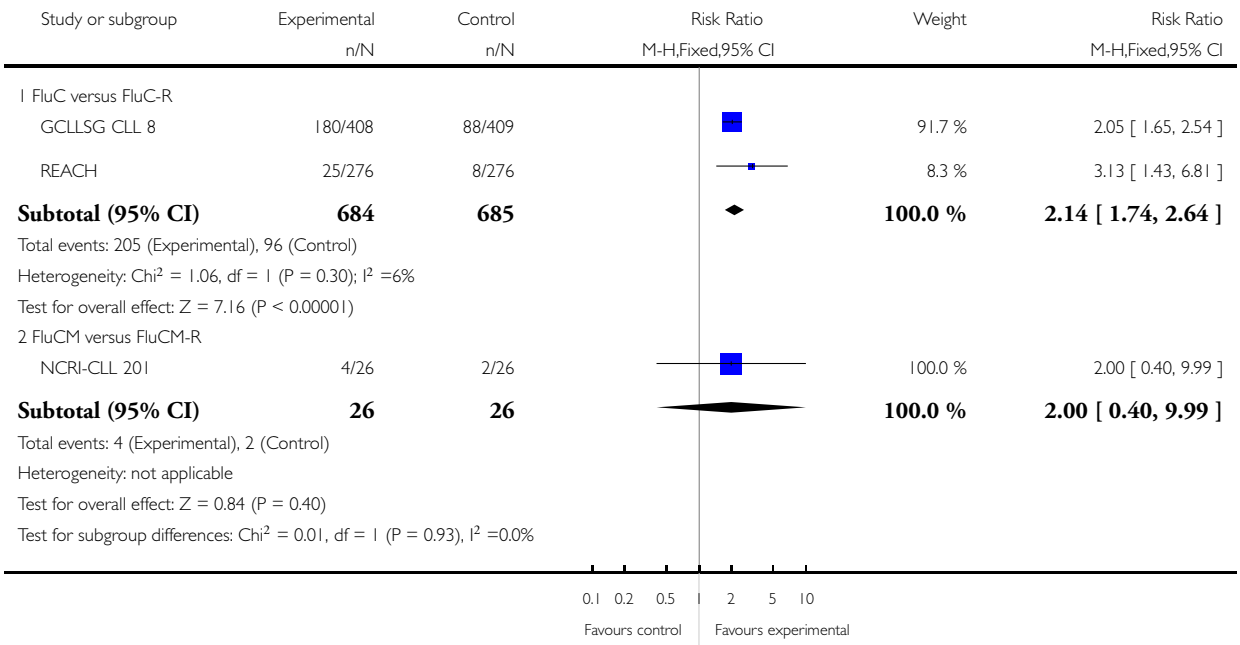


Analysis 1.20. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 20 CRR - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 20 CRR - subgrouped by different treatment regimens



Analysis 1.21. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 21 MRD negativity - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 21 MRD negativity - overall analysis

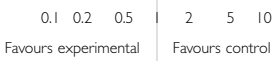
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
NCRI-CLL 201	5/26	3/26		18.6 %	1.67 [0.44, 6.26]
REACH	16/37	10/32		81.4 %	1.38 [0.73, 2.61]
Total (95% CI)	**63**	**58**		**100.0 %**	**1.43 [0.81, 2.54]**

Total events: 21 (Experimental), 13 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable



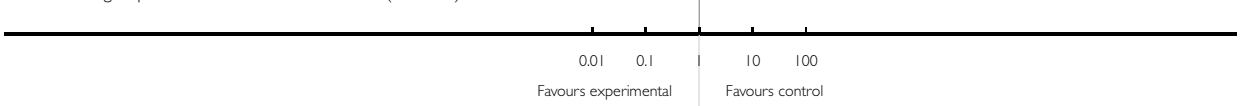
Analysis 1.22. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 22 MRD negativity - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 22 MRD negativity - subgrouped by different treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FluC versus FluC-R					
REACH	16/37	10/32		100.0 %	1.38 [0.73, 2.61]
Subtotal (95% CI)	**37**	**32**		**100.0 %**	**1.38 [0.73, 2.61]**
Total events: 16 (Experimental), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
2 FluCM versus FluCM-R					
NCRI-CLL 201	5/26	3/26		100.0 %	1.67 [0.44, 6.26]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**1.67 [0.44, 6.26]**
Total events: 5 (Experimental), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 =0.0%					

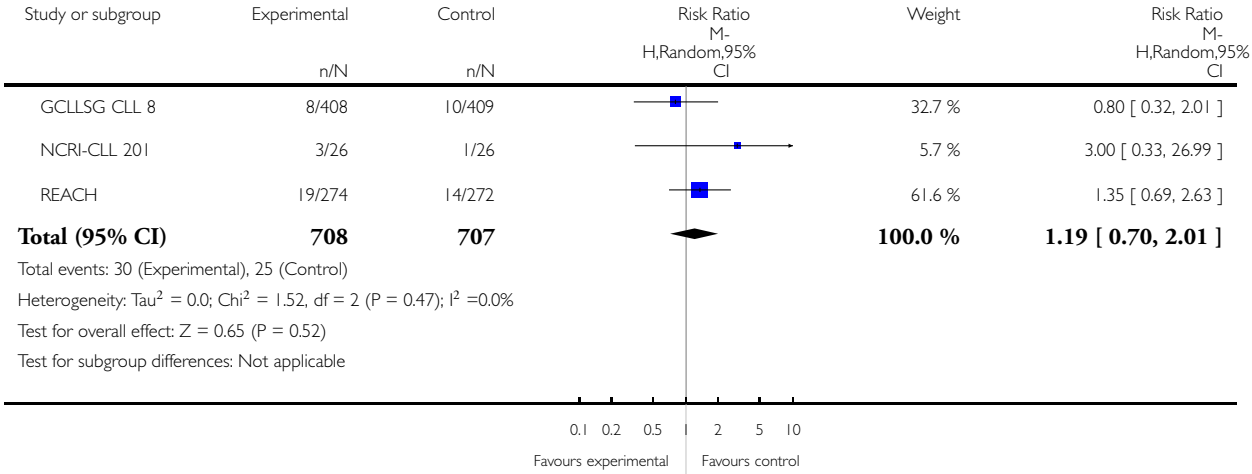


Analysis 1.23. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 23 Treatment-related mortality - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 23 Treatment-related mortality - overall analysis



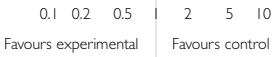
Analysis 1.24. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 24 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 24 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line treatment					
GCLLSG CLL 8	8/408	10/409		100.0 %	0.80 [0.32, 2.01]
Subtotal (95% CI)	**408**	**409**		**100.0 %**	**0.80 [0.32, 2.01]**
Total events: 8 (Experimental), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 previously treated					
NCRI-CLL 201	3/26	1/26		6.6 %	3.00 [0.33, 26.99]
REACH	19/274	14/272		93.4 %	1.35 [0.69, 2.63]
Subtotal (95% CI)	**300**	**298**		**100.0 %**	**1.46 [0.77, 2.75]**
Total events: 22 (Experimental), 15 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Chi^2 = 1.10, df = 1 (P = 0.30), I^2 =9%					

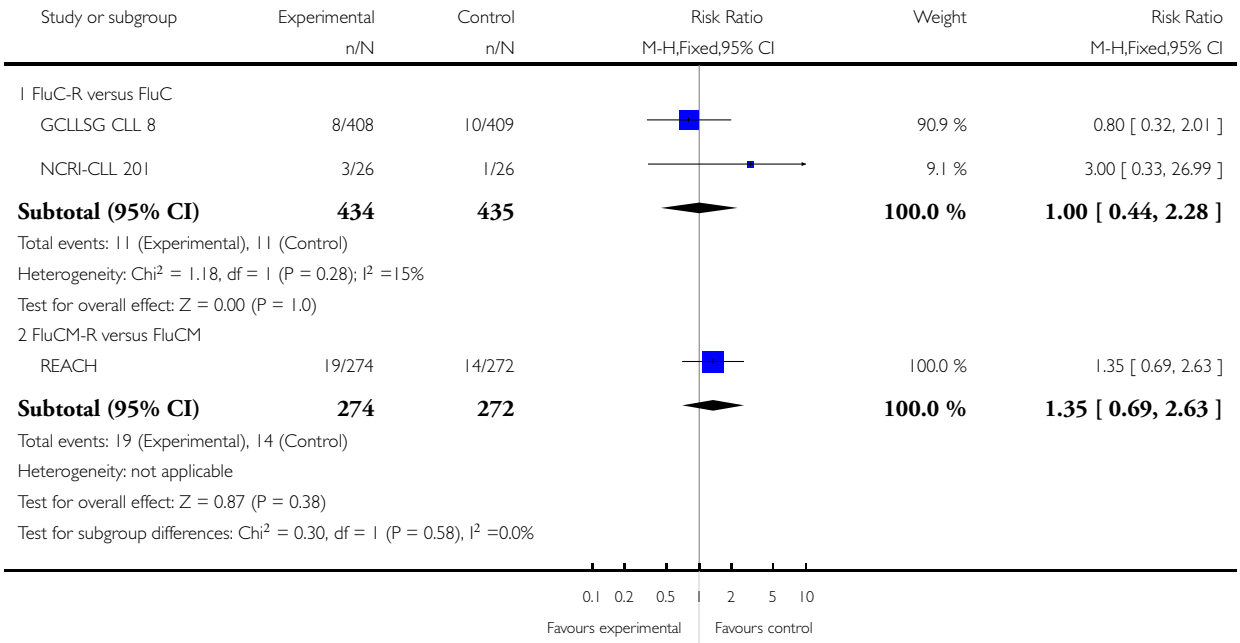


Analysis 1.25. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 25 Treatment-related mortality - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 25 Treatment-related mortality - subgrouped by different treatment regimens



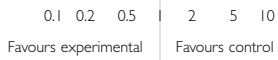
Analysis 1.26. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 26 SAEs - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 26 SAEs - overall analysis

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
NCRI-CLL 201	14/26	13/26		9.1 %	1.08 [0.64, 1.82]
REACH	137/274	130/272		90.9 %	1.05 [0.88, 1.24]
Total (95% CI)	**300**	**298**		**100.0 %**	**1.05 [0.89, 1.23]**
Total events: 151 (Experimental), 143 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					

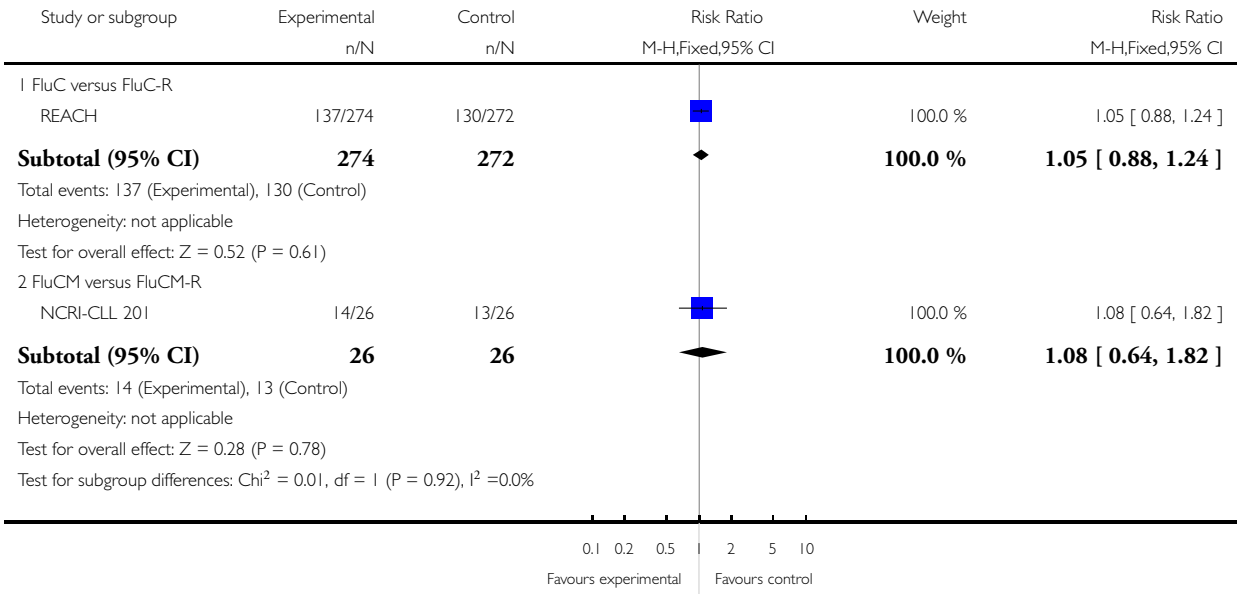


Analysis 1.27. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 27 SAEs - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 27 SAEs - subgrouped by different treatment regimens



Analysis 1.28. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 28 Grade 3/4 AEs - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 28 Grade 3/4 AEs - overall analysis

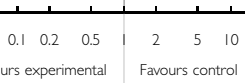
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GCLLSG CLL 8	309/404	249/396		52.9 %	1.22 [1.11, 1.33]
NCRI-CLL 201	24/26	23/26		4.8 %	1.04 [0.87, 1.25]
REACH	219/274	200/272		42.2 %	1.09 [0.99, 1.19]
Total (95% CI)	**704**	**694**		**100.0 %**	**1.15 [1.08, 1.23]**

Total events: 552 (Experimental), 472 (Control)

Heterogeneity: $Chi^2 = 4.04$, df = 2 (P = 0.13); $I^2 = 51\%$

Test for overall effect: Z = 4.38 (P = 0.000012)

Test for subgroup differences: Not applicable



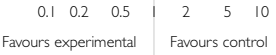
Analysis 1.29. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 29 Grade 3/4 AEs - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 29 Grade 3/4 AEs - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line treatment					
GCLLSG CLL 8	309/404	249/396		100.0 %	1.22 [1.11, 1.33]
Subtotal (95% CI)	**404**	**396**		**100.0 %**	**1.22 [1.11, 1.33]**
Total events: 309 (Experimental), 249 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.13 (P = 0.000037)					
2 previously treated					
NCRI-CLL 201	24/26	23/26		10.3 %	1.04 [0.87, 1.25]
REACH	219/274	200/272		89.7 %	1.09 [0.99, 1.19]
Subtotal (95% CI)	**300**	**298**		**100.0 %**	**1.08 [0.99, 1.18]**
Total events: 243 (Experimental), 223 (Control)					
Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.82 (P = 0.068)					
Test for subgroup differences: Chi^2 = 3.28, df = 1 (P = 0.07), I^2 =69%					



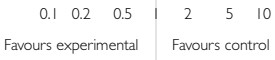
Analysis 1.30. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 30 Grade 3/4 AEs - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 30 Grade 3/4 AEs - subgrouped by different treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FluC versus FluC-R					
GCLLSG CLL 8	309/404	249/396		55.6 %	1.22 [1.11, 1.33]
REACH	219/274	200/272		44.4 %	1.09 [0.99, 1.19]
Subtotal (95% CI)	**678**	**668**		**100.0 %**	**1.16 [1.08, 1.24]**
Total events: 528 (Experimental), 449 (Control)					
Heterogeneity: Chi^2 = 2.87, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 4.36 (P = 0.000013)					
2 FluCM versus FluCM-R					
NCRI-CLL 201	24/26	23/26		100.0 %	1.04 [0.87, 1.25]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**1.04 [0.87, 1.25]**
Total events: 24 (Experimental), 23 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
Test for subgroup differences: Chi^2 = 1.18, df = 1 (P = 0.28), I^2 =15%					



Analysis 1.31. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 31 Anaemia grade 3/4 - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 31 Anaemia grade 3/4 - overall analysis

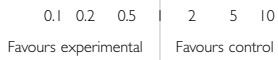
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GCLLSG CLL 8	22/404	27/396		43.7 %	0.80 [0.46, 1.38]
REACH	33/274	35/272		56.3 %	0.94 [0.60, 1.46]
Total (95% CI)	**678**	**668**		**100.0 %**	**0.88 [0.62, 1.24]**

Total events: 55 (Experimental), 62 (Control)

Heterogeneity: $Chi^2 = 0.20$, df = 1 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



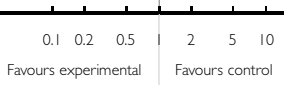
Analysis 1.32. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 32 Anaemia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 32 Anaemia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line treatment					
GCLLSG CLL 8	22/404	27/396		100.0 %	0.80 [0.46, 1.38]
Subtotal (95% CI)	**404**	**396**		**100.0 %**	**0.80 [0.46, 1.38]**
Total events: 22 (Experimental), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 previously treated					
REACH	33/274	35/272		100.0 %	0.94 [0.60, 1.46]
Subtotal (95% CI)	**274**	**272**		**100.0 %**	**0.94 [0.60, 1.46]**
Total events: 33 (Experimental), 35 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.66), I^2 =0.0%					



Analysis 1.33. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 33 Neutropenia grade 3/4 - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 33 Neutropenia grade 3/4 - overall analysis

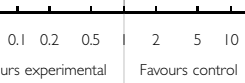
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GCLLSG CLL 8	136/404	83/396		40.6 %	1.61 [1.27, 2.03]
NCRI-CLL 201	14/26	14/26		6.8 %	1.00 [0.60, 1.65]
REACH	116/274	108/272		52.6 %	1.07 [0.87, 1.30]
Total (95% CI)	**704**	**694**		**100.0 %**	**1.28 [1.11, 1.48]**

Total events: 266 (Experimental), 205 (Control)

Heterogeneity: $Chi^2 = 7.67$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 3.30 (P = 0.00098)

Test for subgroup differences: Not applicable

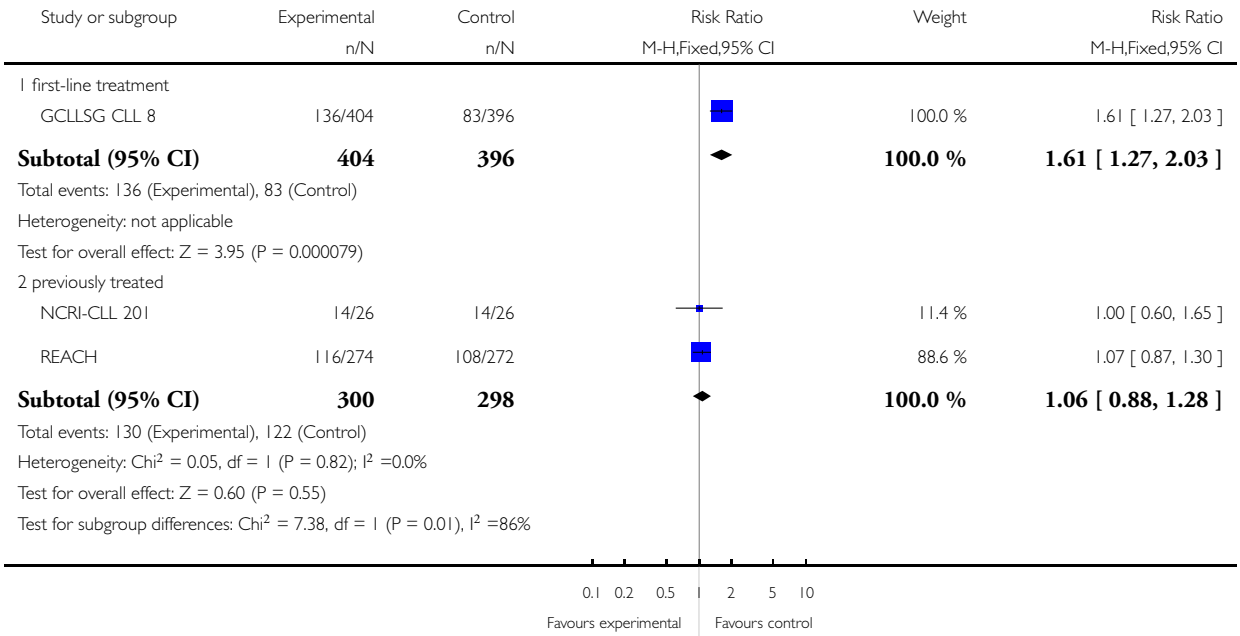


Analysis 1.34. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 34 Neutropenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 34 Neutropenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens

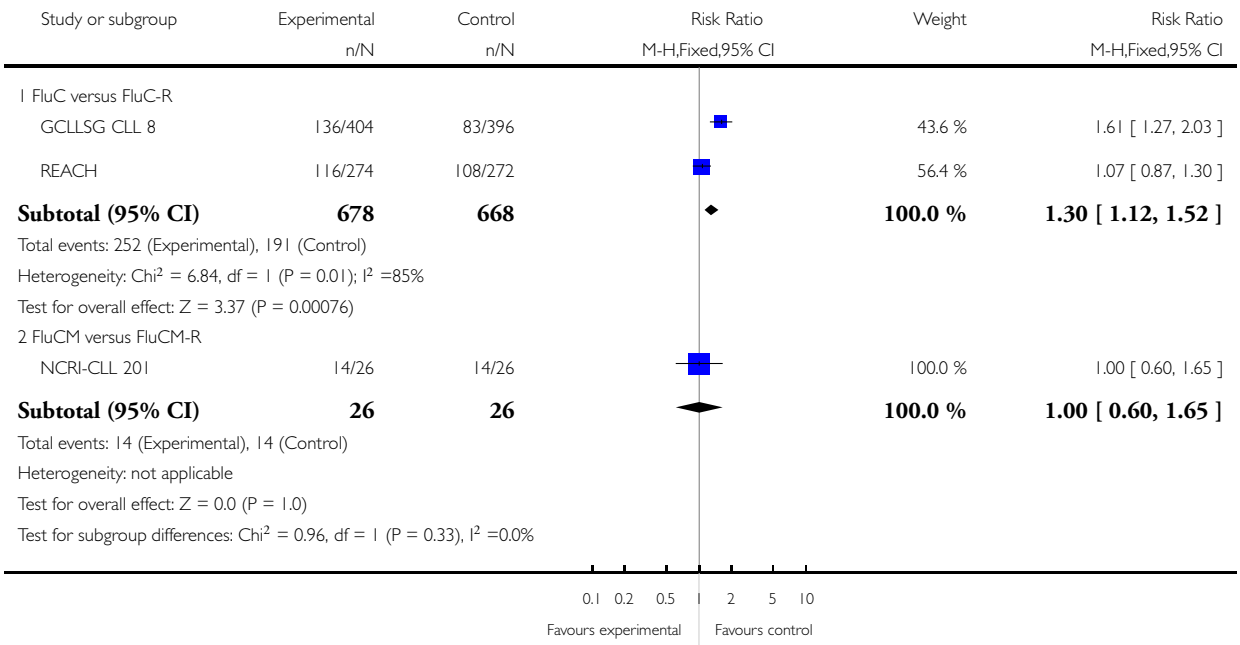


Analysis 1.35. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 35 Neutropenia grade 3/4 - subgrouped by different treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 35 Neutropenia grade 3/4 - subgrouped by different treatment regimens



Analysis 1.36. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 36 Thrombocytopenia grade 3/4 - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 36 Thrombocytopenia grade 3/4 - overall analysis

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GCLLSG CLL 8	30/404	44/396		64.8 %	0.67 [0.43, 1.04]
REACH	29/274	24/272		35.2 %	1.20 [0.72, 2.01]
Total (95% CI)	**678**	**668**		**100.0 %**	**0.86 [0.61, 1.19]**
Total events: 59 (Experimental), 68 (Control)					
Heterogeneity: Chi^2 = 2.85, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 0.92 (P = 0.36)					
Test for subgroup differences: Not applicable					

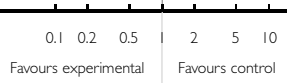
Analysis 1.37. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 37 Thrombocytopenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Outcome: 37 Thrombocytopenia grade 3/4 - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line treatment					
GCLLSG CLL 8	30/404	44/396		100.0 %	0.67 [0.43, 1.04]
Subtotal (95% CI)	**404**	**396**		**100.0 %**	**0.67 [0.43, 1.04]**
Total events: 30 (Experimental), 44 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.78 (P = 0.075)					
2 previously treated					
REACH	29/274	24/272		100.0 %	1.20 [0.72, 2.01]
Subtotal (95% CI)	**274**	**272**		**100.0 %**	**1.20 [0.72, 2.01]**
Total events: 29 (Experimental), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi^2 = 2.85, df = 1 (P = 0.09), I^2 =65%					



Analysis 2.1. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 1 ORR - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 1 ORR - overall analysis

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CLL2007FMP	73/83	70/82		94.9 %	1.03 [0.91, 1.16]
Gribben 2005	3/7	3/4		5.1 %	0.57 [0.20, 1.59]
Total (95% CI)	**90**	**86**		**100.0 %**	**1.01 [0.89, 1.14]**

Total events: 76 (Experimental), 73 (Control)

Heterogeneity: $Chi^2 = 1.31$, df = 1 (P = 0.25); $I^2 = 24\%$

Test for overall effect: Z = 0.11 (P = 0.91)

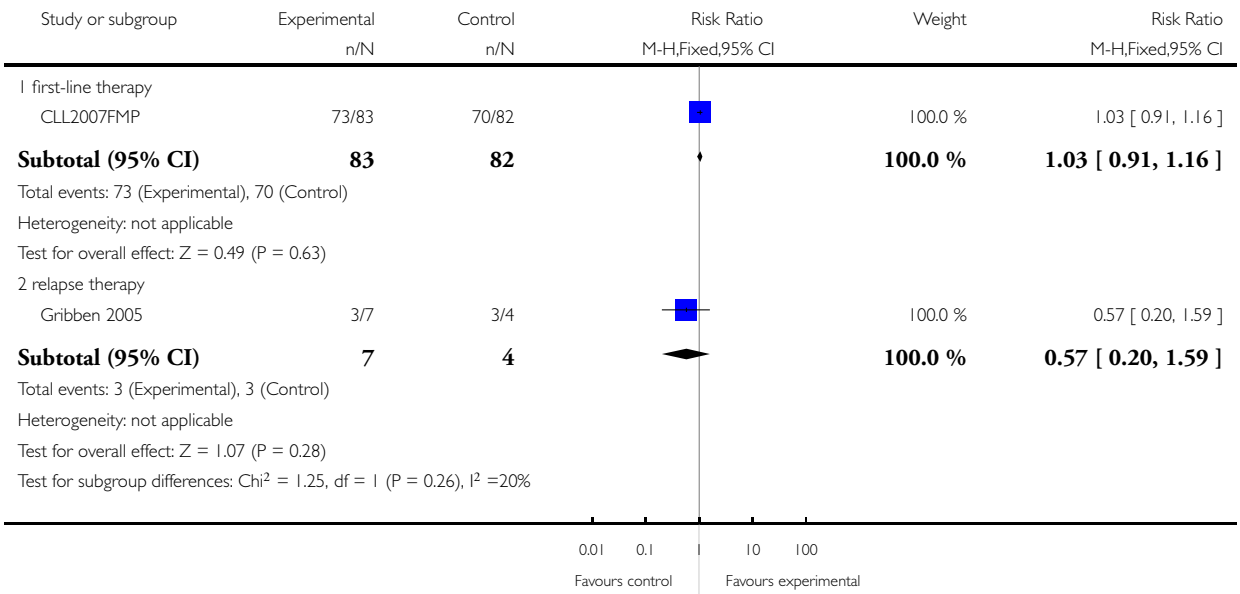
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 2 ORR - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 2 ORR - subgrouped by different anti-CD20 antibody treatment regimens



Analysis 2.3. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 3 CRR - overall analysis.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 3 CRR - overall analysis

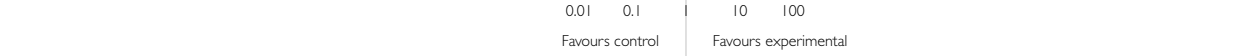
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CLL2007FMP	54/83	42/82		94.3 %	1.27 [0.98, 1.65]
Gribben 2005	1/7	2/4		5.7 %	0.29 [0.04, 2.25]
Total (95% CI)	**90**	**86**		**100.0 %**	**1.21 [0.94, 1.58]**

Total events: 55 (Experimental), 44 (Control)

Heterogeneity: $Chi^2 = 2.00$, df = 1 (P = 0.16); $I^2 = 50\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable



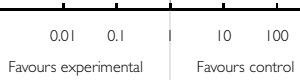
Analysis 2.4. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 4 CRR - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 4 CRR - subgrouped by different anti-CD20 antibody treatment regimens

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 first-line therapy					
CLL2007FMP	54/83	42/82		100.0 %	1.27 [0.98, 1.65]
Subtotal (95% CI)	**83**	**82**		**100.0 %**	**1.27 [0.98, 1.65]**
Total events: 54 (Experimental), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.78 (P = 0.075)					
2 relapse therapy					
Gribben 2005	1/7	2/4		100.0 %	0.29 [0.04, 2.25]
Subtotal (95% CI)	**7**	**4**		**100.0 %**	**0.29 [0.04, 2.25]**
Total events: 1 (Experimental), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.23)					
Test for subgroup differences: Chi^2 = 1.98, df = 1 (P = 0.16), I^2 =49%					



Analysis 2.5. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 5 Treatment-related mortality.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 5 Treatment-related mortality

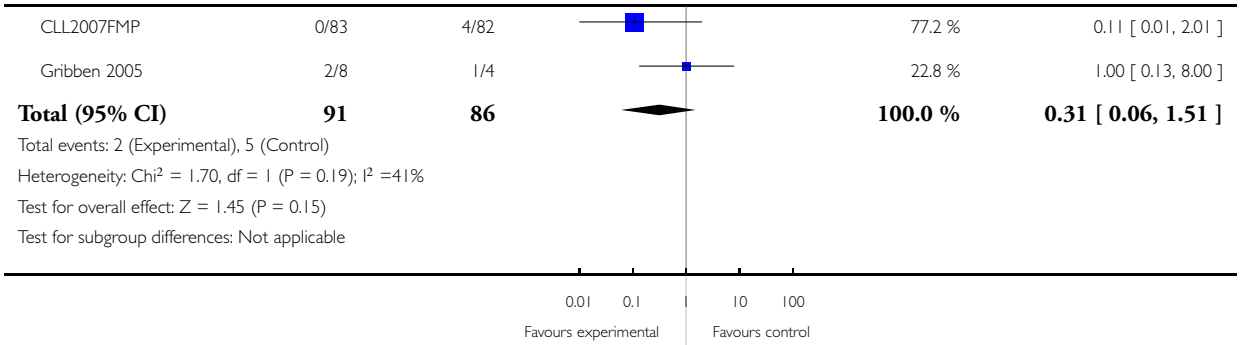
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CLL2007FMP	0/83	4/82		77.2 %	0.11 [0.01, 2.01]
Gribben 2005	2/8	1/4		22.8 %	1.00 [0.13, 8.00]
Total (95% CI)	**91**	**86**		**100.0 %**	**0.31 [0.06, 1.51]**

Total events: 2 (Experimental), 5 (Control)

Heterogeneity: Chi^2 = 1.70, df = 1 (P = 0.19); I^2 =41%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

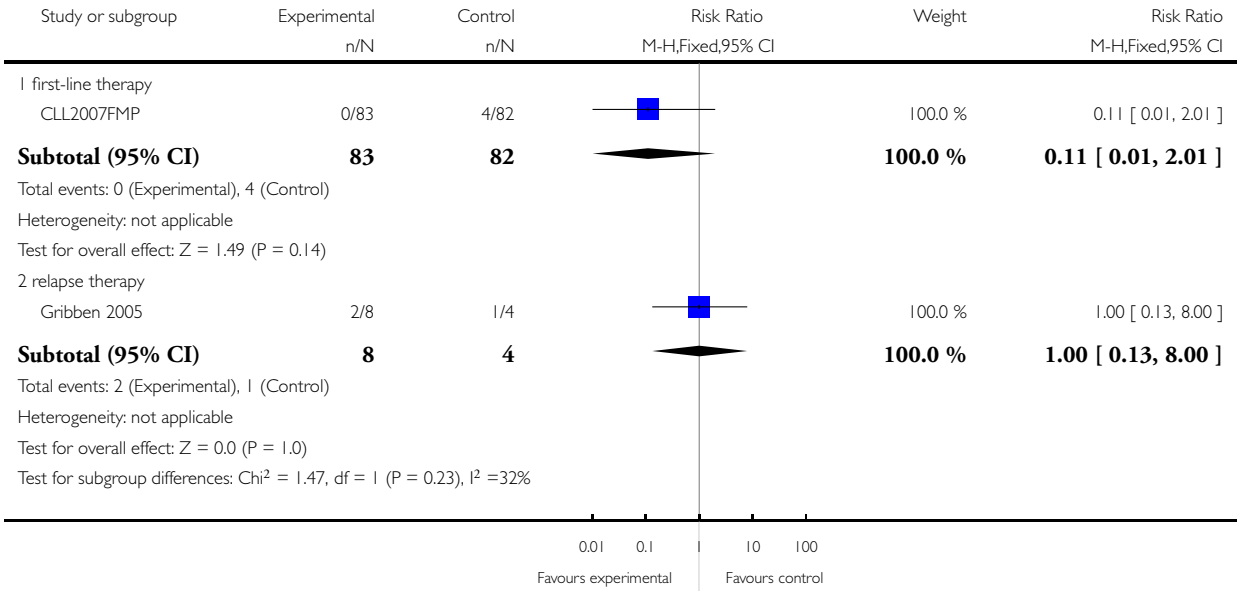


Analysis 2.6. Comparison 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups), Outcome 6 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

Comparison: 2 Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)

Outcome: 6 Treatment-related mortality - subgrouped by different anti-CD20 antibody treatment regimens



ADDITIONAL TABLES

Table 1. Overall survival subgroup results reported by GCLLSG CLL8

Grouped by	Subgroup	Experimental arm (N)	Control arm (N)	Hazard ratio (95% CI)
Age				
	< 65 years	282	290	0·68 (0.46 to 1.02)
	≥ 65 years	126	119	0.63 (0.37 to 1.10)
Stage				
	Binet A	18	22	0.19 (0.02 to 1.61)

Table 1. Overall survival subgroup results reported by GCLLSG CLL8 (*Continued*)

	Binet B	263	259	0.45 (0.30 to 0.69)
	Binet C	126	126	1.48 (0.84 to 2.62)
Prognostic factors				
	del17p	22	29	0.66 (0.32 to 1.36)
	del11q	84	69	0.42 (0.18 to 0.97)
	trisomy 12	30	44	0.23 (0.03 to 1.94)
	del13q	168	182	0.30 (0.13 to 0.71)
	no abnormalities	not reported	not reported	1.56 (0.67 to 3.64)

Table 2. Complete response rate subgroup results reported by GCLLSG CLL8

Grouped by	Subgroup	Experimental arm N (%)	Control arm N (%)	Relative risk (95% CI)
Age				
	< 65 years	126/282 (45)	59/290 (20)	8.10 (4.94 to 13.27)
	≥ 65 years	54/126 (43)	29/119 (24)	4.29 (2.87 to 6.39)
Stage				
	Binet A	18/18 (100)	6/22 (27)	3.45 (1.79 to 6.63)
	Binet B	124/263 (47)	66/259 (25)	0.47 (0.42 to 0.54)
	Binet C	43/126 (34)	16/126 (13)	0.34 (0.27 to 0.44)
Prognostic factors				
	del17p	1/22 (5)	0/29 (0)	3.91 (0.17 to 91.7)
	del11q	41/84 (49)	9/69 (13)	3.74 (1.96 to 7.15)
	trisomy 12	17/24 (71)	7/37 (19)	3.74 (1.83 to 7.65)
	del13q	50/105 (48)	27/119 (23)	0.71 (0.41 to 1.23)
	no abnormalities	28/80 (35)	16/58 (28)	0.75 (0.5 to 1.13)

Table 3. Adverse events (reported by one trial)

Name of trial	Adverse event	Experimental arm (N)	Control arm (N)
GCLLSG CLL 8			
	Cytokine release syndrome grade 3/4	1/404	0/396
	Haematological toxicity grade 3/4	225/404	157/396
	Leukocytopenia grade 3/4	97/404	48/396
	Tumour lysis syndrome grade 3/4	1/404	2/396
	Autoimmune haemolytic anaemia	22/404	27/396
	Infection	103/404	85/396
REACH			
	Febrile neutropenia grade 3/4	33/274	32/272
	Granulocytopenia grade 3/4	18/274	12/272
	Hepatitis B grade 3/4	0/274	5/272
	Pancytopenia grade 3/4	9/274	13/272
	Pneumonia	15/274	17/272

Table 4. Adverse events (dose or time schedule)

Name of trial	Adverse event	Experimental arm (N)	Control arm (N)
CALGB 9712			
	Anaemia grade 3/4	2/51	0/53
	Autoimmune haemolytic anaemia	0/51	1/53
	Chills grade 3/4	0/51	0/53
	Dyspnoea grade 3/4	7/51	3/53
	Fatigue/malaise grade 3/4	0/51	2/53
	Fever grade 3/4	0/51	0/53

Table 4. Adverse events (dose or time schedule) (*Continued*)

	Hypotension grade 3/4	3/51	0/53
	Infections	10/51	12/53
	Myalgias grade 3/4	0/51	0/53
	Nausea grade 3/4	0/51	1/53
	Neurotoxicity	1/51	1/53
	Neutropenia grade 3/4	39/51	21/53
	Thrombocytopenia grade 3/4	10/51	5/53
	Vomiting grade 3/4	0/51	0/53
Wierda 2009			
During treatment and up to 30 days following the last dose		FCO500	FCO1000
	Infections grade 3/4	4/31	7/30
	Febrile neutropenia grade 3/4	3/31	3/30
	Neutropenia	11/31	18/30
	Anaemia	2/31	6/30
	Thrombocytopenia	2/31	7/30
	Haemolytic anaemia grade 3/4	2/31	1/30

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

Searches (1990 to March 2009)

1. exp Leukemia, B-Cell/
2. exp Leukemia, Lymphocytic, Chronic, B-Cell/
3. ((leuk?em$ or leu?em$ or lymph$) adj (lymphocyt$ or lymphoblast$ or linfoid$ or b-cell$)).tw,kf,ot.
4. (chronic$ or cronic$ or chroniq$ or well-differential$).tw,kf,ot. (589526)
5. 3 and 4
6. (lymphom$ and (small cell$ or small-cell$)).tw,kf,ot.
7. (lymphom$ adj2 lymphocyt$).tw,kf,ot.
8. lymphoplasma?ytoid.tw,kf,ot.
9. cll.tw.
10. sll.tw.
11. or/6-10
12. 1 or 2 or 5 or 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. humans.sh.
23. 21 and 22
24. 12 and 23

Searches (update March 2009 to January 2012)

1. exp LEUKEMIA, B-CELL/
2. exp LEUKEMIA, LYMPHOCYTIC, CHRONIC, B-CELL/
3. ((leuk?em$ or leu?em$ or lymph$) adj (lymphocyt$ or lymphoblast$ or linfoid$ or b-cell$)).tw,kf,ot.
4. (chronic$ or cronic$ or chroniq$ or well-differential$).tw,kf,ot.
5. 3 and 4
6. (lymphom$ and (small cell$ or small-cell$)).tw,kf,ot.
7. (lymphom$ adj2 lymphocyt$).tw,kf,ot.
8. lymphoplasma?ytoid.tw,kf,ot.
9. cll.tw.
10. sll.tw.
11. or/6-10
12. 1 or 2 or 5 or 11
13. exp ANTIBODIES, MONOCLONAL/
14. (antibod$ adj2 monoclonal$).tw,kf,ot.
15. mabt$.tw,kf,ot,nm.
16. ritux$.tw,kf,ot,nm.
17. exp ANTIGENS, CD20/
18. ((CD20 or CD-20 or CD 20) adj3 antibod$).tw,kf,ot,nm.
19. (ANTI-CD20 or ANTI CD20).tw,kf,ot,nm.
20. (ANTICD20 or ANTI-CD-20 or ANTICD-20).tw,kf,ot,nm.
21. (IDEC-c2b8 or IDECc2b8).tw,kf,ot,nm.
22. idec$.tw,kf,ot,nm.
23. ofatumumab$.tw,kf,ot,nm.

24. arzerr$.tw,kf,ot.
25. 13 or 14
26. or/15-24
27. 12 and 26
28. 12 and (25 or 26)
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized.ab.
32. placebo.ab.
33. drug therapy.fs.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. or/29-36
38. humans.sh.
39. 37 and 38
40. 28 and 39

Appendix 2. EMBASE search strategy

Searches (1990 to March 2009)

1. exp B CELL LEUKEMIA/
2. exp CHRONIC LYMPHATIC LEUKEMIA/
3. ((leuk?em$ or leu?em$ or lymph$) adj (lymphocyt$ or lymphoblast$ or linfoid$ or b-cell$)).tw.
4. (chronic$ or cronic$ or chroniq$ or well-differential$).tw.
5. 3 and 4
6. (lymphom$ and (small cell$ or small-cell$)).tw.
7. (lymphom$ adj2 lymphocyt$).tw.
8. lymphoplasma?ytoid.tw.
9. cll.tw.
10. sll.tw.
11. or/6-10
12. 1 or 2 or 5 or 11
13. (random$ or placebo$).ti,ab.
14. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
15. controlled clinical trial$.ti,ab.
16. RETRACTED ARTICLE/
17. or/13-16
18. (animal$ not human$).sh,hw.
19. 17 not 18
20. 12 and 19

Appendix 3. CENTRAL search strategy

Searches (1990 to March 2009)

1. MeSH descriptor Leukemia, B-Cell explode all trees
2. MeSH descriptor Leukemia, Lymphocytic, Chronic, B-Cell explode all trees
3. (leu*em* NEAR/ lymphocyt*) or (leu*em* NEAR/ lymphoblast*) or (leu*em* NEAR/ linfoid*) or (leu*em* NEAR/ b-cell*)
4. (leu*em* NEAR/ lymphocyt*) or (leu*em* NEAR/ lymphoblast*) or (leu*em* NEAR/ linfoid*) or (leu*em* NEAR/ b-cell*)
5. (lymph* NEAR/ lymphocyt*) or (lymph* NEAR/ lymphoblast*) or (lymph* NEAR/ linfoid*) or (lymph* NEAR/ b-cell*)
6. (chronic*) or (cronic*) or (chroniq*) or (well-differential*)
7. (#6 AND (#3 OR #4 OR #5))
8. (lymphom*) and (small cell* or small-cell*)
9. (lymphom* NEAR/2 lymphocyt*)
10. (lymphoplasma*ytoid*)
11. (cll or sll)
12. (#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11)

Searches (update March 2009 to January 2012)

1. MeSH descriptor Leukemia, B-Cell explode all trees
2. MeSH descriptor Leukemia, Lymphocytic, Chronic, B-Cell explode all trees
3. (leu*em* NEAR/ lymphocyt*) or (leu*em* NEAR/ lymphoblast*) or (leu*em* NEAR/ linfoid*) or (leu*em* NEAR/ b-cell*)
4. (leu*em* NEAR/ lymphocyt*) or (leu*em* NEAR/ lymphoblast*) or (leu*em* NEAR/ linfoid*) or (leu*em* NEAR/ b-cell*)
5. (lymph* NEAR/ lymphocyt*) or (lymph* NEAR/ lymphoblast*) or (lymph* NEAR/ linfoid*) or (lymph* NEAR/ b-cell*)
6. (chronic*) or (cronic*) or (chroniq*) or (well-differential*)
7. (#6 AND (#3 OR #4 OR #5))
8. (lymphom*) and (small cell* or small-cell*)
9. (lymphom* NEAR/2 lymphocyt*)
10. (lymphoplasma*ytoid*)
11. (cll or sll)
12. (#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11)
13. MeSH descriptor Antibodies, Monoclonal explode all trees
14. (antibod* NEAR/2 monoclonal*)
15. (mabt*)
16. (ritux*)
17. MeSH descriptor Antigens, CD20 explode all trees
18. (CD20 NEAR/3 antibod*) or (CD-20 NEAR/3 antibod*) or (CD 20 NEAR/3 antibod*)
19. (ANTI-CD20 or ANTI CD20)
20. (ANTICD20 or ANTI-CD-20 or ANTICD-20)
21. (IDEC-c2b8 or IDECc2b8)
22. (idec*)
23. (ofatumumab*)
24. (arzerr*)
25. (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
26. (#12 AND #25)

CONTRIBUTIONS OF AUTHORS

Kathrin Bauer (KB): data selection, data extraction, and wrote the first and final draft of the review.

Michaela Rancea (MR): data selection, data extraction, proofread, and commented on the first and final draft.

Thomas Elter (TE): provided clinical expertise, proofread, and commented on the first and final draft.

Nicole Skoetz (NS): methodological expertise, proofread, and commented on first and final draft of the review.

Andreas Engert (AE): provided clinical expertise, proofread, and commented on the first and final draft.

Verena Roloff (VR): methodological expertise, proofread, and commented on first and final draft of the review.

Michael Hallek (MH): provided clinical expertise, proofread, and commented on the first and final draft.

DECLARATIONS OF INTEREST

KB, MR, AE and NS: none known.

TE is a member of the German CLL Study Group and received a grant, honoraria and travel/accommodation/meeting expenses from Bayer Schering AG, Genzyme AG, and Mundipharma for presenting CLL-related data.

MH: has conducted several trials in this field (e.g. GCLLSG CLL8). MH received consultancy fees (Bayer Schering AG, Genzyme AG), payment for lectures (Bayer Schering AG) and research funding (Bayer Schering AG).

VR completed a four-month paid internship at Novartis, working on a general statistical methods project as part of her doctoral training.

SOURCES OF SUPPORT

Internal sources

- Köln Fortune, Germany, Not specified.

Funding programme “Köln Fortune”, Medical Faculty University of Cologne
VR was supported by a UK Medical Research Council studentship.

External sources

- BMBF, Germany, Not specified.

Project grant application NO 01KG0918, Federal Ministry of Education and Research (BMBF)

INDEX TERMS

Medical Subject Headings (MeSH)

Alemtuzumab; Antibodies, Monoclonal [adverse effects; therapeutic use]; Antibodies, Monoclonal, Humanized [adverse effects; therapeutic use]; Antibodies, Monoclonal, Murine-Derived [adverse effects; therapeutic use]; Antineoplastic Agents [adverse effects; *therapeutic use]; Leukemia, Lymphocytic, Chronic, B-Cell [*drug therapy]; Randomized Controlled Trials as Topic; Rituximab; Vidarabine [analogs & derivatives; therapeutic use]

MeSH check words

Humans