Guideline 6-8 Version 3 IN REVIEW

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Rituximab in Lymphoma and Chronic Lymphocytic Leukemia: A Clinical Practice Guideline

A. Prica, F. Baldassarre, L.K. Hicks, K. Imrie, T. C. Kouroukis, M. Cheung, and the Hematology Disease Site Group

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Guideline 6-8 Version 3 is comprised of 4 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/721

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Guideline 6-8 Version 3: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Rituximab in Lymphoma and Chronic Lymphocytic Leukemia: Recommendations Summary

A. Prica, F. Baldassarre, L.K. Hicks, K. Imrie, T. C. Kouroukis, M. Cheung, and the Hematology Disease Site Group

GUIDELINE OBJECTIVES

To provide an updated guideline on the use of rituximab in lymphoma and chronic lymphocytic leukemia (CLL).

TARGET POPULATIONS

Lymphoma

Adult patients with lymphoma of any type, at any stage, and with any histology.

Chronic Lymphocytic Leukemia

Adult patients with CLL at any stage.

INTENDED USERS

Intended users of this updated guideline include hematologists and oncologists treating patients with lymphoma or CLL.

RECOMMENDATIONS

Recommendation 1

Aggressive histology B-cell lymphomas, including Burkitt lymphoma: first-line, second-line and maintenance treatment and patients with human immunodeficiency virus (HIV)-associated lymphomas.

Previously Untreated Patients

a. Previously untreated patients with aggressive histology CD20-positive B-cell lymphomas who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP], CHOP-like, or similar dose-intense regimens) should receive this therapy in combination with rituximab.

Patients with Relapsed/Refractory Disease

b. For previously treated patients with aggressive histology CD20-positive B-cell lymphomas:

i. There is insufficient evidence at this time to support treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated with a rituximab-containing chemotherapy regimen.
ii. If patients have not previously received rituximab as part of their treatment regimen, the addition of rituximab to chemotherapy is reasonable.

Rituxmab Maintenance Treatment

c. There is insufficient evidence at this time to support the use of maintenance rituximab in aggressive histology B-cell lymphomas.

Patients with HIV-Associated Lymphomas

d. Previously untreated patients with HIV-related lymphoma with a CD4 count ≥50/mm^3 who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including CHOP, CHOP-like, or similar dose-intense regimens), should receive this therapy in combination with rituximab. The addition of rituximab to chemotherapy in patients with CD4 <50/mm^3 is not recommended.

Recommendation 2
Indolent histology B-cell lymphomas: first-line, second-line, and maintenance treatment and patients with asymptomatic CD20-positive B-cell lymphomas

Previously Untreated Patients

a. Previously untreated patients with indolent histology CD20-positive B-cell lymphomas, excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive their chemotherapy in combination with rituximab.
b. For patients with indolent histology CD20-positive B-cell–histology lymphomas, excluding SLL, who are candidates for therapy, but not combination chemotherapy, rituximab monotherapy is a reasonable option.

Patients with Relapsed/Refractory Disease

c. For previously treated patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL:
   i. Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab or as rituximab monotherapy.
   ii. Patients who have previously received rituximab (including combination rituximab chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Rituxmab Maintenance Treatment

d. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Patients with Asymptomatic CD20-Positive B-Cell Lymphomas

e. There is insufficient evidence at this time to support or refute upfront treatment with rituximab monotherapy for asymptomatic indolent histology CD20-positive B-cell lymphomas.

Recommendation 3
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Previously Untreated Patients

a. Patients with previously untreated CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.
b. In patients with previously untreated CLL/SLL who are appropriate candidates for chlorambucil chemotherapy, the addition of rituximab can be considered.

Patients with Relapsed/Refractory Disease

c. Patients with relapsed or refractory CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.

Recommendation 4
Hepatitis B virus reactivation in all patients treated with rituximab

The Hematology Disease Site Group recommends that all patients be screened for surface antigen for hepatitis B (HBsAg) and for hepatitis B core antibody (HBcAb) prior to treatment with rituximab. Consultation with an expert in hepatitis B virus (HBV) should be considered for all patients who test positively for HBV. Patients who are HBsAg positive should receive prophylactic antiviral therapy during and after rituximab. Patients who are HbsAg negative/HBcAb positive should be considered for either prophylactic antiviral therapy, close monitoring for viral reactivation, and/or should be followed by an expert in HBV. In the absence of active hepatitis (elevated transaminases), it is not usually necessary to delay rituximab. In most cases, HBV screening and management can occur in parallel with non-Hodgkin lymphoma/CLL treatment.

Guideline 6-8 Version 3: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Rituximab in Lymphoma and Chronic Lymphocytic Leukemia: A Clinical Practice Guideline, Version 3

Guideline

A. Prica, F. Baldassarre, L.K. Hicks, K. Imrie, T.C. Kouroukis, M. Cheung, and the Hematology Disease Site Group

GUIDELINE OBJECTIVES

To provide an updated guideline on the use of rituximab in lymphoma and chronic lymphocytic leukemia (CLL).

TARGET POPULATIONS

Lymphoma

Adult patients with lymphoma of any type, at any stage, and with any histology.

Chronic Lymphocytic Leukemia

Adult patients with CLL at any stage.

INTENDED USERS

Intended users of this updated guideline include hematologists and oncologists treating patients with lymphoma or CLL.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1

Aggressive histology B-cell lymphomas, including Burkitt lymphoma: first-line, second-line, and maintenance treatment and patient with human immunodeficiency virus (HIV)-associated lymphomas.

Previously Untreated Patients

a. Previously untreated patients with aggressive histology CD20-positive B-cell lymphomas who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP], CHOP-like, or similar dose-intense regimens) should receive this therapy in combination with rituximab.

Patients with Relapsed/Refractory Disease

b. For previously treated patients with aggressive histology CD20-positive B-cell lymphomas:
   i. There is insufficient evidence at this time to support treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated with a rituximab-containing chemotherapy regimen.
   ii. If patients have not previously received rituximab as part of their treatment regimen, the addition of rituximab to chemotherapy is reasonable.

Rituxmab Maintenance Treatment

c. There is insufficient evidence at this time to support the use of maintenance rituximab in aggressive histology B-cell lymphomas

Patients with HIV-Associated Lymphomas

d. Previously untreated patients with HIV-related lymphoma with a CD4 count ≥50/mm^3 who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including CHOP, CHOP-like, or similar dose-intense regimens), should receive this therapy in combination with rituximab. The addition of rituximab to chemotherapy in patients with CD4 <50/mm^3 is not recommended.

Summary of Key Evidence for Recommendation 1: Aggressive Histology Lymphoma

Previously Untreated Patients

Ten studies had a population of previously untreated patients [1-10]. These studies compared rituximab in combination with chemotherapy agents (CHOP or CHOP-like) with chemotherapy alone. The studies indicated an overall benefit of adding rituximab without, for the majority of patients, greater adverse events (See Tables 2E and 2AE in Section 3).

A meta-analysis of six studies [2,5-7,9,11], detected that the rituximab combination improved event-free-survival rates (EFS)/failure-free-survival rates (FFS) (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.50 to 0.69; p<0.00001) (Figure 1, Section 3).

A meta-analysis of four studies [5-7,11] found that the rituximab combination improved progression-free survival rates (PFS) (HR, 0.54; 95% CI, 0.45 to 0.65; p<0.00001) (Figure 2, Section 3).

A meta-analysis of seven studies [2-6,10,12] detected that the rituximab combination improved overall survival rates (OS) (HR, 0.67; 95% CI, 0.58 to 0.77; p <0.00001) (Figure 3, Section 3).

The randomized trial reported by Ribrag et al [9] in abstract form, examined the effect of rituximab in patients with Burkitt lymphoma and detected an increase in EFS (76% versus 64%; p=0.05) and OS (82% versus 71%; p=0.016) for patients administered the rituximab combination.

Except for the RICOVER-60 [6], none of the included studies detected a statistically significant difference in adverse events. In the RICOVER-60 [6] study, patients allocated to the arm that received eight treatments of rituximab + CHOP (R-CHOP) at two week intervals experienced significantly more anemia (p=0.001) and mucositis (p=0.03) when compared with patients in the arm that received six treatments of CHOP at two week intervals.

Patients with Relapsed/Refractory Disease

Two studies with different populations presented contrasting results in this group. The HOVON-44 study [13] studied patients who were rituximab-naïve and detected results in favour of rituximab for FFS (50% versus 24%; p<0.001), PFS (52% versus 31%; p<0.002), and complete

response (CR) (46% vs 35%; p=0.003), but no statistically significant differences in OS (59% versus 52%; p=0.15). See Tables 3E and 3AE in Section 3. The study reported by Aviles et al [14] studied elderly patients and did not find any statistically significant differences between the rituximab combination and the chemotherapy-only arm. No statistically significant differences were reported for grade ≥3 adverse events by the authors of both studies.

Rituximab Maintenance Treatment

While the schedule and duration of rituximab maintenance treatments varied across studies, no statistically significant results were observed for PFS or OS (Tables 4E and 4AE, Section 3). One study detected a statistically significant increase in FFS [4]; however, a subgroup analysis of that study found that rituximab maintenance treatments significantly prolonged FFS in patients treated with CHOP, but not in patients treated with R-CHOP. Two studies measured quality of life [15,16], and they reported contrasting results. None of the studies reported a significant difference in grade ≥3 adverse events except the E4494/C9793 study [4], which detected significantly greater rates of lymphopenia in patients treated with rituximab (p=0.008) (Table 4AE, Section 3).

Patients With HIV-Associated Lymphoma

The meta-analysis reported by Barta et al [17] forms the basis of the recommendation. In this meta-analysis, pooled individual patient data from 19 prospective studies detected that rituximab use was associated with improved outcomes for patients with CD4 counts ≥50 cells/μL for CR (odds ratio [OR], 2.84; 95% CI, 1.60 to 5.02; p<0.001), for PFS (HR, 0.48; 95% CI, 0.32 to 0.72, p<0.001), and for OS (HR, 0.55; 95% CI, 3.9 to 0.77; p<0.001). No association was observed for patients with CD4 count <50 cells/μL. Barta et al (17) reported that death due to HIV-related causes did not significantly differ between patients treated with a rituximab combination versus controls (OR, 0.58; 95% CI, 0.30 to 1.12; p=0.14).

Justification for Recommendation 1

The evidence included in this guideline demonstrates that rituximab is an effective agent with a favourable toxicity profile. Rituximab is effective in extending life and prolonging PFS and EFS in previously untreated patients. Concerns about the scarcity and quality of the evidence available, as well as about the variety of doses and schedules used for rituximab maintenance regimens for patients with previously treated lymphoma, determined the recommendation for this population.

Qualifying Statements for Recommendation 1

- Rituximab has a favourable single-agent toxicity profile. The addition of rituximab to chemotherapeutic regimens such as CHOP does not appear to significantly alter the adverse effects of these regimens in lymphoma.
- Rituximab should be administered at a dose of 375 mg/m^2 and administered at the beginning of each treatment cycle of chemotherapy, as this was the dose and schedule used in all the included trials.
- New data is rapidly becoming available regarding the role of rituximab in treating these diseases. Practitioners and patients are advised to review the website of Cancer Care Ontario's Program in Evidence-based Care (PEBC) (https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/hema-ebs/) for updates to this guideline.

RECOMMENDATION 2
Indolent histology B-cell lymphomas first-line, second-line, and maintenance treatment and patients with asymptomatic CD20-positive B-cell lymphomas

Previously Untreated Patients

a. Previously untreated patients with indolent histology CD20-positive B-cell lymphomas, excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive their chemotherapy in combination with rituximab.
b. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who are candidates for therapy, but not combination chemotherapy, rituximab monotherapy is a reasonable option.

Patients with Relapsed/Refractory Disease

c. For previously treated patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL:
    i. Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab or as rituximab monotherapy.
    ii. Patients who have previously received rituximab (including combination rituximab/chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Rituxmab Maintenance Treatment

d. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Patients with Asymptomatic CD20-Positive B-Cell Lymphomas

e. There is insufficient evidence at this time to support or refute upfront treatment with rituximab monotherapy for asymptomatic indolent histology CD20-positive B-cell lymphomas.

Summary of Key Evidence for Recommendation 2

Overall, the studies of patients with indolent histology lymphoma [18-31] were clinically heterogeneous; therefore, no meta-analysis was conducted. A brief summary of the results follows; for more detailed numerical results see Section 3, Tables 5E and 5AE for previously untreated patients, and Tables 6E and 6AE for patients with relapsed/refractory disease.

Previously Untreated Patients

Ten studies, represented by 23 publications, were included. Five studies reported a nonsignificant difference in OS [21,22,24,27,32]: rituximab (alone or in combination) was compared with chorambucil [24], with watchful waiting [27], with cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP), with cyclophosphamide, adriamycin, etoposide and prednisolone plus interferon 2α (CHVP+I) [22], and with CHOP [32]. Four studies reported a statistically significant OS benefit for rituximab [18,33-35]; rituximab and various rituximab combinations were compared with CHOP [33], with cyclophosphamide, vincristine,

and prednisone (CVP) [34], with CHOP and iodine-131-tositumomab [35], and with mitoxantrone, chlorambucil, and prednisone (MCP) [18]. Lengths of follow-up ranged from 18 months to 4.9 years.

Three studies reported on EFS [18,22,24]. Herold et al [18] reported a statistically significant (p=0.0001) benefit for rituximab in combination with MCP (R-MCP) compared with MCP alone at 47 and 60 months; Salles et al [22] found a statistically significant benefit of rituximab in combination with CHVP+I compared with CHVP+I alone (p=0.001), and Zucca et al [24] found a statistically significant benefit of rituximab combined with chlorambucil compared with cholrambucil alone at five-year follow up (p=0.002); a third, rituximab-only arm of this trial was still ongoing at the time of publication in 2013.

Five studies reported on PFS [18,23-25,27]. Herold et al [18] reported statistically significant longer PFS for R-MCP compared with MCP alone; Salles et al [22] reported a median of 35 months survival in the CHVP+I alone arm while median was not reached in the rituximab combination arm. Press et al [23] reported no statistically significant difference between R-CHOP compared with CHOP and iodine-131-tositumumab at two and 4.9 years follow-up. Zucca et al [24] reported no statistically significant difference between rituximab plus chlorambucil and chlorambucil alone (p=0.057). Hoster et al [25] and Lenz et al [32] did not find a statistically significant difference between R-CHOP and CHOP alone (p=0.31). Ardeshna et al [27], in a conference abstract reporting a study that was stopped early for benefit at 18 months follow-up, detected a statistically significant difference of rituximab treatment, and of rituximab treatment and maintenance compared with watchful waiting (log rank test p<0.001).

One study [34] detected a statistically significant benefit for rituximab combined with CVP compared with CVP alone for disease-free survival rates (DFS) (p=0.0001).

One study in abstract form [21] did not find a significant difference in disease-free survival rates (DFS) when comparing rituximab alone, rituximab combined with CNOP, or CNOP alone at 24 months follow-up (p values not reported).

Two studies [18,27], of which one was reported in abstract form [27], reported a statistically significant benefit of rituximab for time to next treatment at 18 and 60 months follow-up, respectively, when comparing R-MCP versus MCP alone and weekly rituximab alone, rituximab treatment, and rituximab maintenance versus watchful waiting (respectively, p=0.0002 and p value of log rank test <0.001).

Four studies [22,32-34] detected a benefit in time to treatment failure. Marcus et al [34] reported a statistically significant benefit of rituximab combined with CVP compared with CVP alone at 53 months follow-up (p<0.0001); Hiddeman et al [33] and Salles et al [22], at five-year follow-up, reported a statistically significant benefit for R-CHOP versus CHOP alone and for rituximab plus CHVP+I versus CHVP+I alone (p<0.0001 and p=0.003, respectively).

Six studies reported a statistically significant benefit for CR [18,22,24,32-34] while four studies did not find a significant difference for CR, for OR, or for both [21,24,26,35].

The majority of the studies did not report on grade ≥3 adverse events or reported nonsignificant between-group differences. Three studies reported statistically significant higher rates of lymphopenia or granulocytopenia in the rituximab arm compared with the chemotherapy-alone arm [22,26,32] (p<0.001; p=0.01 [granulocytopenia]; and p=0.02, respectively). One study reported a higher rate of infections and neutropenia in the rituximab arm when rituximab combined with CNOP was compared with CNOP alone [21], and one study reported a higher rate of thrombocytopenia in the rituximab arm compared with chemotherapy alone [35]. One study [23] reported a statistically significant difference in favour of the non-rituximab arm for cardiac adverse effects (p=0.08), while no statistically significant differences were reported for neurological adverse effects, nausea, and vomiting [23,26,33].

Patients with Relapsed/Refractory Disease

Five studies [28,31,36-38], represented by nine publications, were included.

One study [29] detected a three-year estimated significant benefit in the rituximab arm when rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (FCM) was compared with FCM alone (p=0.003), and two studies did not detect a statistically significant difference when rituximab plus ^{90}Y ibritumomab tiuxetan was compared with no treatment [28] and when R-CHOP was compared with CHOP alone [30].

The CALBG 50401 study [31] reported on EFS and detected a benefit for the combination of rituximab and lenalidomide compared with lenalidomide alone at 18 months follow-up (p=0.006).

The FIT, GLSG, and the EORTC20981 studies [28,37,38] detected a statistically significant benefit for PFS when rituximab combined with chemotherapy was compared with no treatment or with chemotherapy alone at follow-ups ranging from 2.5 to 7.3 years (p<0.0001, p=0.038, and p<0.001, respectively) (see Section 3, Table 6E for numerical results).

Witzig et al [36] reported a nonsignificant between-group difference in time to progression when rituximab alone was compared with ^{90}Y ibritumomab tiuxetan.

The FIT study [28] and the Witzig et al study [36] had contrasting results for time to next treatment. The FIT study follow-up detected a statistically significant benefit for patients in the the rituximab group compared with patients in the no treatment group at 66 and 87.6 months (HR, 0.47; 95%CI, 0.36 to 0.61, p<0.001) [28]; Witzig et al [36] detected no between-group difference at 48 months when rituximab was compared with ^{90}Y ibritumomab tiuxetan (p=0.084).

Three studies reporded a statistically significant benefit of rituximab in CR [36-38] or in overall response [36,38].

The Witzig et al study [36] reported a nonsignificant between-group difference in response duration. The other two studies did not report significant tests on response outcomes. The GLSG study [37] reported a statistically significantly higher incidence of grade $\geq$3 lymphopenia in patients treated with rituximab (see Table 6AE for numerical results). None of the other studies reported any other significant grade ≥3 adverse events.

Justification for Recommendation 2

Rituximab is effective in extending life and prolonging PFS and EFS in previously untreated patients, when administered in combination with CHOP or CHOP-like chemotherapy. Rituximab is effective in prolonging PFS in previously untreated patients, when administered in combination with chlorambucil. Rituximab is also effective in extending PFS in the relapsed setting when added to fludarabine-based chemotherapy, and this consistent benefit formed the basis for the recommendation in this setting.

Qualifying Statements for Recommendation 2

- Rituximab has a favourable single-agent toxicity profile. The addition of rituximab to chemotherapeutic regimens such as CVP, CHOP, bendamustine, and FCM does not appear to significantly alter the adverse effects of these regimens in lymphoma.
- Rituximab should be administered at a dose of 375 mg/m^2 and administered at the beginning of each treatment cycle of chemotherapy, as this was the dose and schedule used in the included studies.
- There is significant variability in the published administration schedules for rituximab maintenance and on the effectiveness of this treatment (Section 3, Table 4E). The members of the Disease Site Group believed that the regimen studied by the EORTC/Intergroup (rituximab 375 mg/m^2 every three months until relapse or two years) was a reasonable and convenient option. Maintenance rituximab should be initiated within eight weeks of completion of the induction regimen as suggested by the PRIMA [39] and EORTC [30] studies.

- Prolonged rituximab therapy may be associated with hypogammaglobulinemia. Testing for immunoglobulin quantitation was a common monitoring strategy in the pivotal clinical trials [39] and should be considered for patients receiving maintenance therapy.

RECOMMENDATION 3
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Previously Untreated Patients

a. Patients with previously untreated CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.
b. In patients with previously untreated CLL/SLL who are appropriate candidates for chlorambucil chemotherapy, the addition of rituximab can be considered.

Patients with Relapsed/Refractory Disease

c. Patients with relapsed or refractory CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.

Summary of Key Evidence for Recommendation 3

Previously Untreated Patients

Four randomized controlled trials [40-43], represented by 12 publications, were included. This body of evidence indicates a benefit in terms of PFS with the use of rituximab in addition to fludarabine-based chemotherapy and cyclophosphamide, when compared with chemotherapy alone (see Section 3, Table 9E for numerical results). Grade 3 or 4 neutropenia and leukocytopenia have been reported [42], however these counts were significantly less than those seen with other monoclonal antibodies [41] (see Section 3, Tables 8E and 8AE for numerical results).

Patients with Relapsed/Refractory Disease

Two studies [44,45], represented by six publications, were included. This body of evidence indicates a benefit for PFS, FFS, and response with the use of rituximab in addition to fludarabine-based chemotherapy when compared with chemotherapy alone (see Section 3, Tables 9E and 9AE for numerical results). The included studies did not detect any statistically significant between-group difference in grade 3 or 4 adverse events.

Justification for Recommendation 3

Rituximab is effective in extending life and prolonging PFS and EFS in previously untreated patients, when administered in combination with fludarabine-based chemotherapy, and in extending PFS when added to chlorambucil. Rituximab is also effective in extending PFS in the relapsed setting when added to fludarabine-based chemotherapy, and this consistent benefit formed the basis for the recommendation in this setting.

Qualifying Statements for Recommendation 3

- Rituximab should be administered at a dose of 375 mg/m^2 given at the beginning of the first cycle, followed by a dose of 500 mg/ m^2 given at the beginning of each subsequent treatment cycle of chemotherapy as this was the treatment dose and schedule used in the included studies.

RECOMMENDATION 4
Hepatitis B virus (HBV) reactivation in all patients treated with rituximab

The Hematology Disease Site Group recommends that all patients be screened for surface antigen for hepatitis B (HBsAg) and hepatitis B core antibody (HBcAb) prior to treatment with rituximab. Consultation with an expert in hepatitis B virus hould be considered for all patients who test positively for HBV. Patients who are HBsAg positive should receive prophylactic antiviral therapy during and after rituximab. Patients who are HBsAg negative/HBcAb positive should be considered for either prophylactic antiviral therapy, close monitoring for viral reactivation, and/or should be followed by an expert in HBV. In the absence of active hepatitis (elevated transaminases), it is not usually necessary to delay rituximab. In most cases, HBV screening and management can occur in parallel with non-Hodgkin lymphoma/CLL treatment.

Summary of Key Evidence for Recommendation 4

A meta-analysis [46] and a randomized controlled trial [47] were identified. This literature found that rituximab is associated with a substantial risk of HBV reactivation (see Table 10E in Section 3 for numerical results). Reactivation has been reported in patients with chronic HBV (HBsAg positive) and in patients with resolved HBV (HBsAg negative/HBcAb positive). Viral reactivation can occur during rituximab treatment or up to 18 months beyond completion of rituximab. Antiviral therapy has been shown to prevent reactivation [47]. Huang et al [47] detected that after 18 months of follow-up there was a significant benefit of antiviral prophylactic therapy in preventing HBV reactivation in patients treated with rituximab (2.4% in the entecavir group versus 17.9% in the control, p=0.027).

RELATED GUIDELINES

- PEBC Evidence-Based Series: #6-7: *Kouroukis T, Browman G, Meyer R. The use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma. Kouroukis T, Ismaili N, reviewers. Toronto (ON): Cancer Care Ontario; 200 3 Jun 25 [Endorsed 2013 May 24]. Program in Evidence-based Care. Practice Guideline No.: 6-7 Version 2.*

UPDATING

All Program in Evidence-Based Care documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC *Document Assessment and Review Protocol*, available on the Cancer Care Ontario (CCO) website at: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

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CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Section 4, Appendix 7A.

Guideline 6-8 Version 3: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Rituximab in Lymphoma and Chronic Lymphocytic Leukemia: Version 3

Evidence Review

A. Prica, F.Baldassarre, L.K. Hicks, K. Imrie, T.C. Kouroukis, M. Cheung and the Hematology Disease Site Group

Report Date: March 31, 2015

INTRODUCTION

Each year, over 2400 patients in Ontario are diagnosed with lymphoma. Indolent non-Hodgkin lymphomas (NHL), with follicular lymphoma (FL) representing the most common subtype, comprise 40% of lymphoma diagnoses and are incurable with conventional therapy. Patients often respond well to initial therapy with intravenous chemotherapy, which is associated with manageable adverse effects. Later in the course of the disease, however, treatment involves more toxic intravenous chemotherapy, generally with a progressively shorter duration of response. The median survival in patients with advanced-stage disease is seven to 10 years from the time of diagnosis. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common type of leukemia in the world, and its disease characteristics and treatment overlap with those of indolent lymphomas. Diffuse large B-cell lymphoma (DLBCL) is a close second in incidence to FL in Canada, although the most common NHL worldwide. Treatment comprises of several cycles of intravenous chemotherapy, yielding cure rates of 60-70%.

Monoclonal antibody therapy is a novel treatment approach being applied to lymphomas and other cancers. Rituximab is the first such agent to be approved for use by the United States Food and Drug Administration and was approved in Canada in March 2000. However, this agent is expensive and has rare life-threatening, infusion-related toxicity. Phase II trials published in the late 1990's reported significant clinical activity and a favourable toxicity profile for this agent when used alone (e.g., McLaughlin et al [48]).

When evidence of the single-agent activity of rituximab in lymphoma became available in 1998, the Hematology Disease Site Group (DSG) of Cancer Care Ontario's (CCO) Program in Evidence-Based Care (PEBC) identified rituximab as a high priority. The DSG developed and regularly updated an evidence summary report (ES #6-8) [49]. The evidence summary identified rituximab as an agent with very manageable toxicity that should be available for selected patients with lymphoma, and facilitated the implementation of an Ontario Ministry of Health and Long-Term Care policy making rituximab widely available as a third-line therapy to patients who had indolent lymphoma other than CLL.

The evidence summary was modified in 2000 after the publication of a randomized trial reported that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and

prednisone (CHOP) improved survival in older patients with DLBCL. In the modified summary, and in an associated practice guideline assessing the treatment for older patients with aggressive histology lymphoma (PEBC Evidence-based Series #6-7), a recommendation was made that rituximab in combination with CHOP (R-CHOP) be considered standard therapy for those patients when the goal of therapy was to achieve an optimum state of disease control and to prolong survival. This evidence summary and the associated practice guideline facilitated a change in the Ontario funding policy to provide rituximab to patients aged ≥60 years of age with previously untreated *de novo* DLBCL. The funding policy implementation in January 2001 was within one month of the presentation of the new data in abstract form.

Presentations at the December 2003 American Society of Hematology (ASH) meeting motivated the Hematology DSG to conduct a third overall review of the available evidence. The DSG anticipated that this review could lead to new recommendations that would warrant the development of a practice guideline (as opposed to an evidence summary). Anticipating that these new recommendations would have important implications for the Ontario Ministry of Health and Long-Term Care's cancer-related New Drug Funding Program, the DSG requested that the Policy Advisory Committee of CCO review a draft version of a practice guideline evaluating rituximab, prior to the completion of the full Practice Guideline Development Cycle [50]. This evidence-based series replaces the original evidence summary.

A fourth modification of the guidelines was requested in 2009 by the New Drug Funding Program, following new data from the December 2008 ASH meeting. At this meeting, two randomized trials studying the addition of rituximab to chemotherapy in patients with CLL were presented. Although no new randomized data were presented on Burkitt lymphoma and immunodeficiency virus (HIV)-related lymphomas, the DSG was requested to present a targeted update on these topics, following requests from Ontario and external practitioners for clarification on the use of rituximab in these histologies. Given the lack of new phase III evidence and the specific interest in safety outcomes for these lymphomas, the DSG completed a targeted literature review that included phase II and population-based controlled studies.

In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature and a clinical expert (MC) reviewed and interpreted the new eligible evidence. The Hematology DSG decided that the existing recommendations required an update, therefore this Version 3 of the guideline was initiated. For Version 3 the studies included in Version 2 were included and they were combined with the results of an updated search of the literature. The updated search included also a separate search for rituximab in HIV-related and Burkitt lymphoma, as well as a seach of hepatitis B reactivation risk with rituximab.

To make recommendations as part of a clinical practice guideline the working group of the Hematology DSG developed this evidence review upon which those recommendations are based. Based on the objectives of the guideline, the working group derived the research questions outlined below.

RESEARCH QUESTIONS

Lymphoma

1. In patients with lymphoma of any type or stage, is rituximab used alone or in combination with chemotherapy more effective than non–rituximab-containing regimens for improving overall survival (OS), disease control (as assessed by measures such as progression-free survival [PFS], event-free survival [EFS], time-to-treatment failure [TTF] , or response duration [RD]), response rate, or quality of life (QOL)?
2. What are the adverse events associated with the use of rituximab used alone or in combination with chemotherapy compared with non–rituximab-containing regimens?

3. Which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with non–rituximab-containing regimens?

Chronic Lymphocytic Leukemia

1. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with CLL? Outcomes of interest are OS, disease control (as assessed by measures such as PFS, EFS, TTF, or RD), and response rate.
2. What is the toxicity associated with the use of rituximab?
3. Which patients are more or less likely to benefit from treatment with rituximab?

METHODS

This evidence review is composed of three parts: the evidentiary base of Version 2, the results of the updated search executed in March 2012 and the content of a further update executed in October 2013. The guideline report history is summarized in Appendix 1. Each of the searches was developed using a planned two-stage method, summarized here and described in more detail below. This document reports the methods used for the most recent update, methods for previous versions are very similar and are available upon request.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then those systematic reviews would form the core of the evidence review.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Stategy

For this update a search for guidelines was undertaken in the Inventory of Cancer Guidelines (SAGE) (http://www.cancerguidelines.ca/Guidelines/inventory/index.php), the National Guideline Clearing House (http://www.guideline.gov/), the CMA Infobase (https://www.cma.ca/en/Pages/cma_default.aspx) and on the web sites of international guidelines developers such as the National Institute for Clinical Excellence (UK) (NICE), the Scottish Intercollegiate Guideline Network (SIGN), the Australian National Health and Medical Research Council, and the New Zealand Guidelines Group.

The literature was systematically searched using the electronic databases MEDLINE (Ovid, March 2006 to October 2013), EMBASE (Ovid, March 2006 to October 2013), and the Cochrane Library (Central Register of Controlled Trials, Database of Systematic Reviews and Database of Abstracts of Effects, October 22, 2013). The search strategies used for the MEDLINE and EMBASE databases are shown in Appendix 2. This search has been adapted for the other database. In addition, abstracts from the ASH (2006 to 2012) and the American Society of Clinical Oncology (ASCO) (2006 to 2013) were searched. Working Group members' files and the reference lists of included articles were searched. The database Clinicaltrials.gov (http://clinicaltrials.gov/ct2/home) was searched for ongoing trials. This report contains studies that were included in previous versions and studies resulting from the newly updated search, therefore, the number of the studies in the evidence tables may appear larger than the number of studies retrieved by the update search.

Study Selection Criteria and Protocol

This update review includes a search specific to Burkitt lymphoma and HIV-associated lymphoma, which was not included in the previous version. Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published

abstracts in the English language comparing rituximab alone with non-rituximab regimens or comparing rituximab combination therapy with non-rituximab regimens and they were:

Lymphoma

1. Randomized controlled trials (RCTs), systematic reviews, meta-analyses, or evidence-based practice guidelines;
2. Studies that included adult patients with lymphoma of any type, at any stage, and any histology;
3. Studies evaluating one or more of the following outcomes: OS, disease control (PFS, EFS, TTF, or RD), response rate, QOL, or toxicity.

Burkitt lymphoma and HIV-associated lymphoma

1. Studies that included adult patients with HIV-associatec lymphoma or Burkitt lymphoma (both HIV and not HIV).
2. RCTs, systematic reviews, meta-analyses, or evidence-based practice guidelines.
3. Other study designs: quasi randomized controlled trials, non-randomized controlled trials, controlled before-and-after studies, prospective cohort studies, retrospective cohort studies, historically controlled trials, nested case-control studies, case-control studies, and before-and-after comparisons (i.e., phase II single arm studies).

Chronic lymphocytic leukemia

1. RCTs, systematic reviews, meta-analyses, or evidence-based clinical practice guidelines;
2. Studies that included patients with CLL or SLL. For studies including patients with various histological subtypes of lymphoproliferative disorders, outcomes of patients with CLL must be identified separately;
3. Studies evaluating at least one of the following outcomes were reported: OS, disease control (PFS, TTF, EFS, or RD), or toxicity. If response rate is reported, at least one of the above outcomes must also be reported to be included.

Exclusion Criteria

Practice guidelines and systematic reviews older than two years, narrative reviews, letters, comments, editorials, cross sectional studies, case reports/case series and the following publications were excluded:

1. Studies where the population is comprised of: cell lines, animals, patients with other conditions (e.g., Castleman disease), and children;
2. No outcomes of interest (i.e., no results for OS, PFS, EFS, TTF, or response duration, response rate, QOL, or toxicity);
3. No comparison to a non-rituximab regimen;
4. Population <10 patients;
5. Abstract of a systematic review;

The following were not considered:

1. Reports evaluating solely patients undergoing stem cell transplantation.

Abstracts that were reports of interim analyses, as well as abstracts of non-comparative studies (as per PEBC policy), and systematic reviews that were more than two years old were also not included.

The methodologist (FB) screened the titles and the abstracts of the citations identified by the electronic databases and the titles of the abstracts from ASCO and ASH conference proceedings and excluded the citations that reported on studies that did not investigate the use of rituximab or that did not meet the inclusion criteria for design (i.e., were not randomized trials or were not systematic reviews for the target populations or were retrospective studies for lymphoma). The methodologist retrieved the full text of the selected articles in the library and reviewed them.

Data Extraction and Assessment of Study Quality and Potential for Bias

The methodologist (FB) extracted data and created evidence tables. Ratios, including hazard ratios (HRs), were expressed with a ratio < 1.0 indicating that patients receiving rituximab had a higher probability of survival. All extracted data and information were audited by an independent auditor.

Important quality features, such as required sample size and actual sample, loss to follow-up, blinding, randomization method, allocation concealment, early termination, intention-to-treat analysis, and ethical approval, for each study were extracted.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.2) provided by the Cochrane Collaboration [51]. For time-to-event outcomes, HRs, rather than the number of events at a certain time point, were the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they were derived from other information reported in the study, if possible, using the methods described by Parmar et al [52]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan 5.2 [51] was used.

Statistical heterogeneity would be calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic ≤10% ($p \leq 0.10$) and/or an I^2 >50% would be considered indicative of statistical heterogeneity.

RESULTS

This report is an update of a previous CCO guideline; the recommendations of the previous version are reported in Appendix 3A and the supporting evidence is summarized in Appendix 3B in Tables 1 and 2.

The flow diagram of this study is presented in Appendix 4.

Search for Existing Systematic Reviews

The search for systematic reviews identified 23 publications, of which four were included [17,53-55] (see Table 1 for general characteristics of included systematic reviews). The remaining systematic reviews were excluded because they were older than two years [56-73], they presented only a protocol [74-76], were duplicate publications [77], or only the abstract was available in English [78]. In addition, from the reference list of one of the included articles, the systematic review by Dong et al [46] was identified and was included for patients with potential hepatitis B virus (HBV) reactivation.

Table 1. Systematic reviews of studies of rituximab in lymphoma and chronic lymphocytic leukemia.

Author, date, Funding source,	Study objectives	Population	Intervention/ Comparison(s)	Outcomes
HIV-associated lymphoma				
Castillo, 2012 [53]; Echenique, 2012 [77] **Funding**: not declared	To test the effectiveness of R-chemo.	Fifteen prospective (RCT and non-RCT) studies with 1,060 patients with HIV-related NHL. Searches cut off from 2001 to 2011.	R-CHOP vs CHOP; R-CDE vs CDE; R-EPOCH vs EPOCH	OR CR OS
Barta, 2013, [17] **Funding**: a combination of grants from US and Spanish government agencies	To pool individual patient data in a meta-analysis and assess the effect of treatment (R and cART) on outcomes after adjusting for baseline covariates.	1546 individual patients data from 19 prospective clinical trials.	R + various chemotherapy regimens	OS* CR PFS
Chronic lymphocytic leukemia				
Lepretre, 2012 [54] **Funding**: F. Hoff mann-La Roche Ltd (Roche)	To evaluate the safety and efficacy of R alone or in combination in patients refractory to F.	Eighteen studies (17 non-RCTs and one RCT) of CLL patients refractory to F.	R in various combinations	PFS OS CR PR SD PD OR
Bauer, 2012 [55] **Funding**: Some of the authors received funding from pharmaceutical companies	To evaluate the benefits and harms of monoclonal antibodies.	Seven trials of patients with CLL, five of which included in a meta-analysis.	Monoclonal antibodies plus chemotherapy vs chemotherapy alone.	OS PFS TTNT CR OR MRD
HBV reactivation				
Dong, 2013 [79] **Funding**: none declared	To research the relashionship between rituximab and HBV reactivation.	Nine retrospective and prospective studies of R in patients with NHL and serological evidence of chronic hepatitis B who were not give prophylactic antiviral therapy.	R in combination with chemo vs chemotherapy.	HBV reactivation (>10-fold rise in serum HBV DNA levels + increase of serum ALT compared withbaseline).

* Primary outcome

ALT = alanine aminotransaminase; cART = combination antiretroviral therapy; CDE = cyclophosphamide, doxorubicine, and etoposide; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunoribicin (adriamycin), Oncovin (vincristine), and prednisone; CLL = chronic lymphocytic leukemia; CR = complete response; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; F = fludarabine; HBV = hepatitis B virus; HIV = human immunodeficiency virus; MRD = minimal residual disease; NHL = non Hodgkin lymphoma; OR = overall response; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; R = rituximab; RCT = randomized controlled trial; SD = stable disease; TTNT = time to next treatment; vs = versus.

Two of the systematic reviews [17,53] included patients with HIV-related NHL, and the others [54,55] included patients with fludarabine-resistant CLL. The reviews by Castillo et al [53], Lepretre et al [54], and Barta et al [17] included randomized and nonrandomized trials.

The AMSTAR tool [80,81] was applied to the reviews of summary data and the ratings are reported in Appendix 5. The review by Bauer et al [55] was of best quality; however, the Working Group decided not to use any of the existing systematic reviews of summary data because of differences in questions, population, or provincial context. Therefore, the reviews by Castillo et al [53], Lepretre et al [54], and Bauer et al [55] will not be discussed further.

The individual patient data meta-analysis by Barta et al [17] forms the basis of the recommendation for HIV-associated lymphoma. In this meta-analysis, pooled individual patient data from 19 prospective studies, with 1060 patients, showed that rituximab use was associated with improved outcomes for patients with CD4 counts ≥ 50 cells/μL for complete response (CR) (odds ratio, 2.84; 95% confidence interval [CI], 1.60 to 5.02; p<0.001), for PFS (HR, 0.48. 95% CI, 0.32 to 0.72), and for OS (HR, 0.55; 95% CI, 3.9 to 0.77; p<0.001). No association was seen for patients with CD4 count <50 cells/μL.

Primary Literature Systematic Review

The primary studies included in this document comprise trials that were included in the previous version and met the inclusion criteria for this new version of the guideline, in addition of trials identified by the updated search.

The body of evidence is composed of RCTs, presented as full-text articles or as conference abstract publications, as well as, for Burkitt lymphoma and HIV-associated lymphoma, of phase II single arm studies. Included, along with the main studies are several corollary publications.

Literature search results

In total, 4330 citations, including 10 guidelines, were captured by the searches. One hundred ninety-five records were from the previous version of this guideline, 3989 were from the searches executed on the electronic databases MEDLINE, EMBASE, and the Cochrane Library, 119 were from conference proceedings, four were from Working Group members' files, and six from review of reference lists of included articles. Seven articles were found during preliminary searches and used as background material. Three hundred seventy-one citations were selected after title and abstract review and the full text of the articles was retrieved in the library; of these, 127 publications representing 56 studies were included after full-text review. Among studies of aggressive lymphoma, 10 RCTs examined previously untreated patients [1-10], including one study of adult Burkitt lymphoma [9]; six non-RCTs had a population of patients with Burkitt lymphoma [82-87]; two studies examined relapsed or refractory patients [13,14]; and four studies examined the efficacy of rituximab maintenance in patients [4,88-90]. One RCT [91] and four non-RCTs [92-95] evaluated the efficacy of rituximab in patients with HIV-associated lymphoma. Among studies of indolent lymphoma, nine RCTs examined the efficacy of rituximab in previously untreated patients [18,21-24,26,32-34]; five RCTs examined relapsed or refractory patients [28,31,36-38]; and nine RCTs examined the efficacy of rituximab maintenance [28,31,36-38]. One study examined HBV reactivation in patients treated with rituximab [47]. Among the studies of CLL, three RCTs examined first-line [40-42] and two RCTs second-line rituximab treatment [44,45].

The results are presented in Tables 2 through 10 with each table composed of four sections: general characteristics, treatment dose and schedule (T), quality (Q), results (E), and adverse events (AE) and accompanying text. The tables are grouped at the end of each section, for each population group. In the text we reference the studies to the main publication,

however data were extracted from all the publications referring to each study, and references to each publication is given in the general characteristics tables for each section.

Aggressive Histology Lymphoma: Previously untreated patients

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 2, and the treatment doses and schedule are summarized in Table 2T.

Ten RCTs [1-6,8-10,12], represented by 22 publications, were included.

The sample size of the studies ranged from 76 to 1222 patients. Nine studies examined patients with diffuse large cell lymphomas, and one study examined patients with Burkitt lymphoma (HIV negative) [9]. Five studies had a population of older adults [1,4,6,10,11], four studied a population of younger adults [2,5,7,9], and one did not report patients' ages [8]. Most studies examined patients with diffuse large B-cell lymphomas, except for Ribrag et al [9] who studied patients with HIV-negative Burkitt lymphoma.

The included studies compared rituximab and a chemotherapy combination with chemotherapy alone. The studies tested rituximab in combination with CHOP or CHOP-like treatment [1,2,4,6,7,10,11]; one study used rituximab combined with etoposide as a component of stem cell mobilization [8]; and one study used rituximab combined with high intensity chemotherapy protocol [9].

The majority of the studies had EFS as the primary outcome [1,2,5-7,9,11]; two studies had failure-free survival (FFS) as the primary outcome [4,10]. Other outcomes reported included measures of survival, such as OS and PFS, measures of response, such as CR, and toxicities (AE).

Additional publications reported on long-term outcome [3,12,96-99], subgroup analyses [100-103], and analyses of prognostic markers [104,105].

Quality of included studies:

The quality of the included studies is summarized in Table 2Q.

Seven studies were reported as full-text publications [1-6,12] and three as conference abstracts [8-10]. The overall quality of the studies was variable. One of the studies blinded outcome assessors [3], the others were open label trials (MinT trial [7], LNH 03-18 trial [5]), or did not report blinding [2,4,6,9]. Four of the studies were terminated early because the formal criterion for stopping was met [4,6], because investigators realized that a meaningful difference in EFS/OS would not detectable with the available sample size [1], or because of benefit [10].

Outcomes

The results of the studies are summarized in Table 2E, the adverse events in Table 2AE.

Overall, this body of evidence indicates a benefit with the use of rituximab in addition to various chemotherapy regimens, when compared with chemotherapy alone. Statistically non-significant results are seen in studies that were underpowered for the primary outcomes of disease control [1,2], or for secondary outcomes such as OS in some of the studies [4-6,8]. Patients treated with rituximab in the included RCTs did not experience statistically significantly greater adverse events than patients in the non-rituximab control groups except for the RICOVER60 study [6], where older patients treated with eight immunochemotherapy cycles with rituximab experienced higher degrees of anemia and mucositis compared with patients who received six cycles of immunochemotherapy alone.

We conducted a meta-analysis of the studies' results for EFS, PFS and OS.

One study, in abstract form [9] examined patients with Burkitt lymphoma; its results are discussed in the following paragraphs but it is not included in any of the statistical pooling due to clinical heterogeneity.

Six non-randomized trials of patients with Burkitt lymphoma represented by 11 publications were also included [82-87,106-110]. Their general characteristics and results are summarized in Tables1, 1E and 1AE in Appendix 6 and they are not discussed any further.

Event-Free-Survival and Failure-Free-Survival.

All the included RCTs that reported on EFS [2,5-7,9,11], except for Aviles et al [1], showed a statistically significantly increased benefit with rituximab plus chemotherapy treatment compared with chemotherapy alone.

The HOVON abstract report [10] and E4494/C9793 [4] studies reported on FFS. These studies showed a statistically significant benefit with the use of rituximab with chemotherapy as compared with chemotherapy alone (HR, 0.60; p=0.004, and HR, 0.78, p=0.008 respectively). The results of six of the studies, with a total of 2,658 patients, were statistically combined in a meta-analysis, (Figure 1). The study by Aviles et al [1] was not included in this analysis because the publication did not report enough data. Only the comparison of six cycles of R-CHOP every two weeks versus six cycles of CHOP every two weeks (6-R-CHOP-14 versus 6-CHOP-14) of the RICOVER60 study [6] was included because the other comparisons either did not contain rituximab (8-CHOP-14 versus 6-CHOP-14) or involved a higher number of cycles (8-R-CHOP-14 vs 6-CHOP-14).

As indicated in Figure 1, the pooled HR for EFS/FFS for the six RCTs was 0.59 (95% CI 0.50 to 0.69). The I^2 value of 47% indicates that statistical heterogeneity among these studies is moderate.

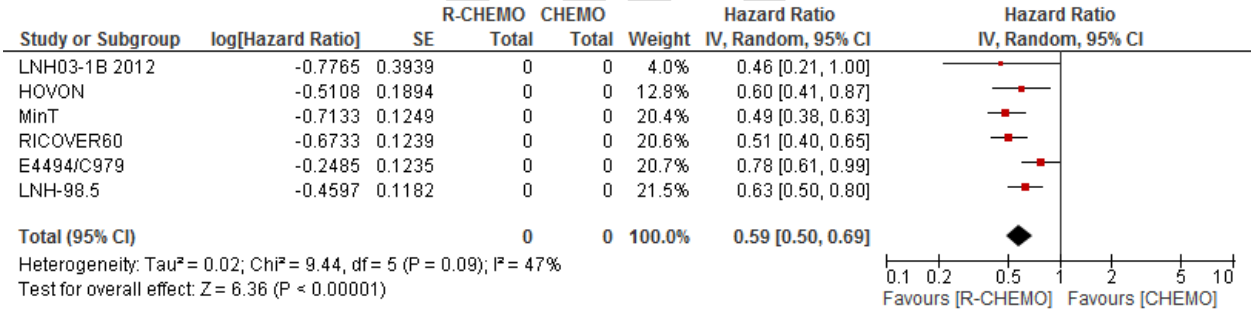

Figure 1. Rituximab in aggressive, previously untreated lymphoma: Event-free survival

Progression-Free-Survival

Four studies, involving 2667 patients, reported on PFS [5-7,11], and all reported a statistically significant benefit in using rituximab with various chemotherapy regimens compared with chemotherapy alone.

The meta-analysis shows that the pooled HR for the four RCTs is 0.54 (95% CI, 0.45 to 0.65) (Figure 2). The statistical heterogeneity of I^2 = 29% can be considerate moderate.

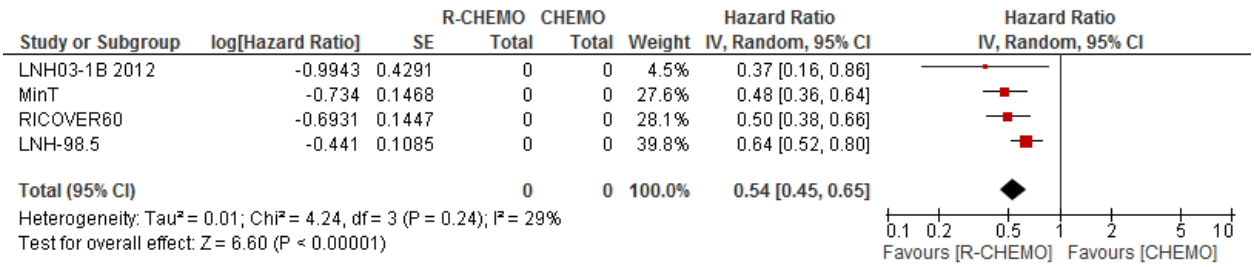

Figure 2. Rituximab in aggressive, previously untreated lymphoma: Progression-free survival

Overall survival (OS)

All the included studies reported on OS. Five studies reported a significant difference in OS in favour of using rituximab, including the study with a population of Burkitt lymphoma patients [3,6,9,10,12], while the remaining six studies reported a non significant difference. Data from seven studies [2-6,10,12], involving 3,738 patients, were statistically combined in a meta-analysis for OS. As illustrated in Figure 3, the pooled HR for OS in the seven RCTs was 0.67 (95% CI, 0.58 to 0.77; p<0.00001). The heterogeneity of the studies was negligeable (I^2=0%)

The studies by Aviles et al [1], and Pohlman et al [8] reported a nonsignificant difference in OS between the rituximab and the chemotherapy alone groups. However, they did not report enough data and were therefore not entered in the meta-analysis.

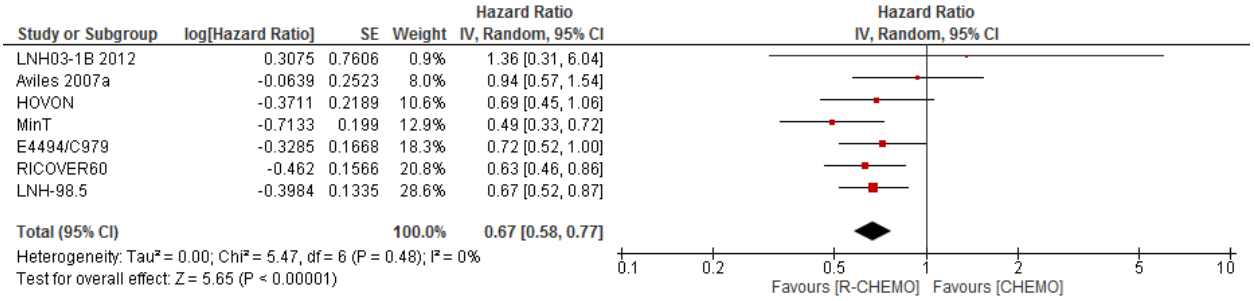

Figure 3. Rituximab in aggressive, previously untreated lymphoma: Overall survival

Disease free survival

Coiffier et al in the LNH-98.5 study [3] showed a better disease-free-survival in the rituximab group compared with the chemotherapy group (respectively median not reached [95% CI, not reached to not reached] versus median 3.4 years [95% CI, 1.6 to not reached]; p value not reported).

Time to progression

Aviles et al [1] reported a time to progression (TTP) nonsignificantly different between the rituximab and chemotherapy and the chemotherapy alone group (respectively 74% versus 72%, median not reached; p value not reported). This outcome was not reported by the other studies.

Response

Seven studies reported on complete remission [1-3,5,6,10,12]. Three of these reported a statistically significant benefit with the use of rituximab and chemotherapy compared with chemotherapy alone [3,6,12] (see Table 2E for results). Two studies reported no between-group difference [1,2]; and two studies did not report any p values [5,10].

Quality of Life

None of the studies measured QOL.

Adverse Events

None of the included studies reported any significant between-group difference in adverse events, except for the RICOVER-60 study [6] in which patients allocated to the 8xR-CHOP-14 arm experienced significantly more anemia and mucositis when compared to patients in the 6xCHOP-14 arm (Table 2AE).

Aggressive Histology Lymphoma: Tables of included studies for previously untreated patients

Table 2. Rituximab in aggressive histology lymphomas: Previously untreated patients including non-HIV Burkitt lymphoma. General characteristics of included randomized controlled trials

Study name, author, date, funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
LNH-98.5 Coiffier, 2010, 2002 [3,11] Feugier, 2005 [98] Rigier, 2011 [101], Mounier, 2003 [111] Groupe d'Étude des Lymphomes de l'Adulte (GELA) **Funding**: Grants from F. Hoffman-La Roche	To evaluate the effectiveness of R-CHOP [11]; five years [98] and ten years follow-up [3]. **Design**: Parallel group **Follow-up:** 10 years	399 elderly patients with previously untreated DLBCL. Median age: 69 years	R-CHOP vs CHOP	*EFS PFS DFS CR PR AE
MabThera International Trial Group MInT Pfreundschuh, 2011, 2008, 2006,[7,12,104], Rieger, 2011 [101], Witzens-Harig, 2012 [96], Murawski, 2010 [99] **Funding**: Roche, Basel, Switzerland	To establish whether younger patients with good prognosis might benefit from R [7,12]. To examine the prognostic significance of max tumour diameter [104]. To examine the effect of chemo + R in PMBCL in comparison to other DLBCLs [96,101]. To examine the effect of different chemo regimens on long-term outcome [99]. **Design:** Parallel group **Follow-up:** median 72 months	823 young patients with good prognosis, previously untreated DLBCL. Median age (years): 47	R+chemo (CHOP-like) vs chemo alone Chemo = CHOP-21 (N=396), CHOEP-21 (N=361), MACOP-B (N=34), PMitCEBO (N=32)	*EFS Response PFS OS AE
RICOVER-60 Pfreundschuh, 2008b, 2012 [abs], 2013 [6], Ott, 2010 [105] Bittenbring, 2013 [abs] [100,102,103] **Funding:** Deutsche Krebshilfe German Federal Minister of Science and Research	Test the use of R in combination with CHOP14 [6]; Test the prognostic impact of immunoblastic morphology [105]; Subgroup of patients with low vitamin D levels [100]. Subgroup of elderly patients with different pharmacokynetics [102]. Analyze the impact of sex on R clearance [103] **Design:** 2×2 factorial design **Follow-up:** the trial was stopped at the 2nd interim analysis	1222 older patients with previously untreated DLBCL Median age (years): not reported	CHOP14 (6 vs 8 cycles) vs R-CHOP14	*EFS RR PFS OS

Study name, author, date, funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Aviles, 2007 [2] **Funding:** none declared	To assess the efficacy and toxicity of R with dose dense chemo **Design:** parallel group **Follow-up:** 53.4 months	196 patients with previously untreated, advanced stage DLCL Median age (years): CEOP-14: 60.4; CEOP-R: 59.1	CEOP-14 vs R-CEOP	*EFS TTP OS
Aviles, 2007b [1] **Funding:** none declared	To assess whether the addition of R to chemo would improve outcomes in patients with poor prognosis **Design:** parallel group **Follow-up:** 58.6 months	204 older patients with previously untreated DLCL Median age (years): CEOP: 69.6 CEOP-R: 68.9	Escalated CEOP vs CEOP-R	*EFS *OS *Response
HOVON Sonneveld, 2006 [abs] [10] **Funding:** none reported	To test the effectiveness of 8 cycles of R-CHOP14 **Design:** RCT multicentre phase III **Follow up:** 20 months	243 elderly patients with intermediate to high risk,previously untreated,B-cell aggressive NHL Median age (years): 72	8 cycles of CHOP14 with or without R	*FFS CR OS
Pohlman, 2005 [abs] [8] **Funding**: Not reported	Test R in combination with etoposide and G-CSF for peripheral stem cell mobilization **Design:** RCT Phase III **Follow-up:** 39 months	76 patients with B-cell NHL. Median age (years): not reported.	Etoposide and G-CSF vs R + etoposide and G-CSF	CD34/kg yield
LNH 03-1B trial Ketterer, 2013 [5] **Funding:** Group d'Ètudes des Lymphomes de l'Adulte and Amgen	To test the addition of 4 R doses to 3 ACVBP cycles **Design:** Phase III multicentre RCT **Follow-up:** 43 months	223 low risk patients with localized DLBCL Median age (years): 49	R+ ACVBP vs ACVBP	*EFS CR PFS DFS OS AE Rate of CNS progression
E4494/C9793 Habermann 2006 [4]; Morrison, 2007 [abs] [112] Morrison, 2010 [abs] [97] **Funding**: Public Health Service Grant, National Cancer Institute; National Institute of Health, Department of Health and Human Services, US	To compare FFS of older patients treated with R-CHOP or CHOP induction. **Design:** Phase III RCT with 2 stage randomization, the first for induction **Follow-up:** 3.5 years	632 patients with untreated DLBCL randomized to induction Median age: IG: 69 years CG: 70 years	R-CHOP vs CHOP	*FFS CR PR TTF OS

Study name, author, date, funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
GRAALL-Lysa LMBA002 Ribrag, 2012 [abs] [9] NCT00180882 **Funding:** some of the authors declared having received support from pharmaceutical companies.	To test R added to an intensive, short-course chemo. **Design:** RCT, phase III **Follow-up:** 38 months	257 adult patients with Burkitt lymphoma and negative to HIV. Median age (years): 47	R + LMBA protocol vs LMBA protocol	*EFS OS AE

*primary outcome
Abs = abstract; ACVBP = dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; AE = adverse effects; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; CG= control group; chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHOEP = cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CNS = central nervous system; CR = complete response; DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; DLCL = diffuse large cell lymphoma; EFS = event-free survival; FFS = failure free survival; G-CSF = granulocyte-colony stimulating factor; HIV = human immunodeficiency virus; IG = intervention group; LMBA protocol = low-dose steroids, vincristine and cyclophosphamide; MACOP-B=cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, prednisone; max = maximum; NHL = non-Hodgkin lymphoma; OS = overall survival; PFS = progression free survival; PMitCEBO=mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; R = rituximab; RCT = randomized controlled trial; RR = response rate; TTF = time to treatment failure; TTP = time to progression.

Table 2T. Treatment details of included randomized trials of rituximab in previously untreated patients with aggressive histology lymphoma

Author, date, study name	Rituximab (375 mg/m^2)	Treatment name	Chemotherapy protocol (mg/m^2)						Comparison
			# Cycles	C	H	O	P	Schedule	
LNH-98.5 Coiffier, 2010, 2002 [3,11] Feugier, 2005 [98].	8 courses	R-CHOP	8	750	50	1.4 max 2 on d 1	40	1 cycle every 3 wks for a total of 8 cycles	CHOP alone
MInT Pfreundschuh, 2011, 2008, 2006,[7,12,104] Rieger, 2011[101], Witzens-Harig, 2012 [96], Murawski, 2010 [99]	6 courses	R-CHOP-like	6	750	50	2	100	CHOP-21: vincristine given IV on ds 1, 22, 43, 64, 85 and 106; prednisone given on ds1-5, 22-26, 43-47,64-68, 85-89 and 106-110	CHOP-like chemotherapy alone
				750	50	2	100	CHOEP-21: Etoposide 50 IV or 200 orally on ds 2-3, 23-24, 44-45, 65-66, 86-87 and 107-108	
				350	50	1.4	40	MACOP-B: C and doxorubicine given IV on ds 1, 15, 29, 43, 57 and 71. Vincristine given IV on ds 8, 22, 36, 50, 64 and 78. Methotrexate 400 on ds 8, 36, and 64 and bleomycin 10 IV on ds 22, 50 and 78; prednisone oral or IM on ds1-84.	
				300		1.4	50	PMitCEBO: Mitoxantrone, 7; C 300; E150 IV on ds 1, 158, 29, 43, 57 and 71; vincristine and bleomycin 10 IV on ds 8, 22, 36, 50, 64, and 78; P 50 on ds 1-28 and on alternating ds 29-84.	
RICOVER-60 [6], Ott, 2010 [105] Bittenbring,	8 courses	R-CHOP-14	6 and 8	750	50	2	100	Vincristine was administered on d 1 and prednisone on ds 1-5. All patients received G-CSF starting on d 6 or on d 4.	6 courses CHOP-14

Author, date, study name	Rituximab (375 mg/m²)	Treatment name	Chemotherapy protocol (mg/m²)						Comparison
			# Cycles	C	H	O	P	Schedule	
2013 [abs] [100], Pfreundschuh, 2012 [102], Pfreundschuh, 2013 [103]									
Aviles, 2007 [2]	6 doses	CEOP-R	6	1500	=	1.4	100	Epirubicin 120 mg/m², and vincristine were given on d 1, prednisone ds 1-5	CEOP-14
Aviles, 2007b [1]	*nr*	CEOP-R	*nr*	750	=	2	*nr*	Epirubicin: 1-degree cycle 70 mg/m²; 2-degree cycle: 90 mg/m²; 3-6 degree cycle 105 mg/m². Total dose 780 mg/m²	CHEOP
Sonneveld, 2006 [abs] [10]	*nr*	R-CHOP	8	*nr*	*nr*	*nr*	*nr*		
Pohlman, 2005 [abs] [8]	3 doses	Etoposide and G-CSF	*nr*	=	=	=	=	Etoposide 2 and G-CSF 10 mcg/kg/day	Etoposide and G-CSF alone
LNH 03-1B trial [5]	4 doses	ACVBP-R	3	=	=	=	=	*nr*	ACVBP
E4494/C9793 (induction) [4];	6 or 8 doses	R-CHOP	7	750	50	1.4	100	R was given 7 and 3 ds before cycle 1 and 2 ds before cycles 3 and 5, and, if administered, 7	CHOP
GRAALL-Lysa LMBA002 [abs] [9]	4 doses	COPADM-R	*nr*	*nr*	*nr*	*nr*	*nr*	R was given on ds 1 and 6 of the first 2 courses of COPADM	COPADM

ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; C = cyclophosphamide; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHOEP = cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CODOX-M/IVAC = cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide and cytarabine Ara-C; COPADM = cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate; d = day; G-CSF = granulocyte-colony stimulating factor; H = doxorubicin; IV = intravenous; M = mitoxantrone; MACOP-B=cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, prednisone; nr = not reported; O = vincristine P = prednisone; PMitCEBO=mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone; R = rituximab; wks = weeks.

Table 2Q. Rituximab in aggressive histology lymphomas: First-line treatment, including non-HIV Burkitt lymphoma. Quality of included randomized controlled trials.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
LNH-98.5 Coiffier, 2010, 2002 [3,11] Feugier, 2005 [98].	R-CHOP vs CHOP	EFS	400 patients recruited for 3 years and followed for a min of 1 yr were required to provide 80% power at 5%, 2-sided significance level to detect an increase in the 3-yr EFS from 30% to 45%.	399	Yes	Yes	Yes, outcome assessors	Yes	No
MInT Pfreundschuh, 2011, 2008 2006,[7,12,104] Rieger, 2011[101], Witzens-Harig, 2012 [96], Murawski, 2010 [99]	R + Chemo (CHOP-like) vs Chemo alone	EFS	820 patients were necessary to provide 80% power at 5%, 2-sided significance level detect a 10% difference in 3-yr EFS	823	Yes	Yes	No, open label	Yes	No
RICOVER-60 Pfreundschuh, 2008b [6], Ott, 2010 [105] Bittenbring, 2013 [abs] [100], Pfreundschuh, 2012 [102], Pfreundschuh, 2013 [103]	CHOP-14 (6 vs 8 cycles) vs R-CHOP-14 (6 vs 8 cycles)	EFS	988 patients were necessary to detect a 9% difference in 3-yr EFS with 80% power and 5%, 2-sided, significance level	1222	Yes	Yes	*nr*	Yes	Yes
Aviles, 2007 [2]	CEOP-14 vs R-CEOP	OS	*nr*	196	Yes	Can't tell	*nr*	Yes	*nr*
Aviles, 2007b [1]	Escalated CEOP vs CEOP-R	EFS OS Response rate	The study was planned to observe a difference of 15% in EFS and OS, but at an analysis performed in 2003 it was observed that over 1000 patients were needed, and the study was closed.	204	Yes	Yes	*nr*	Yes	Yes
Sonneveld, 2006 [abs] [10]	R + CHOP-14 vs CHOP-14	FFS	A target of 400 patients to be accrued in 5 years based on an expected increase in FFS with HR=0.70.	243	No	No	*nr*	No	Yes
Pohlman, 2005 [abs] [8]	R + etoposide and G-CSF vs Etoposide and G-CSF	CD34/kg yield	*nr*	76	No	No	*nr*	No	No
LNH 03-1B trial Ketterer, 2013 [5]	R+ ACVBP vs ACVBP	EFS	400 patients were required over 4 years and followed for1 year to obtain a 90% power at a 5% significance level.	223	Yes	*nr*	No	Yes	No

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
E4494/C9793 Habermann 2006 [4] Morrison, 2010 [abs][97]	R-CHOP vs CHOP	FFS	The study was designed to detect a 33% reduction in the induction FFS HR (82% power), the number of patients is not provided. The data represents 95% of the planned induction information.	546	No	*nr*	*nr*	Yes	Yes
GRAALL-Lysa LMBA002 Ribrag, 2012 [abs] [9] NCT00180882	R + LMBA protocol vs LMBA protocol	EFS	250 patients were required to detect a 15% gain in EFS with 90% power and two-sided 5% significance.	257	No	*nr*	*nr*	*nr*	*nr*

Abs = abstract; ACVBP = dose-intensified doxorubicin, cyclophosphamide, vindesine,bleomycin, and prednisone; Chemo = chemotherapy; CEOP = cyclophosphamide, epirubicine, vincristine, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CR = complete response; EFS = event-free survival; FFS = failure-free survival; G-CSF = granulocyte-colony stimulating factor; HR = hazard ratio; ITT = intention-to-treat; LMBA protocol = low-dose steroids, vincristine and cyclophosphamide; min = minimum; *nr* = not reported; OS = overall survival; R = rituximab.

Table 2E. Efficacy of rituximab in aggressive histology lymphomas: First-line treatment, including non-HIV Burkitt lymphoma. Included randomized controlled trials.

Study	Intervention Control	Primary Outcome	EFS median (months/years) or % surviving	PFS Median (months/years) or % surviving	CR (%)	OS, median (months/years) or % surviving	Follow-up, median (months/years)
LNH-98.5 Coiffier, 2010, 2002 [3,11] Feugier, 2005 [98].	R-CHOP	EFS	$EFS_{60\ months}$ 3.8 years (95% CI, 2.37-not reached)	4.8 years (95% CI, 2.7-7.6)	76	3.5 years (CI, 2.2-5.5)	120 months 60 months 24 months
	CHOP		$EFS_{60\ months}$: 1.1 years (95% CI, 0.8-1.5) *p<0.00002	1.2 years (95% CI, 0.9-1.8) p<0.0001	63 P = 0.005[B]	8.4 years p<0.0001	
MInT Pfreundschuh, 2011, 2008, 2006,[7,12,104], Rieger, 2011[101], Witzens-Harig, 2012 [96], Murawski, 2010 [99]	R+CHOP-like chemo[C]	EFS	Median not reached. $EFS_{72\ mo}$: 74.3% (95% CI, 69.3-78.6)	80.2 (95% CI, 75.4-84.1	86	Median not reached. 90.1% (95% CI, 86.4-92.9)	72 months
	Chemo		$EFS_{72\ months}$: 55.8% (95% CI, 50.4-60.9) *p<0.0001	63.9% (95% CI, 58.4-68.9) p<0.0001	68 P<0.0001	80.0% (95% CI, 75.3-83.9),p=0.0004	
RICOVER-60 Pfreundschuh, 2008b [6], Ott, 2010 [105] Bittenbring, 2013 [abs] [100], Pfreundschuh, 2012 [102], Pfreundschuh, 2013 [103]	6xR-CHOP-14	EFS	*66.5% (95% CI, 60.9-72.0) RR 0.51 (95% CI, 0.40-0.65) p<0.0001[A]	73.4 (68.1-78.7) RR 0.50 (95% CI, 0.38-0.67) p<0.0001[A]	78 P=0.0069[A]	78.1% p=0.018[A]	34.5 months
	8xR-CHOP-14		*63.1% (95% CI, 57.4-68.8) RR 0.54 (95% CI, 0.43-0.69) p<0.0001[A]	68.8 (63.2-74.5) RR 0.59 (95% CI, 0.45-0.77) p=0.0001[A]	76 P=0.0372, NS after Bonferroni corr.[A]	72.5% NS[A]	
	6xCHOP-14		*47.2% (95% CI, 41.2-53.3)	56.9% (50.8-63)[A]	68	67.7%	
	8xCHOP-14		*53.0% (95% CI, 47.0-59.1) RR 0.76 (95% CI, 0.60-0.95) p=0.0172[D]	56.9% (50.8-63) RR 0.92 (95% CI, 0.72-1.18) NS[D]	72 NS[A]	66% NS[A]	
Aviles, 2007a [2]	R-CEOP	OS	*nr*	*nr*	76	Median not reached 67%	53.4 months
	CEOP		*nr*	*nr*	74 NS	65%	
Aviles, 2007b [1]	R-CEOP	EFS	Median not reached *75%	*nr*	*78	Median not reached *81%	58.6 months
	Esc CEOP		*77% NS	*nr*	*74 NS	*82% NS	

Study	Intervention Control	Primary Outcome	EFS median (months/years) or % surviving	PFS Median (months/years) or % surviving	CR (%)	OS, median (months/years) or % surviving	Follow-up, median (months/ years)
HOVON Sonneveld, 2006 [abs] [10]	R-CHOP	FFS	$FFS_{20\ months}$: 55%	*nr*	After 8 cycles: 66	HR=0.69 (95% CI, 0.46-1.05) in favour of R-CHOP p=0.09	20 months
	CHOP		$FFS_{20\ months}$: 33% HR=0.60, p=0.004	*nr*	46, P=*nr*		
Pohlman, 2005 [abs] [8]	R-etoposide G-CSF	CD34/Kg	*nr*	NS	*nr*	NS	39 months
	etoposide G-CSF		*nr*	NS	*nr*	NS	
LNH 03-1B trial Ketterer, 2013 [5]	R+ ACVBP	EFS	*$EFS_{3\ years\ est}$: 93% (95% CI, 87% 97%)	$PFS_{3\ years\ est}$: 95% (95% CI, 89%-98%)	97	NS	43 months
	ACVBP		$EFS_{3\text{-}years\ est}$: 82% (95% CI, 73%-88%) HR 0.46, p = 0.0487	$PFS_{3\text{-}years\ est}$: 83% (95% CI, 74%-89%) HR 0.37, p = 0.02	94, P values *nr*	NS	
GRAALL-Lysa LMBA002 Ribrag, 2012 [abs] [9]	R-LMBA	EFS	*76%	*nr*	*nr*	OS_{3years}: 82%	36 months
	LMBA		64% p=0.05	*nr*	*nr*	$OS_{3\ years}$:71% p=0.016	
E4494/C9793 Habermann 2006 [4], Morrison, 2007 [abs] [112] Morrison, 2010 [abs] [97]	R-CHOP	FFS	$FFS_{36\ months}$: 53% $FFS_{9\ years}$: 35%	*nr*	*nr*	$OS_{36\ months}$: 67% $OS_{9\ years}$: 44%	36 months 9.4 years
	CHOP		$FFS_{36\ months}$: 46% HR = 0.78; 95% CI, 0.61 to 0.99, NS $FFS_{9\ years}$: 25%, p=0.008	*nr*	*nr*	$OS_{36\ months}$: 58% HR = 0.83; 95% CI, 0.63 to 1.09 NS $OS_{9\ years}$: 37%, NS	

*primary outcome
[A] P value derived from comparison with 6xCHOP-14 treatment

Abs = abstract; ACVBP = dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CEOP = cyclophosphamide, epirubicine, vincristine, and prednisone; Chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CI = confidence interval; corr = correction; CR = complete response; EFS = event-free survival; Esc = escalated regimen; FFS = failure-free survival; G-CSF = granulocyte-colony stimulating factor; HR = hazard ratio; LMBA protocol = low-dose steroids, vincristine and cyclophosphamide; min = minimum; mo = months; *nr* = not reported; NS = not significant; OS = overall survival; R = rituximab; RR = relative risk.

Table 2AE. Rituximab in aggressive histology lymphomas – First-line treatment, including non-HIV Burkitt lymphoma. Grade ≥ 3 adverse events in included randomized controlled trials.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vom (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)		Second tumours (%)	Deaths (%)
												Arrhyt.	Card. funct.		
LNH-98.5 Coiffier, 2010, 2002 [3,11] Feugier, 2005 [98].	R-CHOP	202	12	*nr*	*nr*	*nr*	*nr*	4	3	3	5	8		10.4	During treatm: 5.9 After treatm: 16.3
	CHOP	197	20	*nr*	*nr*	*nr*	*nr*	8	2	5	9	8		11.2	During treatm: 5.9 After treatm: 8.1
MInT Pfreundschuh, 2011, 2008 2006,[7,12,104], Rieger, 2011[101], Witzens-Harig, 2012 [96], Murawski, 2010 [99]	R+chemo	404	7	*nr*	*nr*	*nr*	*nr*	<1; 2	*nr*	*nr*	3	2		4.5	10 Treatm Related 1
	chemo	403	8	*nr*	*nr*	*nr*	*nr*	1; 2	*nr*	*nr*	3	1		4	18 Treatm Related: 0.2
RICOVER-60 Pfreundschuh, 2008b [6], Ott, 2010 [105] Bittenbring, 2013 [abs] [100], Pfreundschuh, 2012 [102], Pfreundschuh, 2013 [103]	6xR-CHOP-14	307	28	*nr*	16	NS	12 NS	*nr*	5	*nr*	7	4	3	*nr*	Treatm Related: 6
	8xR-CHOP-14	305	35	*nr*	27	NS	16 NS	*nr*	9	*nr*	8	6	3	*nr*	8
	6xCHOP-14	306	29	*nr*	16	NS	10 NS	*nr*	3	*nr*	7	5	2	*nr*	8
	8xCHOP-14	304	31 NS	*nr*	23 P=0.001	NS	17 NS	*nr*	6 P=0.03	*nr*	11 NS	3 NS	2 NS	*nr*	8 NS
Aviles, 2007 [2]	R-CEOP	98	*nr*	*nr*	*nr*	8	0	3	0	nr	0	0		*nr*	Treatm related: 0
	CEOP-14	98	*nr*[A]	*nr*	*nr*	4	0	5	0	nr	0	0		*nr*	0
Aviles, 2007b [1]	R-CEOP	204	*nr*	*nr*	*nr*	NS	*nr*[B]	*nr*	*nr*	*nr*	NS	NS		*nr*	*nr*
	Esc CEOP		*nr*	*nr*	*nr*	NS	*nr*	*nr*	*nr*	*nr*	NS	NS		*nr*	*nr*
HOVON Sonneveld, 2006 [abs] [10]	R-CHOP-14, 8 cycl	243	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*		<1	*nr*
	CHOP-14, 8 cycl		*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*		<1	*nr*
Pohlman, 2005 [abs] [8]	R-etoposide G-CSF	28	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*		*nr*	After ASCT: 11

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vom (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumours (%)	Deaths (%)
	etoposide G-CSF	27	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	7
LNH 03-1B trial Ketterer, 2013 [5]	R-ACVBP	110	During neuropenia: 14 Without neuroptenia: 4			35 19 *nr*	15	1	11	0	2	0		Treatm related: 1
	ACVBP	112	During neuropenia: 9 Without neuroptenia: 2			44 21 *nr*	13	3	19	2	3	1		0
GRAALL-Lysa LMBA002 Ribrag, 2012 [abs] [9]	R-LMBA	128	NS	NS	NS	*nr*	NS	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Treatm related: 7
	LMBA	129	NS	NS	NS	*nr*	NS	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Treatm related: 5
E4494/C9793 Induction Habermann 2006 [4], Morrison, 2007 [abs] [112] Morrison, 2010 [abs] [97]	R-CHOP	267	17	78	17	*nr*	14	*nr*	*nr*	*nr*	*nr*	9	*nr*	5%
	CHOP	279	16	78 (no fever)	16 NS	*nr*	10	*nr*	*nr*	*nr*	*nr*	9	*nr*	

[A] Bacterial and fungal infections were reported, not viral infections.
[B] Only Grade I and II reported.

Abs = abstract; ACVBP = dose-intensified doxorubicin, cyclophosphamide, vindesine,bleomycin, and prednisone; ASCT = autologous stem cell transplantation; Chemo = chemotherapy; CEOP = cyclophosphamide, epirubicine, vincristine, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CI = confidence interval; CR = complete response; cycl = cycles; EFS = event-free survival; FFS = failure-free survival; G-CSF = cranulocyte-colony stimulating factor; HR = hazard ratio; LMBA protocol = low-dose steroids, vincristine, and cyclophosphamide; min = minimum; *nr* = not reported; NS = not significant; R = rituximab; tox = toxicity; treatm. = treatment; vom = vomiting.

Aggressive Histology Lymphoma: Patients With Relapsed/ Refractory Disease

General Characteristics of Included Studies

The general characteristics of these studies are summarized in Table 3.

Two RCTs [13,14] were included. One study included 100 frail patients with relapsed/refractory DLBCL [14], and the other study included 239 rituximab-naïve, adult patients with relapsed/refractory, aggressive B-cell NHL.

The studies tested rituximab in combination with chemotherapy versus chemotherapy alone and reported on CR, PR, PFS, FFS, and OS.

Patients in the study by Aviles et al [14] were treated with rituximab 375 mg/m^2 on day 1 of every cycle of conventional doses of etoposide, methylprednisolone, high-dose Ara-C, and cisplatin. In the HOVON-44 study [13] the treatment consisted of three cycles of re-induction therapy. The DHAP treatment consisted of cisplatin 100 mg/m^2 on day 1 (24 h intravenous infusion); cytarabine 2 g/m^2 on day 2 (3-h infusion repeated after 12 h); and dexamethasone 40 mg/day for four consecutive days. The VIM treatment consisted of etopostide 90 mg/m^2 on days 1, 3 and 5, ifosfamide 1200 mg/m^2 on days 1 through 5 and methotrexate 30 mg/m^2 on days 1 and 5. Rituximab 375 mg/m^2 was given on day 5 of the DHAP course or on day 6 of the VIM course.

Quality of included studies:

The quality of the studies is summarized in Table 3Q.

Neither study reported on power calculation, methods used for allocating patients to group, and on blinding. Both studies used an intention-to-treat analysis.

Outcomes

The results of the studies are summarized in Table 3E, the adverse events in Table 3AE.

Statistical pooling of the results into a meta-analysis was not considered appropriate for these studies because the population and the interventions were clinically heterogeneous.

Survival and Response

The HOVON 44 study [13] showed a statistically significant benefit with the use of rituximab for PFS, FFS, and CR in rituximab-naïve patients. By contrast, Aviles et al [14] who studied frail patients, did not report any statistically significant between-arm difference.

Quality of Life

These studies did not measure QOL.

Adverse Events

No statistically significant between-group differences were reported for grade $\geq$3 adverse events by either author.

Aggressive Histology Lymphoma: Tables of studies of patients with relapsed/refractory disease

Table 3. Rituximab in aggressive histology lymphomas: General characteristics of included randomized controlled trials of patients with relapsed/refractory disease.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Aviles, 2010 [14] Funding: none declared	To evaluate the efficacy of R-ESHAP Design: single centre, phase III Follow-up: 64.5 months	100 frail patients with refractory/relapsed DLBCL	ESHAP vs R-ESHAP	CR PFS OS
HOVON-44 Vellenga, 2008 [13] Funding: Not reported	To evaluate the role of R during remission induction. Design: parallel group Follow-up: 24 months	239 rituximab-naïve patients with relapse progressive/aggressive CD20+ NHL	DHAP-VIM DHAP +ASCT vs R DHAP-VIM DHAP +ASCT	CR PR FFS PFS

ASCT = autologous stem cell transplantation; CR = complete response; DHAP-VIM DHAP = DHAP (cisplatin cytarabine-dexamethasone)-VIM (etoposide-ifosfamide-methotrexate)-DHAP =cisplatin-cytarabine-dexamethasone; DLBCL = diffuse large B cell lymphoma; ESHAP = etoposide, methylprednisolone, high-dose Ara-C, cisplatin; FFS = failure-free survival; NHL = non-Hodgkin lymphoma; OS = overall survival; PFS = progression free survival; PR = partial response; R = rituximab.

Table 3Q. Rituximab in aggressive histology lymphomas: Quality of included randomized controlled trials of patients with relapsed/refractory disease.

Study	Treatment	Primary outcome	Sample Size N	Randomization method described	ITT Analysis	Early termination
Aviles, 2010 [14]	ESHAP vs R-ESHAP	*nr*	100	No	Yes	No
HOVON-44 Vellenga, 2008 [13]	DHAP-VIM DHAP +ASCT vs R DHAP-VIM DHAP +ASCT	*nr*	239	No	Yes	No

ASCT = autologous stem cell transplantation; CR = complete response; DHAP-VIM DHAP = DHAP (cisplatin cytarabine-dexamethasone)-VIM (etoposideifosfamide-methotrexate)-DHAP (cisplatincytarabine-dexamethasone DLBCL = diffuse large B cell lymphoma; ESHAP = etoposide, methylprednisolone, high-dose Ara-C, cisplatin; ITT = intention-to-treat; nr = not reported; PFS = progression-free-survival; OS = overall survival; PFS = progression-free-survival; PR = partial response; R = rituximab; vs = versus.

Table 3E. Efficacy of rituximab in aggressive histology lymphomas: Included randomized controlled trials of patients with relapsed/refractory disease.

Study	Intervention Control or other disease control measure median	EFS median (months) or % surviving	PFS Median (months) or % surviving	CR (%)	OS, median (months) or % surviving	Follow-up, median (months)
Aviles, 2010 [14]	R-ESHAP	*nr*	50% (95%CI, 42%-58%)	36 (95% CI, 26-43)	Median not reached 26% (95% CI, 21%-39%)	64.5 mo
	ESHAP	*nr*	51% (95% CI, 43%-60% NS	37 (95% CI 30-48) NS	31% (95% CI, 24%-38%) NS	
HOVON-44 Vellenga, 2008 [13]	R DHAP-VIM DHAP +ASCT	$FFS_{24\ mo}$: 50%	$PFS_{24\ mo}$: 52%	46	59%	31 mo
	DHAP-VIM DHAP +ASCT	$FFS_{24\ mo}$: 24% P<0.001	31% P<0.002	35 P = 0.003	52% NS	

ASCT = autologous stem cell transplantation; CI = confidence interval; CR = complete response; DHAP-VIM DHAP = DHAP (cisplatin cytarabine-dexamethasone)-VIM (etoposideifosfamide-methotrexate)-DHAP (cisplatincytarabine-dexamethasone; DLBCL = diffuse large B cell lymphoma; ESHAP = etoposide, methylprednisolone, high-dose Ara-C, cisplatin; FFS = failure-free survival; mo = months; nr = not reported; NS = not significant; OS = overall survival; PFS = progression free survival; PR = partial response; R = rituximab.

Table 3AE. Rituximab in aggressive histology lymphomas: Grade ≥3 adverse events in ranocimized controlled trials of patients with relapsed disease.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vom (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
Aviles, 2010 [14]	R-ESHAP	47	32	26	2	*nr*	4	0	*nr*	*nr*	<1	*nr*	*nr*	0
	ESHAP	53	22	15	3	*nr*	3	0	*nr*	*nr*	<1	*nr*	*nr*	
HOVON-44 Vellenga, 2008 [13]	R DHAP-VIM DHAP +ASCT	113	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Non treatment related: 44
	DHAP-VIM DHAP +ASCT	112	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	54

ASCT = autologous stem cell transplantation; DHAP-VIM DHAP = DHAP (cisplatin cytarabine-dexamethasone)-VIM (etoposideifosfamide-methotrexate)-DHAP (cisplatincytarabine-dexamethasone; ESHAP = etoposide, methylprednisolone, high-dose Ara-C, cisplatin; *nr* = not reported; R = rituximab; tox – toxicity; vom = vomiting.

Aggressive Histology Lymphoma: Rituximab Maintenance Treatment

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 4.

Four studies [4,88-90], represented by eight publications, were included.

The sample size ranged from 269 to 477 patients. All the studies had a population of CD20+ NHL; the median age of the patients varied from 46.2 to 69 years. All the studies compared rituximab maintenance with observation. Two studies were completed in the firstline setting [4,89], one study was completed in the relapsed/refractory setting [88], and one study, published in abstract form, included patients from the firstline and relapsed/refractory populations [90]. Two studies had EFS as primary outcome [88,89], one study had FFS [4], and one study [15] had PFS as primary outcome. Other outcomes reported were PFS, OS, response, and AE.

Additional publications reported on QOL [16,90], and long-term follow-up [97,112].

Three of the trials had two randomizations, the second of which tested for rituximab maintenance [4,88,89]. Therefore, depending on the trials' first phase, some patients in the rituximab maintenance group had been already exposed to rituximab (e.g., all the patients from the CORAL study [88], and some of the patients in the E4494/C9793 study [4]). The maintenance treatment dose and schedule as shown in Table 4T, was quite diverse and this did not allow a statistical pooling of the results.

Quality of Included Studies:

The quality of the included studies is summarized in Table 4Q.

All the studies were represented by at least one full-text publication. The overall quality of this body of evidence appears to be moderate to high. Three studies reported a power calculation. Although the study by Witzens-Harig et al [15,90] included patients with aggressive and patients with indolent histology, the 2011 abstract publication reports data only on DLBCL patients, and we considered it as the primary publication.

Outcomes

The results of the studies are summarized in Table 4E, and the adverse events in Table 4AE.

Overall, while schedule and duration of rituximab maintenance varied across studies, no statistically significant results were seen for PFS or OS. On the other hand, adverse events were mostly not reported in the included studies. Although the schedule of rituximab maintenance varied among studies, we considered them clinically homogeneous, and we statistically pooled their results.

Event-Free-Survival and Failure-Free-Survival.

The CORAL and LNH-98-3 studies reported no statistically significant between-group difference for EFS [88,89]. The E4494/C9793 study [4] showed a statistically significant benefit for rituximab at 36, 66 and 108 months for FFS (Table 4E). Results were not pooled in a meta-analysis because of clinical heterogeneity: the studies' populations belonged to different age groups.

Progression-Free-Survival

This body of evidence indicates no statistically significant difference with the use of rituximab maintenance for PFS. Not enough published data were available to statistically pool the results.

Overall Survival

This body of evidence indicates no statistically significant difference with the use of rituximab maintenance for OS. Not enough published data were available to statistically pool the results.

Quality of Life

The study by Witzens-Harig et al [15] measured QOL with a generic (EQ-5D [113]) and with a cancer-specific tool (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 [114]) and Heutte et al [16] used the EORTC QLQ C30 tool. Witzens-Harig et al [15] found no statistically significant difference between the rituximab maintenance and the observation group while Heutte et al [16] found that rituximab maintenance significantly reduced pain ($p = 0.022$), insomnia ($p=0.013$) and constipation ($p = 0.034$).

Adverse Events

The E4494/C9793 study [4] reported a statistically significantly higher granulocytopenia in the rituximab group (12% versus 4%, $p=0.008$). The CORAL study reported more adverse events in the rituximab group than in the control group during the first 100 days of maintenance (47% versus 42%) with 43 serious adverse events (SAE) in the rituximab group versus 22 serious adverse events in the observation group. Nonhematological toxicity was similar in both groups. None of the included studies reported on infusion reactions.

Aggressive Histology Lymphoma: Tables of studies of rituximab maintenance

Table 4. Rituximab in aggressive histology lymphomas. General characteristics of included randomized controlled trials of patients treated with rituximab maintenance

Study name, author, date, funding source	Study objectives; design; follow-up	Patient population	Intervention, Comparison(s)	Outcomes
Collaborative Trial in Relapsed Aggressive Lymhoma (CORAL) Gisselbrecht, 2012, [88] **Funding**: F. Hoffman La Roche, Baxter, Chugai Laboratories	Examine the effect of R-maint. post transplantation. **Design**: parallel group, phase III, multicentre with 2 randomizations, the first to salvage [115], did not have a non R arm, and the second to maint [88]. **Follow-up**: 44 months	477 patients with relapsed/refractory CD20+ DLBCL Median age (years): 54	R maintenance vs observation after ASCT	*EFS Response PFS OS AE
Witzens-Harig, 2011 [abs], 2009 [15,90] **Funding**: none declared	To test R maint effectiveness. **Design**: Multicentre randomized phase II **Follow-up**: 30 months	326 patients with B-cell NHL 145 patients with DLCBL [90] Median age (years): 58.6 122 patients with CD20+B-cell NHL for QOL [15]	R maint vs obs	*PFS CR PR Response OS *QOL
LNH 98-3 Haioun, 2009 [89] Heutte, 2011 [16] **Funding**: Programme Hospitalier de Recherche Clinique; Ministry of Health; Roche and Agmen.	Evaluate the effectiveness of R consolidation, at a second randomization after ASCT [89]. Assess QOL of patients assigned to R maintenance after ASCT [16]. **Design**: Phase III RCT 2 randomization stages, the first for induction, the other for maint. The first stage is not of interest because no R treatm. **Follow-up**: 4 years	269 newly diagnosed patients with CD20+ DLBCL or other high-grade B-cell lymphomas responders to ASCT. Median age (years): 46.2	R maint vs obs	*EFS CR PR AE QOL
E4494/C9793 Habermann 2006 [4]; Morrison, 2007 [abs] [112], Morrison, 2010 [abs] [97] **Funding:** Public Health Service Grant, National Cancer Institute; National Institute of Health, Department of Health and Human Services, US	To test the effectiveness of R maint **Design**: Phase III RCT with 2 stage random assignement, the second (only responding patients) for maint **Follow-up**: 5.5 years	415 patients >60 years old with untreated DLBCL who responded to induction Median age (years): 69	R maint vs obs	FFS

*primary outcome.

[A] Rituximab maintenance significantly prolonged FFS after CHOP (p=0.003, HR, 0.56, 95% CI, 0.38 to 0.82), but not after R-CHOP (p=0.89, HR, 0.97, 95% CI, 0.64 to 1.47).

Abs = abstract; AE= adverse events; ASCT = autologous stem cell transplant; CI = confidence interval; EFS = event-free survival; FFS = failure-free survival; HR = hazard ratio; maint = maintenance; mo = months; *nr* = not reported; NS = not significant; obs = observation; OS = overall survival; PFS = progression-free survival; R = Rituximab; TTP = time to progression.

Table 4T. Rituximab maintenance versus observation trials in aggressive histology lymphomas: Treatment dose and schedule.

Study	Previous treatment	Rituximab dose	Schedule	Duration	Control
CORAL **Gisselbrecht, 2012,** [88]	R-ICE vs R-DHAP 4 cycles of induction	375 mg\m^2 i.v.	Every 8 weeks	1 years	obs
Witzens-Harig, 2011 [abs] [90]	Standard treatment	375 mg\m^2 i.v.	Every 3 months	2 years	obs
LHN-98-3 **Haioun, 2009 [89]** **Heutte, 2011 [16]**	ACVBP vs AC/ACE	375 mg\m^2 i.v.	Every week	4 weeks	obs
E4494/C9793 **Habermann 2006 [4];** **Morrison, 2007 [abs] [112]** **Morrison, 2010 [abs][97]**	CHOP vs R-CHOP	375 mg\m^2 weekly i.v.	Every 6 months	2 years	obs

AC/ACE = doxorubicin, cyclophosphamide and etoposide; ACVBP = doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone; i.v. = intravenously; obs = observation; R = rituximab; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cysplatin

Table 4Q. Rituximab in aggressive histology lymphomas: Quality of included randomized controlled trials of patients treated with rituximab maintenance.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
CORAL Gisselbrecht, 2012, [88]	R maint vs observation after ASCT	EFS	240 patients who underwent ASCT were needed to detect a 15% change in the 2-year EFS after ASCT in the maint therapy arm vs no maint (50%) to provide 80% power at the 5%, 2-sided significance level.	245	*nr*	*nr*	*nr*	Yes	No
Witzens-Harig, 2011 [abs], 2009 [15,90]	R maint vs observation	PFS QOL	*nr*	91 (evaluable)	*nr*	*nr*	*nr*	No	No
LNH 98-3 Haioun, 2009 [89] Heutte, 2011 [16]	R maint (second randomization) vs obs	EFS QOL	300 patients treated with ASCT over 4 years and followed up for ≥ 1 yr to provide 90% power at the 5% significance level (130 events). The study was stopped early because fewer events than expected and power was 60%.	269	Yes	Yes	*nr*	*nr*	Yes
E4494/C9793	R maint vs obs	FFS	The study was designed to detect a 40% reduction in the maint FFS HR (80% power at a 5%, 2-sided significance level).	415	No	*nr*	*nr*	No	Yes

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
Habermann 2006 [4]; Morrison, 2007 [abs] [112] Morrison, 2010 [abs][97]			The number of patients is not provided. The data represent 75% of the planned maint information.						

Abs = abstract; ASCT = autologous stem cell transplantation; EFS = event-free survival; FFS = failure free survival; ITT = intention-to-treat; maint = maintenance; *nr* = not reported; obs = observation; QOL = quality of life; R = rituximab; vs = versus.

Table 4E. Efficacy of rituximab in aggressive histology lympohmas. Included randomized controlled trials of patients treated with rituximab maintenance.

Study	Intervention Control	EFS or FFS median (months/years) or % surviving	PFS % surviving	CR or other measures of response (%)	OS, median (months/years)	Follow-up, median (months)
CORAL Gisselbrecht, 2012, [88]	R maint after ASCT	EFS: Median not reached *52% (95% CI, 42% - 61%)	NS	*nr*	NS	44
	Obs	EFS: *53% (95% CI, 44% - 62%) NS	NS	*nr*		
Witzens-Harig, 2009, 2011 [abs] [15,90]	R maint	*nr*	*91%	*nr*	NS	30
	Obs	*nr*	*86% NS	*nr*		
LNH 98-3 Haioun, 2009 [89] Heutte, 2011 [16]	R	EFS: Median not reached *80% (95% CI, 72%-86%)	*nr*	*nr*	NS	51
	obs	EFS: *71% (95% CI, 62%-78%)	*nr*	*nr*		
E4494/C9793 Habermann 2006 [4]; Morrison, 2007 [abs], 2010 [abs] [97,112]	R maint	*FFS $rate_{est\ 3\ years}$:53% $FFS_{66\ months}$: 46% $FFS_{9\ years}$: significant improvement	*nr*	*nr*	$OS_{36\ months}$: NS $OS_{9\ years}$: NS	42 66 108
	Obs	FFS $rate_{est\ 3\ years}$:46% (HR, 0.78; 95% CI, 0.61-0.99, p=0.04) $FFS_{66\ months}$: 36% (HR, 0.64, P=0.005) $FFS_{9\ years}$ p=0.018 (HR, 0.71, 95%CI, 0.54 to 0.94)[A]	*nr*	*nr*	$OS_{36\ months}$: NS $OS_{9\ years}$: NS	

*primary outcome.
[A] Rituximab maintenance significantly prolonged FFS after CHOP (p=0.003, HR, 0.56, 95%CI, 0.38 to 0.82), but not after R-CHOP (p=0.89, HR, 0.97, 95% CI, 0.64 to 1.47).
Abs = abstract; ASCT = autologous stem cell transplant; CI = confidence interval; EFS = event-free survival; FFS = failure-free survival; HR = Hazard ratio; maint = maintenance; *nr* = not reported; NS = not significant; obs = observation; OS = overall survival; FS = progression-free-survival; R = rituximab; TTP Time to progression.

Table 4AE. Rituximab in aggressive histology lymphomas: Grade≥3 adverse events in randomized controlled trials of patients treated with rituximab maintenance.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Deaths (%)
CORAL [88]	R maint	122	37[A]	9[B]	All causes: 6
	Obs	120	11[A]	6[B]	3
Witzens-Harig, 2009, 2011 [abs] [15,90]	R maint	73	*nr*	*nr*	*nr*
	Obs	72	*nr*	*nr*	*nr*
LNH 98-3 [89] Heutte, 2011 [16]	R	139	1	6	*nr*
	obs	130	*nr*	*nr*	*nr*
E4494/C9793 Maintenance Habermann, 2006 [4]; Morrison, 2007, 2010 [abs] [abs] [97,112]	R maint	174	17%	*nr*	*nr*
	obs	178	16%	*nr*	*nr*

[A] All grades
[B] Delayed neutropenia after day 100
Abs = abstract; *nr* = not reported; maint = maintenance; obs = observation; R = rituximab.

Patients with HIV-associated Lymphomas

All the studies identified by the searches and included in this review [91-95,116], were also included in the individual patient data (IPD) meta-analysis by Barta et al [17] that forms the basis for the recommendations. Tables of general characteristics, quality and efficacy of these studies are reported in Appendix 6.

Indolent/Mantle Cell Lymphoma (MCL): Previously Untreated Patients

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 5. More details about the treatment doses and schedules are in Table 5T.

Ten studies [18,21-24,26,27,32-34], represented by 22 publications, were included.

The sample size ranged from 123 to 554 patients. The patient population comprised FL (three studies [22,23,34]); non-Hodgkin lymphoma NHL (two studies [18,21]); mantle cell lymphoma (MCL) (two studies [26,32]); lymphoplasmacytoid lymphoma (one study [33]; and marginal zone lymphoma (MZL) (one study [24]).

Rituximab in combination with chemotherapy was compared with chemotherapy alone in seven studies [18,22,23,26,32-34]. In a three-arm design, rituximab/chemotherapy was compared with with rituximab alone, and with chemotherapy alone in two studies [21,24]. In a study presented in an abstract form, rituximab alone was compared with watchful waiting, and with rituximab treatment plus rituximab maintenance [27]. Five studies used a CHOP or CHOP-like treatment [21-23,32,33], and four studies used various chemotherapy combinations: chlorambucil [24]; mitoxantrone, chlorambucil and prednisone [18]; cyclophosphamide, vincristine and prednisone [34], and fludarabine and cyclophosphamide [26].

Three studies had response as the primary outcome [18,26,32]; two studies had EFS [22,24]; one study had TTF [34], one study had risk of treatment failure [33], one had OS [21], and one had PFS [23].

Quality of included studies:
The quality of included studies is summarized in Table 5Q.
All the studies except for Rivas-Vera et al [21] and Ardeshna et al [27] were represented by at least one full-text publication. Although most studies were open label, the overall quality of this body of evidence can be considered moderate to high.

Outcomes
The results of the studies are summarized in Table 5E, and the adverse events in Table 5AE.

Meta-analysis for studies of indolent lymphoma was not considered appropriate because the studies were heterogeneous in outcomes, populations or interventions.

Event-Free-Survival
A statistically significant benefit of rituximab was detected in the IELSG-19 [24], in the FL2000 study [22], and in the OSHO#39 study [18]; the other studies did not report this outcome (Table 5E).

Progression-Free-Survival
A statistically significant benefit of rituximab was detected in three studies [18,23,34] (Table 5E).

The IELSG-19 study at five years follow-up found a PFS of 62% (95% CI, 51% to 71%) for chlorambucil versus 71% (95% CI, 61% to 69%) for the rituximab combination (p =0.057) [24]. The GLSG study [32] found no statistically significant difference between patients treated with CHOP versus those treated with R-CHOP (52% versus 60%; p = 0.31). The study by Ardeshna et al [27] reported significant differences in PFS between the observation and the rituximab arms (p<0.001 for both arms). The other studies did not report on this outcome.

Time-to-Progression, Time-to-Treatment-Failure, and Time-to-Next-Treatment

The study by Marcus et al [34] reported a statistically significant difference in TTP in favour of rituximab (Table 5E).

The studies by Marcus et al [34], Hiddemann et al [33], and by Lenz et al [32] reported statistically significant benefits of rituximab for TTF (see Table 5E).

The OSHO study [18] reported a statistically significant benefit of rituximab for time to next treatment (TTNT).

The Ardeshna et al study [27] reported the TTNT was significantly longer in the rituximab arms compared with watchful waiting (p<0.001 for both arms).

Overall Survival
All the studies except for Eve et al [26] reported on OS. Four studies reported a statistically significant benefit of rituximab [18,23,33,34], and five studies reported a non-significant between-group difference [21,22,24,27,32] (Table 5E).

Response and Response Duration
Five studies reported a statistically significant benefit of rituximab for CR [18,22,24,32,34]. Three studies did not report a statistically significant benefit of rituximab for CR [23,26,33], and three studies did not report a statistically significant benefit of rituximab for overall response [21,23,24] (Table 5E).
One study reported a statistically significant benefit of rituximab for RD [33], (Table 5E).

Quality of Life

None of the included studies reported data on quality of life.

Adverse Events
Three studies reported a significantly greater grade 3-4 lymphopenia in patients treated with rituximab [22,26,32]. One study reported a higher rate of infections and neutropenia [21], and one study reported a higher rate of thrombocytopenia in the rituximab arm compared with chemotherapy alone [35].
Among the non-hematological adverse events, one study reported a statistically significant difference in cardiac toxicity [23] in patients treated with rituximab, while non-significant differences were shown in two studies [22,26]. Non-significant differences were reported by two studies [26,33] for neurological toxicities, and for nausea and vomiting in three studies [23,26,33].

Indolent/mantle-cell lymphomas: Tables of studies of previously untreated patients

Table 5. Rituximab in indolent/mantle cell lymphomas. General characteristics of included ontrolled trials of previously untreated patients.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
OSHO#39 Herold, 2007, 2010 [abs], 2003, [18,117,118], Hirt, 2008 [119] Funding: Hoffmann-La Roche, Germany	To test the effectiveness of adding of R to MCP treatment. To identify molecular markers of lymphoma and determine their correlation with clinical reponse **Design**: Multicentre Phase III RCT: 47 and 60 months follow-up data. **Follow-up**: 47 months	358 patients with indolent NHL. Median age (years): IG: 60 CG: 57	R-MCP vs MCP	*Remission rate: CR, PR EFS *PFS OS TTNT AE
Marcus 2008, 2005, 2010 [19,34,120] **Funding**: Hoffmann-La Roche	To test the effectivess of R added to CVP. **Design**: parallel group **Follow-up**: 53 months	321 patients with FL. Median age (years): R-CVP = 52 CVP = 53	R-CVP vs CVP	*TTF OR CR RD TTNT OS
German Low Grade Lymphoma study group GLSG Buske, 2008 [abs] [20] Hiddermann, 2005 [33] Buske, 2004 [abs], 2009 [121] [122] Funding: Deutsche Krebshilfe; Deutsches Budesministerium fur Bildung und Familie as part of the Competence Network Lymphomas.	To test the efficacy of R in addition to chemotherapy Design: parallel group, open label, Phase III, 2-stage randomization.[A] Follow up: 58 months	552 Patients with FL. Median age (years): 56 72 patients with previously untreated lymphomplastycytoid/ic immunocytoma including Waldenström macroglobulinemia and lymphoplasmacytoid lymphoma Median age (years): 61.5	R-CHOP vs CHOP	*Risk of treatment failure Response TTF RD OS OR TTF
Rivas-Vera, 2005 [abs] [21] **Funding**: Not reported	To evaluate the efficacy of R **Design:** Multicentre parallel group **Follow up:** 24 months	195 patients with indolent NHL Median age (years): 59	R vs CNOP vs R-CNOP	*OS OR DFS
GELA GOELAMS FL2000 Salles, 2008 [22] Le Gouill [123] Canioni, 2008 [124]	To evaluate the benefits of combining R with chemotherapy and interferon [22]. To establish whether intratumoral macrophage count can predict outcome in FL patients [124] **Design:** parallel group, open label, Phase III **Follow-up:** 5 years	360 patients with FL [22]. 194 patients with FL [124]. Median age (years): 61	R-CHVP+I vs CHVP+I	*EFS CR PR Stable disease

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Funding: French Government, Ligue Nationale Contre le Cancer, Roche Pharma France.				
SWOG S0016 Press, 2011 [abs], 2012 [abs], 2013 [23,35,125] **Funding:** PHS Coperative Agreement Grants, National Cancer Institute, and in part from GlaxoSmithKline	To compare safety and efficacy of two immunochemotherapy regimens patients with FL. **Design:** Phase III parallel group **Follow-up:** 4.9 years	554 patients with stage II, III or IV FL of any grade Median age (years): CHOP-R: 54.5 CHOP + Iodine-131-Tositumomab (CHOP-RIT): 53.3	R-CHOP vs CHOP-RIT	*PFS OS Serious toxicities
IELSG-19 Zucca, 2013 [24] **Funding:** Roche	To investigate the addition of R to Chl as initial treatment for MALT lymphoma. **Design:** Phase III RCT[B]	227 patients with marginal-zone, B-cell lymphoma. Median age: 59.8	R-Chl vs Chl vs R	*EFS OR PFS OS Long term AE
GLSG Hoster, 2008 [abs] [25] Lenz, 2005 [32] **Funding:** Deutsche Krebshilfe	Test the efficacy and safety of R in addition to chemotherapy. **Design**: parallel group, open label, phase III **Follow-up**: 18 months	123 patients with MCL. Median age (years): 62	R-CHOP vs CHOP	*OR *CR TTF RD OS AE
NCRN LY05 Eve, 2009 [26] **Funding**: Cancer Research UK	To conduct a phase II feasibility study in preparation of a phase III trial of fludarabine and cyclophosphamide combined with R. **Design**: open label multicentre phase II **Follow-up**: 38.3 months	156 patients with MCL Median age: 63.5 years	FC vs FCR	*Response *AE
Ardeshna, 2010 [27] **Funding**: *nr*	To compare watchful waiting with immediate treatment with R **Design**: open label, parallel group **Follow-up:** 46 months	462 patients with stage 2, 3 and 4 FL	Arm A: watchful waiting Arm B: R 375 mg/m^2 weekly for 4 wks Arm C: R 375 mg/m^2 weekly for 4 wks followed by R maint. every 2 mo for 2 years (starting at mo 3 until mo 25)	TTNT (chemotherapy or radiotherapy) QOL

*primary outcome
[A] The second randomization (patients <60 years of age and responders) was to DexaBEAM vs interferon-α
[B] This study was designed as a two arm comparison: R vs Chl, then, the protocol was amended, and a third arm R alone, was added
Abs = abstract; AE = adverse events; CG = control group; Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVP = cyclophosphamide, adriamycin, etoposide, and prednisolone; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; CR = complete response; CVP = cyclophosphamide, vincristine and

prednisone; DFS = disease-free survival; EFS = event-free survival; FC = fludarabine and cyclophosphamide; FL = follicular lymphoma; IG = intervention group; maint. = maintenance; MCL = mantle cell lymphoma; MALT = mucosa-associated lymphoid tissue; MCP = mitoxantrone, chlorambucil and prednisolone; mo = month; NHL = non Hodgkin lymphoma; *nr* = not reported; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; QOL = quality of life; R = rituximab; RCT = randomized controlled trial; RD = response duration; RIT = consolidation with tositumomab/iodine I-131 tositumomab radioimmunotherapy; TTF = time to failure; TTNT = time to next treatment; vs = versus; wk = week.

Table 5T. Rituximab indolent histology and mantle cell lymphoma: Previously untreated patients

Author, date, study name	R (375 mg/m^2) courses	Treat name	Chemotherapy protocol (mg/m^2)						Comparison
			Cycles	C	H	O	P	Schedule	
OSHO#39 Herold, 2007, 2010 [abs], 2003, [18,117,118], Hirt, 2008 [119]	8	R-MCP	8	NA	NA	NA	NA	Rituximab d 1, Mitoxantrone 8 mg/2 i.v. on d 3 and 4, chlorambucil 3×3 mg/m^2 PO d 3-7, prednisolone 25mg/m^2 PO d 3-7	MCP
Marcus 2008, 2005, 2010 [19,34,120]	8	R-CVP	Max 8 (21 ds durati on)	750	NA	1.4 to 2	40	C, and O given on d 1; P on ds 1 to 5 R i.v. on d 1 of each cycle.	CVP
GLSG Buske, 2008 [abs] [20] Hiddermann, 2005 [33]	6 to 8	R-CHOP	6 to 8	750	50	1.4 to 2	100	C i.v. day 1, H i.v. day 1, O day 1,	6 to 8 cycles
Rivas-Vera, 2005 [abs] [21]	6	R-CNOP	6	NA	NA	NA	NA	"standard doses" of cyclophosphadamide, mitoxantrone, vincristine, and prednisone	CNOP
GELA GOELAMS FL2000 Salles, 2008 [22] Le Gouill [123] Canioni, 2008 [124]	12	R-CHVP+I	12	600	1.25	*nr*	40	Courses were administered every 28 ds for 6 courses and then every 56 ds for another 6 courses combined with 18 months of interferon. C on d 1; H on d 1; Etoposide 100 mg/m^2 on d 1 Prednisolone on ds 1-5 Interferon alpha2a sc 3 times a week at 4.5 million units (MU) for patients <70 years of age and 3 MU for patients >70 years old.	CHVP+I
SWOG S0016 Press, 2011 [abs], 2012 [abs], 2013 [23,35,125]	6	R-CHOP	6	750	50	1.4	100	In the R-CHOP arm: CHOP was administered over 21 days. R was given on days 1, 6, 48, 90, 134, and 141 and CHOP was given on days 8, 29, 50, 71, 92 and 113. In the CHOP-RIT arm: RIT was given 4 to 8 weeks after the 6th cycle of CHOP. The therapeutic infusion of tositumomab/^{131}I-tositumomab was given 7-14 ds after the dosimetric infusion with 450 mg of tositumomab followed by 35 mg of 131I-tositumomab labeled with enough ^{131}I to deliver a 0.75 Gy whole-body dose	CHOP-RIT
IELSG-19 Zucca, 2013 [24]	8	R-Chl	8	NA	NA	NA	NA	Chl arm: 6 mg/m^2 Chl induction was given daily for 42 ds (wks 1 through 6. After re-staging, responders were given Chl at the same dose of 2 wks every 4 wks (=1 cycle) for up to 4 cycles.	Chl

Author, date, study name	R (375 mg/m^2) courses	Treat name	Chemotherapy protocol (mg/m^2)						Comparison
			Cycles	C	H	O	P	Schedule	
								R-Chl arm: R 375 mg/m^2 was added on ds 1,8, 15, 22, at induction. After re-staging it was administered on ds 56, 84, 112, and 140.	
Hoster, 2008 [abs] [25] Lenz, 2005 [32]	6	R-CHOP	6	750	50	1.4 to 2	100	C i.v. day 1, H i.v. day 1, O i.v. day 1, P PO ds 1-5	CHOP
NCRN LY05 Eve, 2009 [26]	8	FCR	8	250	NA	NA	NA	F (oral): 40 mg/m^2 ; C (oral) daily for 3 ds; R was given as i.v. infusion on d 1.	FC
Ardeshna, 2010 [27]	0 4 4+ maint.	watchful waiting	NA	NA	NA	NA	NA	NA	Rituximab induction, rituximab induction + maintenance

Abs = abstract; C = cyclophosphamide, Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVP+I = cyclophosphamide, adriamycin, etoposide, and prednisolone plus interfern-2alpha; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; CVP = cyclophosphamide, vincristine and prednisone; d = day ;F = fludarabine; FC = fludarabine, cyclophosphamide amd rituximab;H = doxorubicin; i.v. = intravenous; maint = maintenance; MCP = mitoxantrone, chlorambucil and prednisolone;; nr = not reported; O = vincristine ; P =prednisolone ; PO = by mouth ; R = rituximab; RIT = consolidation with tositumomab/iodine I-131 tositumomab radioimmunotherapy; sc = subcutaneously; Treat = treatment

Table 5Q. Rituximab in indolent/mantle cell lymphomas – Quality of included randomized controlled trials of previously untreated patients.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
OSHO#39 Herold, 2007, 2010 [abs], 2003, [18,117,118], Hirt, 2008 [119]	R-MCP vs MCP	OR	216 patients, assuming a PFS of 45% at 4 years, were required to provide 80% power at a 5%, 2-sided significance level	358	Yes	Yes	No	Yes	No
Marcus 2008, 2005, 2010 [19,34,120]	R-CVP vs CVP	TTF	318 patients were required to detect a 50% increase in the median TTF in patients in the intervention vs control group to have 85% power at a 2-sided 5% significance level	322	Yes	Yes	*nr*	Yes	No
GLSG Buske, 2009 [122] Hiddermann, 2005 [33]	R-CHOP vs CHOP	Risk of treatment failure	The comparison of CHOP alone with R-CHOP was designed to test whether R-CHOP could reduce the risk for treatment failure by 50% according to a proportional hazards assumption. A one-sided triangular sequential test for log rank analysis with a significance level of 1% was applied. 148 observations would be needed to detect R-CHOP superiority with a probability of 95%.	630	Yes	Yes	No	Yes	Yes
Rivas-Vera, 2005 [abs] [21]	R vs CNOP vs R-CNOP	OR	*nr*	195	*nr*	*nr*	*nr*	*nr*	No
GELA GOELAMS FL2000 Salles, 2008 [22] Le Gouill [123] Canioni, 2008 [124]	R-CHVP+I vs CHVP+I	EFS	360 patients were required to detect a change of 20% at 3 years in the R arm and provide 90% power at a 5% significance level.	358	Yes	Yes	No	Yes	No
SWOG S0016 Press, 2011 [abs] [35], 2012 [abs] [125], 2013 [23]	R-CHOP vs CHOP + Iodine-131-Tositumomab (CHOP-RIT)	PFS	Approximately 500 pt over4.5 years and 2 years of follow-up were required to detect an improvement in PFS of CHOP-RIT over CHOP-R corresponding to a HR of 1.50 to obtain a power of 86% with a one-sided 0.025 significance level.	532	Yes	*nr*	*nr*	Yes	No
IELSG-19 Zucca, 2013 [24][A]	Chl + R vs Chl vs R	EFS	To show a 20% improvement with 80% power at an overall 5% significance level under the assumption that 5-yr EFS for patients treated with Chl would be 50%. 252 patients were needed	252[A]	*nr*	*nr*	No	No	No

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
GLSG Hoster, 2008 [abs] [25] Lenz, 2005 [32]	R-CHOP vs CHOP	OR CR	Primary outcomes were monitored by truncated one-sided sequential probability ratio tests in order to allow a stop of random assignment as soon as a significant difference was detected between arms. The significance level was set at 4% for OR and at 1% for CR. Tests were adjusted to a power of 95% for the expected improvement of 95% with R-CHOP and 85% with CHOP.	123	Yes	Yes	No	No[B]	Yes
NCRN LY05 Eve, 2009 [26]	FC vs FCR	AE	*nr*	156	*nr*	*nr*	No	No	No
Ardeshna, 2010 [27]	Arm A: watchful waiting Arm B: R 375 mg/m^2 weekly for 4 wks Arm C: R 375 mg/m^2 weekly for 4 wks followed by R maint. every 2 mo for 2 years (starting at mo 3 until mo 25)	TTNT	To detect an improvement in the median time to initiation of therapy in each R arm of 18 months, with a significance level of 2.5% and 90% power, a total of 230 events and 600 patients were required. A decision to stop Arm B was taken in September 2007 because of benefit of R maintenance. A total of 360 patients were planned including arms A and C.	462	*nr*	*nr*	*nr*	*nr*	Yes

[A] First 2 arms only, the R alone arm was added subsequently and results are not presented.
[B] A secondary analysis was performed on intention-to-treat.
Abs = abstract; Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; CHVP = cyclophosphamide, adriamycin, etoposide, and prednisolone; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; CR = complete response; CVP = cyclophosphamide, vincristine, and prednisone; EFS = event-free survival; FC = fludarabine and cyclophosphamide; HR = hazard ratio; I = interferon; ITT = intention-to-treat; MCP = mitoxantrone, chlorambucil, and prednisolone; *nr* = not reported; OR = overall response; PFS = progression-free survival; R = rituximab; RIT = Iodine-131-Tositumomab; TTF = time to treatment failure; TTNT = time to next treatment; vs = versus.

Table 5E. Efficacy of rituximab in indolent/mantle cell lymphomas. Included randomized controlled trials of first-line treatment.

Study	Intervention Control	EFS Median (months) or % surviving	PFS Median (months) or % surviving	TTP, RD Median (months) or % surviving	FFS or other disease control measures. Median (months) or % surviving	CR or other measures of response (%)	OS	Follow-up
OSHO#39 Herold, 2007, 2010 [abs], 2003, [18,117,118], Hirt, 2008 [119]	R-MCP	$EFS_{47\ months}$: Median not reached $EFS_{60\ months}$:86	$PFS_{60\ months}$: 86 $RD_{47\ months}$: Not reached	*nr*	*TTNT: Not reached	50	$OS_{60\ months}$: Median not reached	47 60
	MCP	$EFS_{47\ months}$: 26, P<0.0001 $EFS_{60\ months}$: 27, P=0.0001	$PFS_{60\ months}$: 35 p<0.0001 $RD_{47\ months}$: 35 months	*nr*	*TTNT: 29.4 p=0.0002	25 p = 0.0004	$OS_{60\ months}$: 108 p = 0.0278	
Marcus 2008, 2005, 2010 [19,34,120]	R-CVP	*nr*	DFS: Median not reached	34 (95% CI, 27 – 48)	*TTF: 27	41	$OS_{48\ months\ est}$: 83%	53
	CVP	*nr*	DFS: 21, p=0.0001	15 (95% CI, 12-18), p<0.0001	*TTF: 7, p<0.0001	10, p<0.0001	$OS_{48\ months\ est}$: 77% p = 0.029	
GLSG Buske, 2008 [abs] [20] Hiddermann, 2005 [33] Buske, 2004 [abs], 2009 [121] [122]	R-CHOP	*nr*	*nr*	$RD_{5\text{-}years}$: 66%	TTF: Median not reached $TTF_{5\text{-}years}$: 65%	20	Median not reached $OS_{5\text{-}years}$: 90%	18 58
	CHOP	*nr*	*nr*	$RD_{5\text{-}years}$: 35%, p<0.0001	35 $TTF_{5\text{-}years}$: 32%, p<0.0001	17, NS	$OS_{5\text{-}years}$: 84%, p = 0.0493	
Rivas-Vera, 2005 [abs] [21]	R	*nr*	DFS: NS	*nr*	*nr*	OR: NS	NS	24
	CNOP	*nr*	NS	*nr*	*nr*	NS	NS	
	R-CNOP	*nr*	NS	*nr*	*nr*	NS	NS	
GELA GOELAMS FL2000 Salles, 2008 [22] Le Gouill [123] Canioni, 2008 [124]	R-CHVP+I	$EFS_{5\text{-}years}$: Median Not reached, 53% (95% CI 45%-60%)	$PFS_{5\ years}$: Not reached	*nr*	$TTF_{5\ years}$: 63	$CR_{6\ months}$: 63 $CR_{18\ months}$: 67	$OS_{5\ years}$: 84% NS	6 18 5 years

Study	Intervention Control	EFS Median (months) or % surviving	PFS Median (months) or % surviving	TTP, RD Median (months) or % surviving	FFS or other disease control measures. Median (months) or % surviving	CR or other measures of response (%)	OS	Follow-up
	CHVP+I	$EFS_{5\text{-years}}$: 2.9 years, 37% (95% CI 29%-44%), p=0.001	$PFS_{5\ years}$: $35_{mo\ (median)}$ p = *nr*	*nr*	$TTF_{5\ years}$: 22 p = 0.003	$CR_{6\ months}$: 34, p<0.001 $CR_{18\ months}$: 50, p=0.001	$OS_{5\ years}$: 79% NS	
SWOG S0016 Press, 2011 [abs], 2012 [abs], 2013 [23,35,125]	R-CHOP	*nr*	$PFS_{2\ years\ est}$: 76% $PFS_{4.9\ years}$: 76%	*nr*	*nr*	$CR_{4.9\ years}$: 40% OR: 85	Median not reached $OS_{2\text{-}years\ est}$: 97% $OS_{5\ years\ est}$: 92%	4.9 years
	CHOP + Iodine-131-Tositumomab	*nr*	$PFS_{2\ years\ est}$: 80%, NS $PFS_{4.9\ years}$: 80% NS	*nr*	*nr*	$CR_{4.9\ years}$: 45%, NS OR: 86, NS	$OS_{2\text{-}years\ est}$: 93% HR, 1.55 (95% CI, 0.95-2.54), p=0.08 $OS_{5years\ est}$:86%	
IELSG-19 Zucca, 2013 [24]	Chl + R	Median not reached. $EFS_{5\ years}$: 68%, (95% CI 59%-76%)	NS	*nr*	RD not reached	78, 95% CI, 69-85) OR: NS	NS	62 (2 arms)
	Chl	Median not reached $EFS_{5\ years}$: 50% (95% CI, 41%-60%) HR, 0.52 (95% CI, 0.34-0.79) p=0.002	NS	*nr*	RD not reached	65 (95% CI, 55-73) p = 0.025 OR: NS	NS	
	R	Third arm of this trial: still ongoing						
GLSG Hoster, 2008 [abs] [25] Lenz, 2005 [32]	R-CHOP	*nr*	NS	*nr*	$TTF_{18\ months}$: 21 $TTF_{1\text{-}yr\ est}$: 84% $TTF_{65\ months}$: 28 RD: 29	*$CR_{18\ months}$: 34 $CR_{65\ months}$: 33	Median not reached. $OS_{65\ months}$: 59%	18 65
	CHOP	*nr*	NS	*nr*	$TTF_{18\ months}$: 14, p=0.0131 $TTF_{1\text{-}year\ est}$: 52%, p *nr*	*$CR_{18\ months}$: 7, p =0.00024 $CR_{65\ months}$: 8, p=0.0008	46% NS	

Study	Intervention Control	EFS Median (months) or % surviving	PFS Median (months) or % surviving	TTP, RD Median (months) or % surviving	FFS or other disease control measures. Median (months) or % surviving	CR or other measures of response (%)	OS	Follow-up
					$TTF_{65\ months}$: 14, p=0.0003 RD: 18, p=0.0052			
NCRN LY05 Eve, 2009 [26]	FCR	*nr*	*nr*	*nr*	*nr*	43	*nr*	38.3
	FC	*nr*	*nr*	*nr*	*nr*	40, NS	*nr*	
Ardeshna, 2010 [abs] [27]	Watchful waiting	*nr*	*nr*	*nr*	*TTNT 33	*nr*	NS	18
	R weekly for 4 weeks	*nr*	p of log rank test <0.001 for each R arm vs watchful waiting	*nr*	*TTNT *nr* P value of log rank test<0.001 for each R arm vs watchful waiting	*nr*	NS	
	R treatment + R maintenance	*nr*	P of log rank test <0.001 for each R arm vs watchful waiting	*nr*	*TTNT *nr* p value of log rank test<0.001 for each R arm vs watchful waiting	*nr*	NS	

*primary outcome

Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CI = confidence interval; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; CR = complete response; CVP = cyclophosphamide, vincristine and prednisone; CHVP+I = cyclophosphamide, adriamycin, etoposide,and prednisolone plus interferon-2a; DFS = disease-free survival; EFS = event-free survival; FC = fludarabine and cyclophosphamide; FCR = fludarabine, cyclophosphamide and rituximab; FFS = failure-free survival; HR = hazard ratio; MCP = mitoxantrone, chlorambucil and prednisolone; *nr* = not reported; NS = not significant; OR = overall response; OS = overall survival; PFS = progression-free survival; R = rituximab; RCT = randomized controlled trial; RD = response duration; TTF = time to failure; TTNT = time to next treatment; TTP = time to progression.

Table 5AE. Rituximab in previously untreated patients with indolent/mantle cell lymphoma: Grade ≥3 adverse events in randomized controlled trials.

Study	Intervention	N	Infections (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vomiting (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
OSHO#39 Herold, 2007, 2010 [abs], 2003, [18,117,118], Hirt, 2008 [119]	R-MCP	105	7	*nr*	3	72	4	1	*nr*	*nr*	*nr*	*nr*	*nr*	14.2
	MCP	96	8	*nr*	4	58	7	6	*nr*	*nr*	*nr*	*nr*	*26*	14
Marcus 2005, 2008, 2010 [19,34,120]	R-CVP	162	NS	24	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Treatm related: 0
	CVP	159	NS	14 (no fever)	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	0
GLSG Buske, 2008 [abs] [20] Hiddermann, 2005 [33]	R-CHOP	222	NS	*nr*	NS	*nr*	NS	NS	*nr*	*nr*	NS	*nr*	*nr*	Total: 3 During treatm: 1
Buske, 2004 [abs], 2009 [121]	CHOP	205	NS	*nr*	NS	*nr*	NS	NS	*nr*	*nr*	NS	*nr*	*nr*	8 During treatm: 1
Rivas-Vera, 2005 [abs] [21]	R	62	4.8[A]	No fever: 4.8	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
	CNOP	55	5.5[A]	23.6	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
	R-CNOP	66	15.2[A] P=0.07[A]	18.2 P=0.001	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*

Study	Intervention	N	Infections (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vomiting (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
GELA GOELAMS FL2000 Salles, 2008 [22] Le Gouill [123] Canioni, 2008 [124]	R-CHVP+I	70	**Induc:** 2 **Consol:** 1	**Induc:** Fever: 1 **Consol:** Fever: 0	**Induc:** 3 **Consol:** 1	**Induc:** Neutrophil: 59 **Consol:** Neutrophil: 6	**Induc:** 2 **Consol:** 0	*nr*	*nr*	*nr*	*nr*	**Induc:** 2 **Consol:** 0	*nr*	At 18 months: 1
	CHVP+I	105	**Induc:** 0 **Consol:** 1 NS	**Induc:** Fever: 1 **Consol:** Fever: 1 NS	**Induc:** 5 **Consol:** 2 NS	**Induc:** Neutrophil: 62 **Consol:** Neutrophil: 38 P<0.001	**Induc:** 2 **Consol:** 1 NS	*nr*	*nr*	*nr*	*nr*	**Induc:** 2 **Consol:** 1 NS	*nr*	1
SWOG S0016 Press, 2011 [abs], 2012 [abs] 2013 [23,35,125]	R-CHOP	263	23	16	3	*nr*	2	NS	*nr*	*nr*	*nr*	7	NS	Treatm rel: 1
	CHOP + Iodine-131-Tositumomab	263	17, NS	10 P=0.05	3, NS	*nr*	18 P<0.0001	NS	*nr*	*nr*	*nr*	3 P=0.08	NS	Treatm rel: 4, NS
IELSG-19 Zucca, 2013 [24]	Chl + R	114	4	14	0	1.8	1.8	0	0	*nr*	*nr*	*nr*	36	0
	Chl	113	3, P *nr*	2, P *nr*	0.8, P *nr*	1.8	0.8	0.8	0	*nr*	*nr*	*nr*	17, P *nr*	0
GLSG Hoster, 2008 [abs] [25]Lenz, 2005 [32]	R-CHOP	62	5	*nr*	9	Leukocytopenia: 69 Granulocytopenia: 63	5	4	1	*nr*	1	*nr*	*nr*	Not treatm related: 16

Study	Intervention	N	Infections (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vomiting (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
	CHOP	60	6 NS	*nr*	10 NS	Leukocytopenia: 62 NS Granulocytopenia: 53 P=0.01	8 NS	6 NS	2 NS	*nr*	2 NS	*nr*	*nr*	Not treatm related: 18
NCRN LY05 Eve, 2009 [26]	FCR	78	20	NS	13	Leukocyte count: 58	36	Nausea: 3 Vomiting: 6	*nr*	*nr*	2	5	*nr*	*nr*
	FC	78	10 NS	NS	13NS	41 P=0.02	17 NS	Nausea: 6 NS Vomiting: 7 NS	*nr*	*nr*	2 NS	0 NS	*nr*	*nr*

[A] Grade 2-4

Abs = abstract; Chl = chlorambucil; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVP = cyclophosphamide, adriamycin, etoposide, and prednisolone; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; Consol = consolidation; CVP = cyclophosphamide, vincristine and prednisone; Iduc = induction; FC = fludarabine and cyclophosphamide; MCP = mitoxantrone, chlorambucil and prednisolone; *nr* = not reported; NS = not significant; R = rituximab; rel = related; Treatm = treatment.

Indolent/Mantle Cell Lymphoma: Patients With Relapsed/Refractory Disease

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 6. More detail about the treatment doses and schedules can be found in Table 6T.

Five studies [28,31,36-38], represented by nine publications were included. The additional publications studied prognostic markers [126,127], or follow-up of the original studies [30,128]. The sample size ranged from 94 to 461 patients. Three studies had a population of patients with FL or MCL [28,37,38]; the other two studies included patients with NHL [31,36]. Two studies compared rituximab combined with chemotherapy with chemotherapy alone [37,38]; one study compared rituximab alone with ^{90}Y ibritumomab tiuxetan [36]; one study compared rituximab and lenalidomide with lenalidomide alone [31], and one study compared rituximab and ^{90}Y ibritumomab tiuxetan with no treatment.

Four studies had measures of response as primary outcomes [31,36-38], and one study had PFS [28].

Quality of Included Studies:

The quality of the included studies is summarized in Table 6Q.

One of the studies was in abstract form [31], while the others were full-text publications. The overall quality of the studies was variable. One study blinded outcome assessors [36], while the others were either open label or did not report on blinding. Two of the studies were stopped early for benefit [29,38].

Outcomes

The results of the studies are summarized in Table 6E, and the adverse events in Table 6AE.

Meta-analysis for studies of indolent lymphoma was not considered appropriate because the studies were heterogeneous in outcomes, populations, or interventions.

Event-Free-Survival

The CALBG 50401 study showed a benefit for the combination rituximab and lenalidomide compared with lenalidomide alone [31]. The other studies did not report on EFS.

Progression-Free-Survival

A statistically significant benefit of rituximab and various chemotherapy regimens was detected in the FIT, the GLSG, and the EORTC20981 studies, which compared with chemotherapy alone at follow-ups ranging from 2.5 to 7.3 years [28,37,38] (see Table 6E for numerical results).

Time-to-Progression, and Time to Next Treatment

Witzig et al [36] reported a non significant between-group difference in TTP when rituximab alone was compared with ^{90}Y ibritumomab tiuxetan. The FIT study [28] and the Witzig et al study [36] had contrasting results for TTNT: while the FIT study showed a statistically significant benefit at 66 and 87.6 months [28], Witzig et al [36]showed no between-group difference at 48 months.

Overall Survival

The studies that reported on OS had contrasting results: the GLSG study [37] showed a three-year estimate significant benefit for the rituximab combination, while the FIT [28] and the EORTC20981 [38] study reported a non-significant between-group difference.

Response and Response Duration

Three studies reporded a statistically significant benefit of rituximab in CR [36-38], or in overall response [36,38].
The Witzig et al study [36] reported a non significant between-group difference in RD. The other two studies did not report significant tests on response outcomes.

Quality of Life

Witzig et al measured QOL with a generic tool, the Functional Assessment of Cancer Therapy – General (FACT-G) [129] on a subgroup of 81 patients. However, they did not compare treatment and intervention groups, but reported only within-group improvements, so their results are not reported here.

Adverse Events

The GLSG study [37] reported a statistically significantly greater grade ≥3 lymphopenia in patients treated with rituximab (see Table 6AE for numerical results). None of the other studies reported any other significant grade ≥3 adverse events.

Indolent/Mantle Cell Lymphomas: Tables of Studies on Patients withR/Refractory Disease

Table 6. Rituximab in indolent/mantle cell lymphomas: General characteristics of included randomized controlled trials of patients with relapsed disease.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
FIT Morschhauser, 2008, 2013 [28,128] First line indolent trial **Funding**: Bayer Schering Pharma AG, Berlin, Germany	To evaluate the efficacy of consolidation with yttrium-90 (^{90}Y) ibritumomab tiuxetan. **Design**: Phase III, open label RCT. **Follow-up**: 7.3 years	414 patients with advanced-stage FL in first remission. Median age (years): IG: 55 CG: 53	R + (^{90}Y) ibritumomab tiuxetan vs no treatm	*PFS CR OS
German Low Grade Lymphoma Study Group GLSG Forstpointner 2006, 2004 [29,37], Determann, 2008 [126] **Funding**: Deutsche Krebshilfe and German Ministry for Research and Technology	To test the efficacy of R added to a FCM regimen [37] To test the predictive value of Ki-67 [126]. **Design**: Open label phase III with 2 randomizations **Follow-up**: 35 months	147 patients with recurrent or refractory FL and MCL [37] Median age (years): 62.5	R-FCM vs FCM (stopped early for benefit)	*CR PR RD Survival AE
EORTC 20981 Van Oers 2006, 2010, 2010b [30,38,127] **Funding**: National Cancer Institute (US), Queen Wihelmina Fund (The Netherlands)	To evaluate the role of R in induction treatment **Design**: Phase III **Follow-up**: 33 months	465 patients with relapsed/resistant FL Median age (years): R-CHOP: 54 CHOP: 55	Induction: CHOP vs R-CHOP	*Response PFS OS AE
Witzig 2002 [36] **Funding**: None declared	Compare response of patients treated with 90Y ibritumomab tiuxetan and R. **Design**: Phase III **Follow-up**: 4 years	143 with relapsed/refractory low grade or transformed NHL Median age (years): ^{90}Y ibritumomab tiuxetan: 59 R: 57	R vs ^{90}Y ibritumomab tiuxetan	OR RD CR PR TTP TTNT

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
				QOL
CALBG 50401 Leonard, 2012 [abs] [31] **Funding**: none declared	To test R in combination with Len **Design**: RCT phase II initially designed to evaluate 3 regimens: R, R+Len and Len. R arm was discontinued because of low accrual. **Follow-up**: 1.5 years	94 patients with follicular or other B-cell lymphomas Median age (years): 63	R+Len vs Len	OR AE

*primary outcome

Abs = abstract; AE = adverse effects; CG = control group; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CR = complete response; FCM = fludarabine, cyclophosphamide and mitoxantrone; FL = follicular lymphoma; IG = intervention group; Len = lenalidomide; OS = overall survival; OR = overall response; PFS = progression-free survival; PR = partial response; QOL = quality of life; R = rituximab; RCT = randomized controlled trial; RD = response duration;Treatm = treatment; TTNT = time to next treatment; TTP = time to progression; vs = versus.

Table 6T. Rituximab in indolent histology and mantle cell lymphoma: Patients with relapsed/refractory disease

Author, date, study name	R (375 mg/m^2)	Treatment name	Chemotherapy protocol (mg/m$^{2)}$						Comparison
			Cycles	C	H	O	P	Schedule	
FIT Morschhauser, 2008 [28]	R 250 mg/m^2	R and ^{90}Y-ibritumomab tiuxetan	=	=	=	=	=	R 250 mg/m^2 on d -7 and d 0 2 courses of R 250 mg/m^2 + 1 course of 90Y-ibritumomab tiuxetan 14.8 MBq/kg	No treatment
GLSG Forstpointner 2006, 2004 Dreyling 2005, 2006 [abs][29,37,130, 131]	R 375 mg/m^2/d	R-FCM followed by R-maintenance	4	200	=	=	=	4 courses of R d 0, F 25 mg/m^2/day, C 200 mg/m^2/d on ds 1-3, and M 8 mg/m^2 d 1 Treatment cycles repeated every 4 weeks for a total of 4 cycles	FCM
EORTC 20981 Van Oers 2006, 2010, 2010b [30,38,127]	375 mg/m^2 on d 1 of each cycle of CHOP	CHOP or R-CHOP (followed by R Maint)	6	750	50	1.4 to 2	100	C IV day 1, H i.v. d 1, O i.v. d 1, P PO d 1-5, and R-CHOP also received R on d 1	CHOP
CALBG 50401 Leonard, 2012 [abs] [31]	375 mg/m^2 weekly x 4	R vs R-Len	12	=	=	=	=	Len alone (15 mg cycle 1, then escalated to 20 mg cycles 2-12, administered ds 1-21 q 28 ds x 12 cycles)	L

Abs = abstract; C = cyclophosphamide; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; d = day; F = fludarabine; FCM = fludarabine, cyclophosphamide and mitoxantrone; H = doxorubicin; i.v. = intravenous; Len = lenalidomide; Maint = maintenance; O = vincristine; P = prednisolone; PO = by mouth; q = every; R = rituximab

Table 6Q. Rituximab in indolent/mantle cell lymphomas – Quality of included randomized controlled trials of patients with relapsed/refractory disease.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
FIT Morschhauser, 2008, 2013 [28,128]	R and (^{90}Y)-ibritumomab tiuxetan vs no treatment	PFS	364 patients were required to detect a prolongation of PFS of 50% in the R arm and to obtain 80% power with a 5%, 2-sided significance test.	414	No	No	No	Yes	No
GLSG Forstpointner 2004, 2006 [29,37], Determann, 2008 [126]	R-FCM vs FCM	PFS	The comparison of FCM versus R-FCM was designed to test whether R addition could increase remission rate from 57% to 77% with a 1-sided triangular sequential test and a significance level of 5%. This test allowed to detect the superiority of R-FCM with a probability of 95%, and allowed to stop recruitment as soon as the level of significance was reached.	147	Yes	Yes	No	Yes	Yes
EORTC 20981 Van Oers 2006, 2010, 2010b [30,38,127]	Induction: CHOP vs R-CHOP	Response	600 patients were required to detect 10% difference in the overall response rate to induction chemotherapy with significance at 5% and 78% power.	461	No	*nr*	*nr*	Yes	Yes
Witzig, 2002 [36]	^{90}Y ibritumomab tiuxetan vs R	OR	150 patients were required to give 80% power to detect 25% higher OR in the ^{90}Y ibritumomab tiuxetan group compared with R group with a 5% significance level.	143	No	*nr*	Yes (outcome assessors)	Yes	No
CALBG 50401 Leonard, 2012 [abs] [31]	R+Len vs Len	*nr*	*nr*	94	No	*nr*	*nr*	nr	No[A]

[A]This trial was designed with 3 arms initially: R, R+Len, and Len. The R arm was terminated early because of low accrual after 3 enrolled patients. The data reported are for the other two arm of the study.

Abs = abstract; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; FCM = fludarabine, cyclophosphamide and mitoxantrone; Len = lenalidomide; *nr* = not reported; OR = overall response; PFS = progression-free survival; R = rituximab; vs =versus;

Table 6E. Efficacy of rituximab in indolent lymphomas: Included randomized controlled trials of patients with relapsed/refractory disease.

Study	Intervention Control	EFS median (years)	PFS/TTP Median (mo)	FFS or other disease control measure median (months)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
FIT Morschhauser, 2008, 2013 [28,128]	R + (^{90}Y) ibritumomab tiuxetan	*nr*	$PFS_{3.5\ years}$: 36.5 $PFS_{5.5\ years}$: 47% $Median_{5.5\ years}$: 49 $PFS_{7.3\ years}$: 4.1 years $PFS_{est\ 8\ years}$: 41%	$TTNT_{5.5\ years}$: median not reached $TTNT_{7.3\ years}$: 8.1 years	87.4	NS	3.5 years 5.5 years 7.3 years
	no treatment	*nr*	$PFS_{3.5\ years}$: 13.3 p<0.0001 $PFS_{5.5\ years}$: 29% p<0.0001 $Median_{5.5\ years}$: 14 $PFS_{7.3\ years}$: 1.1 years p<0.001 $PFS_{est\ 8\ years}$:22%	$TTNT_{5.5\ years}$: 35 months p<0.0001 $TTNT_{7.3\ years}$: 3 years HR 0.47, (95% CI 0,.36-0.61), p<0.001	53.3 p *nr*	NS	
GLSG Forstpointner 2006, 2004 [29,37], Determann, 2008 [126]	R-FCM	*nr*	$PFS_{2\text{-}years\ est}$: 16	*nr*	13	$OS_{3\text{-}years\ est}$: Not reached	18
	FCM	*nr*	$PFS_{2\text{-}years\ est}$: 10, p=0.0381	*nr*	33, p=0.005	$OS_{3\text{-}years\ est}$: 24 p=0.003	
EORTC 20981 Van Oers 2006, 2010, 2010b [30,38,127]	R-CHOP	*nr*	*PFS: 33.1	*nr*	29.5 OR: 85.1	$OS_{3\text{-}years}$: 82.5%	39.4
	CHOP	*nr*	*PFS: 20.2 HR 0.65; p < 0.001	*nr*	15.6, P<0.001 OR: 72.3, p<0.001	$OS_{3\text{-}years}$: 71.9% HR 0.74, NS	
Witzig 2002 [36]	R	*nr*	PFS: *nr* TTP: 10.1	RD: 12.1 TTNT: 15.4	16 *OR: 56	*nr*	4 years
	^{90}Y ibritumomab tiuxetan	*nr*	PFS: *nr* TTP: 11.2, NS	RD: 14.2, NS TTNT: Not reached, NS	30, p=0.04 *OR: 80, P=0.002	*nr*	
CALBG 50401 Leonard, 2012 [abs] [31]	R+Len	2 years	*nr*	*nr*	32	*nr*	18
	Len	1.2 years p=0.0063	*nr*	*nr*	13	*nr*	

*Primary outcome

Abs = abstract; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR = complete response; EFS =event-free survival; Est = estimate; FCM = fludarabine, cyclophosphamide and mitoxantronel; FFS = failure-free survival; nr = not reported; Len = lenalidomide; mo – months;NS = not significant; OR = overall response; OS = oeverall survival; PFS = progression-free survival; R = rituximab; RD = response duration; TTNT = time to next treatment; TTP = Time-to progression.

Table 6AE. Rituximab in indolent lymphomas: Grade ≥3 adverse events in randomized controlled trials of patients with relapsed/refractory disease.

Study	Intervention	N	Infections* (%)	(Febrile) neutro-penia (%)	Anemia (%)	Lympho-penia (%)	Thrombo - cytopenia (%)	Nausea; vomiting (%)	Mucositis (%)	Liver tox (%)	Neuro -tox (%)	Cardiac tox (%)	2nd tumors (%)	Deaths (%)
FIT Morschhausen, 2008, 2013 [28,128]	R + (^{90}Y) ibritumomab tiuxetan	208	7.9	Neutropenia: 66.7 Fever: 3	3.4	60.3	60.8	*nr*	*nr*	*nr*	*nr*	*nr*	12.5	2.88
	No treatm	206	2.4	Neutropenia: 2.5 Fever: 0	0	10.8	0	*nr*	*nr*	*nr*	*nr*	*nr*	7 NS	2.4
GLSG Forstpointner 2006, 2004 [29,37],	R-FCM	66	1.4% of courses, NS	Fever: 1.1	5.9	51.2	11.7	1.1, NS	0.3	0	0.2	0	*nr*	*nr*
	FCM	62	1.8% of courses, NS	Fever: 0.5, NS	5.3 NS	39.4 P=0.006	11.3, NS	0, NS	0, NS	0, NS	0.1, NS	0.9, NS	*nr*	*nr*
EORTC 20981 Van Oers 2006, 2010b [38,127]	R-CHOP	234	*nr*	No fever: 54.7	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Treatm rel: 0.4
	CHOP	231	*nr*	48.2, NS	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	0.9
Witzig 2002 [36]	R	70	*nr*	*nr*	*nr*	*nr*	*nr*	0	NS	NS	NS	NS	NS	Not treatm rel: 14
	^{90}Y ibritumomab tiuxetan	73	*nr*	*nr*	*nr*	*nr*	*nr*	0	NS	NS	NS	NS	NS	16
CALBG 50401 Leonard, 2012 [abs] [31]	R+Len	44	*nr*	No fever: 19	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
	Len	45	*nr*	16	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*

Abs = abstract; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; FCM = fludarabine, cyclophosphamide, and mitoxantrone; Len = lenalidomide; nr = not reported; NS = not significant; R = rituximab; rel = related; Treatm = treatment; TTNT = time to next treatment.

Indolent/Mantle Cell Lymphoma: Rituximab Maintenance Treatment

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 7.

Nine studies [29,38,39,132-137], represented by 22 publications were included. The additional publications focussed on long-term follow-up [30,138,139], prognostic markers [126,127,140-143], subgroup analyses [144,145], toxicity data [146], and efficacy of rituximab induction [37]. The sample size ranged from 88 to 1019 patients. Six studies had a population of patients with FL [29,38,39,132-134], two studies included patients with MCL [29,137], and two studies included patients with NHL or indolent lymphoma [135,136]. The Hainsworth et al study [136] study compared rituximab maintenance with rituximab re-treatment; all the other studies compared rituximab maintenance with observation. Five studies had PFS as the primary outcome [38,39,132,133,135], two studies had EFS [134,137], one study had risk of relapse [29], and one study duration of benefit [136]. Other outcomes reported were TTNT, OS, response, adverse events, and QOL.

Two of the trials had two randomizations, the second of which tested for rituximab maintenance [38,132]. Therefore, depending on the trials' first phase, some patients in the rituximab maintenance group had already been exposed to rituximab (all the patients from the PRIMA study [39], the FILML17638 study [133], the Forstpointner et al study [29].

Quality of Included Studies:

The quality of the included studies is summarized in Table 7Q.

All the studies were represented by at least one full-text publication. The overall quality of this body of evidence appears to be moderate to high. All the studies reported a power calculation, including the two studies that randomized patients for a second time to study maintenance treatment [38,132]. Six studies concealed patient allocation to groups [29,39,132,134,136,137], and seven conducted an intention-to-treat analysis [29,38,39,132-134,137]. Five studies were stopped early [29,38,39,132,136], and one did not reach the predetermined sample size [132].

Outcomes

The results of the studies are summarized in Table 7E, the adverse events in Table 7AE. Although the studies had somewhat different treatment duration (see Table 7T), populations of resistant follicular or MCLs, rituximab dose and comparisons were homogeneous. Therefore, we decided to conduct a meta-analysis of the studies that had similar comparisons [29,38,39,133-135,137].

Event-Free-Survival and Failure-Free-Survival.

Three studies reported on EFS: two of them showed a statistically significant benefit of rituximab maintenance treatment [39,134], and one showed a statistically non-significant between-group difference [137]. One study reported a statistically significant benefit of rituximab maintenance treatment for FFS [29]. (See Table 7E for numerical results).

As indicated in Figure 4, the pooled HR for EFS for the three RCTs was 0.61 (95% CI 0.51 to 0.72). The I^2 value of 0% indicates that statistical heterogeneity among these studies is negligeable.

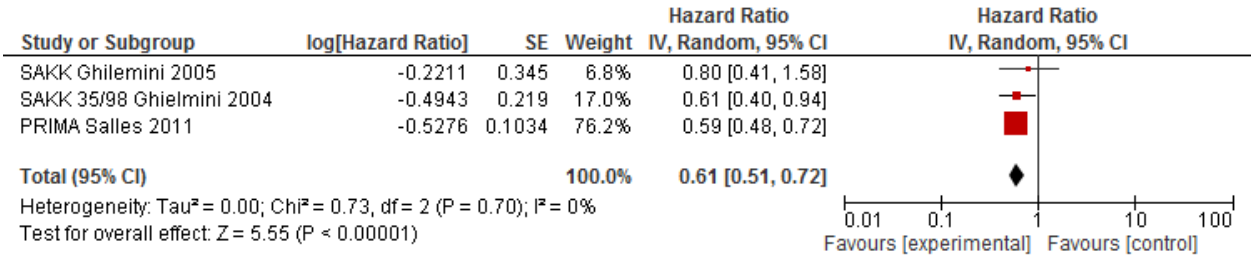

Figure 4. Rituximab maintenance versus observation in indolent lymphoma: Event-free survival.

Progression-Free-Survival

Six studies reported on PFS [38,39,132,133,135,136]. Five studies showed a statistically significant benefit of rituximab maintenance [38,39,132,135,136], and one study showed no difference [133].

The meta-analysis showed a pooled HR for the six RCTs of 0.53 (95% CI, 0.47 to 0.59) (Figure 5). The statistical heterogeneity, represented by I^2, of 38% can be considered moderate.

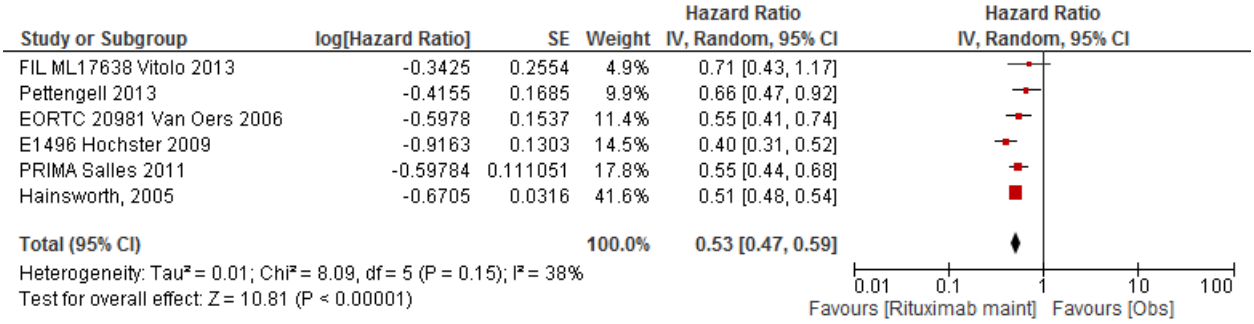

Figure 5. Rituximab maintenance versus observation in indolent lymphoma: Progression-free survival

Overall survival

Seven studies reported on OS [29,38,39,132,134-136].

Four studies included patients naïve to rituximab [30,132,135,136], two studies included patients previously exposed to rituximab [29,39], and one study [138] did not specify if patients were previously exposed to rituximab or not.

Two studies reported a statistically significant benefit in the rituximab group compared with observation at 33 and 26 months [29,38]; however, this advantage waned at five-year follow-up in the EORTC 20981 study [30]. Five studies reported a non-significant between-group difference [39,132,134-136] (see Table 7E for numerical results). In four studies the maintenance treatment lasted 24 months [30,39,135,136], in two studies it lasted eight months [132,134], and in one study it lasted 11 months [29].

The results of the studies were not pooled in a meta-analysis because of clinical heterogeneity.

Quality of Life

The PRIMA study measured QOL [39] with the functional assessment of cancer therapy (general [FACT-G] score and the EORTC QLQ-C30) and failed to detect any statistically significant difference with either tool between the rituximab maintenance and the observation group (mean adjusted FACT-G scores 86.6 [95% CI, 85 to 88.3] versus 87.2 [95% CI, 85.3 to 89.1]; p=0.68, and EORTC QLQ-C30 global health status mean scores 75.5 [95% CI, 72.8 to 78.2] versus 75.2 [95% CI, 72.0 to 78.4], respectively [p=0.89]).

Adverse Events

The EORTC 20981 study [38] reported a statistically significant higher grade ≥3 infections and febrile neutropenia in the rituximab maintenance group than in the observation group; a statistically significant difference in grade 2 to 4 infections has been reported by the PRIMA study [39] (see foot note of Table 7AE for numerical results). The other studies did not report any statistically significant between-group difference. Infusion-related reactions are described by the most part as mild to moderate, or they are not reported.

Patients with indolent/mantle cell lymphoma: Tables of rituximab maintenance treatment

Table 7. Rituximab in indolent lymphomas: General characteristics of included randomized controlled trials of studies of maintenance treatment.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Primary Rituximab and Maintenance (PRIMA) Salles, 2011, [39], Ghesquières, 2012 [140], Trotman, 2010 [145], Zhou 2011 [146], Silva, 2013 [144] **Funding**: Groupe d'Étude des Lymphomes de l'Adulte (GELA) F. Hoffman La Roche Biogen IDEC	To assess the benefit of 2-years R maintenance after first-line treatment with R chemotherapy [39]. To assess the effectiveness of R maintenance in a subgroup of patients with FCGR3A AND FCGR2A polymorphisms [140]. To assess PET imaging as a prognostic factor [145]. To report on symptom burden [146]. **Design:** RCT open label **Follow up:** 36 months	1018 patients with previously untreated FL responding to induction receiving R and chemotherapy treatment (R-CHOP vs R-FCM) Median age (years): IG 57 CG: 55	R Maint vs obs	PFS EFS TTNT OS Response AE QOL
SAKK Ghielmini 2005 [137] **Funding:** Roche Pharma Schweitz AG, Swiss Group for clinical Cancer Research	To evaluate the effect of single agent R at the standard treatment and at maintenance **Design:** parallel group **Follow up:** 29 months	88 patients with newly diagnosed, refractory or relapsed MCL Median age (years): IG: 60 CG: 61	Prolonged R Maint for 8 weeks vs no treatment.	EFS
SAKK 35/98 Ghielmini, 2009, 2004, [abs] [134,138] Martinelli 2010 [139], Lee, 2012 [abs] [142] Ghielmini, 2005 [143] **Funding**: *nr* State Secretariat for Education and Research of Switzerland; Roche Pharma Sweitz	To investigate the proportion of long-term responders to a R regimen and the characteristics predicting long-term response [134,138,139]. To determine the relationship of FcγRIIB expression to clinical outcomes [142]. **Design:** parallel group **Follow-up:** 35 months	Chemotherapy naïve (n=64) or pre-treated (n=138) FL patients. Follow-up at 8.9 years [138] and at 9.5 years [139] Median age (years): IG: 56 CG: 57	4 cycles of maint every 2 months vs obs.	EFS

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
FIL ML17638 Vitolo, 2013 [133], Ladetto, 2012 [abs] [141] **Funding**: Roche Italy	To investigate the efficacy and toxicity of R-maintenance in elderly patients [133]. To test the predictive value of PCR [141]. **Design:** open label phase III **Follow-up:** 42 months	202 elderly patients with FL who respond to a brief chemo-immunotherapy with 4 courses of R-FND + 4 doses of R as consolidation Median age (years): 66	R maintenance with R single dose every 2 months, vs obs	*PFS OS AE
Forstpointner 2006, 2004 [29,37], Determann, 2008 [126] German Low Grade Lymphoma Study Group **Funding**: Deutsche Krebshilfe and German Ministry for Research and Technology	To test the efficacy of R maintenance following induction with an R-based regimen in relapsed indolent lymphoma [29] **Design:** Open label phase III; second randomization **Follow-up:** 26 months	176 patients with recurring FL or MCL who had been previously treated with a R-base regimen participated in the maintenance study. Median age (years): 62	R maintenance: (2 courses of 4 times weekly R after 3 and 9 months) vs obs	Risk of relapse
EORTC 20981 Van Oers 2006, 2010 [30,38] Van Oers, 2010b [127] **Funding:** National Cancer Institute (US), Queen Wihelmina Fund (The Netherlands)	To evaluate the role or R maintenance treatment at 6 years follow-up in relapsed follicular lymphoma in relapsed follicular lymphoma. To study whether preinduction BCL2/IgH levels correlate with level of response and PFS, whether post-induction BCL1/IgH correlate with PFS and whether levels of BCL2/IgH are predictors of R benefit [127] **Design:** Phase III **Follow-up:** 6 years	319 patients with relapsed/resistant follicular lymphoma in complete or patial remission after induction treatment Median age (years): R-CHOP: 55 CHOP: 54	Maint: R every 3 months for a maximum or 2 years vs obs	*PFS OS
Hainsworth, 2005 [136] **Funding:** Genentech Inc and the Minnie Pearl Foundation.	To compare R maintenance with R retreatment. **Design:** Phase II **Follow up:** 41 months	114 previously treated patients with relapsing indolent NHL Median age (years): Maint: 57 Re-treatment: 67	4-week R maintenance courses at 6-months interval vs R re-treatment	*Duration of R benefit PFS OS OR
E1496 Hochster, 2009 [135] **Funding:** Public Health Sevice Grants, National Cancer Institute, National	To determine if R maintenance was effective in improving PFS. **Design:** Phase III **Follow up:** 4 years	311 patients with advanced indolent lymphoma. Median age (years): 58	R maintenance vs obs	*PFS Response OS

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Institutes of Health and Department of Health and Human Services.				
Pettengell, 2013 [132] **Funding:** Some of the authors declared having received support from pharmaceutical companies	To assess the efficacy and safety of R as in vivo purging before transplantation and as maintenance treatment after high dose chemotherapy and autologous stem-cell transplantation **Design:** Open label 2×2 factorial design RCT phase III	280 R-naïve patients with relapsed FL, study stopped after 280 patients Median age (years): 51	R *in* vivo Purging vs No Purging and Maint R vs obs	*PFS OS

*primary outcome

Abs = abstract; AE = adverse effects; BCL2/IgH = BCL2/immunoglobulin heavy chain; CG = control group; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; EFS = event-free survival; FCM = fludarabine, cyclophosphamide and mitoxantrone; FL = follicular lymphoma; FND = fludarabine, mitoxantrone, dexamethasone; IG = intervention group; Maint = maintenance; MCL = mantle cell lymphoma; obs = observation; NHL = non-Hodgkin lymphoma; obs = observation; OS = overall survival; PFS = progression-free survival; QOL = quality of life; R = rituximab; RCT = randomized controlled trial; TTNT = time to next treatment; vs = versus.

Table 7T. Rituximab maintenance in indolent/mantle cell lymphomas: Treatment dose and schedule.

Study	Previous treatment	R maintenance dose	Schedule	Duration	Comparison
PRIMA Salles, 2011, [39]	R-CHOP; R-CVP; R-FCM	375 mg/m^2	every 8 weeks	24 months	obs
SAKK Ghielmini 2005 [137]	Rituximab 375 mg/m^2 for 4 wks	375 mg/m^2	every 8 weeks	8 months	obs
SAKK 35/98 [134]	Rituximab 375 mg/m^2 for 4 wks	375 mg/m^2	every 8/10 weeks	8 months	obs
FIL ML17638 Vitolo, 2013 [133]	4 monthly R-FND	375 mg/m^2	every 8/10 weeks	8 months	obs
Forstpointner 2006 [29]	R-FCM 4 cycles every 4 weeks	375 mg/m^2	One course of 4 weekly doses of R 3 months after completion of salvage therapy and one course 9 months after.	11 months	obs
EORTC 20981 Van Oers 2006 [38]	CHOP vs R-CHOP	2nd randomization: 375 mg/m^2	Every 12 weeks	24 months or until relapse	obs
Hainsworth, 2005 [136]	4-week course of rituximab 375 mg/m^2	375 mg/m^2 for 4 weeks	Every 6 months	24 months or until relapse (i.e., 4 rituximab courses)	R re-treatment
E1496 Hochster, 2009 [135]	6 -8 cycles of CVP	375 mg/m^2 once weekly for 4 weeks	Every 6 months starting 4 weeks after the last CVP cycle	4 courses during 24 months	obs
Pettengell, 2013 [132]	4-week course of rituximab 375 mg/m^2	2nd randomization: 375 mg/m^2	every 8/10 weeks	4 treatments during 8 months	obs

Obs = observation; R = rituximab; R-CHOP = six cycles repeated every 3 wks of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2 on day 1, vincristine 1.4 mg/m^2 [capped at 2 mg] on day 1, doxorubicin 50 mg/m^2 on day 1, and prednisone 100 mg on days 1–5; R-CVP = cyclophosphamide 750 mg/m^2 on day 1, vincristine 1 • 4 mg/m^2 [capped at 2 mg] on day 1, and prednisone 40 mg/m^2 on days 1–5, with each cycle repeated every 3 weeks for 8 cycles; R-FCM = rituximab 375 mg/m^2/day on day 0, fludarabine 25 mg/m^2/day on days 1 - 3, cyclophosphamide 200 mg/m^2/day on days 1 - 3, and mitoxantrone 8 mg/m^2/day on day 1; R-FND = 375 mg/m^2 rituximab on day 1, 25 mg/m^2 fludarabine on days 2 - 4, 10 mg/m^2 mitoxantrone on day 2, and 10 mg of dexamethasone on days 2 - 4.

Table 7Q. Rituximab in indolent lymphomas – Quality of included randomized controlled trials of studies of maintenance treatment.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
PRIMA Salles, 2011, [39] Ghesquières, 2012 [140], Trotman, 2010 [145], Zhou 2011 [146]	R maintenance vs observation	PFS	900 patients were required to detect a prolongation of PFS of 45% in the R arm and to obtain 80% power with a 5%, 2-sided significance test.	1018	Yes	Yes	No	Yes	Yes
SAKK Ghielmini 2005 [137]	R maint vs no treatment	EFS	54 events in 65 patients were required to provide 80% power with a 5%, 2-sided significance to detect an increase of EFS from 6 months in the control arm to 13 months in the intervention arm.	104	Yes	Yes	No	Yes	No
SAKK 35/98 Ghielmini, 2009, [134,138] Martinelli 2010 [139]	Induction with R alone once weekly for 4 wks vs induction followed by 4 cycles of maint every 2 months.	EFS	99 events in 135 patients were required to provide 80% power with a 5%, 2-sided significance to detect an increase of EFS from 9 months in the control arm to 16.2 months in the intervention arm.	151	Yes	Yes	No	Yes	No
FIL ML17638 Vitolo, 2011 [abs] [147] Vitolo, 2009 [148] Vitolo, 2013 [133], Ladetto, 2012 [abs] [141]	R maint vs obs	PFS	186 patients were required to show an improvement in favour of R maintenance with 80% power and a 2-sided significance level of 5%.	202	No	No	No	Yes	No
Forstpointner 2006, 2004 [29,37], Determann, 2008 [126]	R maint: (2 courses of 4-times weekly R after 3 and 9 months) vs obs	Risk of relapse	A 1-sided triangular sequential test with a significance level of 5% was applied to detect the ability of R maintenance to reduce the relative risk of relapse by 50% with a probability of 95%.	195	Yes	Yes	No	Yes[A]	Yes
EORTC 20981 Van Oers 2006, 2010, 2010b [30,38,127]	R maint	PFS	201 progressions or deaths were required to detect a 14% difference in the 2-yr PFS with 80% power and significance at 5%, 2-sided test.	334	No	*nr*	*nr*	Yes	Yes
Hainsworth, 2005 [136]	R maint: 4-week courses at 6-months	Duration of R benefit	50 patients to each group were required to demonstrate a prolongation of the duration of R benefit by 50% (18 to 27 months)	114	Yes	Yes	No	No	Yes

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
	interval vs R re-treatment								
E1496 Hochster, 2009 [135]	R maint vs obs	PFS	300 patients were required over 3.33 years to provide 84% power to detect a 50% improvement in PFS from 2.5 years in the observation arm to 3.75 years for the R arm	311	No	No	No	No[B]	No
Pettengell, 2013 [132]	R *in* vivo Purging vs obs vs maint R vs obs	PFS	480 patients were required to detect 15% difference in PFS at 4 years with 80% power with a significance level of 5%, 2-sided test.	280	Yes	Yes	No	Yes	Yes

[A]For histologic subgroup and overall survival.
[B]ITT analysis was performed but results are not shown

Abs = abstract; EFS = event-free survival; maint = maintenance; nr = not reported; obs = observation; PFS = progression-free survival; R = rituximab; ITT = intention-to-treat; vs = versus; wks = weeks.

Table 7E. Efficacy of rituximab in indolent lymphomas: Included randomized controlled trials of maintenance treatment.

Study	Intervention Control	Measures disease control median (months)	PFS Median (months/years)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
PRIMA Salles, 2011, [39] Ghesquières, 2012 [140]; Trotman, 2010 [145], Zhou 2011 [146]	R maint	EFS: *nr* TTP: Not reached	74.9%	CR: 71.5	NS	36
	obs	EFS: HR 0.59, 95% CI, 0.48-0.72, P *nr* TTP: 48.3 95% CI, 38-not reached	57.6% HR 0.55 (95% CI, 0.44-0.68) p<0.0001	CR: 52.5, p=0.0001	NS	
SAKK Ghielmini 2005 [137]	Maint: Prolongued R (8 wks)	EFS: 12 (95% CI, 8-17)	*nr*	RR: NS	*nr*	29
	No treatment	EFS: 6 (95% CI, 4-14) p = 0.1	*nr*	NS	*nr*	
SAKK 35/98 Ghielmini, 2009, 2004, [abs] [134,138]	Induction: R alone (4 wks) plus no further treatment	EFS: $11.8_{35\ months}$ $13_{9.5\ years}$	*nr*	Response rate: $44_{12\ months}$ CR: NS	NS	35 9.5 years

Study	Intervention Control	Measures disease control median (months)	PFS Median (months/years)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
Martinelli 2010 [139] Lee, 2012 [abs] [142]	Induction + 4 cycles of maint every 2 months	EFS: 23.2 HR 0.61,(95% CI, 0.40-0.93) p = 0.024 $EFS_{9.5\ years}$: 24 p<0.001	*nr*	Response rate: $60_{12\ mo}$ p = 0.046 CR: NS	NS (values not provided)	
FIL ML17638 Vitolo, 2009 [148] Vitolo, 2013 [133] Ladetto, 2012 [abs] [141]	R maint every 2 months	*nr*	$PFS_{2\text{-}years}$: 81% (30 events)	$CR_{18\ mo}$: 87	NS	34
	obs	*nr*	$PFS_{2\text{-}years}$: 69% (35 events) HR 0.71 (95% CI, 0.43-1.17) NS	CR_{18}: 71, p=0.006	NS	
Forstpointner 2006, 2004 [29,37], Determann, 2008 [126]	R maint	RD: Median not reached	*nr*	*nr*	Median Not reached Est $OS_{3\text{-}years}$: 77%	26
	Obs	RD: 17 p<0.001	*nr*	*nr*	Median Not reached Est $OS_{3\text{-}years}$: 57% P = 0.003	
EORTC 20981 Van Oers 2006, 2010 [30,38] Van Oers, 2010b [127]	R maint	*nr*	*$PFS_{33.3\ months}$: 51.5 $PFS_{6\text{-}years}$: 3.7 years	*nr*	$OS_{3\text{-}years}$: 85.1% $OS_{5\text{-}years}$: 74.3%	33.3 6 years
	obs	*nr*	*$PFS_{33.3\ mo}$: 14.9 HR 0.40, p < 0.001 $PFS_{6\text{-}years}$: 1.3 years, HR: 0.55 p<0.0001	*nr*	$OS_{3\text{-}years}$: 77.1% HR, 0.52, P=0.011 $OS_{5\text{-}years}$: 64.7% HR 0.70 (95% CI 0.48-1.03) P=0.07	
Hainsworth, 2005 [136]	R maint	*nr*	31.3	CR: 23	$OS_{3\ years}$: 72%	41
	R re-treatment	*nr*	7.4, P=0.007	CR: 2 p=0.03	$OS_{5\text{-}years}$: 68%, NS	
E1496 Hochster, 2009 [135]	R maint	*nr*	4.3 years	CR: 37	Median not reached; $OS_{3\text{-}years}$: 92%	3.7 years
	Obs	*nr*	1.3 years HR 0.4, 95% CI, 0.3-0.5, $p=4.4x10^{-10}$	CR: 22, P *nr*	$OS_{3\text{-}years}$: 86% HR = 0.6 (95% CI, 0.3-1.2), p=0.05	

Study	Intervention Control	Measures disease control median (months)	PFS Median (months/years)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
Pettengell, 2013 [132]	R *in* vivo Purging vs No Purging	*nr*	*NS	*nr*	NS	8.3 years
		nr	*NS	*nr*	NS	
	Maint R vs No maint	*nr*	*$PFS_{10\ years}$: 54% (95% CI, 45%-62.2%)	*nr*	NS	
		nr	*$PFS_{10\ years}$: 37% (95% CI, 28.6%-45.3%), HR 0.66; (95% CI 0.47-0.91), p=0.01	*nr*	NS	

Abs = abstract; CI = confidence interval; CR = complete response; EFS = event-free survival; FFS = failure-free survival; HR = hazard ratio; maint = maintenance; mo = moths;*nr* = not reported; NS = not significant; obs = observation; OS = overall survival; PFS = progression-free survival; R = rituximab; RR = response rate; TTP = time to progression; wks = weeks.

Table 7AE. Rituximab maintenance in indolent lymphomas: Grade ≥3 adverse events in randomized controlled trials.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Infusion reactions	Deaths (%)
PRIMA Salles, 2011, [39] [39] Ghesquières, 2012 [140], Trotman, 2010 [145], Zhou 2011 [146]	R maint	501	4[A]	Fever: <1 Neutropenia: 4	*nr*	Treatm related: 0.1 NS
	Obs	508	1[A]	Fever: <1 Neutropenia:1	*nr*	0 NS
SAKK Ghielmini 2005 [137]	Prolonged R maint (8 wks)	34	*nr*	*nr*[B]	*nr*[B]	3
	Obs	27	*nr*	*nr*[B]	*nr*[B]	0
SAKK 35/98 Gielmini, 2009 [abs], 2004 [134,138], Martinelli, 2010 [139]	Induction: R once weekly for 4 wks + 4 cycles of maint every 2 months	B: 73	*nr*	*nr*[C]	0	During treatment: 0.7
	induction + no further treatm	A: 78	*nr*	*nr*[C]	0	
Vitolo, 2009 [abs] [148] Vitolo, 2013 [133]	R maint every 2 months	101	1	*nr*	*nr*	During treatm: 0.8
	Obs	101	3	*nr*	*nr*	
GLSG	R maint	80	4	Fever: 4	8%[D]	nr

Forstpointner [29,37]	Obs	82	3 NS	Fever: 0 NS	0	nr
EORTC 20981 Van Oers 2006, 2010 [30,38] Van Oers, 2010b [127]	R maint	167	9.7	Fever: 0 11.5	*nr*	Treatm related: 0
	Obs	167	2.4 P=0.01	6 P=0.01	*nr*	0
Hainsworth, 2005 [136]	R maint	34	*nr*	Fever: 0 Neutropenia:3	5%	*nr*
	R re-treatm	28	*nr*	0	0 P *nr*	*nr*
ECOG1496 Hochster, 2009 [135]	R maint	158	1	Fever: 0 Neutropenia:3	*nr*	*nr*
	Obs	153	1	Fever: 0 Neutropenia:1	*nr*	*nr*
Pettengell, 2013 [132]	Maint R vs No maint	138	NS	NS	*nr*	0
		142	NS	NS	*nr*	0

[A] The most common adverse events were grade 2-4 infections 39% in the rituximab and 24% in the control group (risk ratio 1.62,95% CI, 1.35 to 1.96, P<0.0001). Four per cent of patients in the rituximab group versus 2% in the observation group experienced adverse events that led to treatment discontinuation. P values for grade 3/4 infections and for events that led to treatment discontinuation are not provided.
[B] Hematologic toxicities: 9% for R maint vs 13% for obs group; mild infusion-related toxicities are reported in the induction phase (i.e., first infusion), no p values are given.
[C] Hematologic toxicities: 18 % in the R maint vs 17% in the no treatment group; Non hematologic toxicities: 10% in the R maint vs 3% in the no treatment group.
[D] Infusion reaction are described as mild to moderate.
Abs = abstract; maint = maintenance; *nr* = not reported; NS = not significant; obs = observation; R = rituximab; treatm = treatment; vs = versus; wks = weeks.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Previously Untreated Patients

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 8, the treatment doses and schedules are summarized in Table 8T.

Four RCTs [40-43], represented by 12 publications, were included.

The sample size of the studies ranged from 104 to 817 patients with CLL.

The included studies compared rituximab given concurrently or sequentially with fludarabine [40], rituximab-fludarabine-cyclophosphamide combination with other monoclonal antibodies [41], rituximab-fludarabine-cyclophosphamide with chemotherapy alone [42], and rituximab-chlorambucile with chlorambucile alone and with chlorambucile combined with obinutuzumab (GA101).

Three studies [41-43] had PFS, and one study [40] had complete remission as primary outcome. Other outcomes reported included OS and measures of response, as well as toxicities (AE).

Quality of Included Studies:

The quality of the included studies is summarized in Table 8Q.

Three included studies were reported as full-text publications [40-42], and one as a conference abstract [43]. The CALGB Study 9712 [40] had not been designed for between-arm comparison. The overall quality of the studies was high, although all of the studies were open label.

Outcomes

The results of the studies are summarized in Table 8E, and the adverse events in Table 8AE.

Overall this body of evidence indicates a benefit with the use of rituximab in addition to fludarabine-based chemotherapy and cyclophosphamide, when compared with chemotherapy alone, (see Table 8E for numerical results). Grade 3 or 4 neutropenia and leukocytopenia have been reported [42], however these were significantly less than with other monoclonal antibodies [41] (see Table 8AE for numerical results).

Chronic Lymphocytic Leukemia: Tables of Studies of Previously Untreated Patients

Table 8. Rituximab in chronic lymphocytic leukemia: General characteristics of included randomized controlled trials of previously untreated patients.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
CALGB 9712 Woyach, 2011 [40], Byrd, 2003, 2005, 2006 [149-151] **Funding**: National Cancer Institute	To determine the efficacy, safety and optimal administration schedule of R with F. **Design**: RCT phase II [149] non comparative. Long term follow-up [40] **Follow-up**: 117 months	104 symptomatic, previously untreated, patients with B-cell CLL. Median age (years): 63	Concurrent vs sequential F with R	OR *CR PR AE PFS OS Impact of genomic features Myeloid neoplasms (ther rel)
CLL2007FMP NCT00564512 Lepretre 2012, 2009 [abs] [41], Letestu, 2011 [abs] [152,153] Funding: none declared	To test the efficacy and safety of Cam in combination with FC **Design**: Multicentre RCT phase III – stopped early after 165 patients were randomized because of excess mortality in the Cam arm. **Follow-up**: Median follow-up time: 38 months	178 previously untreated patients with B-CLL Median age (years): 57	FCR vs FCCam	AE OR CR PR *PFS OS
ML17102 CLL8 NCT00281918 Hallek, 2010 [42], Fink, 2011 [154], Bottcher, 2012 [155], Fischer, 2012 [156] Funding: Hoffman La Roche	To test the efficacy of a R-regimen for first line treatment of patients with advanced, symptomatic disease. To characterize patients with poor prognosis [154]. To determine the clinical significance of flow cytometric MRD quantification and to examine its prognostic value [155]. **Design:** RCT Phase III **Follow-up:** 8 years	817 previously untreated patients with CLL. Median age (years): 61	FCR vs FC	*PFS EFS OS DFS DOR TTNT Death CR PR OS AE
CLL 11 Goede, 2013 [abs] [43]	To evaluate three treatments in previously untreated CLL patients with comorbidities.	R + Chl (RChl)GA101: Stage 1b: N = 233 Chl (GChl): Stage 1a N = 238 Chl alone: Stage 1a: N = 118; Stage 1b N = 118 Median age (years): Stage 1a: 73 Stage 1b: 72	R + Chl (RChl)GA101 + Chl (GChl), Chl alone	OR CR *PFS AE

*primary outcome
Abs = abstract; AE = adverse effects; C = cyclophosphamide; Cam = alemtuzumab; Chl = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; DFS = disease free survival; DOR = duration of response; EFS = event-free survival; F = fludarabine; MRD = minimal residual disease; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; OS = overall survival; R = rituximab; RCT = randomized controlled trial; rel = relatedTher = therapy; TTNT = time to next treatment.

Table 8T. Rituximab in chronic lymphocytic leukemia: Dose and schedule for previously untreated patients.

Study	Intervention schedule	Control schedule	Dose	Duration
CALGB 9712 Woyach, 2011 [40], Byrd, 2003, 2005, 2006 [149-151]	FR sequentially: F 28 ds for 6 cycles + restaging, + 2 mo obs, then 4 weekly doses of R	FR concurrently: F every 28 ds for a total of 6 cycles + R on ds 1 and 4 of cycle 1 of F therapy + 2 mo obs + restaging then 4 weekly doses of R	F: 25 mg/m^2 i.v.daily on ds 1 to 5 R:375 mg/m^2 with dose escalation	9 mo
CLL2007FMP NCT00564512 Lepretre, 2012 [41], Letestu, 2011 [abs] [152] Lepretre, 2009 [abs] [153]	FCR 28 ds for 6 cycles	FCCam 6 monthly courses of oral FC	FCR: F: 40 mg/m^2 daily C: 250 mg/m^2 daily on ds 1 to 3 every 28 days R: 375 mg/m^2 i.v. on d 0 in the 1st cycle and 500 mg/m^2 on d 1 for all subsequent cycles every 28 ds FCCam: F: 40 mg/m^2 daily on ds 1 to 3 C: 250 mg/m^2 per d on ds 1 to 3 every 28 ds Cam: 30 mg subcutaneously on ds 1-3 every 28 ds	6 mo
ML17102 CLL8 NCT00281918 Hallek, 2010 [42], Fink, 2011 [154], Bottcher, 2012 [155], Fischer, 2012 [156]	FCR 28 ds for 6 cycles	FC	F: 25 mg/m^2 daily C: 250 mg/m^2 daily on ds 1 to 3 of each course R: 375 mg/m^2 on d 0 of the 1st course, then 500 mg/m^2 on d 1 of the 2nd to 6th courses.	6 mo
CLL 11 Goede, 2013 [abs] [43]	R + Chl (RChl)GA101 + Chl (GChl),	Chl alone	R + Chl (RChl)GA101 + Chl: 375 mg/m^2 i.v. d1 cycle 1, 500 mg/m^2 d1 cycles 2-6 (GChl): 100 mg i.v. d1, 900 mg d2, 1000 mg d8, d 15 of cycle 1, 1000 mg d 1 cycles 2-6 Chl alone: 0.5 mg/kg po d1, d15 every 28 days	6 cycles

Abs = abstract; C = cyclophosphamide; Cam = alentuzumab; Chl = chlorambucil; d = day; F = fludarabine; G = Obinutuzumab; i.v. = intravenously; mo = months; obs = observation; po = by mouth; R = rituximab.

Table 8Q. Rituximab in chronic lymphocytic leukemia: Quality of included randomized controlled trials of previously untreated patients.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
CALGB Study 9712 Woyach, 2011 [40], Byrd, 2003 [149]	Concurrent vs sequential F with R	CR	50 patients per arm were required to allow adequate power to detect an improvement in the CR rate from 20% to 40%.	104	No	*nr*	No	Yes	No
CLL2007FMP NCT00564512 Lepretre, 2012 [41], Letestu, 2011 [abs] [152], Lepretre, 2009 [abs] [153]	FCR vs FCCam	PFS	155 per group were required to detect a difference of 15% in PFS in favour of the FCCam arm with 80% power and a 2-sided significance of 5%.	165	Yes	Yes	No	Yes	Yes excess morality in the FCCam arm
ML17102 CLL8 Hallek, 2010 [42], Fink, 2011 [154], Bottcher, 2012 [155], Fischer, 2012 [156]	FCR vs FC	PFS	357 events were required with an HR of 0.741, and a 2-sided significance level of 5%, to obtain 80% power and a PFS of 66% at 2 years.	817	Yes	Yes	No	Yes	No
CLL 11 Goede, 2013 [43]	R + Chl vs (RChl)GA101 + Chl (GChl), vs Chl alone	PFS	*nr*	Stage 1a: (GChl): N = 238 Chl alone: N = 118 Stage 1b: Chl alone: N = 118 R + Chl : N = 118	*nr*	*nr*	*nr*	*nr*	No

Abs = abstract; C = cyclophosphamide; Cam = alemtuzumab; Chl = chlorambucil; CR = complete response; F = fludarabine; ITT = intention-to-treat; *nr* = not reported; PFS = progression-free survival; R = rituximab; vs = versus

Table 8E. Efficacy of rituximab in chronic lymphocytic leukemia. Included randomized controlled trials of previously untreated patients.

Study	Intervention Control	EFS median (months)	PFS Median (months)	TTP, median (months)	FFS or other disease control measure median (months)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
CALGB Study 9712 Woyach, 2011 [40] Byrd, 2003 [149]	Concurrent F+R	*nr*	Est $PFS_{2\text{-years}}$: 70% PFS_{117}: NS	*nr*	*nr*	47, (95% CI, 0.82-0.98	OS_{117}: NS	23 117
	Sequential F+R	*nr*	Est $PFS_{2\text{-years}}$: 70% PFS_{117}: NS	*nr*	*nr*	28, (95% CI, 0.66-0.99)	OS_{117}: NS	
CLL2007FMP Lepretre 2012 [41], Letestu, 2011 [abs] [152] Lepretre, 2009 [abs] [153]	FCR	*nr*	$PFS_{3\ years}$: 82.6% (95% CI, 74.7%-91.3%)	*nr*	*nr*	33.75 (95% CI, 23.6-45.2)	90.1% (95% CI, 83.2%-97.6%)	38
	FCCam	*nr*	$PFS_{3\ years}$: 72.5% (95% CI, 63.3%-83.0%), NS	*nr*	*nr*	19.2 (95% CI, 11.2-29.7), p=0.04	86.4% (95% CI 79.3%-94.2%), NS	
ML17102 CLL8 Hallek, 2010 [42] Fink, 2011 [154] Bottcher, 2012 [155], Fischer, 2012 [156]	FCR	*nr*	*$PFS_{3\ years}$: 51.8 (95% CI 46.2-57.6) $PFS_{5.9\ years}$: 38%	*nr*	*nr*	CR: 44 OR: 90	$OS_{3\text{-years}}$: 87% $OS_{5.9\ years}$: median not reached	8 years
	FC	*nr*	*$PFS_{3\ years}$: 32.8 (95% CI 29.6-36.0), P<0.0001 $PFS_{5.9\ years}$: 27.4%, p<0.0001	*nr*	*nr*	CR: 22, P<0.0001 OR: 80, P<0.0001	$OS_{3\text{-years}}$: 83%, P=0.012 $OS_{5.9\ years}$: 86 (95% CI 78.7-93.2 months), p=0.001	
					Stage 1b[A]			
CLL 11 Goede, 2013 [abs] [43]	R + Chl	*nr*	15.7	*nr*	*nr*	CR: 8.3 OR: 65.9	*nr*	*nr*
	Chl alone	*nr*	10.8 HR 0.32, CI, 0.24-0.44, p<0.0001	*nr*	*nr*	CR: 0 OR: 30	*nr*	

*primary outcome

[A] Results for a comparison of rituximab and GA101 in the study by Goede were not available.

Abs = abstract; C = cyclophosphamide; Cam = alemtuzumab; CI = confidence interval; F = fludarabine; *nr* = not reported; NS = not significant; OR = overall response; OS = overall survival; PFS = progression-free survival; R = rituximab.

Table 8AE. Rituximab in chronic lymphocytic leukemia. Grade ≥3 adverse events in randomized controlled trials of previously untreated patients.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vomiting (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
CALGB Study 9712 Woyach, 2011 [40] Byrd, 2003 [149]	**Induc:** Concurrent F+R **Consol:** 4 weekly R doses	51	**Induc:** 20 **Consol:** 6	**Induc:** No fever: 76 **Consol:** No fever: 19	**Induc:** 4 **Consol:** 3	*nr*	**Induc:** 20 **Consol:** 0	**Induc:** 0 **Consol:** 0	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
	Induc: Sequential F+R **Consol:** 4 weekly R doses	53	**Induction:** 6 **Consol:** 23	**Induc:** No fever: 39 **Consolidation:** No fever: 8	**Induc:** 0 **Consol:** 0	*nr*	**Induc:** 10 **Consol:** 0	**Induc:** 2 **Consol:** 0	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
CLL2007FMP Lepretre 2012 [41], Letestu, 2011 [abs] [152] Lepretre, 2009 [abs] [153]	FCR	82 patients 448 courses	16	Fever: 0 Grade 3: 29.62 Grade 4: 19.42	*nr*	End of treatm 0.248 × 10^9/L	*nr*	*nr*	*nr*	*nr*	*nr*	1	*nr*	*nr*
	FCCam	83 patients 378 courses	51	Grade 3:38.7 P=0.023 Grade 4: 25.26 NS	*nr*	End of treatm 0.127 ×10^9/L	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	8.4
ML17102 CLL8 Hallek, 2010 [42], Fink, 2011 [abs] [154]	FCR	404	25	No fever: 34	5	Leukocytopenia: 24	7	*nr*	*nr*	*nr*	nr	26	8	Not treatm related 16
	FC	396	21 NS	21 P<0.0001	7 NS	Leukocytopenia: 12 P<0.0001	11 NS	*nr*	*nr*	*nr*	*nr*	17	15	21
CLL 11 Goede, 2013 [abs] [43]	R + Chl	233	8	25	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
	Chl alone	118	11	15	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*

Abs = abstract; C = cyclophosphamide; Consol = consolidation; F = fludarabine; Induc = induction; *nr* = not reported; NS = not significant; R = rituximab; treatm = treatment;

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Patients with Relapsed/Refractory Disease

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in Table 9, the treatment doses and schedules are summarized in Table 9T. Two studies [44,45], represented by six publications, were included. The sample size was 52 patients in one phase II study [44], and 552 in the other [45]. The included studies compared rituximab in combination with fludarabine-based chemotherapy with chemotherapy alone. One study had PFS [45], and one study had overall response as primary outcomes. Other outcomes reported were OS, and QOL.

Quality of Included Studies

The quality of the included studies is summarized in Table 9Q.

The two studies included were reported as full-text publications. The NCRI CLL201 trial [44] was a phase II study with a smaller sample; the BO17072 study [45], was an open-label trial, was at moderate risk of bias because the authors did not report on random sequence generation and allocation concealement; they did not blind patients, clinicians or outcome assessors; and they conducted an intention-to-treat analysis and did report on all outcomes stated in their methods section.

Outcomes

The results of the studies are summarized in Table 9E, the adverse events in Table 9AE.

Overall this body of evidence indicates a benefit with the use of rituximab in addition to fludarabine-based chemotherapy, when compared with chemotherapy alone, (see Table 9E for numerical results). There were no statistically significant between-group difference in grade 3 or 4 adverse events.

Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Tables of Studies of Patients with Relapsed/Refractory Disease

Table 9. Rituximab in chronic lympocytic leukemia. General characteristics of included randomized controlled trials of relapsed disease.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
REACH BO17072 Robak, 2010, 2009 [abs] [45,157], Dornan, 2009 [abs], Li 2009 [abs] [158,159] **Funding:** Hoffman La Roche, Genentech, and Biogen Idec	To test the effectiveness of chemoimmuno therapy **Design:** multicentre parallel group **Follow up:** 25 months	552 previously treated CLL patients Median age (years): IG: 63 CG: 62	FCR vs FC	*PFS CR MRD QOL
NCRI CLL201 Trial Hillmen, 2011 [44], Hillmen 2007 [abs] [160] **Funding:** Roche Pharmaceuticals	To test whether FCM-R eradicates detectable CLL. **Design:** multicentre, open label, two-stage, parallel group phase II **Follow-up:** 38 months	52 patients with relapsed CLL Median age (years): 68	FCM-R vs FCM	*OR CR PR PFS OS

*primary outcome

Abs = abstract; C = cyclophosphamide; CG = control group; CLL = chronic lymphocytic leukemia; CR = complete response; F = fludarabine; IG = intervention group; M = mitoxantrone; MRD = minimal residual disease; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial response; QOL = quality of life; R = rituximab.

Table 9T. Rituximab in chronic lymphocytic leukemia: Dose and schedule for patients with relapsed/refractory disease.

Study	Intervention schedule	Control schedule	Dose	Duration
REACH BO17072 Robak, 2010 [45]; Roback 2009 [abs] [157]; Dornan, 2009 [abs], Li 2009 [abs] [158,159]	FCR R: on d 1 of 1st cycle (the day before chemotherapy) then on d 1 of subsequent cycles (the same day as chemotherapy)	FC	F: 25mg/m^2/d i.v. C: 250mg/m^2/d for 3 ds R: 375 mg/m^2 i.v., and 500 mg/m^2 i.v.	6 cycles of 28 ds each
NCRI CLL201 Trial Hillmen, 2011 [44], Hillmen 2007 [abs] [160]	FCM-R	FCM	F: 24 mg/m^2/d on ds 1 to 5 orally C: at 150 mg/m^2/d on ds 1 to 5 orally M: 6 mg/m^2 on d 1, i.v. R: 375 mg/m^2, amended to increase to 500 mg/m^2 for cycles 2 to 6	6 cycles of 28 ds each

Abs = abstract; C = cyclophosphamide; d =day; F=fludarabine; i.v. = intravenously; M = mitoxantrone; R = rituximab.

Table 9Q. Rituximab in chronic lymphocytic leukemia: Quality of included randomized controlled trials of patients with relapsed/refractory disease.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
BO17072 Robak, 2010 [45]	FCR vs FC	PFS	550 patients and 284 events were required to detect a 40% improvement in median PFS in the R-FC arm corresponding to a 29% risk reduction (HR = 0.714) with 80% power at 5% significance level.	552	*nr*	*nr*	No	Yes	No
NCRI CLL201 Trial Hillmen, 2011 [44], Hillmen 2007 [abs] [160]	FCM vs FCM-R	OR	The sample size was estimated for a single arm trial, then the sample size was doubled to include the randomized concurrent arm. Four patients were required in the first stage and 21 patients in the second stage of the trial to obtain 90% power and an estimate 50% OR in the FCM-R arm at a 10% level of precision.[c]	52	No	*nr*	No	No	No

Abs = abstract; C = cyclophosphamide; F =fludarabine; HR = hazard ratio; ITT = intention to treat; M = mitoxantrone; nr = not reported; OR = overall response; PFS = progression-free survival; R = rituximab.

Table 9E. Efficacy of rituximab in chronic lymphocytic leukemia: Included randomized controlled trials of patients with relapsed/refractory disease.

Study	Intervention Control	EFS median (months)	PFS Median (months)	TTP, median (months)	FFS or other disease control measure median (months)	CR or other measures of response (%)	OS, median (months)	Follow-up, median (months)
BO17072 Robak, 2010 [45]	FCR	*nr*	*PFS_{10}: 30.6	*nr*	DR:39.6 TTNT: Not reached	24.3	Median not reached	25
	FC	*nr*	*PFS_{10}: 20.6 HR 0.65 (95% CI, 0.51-0.82), p<0.001	*nr*	DR: 27.7, HR 0.69 (95% CI, 0.50-0.96), p=0.0252 TTNT: 34.3, HR 0.65 (95% CI 0.49-0.86), p=0.0024	13, P<0.001	52 months, HR 0.83 (95% CI, 0.59-1.17), NS	
NCRI CLL201 Hillmen, 2011 [44], Hillmen 2007 [abs] [160]	FCM-R	*nr*	*nr*	*nr*	*nr*	15 OR: 65% (95% CI, 44%-83%)	*nr*	38
	FCM	*nr*	*nr*	*nr*	*nr*	8 OR: 58% (95% CI, 40%-77%)	*nr*	

*primary outcome
Abs = abstract; C = cyclophosphamide; CI = confidence interval; CLL = chronic lymphocytic leukemia; CR =complete response; DR =duration of response; EFS = event-free survival; F = fludarabine; FFS = failure-free survival;HR = hazard ratio; M = mitoxantrone; *nr* = not reported;NS = not significant; OR = overall response; Os = overall survival; PFS = progression-free survival; R = rituximab; RCT =randomized controlled trial; TTNT = time to next treatment.

Table 9AE. Rituximab in chronic lymphocytic leukemia: Grade ≥3 adverse events in randomized controlled trials of patients with relapsed/refractory disease.

Study	Intervention	N	Infections* (%)	(Febrile) neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; vom. (%)	Mucositis (%)	Liver tox (%)	Neurol. Tox (%)	Cardiac tox (%)	Second tumors (%)	Deaths (%)
BO17072 Robak, 2010† [45]	FCR	276	14	12	12	*nr*	11	Nausea: 40 Vom.: 21	*nr*	*nr*	*nr*	*nr*	*nr*	7
	FC	276	10	12	13	*nr*	9	Nausea: 35 Vom.: 19	*nr*	*nr*	*nr*	*nr*	*nr*	5
NCRI CLL201 Hillmen, 2011 [44], Hillmen 2007 [abs] [160]	FCM-R	26	10.5[A]	*nr*[B]	*nr*[B]	*nr*[B]	*nr*[B]	GI: 0	*nr*	*nr*	*nr*	*nr*	*nr*	Not treatm related: 62
	FCM	26	0 [A]	*nr*[B]	*nr*[B]	*nr*[B]	*nr*[B]	GI: 25	*nr*	*nr*	*nr*	*nr*	*nr*	50

[A] Inflammatory and immunosuppressive
[B] Hematological adverse events: 63.2% in FCM-R arm vs 25% in FCM arm.
Abs = abstract; C = cyclophosphamide; CLL = chronic lymphocytic leukemia; F = fludarabine; GI = gastrointestinal; M = mitoxantrone; nr = not reported; R = rituximab; RCT = randomized controlled trial; tox = toxicity; Treatm = treatment; Vom. = vomiting.

Hepatitis B Virus Reactivation

A systematic review with meta-analysis [46] and a RCT [47] were identified.

The meta-analysis included nine retrospective or prospective trials published from 1997 to 2012 for a total of 971 patients with NHL treated with CHOP, or CHOP-like chemotherapy, and rituximab. The authors found that the cumulative incidence of HBV reactivation was significantly higher in the rituximab than in the chemotherapy-alone group (11.89% versus 4.11, relative risk [RR], 2.14; 95% CI, 1.42 to 3.22; p = 0.0003). To see the risk of HBV reactivation in isolated anti-HBc carriers, the authors pooled in meta-analysis (fixed-effects model) six case series of hepatitis B core antibody positive (HBcAb positive) patients, and they found a RR of 5.52 (95% CI, 2.05 to 14.85; p = 0.0007), for an anti-HBc carrier to develop hepatitis when exposed to rituximab. To explore the effect of rituximab treatment on hepatitis B surface antigen positive (HBsAg positive) patients, the authors combined three case series of NHL patients with HBsAg positive treated with rituximab-based therapy in meta-analysis (random-effects model). The RR of HBV reactivation of rituximab treated patients compared with control was 1.63 (95% CI, 0.65 to 4.09; p = 0.30).

Huang et al [47] randomized 80 patients with CD20+ lymphoma, including DLBCL, FL, MCL, and SLL, and resolved hepatitis B to receive prophylactic entecavir (0.5 mg/day) before chemotherapy to three months after completing chemotherapy or to receive entecavir at the time of HBV reactivation and HBsAg reverse seroconversion since chemotherapy. At 18 months follow-up one patient in the prophylaxis group and seven patients in the control group developed HBV reactivation (p=0.027). The authors found that seroconversion was higher in the control than in the prophylaxis group (p=0.032), and that patients with detectable or undetectable viral load could develop HBV reactivation and HBsAG reverse seroconversion (Table 10, 10Q, and 10E).

In summary, this literature showed that rituximab treatment is associated with a substantial risk of HBV reactivation. Reactivation has been reported in patients with chronic HBV (HBsAg+) and in patients with resolved HBV (HBsAg negative/HBcAb positive). Viral reactivation can occur during rituximab treatment or up to 18 months beyond completion of rituximab. Adverse effects of antiviral therapy are not discussed here because they are out of scope for this review.

Table 10. Rituximab and hepatitis B virus reactivation: General characteristics of the included randomized controlled trial.

Study name, author, date, Funding source,	Study objectives; design; follow-up	Patient population	Intervention/ Comparison(s)	Outcomes
Huang, 2013 [47]	To test the role of antiviral prophylaxis with ETV for the prevention of HBV reactivation in patients treated with R for lymphoma **Design:** RCT, phase IV **Follow-up:** 18.5 months	80 patients with CD20+ lymphoma and resolved hepatitis B	ETV before chemotherapy to 3 months after completing treatment (prophylactic ETV) vs ETV at the time of reactivation and HBsAg reverse seroconversion since chemotherapy (treatment ETV)	*Incidence of R-associated HBV reactivation during and after chemotherapy

ETV = entecavir; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; R = rituximab; RCT Randomized controlled trial; vs = versus.

Table 10Q. Rituximab and hepatitis B virus reactivation: Quality of the included randomized controlled trial.

Study	Treatment	Primary outcome	Required sample size	Sample Size N	Randomization method described	Allocation concealment	Blinding	ITT Analysis	Early termination
Huang, 2013 [47]	Prophylactic ETV vs treatment ETV	Incidence of HBV reactivation	38 patients per group were required for 80% power with 5% error. HBV reactivation was estimated as 25% in the control group and 5% in the ETV prophylaxis group.	80	No	*nr*	*Nr*	Yes	No

ETV = entecavir; HBV = hepatitis B virus; ITT = intention to treat; R = rituximab; vs = versus.

Table 10E. Rituximab and hepatitis B virus reactivation: Efficacy of the included randomized controlled trial.

Study	Intervention Control	HBV react (%)	HBsAg reverse seroconversion (%)	Cumulative reactivation rate at 6, 12 and 18 months(%)	Cumulative HBsAg reverse seroconversion rate at 6, 12 and18 months (%)	Time lag from HBV reactivation to seroconversion	Deaths
Huang, 2013 [47]	Prophylactic ETV vs treatment ETV	2.4	0	0, 0, 4.3	0, 0, 0	0.7 months (range 0 to 6.2)	0
		17.9 p = 0.027	10.3 p = 0.052	8%, 11.2, 25.9% p = 0.019	0, 6.4, 16.3 p = 0.032		

ETV = entecavir; HBsAg = hepatitis B surface antigen; R = rituximab; react = reactivation; vs = versus.

Ongoing, Unpublished, or Incomplete Studies

Table 11 presents the trials that were ongoing at the time of our search of the trial registry Clinicaltrials.gov (available at https://clinicaltrials.gov/) (i.e., October 2013). Table 12 presents the trials that were identified as abstracts of interim analyses and therefore not included in this report.

Table 11. Ongoing trials

Interventions	Official title	Status	Protocol ID	Completion Date	Last updated
GA101 + CHOP vs. R+CHOP	A Study of RO5072759 (GA101) in Combination With CHOP Chemotherapy Versus MabThera/Rituxan (Rituximab) With CHOP in Patients With CD20-Positive Diffuse Large B-Cell Lymphoma	Recruiting	NCT01287741	February 2019	March 16, 2012
Ofatumumab vs. Rituximab	Single Agent Ofatumumab Vs. Single Agent Rituximab in Follicular Lymphoma Relapsed After Rituximab-Containing Therapy	Recruiting	NCT01200589	June 2019	January 5, 2012
LBH589 vs. Rituximab	A Phase II Study of Oral Panobinostat (LBH589) and Rituximab to Tat Diffuse Large B Cell Lymphoma	Recruiting	NCT01238692	NR	December 6, 2011
Rituximab vs. lenalidomide	Lenalidomide With or Without Rituximab After Standard Chemotherapy in Treating Patients With Diffuse Large B-Cell Non-Hodgkin Lymphoma	Recruiting	NCT00765245	May 2014	May 26, 2011
FC + R vs. FC alone	Fludarabine and Cyclophosphamide With or Without Rituximab in Treating Patients With Previously Untreated Mantle Cell Lymphoma	Recruiting	NCT00641095	September 2010	October 6, 2009
RM vs. Observation	Mantel Cell Lymphoma Efficacy of Rituximab Maintenance	Recruiting	NCT00921414	December 2012	October 21, 2011
^{90}Y-ibritumomab tiuxetan vs. RM	ZAR2007: R-CHOP in Folicular Lymphoma Patients no Treated Previously. Consolidation With ^{90}Y Ibritumomab Tiuxetan (ZevalinAr) Versus Maintenance Treatment With Rituximab	Recruiting	NCT00662948	December 2016	December 12, 2011
R-ABVD vs. ABVD	Phase II R-ABVD Versus ABVD for Advanced Stage Classical Hodgkin Lymphoma	Recruiting	NCT00654732	March 2014	March 5, 2012
R+ Chemo vs. Chemo alone	Intergroup Randomized Trial for Children or Adolescents With B-Cell Non Hodgkin Lymphoma or B-Acute Leukemia: Rituximab Evaluation in High Risk Patients	Recruiting	NCT01516580	December 2021	January 24, 2012

ABVD = adriamicin, bleomycin, vinblastine, dacarbazine; Chemo = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; FC = fludarabine, cyclophosphamide; GA101 = obinutuzumab; Len = lenalidomide; R = rituximab; RM = rituximab maintenance;

Table 12. Studies that were captured by the search but not included because abstracts of interim analyses.

Study name, Author, date	Population	Intervention	Control
IELSG-19 Zucca, 2013 [161]	Patients with extranodal marginal zone b-cell lymphoma (malt lymphoma): Final results of the IELSG-19 study.	R/Chl	Chl
BMT CTN 0401 Vose, 2013 [162]	Salles, 2013 [163]	Previously treated patients with INHL	R/GS-1101
O'Brien, 2013 [164]	Patients with previously treated chronic lymphocytic leukemia	R/GS-1101	Placebo +R
Mobasher, 2013 [165]	Patients with previously untreated DLBCL	R-CHOP	GA101 (obinutuzumab) +CHOP
Le Gouill, 2013	Younger MCL patients	RM	observation
AGMT NHL13 Jaeger, 2013 [166]	Patients with aggressive B-cell lymphoma	RM	observation
CLL11 (bo21004) Hallek, 2013 [167]	Patients with CLL and comorbidities	R + Chl	GA101 + Chl
Fingerle-Rowson, 2013 [168]	Patients with advanced FL and MZL	GA101 + chemotherapy followed by GA101 maintenance	rituximab + chemotherapy followed by rituximab maintenance
PCYC-1104 Dreyling, 2013 [169]	Elderly patients with newly diagnosed MCL.	Ibrutinib + BR	BR
stil NHL 7-2008, maintain; nct00877214 Burchardt, 2013 [170]	Patients with indolent lymphomas	RM vs observation	nr
Reddy, 2012 [171]	Patients with high risk DLBCL	Len + R + RM	Len
Le Gouill, 2012 [172]	Untreated mantle cell lymphoma patients	R-DHAP and after autologous stem cell transplantation + R maintenance	Observation
Sehn, 2011 [173]	Patients with relapsed CD20 indolent B-cell NHL	GA101 (Obinutuzumab)	R
Reddy, 2011 [174]	Patients with high/high-intermediate risk diffuse large B-cell lymphoma	Len M	Len +R as M
Zucca, 2010 [175]	Patients with MALT Lymphoma	Chl + R	Chl
Theocharous, 2010 [176]	Patients with follicular lymphoma previously treated with rituximab	Bortezomib with fludarabine	R + F
Pettengell, 2010 [177]	Patients with relapsed or resistant follicular lymphoma prior to high-dose therapy as in vivo purging and to maintain remission following high-dose therapy	R purging	RM
SAKK 35/03 Taverna, 2009 [178]	Patients with FL	Long term R maintenance	Short term maintenance
SAKK 35/98 Martinelli, 2009 [179]	Patients with FL	R prolonged exposure	R standard schedule
Hallek, 2009 [180]	Patients with advanced CLL	FCR	FC
Foussard, 2006 [181]	Previously untreated patients with follicular lymphoma	R- CHVP- Interferon (12 courses)	6 CHVP courses combined with 6 rituximab infusions + 18 months IFN (R-CHVP-I)

B = bendamustine; BEAM = carmustine, etoposide, cytarabine, and melphalan; Chl = chlorambucil; CHOP = cyclophosmphamide, hydroxydaunorubicin, vincristine, and prednisone; CLL = chronic lymphocytic leukemia; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVP = cyclophosphamide-adriamycin-vincristine-prednisone; DLBCL = diffuse large B-cell lymphoma; F = fludarabine; FCR = fludarabine, cyclophosphamide, and rituximab; FL = follicular lymphoma; GA101 = obinutuzumab; GS-1101 = idelalisib; I = interferon; INHL = indolent non-Hodgkin lymphoma; Len = lenalidomide; M = maintenance; MCL = mantle cell lymphoma ; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; R = rituximab;

DISCUSSION AND CONCLUSIONS

In the primary treatment of DLBCL, six trials have evaluated rituximab combined with anthracycline-based chemotherapy in patients with DLBCL. In all of these reports, the duration of disease control was superior in patients allocated to receive rituximab. Coiffier et al [3], Sonneveld et al [10], and two studies by Pfreundschuh et al [6,12] also observed clinically important and statistically significant difference in OS. A second trial authored by Pfreundschuh et al [6] comparing CHOP given every two weeks to the same regimen with rituximab also detected an OS benefit with the antibody addition. Ketterer et al [5] compared intensified chemotherapy (dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) to the same regimen with rituximab, and detected no difference in OS. This was a low-risk young population, and the survival in both arms was 98% and 97% at three years; thus, longer follow-up is likely needed. Habermann et al [4] also detected no difference in OS. The design and analysis of that trial was complex because it included a second randomization to maintenance therapy with rituximab or observation, and there was an interaction between the induction and maintenance randomizations which may have limited the ability to detect a survival advantage from rituximab in induction chemotherapy. The DSG has interpreted these results as a strongly supporting a role for rituximab in the primary treatment of patients with DLBCL. This interpretation is based on the consistent observation of a longer duration of disease control in patients receiving rituximab and the demonstrated survival advantage. This forms the basis for recommendation 1, recommending the addition of rituximab to chemotherapy in upfront aggressive B-cell lymphoma.

The evaluation by Kaplan et al [91] of rituximab in patients with HIV-related lymphoma failed to detect differences between randomized groups with respect to OS. A careful analysis of these data suggests an improvement of lymphoma-associated mortality that is balanced by an increase in infection-related mortality. The increase in infection-related death appears to be pronounced in a selected and identifiable group of high-risk patients (CD4 count $<50/mm^3$) and in those who received maintenance rituximab. A recent individual patient meta-analysis by Barta et al [17] pooled data from 1546 patients enrolled in 19 key trials, and confirmed these findings. On multivariate analysis, the use of rituximab in combination with chemotherapy was associated with significantly improved outcomes, including CR rates, PFS, and OS, in patients with CD4 counts ≥ 50 mm^3 only. The Hematology DSG appreciates that the infection risk associated with treatment of HIV-related lymphoma in general may be evolving in the era of combination antiretroviral therapy. More recent studies suggest that patients treated in the era of combination antiretroviral therapy may not have the same risk of infection with rituximab-associated therapy. Finally, the group was influenced by the extent of data supporting the use of rituximab in DLBCL in general, of which HIV-related DLBCL represents a subgroup (rather than a distinct biological entity). Therefore, the Hematology DSG recognizes that for selected patients who are carefully monitored for infection and immune (CD4 count) parameters, the benefit of rituximab may outweigh the risks and that it is a reasonable therapy to consider, thus our recommendation that if patients have a CD4 count $\geq 50/mm^3$, they should receive chemotherapy in combination with rituximab.

There is one phase III study by Ribrag et al [9] comparing the use of rituximab-based chemotherapy to chemotherapy alone in Burkitt lymphoma. Rituximab was added to dose-intense cyclophosphamide, vincristine, prednisolone, doxorubicin, and methotrexate chemotherapy, demonstrating improved EFS and OS. This confirms the findings of older, nonrandomized but comparative phase II data. These data suggest that the addition of rituximab does not add toxicity to the baseline regimen. The DSG also considered that there was strong biological rationale in treating Burkitt lymphoma with rituximab, given the dense expression of CD20 found in these pathologies. Based on currently available data, the

Hematology DSG believed that the addition of rituximab to a dose-intense regimen in Burkitt lymphoma should be offered.
For previously treated patients with aggressive histology CD20-positive B-cell lymphomas, the use of rituximab prior to stem-cell mobilization for autologous stem cell transplantation has been studied in two randomized trials. Both of these studies were underpowered to detect differences in disease control or OS, and no differences were found in the reporting of these outcomes. The Hematology DSG deliberated over the role of rituximab in salvage therapy of DLBCL and its variants. The systematic review did not identify any randomized trials evaluating the addition of rituximab; however, the Hematology DSG members were aware of small uncontrolled phase II trials reporting outcomes of patients receiving rituximab containing salvage regimens. These data are difficult to interpret given the small number of patients included, patient selection, and variable number of patients previously exposed to rituximab during primary therapy. Therefore, the Hematology DSG considered that the evidence justifying the routine adoption of rituximab as part of a premobilization strategy is currently insufficient, and a definitive recommendation cannot be made.
The Hematology DSG considered the data of Haioun et al [89] evaluating rituximab as maintenance therapy following autologous stem cell transplantation too preliminary to form conclusions.

Follicular and Other Indolent Lymphomas

Nine trials have tested the addition of rituximab to chemotherapy as a first-line therapy in patients with follicular and other indolent lymphomas. Because two of the trials included patients with MCL, discussion of this histology has been included in this section. One report provided very preliminary results for the duration of disease control or OS despite lacking power to detect differences in these outcomes and was not considered further (Rivas-Vera, 2005, #5228}. The remaining trials all reported large differences in disease control with no increase in major toxicity. Two trials also suggest an improvement in OS with the addition of rituximab [1,2,33]. An aggregate-data meta-analysis including these data has also confirmed an OS benefit in both FL and MCL patients treated with rituximab and chemotherapy. Finally, a practice guideline prepared by the Italian Society of Hematology [182] recommends the addition of rituximab to conventional chemotherapy for the treatment of nodal indolent lymphoma.

In addition to the early data demonstrating a survival benefit when rituximab is added to upfront chemotherapy, the DSG was also influenced by the magnitude of the benefit in disease control (a 15-month delay in time to re-treatment in the rituximab plus cyclophosphamide, vincristine, and prednisone trial, for example) and the lack of significant toxicity with this therapy. Furthermore, given the inclusion of a number of non-follicular indolent histologies in three of the seven trials, and the comparable activity of rituximab in FL and other non-follicular indolent histologies (excluding SLL/CLL), the DSG recommends that data from FL be generalized to these histologies. For these reasons, the DSG recommends that previously untreated patients with follicular or other indolent histology B-cell lymphoma (such as MCL, MZL, and lymphoplasmacytoid lymphoma), excluding SLL, who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab.

One trial has tested the use of rituximab monotherapy compared with watchful waiting in asymptomatic low-bulk FL patients and demonstrated improvement in the primary outcome of TTNT, as well as PFS. The DSG discussed these data, and felt the outcome of TTNT may be subjective, and in the absence of longer follow-up data, including the effects of this treatment on future response to subsequent therapies, there was insufficient data to make a recommendation.

The DSG also considered the role of rituximab beyond first-line therapy. For previously treated patients with follicular or other indolent histology B-cell lymphoma (such as MCL, MZL,

and lymphoplasmacytoid lymphoma), excluding SLL, who are appropriate candidates for chemotherapy and who have not previously received rituximab, should receive this chemotherapy in combination with rituximab. This recommendation is based on the improved survival and TTP observed with the addition of rituximab to FCM reported by Forstpointner et al [37] and Dreyling et al [131], and the improved TTP reported in the study of CHOP ± rituximab by Van Oers et al [38]. This forms the basis for the above recommendation in previously treated patients.

There are now nine RCTs of maintenance rituximab (MR) in patients with indolent B-cell lymphoma [29,30,39,132-137]; the majority of studies have demonstrated clinically important improvements in disease control and three trials have shown prolongation of survival [29,30,135]. In patients receiving therapy for relapsed follicular lymphoma, there are clear benefits in disease control and survival attained with the use of MR. The benefit in disease control is preserved even in patients who have received combination chemotherapy that includes rituximab. Following front-line therapy, MR has similarly resulted in prolonged PFS and OS. However, this strategy has only been studied following combination chemotherapy without rituximab. The DSG believed strongly that the body of evidence to date supports extending the use of MR to the front-line setting following chemotherapy with rituximab. The group consensus was influenced by the sizable magnitude of benefit in disease control in this setting and the preservation of this benefit following rituximab-based chemotherapy noted in the relapsed setting.

Data are available on the use of MR following rituximab monotherapy in both front-line and relapsed settings. Based on the improvement in PFS in those trials as well as the consistent benefit of this strategy, the DSG also recommends the use of MR in those patients initially receiving rituximab monotherapy. Thus, rituximab maintenance is recommended for patients with CD20-positive indolent B-cell histology lymphomaswho respond to treatment with combination chemotherapy and/or rituximab.

The role of rituximab in combination with chemotherapy for patients previously treated with rituximab (alone or in combination) is much less clearly defined. None of the randomized trials included patients who had previously received rituximab. The DSG is unable to offer definitive recommendations where no direct evidence exists but recognizes the need of practitioners and policy-makers for guidance in this situation. The addition of rituximab to chemotherapy in patients beyond first-line treatment is associated with improved TTP and, in one trial, survival. The re-use of therapies that have previously been effective for a given patient is a common strategy when managing patients with indolent lymphomas. Data from trials of rituximab monotherapy suggest that in a selected population of rituximab-sensitive patients, a response rate comparable to that observed in first-line treatment can be observed [136]. Cumulative toxicity from multiple treatments with rituximab is not expected.Based upon these data, and the consensus of the members of the Hematology DSG, the group recommends that patients previously treated with rituximab who remain sensitive to this agent, and who are appropriate candidates, should receive chemotherapy in combination with rituximab. While no evidence-based definition of rituximab sensitivity exists, the DSG considers relapse one year or more after treatment with rituximab to be a reasonable threshold. In addition, the group considered patients who remained stable for one year following the last dose of maintenance rituximab to be rituximab-sensitive. Thus, patients who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Given the inclusion of a number of non-follicular indolent histologies in four of the six trials and the comparable activity of rituximab in FL and other non-follicular indolent

histologies, the DSG recommended that data from FL be generalized to these histologies (including MZL, and lymphoplasmacytoid lymphoma). The DSG did recognize that MCL was specifically studied in the trial by Ghielmini et al [137] and no difference in EFS was detected with MR. However, given the small sample size tested, the group questioned the power of this study to find any benefit of MR. Moreover, in a subgroup analysis of the trial reported by Dreyling et al [130], there remained a statistically significant benefit in RD in the subset of patients with MCL. Therefore, the DSG supported extrapolating the data supporting MR use to patients with MCL.

Chronic Lymphocytic Leukemia

There are now five randomized studies [40-42,44,45] that document the addition of rituximab to fludarabine-based chemotherapy in CLL. Three trials in the upfront setting [40-42] have demonstrated improved response rates; however, two of the trials have short follow-up [40,41], without demonstration of improved disease control or survival. A single RCT by Hallek et al [42] has adequate follow-up of over eight years and demonstrated an improvement in response and disease control (PFS) with the addition of rituximab to chemotherapy (fludarabine, cyclophosphamide, and rituximab) as well as significant improvement in OS with longer follow-up. One RCT in the relapsed/refractory CLL population has comprehensive data reported [45], and similarly demonstrated a 10-month extension in progression-free survival. The Hematology DSG noted that this built upon phase II historically controlled data that documented improvements in disease control and survival when rituximab was added to fludarabine alone. In the phase III studies, the group also noted that the addition of rituximab was not associated with a dramatic increased risk of infection-related toxicity. Finally, the group recognized these trials studied the addition of rituximab to a fludarabine-based chemotherapy backbone, which may not be applicable to older, frail CLL patients. The Hematology DSG does recognize the consistent and moderate benefit in PFS and OS in the phase III setting and the acceptable toxicity profile of rituximab; the DSG felt that the addition of rituximab to fludarabine-based chemotherapy should be recommended in the treatment of CLL and SLL. More recently, the comparison of chlorambucil alone to rituximab and chlorambucil in the older, frail patient population also demonstrated a significant improvement in PFS. Thus, the DSG felt the addition of rituximab to single-agent chlorambucil can be considered.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 4.

JOURNAL REFERENCE(S)

A previous version of this EBS report was published in *Current Oncology*:
Imrie K, Esmail R, Buckstein R, Berinstein N, Meyer R, Zahra HA, et al. Use of rituximab in the treatment of lymphoma: an evidence summary. Curr Oncol. 1999;6(4):228-35.

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A complete list of the members of the Hematology DSG and the Working Group, with their affiliations and conflict of interest information, is provided Appendix 7.

Guideline 6-8 Version 3: Section 4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Rituximab in Lymphoma and Chronic Lymphocytic Leukemia: Version 3

Development Methods, Recommendations Development and External Review Process

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Report Date: March 31, 2015

FORMATION OF WORKING GROUP

The Hematology Disease Site Group (DSG) asked the PEBC to develop a guideline on the use of rituximab for lymphoma and chronic lymphocytic leukemia (CLL). In consultation with the Hematology DSG; a Working Group was identified from the DSG membership. This Working Group consisted of five medical oncologists and one methodologist. The Hematology DSG would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

OBJECTIVES AND RESEARCH QUESTIONS

This Working Group developed the following objective for this guideline in consultation with the Hematology DSG:

- **Provide an updated guideline on the use of rituximab in patients with lymphoma and CLL.**

From this objective, the following research questions were derived to direct the search for available evidence to inform recommendations.

Lymphoma

1. In patients with lymphoma of any type or stage, is rituximab used alone or in combination with chemotherapy more effective than nonrituximab-containing regimens for improving overall survival rates (OS), disease control (as assessed by measures such as progression-free survival rates [PFS], event-free survival rates [EFS], time-to-treatment failure [TTF], or response duration), response rate, or quality of life (QOL)?

2. What is the toxicity associated with the use of rituximab used alone or in combination with chemotherapy compared with nonrituximab-containing regimens?
3. Which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with nonrituximab-containing regimens?

Chronic Lymphocytic Leukemia

4. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with CLL? Outcomes of interest are OS, disease control (as assessed by measures such as PFS, EFS, TTF, or response duration), and response rate.
5. What is the toxicity associated with the use of rituximab?
6. Which patients are more or less likely to benefit from treatment with rituximab?

GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context" [183]. This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, a search was conducted of the Inventory of Cancer Guidelines (available at: http://www.cancerguidelines.ca/Guidelines/inventory/index.php), the National Guideline Clearing House (http://www.guideline.gov/), and the CMAJ Infobase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx), as well as of international guideline developers such as: NICE (UK) (http://www.nice.org.uk/guidance/index.jsp), SIGN (UK) (http://www.sign.ac.uk/guidelines/index.html), ASCO (US) (http://www.instituteforquality.org/practice-guidelines), National Health and Medical Research Council (Aus) (http://www.nhmrc.gov.au/publications/subjects/cancer.htm), and New Zealand Guidelines Group (http://www.nzgg.org.nz/index.cfm?fuseaction=fuseaction_10&fusesubaction=docs&documentid=22#Cancer). In addition, the Medline and Embase databases were searched for guidelines (see Appendix 2 for search strategies). Only guidelines published after 2011 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument.

Results of Guideline Review

The search for guidelines identified 10 guidelines [184-193]; of these, four were included after full-text review [185,191-193]; the remainder were excluded since they were two or more years old. The Working Group decided *a priori* not to endorse any of the existing guidelines, because none was focused on the context of Ontario. The included guidelines were used as a source of evidence.

EVIDENCE REVIEW DEVELOPMENT

Using the research questions described above, a search for existing systematic reviews and a systematic review of the primary literature was conducted, as described in Section 3 of this guideline.

INITIAL RECOMMENDATIONS

Using the evidence review in Section 3, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of

the aggregate evidence quality, the potential for bias in the evidence, and the likely benefits and harms of rituximab in patients with lymphoma and CLL. The members of the Working Group considered the values they used in weighing benefits compared with harms, and then made a considered judgement. This process is described in detail for each topic area described below.

Aggressive Histology B-cell Lymphomas

Key Evidence for Benefits and Harms

Previously Untreated Patients

Ten studies had a population of previously untreated patients [1-10]. These studies compared rituximab in combination with chemotherapy agents (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or CHOP-like) with chemotherapy alone. The studies indicated an overall benefit of adding rituximab without, for the majority of patients, greater adverse events (See Tables 2E and 2AE in Section 3).

A meta-analysis of six studies [2,5-7,9,11], detected that the rituximab combination improved EFS/failure-free-survival rates (FFS) (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.50 to 0.69; p<0.00001) (Figure 1, Section 3).

A meta-analysis of four studies [5-7,11] found that the rituximab combination improved PFS (HR, 0.54; 95% CI, 0.45 to 0.65; p<0.00001) (Figure 2, Section 3).

A meta-analysis of seven studies [2-6,10,12] detected that the rituximab combination improved overall survival rates (OS) (HR 0.67, 95% CI 0.58 to 0.77; p <0.00001)(Figure 3, Section 3).

The randomized trial reported by Ribrag et al [9], in abstract form, examined the effect of rituximab in patients with Burkitt lymphoma and detected a benefit for EFS (76% versus 64%; p=0.05) and OS (82% versus 71%; p=0.016) for patients administered the rituximab combination.

Except for the RICOVER-60 study [6], none of the included studies detected a statistically significant difference in adverse events. In the RICOVER-60 [6] study, patients allocated to the arm that received eight treatments of rituximab +-CHOP (R-CHOP) at two week intervals experienced significantly more anemia (p=0.001) and mucositis (p=0.03) when compared with patients in the arm that received six treatments of CHOP at two week intervals.

Patients with Relapsed/Refractory Disease

Two studies [13,14] with different populations presented contrasting results in this group. The HOVON-44 study [13] studied in patients who were rituximab-naïve and detected results in favour of rituximab for FFS (50% versus 24%; p<0.001), PFS (52% versus 31%; p<0.002), and complete response (CR) (46% versus 35%; p=0.003), but no statistically significant differences in OS (59% versus 52%; p=0.05). The study reported by Aviles et al [14] studied frail patients and did not find any statistically significant differences between the rituximab combination and the chemotherapy-only arm.

No statistically significant differences were reported for grade ≥3 adverse events by the authors of both studies.

Rituximab Maintenance Treatment

Four studies of patients with diffuse large B-cell lymphoma examined the efficacy of rituximab maintenance [4,88-90]. None of them detected a significant between-group difference at their longest follow-up for EFS. One study [4] reported a significant benefit of rituximab at 42, 66, and 108 months (HR, 0.78, 0.64; and 0.71, respectively), but none of the studies reported a significant difference in OS. In the E4494/C9793 study, a subgroup analysis found that rituximab maintenance significantly prolonged FFS in patients treated with CHOP, but not in patients treated with R-CHOP. None of the studies reported a significant difference in grade ≥3 adverse events except the E4494/C9793 study [4], which detected significantly greater rates of lymphopenia in patients treated with rituximab (p=0.008) (Table 4AE, Section 3).

Patients with Human Immunodeficiency Virus-Associated Lymphoma

The meta-analysis reported by Barta et al [17] forms the basis of the recommendation. In this meta-analysis, pooled individual patient data from 19 prospective studies detected that rituximab use was associated with improved outcomes for patients with CD4 counts ≥50 cells/μL for CR (odds ratio, 2.84; 95% CI, 1.60 to 5.02; p<0.001), for PFS (HR, 0.48; 95% CI, 0.32 to 0.72, p<0.001), for OS (HR, 0.55; 95% CI, 3.9 to 0.77; p<0.001). No association was observed for patients with CD4 count <50 cells/μL.

Barta et al [17] reported that death due to human immunodeficiency virus (HIV)-related causes did not significantly differ between patients treated with a rituximab combination versus controls (odds ratio [OR], 0.58; 95% CI, 0.30 to 1.12; p=0.14).

Aggregate Evidence Quality and Potential for Bias

The overall quality of the included studies was variable.

Recommendation 1

This recommendation covers first-line, second-line, and maintenance treatment for patients with aggressive histology B-cell lymphomas, including Burkitt lymphoma. It also covers first-line treatment for patients with human immunodeficiency virus (HIV)-associated lymphomas.

Previously Untreated Patients

a. Previously untreated patients with aggressive histology CD20-positive B-cell lymphomas who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including CHOP, CHOP-like, or similar dose-intense regimens) should receive this therapy in combination with rituximab.

Patients with Relapsed/Refractory Disease

b. For previously treated patients with aggressive histology CD20-positive B-cell lymphomas:
   i. There is insufficient evidence at this time to support treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated with a rituximab-containing chemotherapy regimen.
   ii. If patients have not previously received rituximab as part of their treatment regimen, the addition of rituximab to chemotherapy is reasonable.

Rituxmab Maintenance Treatment

c. There is insufficient evidence at this time to support the use of maintenance rituximab in aggressive histology B-cell lymphomas.

Patients with HIV-Associated Lymphomas

d. Previously untreated patients with HIV-related lymphoma who are candidates for treatment with curative intent, will receive combination chemotherapy with curative intent (including CHOP, CHOP-like, or similar dose-intense regimens) and, if they have a CD4 count ≥50/mm^3, should receive this therapy in combination with rituximab. The addition of rituximab to chemotherapy in patients with CD4 <50/mm^3 is not recommended.

Indolent Histology B-cell Lymphomas

Key Evidence for Benefits and Harms

Overall, the studies of patients with indolent histology lymphoma [18-31] were clinically heterogeneous; therefore, no meta-analysis was conducted. A brief summary of the results follows; for more detailed numerical results see Section 3, Tables 5E and 5AE for previously untreated patients, and Tables 6E and 6AE for patients with relapsed/refractory disease.

Previously Untreated Patients.

Three studies detected a statistically significant benefit of rituximab for EFS [18,22,24] and four studies detected a benefit for PFS [18,23,27,34]. One study detected a statistically significant benefit of rituximab for disease-free-survival rates (DFS) [34] and one study in abstract form reported a nonsignificant difference in DFS [21]. Two studies, one in abstract form, reported a benefit of rituximab for time to next treatment [18,27]. The studies reported by Marcus et al [34], Hiddemann et al [33], and Lenz et al [32] reported statistically significant benefits for rituximab for TTF.

Six studies reported a statistically significant benefit for CR [18,22,24,32-34] while four studies reported nonsignificant difference for CR, for overall response, or for both [21,24,26,35].

Five studies reported a nonsignificant difference in OS [21,22,24,27,32] and four studies reported a statistically significant benefit in OS for patients allocated to the rituximab arm [18,33-35].

The majority of the studies did not report on grade ≥3 adverse events or reported nonsignificant between-group differences. Three studies reported a statistically significant higher rate of lymphopenia in the rituximab arm compared with the chemotherapy-alone arm [22,26,32]. One study reported a higher rate of infections and neutropenia [21], and one study reported a higher rate of thrombocytopenia, in the rituximab arm compared with chemotherapy alone [35]. One study reported a statistically significant difference in cardiac toxicity [23] in patients treated with rituximab, while no statistically significant differences were reported for neurologic toxicities, nausea, and vomiting [23,26,33].

Patients with Relapsed/Refractory Disease.

Five studies [28,31,36-38] were included. The CALBG 50401 study [31] detected a benefit for the combination rituximab and lenalidomide compared with lenalidomide alone. The FIT [28], the GLSG [37], and the EORTC20981 [38] detected a significant benefit of rituximab and various chemotherapy regimens compared with chemotherapy alone at follow-ups ranging from 2.5 to 7.3 years. The FIT study [28] and the Witzig et al study [36] had contrasting results for time to next treatment: while the FIT study [28] detected a statistically significant benefit for added rituximab at 66 and 87.6 months, Witzig et al [36] detected no between-group difference at 48 months. As well, the studies that reported on OS had contrasting results: the GLSG study [37] detected a three-year estimated significant benefit for the rituximab combination, while the FIT [28] and the EORTC20981 [38] studies reported a nonsignificant between-group difference. Three studies reported a statistically significant benefit of rituximab in CR [36-38], or in overall response [36,38]. None of the included studies detected any significant grade ≥3 adverse events, except for the GLSG study, which reported statistically significant rates of grade ≥3 lymphopenia.

Aggregate Evidence Quality and Potential for Bias

The overall quality of the studies included for the relapsed/refractory population was moderate to high.

Recommendation 2

This recommendation covers first-line, second-line, and maintenance treatment for patients with indolent histology B-cell lymphomas. It also addresses patients with asymptomatic CD20-positive B-cell lymphomas.

Previously uUtreated Patients

a. Previously untreated patients with indolent histology CD20-positive B-cell lymphomas, excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive their chemotherapy in combination with rituximab.
b. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who are candidates for therapy, but not combination chemotherapy, rituximab monotherapy is a reasonable option.

Patients with Relapsed/Refractory Disease

c. For previously treated patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL:
   i. Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab or as rituximab monotherapy.
   ii. Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Rituximab Maintenance Treatment

d. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Patients with Asymptomatic CD20-Positive B-Cell Lymphomas

e. There is insufficient evidence at this time to support or refute upfront treatment with rituximab monotherapy for asymptomatic indolent histology CD20-positive B-cell lymphomas.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Key Evidence for Benefits and Harms

Studies of Previously Untreated patients

Four randomized controlled trials [40-43] were reviewed. This body of evidence indicates a benefit with the use of rituximab in addition to fludarabine-based chemotherapy and cyclophosphamide, when compared with chemotherapy alone (see Section 3, Table 9E for numerical results). Grade 3 or 4 neutropenia and leukocytopenia have been reported [42], however, these counts were significantly less than those seen with other monoclonal antibodies [41] (see Section 3, Table 9AE for numerical results).

Studies of Patients with Relapsed/Refractory Disease

Two studies [44,45], represented by six publications, were included. This body of evidence indicates a benefit with the use of rituximab in addition to fludarabine-based chemotherapy, when compared with chemotherapy alone (see Section 3, Table 9E for numerical

results). The included studies did not detect any statistically significant between-group difference in grade 3 or 4 adverse events.

Aggregate Evidence Quality and Potential for Bias

The overall quality of the studies of first-line treatment was high, although all of the studies were open label. Among the studies of second-line treatment, one was a phase II smaller study [44] and the other [45] was considered to be of moderate quality because it was at risk for selection bias.

Recommendation 3

This recommendation covers first- and second-line treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.

Previously Untreated Patients

a. Patients with previously untreated CLL/SLL who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.
b. In patients with previously untreated CLL/SLL who are appropriate candidates for chlorambucil chemotherapy, the addition of rituximab can be considered.

Patients with Relapsed/Refractory disease

c. Patients with relapsed or refractory CLL/SLL who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.

Rituximab-Induced Hepatitis B Virus Reactivation

Key Evidence for Benefits and Harms

Rituximab is associated with a substantial risk of hepatitis B virus (HBV) reactivation. Reactivation has been reported in patients with chronic HBV (HBsAg positive) and in patients with resolved HBV (HBsAg negative/HBcAb positive). Viral reactivation can occur during rituximab treatment or up to 18 months beyond completion of rituximab [46,47]. Antiviral therapy has been shown to prevent reactivation [47]. Huang et al [47] found that after 18 months of follow-up there was a significant benefit of antiviral prophylactic therapy in preventing HBV reactivation in patients treated with rituximab (2.4% in the entecavir group versus 17.9% in the control, p=0.027).

Aggregate Evidence Quality and Potential for Bias

The systematic review included mostly retrospective studies, and did not perform an assessment of the quality of the included studies. The randomized controlled trial was at moderate to high risk of bias because the authors did not report how the random sequence was generated, did not report whether allocation was concealed, and did not blind patients, clinicians or outcome assessors. Overall, this body of evidence is consistent in indicating that treatment with rituximab can cause reactivation of HBV, and this can lead to very severe adverse effects, including death of the patients.

Recommendation 4

This recommendation covers all patients to be treated with rituximab who have hepatitis B virus.

The Hematology DSG recommends that all patients be screened for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) prior to treatment with rituximab. Consultation with an expert in HBV should be considered for all patients who test positively for HBV. Patients who are HBsAg-positive should receive prophylactic antiviral therapy during and after rituximab. Patients who are HBsAg-negative/HBcAb-positive should be considered for either prophylactic antiviral therapy, close monitoring for viral reactivation, or should be followed by an expert in HBV. In the absence of active hepatitis (elevated transaminases), it is not usually necessary to delay rituximab. In most cases, HBV screening and management can occur in parallel with non-Hodgkin lymphoma/CLL treatment.

VALUES OF THE WORKING GROUP

The Working Group aimed to make this guideline widely applicable across patient populations and settings. The members of the Group value the effectiveness of rituximab in extending life, in prolonging time without progression in previously untreated patients with aggressive disease, including Burkitt lymphoma and HIV-associated lymphoma. The members of the Group value the effectiveness of rituximab-based induction and maintenance therapy in extending life and prolonging progression in patients with indolent lymphoma. In the subgroup of patients with CLL/SLL, the Group again identified evidence of improved disease control when rituximab was added to fludarabine-based chemotherapy or chlorambucil. The benefit attained with rituximab was believed to be clinically meaningful, in alignment with patient preferences, and associated with reasonable and manageable toxicity. To further minimize the potential toxicity associated with rituximab, the Group members believed it was important to emphasize the risk of hepatitis B reactivation and the measures to prevent this complication.

The Working Group members phrased these statements in a more general and inclusive way than they were worded in the previous version of this guideline, to facilitate implementation.

Considered Judgement

The new evidence available indicates that rituximab is an effective agent with a favourable toxicity profile, and it can extend life and PFS/EFS in previously untreated patients. At the present time, not enough good-quality, consistent evidence is available to formulate a recommendation for previously treated patients. Of note, as compared with the previous version of this document, is the change in direction of the recommendation regarding patients with HIV-associated lymphomas. The new version of this recommendation is supported by the individual patient data meta-analysis reported by Barta et al [17].

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel (RAP). The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Hematology DSG acted as the Expert Panel for this document. The members of this group were required to submit conflict-of-interest declarations prior to reviewing the document. These declarations are described in Appendix 7. The document was approved by formal vote. To be approved, 75% of the Hematology DSG membership must cast a vote or abstain, and of those that vote 75% must approve the document. On November 6, 2014 the Hematology DSG reviewed the document and 80% of the DSG membership cast a vote (20 of 25), either face-to-face or by email. All the voters approved the document as is.

Report Approval Panel Review and Approval

The purpose of the RAP review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document; the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In December 2014 the RAP reviewed this document. The RAP approved the document, and made a few suggestions for improvement. Key issues raised by the RAP are listed in Table 13 with the response of the Working Group:

Table 13. Comments of the Report Approval Panel and responses by the Working Group

RAP members' suggestions	Response by the Working Group
Consider a page with just the recommendations	A front section was added with just the recommendations. The document is now composed of four sections.
Recommendation 4 specifically discusses the risk of HBV reactivation. Although some of the research questions aim at discussing the toxicity profile of rituximab in the studied population, the authors should have a specific objective addressing this question, or at least a specific mention of this toxicity in the research questions.	The term "toxicity" was changed to "adverse events" in research question 2. This more inclusive term better describes events such as HBV reactivation.
Although long, the front end of this document is very clearly written (congratulations to the writer) in contrast to the Discussion where points were being made but it wasn't always clear what the recommendation was. It might be clearer if each paragraph, like the early ones in this section, comments on the issues, the findings and the subsequent recommendation. Many paragraphs are missing the final recommendation and I find myself going back to section 1 to figure out where the group landed on each issue.	The discussion was partly rewritten to incorporate recommendations for each section.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Hematology Disease Site Group circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, five targeted peer reviewers from Ontario who are considered clinical and/or methodological experts on the topic were identified by the Working Group and the Hematology DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and asking whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on January 14, 2015. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Hematology DSG reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. All all medical oncologists and hematologists in the PEBC database were contacted by email to inform them of the survey. One hundred and fifteen individuals were from Ontario and one from New Brunwick. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidence review (Section 2). The notification email was sent on January 14, 2015. The consultation period ended on February 25, 2015. The Hematology DSG reviewed the results of the survey.

Results

Targeted Peer Review

Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 14.

Table 14. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**				67%	33%
2. **Rate the guideline presentation.**				33%	67%
3. **Rate the guideline recommendations.**			33%	33%	33%
4. Rate the completeness of reporting.				100%	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				67%	33%
6. Rate the overall quality of the guideline report.	NA*	NA	NA	NA	NA
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				67%	33%
8. I would recommend this guideline for use in practice.		33%		67%	
9. What are the barriers or enablers to the implementation of this guideline report?		33%	33%	33%	

* NA = not applicable.

Summary of Written Comments and Working Group Responses

The main points contained in the written comments and the responses of the Working Group are presented in Table 15.

Table 15. Summary of Targeted Peer Reviewers written comments and responses by the Working Group

Item	Comment	Response
1	Patients and external consultants were not involved. The guidelines do not include all relevant study results, or consider alternative chemotherapy partners for rituximab. Overall, the studies considered prove a role for rituximab with chemotherapy (relative to chemotherapy alone) in several disease situations, but do not prove the best or only chemotherapy partner for rituximab. This issue is neglected by the group that developed the guideline, and as a result, will adversely impact patient care and outcomes.	A patient representative is a member of the Disease Site Group (see Appendix 7B), and reviewed and approved the document at the internal review stage. This evaluation is part of external review. The ideal chemotherapy partner or combination was outside the scope of this review.

2	The guidelines for initial therapy of aggressive B-cell lymphoma, as well as initial therapy and subsequent therapy for indolent B-cell lymphoma are clinically sound and appropriate. The guidelines for CLL omit important studies related to other chemotherapy partners for rituximab, especially bendamustine. The guideline provides only two alternative regimens for patients with CLL: R-fludarabine (i.e. FCR) for very fit healthy patients, and R-chlorambucil for frail patients. The majority of patients with CLL, however, are neither very fit, nor frail, and therefore, are inappropriately managed with either FCR or CBL-R. The German CLL8 and CLL11 studies prove beneficial effects of adding rituximab to chemotherapy, and support numerous other studies demonstrating benefits of R-chemo for every other CD20 lymphoid malignancy, regardless of chemotherapy partner. It stands to reason, therefore, that adding rituximab to other partners, such as bendamustine, will also improve outcome relative to that chemotherapy alone. There is no rationale to conclude otherwise. That extrapolation is completely supported by evidence-based medicine practice. In addition, there are studies to show that bendamustine provides superior response rates and PFS compared with chlorambucil, BR gives higher CR rates than CBL-R without added adverse effects (interim analysis of MABLE RCT) and BR gives similar PFS and OS with far fewer adverse effects than FCR for "fit" patients with CLL over age 65 years (CLL10). To avoid considering BR as an initial treatment option for patients with CLL will result in substandard care of CLL within Ontario, and adversely impact patient outcome.	The ideal chemotherapy partner or combination for rituximab was outside the scope of this review.
3	Guidelines are clear on the use of rituximab but do not elaborate enough on the management of these cancers in general so that their use as a guideline for the care of individual patients is limited.	General lymphoma management was outside the scope of this guideline that was looking only at rituximab.
4	Some important studies and treatment alternatives are missing.	We captured all available randomized controlled studies through the PEBC methodology.
5	Key issue is the translation of recommendations to funding in Ontario.	Translation of recommendations to funding in Ontario is outside the scope of our mandate.
6	As listed above, does not give a detailed approach to the treatment of patients with these diseases; rather, it gives general statements about the use of rituximab, which I realize is the objective of the exercise. However, in daily practice, more direction may be appreciated by physicians. For policy makers, this document is quite adequate and quite clear.	A detailed approach to the treatment of patients with these diseases will be the focus of clinical pathways that will be produced in the future.
	The guidelines for initial therapy of aggressive and indolent B-cell lymphomas have been implemented. The guidelines for relapsed aggressive B-cell lymphoma (not allowing rituximab with salvage chemotherapy for potentially curable transplant-eligible patients) and the guidelines for	The group members did discuss these indications. It was not felt that the randomized controlled data of rituximab alone or in combination versus

	initial therapy of CLL (not allowing BR) do not follow established practices in other Canadian provinces, or in other countries within the developed world. Physicians, patients, and lymphoma advocacy groups will be upset with these recommendations as stated in these guidelines.	some other therapy that did not include rituximab supported these indications at present, despite the practice in other jurisdictions.
	Was the rituximab maintenance data from NCIC LY12 (report in abstract form) in REL/REF aggressive CD20+ NHL missed?	This abstract was captured by the search but it was an interim report. Recommendations would not be based on an abstract report only.
	For recommendation 2E, wonder why the word "refute" is used since nowhere else where rituximab cannot be supported for use is "refute" used. Is there some stronger statement that is being made here? If so, it may be worth a more elaborate statement.	We used the wording "support or refute" to imply that there was insufficient evidence to guide the use of rituximab at present. The wording was meant to imply the uncertainty in the evidence to guide a stronger recommendation.
	For the Ribrag study, it is not clear what the study design is. Since it is the only comparative study, perhaps it warrants a small statement to understand the basis for use of rituximab in Burkitt lymphoma, data people are generally less familiar with.	The Ribrag study was identified in the tables as a phase III randomized controlled trial (RCT); we added this specification also in the text.

Professional Consultation

Nine responses were received. Key results of the feedback survey are summarized in Table 15.

Table 15. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment*	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	1 (11%)	0	2 (22%)	5 (56%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	1 (11%)	0	2 (22%)	5 (56%)
3. I would recommend this guideline for use in practice.	0	1 (11%)	0	3 (33%)	4 (44%)

* One respondent rated not applicable for all questions

4. What are the barriers or enablers to the implementation of this guideline report?

1) Some funding gaps would need to be closed.
2) None
3) Lack of guidance for use of rituximab with newer therapies, now becoming the standard of care: bendamustine, idelalisib,...
4) Need to revise CCO guidelines in CLL/SLL.

Summary of Written Comments

The main points contained in the written comments were:

1) Excellent.
2) It would be useful to be more explicit about relapsed/refractory low-grade disease. My interpretation of the principles in Recommendation 2 c(ii) and 2(d) suggest that rituximab can be used past second-line and that maintenance can be repeated after a reresponse. If my interpretation is correct, these are currently areas where there are funding gaps and would benefit from clarity.
3) An excellent report. I agree with the vast majority of it. Here are a couple of points for consideration. 1) There is insufficient evidence to rule out a benefit for rituximab in the treatment of relapsed aggressive CD20+ ?B cell lymphoma and its use is standard in many places, despite there being no level I evidence of its benefit as stated in the report (although there is some evidence - e.g., post hoc analysis of LY.12). 2) Do you really want to exclude patients in Ontario with HIV+ lymphoma and a low CD4 count from access to rituximab, given the overwhelming evidence of the drug's benefit in every other situation, the changing landscape of HIV therapy over time, the relatively small budget impact/patient numbers, and the very limited quality of evidence that it is not effective in this setting? This may be unwise.
4) There is no comment made about bendamustine-rituximab as front line therapy for indolent lymphoma despite the fact that there are two randomized trials published on this in comparison to other forms of chemo. This must be included in order to be up to date.
5) No discussion of what to do in hepatitis B positive for prophylaxis (i.e., HbC, HepB Sag, that must be done pre-rx , how it should be prophylaxed and in whom) monitoring of viral load etc..
6) No discussion of how to handle hepatitis C

Modifications/Actions

No further modificiation.

Conclusion

This report reflects the integration of feedback obtained through the external review process with final approval given by the Hematology DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Conflict of Interest

In accordance with the PEBC Conflict of Interest Policy, the guideline authors, the Hematology DSG Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Declarations of conflict of interest are reported in Appendix 7.

Contacting the Hematology DSG

Contact information for the Disease Site Group members can be found at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/hema-ebs/hema-dsg/

APPENDICES

Appendix 1. Guideline report history.

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Evidence Summary 1999	1966-1999	Full Report	Web publication Journal publication	Not applicable
Original version 2 December 2006	1966-2006	Full Report	Web publication Journal publication	This document replaced the evidence summary that was completed in 1999
Updated search March 2012	2006- 2012	Full Report	Web publication	This document integrates data included in all previous reports with new data
Present report 2015	2012-2013			

Appendix 2. Search strategies.
Literature Search Strategy:

MEDLINE
Lymphoma
1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp lymphoma/
42. lymphoma.mp.
43. 41 or 42
44. rituxan.mp.

45. rituximab.mp.
46. ritux:.mp.
47. idec.mp.
48. 44 or 45 or 46 or 47
49. c2b8.mp.
50. c2b?.mp.
51. anti-cd20.mp.
52. anticd20.mp.
53. mabthera.mp.
54. 49 or 50 or 51 or 52 or 53
55. 48 or 54
56. 43 and 55
57. 40 and 56
58. (200606: or 2007: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
59. 57 and 58

MEDLINE: **CLL**

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32

34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp leukemia/
42. chronic lymphocytic leukemia.mp.
43. chronic lymphocytic leukaemia.mp.
44. CLL.mp.
45. 41 or 42 or 43 or 44
46. rituxan.mp.
47. rituximab.mp.
48. ritux:.mp.
49. idec.mp.
50. 46 or 47 or 48 or 49
51. c2b8.mp.
52. c2b?.mp.
53. anti-cd20.mp.
54. anticd20.mp.
55. mabthera.mp.
56. 51 or 52 or 53 or 54 or 55
57. 50 or 56
58. 45 and 57
59. 40 and 58
60. (200606: or 2007: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
61. 59 and 60

EMBASE
Lymphoma:
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/

21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp lymphoma/
37. lymphoma.tw.
38. 36 or 37
39. rituxan.tw.
40. rituximab.tw.
41. ritux:.tw.
42. idec.tw.
43. 39 or 40 or 41 or 42
44. c2b8.tw.
45. c2b?.tw.
46. anti-cd20.tw.
47. anticd20.tw.
48. mabthera.tw.
49. 44 or 45 or 46 or 47 or 48
50. 43 or 49
51. 38 and 50
52. 35 and 51
53. (200606$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
54. 52 and 53

EMBASE – CLL

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/

17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp leukemia/
37. exp lymphocytic/
38. exp chronic/
39. 36 and 37 and 38
40. chronic lymphocytic leukemia.tw.
41. CLL.tw.
42. 39 or 40 or 41
43. rituxan.tw.
44. rituximab.tw.
45. ritux:.tw.
46. idec.tw.
47. 43 or 44 or 45 or 46
48. c2b8.tw.
49. c2b?.tw.
50. anti-cd20.tw.
51. anticd20.tw.
52. mabthera.tw.
53. 48 or 49 or 50 or 51 or 52
54. 47 or 53
55. 42 and 54
56. 35 and 55
57. (200606$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
58. 56 and 57

Search for rituximab in HIV and Brukitt lymphoma: Medline

Search Strategy: Executed on July 2, 2012

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1 *Antibodies, Monoclonal/tu [Therapeutic Use]
2 ritux:.mp.
3 idec.mp.
4 c2b8.mp.
5 c2b?.mp.
6 anti-cd20.mp.
7 anticd20.mp.
8 mabthera.mp.
9 human immunodeficiency virus.mp. or exp HIV/
10 HIV.tw.
11 (acquired immune deficiency syndrome or aids).tw.
12 exp Acquired Immunodeficiency Syndrome/
13 lymphoma, aids-related/
14 burkitt lymphoma/ or burkitt.tw.
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
16 (9 or 10 or 11 or 12) and 13
17 15 and (14 or 16)
18 limit 17 to english language
19 17 not 18
20 limit 18 to (addresses or autobiography or bibliography or biography or case reports or dictionary or directory or in vitro or interview or legal cases or legislation or letter or newspaper article or patient education handout or periodical index or portraits or video-audio media) (64)
21 animal/ not (animal/ and human/)
22 18 not 20
23 22 not 21

Search for rituximab in HIV and Brukitt lymphoma: Embase

Search Strategy:

---

1 ritux:.tw.
2 idec.tw.
3 c2b8.tw.
4 c2b?.tw.
5 anti-cd20.tw.
6 anticd20.tw.
7 mabthera.tw.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Human immunodeficiency virus infection/ or human immunodeficiency syndrome.mp.
10 exp acquired immune deficiency syndrome/
11 aids.mp.
12 Burkitt lymphoma/ or lymphoma/
13 aids related lymphoma.mp.
14 burkitt.tw.
15 9 or 10 or 11 or 12 or 13 or 14
16 8 and 15
17 limit 16 to english language
18 limit 17 to (editorial or letter or note or short survey or trade journal)
19 17 not 18
20 animal/ not (animal/ and human/)
21 19 not 20

Appendix 3A. Recommendations of Version 2 of this guideline.

Recommendations

Lymphoma

d. Previously untreated patients with diffuse large B-cell lymphoma (DLBCL), or a variant of DLBCL (such as mediastinal sclerosing B-cell lymphoma, T-cell–rich B-cell lymphoma, Burkitt-like lymphoma, or intravascular lymphoma), who are candidates for treatment with curative intent and will receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), should receive this therapy in combination with rituximab. This grouping includes patients with untreated DLBCL that has transformed from follicular or other indolent lymphoma.

e. There is insufficient evidence at this time to support or refute treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated for diffuse DLBCL or a variant of DLBCL.

f. There is insufficient evidence to support combining rituximab with chemotherapy when treating patients with human immunodeficiency virus (HIV)-related lymphoma. These patients may be at an increased risk for life-threatening infections when rituximab is combined with CHOP.

g. Previously untreated patients with follicular or other indolent B-cell–histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab.

h. For patients with follicular lymphoma or other indolent B-cell lymphomas who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

i. For previously treated patients with follicular or other indolent B-cell–histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding SLL:

iii. Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.

iv. Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration to the last rituximab administration and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.

Chronic Lymphocytic Leukemia

j. There is insufficient evidence at this time to support or refute the use of single-agent rituximab or a rituximab-containing chemotherapy regimen in patients with CLL.

Qualifying Statements

k. Rituximab has a favourable single-agent toxicity profile. The addition of rituximab to chemotherapeutic regimens such as cyclophosphamide, vincristine, and prednisone (CVP), CHOP, and fludarabine, cyclophosphamide, and mitoxantrone (FCM) does not appear to significantly alter the toxicity of these regimens in lymphoma.

l. Rituximab should be administered at a dose of 375 mg/m^2 and given at the beginning of each treatment cycle of chemotherapy.

m. There is significant variability in the published administration schedules for rituximab maintenance. The DSG felt that the regimen studied by the EORTC/Intergroup (rituximab 375mg/m^2 every 3 months until relapse or 2 years) was a reasonable and convenient option. Maintenance rituximab should be initiated within 8 weeks of completion of the induction regimen.

n. Prolonged rituximab therapy may be associated with hypogammaglobulinemia. Immunoglobulin quantitation was a common monitoring strategy in the pivotal clinical trials and should be considered for patients receiving maintenance therapy.

o. In the absence of randomized data evaluating the role of rituximab re-treatment, the recommendation that rituximab be reused in combination with chemotherapy is based on the consensus opinion of the Hematology Disease Site Group.

- There is a rapid availability of new data regarding the role of rituximab in treating these diseases. Practitioners and patients are advised to review the Web site of Cancer Care Ontario's Program in Evidence-based Care (PEBC) to learn the status of this practice guideline.

Key Evidence

Lymphoma

- A total of 22 randomized controlled trials were identified: 9 trials assessed patients with aggressive histology and 13 assessed patients with indolent histology. Three trials in aggressive histology were published in article form, as were seven trials in indolent histology; all remaining reports were preliminary publications in abstract form. The Hematology DSG was compelled by these data despite the limitation of their being primarily in abstract form.
- In one randomized trial comparing CHOP plus rituximab (CHOP-rituximab) with CHOP alone in previously untreated patients with DLBCL (aged 60 to 80 years), complete response, disease control (event-free survival), and overall survival were superior in patients allocated to receive CHOP-rituximab. In another randomized (reported in abstract form) comparing CHOP-14 (administered every 14 days) plus rituximab with CHOP-14 alone in patients aged 65 and older with DLBCL, mantle cell lymphoma, or grade III follicular lymphoma, disease control (event-free survival) and overall survival were again superior in the R-CHOP-14 group. A third randomized trial in elderly patients (age 61 to 80 years) with DLBCL similarly randomized patients to R-CHOP-14 vs. CHOP-14 and demonstrated improved disease control (freedom from treatment failure). No difference in overall survival has been detected in the preliminary analysis of this trial (presented in abstract form).
- In one randomized trial comparing CHOP-rituximab with CHOP alone (reported in abstract form), in previously untreated patients with DLBCL (age 60 years and greater), disease control (time-to-treatment failure) was superior in patients allocated to receive CHOP-rituximab. No difference between randomized groups in overall survival was detected. In that trial, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or observation. Disease control (time-to-treatment failure) was superior in patients allocated to receive rituximab; no difference between randomized groups in overall survival was detected.
- In one randomized trial of younger patients (age 60 and younger) with low-risk DLBCL (reported in abstract form), patients received CHOP-like chemotherapy with or without rituximab. Disease control (time-to-treatment failure), and overall survival were superior in patients that received rituximab in addition to chemotherapy compared to patients that received chemotherapy alone.
- In a randomized trial of CHOP-rituximab compared with CHOP alone in patients with previously untreated human immunodeficiency virus (HIV)-related lymphoma, no overall survival benefit was derived from the addition of rituximab therapy. Although there was a trend to improvement in the primary outcome of response rate for R-CHOP, this benefit was offset by a statistically significant increased risk of treatment-related infectious death.
- In three trials comparing chemotherapy with or without rituximab in previously untreated patients with advanced-stage follicular lymphoma, disease control (time-to-treatment failure, time to progression, or two-year event-free survival) was superior in patients allocated to receive rituximab. An overall survival benefit was demonstrated with rituximab-based therapy in one full publication report, despite a brief median follow-up period of only 18 months. In another study, a strong trend to improved overall survival in the rituximab arm has been reported. An aggregate-data meta-analysis including these data has also confirmed an overall survival benefit in patients treated with rituximab and chemotherapy.
- In one trial comparing FCM to FCM-R in previously treated patients with indolent lymphomas, response rate, disease control (progression-free survival) and overall survival were superior in patients allocated to receive FCM-R. In another trial comparing CHOP to CHOP-R in patients with follicular lymphoma relapsed or resistant to a maximum of two non-anthracycline regimens, complete response and disease control (three-year progression-free survival) were superior in patients allocated to receive CHOP-R compared to patients that received CHOP alone. In both trials, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or observation. Disease control (response duration or progression-free survival) was superior in patients allocated to receive maintenance rituximab; overall survival was not reported in the abstract reports of these studies.
- In one randomized trial comparing maintenance rituximab to observation in patients with untreated indolent lymphoma who initially responded to CVP induction, disease control (progression-free survival) and overall survival were superior in patients allocated to receive rituximab maintenance.
- There were no trials that compared chemotherapy to the same chemotherapy plus rituximab in patients who had previously received rituximab and achieved a response duration of at least one year. Two randomized trials comparing chemotherapy plus rituximab to chemotherapy alone in patients previously treated with rituximab alone showed improvement in survival or progression-free survival. One randomized trial that compared maintenance rituximab to re-treatment with rituximab at disease progression following induction treatment with rituximab monotherapy, reported a response rate for re-treatment that was comparable to first-line treatment.
- No important additional hematologic or non-hematologic toxicities were observed when rituximab was combined with chemotherapy.

Chronic Lymphocytic Leukemia

- No randomized controlled trials were located.

Appendix 3B. Supporting evidence for the recommendations: Version 2.

Table 1. Randomized controlled trials evaluating chemotherapy plus rituximab versus nonrituximab regimens in aggressive histology lymphoma.

Author, Type of Study	N rand	Patients	Treatment[A]	Follow-up Time	Response Rate[B]	Disease Control[B]	Overall Survival Rate[B]	Comments
Coiffier [11], full Feugier [98], full, update	399	Untreated DLBCL[CD], age 60 to 80 y	R-CHOP vs. CHOP[E]	Median 24 mo Median 5 y	76% vs. 63%; p=0.005 (CR+CRu)	2 y EFS: 57% vs. 38% ; p<0.001[F] 5 y EFS: 47% vs 29% ; p=.00002	At 2 y: 70% vs. 57% ; p=0.007[F] 5 y: 58% vs 45% ; p=.0073	ITT analysis with all randomized patients
Habermann [194], abstn	632	Untreated[G] DLBCL, age ≥60 y	R-CHOP vs. CHOP[E] MR vs. observation for responders	Median 2.7 y	77% vs. 76%[H]; p=0.76 N/A	TTF superior in R-CHOP[FI]; p=0.025 TTF superior for MR; p=0.01	p=0.25[FI] p=0.67	Eval: 540 patients for induction; 348 patients for maintenance.
Sonneveld [195], abst	250	Untreated DLBCL, mantle cell lymphoma, FL grade III, intermediate/high-risk IPI, age ≥65 y	R-CHOP-14 vs. CHOP-14	Median 4 mo[J]	NR	EFS superior in R-CHOP-14[I]; p-value NR	OS superior in R-CHOP-14[I]; p-value NR	Eval: 171 patients at first interim analysis
Pfreundschuh [196], abst	1300[KL]	Untreated DLBCL, age 61-80y	R-CHOP-14 vs. CHOP-14	Median 26 mo	NR	FFTF superior in R-CHOP-14[FI]; p=0.000025	At 26 mo: 74% vs. 78%; p=0.13	Eval: 828 patients
Pfreundschuh [197], abst	824	Untreated DLBCL, IPI 0-1, age 18 to 60 y	CT[M] + R vs. CT[M]	Median 24 mo	85% vs. 65%; p<0.005 (CR)	2 y TTF: 79.9% vs. 60.8%; p=0.000000007[F]	95% vs. 86%; p=0.0002[F]	Eval: 823 patients
Kaplan [91], full	150[N]	Untreated HIV lymphoma (aggressive B-cell)	CHOP-R (+R maint for patients with CR or PR) vs. CHOP[E]	Median 137 wk	57.6% vs. 47.0%; p=0.147 (CR+CRu)	Median PFS: 45 vs. 38 wk; p=0.67	Median: 139 vs. 110 wk; p=0.76	Age range: 26 to 73y
Van Heeckeren [198], full	34	B-cell NHL – high-risk, relapsed, or transformed disease – undergoing HDC and ASCT (aggressive histology, n=17; indolent histology, n=10)	*In vivo* purge with premobilisation R vs. *ex vivo* CD34+ cell enrichment using immuno-magnetic beads[E]	Median 796 days	N/A	2 y EFS: 81% vs. 76%; p=0.66	3 y OS: 67% vs 100%; p=0.16	Eval: 27 patients
Pohlman [8], abst	76	B-cell NHL eligible for ASCT	Premobilisation R vs. no R premobilisation	Median 39 mo	N/A	No difference in PFS at 39 mo; p-value NR	No difference in OS at 39 mo; p-value NR	Eval: 55 patients
Maintenance therapy								
Habermann [194], abst	632	Untreated[G] DLBCL, age ≥60 y	R-CHOP vs. CHOP[E] MR vs. observation for responders	Median 2.7 y	77% vs. 76%[H]; p=0.76 N/A	TTF superior in R-CHOP[FI]; p=0.025 TTF superior for MR; p=0.01	p=0.25[FI] p=0.67	Eval: 540 patients for induction; 348 patients for maintenance.

Haioun [199], abst	269	DLBCL, 2 mo post-ASCT (+HDC), age <60 y	R vs. obs post-ASCT[L]	Median 3 y	N/A	3 y EFS: 80% vs. 72%; p=0.10	NR	high-risk patients (aaIPI 2 or 3)

aaIPI=adverse age-adjusted International Prognostic Index factors; abst=abstract; ASCT=autologous stem cell transplantation; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP-14=CHOP administered every 14 days; CR=complete response; CRu=unconfirmed CR; CT=chemotherapy; DLBCL=diffuse large B-cell lymphoma; EFS=event-free survival rate; eval=evaluable; FFTF=freedom from treatment failure; FL= follicular lymphoma; full=full paper; HDC=high-dose consolidative chemotherapy; HIV=human immunodeficiency virus; IPI=International Prognostic Index factor; ITT=intention-to-treat; maint=maintenance; mo=month(s); MR=maintenance rituximab; N=number; N/A=not applicable; NHL=non-Hodgkin's lymphoma; NR=not reported; obs=observation; OS=overall survival rate; PFS=progression-free survival rate; PR=partial response; R=rituximab; rand=randomized; R-CHOP=rituximab plus CHOP; RR=response rate; TTF=time-to-treatment failure; vs.=versus; wk=week(s); y=year(s).

[A]Treatment details are provided in Appendix 1.

[B]Data provided in order of intervention versus control.

[C]Of patients with central pathologic review (n=385), 87% had confirmed DLBCL.

[D]Some patients with T-cell lymphoma (exclusion criterion) were discovered on central pathologic review.

[E]No difference between groups for baseline/clinical characteristics.

[F]Log-rank.

[G]Information provided in study protocol (Protocol ID E-4494, date last modified 2002-03-01; National Cancer Institute Clinical Trials, http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=65935&version=HealthProfessional &protocolsearchid=1000667).

[H]Overall RR; no definition provided.

[I]Data in each arm not provided.

[J]Median time off protocol.

[K]Authors did not indicate whether groups similar at baseline.

[L]1300 patients recruited. Authors did not indicate number of patients randomized.

[M]CT included CHOP-21, CHOEP-21 (cyclophosphamide, doxorubicin, etoposide, vincristine , prednisone, administered every 21 days), MACOP-B (methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, bleomycin), or PMitCEBO (prednisolone, mitoxantrone, cyclophosphamide, etopside, belomycin, vincristine); doses and schedules not reported.

[N]Randomized in 2:1 ratio in favour of rituximab.

Table 2. Randomized controlled trials evaluating chemotherapy plus rituximab versus nonrituximab regimens in indolent histology lymphoma.

Author, Type of Study	N rand	Patients	Treatment[A]	Follow-up Time	Response Rate[B]	Disease Control[B]	Overall Survival Rate[B]	Comments
First-line therapy								
Marcus [34], full Solal-Celigny [200], abst	321	First-line follicular (stg III, IV)	CVP-R vs.CVP[C]	Median 42 mo	81% vs. 57%[D]; p<0.0001	Median TTP, 34 vs. 15 mo; p<0.0001[E]	3 y OS: 89% vs. 81%; p=0.07[E]	Age range: 27 to 80 y
Hiddemann [33], full	428	First-line follicular		Median 18 mo	96% vs. 90%; p=0.011	Median TTF, not reached in either group; TTF superior in R-CHOP group (relative risk 0.40); p<0.0001	Median OS not reached in either group; est probability of survival at 2 y, 95% vs. 90%; p=0.016	
Rivas-Vera [21], abst	195	First-line indolent	CNOP vs. CNOP-R vs. R[C]	NR	83% vs. 90% vs. 85%[D]; p=0.545	2 y DFS: 65% vs. 70% vs. 68%; p=0.93	2 y OS: 84% vs. 78% vs. 87%; p=0.89	Stg III, IV in analysis; eval 183. Age 25 to 85 y
Herold [118,201], prelim report/abst	358[FG]	First-line indolent NHL (follicular, mantle cell, and immunocytoma) (all stg III, IV)	MCP-R vs. MCP[C]	Accrual: 10/98 to 09/03	85.5% vs. 65.5%; p<0.0001 (CR+PR)	2 y EFS, 69% vs. 44%; p<0.001	NR	56% of patients had follicular NHL
Salles [202], abst	359	First-line follicular NHL (stage II to IV)	αIFN+CHVP-R vs. αIFN+CHVP	Median 30 mo	At 18 mo: 84% vs. 73%; p=0.004 (CR+PR)	2.5 y EFS, 78% vs. 62%; p=0.003	NR	Age 18 to 75 y
Buske [121], abst	72[F]	First-line lymphoplasmocytoid/ic immunocytoma	R-CHOP vs. CHOP[C]	Maximum 4 y	94% vs. 69%; p=0.012 (CR+PR)	Median TTF, not reached vs. 22 mo; p=0.0057	NR	Median age 61.5 y 24% of patients had IPI>2.
Lenz [32], full	128	First-line mantle cell lymphoma (stg III or IV)	R-CHOP vs. CHOP	Median 18 mo	94% vs. 75%; p=0.0054 (CR+PR)	Median TTF, 21 mo vs. 14 mo p=0.0131	2 y: 76% (both arms, p=0.93)	Eval: 62 R-CHOP, 60 CHOP Median age 61.5 y
Second-line or later therapy								
Forstpointner [37], full Dreyling [130], abst	147	Relapsed follicular and mantle Maintenance randomization described below (Dreyling 37)	FCM-R vs. FCM	Median 18 mo	79% vs. 58%; p=0.01 (CR+PR)	Median PFS, 16 vs. 10 mo; p=0.0381	Median, not reached vs. 24 mo; (p=0.0030	Eval: 128 patients; 10 patients had incomplete documentation, 9 patients withdrew after randomization prior to starting therapy Age 35 to 80 y
Van Oers [203], abst	461	Relapsed/ resistant[Q] follicular NHL (stg III or IV)	R-CHOP vs. CHOP	NR	CR after induction: 30.4% vs. 18.1%; p=0.0004	3 y PFS 67.7% vs. 31.2%; p<0.0001	NS	Eval: 369 patients for induction response;

Author, Type of Study	N rand	Patients	Treatment[A]	Follow-up Time	Response Rate[B]	Disease Control[B]	Overall Survival Rate[B]	Comments
		Maintenance randomization described below (Van Oers 38)						268 patients for maintenance
Maintenance therapy								
Hochster 2005 [204], abst	304	**Untreated,** advanced indolent NHL (stg III to IV follicular grade 1 to 2 and SLL)	CVP	R maint vs. obs[L],	Median 3 y	PFS superior in R maint group; HR=0.38; p=3x10^{-8}. FL only: 4 y PFS, 56% vs. 33%; p-value NR	OS superior in R maint group; HR=0.66, p=0.09. FL only: 4 y OS, 88% vs. 72%, p=0.03	237 patients with FL
Ghielmini [134], full	202	**Untreated and relapsed**[J] follicular lymphoma[N].	R	R maint vs. obs[L]	Median 35 mo	Median EFS[O,] 23.2 vs. 11.8 mo; p=0.024. Response duration[P] at 24 mo, 58% vs. 35%;p=0.022	NR	Patients rand after induction. Eval: 185 patients for induction phase; 151 patients for maintenance phase. Median age 57 y
Ghielmini [137], full	61	Untreated and relapsed[J] mantle cell lymphoma	R	R maint vs. obs	Median 29 mo	Median EFS[O,] 12 mo vs. 6 mo; p=0.45	NR	Patients rand after induction. Eval
Hainsworth [136], full	90[FI]	**Relapsed**[J] indolent NHL (grade 1 or 2 follicular, or SLL)	R[L]	R maint vs. obs[K]	Median 41 mo	Median PFS, 31.7 vs. 7.4 mo; p=0.007. Median duration of R benefit 31.3 vs. 27.4 mo; p=0.94[M]	3 y, 72% vs. 68%; p=NS	R at progression in obs arm
Dreyling [131], abst	195[F]	**Relapsed** follicular or mantle cell lymphoma	FCM or R-FCM (first random-ization)[Q]	R maint vs. obs[C] (second randomization)	NR	Median PFS, not reached vs. 17 mo[R]; p=0.001	3 y, 82% vs. 55%; p=0.056	Eval: 176 patients
Van Oers [205], abst	319	Relapsed/ resistant[S] follicular NHL (stg III or IV)	R-CHOP vs. CHOP (first randomization)	R maint vs. obs[C] (second randomization)	NR	Median PFS, 52 vs. 15 mo; p<0.0001)[T]	3 y, 85% vs. 77%; p=0.011[T]	Eval: 268 patients

abst=abstract; αIFN= interferon-alpha; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP= cyclophosphamide, adriamycin, etoposide, prednisolone; CNOP=cyclophosphamide, mitoxantrone, vincristine, prednisone; CR=complete response; CVP=cyclophosphamide, vincristine, prednisone; EFS=event-free survival rate; DFS=disease-free survival rate; est=estimated; eval=evaluable; FCM=fludarabine, cyclophosphamide, mitoxantrone; FL= follicular lymphoma; full=full paper; HR=hazard ratio; IPI=International Prognostic Index factor; ITT=intention to treat; maint=maintenance; max=maximum; MCP=mitoxantrone, chlorambucil, prednisone; mo=month(s); N=number; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; obs=observation; OS=overall survival rate; PFS=progression-free survival rate; PR=partial response; prelim=preliminary; rand=randomized; R=rituximab; SLL=small lymphocytic lymphoma; stg=stage; TTF=time-to-treatment failure; TTP=time to progression; vs.=versus; y=year(s).

[A]Treatment details are provided in Appendix 1.

[B]Data provided in order of intervention versus control.

[C]Authors did not indicate whether groups similar at baseline.

[D]Overall response rate; no definition provided.

[E]Log-rank.

[F]Number of patients in each group not given.

[G]Number of patients in analysis unknown.

[H]Responders in this trial received IFN-alpha maintenance or received myeloablative consolidation plus autologous stem cell transplant.
[I]13 patients randomized to maintenance rituximab progressed before starting treatment.
[J]No previous treatment with rituximab.
[K]Obs=retreatment at progression.
[L]Authors indicate groups balanced for characteristics or for a list of characteristics.
[M]Duration of rituximab benefit=date of documented remission until date of other treatment necessary
[N]Newly diagnosed or relapsed/refractory.
[O]EFS measured from start of induction.
[P]Among those responding with induction.
[Q]First randomization stopped after 147 patients; all subsequent patients received induction R-FCM (136 of 174 evaluable patients for the second randomization received R-FCM).
[R]Median PFS reported for patients who received R-FCM and subsequent randomization to maintenance rituximab versus observation; median follow-up not reported.
[S]Resistant to a maximum of 2 non-anthracycline regimens.
[T]Overall and progression-free survival rates were reported in an oral presentation at the 2005 ASH Annual Meeting (40).

Table 3. Trials evaluating rituximab monotherapy or combination therapy in chronic lymphocytic leukemia (CLL).

Author, Type of Study	Patients	N (eval)	Treatment[A]	Line	Follow-up Time	Response Rate	Response Duration	Disease Control	Overall Survival Rate
Rituximab Monotherapy									
Huhn [206], fFull	relap/refract B-CLL/PLL[BC]	28	R	>1	Accrual 09/98 to 07/99; manuscript accepted 04/01.	25%[D] (PR)	Median 20 wk (5 mo)	Median TTP 16 wk (n=29)	n=21 survivors at time of reporting
Itala [207], full	CLL	23	R	>1	28-wk study period	35% (PR)	Median 12.5 wk (3 mo)	NR	NR
Thomas [208], abst	high-risk, early-stg CLL	21	R	First-line	Median 8 mo	90% (CR+nPR+PR)	NR; 1 pt with PR progressed	NR	NR
Hainsworth [209], abst	Stg III, IV SLL/CLL[EF]	56	R (+R maint)	First-line	Of initial 24 patients, median 26 mo	44% at 6 wk (before maint)[G]	NR	Median PFS 35 mo (n=24 patients)	NR
Byrd [210], full	SLL/CLL	29 (33 enrolled)	R (different dose cohorts)	Mixed	Accrual 01/99 to 08/99; manuscript accepted 01/01	52%[E] (45% all enrolled) (CR+PR); CLL subgroup 46%[H]	Median 10 mo[E]	Median PFS 6 mo (entire group)[E]	n=6 deaths[E]
O'Brien [211], full	CLL subset	40	R (different dose cohorts)	>1	No information provided	36% among all doses (75% at highest dose) (PR)	NR	NR	NR
Hainsworth [212], full	CLL/SLL[E]	43 (44 enrolled)	R (+R maint[I])	First-line	Median 24 mo	51% before maintenance (CRu+PR); 58% at time of reporting (CR+CRu+PR)	NR	Actuarial 2 y PFS 49%; median 19 mo (n=44 in analysis)	Of n=44, 6 deaths at time of reporting
Hainsworth [213] and [214], full and abst	SLL subset	24 (enrolled; eval unknown)	R (+R maint)	First-line[J]	Median 55 mo	70% (CR+PR)	NR	Median PFS 31mo	NR
Mauro [215], abst	CP responders, CLL	19 (all in PR)	R as maint	>1	Median 17 mo	68% showed clinical improvement to CR	NR	Median PFS 16 mo	NR

Author, Type of Study	Patients	N (eval)	Treatment[A]	Line	Follow-up Time	Response Rate	Response Duration	Disease Control	Overall Survival Rate
Rituximab Combination Therapy									
Byrd [149], full	randomized phase II	51	FR (concurrent) + R consolid	First-line	Median 23 mo	90% (PR+CR)	Median not reached	Est. 2 y PFS 70%	n=6 deaths
		53	FR (sequential); R consolid	First-line		77% (PR+CR)	Median not reached	Est. 2 y PFS 70%	n=2 deaths
Gupta [216], full	Stg III, IV	22	RCD	>1[K]	Accrual: 03/98 to 05/00	77% (after median 4 cycles) (CR+PR)	Median 7 mo	NR	NR
Drapkin [217], abst		54	R+ pentostatin +pr maint	Mixed	Final evaluations done on days 113 to 119 of study.	33% (CR+CRu+PR +PRu)	Median 9.8 mo	NR	n=8 deaths
Schulz [218], full	B-CLL	31	FR	Mixed	Median 54 wk	87% (CR+CRu+PR)	Median 75 wk (19 mo)	NR	NR
Del Principe [219], abst	B-CLL	49	FR	First-line	Median 29 mo	97.9% (CR+PR)	Median not reached	3 y PFS 72%	NR
Faderl [220], abst	relap/refract adv CLL	32	R + alemtuzumab	>1	No information provided	63% (CR+nPR+PR)	NR	NR	NR
Keating [221], full	CLL	224	FCR	First-line	Minimum 27 mo Maximum 48 mo	95% (CR+nPR+PR)	NR	2 y FFS 84%	2 y 93%
Garcia-Manero [222], abst		102	FCR	>1	Accrual: 11/99 to 07/01; median >13 mo	72.2% (CR+nPR+PR)	NR	NR	At time of reporting, n=26 deaths (74.5% survival)
Wierda [223], abst		79	FCR	First-line	Median 24 mo	95% (CR+nPR+PR)	NR	NR	94% at median 2 y follow-up
Wierda [224], full		177	FCR	>1	Median 28 mo	73% (CR+nPR+PR)	NR	Median TTP 28 mo	Median 42 mo
Weide [225], full	relap/ refract, CLL/PLL subset[B]	22 (21 B-CLL, 1 B-PLL)	BMR followed by BM	>1	No information provided	95% (CR+PR)	NR	Median TTP 17 mo	NR
Weiss [226], abst	intermediate/ high-risk CLL subset	20	PCR	>1	No information provided	80% (CR+nR+PR)	NR	NR	NR

Author, Type of Study	Patients	N (eval)	Treatment[A]	Line	Follow-up Time	Response Rate	Response Duration	Disease Control	Overall Survival Rate
Kay [227], abst	B-CLL	15	PCR	First-line	Median 258 d (~8.6 mo)	100% (best response ≥PR: CR+CCR+PR)	2 patients progressed at 172 and 200 d	NR	NR
Reynolds [228], abst	progressive CLL	20	PCR	First-line	Accrual: 04/02 to 11/02; analysis as of 18/06/03	90% (CR+PR)	Median 3.4 mo	NR	Est. 1 y 76.7%
Robak [229], full	CD20+ B-CLL	15	R + cladribine	>1	Median 9 mo	73.3% (CR+PR)	Median 6+ mo	Est. FFS 9 mo 78%	NR
Nabhan [230], full	failed/ relap	12 (11)	R + alemtuzumab	>1	No information provided	9.1% (CR+PR)	10 wk	NR	NR
Castro [231], abst	relaps/ refract CLL	14	HDMP + R	>1	Median 26 mo	100% (CR+PR)	NR	Median TTP 12 mo	NR

abst=abstract; adv=advanced; B=B-cell; BM=bendamustine, mitoxantrone; BMR=bendamustine, mitoxantrone, rituximab; CLL=chronic lymphocytic leukemia; CP=chlorambucil, prednisone; consolid=consolidation; CR=complete response/remission; CRu=unconfirmed CR; CCR=clinical CR; d=day(s); est.=estimated; eval=evaluable; FCR=fludarabine, cyclophosphamide, rituximab; FFS=failure-free survival rate; FR=fludarabine plus rituximab; intermed=intermediate; HDMP=high dose methylprednisolone; mo=month(s); N/n=number; nPR=nodular partial remission/response; nR=nodular response; NR=not reported; maint=maintenance; PCR=pentostatin, cyclophosphamide, rituximab; PFS=progression-free survival rate; PLL=prolymphocytic leukemia; pr=pentostatin, rituximab; PR=partial response/remission; PRu=unconfirmed PR; R=rituximab; RCD=rituximab, cyclophosphamide, decadron; relap=relapsed; refract=refractory; SLL=small lymphocytic lymphoma; stg=stage; TTP=time to progression; wk=week(s); y=year(s).

[A]Treatment details are provided in Appendix 1.

[B]Data for CLL and PLL reported together.

[C]Divided patients into cohorts according to tumour mass, but pooled cohort data together in analyses.

[D]By intention to treat (n=30), 23% PR.

[E]Data for CLL and SLL reported together.

[F]Authors indicate patients treated in two sequential trials, but no other details provided.

[G]Objective response (includes CR).

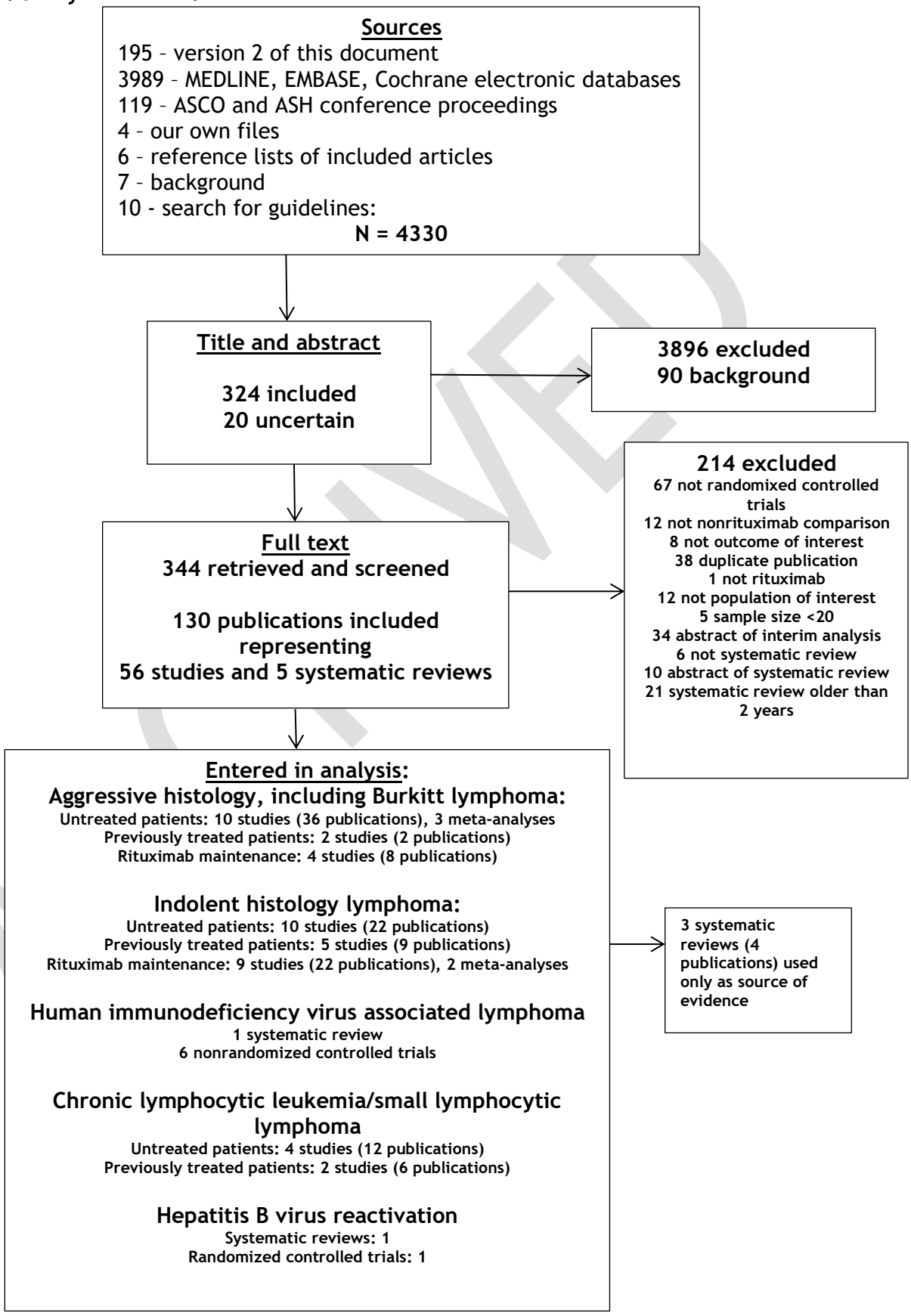
[H]Unknown if both CR and PR occurred in the CLL subgroup.

[I]Patients with objective response or stable disease received maintenance.

[J]Two patients received initial radiotherapy, but not indicated whether they were patients with SLL.

[K]Rituximab included as previous treatment.

Appendix 4. Study flow chart.



Appendix 5. Quality assessment of included systematic reviews, rated by two independent reviewers, AMSTAR (3).

AMSTAR item	Rating				
	Bauer, 2012 [55]	Castillo, 2012 [53]	Lepretre, 2012 [54]	Barta, 2013 [17]	Dong, 2013 [46]
1. Was an *a priori* design provided?	Y	CA	CA	Y	Y
2. Was there duplicate study selection and data extraction?	Y	CA	CA	CA	Y
3. Was a comprehensive literature search performed?	Y	N	Y	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	N	Y	N
5. Was a list of studies (included and excluded) provided?	Y	N	N	Y	Y
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	N	N	NA	N
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	N	N	NA	N
9. Were the methods used to combine the findings of studies appropriate?	Y	N	N	Y	Y
10. Was the likelihood of publication bias assessed?	NA	Y	N	Y	Y
11. Was the conflict of interest stated?	Y	Y	Y	Y	Y

Y=yes; N=no; CA=cannot answer; NA=not applicable

Appendix 6. Rituximab in patients with Burkitt lymphoma and human immunodeficiency virus-related lymphoma: nonrandomized studies.

Table 1. Rituximab in Burkitt lymphomas: general characteristics of included nonrandomized controlled trials.

Study; Funding Source	Study Objectives; Design; Follow-up	Patient Population	Intervention/ Comparison(s)	Outcomes
Evens, 2011 [abst] [82], 2012 [abst] [108], 2013 [abst] [109] Funding: Ortho-Biotec	To test the efficacy of liposomal doxorubicin and R + chemotherapy [82,108] **Design**: Phase II **Follow up:** 24 mo	25 patients with HIV+ or HIV- Burkitt L Median age (y): 44	Noncomparative. All patients were administered CODOX-M/IVAC and R. Liposomal doxorubicin was substituted for doxorubicin	Response PFS OS AE
Kasamon, 2013 [full] [84] Funding: National Institute of Health, National Cancer Institute Lymphoma SPORE, and philanthropic support of research	To test whether cyclophosphamide intensification might reduce the need for other cytotoxic agents and shorten treatment duration **Design**: single arm phase 2 trial **Follow up**: 52 mo	21 older adults with Burkitt L or unclassifiable B-cell L/leukemia Median age (y): 53	Cycles 1 and 2: cyclophosphamide, vincristine, prednisone and R with CNS prophylaxis or treatment. Cyclophosphamide intensification: R day 1; high-dose cyclophosphamide without stem-cell rescue; filgrastim; and, when the ANC was > 1000/ m L, once-weekly R for 4 wk	EFS OS Relapse incidence
Wästerlid, 2013 [full] [87] Funding: Swedish Cancer Society	1) To examine the outcome of treatment with various chemotherapy agents 2) To assess possible improvement within the time frame of the study **Design**: Retrospective, population-based study **Follow up:** 9 y	163 adults, HIV-negative, Burkitt L treated with various regimens Median age (y): 56	R (once per cycle) + CHOP/CHEOP R (twice per cycle) + hyper-CVAD CODOX-M/IVAC	OS
Hoelzer, 2012 [abst] [83] Funding: none declared	To test the efficacy and safety of R + intensive-short chemotherapy **Design:** Prospective multicentre single arm **Follow up:** not reported	363 adolescent and adult patients with Burkitt lymphoma (N=229) and Burkitt leukemia (N=134) Median age (y): Burkitt leukemia: 47 Burkitt lymphoma: 40	R + high-dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, ifosphamide, corticosterioids, and a triple intrathecal therapy (MTX, AraC, Dexa)	CR OS PFS
CALGB 10002 Rizzieri, 2010 [full] [85]	To assess the benefit of adding R + growth factor to the intensive chemotherapy used in study CALGB 9251	105 patients with untreated HIV-negative Burkitt L Median age (y): not reported	All patients were treated with R and intensive short chemotherapy without cranial irradiation	CR EFS OS

Study; Funding Source	Study Objectives; Design; Follow-up	Patient Population	Intervention/ Comparison(s)	Outcomes
Funding: None declared	**Design:** Phase II, single arm **Follow up:** 2 y			
MD Anderson study Thomas, 2006, 2010, 2011 [full] [86,106,107] Fayad, 2007 [full] [110] Funding: Biogen-Idec; Genentech, Bio-Oncology	To evaluate the effectiveness of R added to intensive chemotherapy. Update [110] **Design:** Phase II, single arm **Follow up:** 22 mo	31 patients [86] + 26 patients [107] with newly diagnosed Burkitt L and acute lymphoblastic leukemia 97 patients with newly diagnosed MCL [110] Median age (y): Burkitt L: 46 MCL: 61	R-hyper-CVAD	Response CR PR OS

Abst=abstract; AE=adverse effects; ANC=absolute neutrophil count; Ara-C= cytarabine; CHEOP=cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CNS=central nervous system; CODOX-M/IVAC=cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; CR=complete response; Dexa=dexamethasone; EFS=event free survival rate; full=full text; HIV=human immunodeficiency virus; hyper-CVAD= hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; L=lymphoma; MCL=mantle cell lymphoma; mo=month(s); MTX= methotrexate; PFS=progression-free survival rate; PR=partial response; OS=overall survival rate; R=rituximab; wk=week(s); y-year(s).

Table 1E. Efficacy of rituximab in Burkitt lymphomas: included nonrandomized controlled trials.

Study	Intervention Control	EFS Median (mo)	PFS Median (mo)	TTP, Median (mo)	FFS or Other Disease Control Measure Median (mo)	CR or Other Measures of Response	OS, Median (mo)	Follow-up, Median (mo)
Evens, 2011 [abst] [82], 2012 [abst] [108], 2013 [abst] [109]	CODOX-M/IVAC and R. Liposomal doxorubicin was substituted for doxorubicin	*nr*	2 y: 86%	NR	NR	67%	$OS_{2\,y}$: 86%	34
Kasamon, 2013 [full] [84]	Cycles 1 and 2: C, vincristine, prednisone and R with CNS prophylaxis Cyclophosphamide intensification: R day 1; high-dose C, filgrastim; and, R once-weekly for 4 wk	EFS_{3y}: 52% (95% CI 35% to 79%)	*nr*	*nr*	*nr*	Of 17 evaluable patients: 47%	Estimated $OS_{1\,y}$ and $OS_{3\,y}$: 57% (95% CI 40%-83%)	52
Wästerlid, 2013 [full] [87]	R (once per cycle) + CHOP/CHEOP R (twice per cycle) + hyper-CVAD	*nr*	*nr*	*nr*	*nr*	*nr*	NS for patients receiving R	58

Study	Intervention Control	EFS Median (mo)	PFS Median (mo)	TTP, Median (mo)	FFS or Other Disease Control Measure Median (mo)	CR or Other Measures of Response	OS, Median (mo)	Follow-up, Median (mo)
	CODOX-M/IVAC							
Hoelzer, 2012 [abst] [83] (Only results for patients with Burkitt lymphoma reported)	R + HD MTX, HD cytosine arabinoside, cyclophosphamide, etoposide, ifosphamide, corticosterioids , intrathecal MTX, AraC, and Dexa	*nr*	83%	*nr*	*nr*	91%	88%	>7 y
CALGB 10002 **Rizzieri, 2010 [abst] [85]**	Intensive chemotherapy + R + GF	77%	*nr*	*nr*	*nr*	82%	79%	38.4
MD Anderson **Thomas, 2006, 2010, 2011 [full] [86,106,107] Fayad, 2007 [full] [110]**	R-hyper-CVAD	80%	*nr*	*nr*	FFS_{5y}: 48%	86%	Median not reached $OS_{est.\ 3\ y}$: 89%	22

Abst=abstract; Ara-C= cytarabine; C=cyclophosphamide; CI,=confidence interval; CHEOP= cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone; CI=confidence interval; CNS=central nervous system; CODOX-M/IVAC=cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide and cytarabine Ara-C; CR=complete response; Dexa=dexamethasone; EFS=event-free survival rate; est.=estimated; FFS=failure-free survival rate; full=full text; GF=growth factor; HD=high dose; hyper CVAD=hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; mo=month(s); MTX=methotrexate; NR=not reported; NS=not significant; OS=overall survival rate; PFS=progression-free survival rate; R=rituximab; TTP=time to progression; wk=week(s); y=year(s).

Table 1AE. Rituximab in Burkitt lymphomas: grade >3 adverse events in nonrandomized controlled trials.

Study	Intervention	N	Infections* (%)	(Febrile) Neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; Vomiting (%)	Mucositis (%)	Liver Tox (%)	Neurol. Tox (%)	Card. Tox (%)	Second Tumors (%)	Deaths (%)
Evens, 2011 [abst] [82], 2012 [abst] [108], 2013 [abst] [109]	CODOX-M/IVAC and R. Liposomal doxorubicin was substituted for doxorubicin	25	38[A]	29 [A]	4	*nr*	62	4[A]	46	*nr*	0	8	*nr*	Not treatm/ related: 12
Kasamon, 2013 [84]	Cycles 1 and 2: cyclophosphamide, vincristine, prednisone and R with CNS prophylaxis or treatment. Cyclophosphamide intensification	21	52	Grade 4: 85 during cycle 1 and 78 during cycle 2	*nr*	*nr*	*nr*	*nr*	0	*nr*	24	5	*nr*	Treatm related 24
Wästerlid, 2013 [87]	R + CHOP/CHEOP R + hyper CVAD CODOX-M/IVAC	163[B]	nr	nr	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	nr	nr	*nr*	nr
Hoelzer, 2012 [abs] [83]	R + HD MTX, HD cytosine arabinoside, cyclophosphamide, etoposide, ifosphamide and corticosterioids and intrathecal MTX, AraC and Dexa	363	23	Neutropenia: 64	*nr*	*nr*	*nr*	*nr*	31	*nr*	nr	nr	*nr*	nr

Study	Intervention	N	Infections* (%)	(Febrile) Neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopenia (%)	Nausea; Vomiting (%)	Mucositis (%)	Liver Tox (%)	Neurol. Tox (%)	Card. Tox (%)	Second Tumors (%)	Deaths (%)
CALGB 10002														
Rizzieri, 2010 [abs] [85]	Intensive chemo + R + GF	105	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
MD Anderson														
Thomas, 2006 [abs], 2010, 2011 [abs] [86,106,107] Fayad, 2007 [110]	R-hyper-CVAD	31	*nr*	45	*nr*	*nr*	22	*nr*	*nr*	*nr*	0	*nr*	*nr*	0

[A] Data from Evens et al, 2012 [108]
[B] Information on patients treated with rituximab only
Abst=abstract; Ara-C= cytarabine; card.=cardiac; CHEOP=cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; chemo=chemotherapy; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone; CNS= central nervous system; CODOX-M/IVAC=cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine Ara-C; CR=complete response; Dexa=dexamethasone; FFS=failure-free-survival rate; GF=growth factor; HD=high dose; hyper-CVAD =hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX=methotrexate; neurol.=neurological; NR=not reported; OS=overall survival rate; PFS=progression-free-survival rate; R=rituximab; tox=toxicity; treatm=treatment; TTP=time-to-progression.

Table 2. Rituximab in human immunodeficiency virus-associated lymphomas: general characteristics of included nonrandomized controlled trials.

Study; Funding Source	Study Objectives; Design; Follow-up	Patient Population	Intervention/ Comparison(s)	Outcomes
Boué, 2006 [full] [92] **Funding:** French National Agency for AIDS and Viral Hepatitis Research (ANRS)	To evaluate the efficacy of R-CHOP **Design:** Multicentre, phase II, single arm **Follow-up:** 33 mo	61 patients with newly diagnosed AIDS-related NHL Median age (y): 41	Noncomparative; all patients received R-CHOP	CR DFS
Ribera, 2008 [full] [94] **Funding:** José Carreras International Leukæmia Foundation	To evaluate the efficacy and safety of R-CHOP and determine the prognostic impact of response to HAART **Design**: Multicentre, phase II, single arm **Follow-up**: 5 y and 8 mo	86 patients with HIV-related DLBCL. Median age (y): 44	Noncomparative; all patients received R-CHOP	CR OS DFS
Spina, 2005 [full] [95] Spina, 2009 [abst], 2010, [abst] [232,233] **Funding:** Istituto Superiore della Sanità, Associazione Italiana per la Ricerca sul Cancro	To test the safety and efficacy of R in combination with infusional chemotherapy **Design**: Pooled results of 3 phase II trials. Long-term follow-up **Follow-up**: N/A	74 patients withHIV-associated, B-cell NHL Median age (y): 38	Noncomparative. All patients received R in combination with 96 hours infusion of cyclophosphamide, doxorubicin, and etoposide	CR OS FFS
Dunleavy, 2010 [full] [93] **Funding:** National Cancer Institute	To study whether DLBCL can be treated with 50% fewer cycles than a standard course, to assess the role,specificity and sensitivity of FDG-PET ,and to examine the role of tumour biology in the outcome of HIV-associated DLBCL **Design**: Phase II, single arm **Follow-up:** 5 y	33 patients with untreated HIV-associated CD20+ diffuse large B-cell lymphoma Median age (y): 42	Short course etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with dose dense R (SC-EPOCH-RR)	Number of chemotherapy cycles PFS OS

Abst=abstract; AIDS=acquired immune deficiency syndrome; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CR=complete response; DFS=disease-free survival rate; DLBCL=diffuse large B-cell lymphoma; FFS=failure-free survival rate; FDG-PET=positron emission tomography with fluorodeoxyglucose; full=full text; HAART=Highly Active AntiRetroviral Therapy; HIV=human immunodeficiency virus; mo=month(s); N/A=not applicable; NHL=non-Hodgkin lymphoma; OS =-overall survival rate; PFS=progression free survival rate; R=rituximab; SC-EPOCH-RR=short-course EPOCH (etoposide, doxorubicin, cyclophosphamide vincristine, prednisone) with double-dose R; y=year(s).

Table 2E. Efficacy of rituximab in human immunodeficiency virus-associated lymphomas: included nonrandomized controlled trials.

Study	Intervention Control	EFS Median (mo)	PFS Median (mo)	TTP, Median (mo)	FFS or Other Disease Control Measure Median (mo)	CR or Other Measures of Response	OS, Median (mo)	Follow-up, Median (mo)
Boué, 2006 [full] [92]	R-CHOP	*nr*	$PFS_{est.\ 2\ y}$: 69% (95% CI, 56% to 82%)	*nr*	*nr*	77% (95% CI, 63 to 87)	$OS_{est.\ 2\ y}$: 75% (95% CI, 64 to 86)	33
Ribera, 2008 [full] [94]	R-CHOP	$EFS_{est.\ 2\ y}$ DFS: 77% (95% CI, 62%-92%)	*nr*	*nr*	*nr*	69%	$OS_{est.\ 3\ y}$: 56% (95% CI, 43 to 69)	24
Spina, 2005 [full] [95] 2010a, [full] [233]	R + 96 hours infusion of cyclophosphamide, doxorubicin, and etoposide	$EFS_{23\ mo}$: 52% (95% CI, 42-62)	NR TTF: 52% DFS: 81%	*nr*	at 23 mo follow-up: 59% (95% CI, 47 to 71)	at 23 months follow-up 70 (95% CI, 59 to 81)	56%	61
Dunleavy, 2010 [full] [93]	SC-EPOCH-RR	*nr*	Est. at 5 years: 84%	*nr*	*nr*	91% (95% CI, 76 to 98)	$OS_{est.\ 5\ y}$: 68%	60

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CI=confidence interval; CR=complete response; DFS=disease-free survival rate; EFS=event-free survival rate; est.=estimated; FFS=failure-free survival rate; full=full text; mo=month(s); NR=not reported; OS=overall survival rate; PFS=progression-free survival rate; R=rituximab; SC-EPOCH-RR=short-course EPOCH (etoposide, doxorubicin, cyclophosphamide vincristine, prednisone) with double-dose R; TTF=time to treatment failure; TTP=time to progression; y=year(s).

Table 2AE. Rituximab in human immunodeficiency virus-associated lymphomas: grade ≥3 adverse events in nonrandomized controlled trials.

Study	Intervention	N	Infections* (%)	(Febrile) Neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopemia (%)	Nausea; Vomiting (%)	Mucositis (%)	Liver Tox (%)	Neurol. Tox (%)	Card. Tox (%)	Second Tumors (%)	Deaths (%)
Boué, 2006 [full] [92]	R-CHOP	52	*nr*	17	31	*nr*	10	2	0	0	0	0	*nr*	Treatm/ related: 2
Ribera, 2008 [full] [94]	R-CHOP	426	10	49 (no fever)	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	2
Spina, 2005 [full] [95], 2010a [full] [233]	R + cyclo doxo etopo	74	31[A]	78[A] (no fever) 5 (with fever and no infection)	32[A]	*nr*	24[A]	*nr*	11[A]	*nr*	*nr*	*nr*	5[B]	Total 35 Treatm/ related: 3 (sepsis)
Dunleavy, 2010 [full] [93]	R (SC-EPOCH-RR)	109 cycles evaluable in 33 patients	*nr*	46% of 109 cycles (no fever) 31% of cycles	*nr*	*nr*	33% of 109 cycles	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Treatm/ related: 0

[A] Data from Spina et al, 2005 [95]
[B] Data from Spina et al, 2010 [233]
Card.=cardiac; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; cyclo=cyclophosphamide; doxo= doxorubicin; etopo=etoposide; full=full text; neurol.=neurologic; NR=not reported; R=rituximab; SC-EPOCH-RR=short-course EPOCH (etoposide, doxorubicin, cyclophosphamide vincristine, prednisone) with double-dose R; tox=tosicity; Treatm=treatment;

Table 3. Rituximab in human immunodeficiency virus-associated lymphomas: general characteristics of included randomized controlled trials.

Study; Funding Source	Study Objectives; Design; Follow-up	Patient Population	Intervention/ Comparison(s)	Outcomes
AIDS Malignancy Consortium (AMC) 010 Kaplan, 2005 [full] [91] Barta 2012 [full] [234] Chadburn, 2009 [full] [235] **Funding**: National Cancer Institute, US	To determine if R + CHOP improve outcomes in patients with HIV-associated lymphoma	150 patients with HIV-associated NHL. Mean age (y): 42	R-CHOP vs. CHOP	*CR *TTP PR AE
	Barta 2010, 2012 is a pooled analysis of 2 RCTs [91,116] to determine the influence of the IPI, CD4 count, and treatment on outcomes	150 patients in the treatment arms of the included studies		CD4 and IPI
	Chadburn 2009 is a subanalysis of the studies reported by Sparano (AMC034) [116] and Kaplan (AMC010) [91] to determine if immunohistochemical analyses of biopsies from patients with HIV-related DLBCL potential prognostic markers **Design:** Parallel group **Follow up:** 137 wk	45 patients from AMC 010 and 36 patients from AMC034 with HIV and DLBCL	Correlation of germinal centre immunophenotype, proliferation index, expression of BCL-2, FOXP1, or B-lymphocyte-induced maturation protein (Blimp-1)/PRDM1 with outcomes	Immunohistochemical markers predictors of better survival rates

*primary outcome
AE=adverse effects; BCL=B-cell lymphoma; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CR=complete response; DLBCL=diffuse large B cell lymphoma; FOXP1=forkhead box protein P1; full=full text; HIV=human immunodeficiency virus; IPI=International Prognostic Index; NHL=non-Hodgkin's lymphoma; PR=partial response; PRDM1=PR domain zinc finger protein 1; R=rituximab; RCT=randomized controlled trial; TTP=time to progression; vs.=versus; wk=week(s); y=year(s).

Table 3Q. Rituximab in human immunodeficiency virus-associated lymphomas: quality of included randomized controlled trials.

Study	Treatment	Primary Outcome	Required Sample Size	Sample Size N	Randomization Method Described	Allocation Concealment	Blinding	ITT Analysis	Early Termination
AMC 010 **Kaplan, 2005 [full] [91]** **Barta 2010 [full], 2012 [full] [234,236]** **Chadburn, 2009 [full] [235]**	R-CHOP vs. CHOP	CR	120 patients in a ratio of 2:1 was sufficient to detect an improvement in CR from 50% with CHOP to 75% with R-CHOP at a one-sided 5% significant level with a power of 81%, and to detect a 50% increase in the median TTP from 35 wk on CHOP alone to 53 wk with R-CHOP at the one-sided 5% significance level with power of 67%	150	Yes	Yes	NR	Yes	No

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CR=complete response; full=full text; ITT=intention to treat; NR=not reported; R=rituximab; TTP=time to progression; vs.=versus; wk=week(s).

Table 3E. Efficacy of rituximab in human immunodeficiency virus-associated lymphomas: included randomized controlled trials.

Study	Intervention Control	EFS Median (mo)	PFS Median (mo)	TTP, Median (mo)	FFS or Other Disease Control Measure Median (mo)	CR or Other Measures of Response	OS, Median (mo)	Follow-up, Median (mo)
(AMC) 010 Kaplan, 2005 [full] [91]	R-CHOP	*nr*	NS	NS	*nr*	57.6%	NS	137 wk
	CHOP	*nr*	NS	NS	*nr*	47%, NS	NS	

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; CR=complete response; EFS=event-free survival rate; FFS=failure-free survival rate; full=full text; mo=month(s); NR=not reported; NS=not significant; OS=overall survival rate; PFS=progression-free survival rate; R=rituximab; TTP=time to progression; wk=week(s).

Table 3AE. Rituximab in human immunodeficiency virus-associated lymphomas: grade ≥3 adverse events in included randomized controlled trials.

Study	Intervention	N	Infections* (%)	(Febrile) Neutropenia (%)	Anemia (%)	Lymphopenia (%)	Thrombocytopemia (%)	Nausea; Vomiting (%)	Mucositis (%)	Liver Tox (%)	Neurol. Tox (%)	Card. Tox (%)	Second Tumors (%)	Deaths (%)
AMC 010 Kaplan, 2005 [full] [91]	R-CHOP	99	1	31	8	62	8	*nr*	*nr*	NS	*nr*	*nr*	*nr*	Total: 42 Treatm/ related infection: 14
	CHOP	51	0	24 NS	6 NS	48 NS	3 NS	*nr*	*nr*	NS	*nr*	*nr*	*nr*	Total: 45, NS Treatm/ related infection: 2, p=0.035

Card.=cardiac; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; full=full text; neurol.=neurologic; NR=not reported; NS=not significant; R=rituximab; tox=toxicity; treatm=treatment.

Appendix 7A. Members of the Rituximab in Lymphoma and Chronic Lymphocytic Leukemia Update Working Group, their affiliations, and their declared conflicts of interest.

Working Group Member Affiliation	Declared Conflict of Interest
Dr. Anca Prica Hematologist/internist Odette Cancer Centre at Sunnybrook Health Sciences, 2075 Bayview Ave., Toronto, Ontario	Declared no conflict of interest
Ms. Fulvia Baldassarre Research Coordinator Program in Evidence-based Care, Cancer Care Ontario McMaster University, Juravinski Hospital Site G Wing, 2nd Floor, Rm 220 711 Concession Street, Hamilton, Ontario	Declared no conflict of interest
Dr. Tom Kouroukis Hematologist/Internist Juravinski Cancer Centre 711 Concession Street, Hamilton, Ontario	Declared no conflict of interest
Dr. Lisa Hicks Hematologist/Internist St Michael's Hospital 30 Bond Street, Toronto, Ontario	Received grants/research support from pharmaceutical industry
Dr. Kevin Imrie Sunnybrook Health Sciences Centre 2075 Bayview Avenue, Toronto, Ontario	Declared no conflict of interest
Dr. Matthew Cheung Hematologist/Internist Odette Cancer Centre at Sunnybrook Health Sciences 2075 Bayview Ave., Toronto, Ontario	Declared no conflict of interest

Appendix 7B. Disease Site Group members of the Expert Panel who reviewed this guideline, their affiliations, and their declared conflicts of interest.

Dr. Chris Bredeson Hematologist/Internist The Ottawa Hospital General Campus 501 Smyth Road, Ottawa, Ontario Declared having received financial support >$5000 from pharmaceutical industry.	Dr. Michael R. Crump Hematologist/Internist Princess Margaret Hospital 610 University Avenue, Toronto, Ontario Declared having received grants/research support from pharmaceutical industry and being a principal investigator in a trial of the object of study.
Dr. Patricia Disperati Community hematologist/oncologist Toronto East General Hospital 825 Coxwell Ave, East York, Ontario Declared no conflict of interest.	Dr. Graeme Fraser Hematologist/Internist Juravinski Cancer Centre 711 Concession Street, Hamilton, Ontario Declared no conflict of interest.
Dr. Jordan Herst Hematologist/Internist Northeastern Ontario Regional Cancer Centre at Sudbury Regional Hospital 680 Kirkwood Drive, Sudbury, Ontario Declared no conflict of interest.	Dr. Irwin Walker Hematologist/Internist McMaster University Medical Centre 1200 Main Street West, Hamilton, Ontario Declared no conflict of interest.
Dr. David Hodgson Princess Margaret Hospital 610 University Avenue, Toronto, Ontario Declared having published an opinion paper on the object of study.	Dr. Nicole Laferriere Hematologist/Internist Northwestern Ontario Regional Cancer Centre at Thunder Bay Regional Health Sciences Centre 980 Oliver Road, Thunder Bay, Ontario Declared no conflict of interest.
Dr. Sindu Kanjeekal Hematologist/Medical Oncologist Windsor Regional Cancer Centre at Windsor Regional Hospital 2220 Kildare Rd., Windsor, Ontario Declared having received an educational grant from pharmaceutical industry.	Dr. Janet MacEachern Hematologist/Internist Grand River Regional Cancer Centre 835 King Street West, Kitchener, Ontario Declared no conflict of interest.
Dr. Andrea Lee Suite 118 1060 Speers Road, Oakville Ontario Declared no conflict of interest.	Dr. Mitchell Sabloff Ottawa General Hospital 501 Smyth Road, Box 704 Ottawa, Ontario Declared having received financial support in the past 5 years from pharmaceutical industry.
Dr. Leonard Minuk Hematologist Victoria Hospital & Children's Hospital	Dr. Robert Stevens Grand River Regional Cancer Centre 835 King Street West, Kitchener, Ontario

800 Commissioners Rd E, London, Ontario Declared no conflict of interest.	Declared no conflict of interest.
Dr. David Robinson Patient representative Economist/Professor Department of Economics Laurentian University 935 Ramsey Lake Road, Sudbury, Ontario Declared no conflict of interest.	Dr. Jason Tay Radiation oncologist Juravinski Cancer Centre 711 Concession Street, Hamilton, Ontario Declared no conflict of interest.
Dr. Andre Schuh Hematologist/Internist Princess Margaret Hospital 610 University Avenue, Toronto, Ontario Declared owning a relevant business entity and having received financial support by pharmaceutical industry.	Mr. Ivan Tyono Pharmacist Odette Cancer Centre at Sunnybrook Health Sciences, 2075 Bayview Avenue, Toronto, Ontario Declared no conflict of interest.
Dr. Jonathan Sussman Radiation Oncologist Juravinski Cancer Centre 711 Concession Street, Hamilton, Ontario Declared no conflict of interest.	Dr. Yael Zaretsky Hematologist/Internist Odette Cancer Centre at Sunnybrook Health Sciences, 2075 Bayview Ave., Toronto, Ontario Declared no conflict of interest.
Dr. William Thomas Patient representative Declared no conflict of interest.	

Appendix 8. Recommendations submitted for external review.

DRAFT RECOMMENDATIONS (approved for external review January 14, 2015)

Aggressive histology B-cell lymphomas, including Burkitt lymphoma: first-line, second-line and maintenance treatment and patients with human immunodeficiency virus (HIV)-associated lymphomas.

RECOMMENDATION 1

Previously untreated patients

e. Previously untreated patients with aggressive histology CD20-positive B-cell lymphomas who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP], CHOP-like, or similar dose-intense regimens) should receive this therapy in combination with rituximab.

Patients with relapsed/refractory disease

f. For previously treated patients with aggressive histology CD20-positive B-cell lymphomas:
   i. There is insufficient evidence at this time to support treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated with a rituximab-containing chemotherapy regimen.
   ii. If patients have not previously received rituximab as part of their treatment regimen, the addition of rituximab to chemotherapy is reasonable.

Rituxmab maintenance treatment

g. There is insufficient evidence at this time to support the use of maintenance rituximab in aggressive histology B-cell lymphomas

Patients with HIV-associated lymphomas

h. Previously untreated patients with HIV-related lymphoma with a CD4 count ≥50/mm^3 who are candidates for treatment with curative intent and will receive combination chemotherapy with curative intent (including CHOP, CHOP-like, or similar dose-intense regimens) should receive this therapy in combination with rituximab. The addition of rituximab to chemotherapy in patients with CD4 <50/mm^3 is not recommended.

Indolent histology B-cell lymphomas: first-line, second-line, and maintenance treatment and patients with asymptomatic CD20-positive B-cell lymphomas

RECOMMENDATION 2

Previously untreated patients

f. Previously untreated patients with indolent histology CD20-positive B-cell lymphomas, excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive their chemotherapy in combination with rituximab.

g. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who are candidates for therapy, but not combination chemotherapy, rituximab monotherapy is a reasonable option.

Patients with relapsed/refractory disease

h. For previously treated patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL:

i. Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab or as rituximab monotherapy.
ii. Patients who have previously received rituximab (including combination rituximab chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Rituxmab maintenance treatment

i. For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Patients with asymptomatic CD20-positive B-cell lymphomas

j. There is insufficient evidence at this time to support or refute upfront treatment with rituximab monotherapy for asymptomatic indolent histology CD20-positive B-cell lymphomas.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

RECOMMENDATION 3

Previously untreated patients

d. Patients with previously untreated CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.
e. In patients with previously untreated CLL/SLL who are appropriate candidates for chlorambucil chemotherapy, the addition of rituximab can be considered.

Patients with relapsed/refractory disease

f. Patients with relapsed or refractory CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.

Hepatitis B virus reactivation in all patients treated with rituximab

RECOMMENDATION 4

The Hematology Disease Site Group recommends that all patients be screened for surface antigen for hepatitis B (HBsAg) and hepatitis B core antibody (HBcAb) prior to treatment with rituximab. Consultation with an expert in hepatitis B virus (HBV) should be considered for all patients who test positively for HBV. HBsAg-positive patients should receive prophylactic antiviral therapy during and after rituximab. HbsAg-negative/HBcAb-positive patients should be considered for either prophylactic antiviral therapy, close monitoring for viral reactivation, and/or should be followed by an expert in HBV. In the absence of active hepatitis (elevated transaminases), it is not usually necessary to delay rituximab. In most cases, HBV screening and management can occur in parallel with non-Hodgkin lymphoma/CLL treatment.

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