Cochrane Library

Cochrane Database of Systematic Reviews

Alemtuzumab for patients with chronic lymphocytic leukaemia (Review)

Skoetz N, Bauer K, Elter T, Monsef I, Roloff V, Hallek M, Engert A

Skoetz N, Bauer K, Elter T, Monsef I, Roloff V, Hallek M, Engert A.
Alemtuzumab for patients with chronic lymphocytic leukaemia.
Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008078.
DOI: 10.1002/14651858.CD008078.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 6
OBJECTIVES 7
METHODS 7
RESULTS 9
Figure 1. 10
Figure 2. 12
Figure 3. 13
DISCUSSION 17
AUTHORS' CONCLUSIONS 18
ACKNOWLEDGEMENTS 18
REFERENCES 19
CHARACTERISTICS OF STUDIES 23
DATA AND ANALYSES 43
Analysis 1.1. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 1 PFS - overall analysis. 47
Analysis 1.2. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 2 PFS - subgrouped by treatment regimens. 47
Analysis 1.3. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 3 PFS - subgrouped by starting point of alemtuzumab. 48
Analysis 1.4. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 4 Treatment related mortality. 48
Analysis 1.5. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 5 ORR - overall analysis. 48
Analysis 1.6. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 6 ORR - subgrouped by treatment regimens. 49
Analysis 1.7. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 7 ORR - subgrouped by starting point of alemtuzumab. 49
Analysis 1.8. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 8 CRR - overall analysis. 50
Analysis 1.9. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 9 CRR - subgrouped by treatment regimens. 50
Analysis 1.10. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 10 CRR - subgrouped by starting point of alemtuzumab. 50
Analysis 1.11. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 11 CMV reactivation - overall analysis. 51
Analysis 1.12. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 12 CMV reactivation - subgrouped by treatment regimens. 51
Analysis 1.13. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 13 CMV reactivation - subgrouped by starting point of alemtuzumab. 52
Analysis 1.14. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 14 Infections (all grades) - overall analysis. 52
Analysis 1.15. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 15 Infections (all grades) - subgrouped by treatment regimens. 53
Analysis 1.16. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 16 Infections (all grades) - subgrouped by starting point of alemtuzumab. 53
Analysis 1.17. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 17 Anaemia grade 3/4 - overall analysis. 54
Analysis 1.18. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 18 Anaemia grade 3/4 - subgrouped by treatment regimens. 54

Analysis 1.19. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 19 Anaemia grade 3/4 - subgrouped by starting point of alemtuzumab. 54
Analysis 1.20. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 20 Neutropenia grade 3/4 - overall analysis. 55
Analysis 1.21. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 21 Neutropenia grade 3/4 - subgrouped by treatment regimens. 55
Analysis 1.22. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 22 Neutropenia grade 3/4 - subgrouped by starting point of alemtuzumab. 56
Analysis 1.23. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 23 Thrombocytopenia grade 3/4 - overall analysis. 56
Analysis 1.24. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 24 Thrombocytopenia grade 3/4 - subgrouped by treatment regimens. 56
Analysis 1.25. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 25 Thrombocytopenia grade 3/4 - subgrouped by starting point of alemtuzumab. 57
Analysis 1.26. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 26 SAEs - overall analysis. 57
Analysis 1.27. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 27 SAEs - subgrouped by treatment regimens. 58
Analysis 1.28. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 28 SAEs - subgrouped by starting point of alemtuzumab. 58
Analysis 2.1. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 1 Treament related mortality. 59
Analysis 2.2. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 2 Treatment related mortality - subgrouped by alemtuzumab treatment regiment. 60
Analysis 2.3. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 3 ORR - overall analysis. 60
Analysis 2.4. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 4 ORR - subgrouped by alemtuzumab treatment regimen. 60
Analysis 2.5. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 5 CRR - overall analysis. 61
Analysis 2.6. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 6 CRR - subgrouped by alemtuzumab treatment regimens. 61
ADDITIONAL TABLES 62
APPENDICES 63
CONTRIBUTIONS OF AUTHORS 66
DECLARATIONS OF INTEREST 67
SOURCES OF SUPPORT 67
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 67
INDEX TERMS 67

[Intervention Review]

Alemtuzumab for patients with chronic lymphocytic leukaemia

Nicole Skoetz[1], Kathrin Bauer[1], Thomas Elter[2], Ina Monsef[1], Verena Roloff[3], Michael Hallek[2], Andreas Engert[1]

[1]Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany. [2]Department I of Internal Medicine, Center of Integrated Oncology Köln Bonn, University Hospital of Cologne, Cologne, Germany. [3]MRC Biostatistics Unit, Cambridge, UK

Contact: Nicole Skoetz, Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Kerpener Str. 62, Cologne, 50924, Germany. nicole.skoetz@uk-koeln.de.

Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 2, 2012.

Citation: Skoetz N, Bauer K, Elter T, Monsef I, Roloff V, Hallek M, Engert A. Alemtuzumab for patients with chronic lymphocytic leukaemia. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008078. DOI: 10.1002/14651858.CD008078.pub2.

ABSTRACT

Background

Chronic lymphocytic leukaemia (CLL) accounts for 25% of all leukaemias and is the most common lymphoid malignancy in Western countries. Standard treatment includes mono- or poly-chemotherapies. Nowadays, monoclonal antibodies are added, especially alemtuzumab and rituximab. However, the impact of these agents remains unclear, as there are hints of an increased risk of severe infections.

Objectives

To assess alemtuzumab compared with no further therapy, or with other anti-leukaemic therapy in patients with CLL.

Search methods

We searched CENTRAL and MEDLINE (from January 1985 to November 2011), and EMBASE (from 1990 to 2009) as well as conference proceedings for randomised controlled trials (RCTs). Two review authors (KB, NS) independently screened search results.

Selection criteria

We included RCTs comparing alemtuzumab with no further therapy or comparing alemtuzumab with anti-leukaemic therapy such as chemotherapy or monoclonal antibodies in patients with histologically-confirmed B-cell CLL. Both pretreated and chemotherapy-naive patients were included.

Data collection and analysis

We used hazard ratios (HR) as an effect measure for overall survival (OS) and progression-free survival (PFS) and risk ratios (RRs) for response rates, treatment-related mortality (TRM) and adverse events. Two review authors independently extracted data and assessed the quality of trials.

Main results

Our search strategies led to 1542 potentially relevant references. Of these, we included five RCTs involving 845 patients. Overall, we judged the quality of the five trials as moderate. All trials were reported as 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. Because of the small number of studies in each analysis (two), the quantification of heterogeneity was not reliable.

Two trials (N = 356) assessed the efficacy of alemtuzumab compared with no further therapy. One trial (N = 335), reported a statistically significant OS advantage for all patients receiving alemtuzumab (HR 0.65 (95% confidence interval (CI) 0.45 to 0.94; P = 0.021). However,

no improvement was seen for the subgroup of patients in Rai stage I or II (HR 1.07; 95% CI 0.62 to 1.84; P = 0.82). In both trials, the complete response rate (CRR) (RR 2.61; 95% CI 1.26 to 5.42; P = 0.01) and PFS (HR 0.58; 95% CI 0.44 to 0.76; P < 0.0001) were statistically significantly increased under therapy with alemtuzumab. The potential heterogeneity seen in the forest plot could be due to the different study designs: One trial evaluated alemtuzumab additional to fludarabine as relapse therapy; the other trial examined alemtuzumab compared with no further therapy for consolidation after first remission.There was no statistically significant difference for TRM between both arms (RR 0.57; 95% CI 0.17 to 1.90; P = 0.36). A statistically significant higher rate of CMV reactivation (RR 10.52; 95% CI 1.42 to 77.68; P = 0.02) and infections (RR 1.32; 95% CI 1.01 to 1.74; P = 0.04) occurred in patients receiving alemtuzumab. Seven severe infections (64%) in the alemtuzumab arm in the GCLLSG CLL4B study led to premature closure.

Two trials (N = 177), evaluated alemtuzumab versus rituximab. Neither study reported OS or PFS. We could not detect a statistically significant difference for CRR (RR 0.85; 95% CI 0.67 to 1.08; P = 0.18) or TRM (RR 3.20; 95% CI 0.66 to 15.50; P = 0.15) between both arms. However, the CLL2007FMP trial was stopped early due to an increase in mortality in the alemtuzumab arm. More serious adverse events occurred in this arm (43% versus 22% (rituximab), P = 0.006).

One trial (N = 297), assessed the efficacy of alemtuzumab compared with chemotherapy (chlorambucil). For this trial, no HR is reported for OS. Median survival has not yet been reached, 84% of patients were alive in each arm at the data cut-off or at the last follow-up date (24.6 months). The TRM between arms shows no statistical significant difference (0.6% versus 2.0%; P = 0.34). Alemtuzumab statistically significantly improves PFS (HR 0.58; 95% CI 0.43 to 0.77; P = 0.0001), time to next treatment (23.3 compared with 14.7 months; P = 0.0001), ORR (83.2% versus 55.4%; P < 0.0001), CRR (24.2% versus 2.0%; P < 0.0001), and minimal residual disease rate (7.4% versus 0%; P = 0.0008) compared with chlorambucil. Statistically, significantly more asymptomatic (51.7% versus 7.4%) and symptomatic cytomegalovirus (CMV) infections (15.4% versus 0%) occurred in the patients treated with alemtuzumab.

Authors' conclusions

In summary, the currently available evidence suggests an OS, CRR and PFS benefit for alemtuzumab compared with no further therapy, but an increased risk for infections in general, CMV infections and CMV reactivations. The role of alemtuzumab versus rituximab still remains unclear, further trials with longer follow-up and overall survival as primary endpoint are needed to evaluate the effects of both agents compared with each other. Alemtuzumab compared with chlorambucil seems to be favourable in terms of PFS, but a longer follow-up period and trials with overall survival as primary endpoint are needed to determine whether this effect will translate into a survival advantage.

PLAIN LANGUAGE SUMMARY

The role of the monoclonal antibody alemtuzumab for treatment of people with chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a cancer and accounts for 25% of all leukaemias. The disease is the most common cancer of the lymphatic system 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. Others are symptomatic at diagnosis or early thereafter and can experience infectious and autoimmune complications, leading to a reduced lifespan. Standard treatment includes chemotherapy with one or more agents. Nowadays monoclonal antibodies are added, especially alemtuzumab and rituximab. However, the impact of these agents remains unclear, as there were hints for increased overall survival, but also risk for severe infections in non-randomised trials. In this systematic review we summarised and analysed the evidence from randomised controlled trials (RCTs) on efficacy and safety of alemtuzumab in the treatment of CLL. We searched several important medical databases such as CENTRAL, MEDLINE and EMBASE and found five RCTs fulfilling our pre-defined inclusion criteria. We included trials that compared alemtuzumab with no further therapy or with anti-cancer therapy in newly-diagnosed or relapsed patients with CLL. In total, 845 patients were treated within the five trials.

Two trials assessed whether alemtuzumab is favourable compared with no further therapy. One trial reported data on overall survival, showing a significant advantage for those patients receiving additional alemtuzumab. The time without progression was statistically significantly improved in both trials with alemtuzumab, but more patients had an infection, especially a virus infection (cytomegalovirus infection). Because of severe infections, one trial was closed prematurely.

Two trials evaluated alemtuzumab versus rituximab. Neither study reported data on survival or survival without a relapse of the disease. We found no statistically significant differences for response to therapy or for deaths during study treatment. One trial was stopped early due to an increase in mortality in the alemtuzumab arm.

In the fifth trial alemtuzumab was compared with chemotherapy (chlorambucil). In this trial no difference in survival could be detected until the last publication of the study. Alemtuzumab statistically significantly improves the survival without a relapse, the time to anti-cancer treatment for relapse, and the response rate. Again, more infections occurred in the patients treated with alemtuzumab, especially infections with the cytomegalovirus that could lead to lung and retina infections.

In summary, the currently available evidence suggests an survival advantage for alemtuzumab compared with no further therapy, but an increased risk for infections in general and for cytomegalovirus.

Summary of findings for the main comparison. Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded) for chronic lymphocytic leukaemia

Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded) for chronic lymphocytic leukaemia

Patient or population: patients with chronic lymphocytic leukaemia
Settings:
Intervention: Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded)				
Overall survival (median 2 years)	**Moderate risk**		**HR 0.65** (0.45 to 0.94)	335 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
	250 per 1000	**171 per 1000** (121 to 237)				
Progression free survival (median 2 years)	**Moderate risk**		**HR 0.61** (0.47 to 0.81)	356 (2 studies)	⊕⊕⊖⊖ **low** [2,3]	
	500 per 1000	**345 per 1000** (278 to 430)				
Treatment related mortality	**Study population**		**RR 0.57** (0.17 to 1.9)	356 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	
	40 per 1000	**23 per 1000** (7 to 75)				
Cytomegalovirus reactivation	**Study population**		**RR 10.52** (1.42 to 77.68)	350 (2 studies)	⊕⊕⊕⊕ **high** [2,4]	
	10 per 1000	**105 per 1000** (14 to 777)				

Complete response rate	**Study population**		**RR 2.61** (1.26 to 5.42)	356 (2 studies)	⊕⊕⊝⊝ **low** [2,3]
	51 per 1000	**133 per 1000** (64 to 276)			
Infections (all grades)	**Study population**		**RR 1.32** (1.01 to 1.74)	356 (2 studies)	⊕⊕⊝⊝ **low** [2,3]
	331 per 1000	**437 per 1000** (335 to 577)			
Serious adverse events	**Study population**		**RR 1.34** (0.95 to 1.89)	350 (2 studies)	⊕⊕⊕⊝ **moderate** [2]
	234 per 1000	**314 per 1000** (223 to 443)			

*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; **RR:** Risk ratio; **HR:** Hazard 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 only
[2] One trial stopped early due to high incidence of CMV reactivation in alemtuzumab arm; two of 23 patients randomised refused initiation of study treatment after randomisation and were excluded from analysis (no ITT analysis)
[3] Heterogeneity between trials
[4] Large effect

Summary of findings 2. Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded) for chronic lymphocytic leukaemia

Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded) for chronic lymphocytic leukaemia

Patient or population: patients with chronic lymphocytic leukaemia
Settings:
Intervention: Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded)				
Overall survival not reported	See comment	See comment	Not estimable	-	See comment	Neither study provided data with regard to this outcome.
Progression free survival not reported	See comment	See comment	Not estimable	-	See comment	Neither study provided data with regard to this outcome.
Treament related mortality	**Study population**		**RR 3.2** (0.66 to 15.5)	177 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	
	22 per 1000	**70 per 1000** (15 to 341)				
Complete response rate	**Study population**		**RR 0.85** (0.67 to 1.08)	170 (2 studies)	⊕⊕⊕⊝ **moderate** [1]	
	655 per 1000	**557 per 1000** (439 to 707)				

*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; **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 due to an increase in mortality in the alemtuzumab arm.
[2] Few events were observed for this outcome, leading to a wide confidence intervals.

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 minimal or no symptoms for many years with a normal life expectancy, without requiring treatment. Others are symptomatic at diagnosis or early thereafter. They experience infectious or autoimmune complications and may die of drug-resistant disease much earlier than the normal life expectancy.

The extent of the disease is reflected by enlargement of lymph nodes, liver, and spleen; a raised lymphocyte count in the blood; and a 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 diagnosis, when most patients are in the early stages of the disease (Binet 1981; Hallek 2008; Rai 1975). Recently, other prognostic factors have been identified which 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 of less than one year (Dohner 2000).

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

While fludarabine leads to higher response rates and longer progression-free survival (PFS) compared with other monotherapies, CHOP, or COP do not improve the overall survival (OS), as shown in a Cochrane Review (Steurer 2006). The same is true for the combination of fludarabine and cyclophosphamide compared with fludarabine alone in randomised trials (Eichhorst 2006; Flinn 2007). So far, there are no randomised data showing an impact on OS for the various treatment options. On the other hand, patients with CLL are at increased risk of infections 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 (for example fludarabine, or the combination of fludarabine with cyclophosphamide) (Hallek 2008).

Monoclonal antibodies against surface proteins expressed in CLL cells may allow a more targeted therapy for 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 with treatment without antibodies (Hallek 2008a; Hillmen 2007). In a retrospective analysis comparing FC with FC-rituximab (FCR), Wierda et al showed a possible benefit on OS (Wierda 2006). A benefit for OS was also shown for relapsed or refractory patients with minimal residual disease (MRD) negativity after alemtuzumab treatment (Moreton 2005). This review is part of a series of reviews examining the role of monoclonal antibodies in CLL (for the role of rituximab in patients with CLL see (Weingart 2009)).

Description of the intervention

In a first small phase II trial, treatment of 93 fludarabine refractory patients with alemtuzumab resulted in an overall response rate (ORR) of 33% and a median OS of 16 months (32 months OS for patients who responded) (Keating 2002). Results seemed to improve when combining alemtuzumab with chemotherapy in other phase II trials for relapsed and refractory patients (Elter 2005; Wierda 2005).

A recently published randomised controlled trial (RCT) comparing alemtuzumab with chlorambucil in the first-line therapy of patients with CLL showed a significantly improved PFS (hazard ratio (HR) log rank 0.58 confidence interval (CI): 0.43 to 0.77) (Hillmen 2007). The OS after a median follow-up of 24.6 months showed no difference, with 84% of participants surviving in each arm. Patients receiving chlorambucil did not have cytomegalovirus (CMV) infections with symptoms but 15.6% of patients receiving alemtuzumab had symptomatic PCR-positive CMV infections. Based on similar results, screening for asymptomatic CMV infections and prophylactic treatment of CMV has been advocated (Thursky 2006).

Patients in complete or partial remission after first-line chemotherapy with either fludarabine or fludarabine plus cyclophosphamide were randomised to alemtuzumab or no intervention. At 21.4 months median follow-up, patients receiving alemtuzumab showed a significant longer PFS (no progression versus 24.7 months, P = 0.036). However, this trial was stopped early due to severe toxicity and infectious complications in the alemtuzumab group (Wendtner 2004). Further randomised studies evaluating the effectiveness of alemtuzumab alone or in combination with chemotherapy are currently underway (see Ongoing studies).

How the intervention might work

The new age of cancer therapy started in 1975, when hybridoma technology led to the development of monoclonal antibodies. These antibodies, applied as a single-agent or combination therapy, attempt to improve anti-tumour activities or decrease the treatment-associated toxicity on the basis of a targeted therapy. One of these antibodies is alemtuzumab (drug name e.g. Campath, MabCampath), a humanised antibody specific for CD52, a surface protein present on CLL B-cells as well as normal B and T-cells (Wierda 2005). Alemtuzumab was approved by the FDA for CLL in 2001 and is also successfully used in patients with multiple sclerosis (Coles 2011).

Why it is important to do this review

Based on published trials, alemtuzumab may be an effective treatment option for patients with CLL with possible benefits on OS (Moreton 2005). On the other hand, there are serious side effects and the non-randomised design of most of the trials may introduce biases that can overestimate the benefit of these

new therapeutic agents (Flynn 2007). At this stage, no systematic review or meta-analysis of alemtuzumab in patients with CLL is available. We are aiming to obtain more evidence regarding the clinical benefit (OS, PFS, response rate) and the therapy-related risks (treatment-related mortality (TRM), adverse events), by systematically analysing the reliability and validity of the data and by considering only RCTs for our review. If this is reasonable, we will summarise these results in a meta-analysis and re-evaluate the use of alemtuzumab in the treatment of CLL. Our review is intended to contribute to decision support for effective treatment strategies with the best balance between benefits and harms for the individual patient.

OBJECTIVES

The objectives of this review are to assess and summarise the evidence on efficacy and safety of alemtuzumab in the treatment of CLL, both in newly diagnosed and relapsed patients.

METHODS

Criteria for considering studies for this review

Types of studies

We only considered 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. We included trials with both pretreated and chemotherapy-naive patients. If we had found trials with mixed populations, i.e. patients with different haematological malignancies, we would only have used the data from the CLL subgroups. If subgroup data for patients with CLL had not have been provided (after contacting the authors of the trial), we would have excluded the trial if less than 80% of patients had CLL.

Types of interventions

We included RCTs evaluating alemtuzumab alone or in combination with chemotherapy as primary treatment, maintenance treatment, or treatment in refractory patients. We considered different treatment approaches for CLL considered as the control group, including conventional therapy such as fludarabine or chlorambucil monotherapy, fludarabine in combination with other chemotherapeutic agents, or another antibody therapy.

We considered trials of alemtuzumab in designs where the only difference between the treatment and control arms is the addition of alemtuzumab and in designs where there are additional differences between the treatment arms. We also considered dose comparison studies of alemtuzumab.

We examined the following types of comparisons:

1. anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups);
2. anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups);
3. alemtuzumab versus anti-leukaemic therapy.

We would have examined different dosages or time schedules of alemtuzumab, but we did not identify any trial fulfilling these criteria.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

We analysed the following outcomes as secondary outcomes:

- progression-free survival (PFS);
- time to next treatment;
- treatment-related mortality (TRM);
- complete response rate (CRR);
- overall response rate (ORR);
- minimal residual disease (MRD);
- adverse events;
- number of patients discontinuing the study because of drug-related adverse events.

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

- Cochrane central register of controlled trials (CENTRAL) (*The Cochrane Library* 2011, Issue 11), search strategy see Appendix 1;
- Ovid MEDLINE (1990 to 18.11.2011), search strategy see Appendix 2;
- Ovid EMBASE (1990 to 20.03.2009), search strategy see Appendix 3.

Conference proceedings

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

- American Society of Clinical Oncology (ASCO) (2009; 2010);
- American Society of Haematology (ASH) (2009; 2010);
- European Haematology Association (EHA) (2009; 2010);
- European Society of Medical Oncology (ESMO) (2010).

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:

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

Institutions

We searched the websites of relevant institutions, agencies (for example, the Food and Drug Administration (FDA (www.fda.gov)), organisations (CLL study groups), and the pharmaceutical company (Genzyme Oncology) for completed and ongoing studies.

Personal contacts

We contacted the authors of relevant studies for unpublished material.

Data collection and analysis

Selection of studies

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

We documented the study selection process 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 (NS, KB) independently extracted the data according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011). We would have contacted the authors of individual studies 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 alemtuzumab; 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; minimal residual disease rate; adverse events; number of patients discontinuing the study because of drug-related adverse events; number of patients evaluated for primary outcomes; number of patients evaluated for secondary outcomes; length of follow-up for survival endpoints;, and definitions for the outcomes.

We used both full-text versions and abstracts including additional information (for example slides) of eligible studies to retrieve the data. We extracted trials reported in more than one publication on one form only. Where these sources did not provide sufficient information, we had planned to contact the authors for additional details, however, this was not necessary.

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 2011a):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

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

- 'Low risk': if the criterion is adequately fulfilled in the study, i.e. the study is at a low risk of bias for the given criterion;
- 'High risk': if the criterion is not fulfilled in the study, i.e. the study is at high risk of bias for the given criterion;
- 'Unclear': if the study report does not provide sufficient information to allow for a judgement of 'Yes' or 'No' 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 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 hazards 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 2011b), there are many potential sources of missing data which have to be taken into account: at study level, at outcome level, and at summary data level. Firstly, it is important to distinguish between "missing at random" and "not missing at random".

We contacted the original investigator to request missing data. We performed sensitivity analysis to assess how sensitive results were to reasonable changes in the assumptions that we made. We addressed the potential impact of missing data on the finding of the review in the discussion.

Assessment of heterogeneity

Because of the small number of studies in each analysis (two), the quantification of heterogeneity is not reliable, since the confidence interval is huge. 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 where possible.

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. One review author (NS) entered data into RevMan software and a second review author (KB) checked it for accuracy. We performed meta-analyses using a fixed-effect model (generic inverse variance method for survival data outcomes and Mantel-Haenszel method for dichotomous data outcomes). With more included trials, we would have used the random-effects model in terms of sensitivity analyses.

If appropriate, we calculated the number needed to treat to benefit and the number needed to treat to harm.

We used the software GRADEpro 3.2 to create 'Summary of Finding' tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

Because of the small number of studies in each analysis and missing subgroup data, it was not possible to explore heterogeneity in full detail. We would have taken the following parameters into consideration for subgroup analyses as there is some evidence that these parameters could cause heterogeneity, but the study authors did not provide subgroup data:

- age (e.g. adults < 50 years versus adults ≥ 50 years);
- stage of disease;
- influence of prognostic factors; e.g. 11q- or 17p-deletion.

We evaluated the following parameters in subgroup analyses:

- different treatment approaches (e.g. combination with chemotherapy or not);
- different alemtuzumab approaches (e.g. primary therapy, maintenance or relapse).

Sensitivity analysis

We assessed robustness of the overall results by sensitivity analysis with respect to the quality and design of trials. Due to the low number of trials included in each analysis (two), we evaluated the influence of full-text versus abstract publication only.

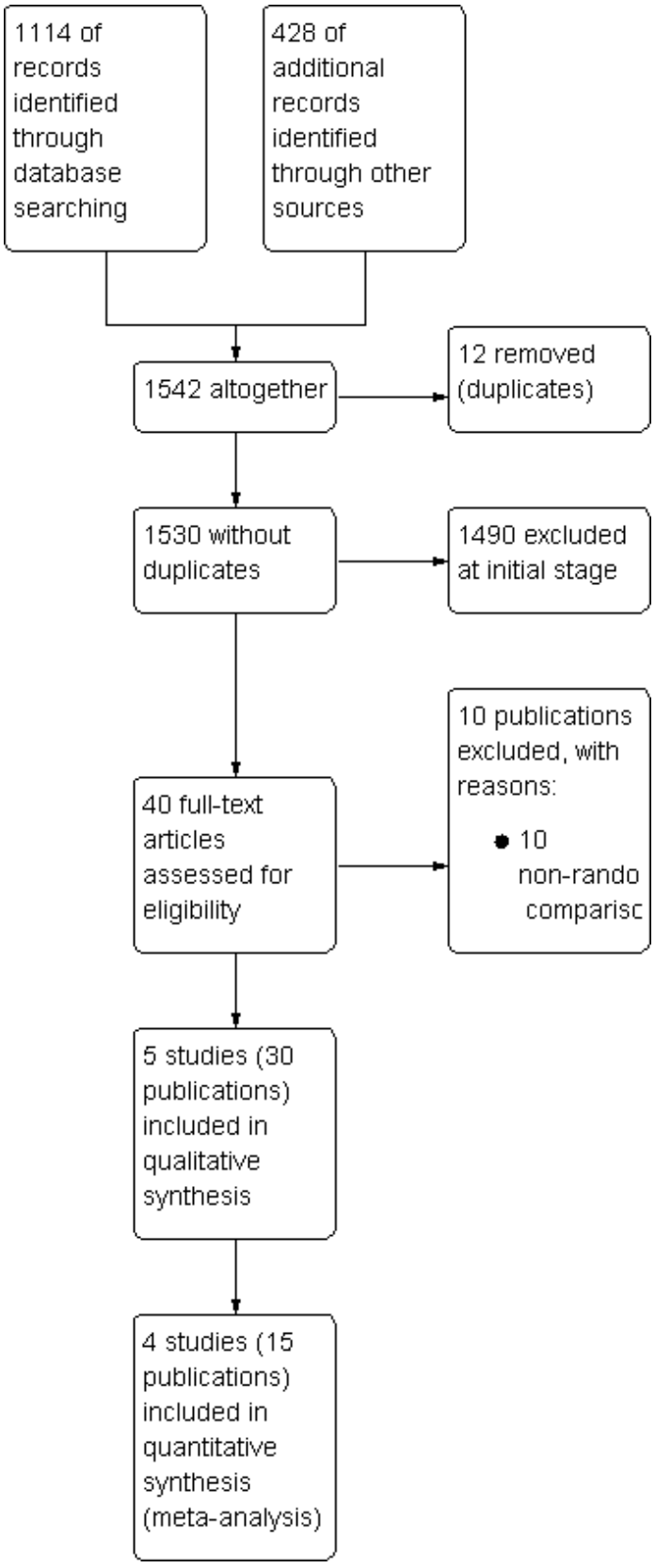
RESULTS

Description of studies

Results of the search

We identified 1542 potentially relevant references through database searches and handsearching. Of these, 1502 were excluded at the initial stage of screening because they did not fulfil our pre-defined inclusion criteria or were duplicates. The remaining 40 publications were retrieved as full-text publications or abstract publications for detailed evaluation. Of these 40 publications, we excluded 10 publications and finally 30 publications (five trials) with 845 patients were formally included in this systematic review. We included two trials in the main meta-analyses of this review. The overall number of references screened, identified, selected, excluded and included are documented according to the PRISMA flow diagram (Figure 1).

Figure 1. Flow diagram.



One guideline was identified but with no additional RCT (Fraser 2006).

Included studies

Five trials in 30 publications including a total of 845 patients (range 12 to 335 patients per trial), fulfilled the inclusion criteria (CAM 307; CAM 314; CLL2007FMP; GCLLSG CLL4B; Gribben 2005).

The characteristics of included trials are summarised in Characteristics of included studies.

For two trials no dates on trial recruitment were provided. One trial recruited from 2001 to 2004 (CAM 307), one from July 2004 to October 2008 (CAM 314), and the other trial from 2007 to 2009 (CLL2007FMP). Two review authors extracted data from full-text publications for three trials (CAM 307; CAM 314; GCLLSG CLL4B) and from abstract publications for two trials (CLL2007FMP; Gribben 2005).

Design

All five included trials were two-armed RCTs.

Sample sizes

The smallest trial (Gribben 2005) randomised 12 patients and the largest trial 335 patients (CAM 314).

Location

Four included trials were conducted in Europe and the US (CAM 307; CAM 314; CLL2007FMP; GCLLSG CLL4B); the other trial (Gribben 2005), did not report where the trial took place.

Participants

A total of 832 male and female patients with histologically-proven CLL were randomised. In two trials alemtuzumab was evaluated in patients receiving first-line therapy (CAM 307; CLL2007FMP), in one trial as maintenance therapy after response to primary therapy (GCLLSG CLL4B) and in two trials in relapsed or refractory patients (CAM 314; Gribben 2005).

Interventions

In two trials, alemtuzumab was evaluated versus no further therapy and observation (CAM 314; GCLLSG CLL4B). Two trials assessed the role of alemtuzumab compared with rituximab (CLL2007FMP; Gribben 2005) and one trial evaluated alemtuzumab compared with chemotherapy (chlorambucil) (CAM 307).

Outcomes

Primary outcome measure

Overall survival was reported in one trial only (CAM 314), although two further trials were reported as full-texts (CAM 307; GCLLSG CLL4B).

Secondary outcome measures

Three trials reported PFS (CAM 307; CAM 314; GCLLSG CLL4B). Response rate was analysed in all five trials, minimal residual disease was evaluated in three trials (CAM 307; CLL2007FMP; GCLLSG CLL4B). Four trials mentioned TRM (CAM 307; CAM 314; GCLLSG CLL4B; CLL2007FMP), and all trials reported adverse events.

Conflict of interest

One trial did not provide conflict of interest statements (abstract publication) Gribben 2005). In one trial, the authors indicated no potential conflict of interest (CLL2007FMP). One trial was supported by a research grant of Schering AG, Berlin and MedacSchering Onkologie, Germany (GCLLSG CLL4B). All authors of CAM 307 are either employees or consultants for Genzyme Corp or have received research grants from Genzyme Corp. One author is a consultant or has a advisory role for Bayer Schering Pharma. Most authors of (CAM 314) received honorariums as members of a board of directors or advisory committees for Genzyme. Two authors of this trial are employees of Genzyme.

Excluded studies

We excluded 10 trials of the retrieved full-text publications, because they were not RCTs (Bolli 2004; Byrd 2009; Elter 2009; Faderl 2010; Hale 2004; Karlsson 2006; Kennedy 2000; Lin 2010; Osterborg 1996; Pettitt 2006).

Risk of bias in included studies

Overall, the quality of included trials was moderate. Two included trials were published as abstracts only, therefore, we were not able to assess the potential risk of bias for these trials in detail. For more information see the 'Risk of bias' tables of included trials and for an overview of the results, please see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

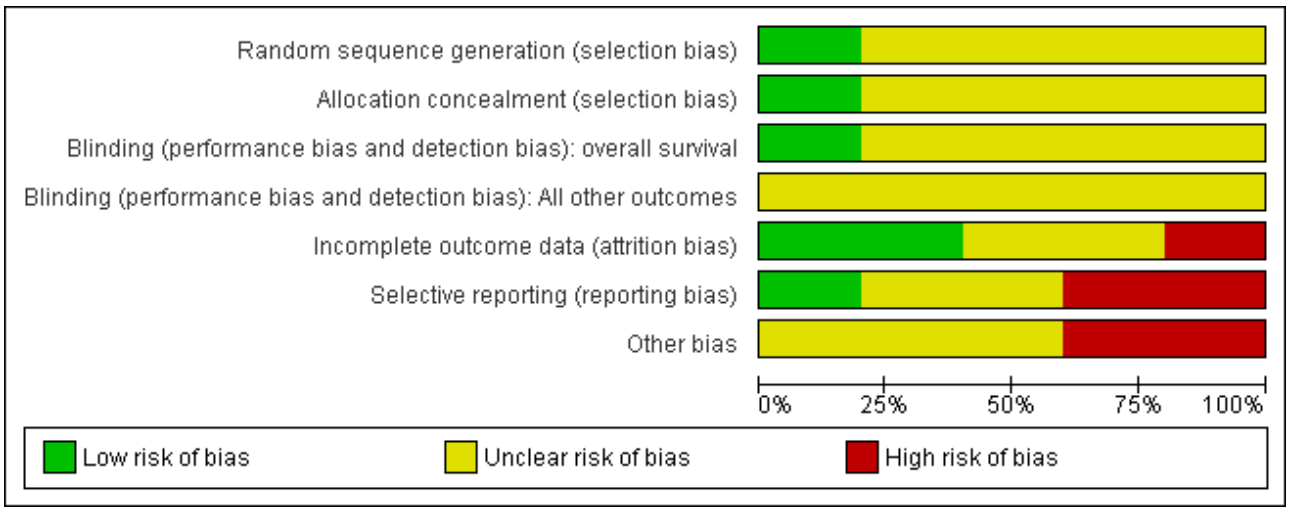
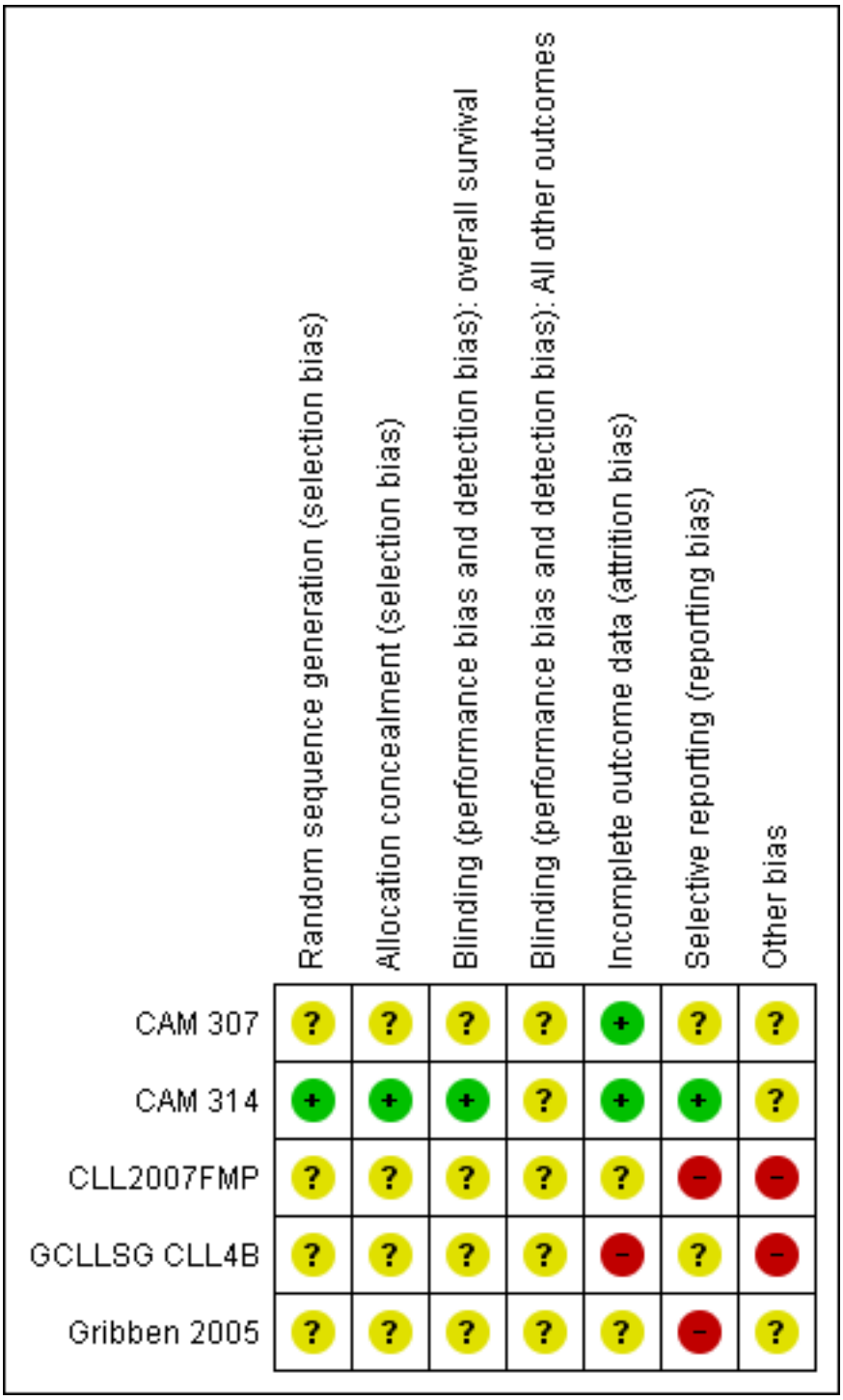


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In one trial, the random sequence generation (minimisation method) and the allocation concealment were adequate (CAM 314); no information was available for the other trials.

Blinding

Patients and physicians were not blinded in the five included trials; no information is given for blinding of the outcome assessor or statistician.

Primary outcome (overall survival)

Although the trial evaluating OS did not report blinding of the outcome assessor, we judged the potential risk of bias for this

outcome as "low" in this trial, as death is an endpoint not susceptible to be biased by the outcome assessor (CAM 314).

Secondary outcomes

As blinding of the outcome assessors is considered important for this review, we judged all trials as "unclear" for the question of blinding.

Incomplete outcome data

Two of the three trials published as full-texts described missing outcome data in detail and stated that they performed analyses according to the intention-to-treat-principle (CAM 307; CAM 314), we therefore, judged risk of attrition bias for this trial as "low". In the other trial published as full-text, two of 23 patients refused treatment after randomisation and were not included in the final analysis (GCLLSG CLL4B). We judged risk of incomplete outcome data for this trial as "high".

There were no obvious missing data among the two trials published as abstracts only, but no detailed information on statistical methods and patients analysed were given, therefore, we judged the risk of attrition bias for these trials as "unclear" (CLL2007FMP; Gribben 2005).

Selective reporting

For one trial, there is no study protocol in http://www.controlled-trials.com/mrct/ available, therefore, we were not able to judge on the potential risk of reporting bias (GCLLSG CLL4B). For one study, a protocol is registered, but no information for pre-planned outcomes is given (CAM 307). For those two studies, we judged the risk of bias as "unclear". Most of the patient-important pre-planned outcomes and the primary endpoint are reported in the full-text publication of CAM 314, however, quality of life is not reported. Although this outcome is not reported, we judged the risk of bias for this trial as "low", as quality of life often is reported in separate publications. The other two studies were published as abstracts and only a few outcomes of the pre-planned outcomes were reported. Therefore, we judged the risk of reporting bias for these three trials as "high".

Other potential sources of bias

Two trials were stopped prematurely due to an increased incidence of severe infections or an increase in mortality in the alemtuzumab arm (CLL2007FMP; GCLLSG CLL4B). Both trials were judged as having a potential "high risk" of bias. One trial recruited more patients than planned (335 instead of 300) without a clear rationale (CAM 314). The risk of bias for this trial was judged as "unclear".

Effects of interventions

See: **Summary of findings for the main comparison** Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded) for chronic lymphocytic leukaemia; **Summary of findings 2** Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded) for chronic lymphocytic leukaemia

Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

Two RCTs (N = 356) evaluated the efficacy and safety of alemtuzumab in an unfounded design (CAM 314; GCLLSG CLL4B).

Overall survival (OS)

Only one of the two trials provided HR for the primary endpoint OS (CAM 314). The authors of CAM 314 reported a statistically significant Improvement in OS for patients receiving fludarabine plus alemtuzumab compared with fludarabine only (HR 0.65 (95% CI 0.45 to 0.94, P = 0.021)) (CAM 314). No improvement in OS was seen in the subgroup of patients with Rai stage I or II (HR 1.07; 95% CI 0.62 to 1.84; P = 0.82).

The authors of the trial by the German CLL study group (GCLLSG) reported that 19 patients were alive at last follow-up (median 48 months), without providing HRs or survival curves (GCLLSG CLL4B). Two patients died because of progressive disease (one patient in each arm).

Progression-free survival (PFS)

Both trials (N = 356) reported a statistically significant improvement for PFS through the addition of alemtuzumab (HR 0.58; 95% CI 0.44 to 0.76; P < 0.0001). There could be some heterogeneity, visible in the forest plot between trials, probably due to the different study designs: CAM 314 evaluated alemtuzumab additional to fludarabine as relapse therapy. GCLLSG CLL4B examined alemtuzumab compared with no further consolidation after the first remission.

Nevertheless, the statistically significant effect is visible in both single trials: In CAM 314, additional alemtuzumab led to improved PFS (HR 0.61; 95% CI 0.47 to 0.81; P = 0.0003); an even more pronounced effect is seen in GCLLSG CLL4B (HR 0.17; 95% CI 0.05 to 0.60; P = 0.006).

Time to next treatment

Neither study reported on this outcome.

Treatment-related mortality (TRM)

Although less treatment-related mortality occurred in the alemtuzumab arm, there is no statistically significant difference for TRM in these two studies between both arms (N = 356; RR 0.57; 95% CI 0.17 to 1.90; P = 0.36).

Engert et al reported TRM, defined as death occurring on therapy or within 30 days after the last dose. Four of 168 patients (2%) died on fludarabine plus alemtuzumab arm versus seven of 167 (4%) on fludarabine-only arm. For the subgroup of patients in the advanced stage, two patients (3%) died in the additional alemtuzumab arm versus five patients (8%) in the fludarabine-only arm (CAM 314).

Wendtner et al reported that no patient died during treatment (altogether two patients died during the follow-up phase, both because of progressive disease) (GCLLSG CLL4B).

Overall response rate (ORR)

Although the overall response rate is increased in patients receiving alemtuzumab, there is no statistically significant difference for the

ORR between patients who did, or did not, receive alemtuzumab (RR 1.10; 95% CI 0.99 to 1.23; P = 0.09).

The relative chance for overall response in CAM 314 (relapse therapy; alemtuzumab combined with fludarabine) is RR = 1.08 (95% CI 0.97 to 1.21; P = 0.18).

The relative chance in GCLLSG CLL4B (consolidation after first remission; alemtuzumab not combined with other chemotherapy) is RR = 1.41 (95% CI 0.92 to 2.14; P = 0.11). However, there is a difference in response to pretreatment prior to randomisation and alemtuzumab therapy: in the alemtuzumab arm there were: one complete response (CR) and 10 partial responses (PR) compared with two CR, five PR, and three nodular PR in the arm without further therapy.

Complete response rate (CRR)

The CRR is statistically significantly higher in the alemtuzumab arm (RR 2.61; 95% CI 1.26 to 5.42; P = 0.01). The potential heterogeneity seen in the forest plot could be explained by the baseline imbalance in the GCLLSG CLL4B study: prior to randomisation to alemtuzumab there were one CR and 10 PR in the alemtuzumab arm versus two CR, five PR and three nodular PR in the arm without any further treatment.

In CAM 314 (relapse therapy; alemtuzumab combined with fludarabine), the relative chance for CR is statistically significantly higher in the alemtuzumab arm (RR 2.98; 95% CI 1.30 to 6.83; P = 0.01).

In GCLLSG CLL4B (consolidation after first-remission; alemtuzumab not combined with other chemotherapy) there is no statisticallysignificant effect between both arms (RR 1.36; 95% CI 0.28 to 6.56; P = 0.70).

Minimal residual disease (MRD)

CAM 314 did not report any information regarding MRD.

GCLLSG CLL4B reported data for 9 of 21 participants (six in the alemtuzumab and three in the observation arm). Due to the high proportion of missing data, we did not calculate a MRD rate.

Adverse events

CMV reactivation

Both studies reported on various adverse events. A statistically significant higher rate of CMV reactivation and symptomatic CMV infection occurred in patients receiving alemtuzumab (RR 10.52; 95% CI 1.42 to 77.68; P = 0.02).

In both single studies, more CMV infections occurred in the alemtuzumab arm, but this effect is is not statistically significantly increased. In CAM 314 (relapse therapy; alemtuzumab combined with fludarabine) the relative risk of symptomatic CMV infection is RR = 9.05 (95% CI 0.49 to 166.84; P = 0.14).

In GCLLSG CLL4B (consolidation after first-remission therapy; alemtuzumab not combined with other chemotherapy) the effect is RR = 11.92 (95% CI 0.76 to 187.84; P = 0.08).

All grade infections

Statistically significant more infections occurred in patients receiving alemtuzumab (RR 1.32; 95% CI 1.01 to 1.74; P = 0.04). However, there could be heterogeneity between trials, visible in the forest plot.

In CAM 314 (relapse therapy; alemtuzumab combined with fludarabine), the relative risk for all grade infections is not statistically significantly different between groups (RR 1.16; 95% CI 0.88 to 1.53; P = 0.29).

In GCLLSG CLL4B (consolidation after first-remission therapy; alemtuzumab not combined with other chemotherapy), we found a statistically significant higher infection rate in the alemtuzumab arm (RR 19.25; 95% CI 1.27 to 291.20; P = 0.03). The incidence of seven severe infections in the alemtuzumab arm led to premature closure of the trial.

Haematological toxicity

Slightly less grade 3 or 4 haematological toxicities occurred in the alemtuzumab arm, but these differences were not statistically significant (anaemia: (RR 0.63; 95% CI 0.33 to 1.20; P = 0.16); neutropenia (RR 1.25; 95% CI 0.97 to 1.61); P = 0.09); thrombocytopenia (RR 1.05; 95% CI 0.58 to 1.89; P = 0.88).

Elter et al reported that adverse events occurring in >10% in the additional alemtuzumab arm relative to fludarabine-only arm include pyrexia, leucopenia, chills, lymphopenia, urticaria, infusion-related reactions, and rash (CAM 314).

Serious adverse events (SAEs)

More serious adverse events were found in the alemtuzumab arm, but there is no statistically significant difference between patients who received additional alemtuzumab and those who did not (RR 1.34; 95% CI 0.95 to 1.89; P = 0.09).

Serious AEs occurred in 33% of participants in the additional alemtuzumab and 25% in the fludarabine arm (CAM 314).

Number of patients discontinuing the study because of drug-related adverse events

In CAM 314, 37 patients (23%) in the alemtuzumab arm and 32 patients (19%) in the fludarabine-only group had to discontinue the study because of adverse events. However, they were assessed for the study outcomes and their data included in the analyses.

GCLLSG CLL4B reported no data on how many patients in both arms discontinued the study because of drug-related adverse events. However, seven patients (63.6%) in the alemtuzumab-arm developed acute severe infection and the trial had to be stopped prematurely.

Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups)

Two RCTs (N = 177) evaluated the role of anti-leukaemic therapy with alemtuzumab compared to another anti-leukaemic therapy without alemtuzumab (CLL2007FMP; Gribben 2005). In both studies, patients were randomised to receive additional alemtuzumab or additional rituximab.

Overall survival (OS)

Neither study provided data with regard to this outcome.

Progression-free survival (PFS)

Neither study reported PFS data.

Time to next treatment

In both studies there were no data provided for time to next treatment.

Treatment related mortality (TRM)

Both trials reported on TRM (N = 177 patients). Treatment related mortality was increased in the alemtuzumab arm compared to the rituximab arm and one trial (CLL2007FMP) was stopped prematurely due to an increase in mortality in the alemtuzumab arm. Although no statistically significant difference was detectable between patients receiving additional alemtuzumab compared with those receiving additional rituximab (RR 3.20; 95% CI 0.66 to 15.50; P = 0.15), a RR 0f 3.20 could b of concern if maintained on more robust data. The potential heterogeneity seen in the forest plot between trials could be due to different patients characteristics:

In CLL2007FMP, patients received alemtuzumab or rituximab for first-line treatment (RR 9.11; 95% CI 0.50 to 166.53; P = 0.14).

Gribben 2005 reported results for relapsed disease (RR 1.00; 95% CI 0.13 to 8.00; P = 1.00).

Overall response rate (ORR)

Both trials reported on ORR (N = 170 patients). No statistically significant difference could be found for the ORR (RR 0.95; 95% CI 0.85 to 1.07; P = 0.43).

In CLL2007FMP (first-line treatment), the chance for OR was RR = 0.93 (95% CI 0.83 to 1.04; P = 0.21). In Gribben 2005 (relapse therapy) RR = 1.75 (95% CI 0.63 to 4.88; P = 0.28).

Complete response rate (CRR)

There was no statistically significant difference in terms of CRR between the patients receiving additional alemtuzumab and those receiving additional rituximab (RR 0.85; 95% CI 0.67 to 1.08; P = 0.18).

In CLL2007FMP (first-line treatment), the chance for CR was RR = 0.81 (95% CI 0.64 to 1.03; P = 0.09). In Gribben 2005 (relapse therapy) RR = 3.50 (95% CI 0.45 to 27.52; P = 0.23).

Minimal residual disease (MRD)

CLL2007FMP reported that at nine months, 21 patients (26%) in the alemtuzumab arm and 36 patients (45%) in the rituximab arm were MDR-negative.

Gribben 2005 did not report any data for this outcome.

Adverse events

In the Gribben 2005 trial, two CMV reactivations (50%) were reported in the additional alemtuzumab arm. The number of CMV reactivations for patients receiving additional rituximab was not reported.

CLL2007FMP provided data for all grade 3/4 adverse events (72 patients (87%) in the alemtuzumab arm versus 75 patients (90%) in the rituximab arm, P = 0.76). There was no statistically significant difference for grade 3/4 neutropenia (65 patients (79%) in the alemtuzumab arm versus 62 patients (75%), P = 0.49). However, SAEs were statistically significantly more frequent in the alemtuzumab arm (in 35 patients (43%) compared with 18 patients (22%) in the rituximab arm, P = 0.006). Additionally, serious febrile neutropenia was statistically significantly more frequent in the alemtuzumab arm (27 patients (33%) versus 13 patients (16%), P = 0.01).

Number of patients discontinuing the study because of drug-related adverse events

In the Gribben 2005 study, one patient (24%) in the alemtuzumab arm discontinued treatment due to adverse events, while in the rituximab arm, there were six patients (75%) (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 additional alemtuzumab arm, 59 patients (71.4%) received all six cycles and, in the additional rituximab arm 63 patients (76.5%).

Alemtuzumab versus anti-leukaemic therapy

One RCT (N = 297), evaluated the efficacy and safety of alemtuzumab compared with chemotherapy (chlorambucil) in patients with relapsed CLL (CAM 307).

Overall survival

CAM 307 did not report a HR or survival curve for OS. Median survival had not yet been reached; 84% of patients were alive in each arm at the data cut-off or at the last follow-up date (24.6 months).

Progression-free survival (PFS)

In CAM 307 (N = 297), alemtuzumab statistically significantly improved PFS compared with chlorambucil (HR 0.58; 95% CI 0.43 to 0.77; P = 0.0001).

Time to next treatment

Patients receiving alemtuzumab had a statistically significant longer median time to alternative treatment (23.3 months) compared with those receiving chlorambucil (14.7 months, P = 0.0001).

Treatment related mortality

CAM 307 reported the following statistical non-significant information regarding TRM, defined as death occurring on therapy, or within 30 days: one patient (0.6%) died in the alemtuzumab arm versus three patients (2.0%) in the chlorambucil arm (P = 0.34).

Overall response rate (ORR)

Statistically, significantly more patients in the alemtuzumab arm achieved an OR: 124 patients (83.2%) on alemtuzumab versus 82 patients (55.4%) on chlorambucil (P < 0.0001).

Complete response rate (CRR)

There is a statistically significant advantage in terms of CRR for those patients receiving alemtuzumab (36 patients (24.2%) compared with those who received alemtuzumab compared with the three patients (2.0%)) who received chlorambucil (P < 0.0001).

Minimal residual disease (MRD)

The MRD is statistically significantly higher in the alemtuzumab arm (11 patients; 7.4%) versus no patients (0%) in the chlorambucil arm (P = 0.0008).

Adverse events

Detailed adverse events are listed in Table 1. For most adverse events, there is no statistically significant difference in grade 3/4 adverse events between both arms (chills, urticaria, hypotension, rash, nausea, vomiting, anaemia, thrombocytopenia, haemolytic anaemia, febrile neutropenia, and bacteria/sepsis, symptomatic CMV infection). However, there were statistically, significantly more adverse events (all grades) for asymptomatic CMV infection (77 patients (51.7% versus 11 patients (7.4%) and symptomatic CMV infection (23 patients (15.4%) versus no patients (0%)). Patients receiving alemtuzumab statistically significantly developed more grade 3/4 pyrexia (8.2% versus 0%; P = 0.03), neutropenia (41% versus 25%; P = 0.004) and SAEs (39 patients (26.5%) in the alemtuzumab arm compared with 10 patients (6.8%) in the chlorambucil arm (P < 0.0001)).

Number of patients discontinuing the study because of drug-related adverse events

Statistically, significantly more patients in the alemtuzumab arm permanently withdrew from the study because of adverse events (29 patients (19.7%) versus six patients (4.1%) in the chlorambucil arm (P = 0.0003)).

Different dosages or time schedules of alemtuzumab

We did not identify any RCT regarding this comparison.

DISCUSSION

Summary of main results

The following findings emerge from this systematic review, evaluating the role of alemtuzumab in newly diagnosed patients as well as in relapsed patients.

- In trials evaluating anti-leukaemic therapy with alemtuzumab versus identical anti-leukaemic therapy alone the results are as follows (two trials, N = 356 patients).
  - OS, PFS and CRR are statistically significantly improved in patients receiving alemtuzumab compared with those not receiving alemtuzumab.
  - There is no evidence that TRM or ORR is different in patients with CLL receiving additional alemtuzumab compared with those not receiving alemtuzumab.
  - There is a statistically significantly higher rate of infections in general and CMV reactivation in patients receiving alemtuzumab.
  - No statistically significant difference is detectable for haematological grade 3 or 4 adverse events and serious adverse events, although one of the two included trials was closed prematurely due to an increase of acute severe infections.
- For the comparison of anti-leukaemic therapy with alemtuzumab versus different anti-leukaemic therapy without alemtuzumab we found two studies evaluating additional alemtuzumab compared to additional rituximab) (N = 177 patients).
  - There are no data provided for OS, PFS and time to next treatment.
  - Due to the small number of patients, no statistically significant difference is seen for TRM, ORR, CRR, and grade 3 or 4 neutropenia.
  - Statistically, significantly more serious adverse events and serious febrile neutropenia occurred in patients receiving alemtuzumab compared with those receiving rituximab. One of the two included trials had to be stopped early because of an increase in mortality in the alemtuzumab arm.
- The following results emerge for the comparison of alemtuzumab versus anti-leukaemic therapy) (one trial; N = 297 patients),
  - There is no HR reported for OS. Median survival has not yet been reached, 84% of patients were alive in each arm at the data cut-off or at the last follow-up date (24.6 months).
  - Alemtuzumab statistically significantly improves PFS, time to next treatment, ORR, CRR and MRD rate compared with chlorambucil.
  - No statistically significant differences were visible for most grade 3 or 4 adverse events (chills, urticaria, hypotension, rash, nausea, vomiting, anaemia, thrombocytopenia, haemolytic anaemia, febrile neutropenia, and bacteria/sepsis, symptomatic CMV infection).
  - Statistically, significantly more adverse events (all grades), more asymptomatic CMV infections and symptomatic CMV infections occurred in the patients treated with alemtuzumab compared with those treated with chlorambucil. Statistically, significantly more patients in the alemtuzumab arm permanently withdrew from the study because of adverse events.

Due to the small number of identified RCTs, subgroup analyses included one trial only in each comparison and are of limited power. We could not detect any difference in the total effect estimate compared with all kinds of subgroups (newly diagnosed versus relapsed patients, first-line treatment versus consolidation treatment, combined with chemotherapy versus without further chemotherapy).

Overall completeness and applicability of evidence

Five published studies addressed the use of alemtuzumab in patients with CLL and are included in this systematic review and meta-analysis. However, two trials were published as abstracts only and the full-text publications are likely to provide more data on relevant outcomes such as, OS, PFS and time to next treatment. It is a serious failure that two trials did not report overall survival (no HR or survival curve), although both trials were published as full-texts.

The five included trials are clinical heterogenous and we therefore, did not pool them in one meta-analysis but in three main analyses.

Moreover, we are aware of six ongoing studies. We will include the findings of these trials in an update of this review and they could lead to different conclusions. One trial mentioned as ongoing was terminated prematurely due to a low recruitment rate. Probably no results of this trial will be published, because only one patient was enrolled.

Quality of the evidence

Overall, the quality of the five included trials (845 patients) was moderate. Two included trials were published as abstracts only, therefore, we were not able to assess the potential risk of bias for these trials in detail. All the included trials were reported as randomised and as open-label studies. One of the included trials reported allocation concealment. The open-label design and unclear allocation concealment could lead to selection, performance or detection biases. Due to the limited abstract publication of two trials, we judged selective reporting as high for these trials, indicating a potential risk of reporting bias. The premature closure of two trials due to an increased incidence of severe infections or increase in mortality in the alemtuzumab arm could lead to other sources of bias. In one of these trials the strongly improved PFS in patients treated with alemtuzumab could be too good to be true and could be caused by the low number of patients randomised (21 instead of 90 patients). Another potential source of bias is this trial is the uncertainty in the HR calculation. In this trial the HR for PFS was calculated from a survival curve with a constant censoring as described by Tierney 2007.

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

Potential biases in the review process

We tried to avoid bias by doing all relevant processes in duplicate. We are not aware of any obvious flaws in our review process.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first comprehensive systematic review and meta-analysis focusing on the treatment of patients with CLL using the monoclonal antibody alemtuzumab.

Individual non-randomised studies in patients with CLL reported an improved rate of complete and partial responses compared with historical data that might have an positive effect on overall and progression-free survival (Byrd 2009a; Hainsworth 2008; Kaufman 2011). However, in accordance with this systematic review, these authors demonstrated an increased rate of CMV reactivation and other opportunistic infections, in some cases even life-threatening (Byrd 2009a; Hainsworth 2008; Kaufman 2011). Some recent publications have pointed out the requirement of close monitoring for CMV infections and pre-emptive therapy using intravenous ganciclovir (Byrd 2009a; Elter 2009a).

Faderl et al. showed promising results on CRR for the combination of intravenous alemtuzumab followed by subcutaneous alemtuzumab injection (Faderl 2010). According to some authors, subcutaneous alemtuzumab might be an alternative to intravenous alemtuzumab to treat safely residual disease in patients with CLL without an increased infection rate (Cortelezzi 2009; Stilgenbauer 2009; Wierda 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently evidence from one single large trial that alemtuzumab compared to no further therapy improves overall survival in patients with CLL. Progression-free survival is increased if alemtuzumab is compared with no further therapy; the effect on PFS for the comparison alemtuzumab versus rituximab awaits further evaluation. As examined here, there is insufficient direct evidence from RCTs to recommend alemtuzumab over rituximab. We demonstrated that alemtuzumab statistically significantly increases the rate of CMV reactivations, infections and SAEs.

Implications for research

More RCTs with the primary endpoint overall survival and a longer follow up period are needed to assess the effect of alemtuzumab on OS. This may be particularly important in situations where PFS is improved to evaluate whether this effect will translate in an OS advantage. Moreover, the optimal dose, schedule and route of alemtuzumab administration should be evaluated in RCTs. To avoid CMV reactivation, CMV prophylaxis or pre-emptive treatment should be considered in the trial design. Additionally, further research is needed to clarify the efficacy and safety of alemtuzumab compared with other monoclonal antibodies such as rituximab or ofatumumab or, in addition to these antibodies.

ACKNOWLEDGEMENTS

Verena Roloff was supported by an Medical Research Council studentship.

We are grateful to the following persons for their comments and improving the protocol:

Prof. Lena Specht and Prof. Keith Wheatley, Editors of the Cochrane Haematological Malignancies Group,

Céline Fournier, Consumer Editor of the Cochrane Haematological Malignancies Group,

Sabine Kluge from the Editorial Base of the Cochrane Haematological Malignancies Group for proof reading and Janet Wale for copy editing.

REFERENCES

References to studies included in this review

CAM 307 *{published data only}*

Demko S, Summers J, Keegan P, Pazdur R. FDA drug approval summary: alemtuzumab as single-agent treatment for B-cell chronic lymphocytic leukemia. *Oncologist* 2008;**13**:167-74.

Dmoszynska A, Fetni R, Wang Y, Belkaci M, Sirard C, Goldberg M, et al. Cytogenetic correlation with efficacy on alemtuzumab (CAM) vs chlorambucil (CHLO) as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia (BCLL) [abstract]. Journal of Clinical Oncology 2006; Vol. 24:361.

Genzyme. A phase III study to evaluate the efficacy and safety of front-line therapy with alemtuzumab (Campath, MabCampath) vs chlorambucil in patients with progressive B-cell chronic lymphocytic leukemia (ClinicalTrials.gov identifier: NCT00046683). http://www.clinicaltrials.gov 2003.

Hillmen P, Skotnicki A, Robak T, Jaksic B, Dmoszynka A, Sirard C, et al. Preliminary phase III efficacy and safety of alemtuzumab vs chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia (BCLL) [abstract]. Journal of Clinical Oncology 2006; Vol. 24:339.

Hillmen P, Skotnicki A, Robak T, Jaksic B, Sirard C, Mayer J. Alemtuzumab (Campath, MabCampath) Has superior progression free survival (PFS) vs chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia (BCLL) [Abstract]. Blood 2006; Vol. 108:93.

Hillmen P, Skotnicki A, Robak T, Jaksic B, Sirard C, Mayer J. Progression free survival is superior with alemtuzumab vs chlorambucil as front-line therapy for patients with B-cell chronic lymphocytic leukemia [Abstract] 1996. *Haematologica* 2007;**92**:45-6.

* Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *Journal of Clinical Oncology* 2007;**25**:5616-23.

Hillmen P, Skotnicki AB, Robak T, Mayer J, Jaksic B, Vukovic V, et al. Preliminary safety and efficacy report of a randomized trial of alemtuzumab vs chlorambucil as front-line therapy in 297 patients with progressive B-cell chronic lymphocytic leukemia. Blood 2004; Vol. 104:687a.

Hillmen PH, Skotnicki AS, Robak TR, Jaksic BJ, Dmoszynska AD, Sirard CS, et al. Preliminary results for the phase III trial of alemtuzumab (Campath, MabCampath) vs chlorambucil as first-line treatment for B-cell chronic lymphocytic leukemia (B-cll) [Abstract]. *Haematologica* 2006;**91**:381.

Mayer J, Robak T, Skotnicki A, Jaksic B, Dmoszynka A, Sirard C, et al. Impact of prognostic factors on outcome in a phase III study comparing alemtuzumab to chlorambucil as first-line therapy for B-cell chronic lymphocytic leukemia (BCLL) [abstract]. Journal of Clinical Oncology 2007; Vol. 25:365.

Mayer J, Robak T, Skotnicki A, Jaksic B, Vukovic V, Weitman S. Interim safety summary of alemtuzumab (Campath, Mabcampath) vs chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia [abstract]. *Hematology Journal* 2004;**5**:28.

Robak T, Dmoszynska A, Fetni R, Wang Y, Belkacz M, Sirard C. Incidence of genomic aberrations and associated efficacy from a phase III study comparing alemtuzumab (Campath, MabCampath) vs chlorambucil as first line therapy for B-cell chronic lymphocytic leukemia (BCLL). Blood 2006; Vol. 108.

Robak T, Skotnicki A, Dmoszynka A, Hebert J, Wang Y, Belkaci M, et al. Cytogenic abnormalities and associated efficacy from a phase iii study comparing alemtuzumab vs. Chlorambucil as first line therapy for b-cell chronic leukemia [Abstract] 1997. *Haematologica* 2007;**92**:46.

Robak T, Skotnicki AB, Mayer J, Vukovic V, Weitman S. Interim safety summary of alemtuzumab vs. chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukemia (BCLL) [abstract]. Journal of Clinical Oncology 2004; Vol. 22:571.

Skotnicki AB, Robak T, Mayer J, Craig A, Weitman S. Phase III study to evaluate the efficacy and safety of front-line therapy with alemtuzumab (Campath, MabCampath) vs. chlorambucil in patients with progressive B-cell chronic lymphocytic leukemia (CAM307). *Blood* 2003;**102**:439a.

CAM 314 *{published data only}*

* Elter T, Gercheva-Kyuchukova L, Pylylpenko H, Robak T, Jaksic B, Rekhtman G, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. The Lancet Oncology published online 2011 October 10 [Epub ahead of print]. [PUBMED: 21992852]

Engert A, Gercheva L, Pilipenko G, Robak T, Wu J, Barry A, et al. Fludarabine (Flu) plus alemtuzumab (FluCam) improves progression free survival versus fludarabine in previously treated chronic lymphocytic leukemia and demonstrates activity in high risk patients. *Haematologica* 2010;**95**:Suppl 2.

Engert A, Gercheva L, Pilipenko G, Robak T, Wu J, Sirard CA, et al. Overall survival advantage and acceptable safety profile with fludarabine in combination with alemtuzumab (FluCam) in previously treated patients with advanced stage chronic lymphocytic leukemia. *Blood* 2010;**116**:919.

Engert A, Gercheva L, Robak T, Galina P, Wu J, Sirard CA, et al. Improved progression-free survival (PFS) of alemtuzumab (Campath, MabCampath) plus fludarabine (Fludara) versus fludarabine alone as second-line treatment of patients with B-cell chronic lymphocytic leukemia: preliminary results from a phase III randomized trial. *Blood* 2009;**114**:537.

CLL2007FMP *{published data only}*

Lepretre S, Aurran T, Mahe B, Cazin B, Tournihlac O, Maisonneuve H, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine (F), cyclophosphamide (C) and MabCampath (Cam) (FCCam) in previously untreated patients (pts) with advanced

B-chronic lymphocytic leukemia (B-CLL) : experience on safety and efficacy within a randomised multicenter phase III trial of the French Cooperative Group on CLL and WM (FCGCLL/MW) and the "Groupe Ouest-Est d'Etudes Des Leucemies Aigues Et Autres Maladies Du Sang" (GOELAMS) : CLL2007FMP (for fit medically patients). *Blood* 2009;**114**:538.

* Remi L, Lepretre S, Arnoulet C, Baseggio L, Campos L, Chatelain B, et al. CLL2007FMP, a phase III randomized multicentric trial of the French Cooperative Group on CLL and WM (FCGCLL/MW) and the "Groupe Ouest-Est D'etudes Des Leucemies Aigues Et Autres Maladies Du Sang" (GOELAMS): immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) yields a significantly better response than fludarabine (F), cyclophosphamide (C) and MabCampath (Cam) (FCCam) in previously untreated B-chronic lymphocytic leukemia patients as evaluated by a sensitive 6 color flow cytometry MRD. *Blood* 2010;**116**:698.

GCLLSG CLL4B *{published data only}*

Ritgen M, Schweighofer C, Fingerle-Rowson G, Eichhorst B, Busch R, Stilgenbauer S. Consolidation with alemtuzumab in first remission induces pronounced MRD reduction and clinical remissions update on a randomized phase III trial of the German CLL Study Group (GCLLSG). Blood 2004; Vol. 104:687a.

Schweighofer C, Ritgen M, Eichhorst B, Busch R, Kneba M, Hallek M, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukemia (CLL) in first remission long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG) [abstract]. *Blood* 2006;**108**:14.

Schweighofer CD, Ritgen M, Eichhorst BF, Busch R, Abenhardt W, Kneba M, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). *British Journal of Haematology* 2009;**144**:95-8.

Schweighofer CD, Ritgen M, Fingerle-Rowson G, Eichhorst B, Busch R, Stilgenbauer S, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission - update on a randomized phase III trial of the German CLL Study Group (GSLLSG). *Onkologie* 2004;**27**:28-9.

Wendtner CM, Ritgen M, Fingerle-Rowson G, Jaeger G, Campe H, Engert A, et al. High efficacy but considerable toxicity of campath-1H consolidation therapy in CLL patients responding to fludarabine - results of a randomized phase III trial [abstract]. *Journal of Clinical Oncology* 2003;**22**:579.

Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jaeger G. Consolidiation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission - experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Blood* 2003;**102**:676.

* Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jager G, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission--experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Leukemia* 2004;**18**:1093-101.

Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jager G, et al. High efficacy but considerable toxicity of Alemtuzumab (MabCampath) consolidation therapy in CLL patients responding to Fludarabine or Fludarabine/cyclophosphamide - results of a randomized phase III trial of the GCLLSG. *Onkologie* 2003;**26**:173.

Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jager G, et al. High efficacy but considerable toxicity of alemtuzumab (Campath-1H) consolidation therapy in CLL patients responding to fludarabine - results of a randomized phase III trial of the GCLLSG [abstract: 0610]. *Haematologica* 2003;**88**:Suppl.

Gribben 2005 *{published data only}*

Gribben J, Stephans K, Blossom M. Fludarabine and alemtuzumab versus fludarabine and rituximab in the treatment of relapsed B-cell chronic lymphocytic leukemia: Results from a phase II study [abstract]. *Blood* 2005;**106**:343.

References to studies excluded from this review

Bolli 2004 *{published data only}*

Bolli N, Di Ianni M, Simonetti S, Cerroni L, Liso A, Falini B, et al. Treating two concurrent B-cell and T-cell lymphoid neoplasms with alemtuzumab monotherapy. *Lancet Oncology* 2004;**5**:64-5.

Byrd 2009 *{published data only}*

Byrd JC, Peterson BL, Rai KR, Hurd D, Hohl R, Perry MC, et al. Fludarabine followed by alemtuzumab consolidation for previously untreated chronic lymphocytic leukemia: final report of Cancer and Leukemia Group B study 19901. *Leukemia & Lymphoma* 2009;**50**:1589-96.

Elter 2009 *{published data only}*

Elter T, Kilp J, Borchmann P, Schulz H, Hallek M, Engert A. Pharmacokinetics of alemtuzumab in combination with fludarabine in patients with relapsed or refractory B-cell chronic lymphocytic leukemia. *Haematologica* 2009;**94**:150-2.

Faderl 2010 *{published data only}*

Faderl S, Ferrajoli A, Wierda W, O'Brien S, Lerner S, Keating M J. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. [Erratum appears in Cancer. 2010 Aug 15;116(16):3982 Note: Dosage error in article text]. *Cancer* 2010;**116**:2360-5.

Hale 2004 *{published data only}*

Hale G, Rebello P, Brettman LR, Fegan C, Kennedy B, Kimby E, et al. Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood* 2004;**104**:948-55.

Karlsson 2006 *{published data only}*

Karlsson C, Norin S, Kimby E, Sander B, Porwit Macdonald A, Nilsson B, et al. Alemtuzumab as first-line therapy for B-

cell chronic lymphocytic leukemia: long-term follow-up of clinical effects, infectious complications and risk of Richter transformation. *Leukemia* 2006;**20**:2204-7.

Kennedy 2000 *{published data only}*

Kennedy B, Forsyth PD, Smith GM, Rawstrom AC, Byrne J, Haynes A, et al. Campath - 1h therapy does not affect pbsc collection and engraftment in patients with CLL previously treated with fludarabine [abstract]. *Hematology Journal* 2000;**1**:201.

Lin 2010 *{published data only}*

Lin TS, Donohue KA, Byrd FC, Lucas MS, Hoke EE, Bengtson EM, et al. Consolidation therapy with subcutaneous alemtuzumab after fludarabine and rituximab induction therapy for previously untreated chronic lymphocytic leukemia: final analysis of CALGB 10101. *Journal of Clinical Oncology* 2010;**28**:4500-6.

Osterborg 1996 *{published data only}*

Osterborg A, Fassas AS, Anagnostopoulos A, Dyer MJ, Catovsky D, Mellstedt H. Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia. *British Journal of Haematology* 1996;**93**:151-3.

Pettitt 2006 *{published data only}*

Pettitt AR, Matutes E, Oscier D. Alemtuzumab in combination with high-dose methylprednisolone is a logical, feasible and highly active therapeutic regimen in chronic lymphocytic leukaemia patients with p53 defects. *Leukemia* 2006;**20**:1441-5.

References to ongoing studies

2006-0767 *{published data only}*

Alemtuzumab + rituximab consolidation in CLL (NCT00771602). Ongoing study August 2008.

39338 *{published data only}*

Low dose alemtuzumab for consolidation and maintenance of patients with B-cell CLL (NCT00336206). Ongoing study June 12, 2006.

CAM203 *{published data only}*

Subcutaneous alemtuzumab (CAMPATH®, MabCampath®) in relapsed/refractory B-CLL. Ongoing study May 18, 2006.

CLL8 *{published data only}*

CLL8: a randomised, phase III study to assess alemtuzumab consolidation therapy in patients with CLL who have responded to previous therapy (ISRCTN63375144). Ongoing study June 2008.

DMS-F0334 *{published data only}*

Fludarabine combined with either alemtuzumab or rituximab in treating patients with refractory or relapsed B-CLL (NCT00086775). Ongoing study July 2003.

Hovon 68 CLL *{published data only}*

A randomised phase III study in previously untreated patients with biological high-risk CLL: fludarabine and cyclophosphamide (FC) versus FC and low-dose alemtuzumab (ISRCTN25180151). Ongoing study December 2005.

P04715 *{published data only}*

SCH 727965 in patients with mantle cell lymphoma or B-CLL (study P04715AM2) (NCT00871546). Ongoing study March 2009.

Additional references

Binet 1981

Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981;**48**(1):198-206.

Byrd 2009a

Byrd JC, Peterson BL, Rai KR, Hurd D, Hohl R, Perry MC, et al. Fludarabine followed by alemtuzumab consolidation for previously untreated chronic lymphocytic leukemia: final report of Cancer and Leukemia Group B study 19901. *Leukemia and Lymphoma* 2009;**50**:1589-96.

Chiorazzi 2005

Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. *The New England Journal of Medicine* 2005;**352**(8):804-15.

Coles 2011

Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurology* 2011;**10**(4):338-48.

Cortelezzi 2009

Cortelezzi A, Pasquini MC, Gardellini A, Gianelli U, Bossi A, Reda G, et al. Low-dose subcutaneous alemtuzumab in refractory chronic lymphocytic leukaemia (CLL): results of a prospective, single-arm multicentre study. *Leukemia* 2009;**23**:2027-33.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Dohner 2000

Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *The New England Journal of Medicine* 2000;**343**(26):1910-6.

Eichhorst 2006

Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood* 2006;**107**(3):885-91.

Elter 2005

Elter T, Borchmann P, Schulz H, Reiser M, Trelle S, Schnell R, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. *Journal of Clinical Oncology* 2005;**23**(28):7024-31.

Elter 2009a

Elter T, Vehreschild JJ, Gribben J, Cornely OA, Engert A, Hallek M. Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Annals of Hematology* 2009;**88**:121-32.

Flinn 2007

Flinn IW, Neuberg DS, Grever MR, Dewald GW, Bennett JM, Paietta EM, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *Journal of Clinical Oncology* 2007;**25**(7):793-8.

Flynn 2007

Flynn JM, Byrd JC. Have we forgotten the purpose of phase III studies?. *Journal of Clinical Oncology* 2007;**25**(35):5553-5.

Fraser 2006

Fraser G, Smith CA, Imrie K, Meyer R, Hematology Disease Site Group. Alemtuzumab in chronic lymphocytic leukemia: a clinical practice guideline. Program in Evidence-based Care. Evidence-based series. Vol. **6-16**, Toronto (ON): Cancer Care Ontario (CCO): AHRQ - Agency for Healthcare Research + Quality, 2006.

GRADEpro [Computer program]

Jan B, Andrew O, Holger S. GRADEpro. Version 3.2 for Windows. Cochrane IMS, 2008.

Hainsworth 2008

Hainsworth JD, Vazquez ER, Spigel DR, Raefsky E, Bearden JD, Saez RA, et al. Combination therapy with fludarabine and rituximab followed by alemtuzumab in the first-line treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase 2 trial of the Minnie Pearl Cancer Research Network. *Cancer* 2008;**112**:1288-95.

Hallek 2008

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;**111**(12):5446-56.

Hallek 2008a

Hallek M, Fingerle-Rowson G, Fink A, Busch, R, Mayer J, Hensel M, et al. Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL). ASH Conference Proceedings. 2008:abstract 325.

Higgins 2011

Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Higgins 2011a

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Hillmen 2007

Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *Journal of Clinical Oncology* 2007;**25**(35):5616-23.

Kaufman 2011

Kaufman MS, Caramanica A, Janson D, Driscoll N, Johnson C, Kohn N, et al. Alemtuzumab maintenance may safely prolong chemotherapy-free intervals in chronic lymphocytic leukemia. *Med Oncol* 2011;**28**:532-8.

Keating 2002

Keating MJ, Flinn I, Jain V, Binet JL, Hillmen P, Byrd J, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* 2002;**99**(10):3554-61.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

Moreton 2005

Moreton P, Kennedy B, Lucas G, Leach M, Rassam SM, Haynes A, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *Journal of Clinical Oncology* 2005;**23**(13):2971-9.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Rai 1975

Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;**46**(2):219-34.

Review Manager (RevMan) [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Schünemann 2011

Schnemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings tables'. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Sterne 2011

Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Steurer 2006

Steurer M, Pall G, Richards S, Schwarzer G, Bohlius J, Greil R. Purine antagonists for chronic lymphocytic leukaemia. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD004270.pub2]

Stilgenbauer 2009

Stilgenbauer S, Zenz, T, Winkler D, Buhler A, Schlenk R, Groner S, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *Journal of Clinical Oncology* 2009;**27**(24):3994-4001.

Thursky 2006

Thursky KA, Worth LJ, Seymour JF, Miles PH, Slavin MA. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab*. *British Journal of Haematology* 2006;**132**(1):3-12.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

Weingart 2009

Weingart O, Elter T, Bauer K, Brillant C, Herbst C, Monsef I, et al. Monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD008079]

Wendtner 2004

Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jager G, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission--experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Leukemia* 2004;**18**(6):1093-101.

Wierda 2005

Wierda WG, Kipps TJ, Keating MJ. Novel immune-based treatment strategies for chronic lymphocytic leukemia. *Journal of Clinical Oncology* 2005;**23**(26):6325-32.

Wierda 2006

Wierda W, O'Brien S, Faderl S, Ferrajoli A, Wang X, Do KA, et al. A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukemia treated with fludarabine-based regimens. *Cancer* 2006;**106**(2):337-45.

Wierda 2011

Wierda WG, Kipps TJ, Keating MJ, Brown JR, Gribben JG, Browning M, et al. Self-administered, subcutaneous alemtuzumab to treat residual disease in patients with chronic lymphocytic leukemia. *Cancer* 2011;**117**:116-24.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

CAM 307

Methods	Randomisation • Two arms: up to 12 weeks alemtuzumab versus up to 12 cycles (4 weeks) of chlorambucil Recruitment period • December 2001 to June 2004 Median follow-up time

CAM 307 *(Continued)*

	• 24.6 months (range not reported)
Participants	Eligibility criteria • Flow cytometry–confirmed diagnosis of B-cell CLL • No previous chemotherapy • Clinical stage: Rai stage I to IV with evidence of progression according to National Cancer Institute Working Group (NCIWG) 1996 criteria • WHO performance status of 0 to 2 • At least 18 years of age • A life expectancy of at least 12 weeks • Adequate renal and liver function, no chronic oral corticosteroid use, no autoimmune thrombocytopenia, no CLL with CNS involvement, no positive quantitative CMV, PCR, no positivity for HIV, no presence of active infection • Patients must have provided written informed consent Patients (N = 297) • Alemtuzumab (N = 149); (N = 2 withdrew consent before treatment, and were not included in safety analysis) • Chlorambucil (N = 148); (N = 1 withdrew consent before treatment, and were not included in safety analysis) Mean age • Alemtuzumab: 59 years (range 35 to 86 years); chlorambucil: 60 years (range 36 to 83 years) Gender (male) • Alemtuzumab: 106 (71.1%); chlorambucil: 107 (72.3%) Stage of disease (Rai) • Stage 0 or missing: alemtuzumab: 4.0%; chlorambucil: 2.0% • Stage I-II: alemtuzumab: 62.4%; chlorambucil: 64.9% • Stage III-IV: alemtuzumab: 33.6%; chlorambucil: 33.1% Country • 44 centres (nine in the United States, 35 in Europe)
Interventions	Alemtuzumab • Alemtuzumab was escalated daily (3, 10, and 30 mg) until tolerated at an IV dose of 30 mg over 2 hours. Patients received alemtuzumab 30 mg three times a week for no more than 12 weeks, including the dose-escalation phase. • Premedication: diphenhydramine and acetaminophen or paracetamol orally (PO) 30 minutes before dosing, with optional IV meperidine or hydrocortisone. • During the first month, patients received allopurinol days -1 to 13. Patients received prophylactic trimethoprim/ sulfamethoxazole DS and famciclovir during therapy and for at least 2 months after the last dose or until CD4 counts were 200 cells/L or higher. Chlorambucil (every 28 days) • 40mg/m^2 PO for 28 days for no more than 12 cycles. • Allopurinol days -1 to 8 for the first three cycles. • Prophylactic antibiotics were not required.

CAM 307 *(Continued)*

	Treatment was to be discontinued in both arms if a patient experienced progressive disease, unacceptable toxicity, autoimmune anaemia, or autoimmune thrombocytopenia. Subsequent treatment was at the discretion of the treating physician.
Outcomes	Reported Primary outcome: • PFS Secondary outcomes • OS • Time to alternative treatment • TRM • ORR • CRR • MRD-negativity • Adverse events • Number of patients discontinuing the study because of drug-related adverse events
Notes	All authors are either employees or consultants for Genzyme Corp or have received research grants from Genzyme Corp. One author is a consultant or has a advisory role for Bayer Schering Pharma.

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	Unclear risk	Comment: The study did not report this outcome.
Blinding (performance bias and detection bias) All other outcomes	Unclear risk	Comment: Patient and physician unblinded. Quote (for outcome assessor): "All the efficacy analyses were based on the independent response review panel's assessment of eligibility, response and, data of progression".
Incomplete outcome data (attrition bias) All outcomes	Low risk	297 recruited patients Quote: "Three patients (two assigned to alemtuzumab and one to chlorambucil) withdrew consent before treatment administration and were not included in the safety analysis." Quote: "All randomly assigned patients were included in the efficacy analysis per the intent-to-treat principle."
Selective reporting (reporting bias)	Unclear risk	Comment: A study protocol is registered (clinical.trials.gov: NCT00046683), but it does not provide any information of the pre-planned primary and secondary outcomes.
Other bias	Unclear risk	Comment: The study appears to be free of other sources of bias.

CAM 314

Methods	Randomisation • Two arms: up to 6 cycles fludarabine plus alemtuzumab (Flu-Cam) versus up to 6 cycles fludarabine (Flu) alone Recruitment period • July 2004 to October 2008 Median follow-up time • 29.5 months
Participants	Eligibility criteria • Relapsed or refractory disease after 1 prior regimen ○ Except patients who were refractory to (i.e., progressed on) fludarabine or alemtuzumab therapy. Patients who previously responded (CR or PR) to fludarabine or alemtuzumab therapy, but who have relapsed at the time of study entry, may be eligible but response to fludarabine or alemtuzumab therapy must have lasted >12 months • Clinical stage: Rai stage I to IV with evidence of progression Patients randomised (N = 335) • Flu-Cam (N = 168): (N = 4 were not treated and were not included in safety analysis) • Flu (N = 167): (N = 2 were not treated and were not included in safety analysis) Mean age • Flu-Cam: 60.0 years; Flu: 60.8 years Gender (male): • Flu-Cam: 109 (65%); Flu: 108 (65%) Stage of disease (Rai stage group) • Stage I-II: Flu-Cam: 104 (62%); Flu: 102 (61%) • Stage III-IV: Flu-Cam: 62 (37%); Flu: 63 (38%) Country • 18 centres in North America and 317 in Europe
Interventions	Flu-Cam (every 28 days; up to 6 cycles) • FluCam patients received escalating doses of alemtuzumab IV until the 30 mg dose was tolerated. • Then, they received Flu 30 mg/m2 IV followed by alemtuzumab 30 mg IV days 1 to 3 every 28 days. Flu (every 28 days, up to 6 cycles) • Patients received 25 mg/m2 IV days 1 to 5 every 28 days. All patients received prophylaxis with cotrimoxazole and famciclovir until CD4+ counts were > 200 cells/mcL.
Outcomes	Primary outcome • PFS Secondary outcomes

CAM 314 *(Continued)*

- OS
- PFS
- TRM
- CRR
- ORR
- Time to alternative therapy
- Health related quality of life
- Pharmacokinetics of fludarabine alone to the pharmacokinetics of fludarabine when concomitantly administered with alemtuzumab
- Adverse events

Reported (relevant for this review)

- OS
- PFS
- TRM
- CRR
- ORR
- Adverse events

Not reported (relevant for this review)

- Time to alternative treatment
- MRD

Not evaluated (relevant for this review)

- Number of patients discontinuing the study because of drug-related adverse events

Notes	Most of the authors are either employees or consultants for Genzyme Corp or have received research grants from Genzyme Corp. Two authors are employees of Genzyme Corp. More patients than planned were randomised without a clear rationale.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients (..) were randomized to FluCam or Flu using the minimization method" Comment: The authors used a adequate method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated allocation schedule"
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 other 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	Quote: "Analysis was by intention to treat" Comment: all randomised patients were analysed

CAM 314 *(Continued)*

Selective reporting (reporting bias)	Low risk	Preplanned outcomes (ClinicalTrials.gov: NCT00086580) in the publication for all pre-defined outcomes reported except • Time to alternative therapy • Incidence of MRD negativity • Health related quality of life • Pharmacokinetics of fludarabine alone to the pharmacokinetics of fludarabine when concomitantly administered with alemtuzumab Comment: The primary endpoint and the patient-important outcomes except quality of life are reported
Other bias	Unclear risk	Quote: "The planned sample size for this study of 300 patients..." "... 335 patients were enrolled..." "More patients than planned were enrolled to enable an analysis of potential drug-drug interactions." Comment: The rationale for randomising more than the planned number of patients is unclear

CLL2007FMP

Methods	Randomisation • Two arms: 6 courses of fludarabine and cyclophosphamide (FluC) plus alemtuzumab (Cam) versus 6 courses of fludarabine and cyclophosphamide (FluC) plus rituximab (R) 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 (cumulative illness rating scale (CIRS) score < or = 6); creatinine clearance at least 60 ml/min • No 17p deletion Patients randomised (N = 165) • FluC-Cam (N = 82): (withdrawals or exclusions not stated) • FluC-R (N = 83): (withdrawals or exclusions not stated) The trial was stopped early due to unacceptable toxicity in the FluC-Cam arm (6 deaths versus 0 in FluC-R arm) Mean age • Not stated Gender (male, female) • Not stated Stage of disease (Rai stage group)

CLL2007FMP *(Continued)*

	• Not stated Countries • France and Belgium
Interventions	FluC-Cam (every 28 days; up to 6 cycles) • Patients received fludarabine 40mg/m^2 days 1 to 3 and cyclophosphamide 250 mg/m^2 days 1 to 3 plus alemtuzumab 30 mg subcutaneous days 1 to 3 FluC-R • Patients received fludarabine 40mg/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 Anti-infective prophylaxis included trimethoprim-sulfamethoxazole and valaciclovir during immunochemotherapy and until the CD4-positive lymphocyte count reached 0.2 10^9/L.
Outcomes	Primary outcome • 36-month PFS Secondary outcomes • OS • Disease-free survival • Event-free survival • Time to next treatment • ORR (CRR and PR) • Rate of phenotypic and molecular response • Duration of phenotypic, molecular, complete and partial responses • Response rates and survival times in biological subgroups • Adverse effects • Quality of life • Minimal residual disease study Reported (relevant for this review) • CRR • ORR • TRM • MRD • Adverse events Not reported (relevant for this review) • OS • PFS • Time to next treatment Not evaluated (relevant for this review) • Number of patients discontinuing the study because of drug-related adverse events
Notes	The trial was discontinued after randomisation of 165 patients for unacceptable toxicity in the FluC-Cam arm (6 deaths 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

CLL2007FMP *(Continued)*

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	Comment: The study did not report this outcome.
Blinding (performance bias and detection bias) All other 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: CR (FCR: 56/80 = 70%, FCCam: 45/79 = 59%, ns)" Reasons of exclusions are not provided.
Selective reporting (reporting bias)	High risk	Pre-planned outcomes (ClinicalTrials.gov: NCT00564512) in the abstract-publications reported for all pre-defined outcomes except • OS • Disease-free survival • Event-free survival • PFS • Time to next treatment • Rate of phenotypic and molecular response • Duration of phenotypic, molecular, complete and partial responses • Response rates and survival times in biological subgroups • Quality of life
Other bias	High risk	Quote: "The trial recruitment was discontinued because of an increase in mortality in the FCCam arm (6 deaths versus 0 in FCR arm), and the last 13 patients enrolled were not randomized" Comment: The trial was stopped early due to data-dependent process.

GCLLSG CLL4B

Methods	Randomisation • Two arms: up to 12 weeks alemtuzumab consolidation therapy versus observation Recruitment period • Not stated Median follow-up time

GCLLSG CLL4B *(Continued)*

- 48 months from start of chemotherapy with Flu or FluC (range not stated).

Participants	Eligibility criteria • B-cell CLL in first complete or partial remission after fludarabine or fludarabine/cyclophosphamide first-line therapy • Between 18 and 66 years of age • Alemtuzumab had to be started no less than 30 days and no more than 90 days after the last dose of fludarabine or fludarabine/cyclophosphamide • No autoimmune cytopenia or severe infections during first line treatment; no medical conditions requiring long-term use of oral corticosteroids Patients recruited (N = 23) Two patients refused initiation of study treatment after randomisation and were excluded from analysis • Alemtuzumab (N = 11): (withdrawals or exclusions not stated) • Observation (N = 10): (withdrawals or exclusions not stated) Mean age • Alemtuzumab: 60 years (range 38 to 63 years); observation: 58 years (range 37 to 66 years) Gender (male) • Alemtuzumab: 8 (72.7%); observation: 7 (70.0%) Stage of disease (according to Rai) • Alemtuzumab: 1 Rai I, 10 Rai II; observation: 1 Rai I, 6 Rai II, 1 Rai III; 2 Rai IV Countries • Germany and Austria
Interventions	Patients received six cycles of fludarabine (25 mg/m^2 days 1 to 5 IV every 28 days) or fludarabine/cyclophosphamide (fludarabine 30 mg/m^2 d1 to 3 IV, cyclophosphamide 250 mg/m^2 days 1 to 3 IV every 28 days). Patients were stratified according to induction treatment and response to induction treatment and randomised for treatment with alemtuzumab or observation. Alemtuzumab • Patients received 3 mg on day 1; if well tolerated, dose was increased to 10 mg on day 2 and to the target dose of 30 mg on day 3. The 30 mg dose was subsequently given three times per week as a 2-h infusion for a maximum of 12 weeks. Therapy was discontinued, if an unacceptable toxicity occurred and stopping criteria for the trial were set as grade 3 or 4 infections occurring in the alemtuzumab arm in five of the first 10 patients. Premedication with antihistamines (e.g., 2 mg IV clemastin), paracetamol (500 mg PO) and prednisone (100 mg IV) was given with the first dose at each escalation and thereafter only if clinically indicated. Anti-infective prophylaxis including cotrimoxazole (960 mg PO twice daily, three times per week) and famciclovir (250 mg PO, twice daily) was given during and up to a minimum of 2 months following the discontinuation of alemtuzumab therapy. Control • No further treatment
Outcomes	Reported Primary outcome

GCLLSG CLL4B *(Continued)*

- PFS

Secondary outcomes

- OS
- Time to next treatment
- TRM
- CRR
- ORR
- MRD
- Adverse events
- Number of patients discontinuing the study because of drug-related adverse events

Not reported

- None

Notes	The study was supported by a research grant of Schering AG, Berlin and MedacSchering Onkologie, Germany

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	Comment: The study did not report this outcome.
Blinding (performance bias and detection bias) All other outcomes	Unclear risk	Comment: Patient and physician unblinded. No information about blinding of outcome assessor provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In all, 23 patients were recruited for this study, two patients refused initiation of study treatment after randomisation and were excluded from analysis." Comment: It is unclear in which group the two patients (8.7%) were randomised, why they refused treatment according to randomisation and why they were not analysed as randomised.
Selective reporting (reporting bias)	Unclear risk	Comment: The study has no registered study protocol. The review authors have not information to permit judgement.
Other bias	High risk	Quote: "This randomized phase III trial shows that a consolidation with alemtuzumab in a standard dose of 30mg IV TIW in CLL patients responding to fludarabine-based chemotherapy is associated with an increased incidence of severe infections and myelotoxicity. Therefore, this multicenter trial was prematurely closed."

Gribben 2005

Methods	Randomisation • To arms: up to 6 cycles fludarabine plus alemtuzumab (Flu-Cam) versus up to 6 cycles fludarabine plus rituximab (Flu-R) 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-Cam (N = 4): (withdraws or exclusions not stated) • Flu-R (N = 8): (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-Cam: 2 patients (50.0%); Flu-R: 1 patient (12.5%) • Stage III-IV: Flu-Cam: 2 patients (50.0%); Flu-R: 7 patients (87.5%) Country • Not stated
Interventions	Patients were assessed monthly for response while on therapy, and interim restaging occurred at cycle 4. Those who achieved a CR received no further therapy, whereas those who achieved a PR or SD received 2 additional cycles. Flu-Cam • Patients received fludarabine 25 mg/m^2 IV and alemtuzumab 30 mg subcutaneus, on days 1 to 5 of each cycle. 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.
Outcomes	Outcomes Reported • CRR • ORR • Adverse events • Number of patients discontinuing the study because of drug-related adverse events

Gribben 2005 *(Continued)*

	Not evaluated or reported • OS • PFS • Time to next treatment • TRM • MRD
Notes	No conflict of interest statement in the abstract.

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	Comment: The study did not report this outcome.
Blinding (performance bias and detection bias) All other 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	The information about completeness of outcome data is insufficient to permit judgement.
Selective reporting (reporting bias)	High risk	Preplanned outcomes (ClinicalTrials.gov: NCT00086775) in the abstract-publications reported for all pre-defined outcomes except: • 1-year survival • Time to progression • Duration of response • Adverse events • Molecular response rate • Lymphocyte and lymphocyte subset recovery (CD3, CD3/CD4, CD3/CD8, CD20) • Time to complete response
Other bias	Unclear risk	In this phase II trial 12 patients only were randomised, without providing a rationale for the uneven distribution (4 patients alemtuzumab arm versus 8 patients in the rituximab arm). Comment: The review authors have no further information on the uneven distribution to permit judgement.

CLL: Chronic lymphocytic leukaemia; CMV: cytomegalovirus; CNS: central nervous system; CR: complete response; CRR: complete response rate; HIV: human immunodeficiency virus; IV: intravenous; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PCR: polymerase chain reaction; PFS: progression-free survival; PO: orally; PR: partial response; TRM: treatment-related mortality; WHO: World Health Organization.

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

Study	Reason for exclusion
Bolli 2004	Not a randomised controlled trial.
Byrd 2009	Not a randomised controlled trial.
Elter 2009	Not a randomised controlled trial.
Faderl 2010	Not a randomised controlled trial.
Hale 2004	Not a randomised controlled trial.
Karlsson 2006	Not a randomised controlled trial.
Kennedy 2000	Not a randomised controlled trial.
Lin 2010	Not a randomised controlled trial.
Osterborg 1996	Not a randomised controlled trial.
Pettitt 2006	Not a randomised controlled trial.

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

2006-0767

Trial name or title	Alemtuzumab + rituximab consolidation in CLL (NCT00771602)
Methods	Consolidation therapy for patients with CLL with evidence of residual disease following prior chemo(immuno)therapy. Randomisation: • Three arms: rituximab versus alemtuzumab versus alemtuzumab + rituximab
Participants	Inclusion Criteria • Patients with CLL, CLL/PLL, or SLL who have achieved an NCI-WG nodular partial (nPR) or CR with documentation of residual disease by MRD flow cytometry following chemotherapy or chemo-immunotherapy. • Age >/=18 years. • ECOG performance status </=2; serum creatinine </= 2 mg/dL; serum total bilirubin </= 2 mg/dL; serum AST or ALT < 4 x ULN.
Interventions	Rituximab • Rituximab 375 mg/m^2 by standard IV infusion on days 1, 8, 15, and 22 of weeks 1 to 4. Alemtuzumab • Alemtuzumab 30 mg SC during week 1 Rituximab plus alemtuzumab • Rituximab 375 mg/m^2 by standard IV infusion on days 1, 8, 15, and 22 of weeks 1 to 4.

2006-0767 *(Continued)*

	• Alemtuzumab 30 mg SC during week 1
Outcomes	Primary outcome • Number of patients with molecular remissions at 52 weeks • MRD Secondary outcomes • PFS • 52 week toxicity rate
Starting date	August 2008
Contact information	The University of Texas M.D. Anderson Cancer Center (Stefan Faderl M.D./ Associate Professor)
Notes	Sponsor: Genzyme Estimated enrolment: 100 Estimated primary completion date: December 2010 (Final data collection date for primary outcome measure) Study status according to ClinicalTrials.gov: This study is terminated - 1 patient enrolled

39338

Trial name or title	Low dose alemtuzumab for consolidation and maintenance of patients with B-cell CLL (NCT00336206)
Methods	SC injection of low dose alemtuzumab for consolidation and maintenance of patients in clinical response after having achieved partial or complete remission after 1st or 2nd line anti-tumour therapy for B-Cell CLL Randomisation • Two arms: alemtuzumab versus placebo
Participants	Inclusion criteria • B-CLL diagnosis taken consideration of NCI criteria. • In case of CR: positive MRD status • At least achieving a PR to the last line of anti-tumour therapy given and than at least PR is still present after a follow-up of 3 to 6 months after the last anti-tumour course (wash-out period) • Age >=18 years and <= 75 years. • WHO performance status 0 to 2. Exclusion criteria • Elapsed time of less than 3 months or more than 6 months since last dose of previous anti-tumour therapy • Previous alemtuzumab administration • Contraindication for alemtuzumab • More than 2 previous treatment regimens • SD or PD on last anti-tumour therapy • Persistent CLL symptoms in clinical need of further anti-tumour therapy
Interventions	Alemtuzumab

39338 *(Continued)*

	• No further information provided Placebo
Outcomes	Primary outcome • Time to treatment failure (TTF) Secondary outcomes • CRR • PRR • MRD • ORR • Duration of response • Safety
Starting date	June 12, 2006
Contact information	Contact: Jorgen Kristensen, MD PhD jkr@emirates.net.ae
Notes	Estimated enrolment: 60 Estimated primary completion date: October 2009 Study status according to ClinicalTrials.gov: The recruitment status is unknown because the information has not been verified recently

CAM203

Trial name or title	Subcutaneous alemtuzumab (CAMPATH®, MabCampath®) in relapsed/refractory B-CLL
Methods	A phase II trial to evaluate the efficacy and safety of SC administered alemtuzumab in patients with previously treated B-CLL. Randomisation • Two arms: alemtuzumab (dose escalation) versus alemtuzumab (no escalation)

Participants	Inclusion criteria
	
	• A diagnosis of B-cell CLL; according to the NCI WG Criteria
	• WHO performance status of 0, 1, or 2
	• Previous therapy with at least one but no more than 5 regimens (single agent or combination regimen). One therapy regimen is defined as consecutive, contiguous cycles of the same drug(s) with no treatment interruptions lasting > 3 months
	• Patient requires treatment for CLL per the following criteria:
	  ◦ Rai stage III or IV;
	  ◦ Rai stage 0-II with at least one of the following - evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia; Massive or progressive splenomegaly; Progressive lymphocytosis with an increase of greater than 50% over a 2-month period or an anticipated doubling time of less than 6 months; Lymphocyte count > 100 x 10^9/L; B-symptoms
	• More than 3 weeks since prior chemotherapy. Patient must have recovered from the acute side effects incurred as a result of previous therapy

CAM203 *(Continued)*

	Exclusion criteria • Previously treated with alemtuzumab • Previous bone marrow transplant
Interventions	Alemtuzumab (dose escalation) • The dose is escalated as tolerated using 3mg,10mg, and 30mg, administered SC (if tolerated). When escalation to 30 mg dose is tolerated, all subsequent doses are administered at 30 mg SC 3 times per week at alternating injection sites for up to 18 weeks. Alemtuzumab (no escalation) • All patients will be treated with 30mg of alemtuzumab (with no escalation period) administered SC (at alternating injection sites) 3 times per week for up to 18 weeks.
Outcomes	Primary outcome • Best disease response to alemtuzumab treatment administered SC for up to 18 weeks in patients with (B-cell CLL) [Time Frame: 44 weeks with additional observation period thereafter] Secondary outcome • PFS • Duration of response • OS • MRD • Safety
Starting date	May 18, 2006
Contact information	Genzyme
Notes	Sponsor: Genzyme Estimated enrolment: 85 Estimated primary completion date: July 2011 (Final data collection date for primary outcome measure) Study status according to ClinicalTrials.gov: This study is ongoing, but not recruiting participants.

CLL8

Trial name or title	CLL8: a randomised, phase III study to assess alemtuzumab consolidation therapy in patients with CLL who have responded to previous therapy (ISRCTN63375144)
Methods	The trial is intended to assess the effect on PFS of SC alemtuzumab in B-CLL patients who have responded to previous chemotherapy. Randomisation • Two arms: alemtuzumab versus observation
Participants	Inclusion criteria • At least 18 years old, either sex • Previous confirmation of B-CLL with a characteristic immunophenotype on peripheral blood flow cytometry

CLL8 *(Continued)*

	• Maximum of three prior therapies received for CLL treatment • Between 6 and 12 months since completing most recent therapy for CLL • Response to most recent chemotherapy treatment for CLL with PR, nCR or CR • No prior alemtuzumab therapy • Absence of clinically evident lymphadenopathy (largest lymph node less than 2 cm in minimum diameter) Exclusion criteria • Disease progression after response to latest therapy • Persisting severe pancytopenia (neutrophils less than 0.5 x 10^9/L or platelets less than 50 x 10^9/L) • Patients previously treated with allogeneic SCT
Interventions	Alemtuzumab • Patients will receive 30 mg SC infusion three times a week for six weeks. After six weeks of treatment patients will undergo an assessment of response. Patients who are assessed as having no detectable CLL (MRD negative) after six weeks of treatment will receive no further treatment with alemtuzumab. Patients who are assessed as having detectable CLL (MRD positive) but showing no improvement will also stop treatment. Patients who are assessed as having detectable CLL (MRD positive) with a reduction in levels after six weeks of treatment will receive a further six weeks of treatment with alemtuzumab. Again such patients will receive 30 mg SC infusion three times a week for six weeks. Patients will then be assessed for response at the end of treatment which will include a blood and bone marrow sample being taken No consolidation therapy • Not any treatment

Outcomes	Primary outcome
	
	• PFS
	
	Secondary outcomes
	
	• Proportion of patients with undetectable minimal residual disease (MRD), measured at the six month post-randomisation follow-up visit
	• Response
	  ◦ For patients receiving treatment with alemtuzumab: after six weeks of treatment (and 12 weeks if applicable)
	  ◦ For patients not receiving treatment with alemtuzumab: three months post-randomisation
	  ◦ For all patients: six months after randomisation (omitted if within four weeks of prior assessment) and 12 months after randomisation
	• OS
	• Time to MRD relapse for patients who are or who become MRD negative
	• Safety and toxicity
	• Quality of life: measured at baseline and 3, 6, 12, 24 and 36 months after randomisation
	• Quality adjusted life years (QALYs)

Starting date	June 2008
Contact information	Prof Peter Hillmen Department of Haematology Level 3 Bexley Wing St James's University Hospital Beckett Street Leeds United Kingdom: peter.hillmen@nhs.net

CLL8 *(Continued)*

Notes	Sponsor: Leeds Teaching Hospitals NHS Trust (UK) Target number of participants: 288 Anticipated end date: December 214

DMS-F0334

Trial name or title	Fludarabine combined with either alemtuzumab or rituximab in treating patients with refractory or relapsed B-CLL (NCT00086775)
Methods	Phase II trial comparing combination treatment with fludarabine and alemtuzumab to fludarabine and rituximab in patients with B-CLL requiring treatment after first line therapy Randomisation • Two arms: fludarabine plus alemtuzumab versus fludarabine plus rituximab
Participants	Inclusion criteria • Diagnosis of B-cell CLL • Refractory to OR relapsed after prior first-line therapy • Age 18 and over • Performance status: ECOG 0-2 • Biologic therapy: more than 4 weeks since prior alemtuzumab and/or rituximab; no prior bone marrow transplantation; no concurrent thrombopoietin or pegfilgrastim • Chemotherapy: more than 3 weeks since prior fludarabine • More than 3 months since prior investigational drugs • No other concurrent cytotoxic therapy
Interventions	Fludarabine plus alemtuzumab • Patients receive fludarabine IV over 30 minutes on days 1 to 5. At least 30 minutes before fludarabine administration, patients receive alemtuzumab SC on days 1 to 5. Fludarabine plus rituximab • Patients receive fludarabine IV over 30 minutes on days 1 to 5. At least 30 minutes before fludarabine administration, patients receive rituximab IV on days 1 and 4 of course 1 and on day 1 only in subsequent courses.
Outcomes	Primary outcome • CRR Secondary outcomes • ORR • 1-year survival • Time to progression • Duration of response • Adverse event • Molecular response rate • Lymphocyte and lymphocyte subset recovery (CD3, CD3/CD4, CD3/CD8, CD20) • Time to complete response • Rate of cytomegalovirus reactivation and time to reactivation

DMS-F0334 *(Continued)*

Starting date	July 2003
Contact information	Ann S. LaCasce, MD, Dana-Farber Cancer Institute
Notes	Sponsor: Bayer Estimated enrolment: no information provided Estimated primary completion date: June 2005 (Final data collection date for primary outcome measure) Study status according to ClinicalTrials.gov: This study has been completed

Hovon 68 CLL

Trial name or title	A randomised phase III study in previously untreated patients with biological high-risk CLL: fludarabine and cyclophosphamide (FC) versus FC and low-dose alemtuzumab (ISRCTN25180151)
Methods	Prospective, multicenter, randomised controlled trial Randomisation • Two arms: fludarabine and cyclophosphamide plus alemtuzumab versus fludarabine and cyclophosphamide
Participants	Inclusion criteria • Biological high-risk CLL • Patients with symptomatic stage A, symptomatic stage B or stage C • Age 18 to 75 years inclusive Exclusion criteria • WHO performance status >/= 3, unless related to CLL • Previously treated with chemotherapy, radiotherapy or immunotherapy for CLL • History of active cancer during the past 5 years, except non-melanoma skin cancer or stage 0 cervical carcinoma
Interventions	Fludarabine and cyclophosphamide plus alemtuzumab • 6 cycles of oral FluC combined with SC alemtuzumab Fludarabine and cyclophosphamide • 6 cycles of oral FluC
Outcomes	Primary outcome • PFS Secondary outcomes • Event free survival • Clinical, flow cytometric and molecular response rate • Overall survival • Disease free survival • Toxicity

Hovon 68 CLL *(Continued)*

Starting date	December 2005
Contact information	Prof M.H.J. Oers, van Academic Medical Center Department of Hematologie P.O. Box 22660 Amsterdam Netherlands m.h.vanoers@amc.uva.nl
Notes	Sponsor: Rigshospitalet (Denmark) Target number of participants: 300 Status of trial: completed

P04715

Trial name or title	SCH 727965 in patients with mantle cell lymphoma or B-CLL (study P04715AM2) (NCT00871546)
Methods	A randomised phase 2 study of SCH 727965 in subjects with relapsed or refractory mantle cell lymphoma (MCL) or B-cell CLL Randomisation • Four arms: B-CLL patients treated with SCH 727965 versus B-CLL patients treated with alemtuzumab; MCL patients treated with SCH 727965 versus MCL patients treated with bortezomib

Participants	Inclusion criteria
	
	• Age >=18 years, either sex, any race.
	• ECOG performance status of 0 or 1.
	• For subjects with MCL:
	  ◦ Diagnosis of MCL according to the World Health Organization (WHO) criteria. Received at least one prior chemotherapeutic regimen, but no more than two regimens including stem cell transplantation. Measurable or assessable disease by the Revised Response Criteria for Malignant Lymphoma
	• For subjects with B-CLL
	  ◦ Documented B-CLL according to the National Cancer Institute Working Group (NCI-WG) criteria. Received at least one prior alkylating agent-based regimen and one fludarabine- or pentostatin-containing regimen, but must not have received more than two prior regimens. Measurable or assessable disease by NCI-WG criteria
	
	Exclusion criteria
	
	• Previous treatment with SCH 727965 or other cyclin-dependent kinase inhibitors
	• For MCL, previous treatment with bortezomib
	• For B-CLL, previous treatment with alemtuzumab

Interventions	B-CLL patients • SCH 727965: ◦ SCH 727965 50 mg/m2 IV on day 1 of each 21-day cycle until disease progression • Alemtuzumab:

P04715 *(Continued)*

	○ Alemtuzumab dose-titrated to the goal maintenance dose of 30 mg/day IV or SC three times a week on alternate days for a total of 12 weeks. MCL patients • SCH 727965: ○ SCH 727965 50 mg/m2 IV on day 1 of each 21-day cycle until disease progression. • Bortezomib: ○ Bortezomib 1.3 mg/m2 IV on days 1, 4, 8, and 11 of each 21-day cycle until disease progression.
Outcomes	Primary outcome • Response rate Secondary outcomes • Time to disease progression
Starting date	March 2009
Contact information	No contacts provided
Notes	Sponsor: Schering-Plough Estimated enrolment: 200 Estimated primary completion date: March 2011 (Final data collection date for primary outcome measure) Study status according to ClinicalTrials.gov: This study is ongoing, but not recruiting participants.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; B-CLL: B-cell chronic lymphocytic leukaemia: CLL: chronic lymphocytic leukaemia; CR: complete response; CRR: complete response rate; IV: intravenous; MRD: minimal residual disease; nCR: near complete response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PLL: prolymphocytic leukaemia; PR: partial response; SC: subcutaneous; SCT: stem cell transplantation; SLL: small lymphocytic lymphoma.

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PFS - overall analysis	2	356	Hazard Ratio (Fixed, 95% CI)	0.58 [0.44, 0.76]
2 PFS - subgrouped by treatment regimens	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
2.1 combinations with chemotherapy	1	335	Hazard Ratio (Fixed, 95% CI)	0.61 [0.47, 0.81]
2.2 not combined with another chemotherapy	1	21	Hazard Ratio (Fixed, 95% CI)	0.17 [0.05, 0.60]
3 PFS - subgrouped by starting point of alemtuzumab	2	356	Hazard Ratio (Fixed, 95% CI)	0.58 [0.44, 0.76]

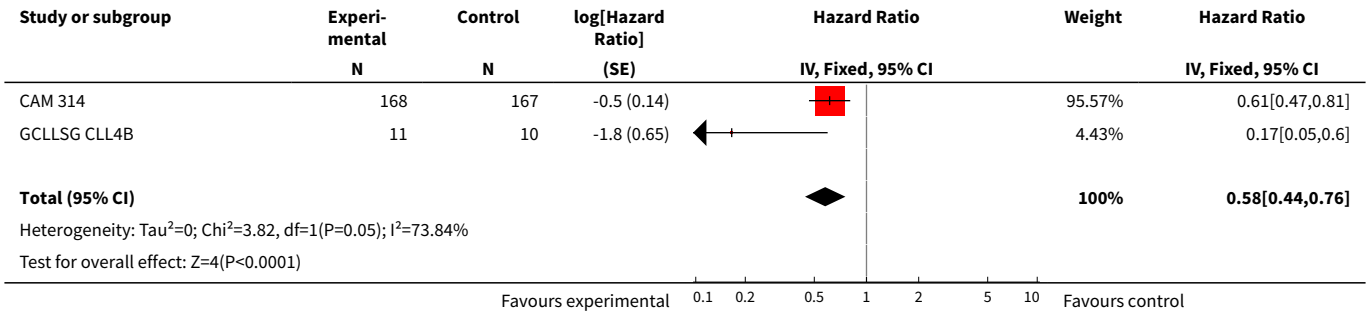
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 relapse therapy	1	335	Hazard Ratio (Fixed, 95% CI)	0.61 [0.47, 0.81]
3.2 consolidation therapy	1	21	Hazard Ratio (Fixed, 95% CI)	0.17 [0.05, 0.60]
4 Treatment related mortality	2	356	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.17, 1.90]
5 ORR - overall analysis	2	356	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.23]
6 ORR - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 combinations with chemotherapy	1	335	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.97, 1.21]
6.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.92, 2.14]
7 ORR - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 relapse therapy	1	335	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.97, 1.21]
7.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.92, 2.14]
8 CRR - overall analysis	2	356	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.26, 5.42]
9 CRR - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 combinations with chemotherapy	1	335	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [1.30, 6.83]
9.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.28, 6.56]
10 CRR - subgrouped by starting point of alemtuzumab	2	356	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.26, 5.42]
10.1 relapse therapy	1	335	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [1.30, 6.83]
10.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.28, 6.56]
11 CMV reactivation - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	10.52 [1.42, 77.68]
12 CMV reactivation - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	9.05 [0.49, 166.84]
12.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	11.92 [0.76, 187.84]
13 CMV reactivation - subgrouped by starting point of alemtuzumab	2	350	Risk Ratio (M-H, Fixed, 95% CI)	10.52 [1.42, 77.68]
13.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	9.05 [0.49, 166.84]
13.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	11.92 [0.76, 187.84]
14 Infections (all grades) - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.01, 1.74]
15 Infections (all grades) - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.88, 1.53]
15.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	19.25 [1.27, 291.20]
16 Infections (all grades) - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.88, 1.53]
16.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	19.25 [1.27, 291.20]
17 Anaemia grade 3/4 - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.33, 1.20]
18 Anaemia grade 3/4 - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.26, 1.06]
18.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [0.25, 85.33]
19 Anaemia grade 3/4 - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.26, 1.06]

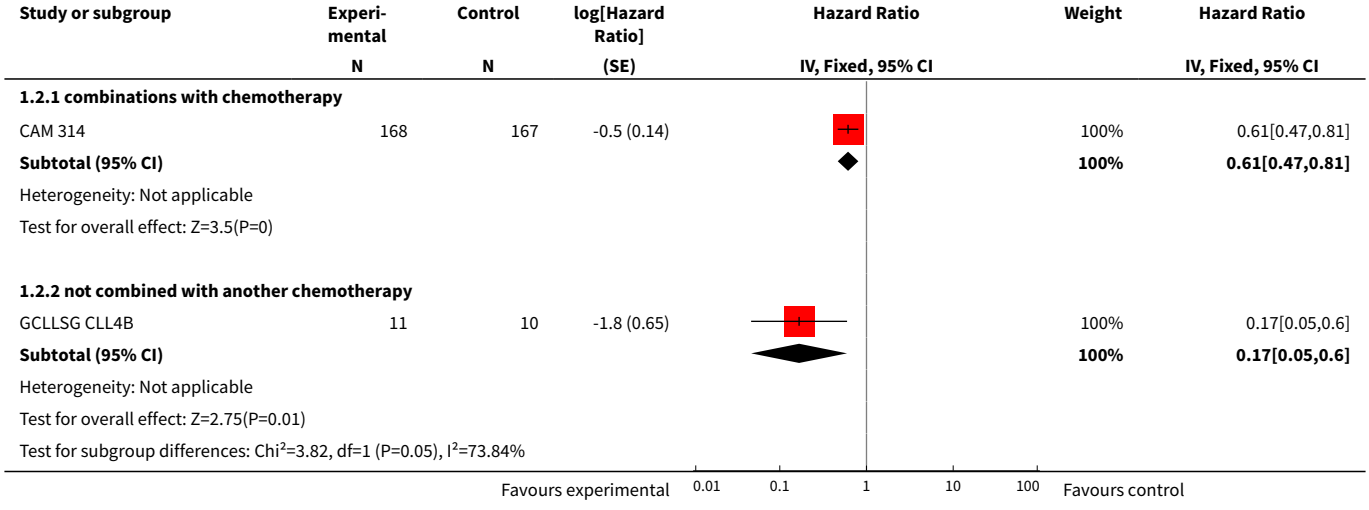
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [0.25, 85.33]
20 Neutropenia grade 3/4 - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.97, 1.61]
21 Neutropenia grade 3/4 - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.89, 1.48]
21.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	13.75 [0.88, 213.65]
22 Neutropenia grade 3/4 - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.89, 1.48]
22.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	13.75 [0.88, 213.65]
23 Thrombocytopenia grade 3/4 - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.58, 1.89]
24 Thrombocytopenia grade 3/4 - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.45, 1.59]
24.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [0.50, 136.33]
25 Thrombocytopenia grade 3/4 - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.45, 1.59]
25.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [0.50, 136.33]
26 SAEs - overall analysis	2	350	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.95, 1.89]
27 SAEs - subgrouped by treatment regimens	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 combinations with chemotherapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.94, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.2 not combined with another chemotherapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.12, 60.70]
28 SAEs - subgrouped by starting point of alemtuzumab	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 relapse therapy	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.94, 1.87]
28.2 consolidation therapy	1	21	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.12, 60.70]

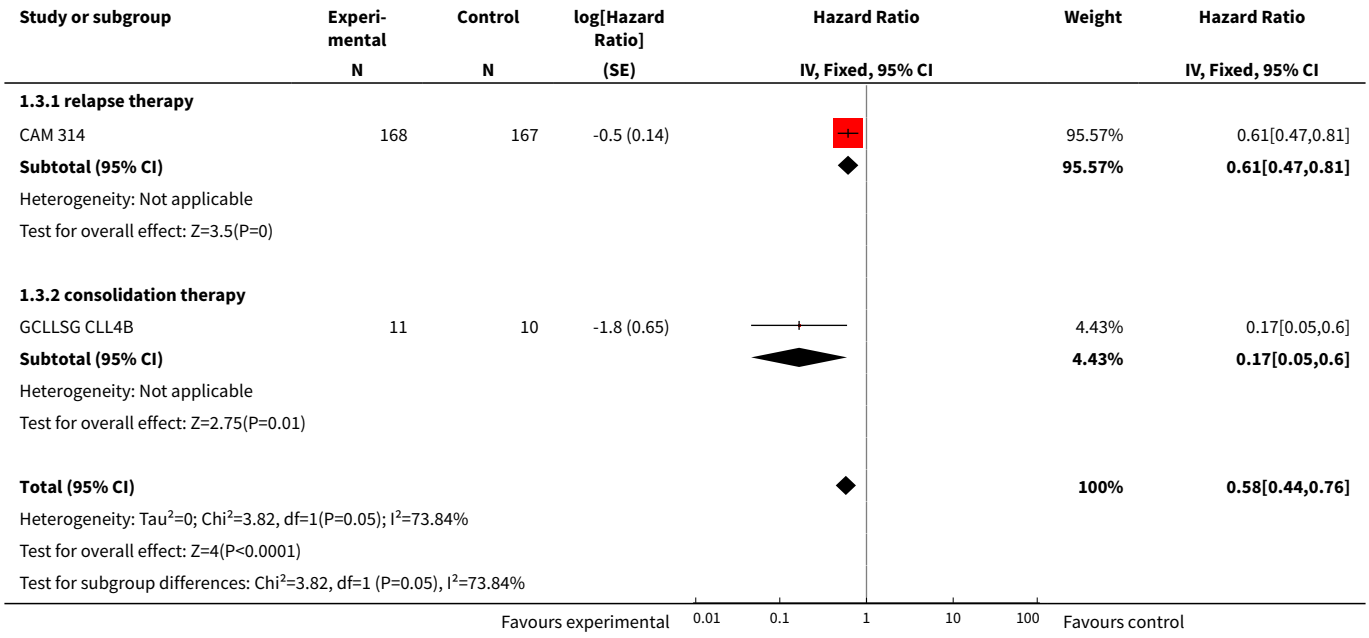
Analysis 1.1. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 1 PFS - overall analysis.



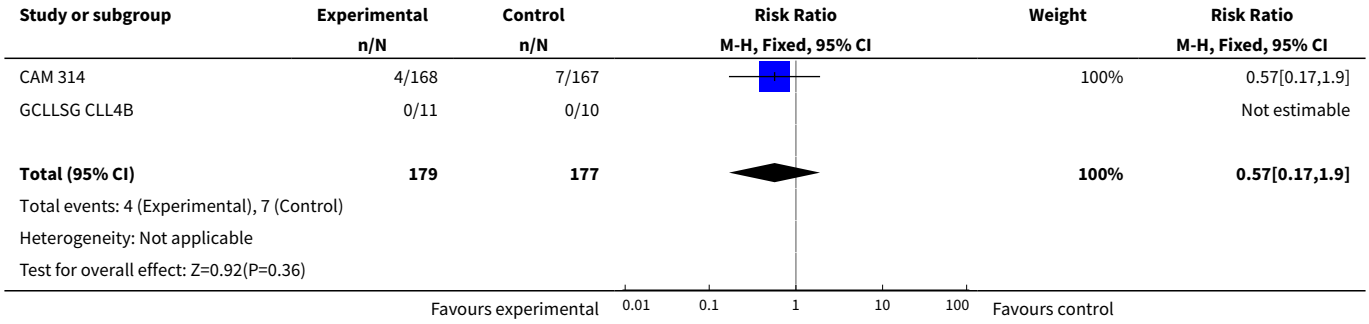
Analysis 1.2. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 2 PFS - subgrouped by treatment regimens.



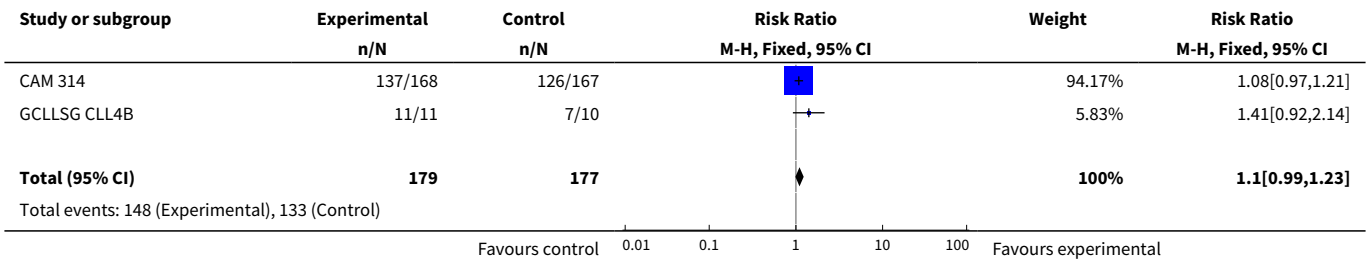
Analysis 1.3. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 3 PFS - subgrouped by starting point of alemtuzumab.

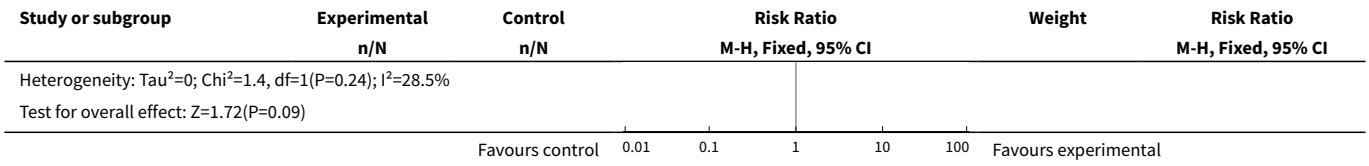


Analysis 1.4. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 4 Treatment related mortality.

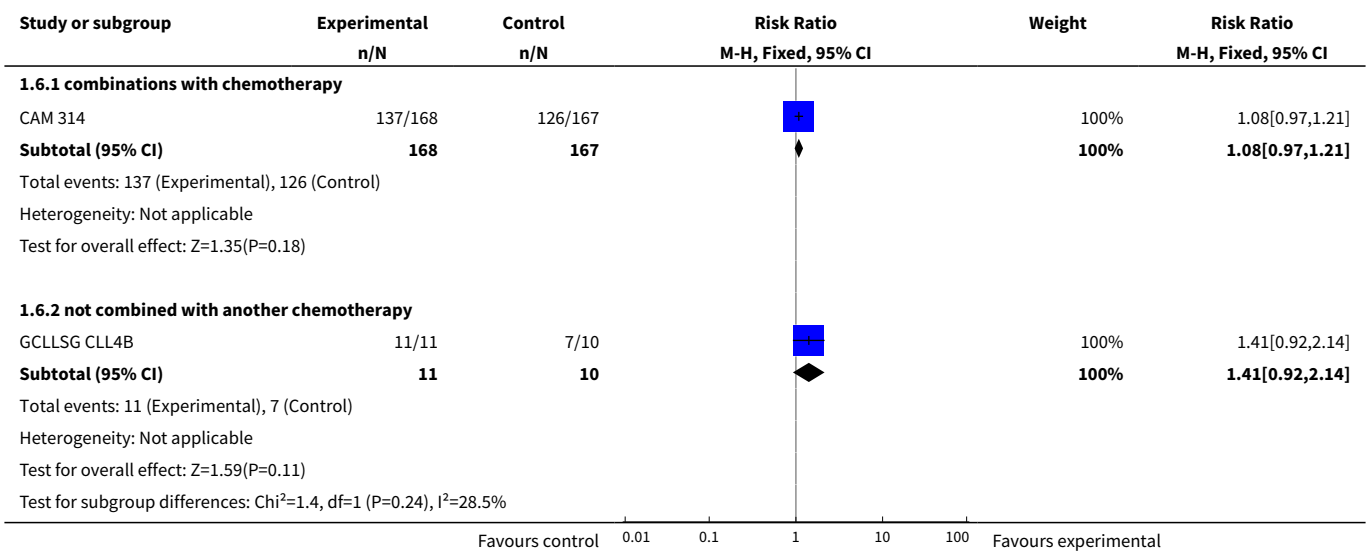


Analysis 1.5. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 5 ORR - overall analysis.

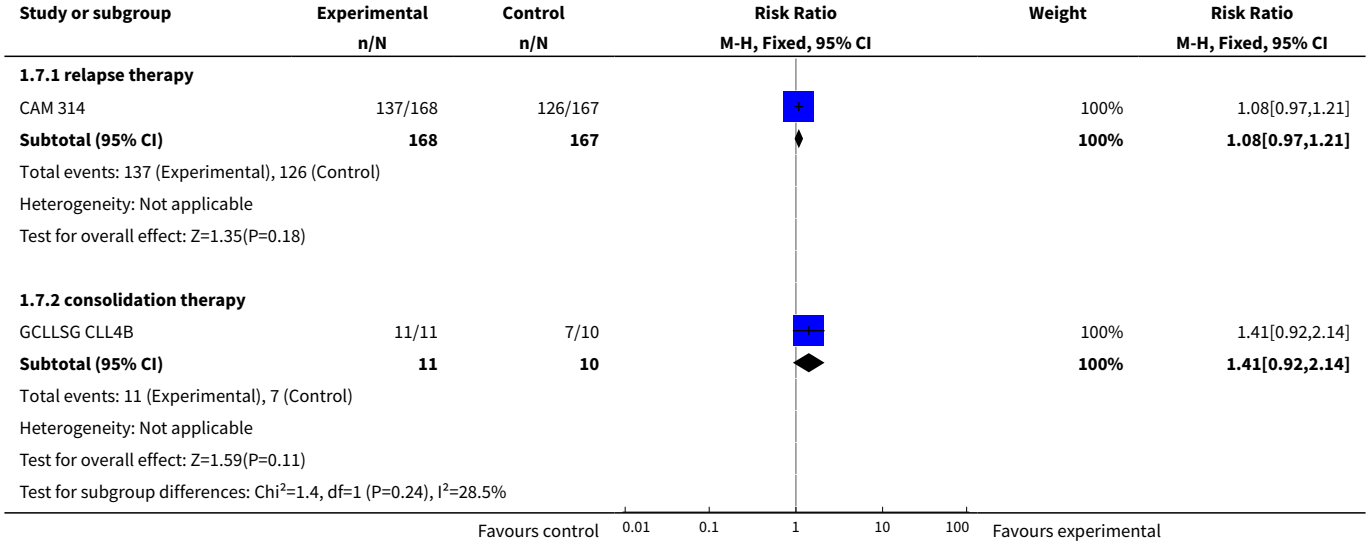




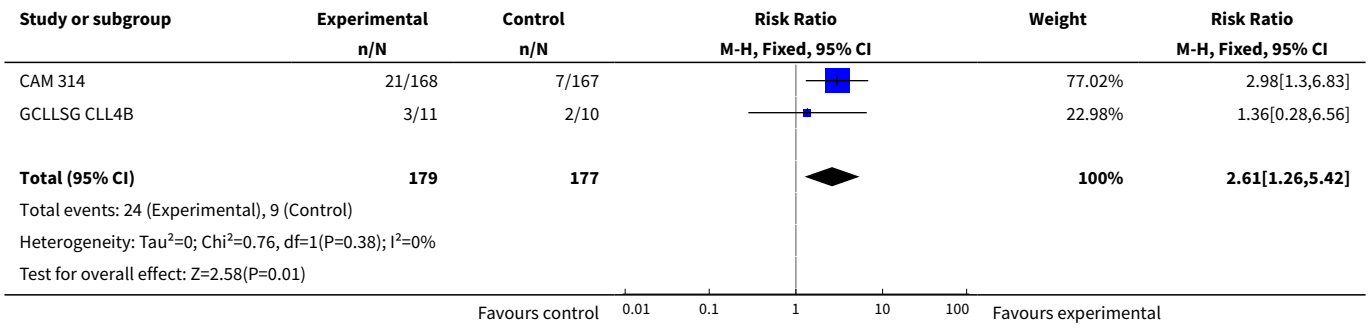
Analysis 1.6. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 6 ORR - subgrouped by treatment regimens.



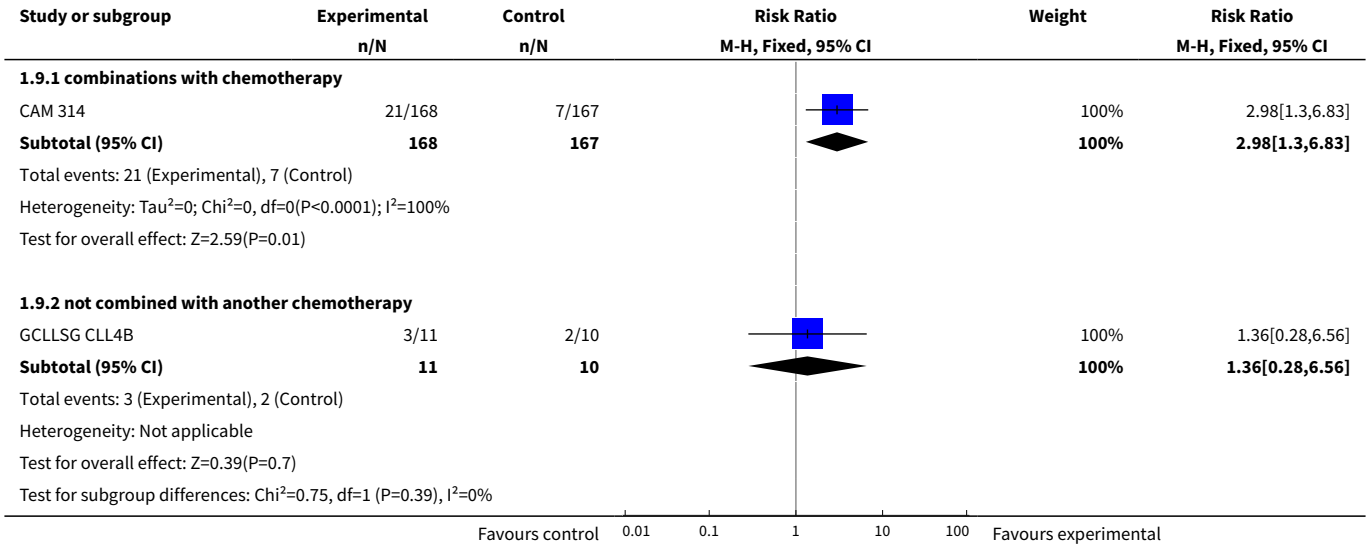
Analysis 1.7. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 7 ORR - subgrouped by starting point of alemtuzumab.



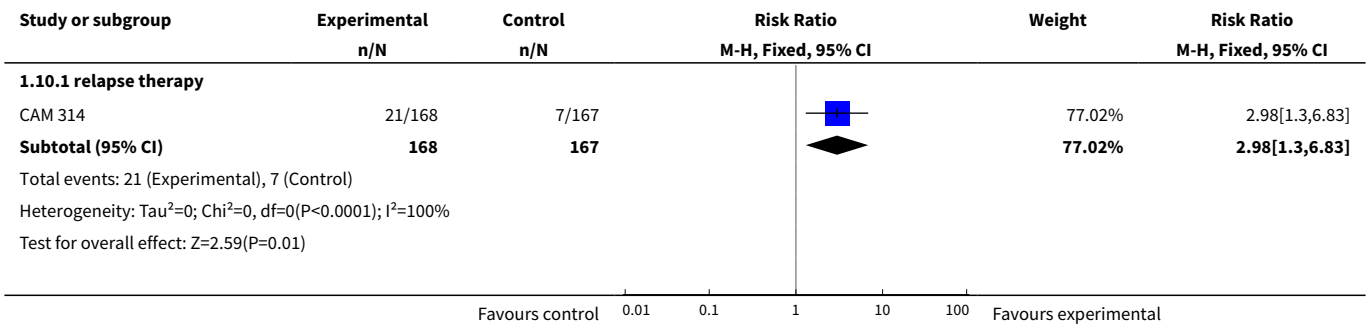
Analysis 1.8. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 8 CRR - overall analysis.

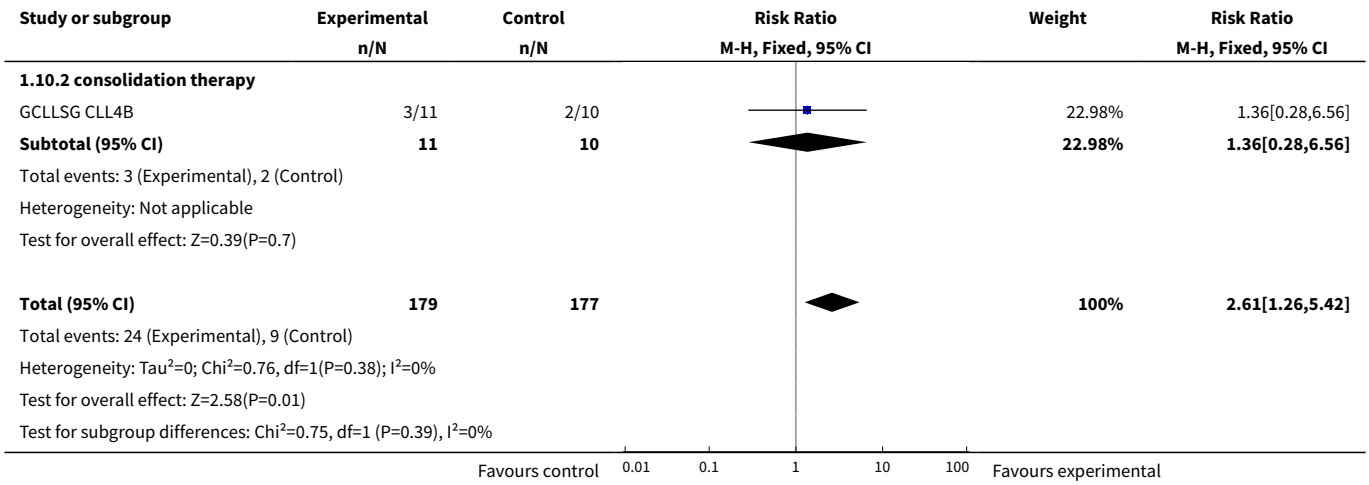


Analysis 1.9. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 9 CRR - subgrouped by treatment regimens.

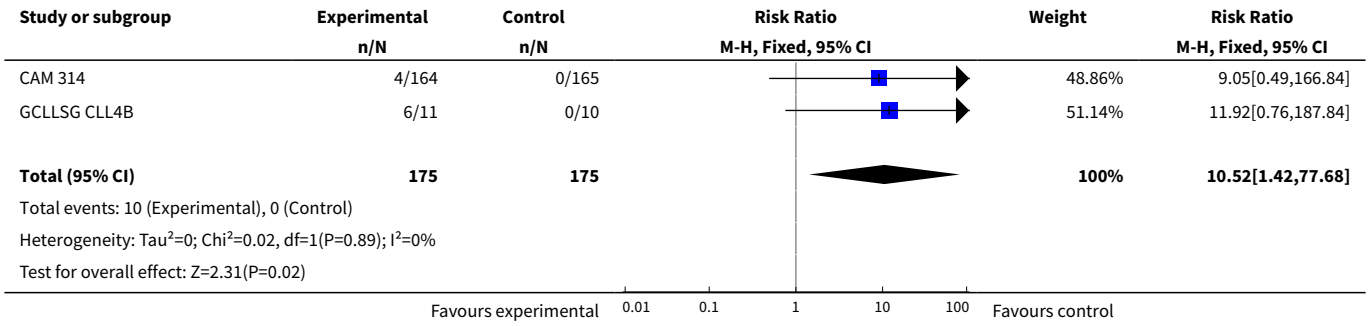


Analysis 1.10. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 10 CRR - subgrouped by starting point of alemtuzumab.

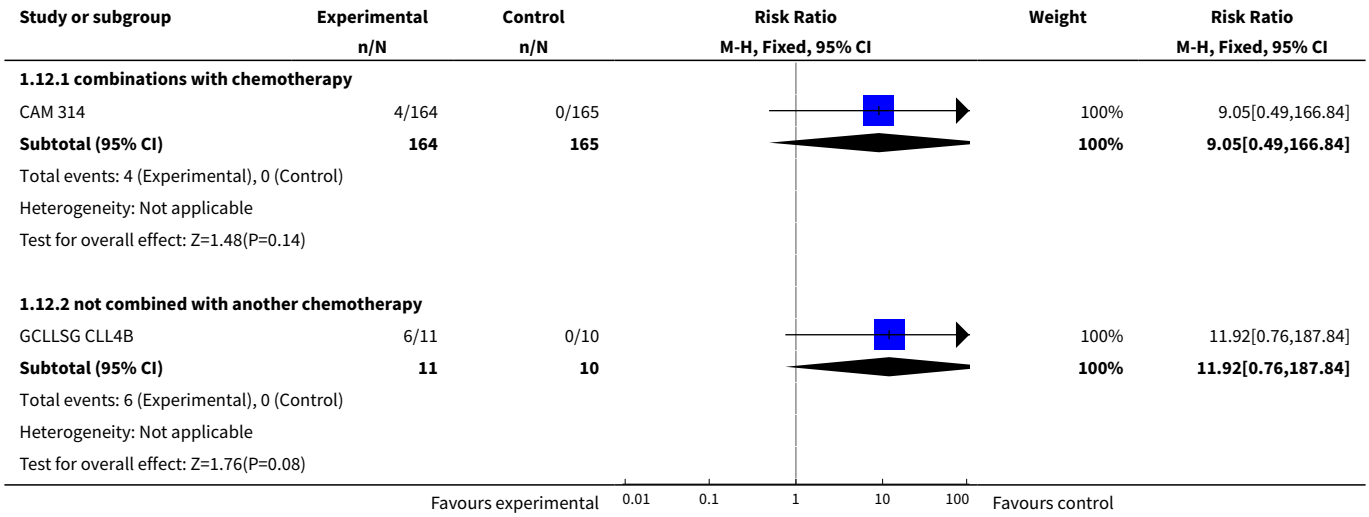


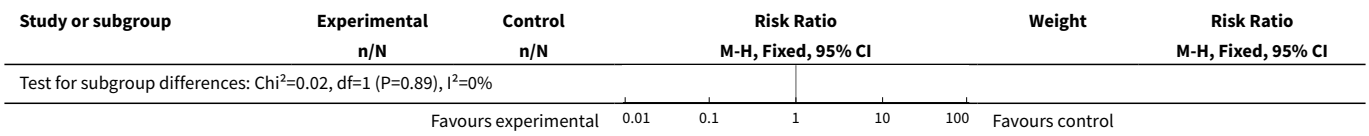


Analysis 1.11. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 11 CMV reactivation - overall analysis.

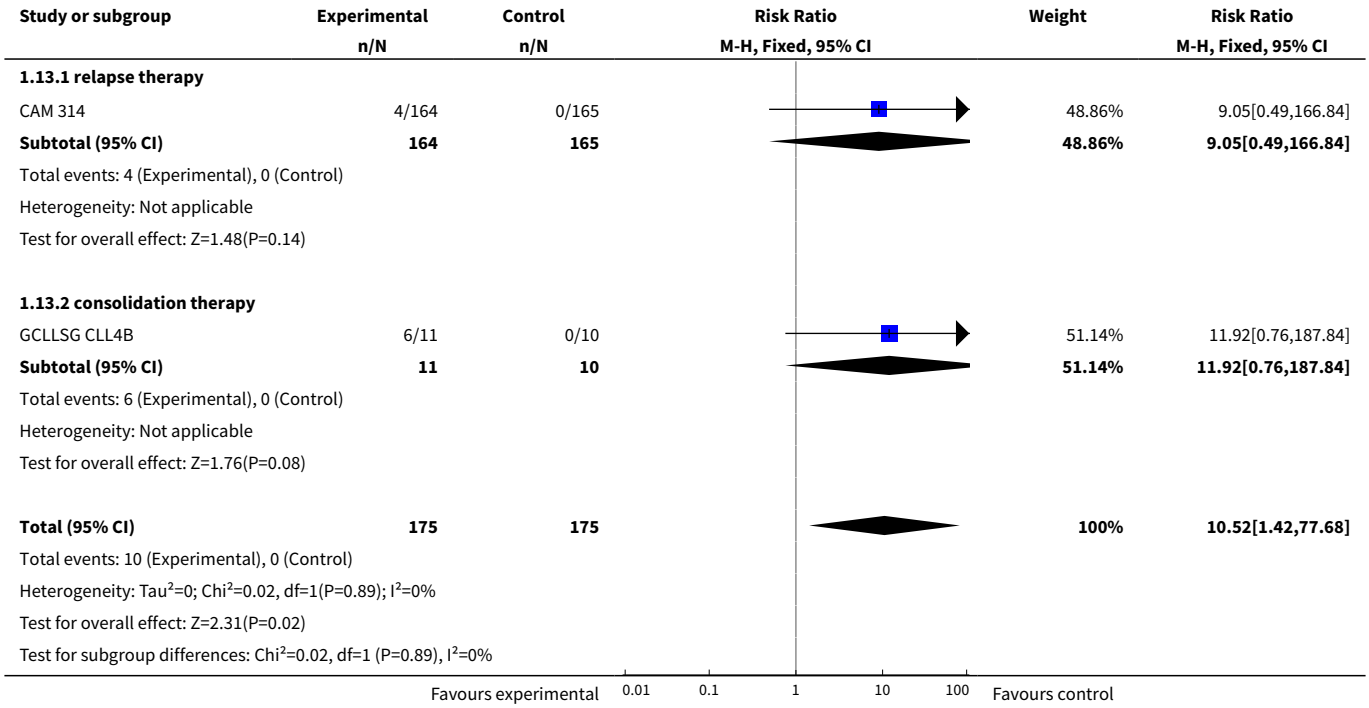


Analysis 1.12. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 12 CMV reactivation - subgrouped by treatment regimens.

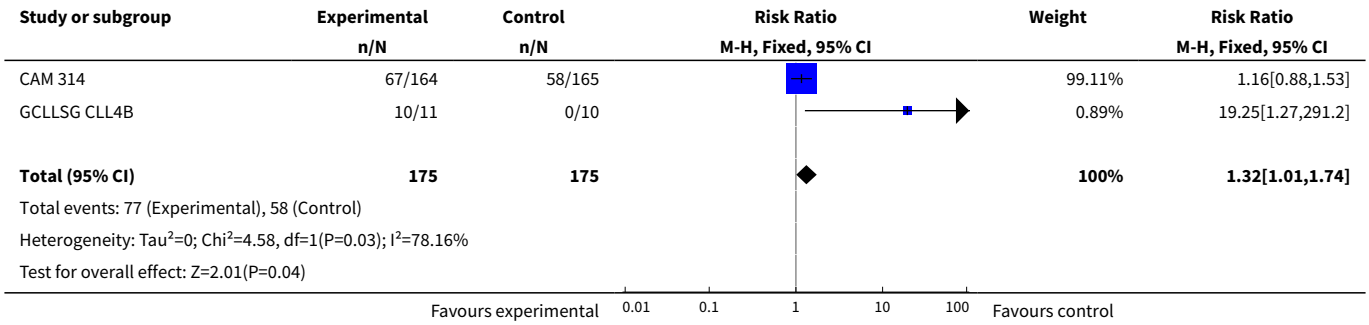




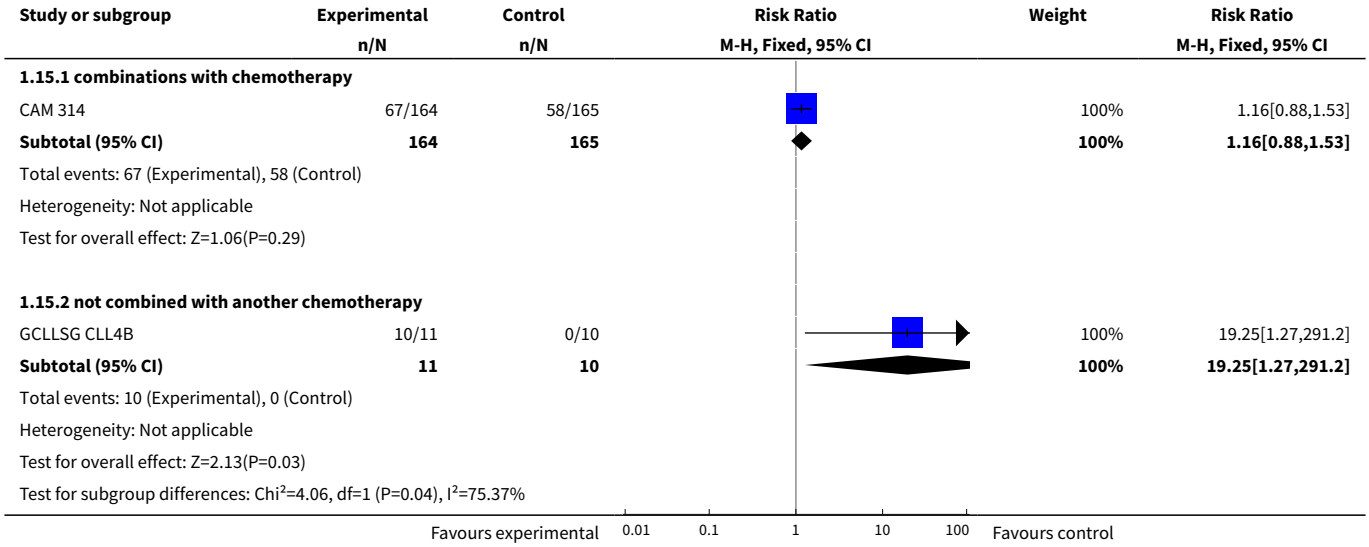
Analysis 1.13. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 13 CMV reactivation - subgrouped by starting point of alemtuzumab.



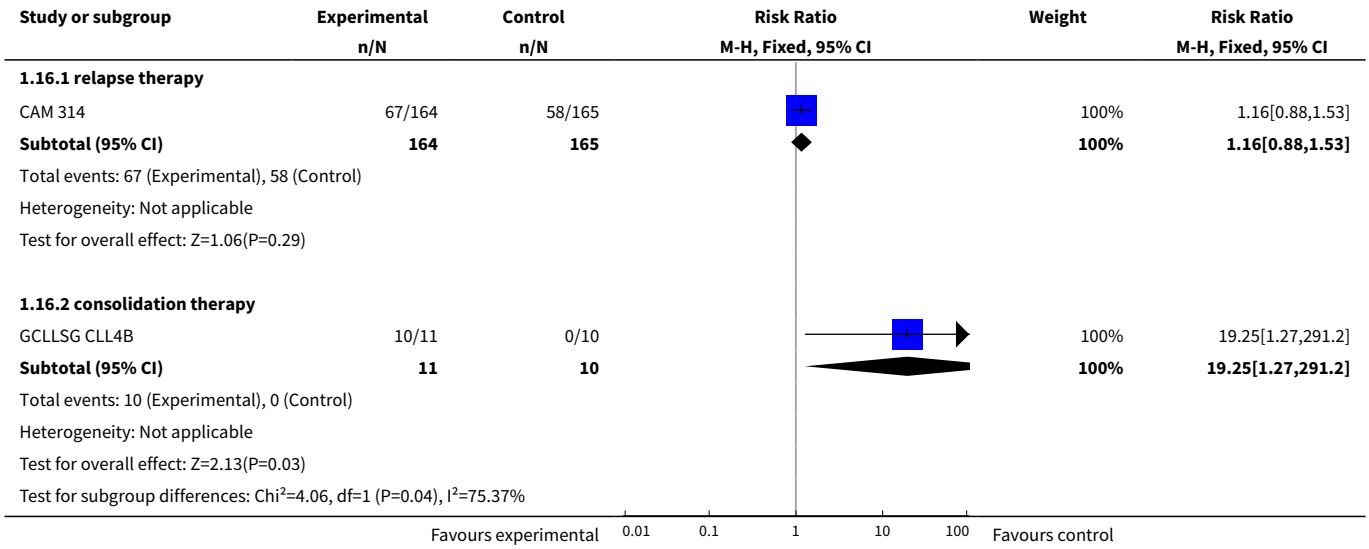
Analysis 1.14. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 14 Infections (all grades) - overall analysis.



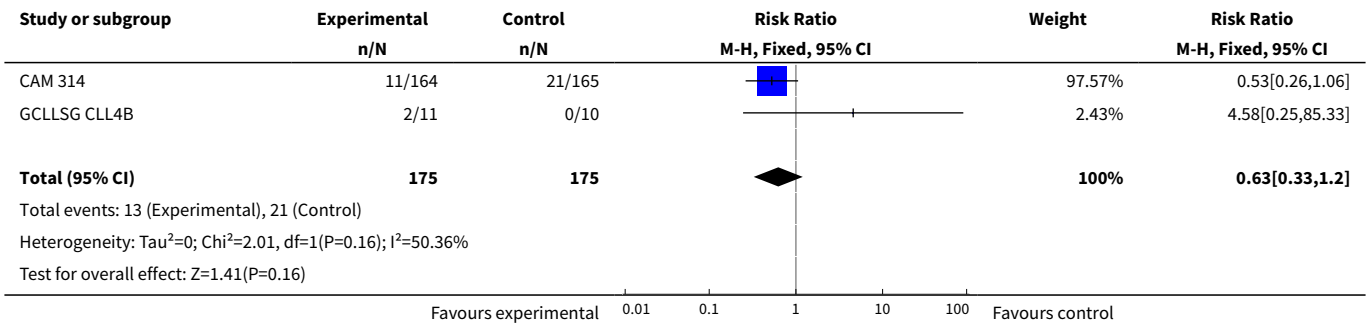
Analysis 1.15. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 15 Infections (all grades) - subgrouped by treatment regimens.



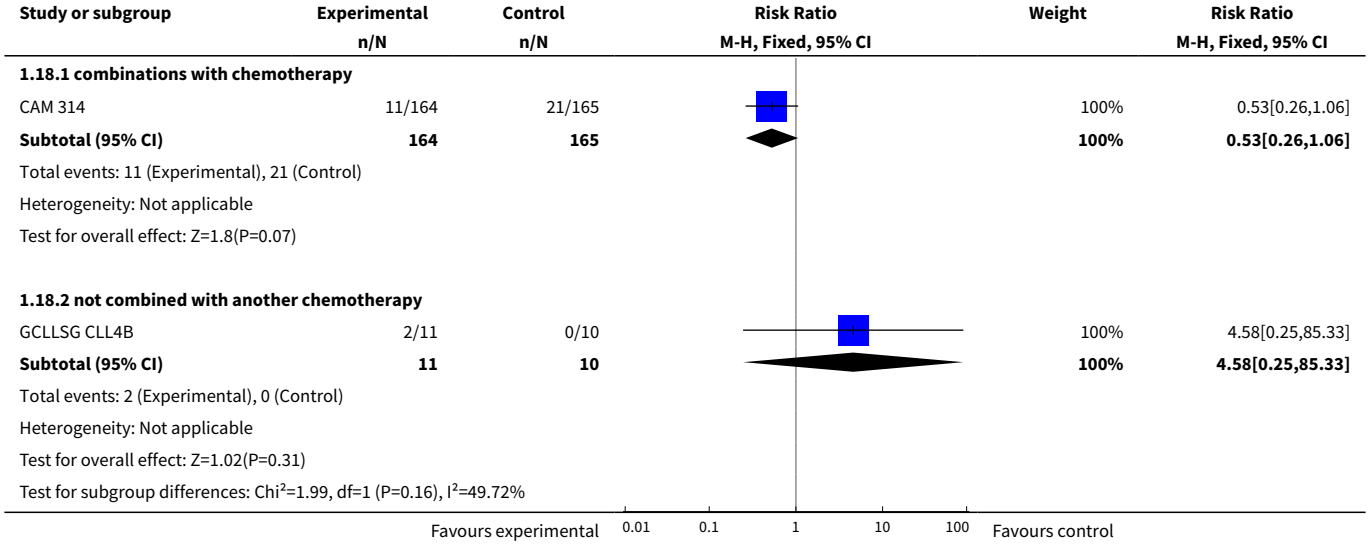
Analysis 1.16. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 16 Infections (all grades) - subgrouped by starting point of alemtuzumab.



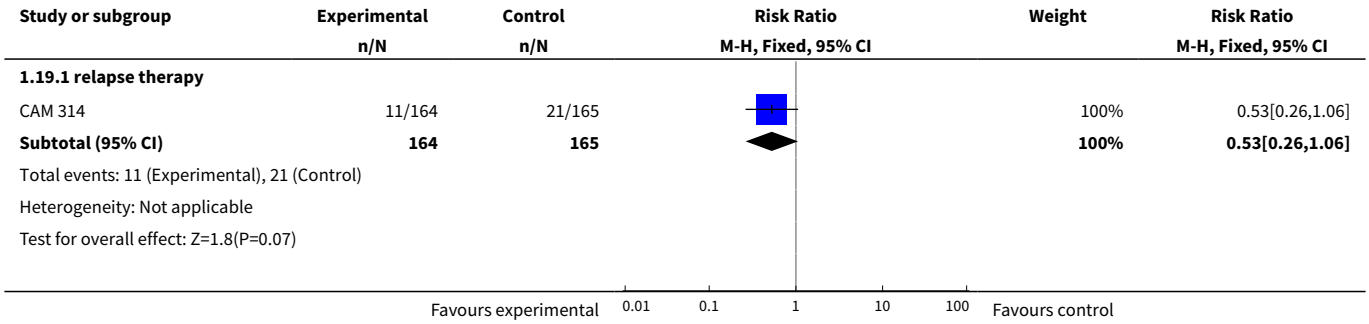
Analysis 1.17. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 17 Anaemia grade 3/4 - overall analysis.

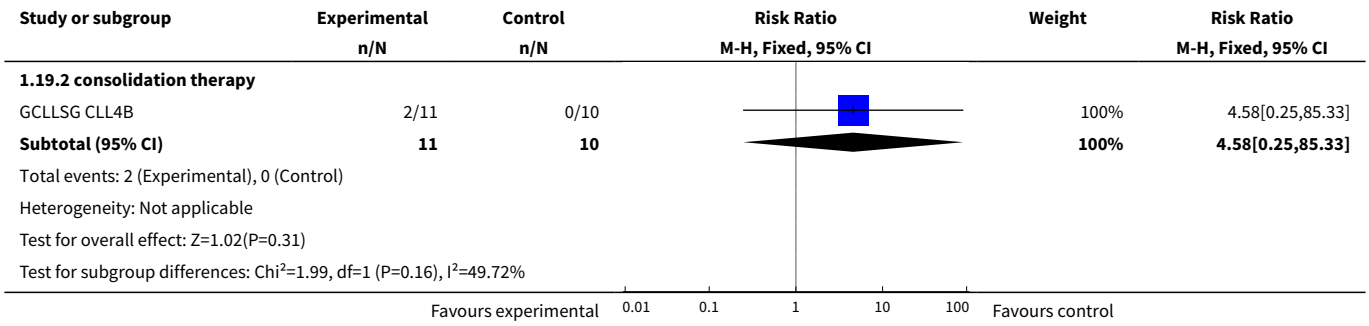


Analysis 1.18. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 18 Anaemia grade 3/4 - subgrouped by treatment regimens.

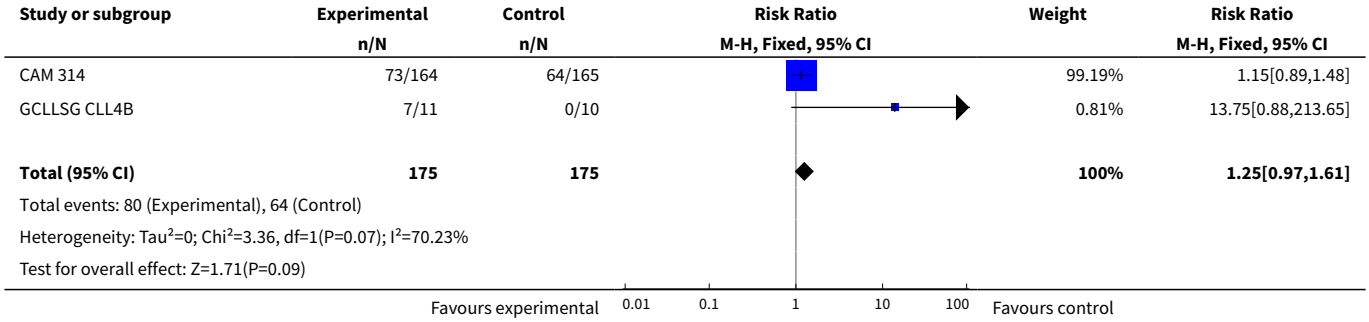


Analysis 1.19. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 19 Anaemia grade 3/4 - subgrouped by starting point of alemtuzumab.

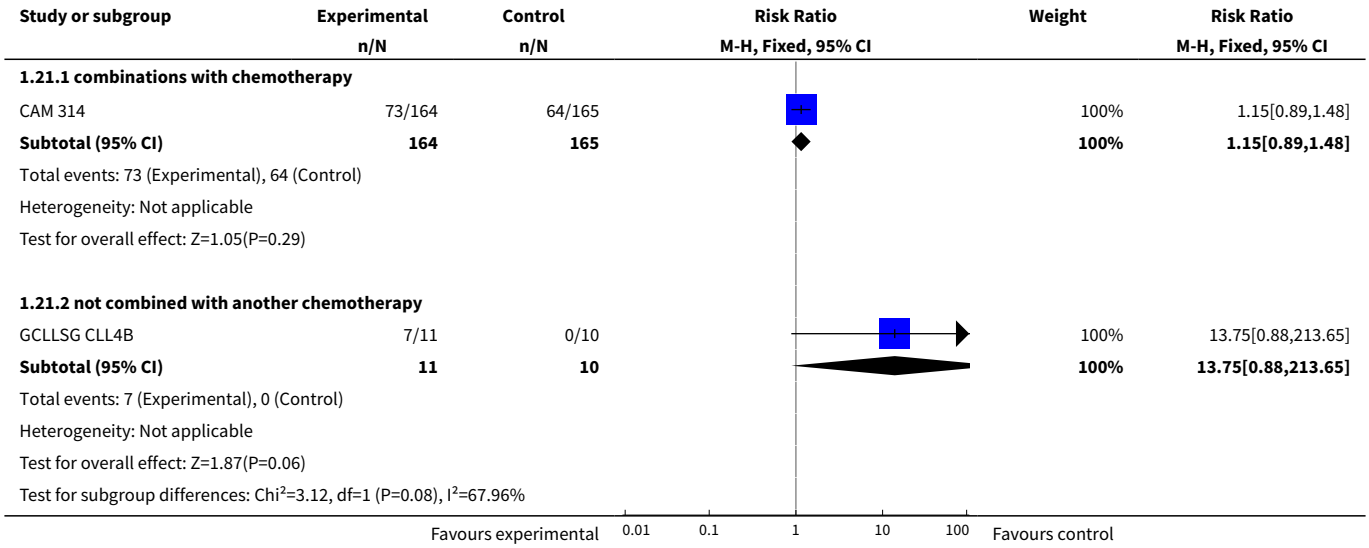




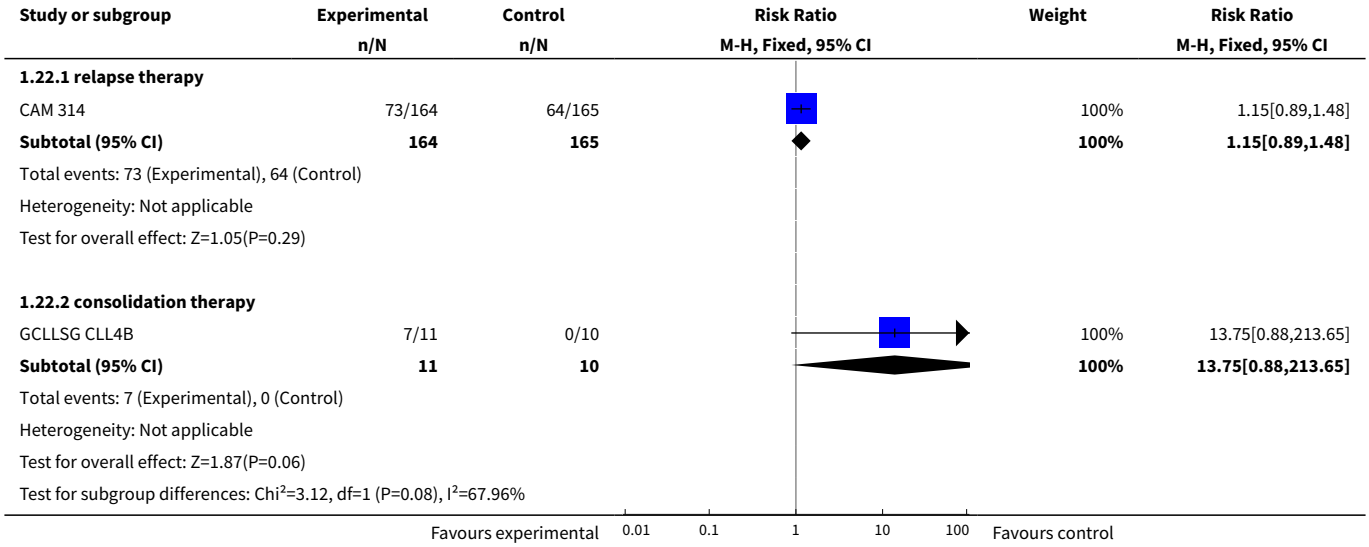
Analysis 1.20. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 20 Neutropenia grade 3/4 - overall analysis.



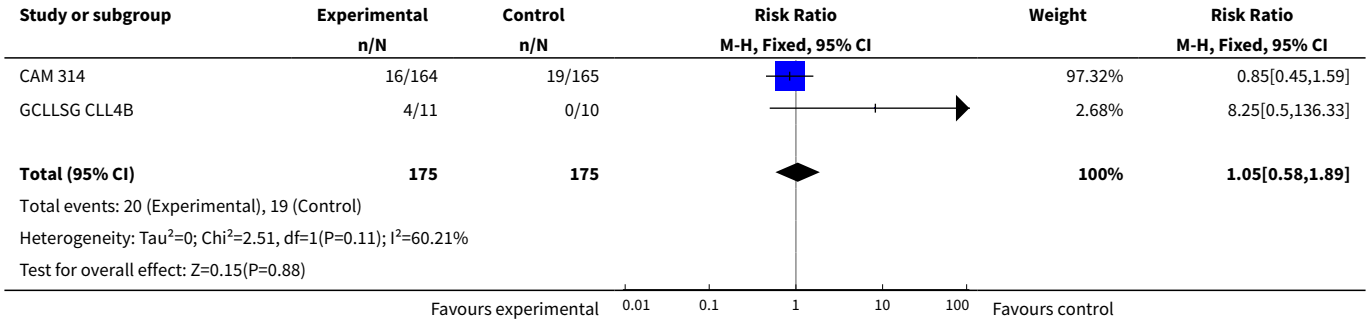
Analysis 1.21. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 21 Neutropenia grade 3/4 - subgrouped by treatment regimens.



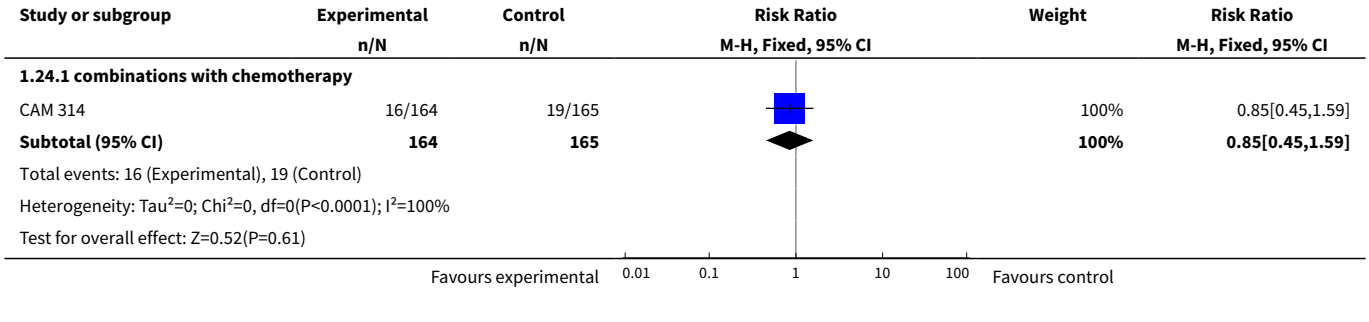
Analysis 1.22. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 22 Neutropenia grade 3/4 - subgrouped by starting point of alemtuzumab.

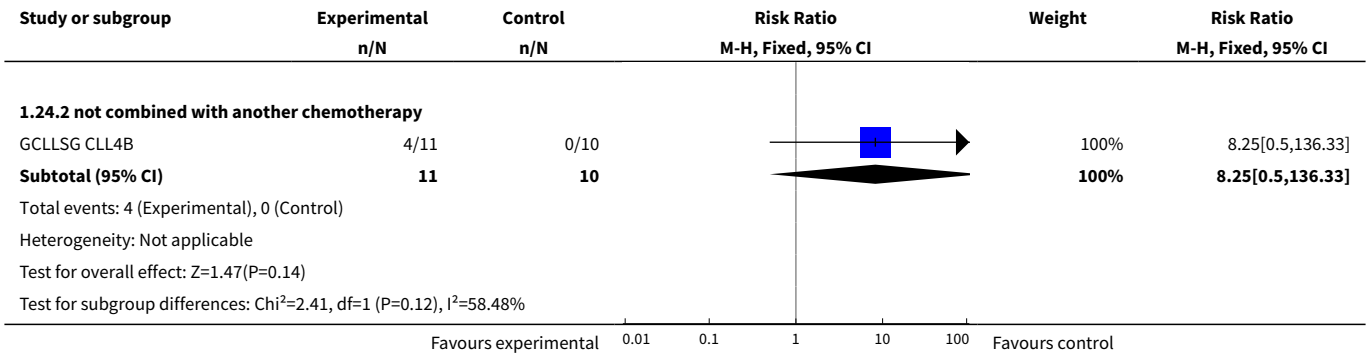


Analysis 1.23. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 23 Thrombocytopenia grade 3/4 - overall analysis.

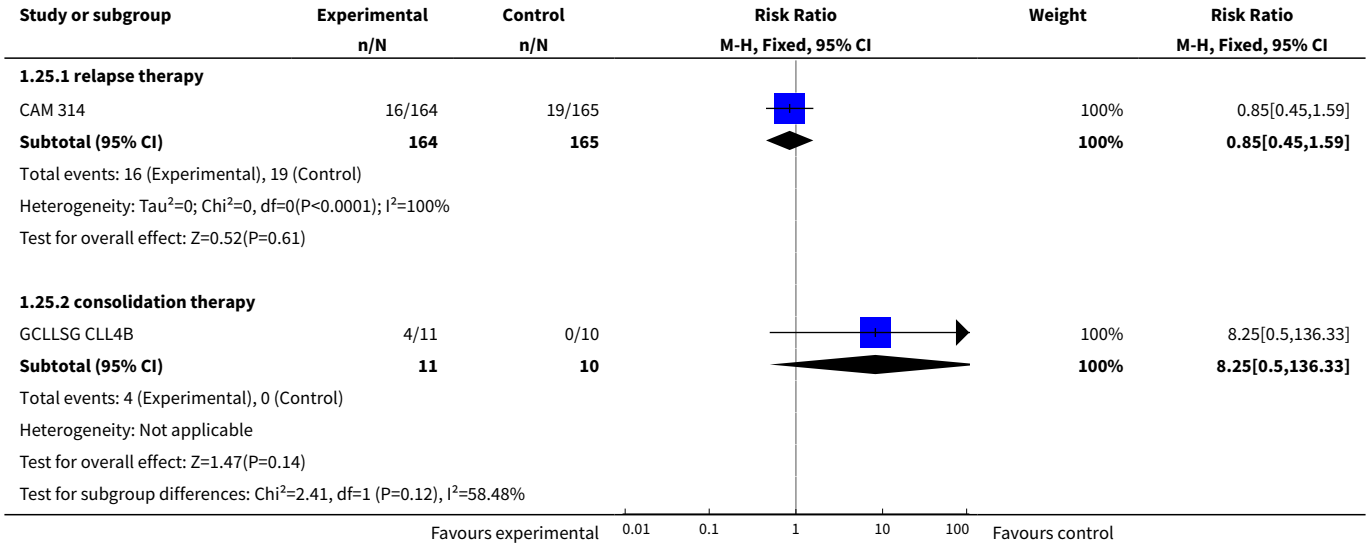


Analysis 1.24. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 24 Thrombocytopenia grade 3/4 - subgrouped by treatment regimens.

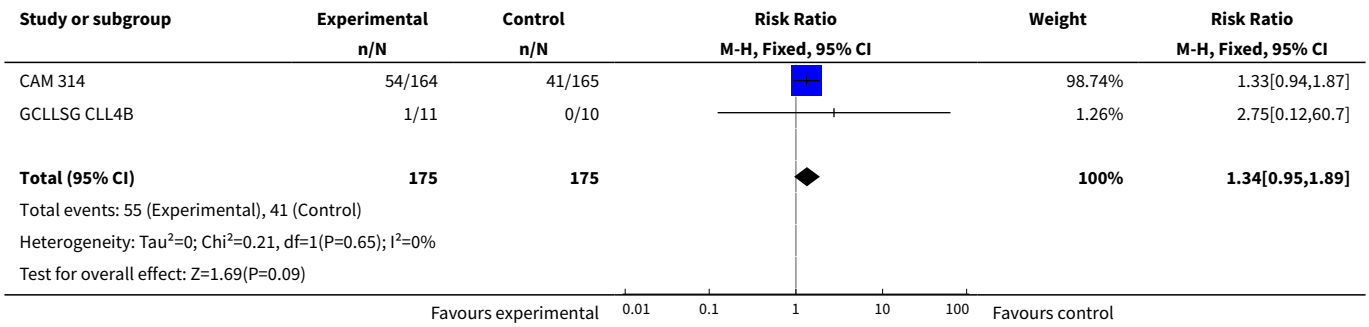




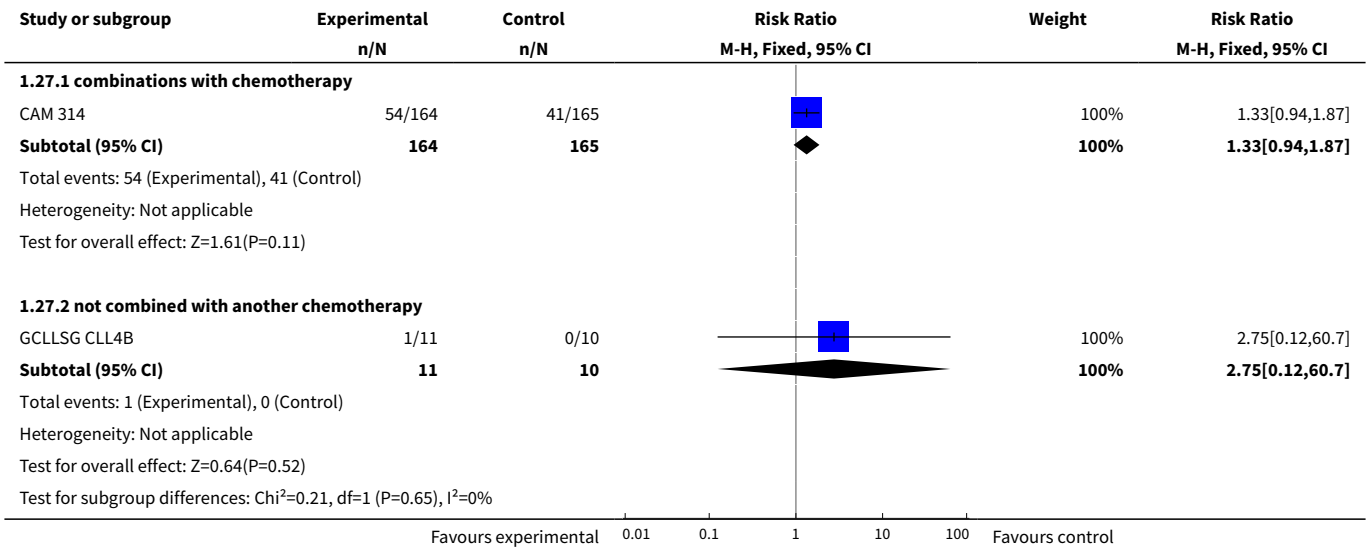
Analysis 1.25. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 25 Thrombocytopenia grade 3/4 - subgrouped by starting point of alemtuzumab.



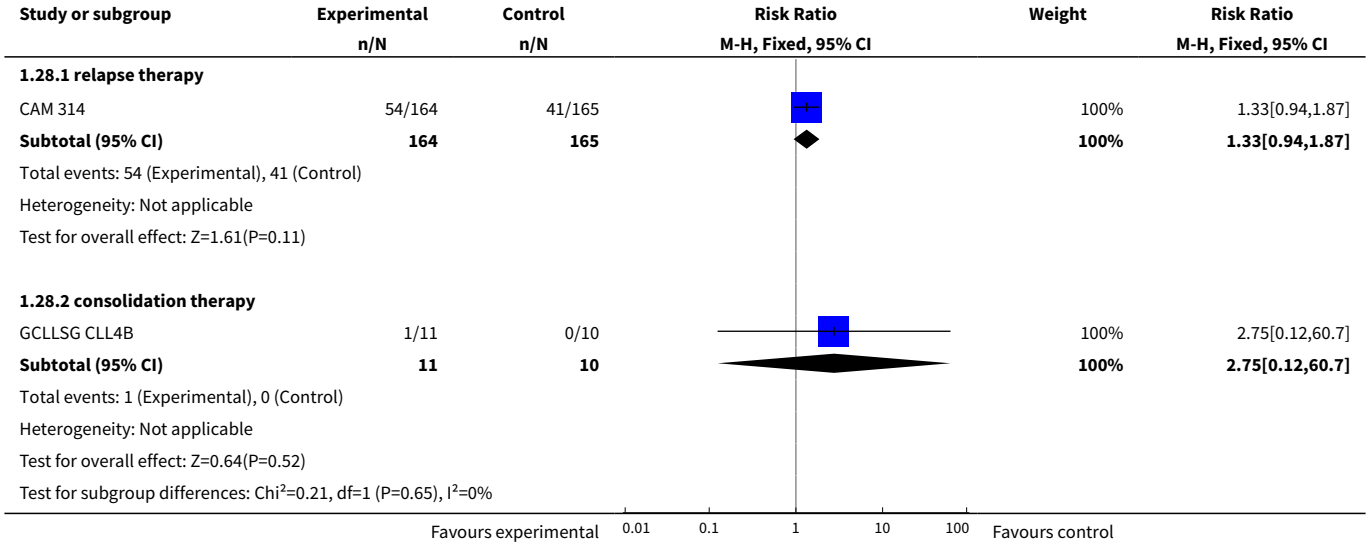
Analysis 1.26. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 26 SAEs - overall analysis.



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



Analysis 1.28. Comparison 1 Anti-leukaemic therapy plus alemtuzumab versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups; unconfounded), Outcome 28 SAEs - subgrouped by starting point of alemtuzumab.

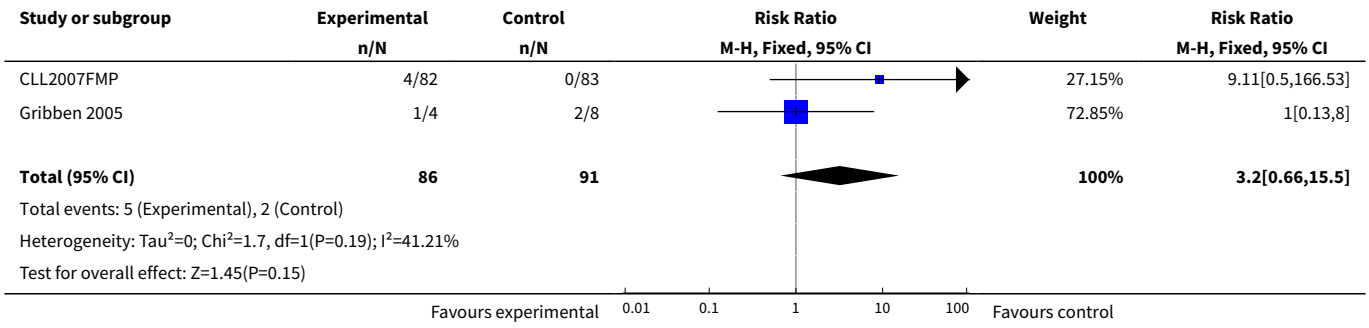


Comparison 2. Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded)

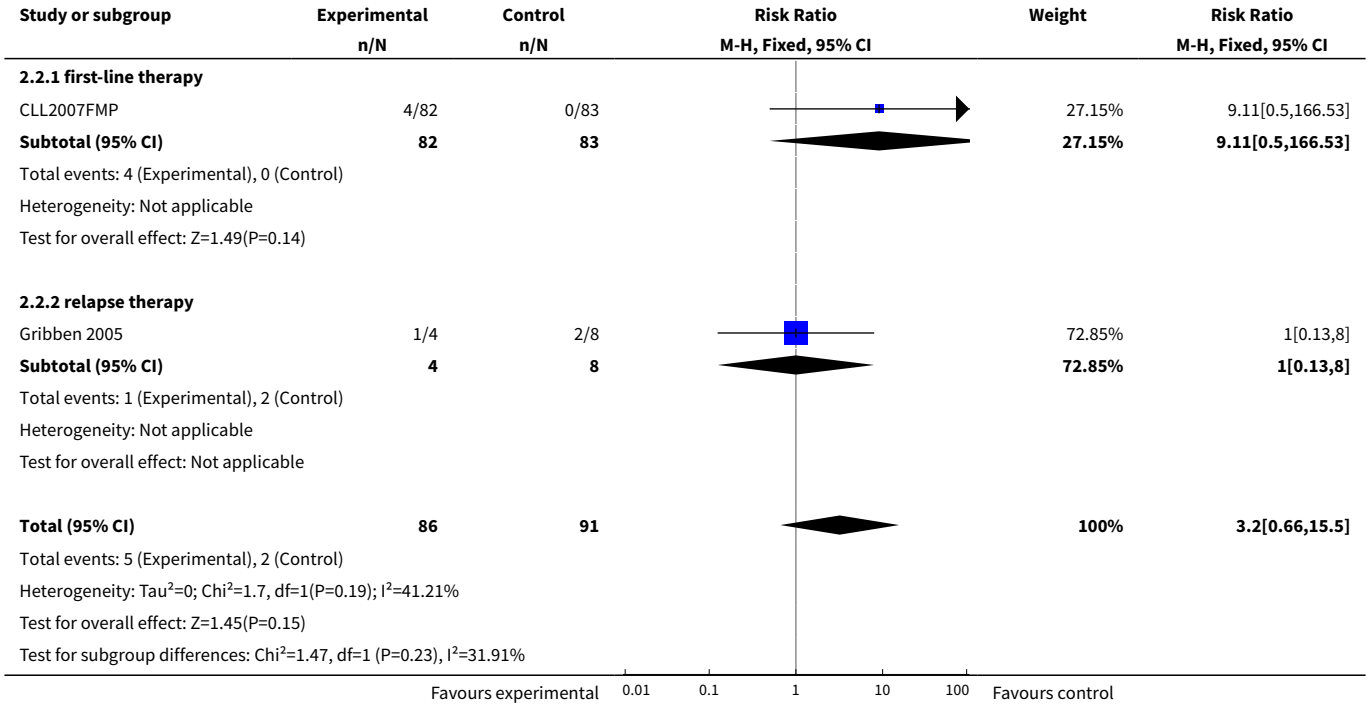
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treament related mortality	2	177	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [0.66, 15.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Treatment related mortality - subgrouped by alemtuzumab treatment regiment	2	177	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [0.66, 15.50]
2.1 first-line therapy	1	165	Risk Ratio (M-H, Fixed, 95% CI)	9.11 [0.50, 166.53]
2.2 relapse therapy	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 8.00]
3 ORR - overall analysis	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
4 ORR - subgrouped by alemtuzumab treatment regimen	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 first-line therapy	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.04]
4.2 relapse therapy	1	11	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.63, 4.88]
5 CRR - overall analysis	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.08]
6 CRR - subgrouped by alemtuzumab treatment regimens	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.08]
6.1 first-line therapy	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.03]
6.2 relapse therapy	1	11	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [0.45, 27.52]

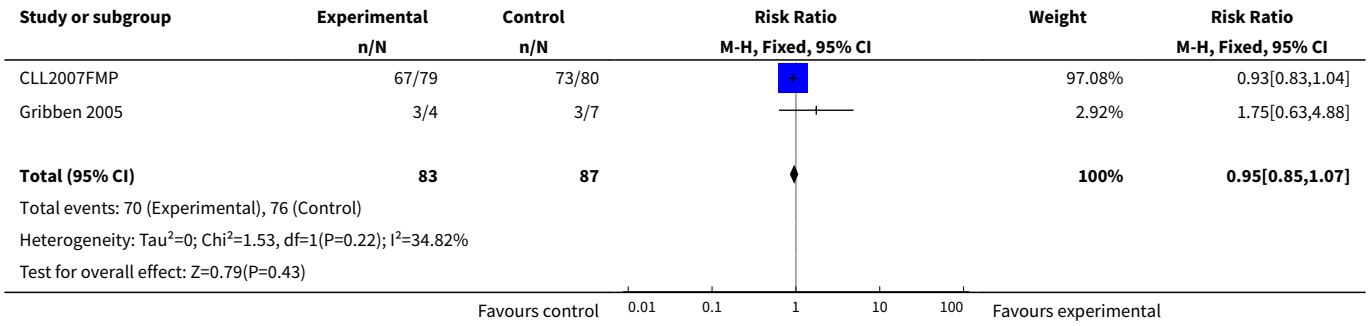
Analysis 2.1. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 1 Treament related mortality.



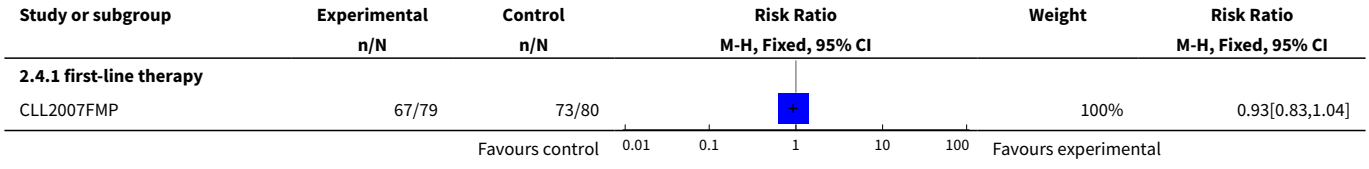
Analysis 2.2. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 2 Treatment related mortality - subgrouped by alemtuzumab treatment regiment.

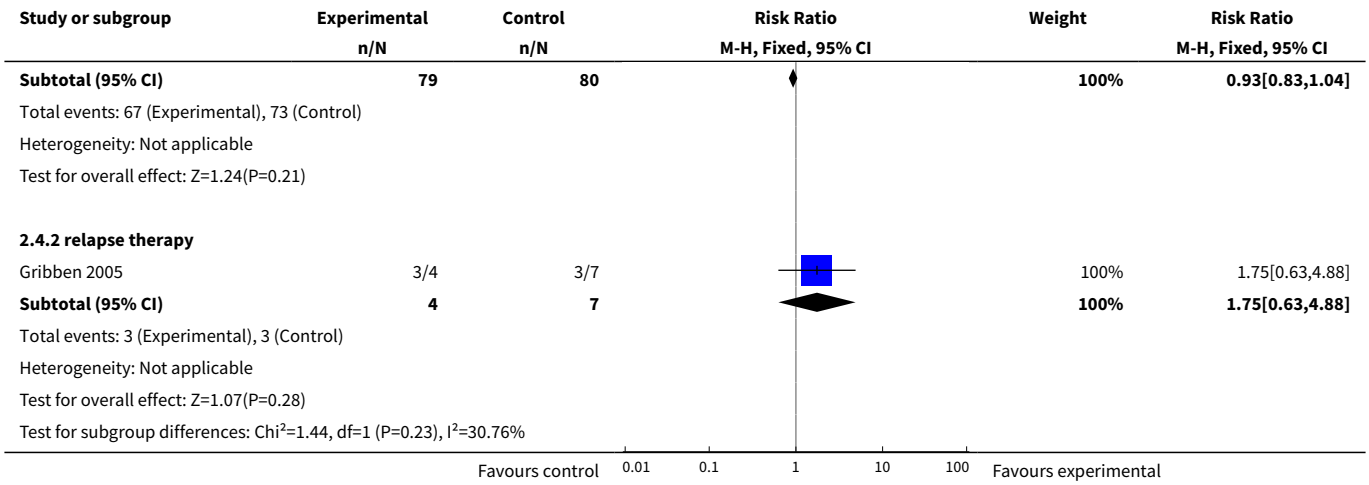


Analysis 2.3. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 3 ORR - overall analysis.

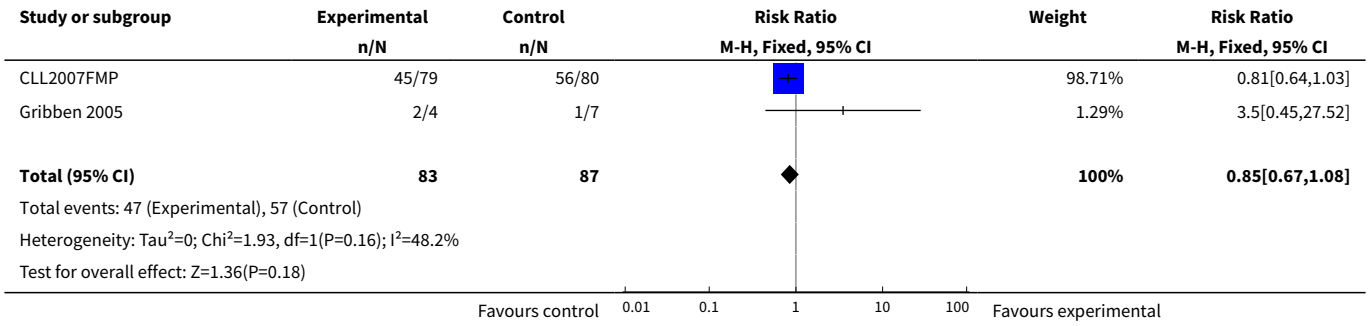


Analysis 2.4. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 4 ORR - subgrouped by alemtuzumab treatment regimen.

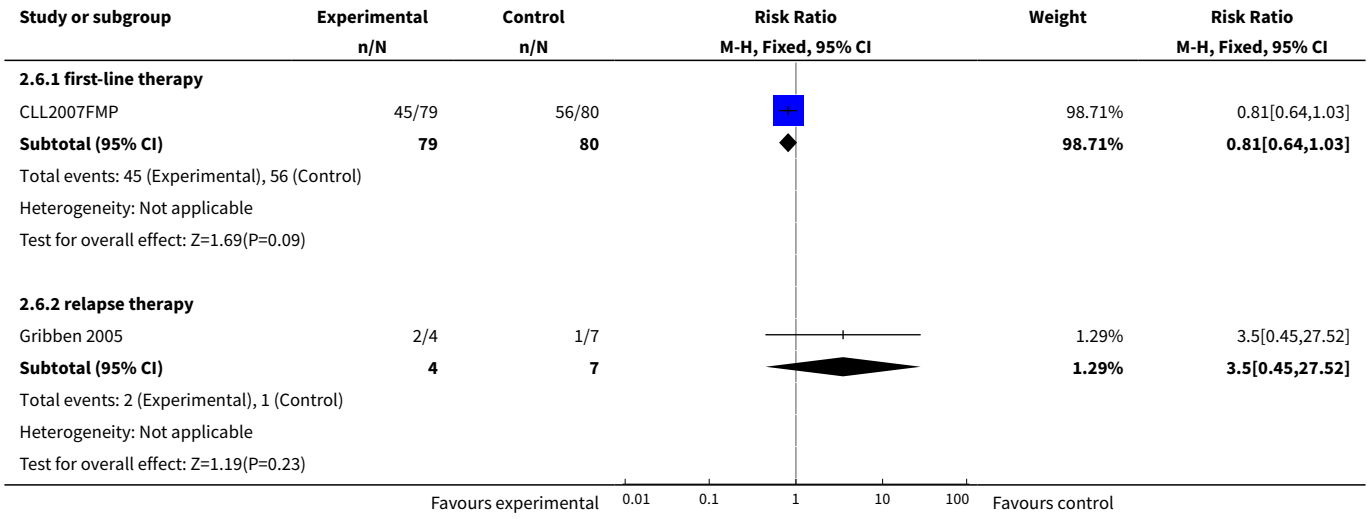


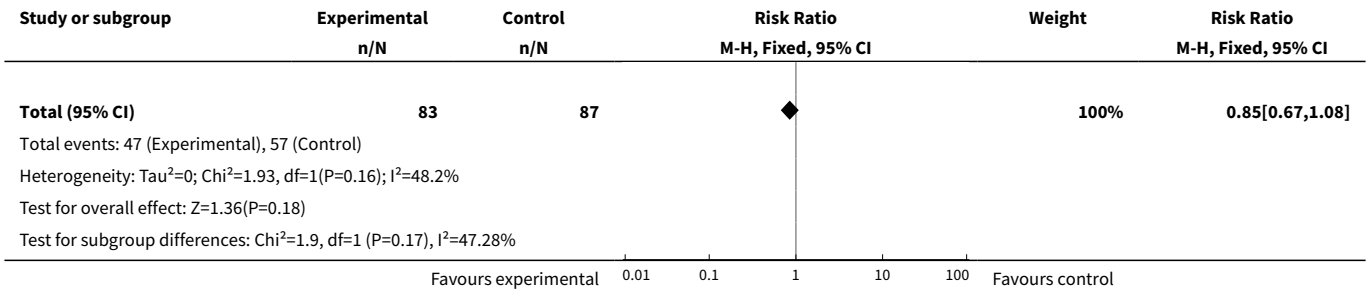


Analysis 2.5. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 5 CRR - overall analysis.



Analysis 2.6. Comparison 2 Anti-leukaemic therapy with alemtuzumab versus anti-leukaemic therapy without alemtuzumab (anti-leukaemic therapy not identical in both groups, confounded), Outcome 6 CRR - subgrouped by alemtuzumab treatment regimens.





ADDITIONAL TABLES

Table 1. Adverse events (alemtuzumab versus chlorambucil); CAM 307

Adverse event	Alemtuzumab arm; N (%)	Chlorambucil arm; N (%)	P value
Grade 3/4 pyrexia	12 (8.2%)	0 (0%)	0.03
Grade 3/4 chills	5 (3.4%)	0 (0%)	0.10
Grade 3/4 urticaria	3 (2.0%)	0 (0%)	0.20
Grade 3/4 hypotension	2 (1.4%)	0 (0%)	0.30
Grade 3/4 rash	1 (0.7%)	0 (0%)	0.50
Grade 3/4 asymptomatic CMV with PCR positivity	6 (4.1%)	0 (0%)	0.08
Grade 3/4 symptomatic CMV infection	6 (4.1%)	0 (0%)	0.08
All grades asymptomatic CMV with PCR positivity	77 (52.4%)	11 (7.5%)	<0.0001
All grades symptomatic CMV infection	23 (15.6%)	0 (0%)	0.007
Grade 3/4 nausea	0 (0%)	1 (0.7%)	0.50
Grade 3/4 vomiting	0 (0%)	1 (0.7%)	0.50
Grade 3/4 anaemia	16 (11%)	26 (18%)	0.10
Grade 3/4 neutropenia	60 (41%)	36 (25%)	0.004
Grade 3/4 thrombocytopenia	18 (12%)	17 (12%)	0.87
Haemolytic anaemia	1 (0.7%)	2 (1.4%)	0.57
Febrile neutropenia	7 (4.8%)	4 (2.7%)	0.37
Bacteria/sepsis	4 (3.0%)	2 (1.4%)	0.42
SAE	39 (26.5%)	10 (6.8%)	<0.0001
Richter's transformation	0 (0%)	0 (0%)	

CMV: cytomegalovirus
PCR: polymerase chain reaction
SAE: serious adverse event

APPENDICES

Appendix 1. Search strategy CENTRAL

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 18. April 2011)

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. (alemtuzumab*)
16. (campath*)
17. (CD52 NEAR/3 antibod*) or (CD-52 NEAR/3 antibod*) or (CD 52 NEAR/3 antibod*)
18. (ANTI-CD52 or ANTI CD52)
19. (#13 OR #14 OR #15 OR #16 OR #17 OR #18)
20. (#12 AND #19)

Appendix 2. Search strategy (Ovid MEDLINE)

Search strategy (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

Search strategy (Update March 2009 to April 2010)

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$)).tw,kf,ot.
4. (chronic$ 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$).tw,kf,ot.
15. 13 or 14
16. alemtuzumab$.tw,kf,ot,nm.
17. campath$.tw,kf,ot.
18. ((CD52 or CD-52 or CD 52) adj3 antibod$).tw,kf,ot,nm.
19. (ANTI-CD52 or ANTI CD52).tw,kf,ot,nm.
20. or/16-19
21. 12 and 20
22. 12 and (15 or 20)
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. drug therapy.fs.
28. randomly.ab.
29. trial.ab.
30. groups.ab.
31. or/23-30

32.humans.sh.
33.31 and 32
34.22 and 33

Search strategy (Update April 2010 to 18. November 2011)

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$).tw,kf,ot.
15. 13 or 14
16. alemtuzumab$.tw,kf,ot,nm.
17. campath$.tw,kf,ot.
18. ((CD52 or CD-52 or CD 52) adj3 antibod$).tw,kf,ot,nm.
19. (ANTI-CD52 or ANTI CD52).tw,kf,ot,nm.
20. or/16-19
21. 12 and 20
22. 12 and (15 or 20)
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. drug therapy.fs.
28. randomly.ab.
29. trial.ab.
30. groups.ab.
31. or/23-30
32. humans.sh.
33. 31 and 32
34. 21 and 33
35. 22 and 33
36. limit 35 to ed=20100401-20111118

Appendix 3. Search strategy (EMBASE)

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

Searches (Update March 2009 to 2010)

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$)).tw.
4. (chronic$ 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$).tw.
8. lymphoplasma?ytoid.tw.
9. cll.tw.
10. sll.tw.
11. or/6-10
12. 1 or 2 or 5 or 11
13. exp MONOCLONAL ANTIBODY/
14. (antibod$ adj2 monoclonal$).tw.
15. ALEMTUZUMAB/
16. alemtuzumab$.tw.
17. campath$.tw.
18. ((CD52 or CD-52 or CD 52) adj3 antibod$).tw.
19. (ANTI-CD52 or ANTI CD52).tw.
20. or/15-19
21. 12 and 20
22. 12 and (13 or 14 or 20)
23. (random$ or placebo$).ti,ab.
24. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
25. controlled clinical trial$.ti,ab.
26. RETRACTED ARTICLE/
27. or/23-26
28. (animal$ not human$).sh,hw.
29. 27 not 28
30. 22 and 29

CONTRIBUTIONS OF AUTHORS

- Nicole Skoetz (NS): methodological expertise, wrote the first and final draft of the review
- Kathrin Bauer (KB): data selection, data extraction, proof read and commented on the first and final draft
- Ina Monsef (IM): developed the search strategies and ran the database searches, provided reference databases
- Thomas Elter (TE): provided clinical expertise, proof read and commented on final draft
- Verena Roloff (VR): statistical expertise, HR calculation, proof read and commented on final draft
- Michael Hallek (MH): clinical expertise, proof read and commented on final draft

- Andreas Engert (AE): provided clinical expertise, proof read and commented on the first and final draft

DECLARATIONS OF INTEREST

NS, KB and IM: none known.

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

AE conducted several trials in this field. He received research funding and lecture fees from Bayer Schering and Genzyme AG.

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

MH received lecture fees from Bayer AG and Genzyme AG and honoraria for consultancy from Bayer AG, Schering AG and Genzyme AG.

SOURCES OF SUPPORT

Internal sources

- Köln Fortune, Germany.

  Funding programme “Köln Fortune”, Medical Faculty University of Cologne

External sources

- BMBF, Germany.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans