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REVIEW

Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience

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Abstract: Rituximab is a human/murine, chimeric anti-CD20 monoclonal antibody with established efficacy, and a favorable and well-defined safety profile in patients with various CD20-expressing lymphoid malignancies, including indolent and aggressive forms of B-cell non-Hodgkin lymphoma. Since its first approval 20 years ago, intravenously administered rituximab has revolutionized the treatment of B-cell malignancies and has become a standard component of care for follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and mantle cell lymphoma. For all of these diseases, clinical trials have demonstrated that rituximab not only prolongs the time to disease progression but also extends overall survival. Efficacy benefits have also been shown in patients with marginal zone lymphoma and in more aggressive diseases such as Burkitt lymphoma. Although the proven clinical efficacy and success of rituximab has led to the development of other anti-CD20 monoclonal antibodies in recent years (e.g., obinutuzumab, ofatumumab, veltuzumab, and ocrelizumab), rituximab is likely to maintain a position within the therapeutic armamentarium because it is well established with a long history of successful clinical use. Furthermore, a subcutaneous formulation of the drug has been approved both in the EU and in the USA for the treatment of B-cell malignancies. Using the wealth of data published on rituximab during the last two decades, we review the preclinical development of rituximab and the clinical experience gained in the treatment of hematologic B-cell malignancies, with a focus on the well-established intravenous route of administration. This article is a companion paper to A. Davies, et al., which is also published in this issue.
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INTRODUCTION

Hematologic B-cell malignancies comprise a large, heterogeneous group of lymphoproliferative disorders that range from slow-growing, indolent non-Hodgkin lymphomas (NHLs), such as follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL), to more aggressive forms of NHL, such as diffuse large B-cell lymphoma (DLBCL) [1, 2]. B-cell disorders represent more than 85% of all NHL cases [3]. In 2012, there were an estimated 385,700 new cases of NHL worldwide, with an estimated 199,700 patients dying from the disease [4], and evidence from US and UK statistics suggests that the annual incidence has been rising steadily since the 1970s [5, 6]. NHL incidence rates are higher among the elderly population than in the younger population, with diagnoses of NHL most common among patients aged 65–74 years [7], and a projection of population dynamics for CLL patients in the USA predicts that 199,000 patients will have the disease in 2025, partly driven by improved survival [8]. In view of the aging population worldwide, the diagnosis and treatment of B-cell hematologic malignancies are likely to remain an important focus for healthcare providers for the foreseeable future.

The treatment strategy for NHL is largely determined by histologic features, disease stage, patient age, prognosis, and the presence of comorbid disease. Staging is established using validated systems, which include the Ann Arbor staging classification for DLBCL [9] and FL [10], and the Binet and Rai staging systems for CLL [11]. Prognostic assessments at initial diagnosis are based on the International Prognostic Index (IPI) and age-adjusted IPI for DLBCL [9], the Follicular Lymphoma International Prognostic Index for FL [10], and the Mantle Cell Lymphoma International Prognostic Index for mantle cell lymphoma (MCL) [12]. In CLL, the Binet and Rai staging systems are both used to categorize patients into three groups according to their prognosis [11], and the International Prognostic Index for patients with CLL may also be applied [13]. In DLBCL, gene expression profiling can now be used to determine prognosis by identifying distinct disease subtypes according to their cell of origin [14, 15].

The development of monoclonal antibodies (mAbs) as a therapeutic treatment began in 1975 by researchers funded by the National Cancer Institute, César Milstein and Georges Köhler [16], who described the formation of hybridomas to rescue and produce a limitless supply of mAbs from a single B cell. For this work, Milstein and Köhler received the Nobel Prize for Physiology or Medicine in 1984 jointly with Niels Jerne [17]. Treatment with the first mAb occurred in 1980 [18], and this was followed by pioneering studies by Ron Levy's group at Stanford University, which produced patient-specific monoclonal anti-idiotype antibodies for treating lymphoma patients [19]. These studies proved the concept that mAbs could have a dramatic antitumor effect and that they were safe, but commercialization was limited by the fact they were patient specific. At the same time, antibodies were being used to investigate cell-surface proteins, resulting in the identification of B-cell-restricted antigens such as CD19 and CD20. This discovery paved the way for the production of therapeutic mAbs that could be used in patients whose tumors expressed those antigens. Given the widespread expression of CD20 on malignant B cells, treatment with a murine mAb against CD20 was undertaken [20], and demonstrated safety, albeit with limited clinical activity. This ultimately led to the development of a chimeric anti-CD20 mAb with increased antitumor activity; namely, rituximab.

Rituximab (MabThera®/Rituxan®/Rituxan HYCELA™, F. Hoffmann-La Roche Ltd.) is a human/murine chimeric, glycosylated immunoglobulin (Ig) G1-κ mAb containing murine light- and heavy-chain variable region sequences, and human kappa and human IgG1 constant region sequences. Rituximab has specific affinity for the B-lymphocyte transmembrane protein, CD20, which is expressed on normal B cells (excluding stem cells, pro-B

cells, and plasma B cells) and on most malignant B cells [21].

Intravenously administered rituximab was granted regulatory approval in 1997 by the US Food and Drug Administration and in 1998 by the European Medicines Agency for use in relapsed/refractory indolent NHL. Approvals for use in CLL followed in 2009 and 2010, respectively. Intravenously administered rituximab was the first therapeutic mAb to be used in the field of oncology, establishing a new class of anticancer drugs. Since its approval, rituximab has revolutionized the treatment of B-cell malignancies, becoming a standard component of care for FL [10, 22], DLBCL [9, 22], and CLL [11, 23]. Rituximab has also been included in the WHO Model List of Essential Medicines since 2015 [24]. A new formulation of rituximab for subcutaneous administration has also been approved in the EU and USA for the treatment of patients with NHL and CLL, based primarily on the results of the SABRINA and SAWYER clinical trials [25, 26]. Subcutaneously administered rituximab was developed primarily to simplify administration and shorten the administration time, and thus improve the patient experience by decreasing the burden of treatment. In addition, this may facilitate access to this important drug in resource-poor settings where intravenous administration may pose a particular challenge.

Clinical experience with intravenously administered rituximab in B-cell hematologic malignancies is extensive, currently extending to 20 years and to more than four million patient exposures worldwide, including data from an estimated 18,000 patients treated with rituximab in corporate-sponsored or supported clinical trials (Roche, data on file not publically available). Clinical experience with rituximab also extends to off-label use in MCL, for which rituximab is a standard component of care [27], and in other hematologic malignancies, including marginal zone lymphoma, Hodgkin lymphoma, Burkitt lymphoma, and B-lineage acute lymphoblastic leukemia (see "Clinical Efficacy of Rituximab"), as well as to non-hematologic licensed indications, including rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis

[28–30], which are outside the scope of this review.

This article reviews the preclinical development of rituximab and clinical experience with the intravenous formulation in B-cell hematologic malignancies. Discussion of the preclinical and clinical experience with subcutaneously administered rituximab is outside the scope of this review, but is covered extensively in a recent publication by Davies et al. [31].The information reported in this article is derived from previously conducted studies, and does not include any new studies of human or animal subjects performed by any of the authors.

MECHANISM OF ACTION OF RITUXIMAB

Rituximab binds with high affinity and specificity to the CD20 antigen, which is expressed on the vast majority of malignant B cells. The apparent affinity constant of rituximab for human CD20, as determined by Scatchard analysis using a human lymphoblastoid cell line (SB), is approximately 5.2 nmol/L [32]. The characteristics of rituximab binding to the CD20 molecule led to the definition of the "type I" anti-CD20 mAbs, which share several properties and are distinct from type II mAbs such as obinutuzumab. At least four mechanistic pathways are thought to be responsible for the elimination of CD20$^+$ cells by rituximab (Fig. 1): antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity (CDC), and direct antitumor effects via either apoptosis or other cell death pathways [33–36]. Binding of the fragment crystallizable (Fc) portion of the rituximab mAb to tumor cells results in the reorganization of CD20 molecules into lipid rafts and subsequent activation of the classical pathway of the complement cascade. This leads to CDC, including tumor cell lysis and augmentation of phagocytosis. ADCC occurs as a result of an interaction between the Fc portion of rituximab in antibody-coated tumor cells and membrane-bound Fcγ receptors expressed on the surface of
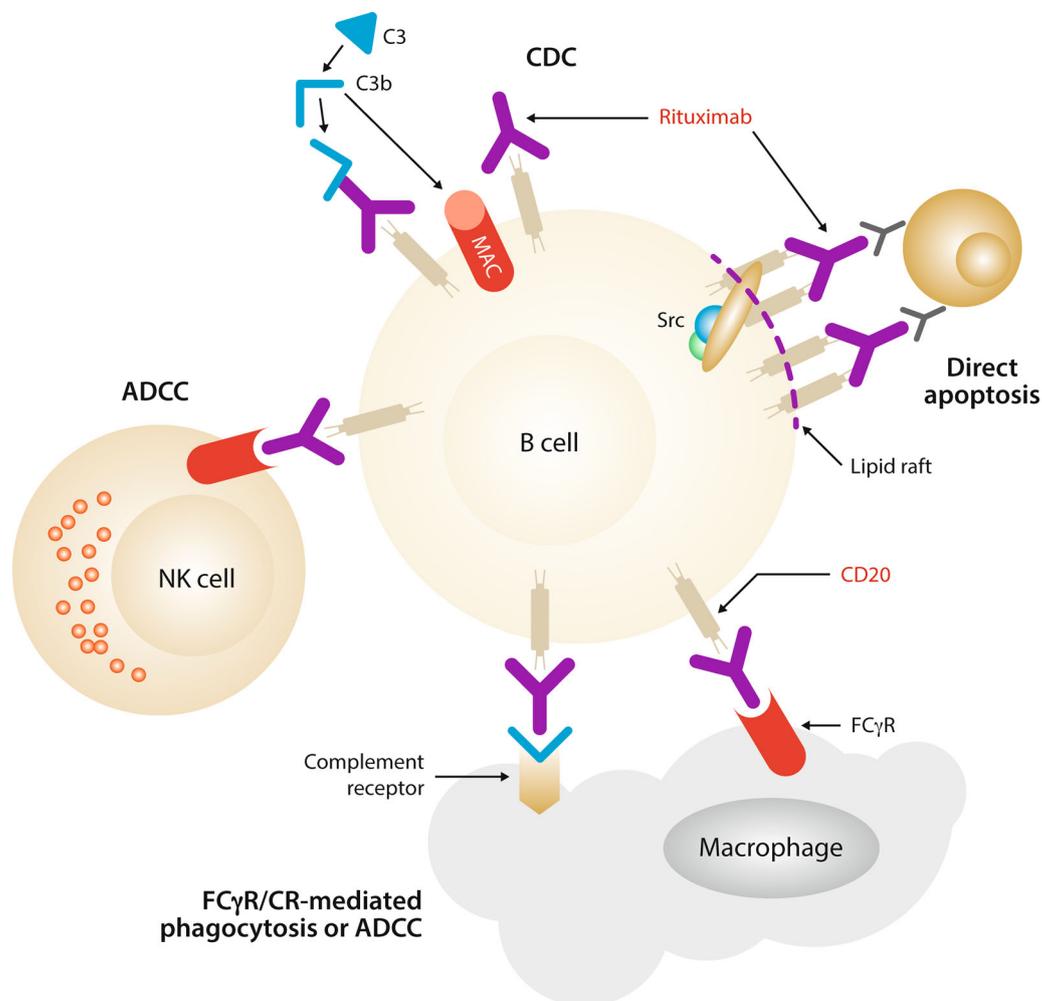
Fig. 1 Mechanisms of rituximab-mediated cell death. Rituximab-coated B cells are killed by at least four different mechanisms: (1) binding of rituximab to CD20 on the B-cell surface causes activation of the complement cascade, which generates the membrane attack complex (MAC), which can directly induce B-cell lysis by complement-dependent cytotoxicity (CDC). (2) Binding of rituximab allows interaction with natural killer (NK) cells via Fc receptors (FcRs) III, which leads to antibody-dependent cellular cytotoxicity (ADCC). (3) The Fc portion of rituximab and the deposited complement fragments allow recognition by both FcRs and complement receptors on macrophages, which leads to phagocytosis and ADCC. (4) The crosslinking of several molecules of rituximab and CD20 in the lipid raft determines the interaction of these complexes with elements of a signaling pathway involving Src kinases that mediate direct apoptosis. FCR Fc receptor, FCγR Fcγ receptor. (Republished with permission of the American Society of Hematology from Jaglowski et al. [166]; permission conveyed through the Copyright Clearance Center)

effector cells (natural killer cells, granulocytes, and macrophages) [37]. This interaction triggers the onset of cellular immune responses central to ADCC, including the release of cytokines, chemokines, and mediators that kill target cells.

In addition, rituximab binding to CD20 on B lymphocytes is thought to induce cell death via nonclassical apoptosis by triggering the crosslinking of multiple CD20 molecules [34–36].

PHARMACODYNAMICS OF RITUXIMAB

Potent B-cell-depleting activity in peripheral blood and lymphoid tissues was reported with rituximab in phase I and phase II studies [38, 39]. Circulating $CD20^+$ B cells underwent rapid depletion in the peripheral blood of patients with recurrent B-cell lymphoma treated with a single dose of rituximab. This effect was dose dependent and persisted for at least 2–3 months in most patients. In addition, there was evidence of a fall in the number of B cells in lymph node biopsy samples 2 weeks after administration of rituximab compared with pretreatment [38]. In a second group of patients with relapsed low-grade NHL treated with multiple doses of rituximab, B-cell depletion was maintained until nearly 6 months after treatment, followed by a slow recovery [39].

PHARMACOKINETIC PROFILE OF RITUXIMAB

The pharmacokinetic (PK) profile of rituximab in a variety of B-cell malignancies has been characterized throughout the product's life cycle, with use of original data from clinical studies as described herein, and by integration of these data into population PK analyses.

Among patients with low-grade or follicular NHL treated with intravenously administered rituximab, serum concentrations of rituximab were detectable after the first infusion and increased with subsequent administrations [38–40]. In 203 patients with relapsed low-grade lymphoma who received four weekly intravenous infusions of rituximab (375 mg/m^2) in two clinical studies [39, 40], the mean maximum plasma concentration (C_{max}) of rituximab was 486 µg/mL (range $77.5–996.6 \text{ µg/mL}$) after the fourth dose, and the drug was detectable in serum for up to 6 months after completion of dosing [29, 30]. In another study, the median serum rituximab concentration after the last of four weekly infusions in a group of 22 FL patients with low tumor burden was approximately 380 µg/mL, and the study authors predicted a steady-state plasma concentration in this group of 438 µg/mL if the drug had been administered once weekly for 8 weeks [41].

Elimination of rituximab in patients with B-cell malignancies is target mediated (i.e., binding of the drug to CD20 on B cells clears the antibody from the serum during the initial infusions, leading to a reduction in or saturation of accessible CD20-binding sites at lymph nodes). This was seen in the phase III study by Berinstein et al. [40], which found a marked increase in mean elimination half-life ($t_{1/2}$) from 76.3 to 205.8 h from the first to the fourth rituximab infusion, which corresponded to a nearly fourfold decrease in clearance (from 38.2 to 9.2 mL/h) and an increase in rituximab C_{max} from 205.6 to 464.7 µg/mL. Later studies reported even slower clearance (i.e., $t_{1/2}$ for rituximab of approximately 3 weeks), although with large intersubject variability [41, 42]; total systemic clearance was estimated at $3.1–11.9 \text{ mL/h/m}^2$ in the earlier study [41].

No notable differences were observed between the PK profiles of rituximab when it was administered as monotherapy and when rituximab therapy was combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy [43]. A population PK analysis in 298 patients with NHL from six clinical studies who were treated with rituximab alone or rituximab combined with CHOP (R-CHOP) showed that age, sex, race, and WHO performance status had no effect on rituximab pharmacokinetics [44]. Higher B-cell counts and greater baseline tumor burden were associated with increased clearance rates, and the volume of distribution varied depending on body surface area and CHOP chemotherapy. Rituximab elimination was reduced following multiple infusions. This analysis found that the PK profile of rituximab in NHL patients is best described by a two-compartment model with a nonspecific time-independent clearance component and a time-dependent clearance component exhibiting first-order kinetics [44].

In a population PK analysis in previously treated patients with relapsed or refractory CLL treated with rituximab (375 mg/m^2 in cycle 1 then 500 mg/m^2 in cycles 2–6) and

standard-dose fludarabine and cyclophosphamide (FC), PK data for rituximab in 21 patients showed a time-dependent PK profile with wide interpatient variability [45]. The study authors noted differences in PK parameters in these CLL patients compared with patients with NHL from a previous population analysis [44]: CLL patients had faster clearance (1260 mL/day vs 585 mL/day), a larger volume of distribution (central 4150 mL vs 2700 mL, peripheral 2320 mL vs 1500 mL), and a lower rate of change from the target-mediated clearance pathway (via CD20) to catabolic elimination (via IgG1) compared with NHL patients [45].

Rituximab serum concentrations have been reported to correlate with clinical response. In a detailed analysis of 166 patients with low-grade or follicular NHL, median serum concentrations of rituximab were higher in responders than in nonresponders after each of the four weekly infusions and up to 3 months after treatment (e.g., 502.8 and 412.4 µg/mL, respectively, after the fourth infusion; $P = 0.01$) [40]. There was an inverse relationship between serum rituximab concentrations and baseline tumor burden indicators. Linear regression showed the inverse correlation between absolute levels of circulating peripheral B cells at the baseline and rituximab concentration to be statistically significant from the second infusion until 1 month after treatment. Inverse correlations between rituximab concentrations in serum and (1) the maximum diameter of the largest lesion and (2) the sum of the product of the perpendicular diameters of the six largest lesions were statistically significant at all time points measured with the exception of the period following the first infusion.

A similar relationship between exposure and response was seen in a phase II study of 68 Japanese patients with aggressive B-cell lymphoma [46]. Serum rituximab concentrations were evaluated in seven responders and five nonresponders. The mean (± standard deviation) trough levels and areas under curves of serum antibody concentration versus time (AUC) for responders and nonresponders were 59.7 ± 11.4 and 43.0 ± 6.4 µg/mL, respectively, and $608,585 \pm 147,373$ and $383,053 \pm$ 176,903 µg h/mL, respectively, with significant differences between groups ($P = 0.021$ and $P = 0.037$). Pretreatment tumor size (sum of the product of the perpendicular diameters) was inversely correlated with AUC ($P < 0.05$ by Spearman's rank correlation coefficient).

Other studies have shown that rituximab exposure falls as tumor volume increases, and that higher exposure correlated with better response and/or outcome [47–50]. A recent report from Tout et al. [50] in 108 previously untreated DLBCL patients demonstrated that rituximab exposure decreased as baseline total metabolic tumor volume increased, with a high AUC in cycle 1 being associated with better PET response after cycle 4 (odds ratio 5.56, $P = 0.0006$) and longer progression-free-survival (PFS; hazard ratio, HR, 0.38, $P = 0.011$) and overall survival (OS; HR 0.17, $P = 0.001$). Sex and body weight may also influence rituximab pharmacokinetics [51, 52]. In a study of 20 elderly patients (aged 61–79 years) with DLBCL, Müller et al. [51] found that rituximab clearance was reduced and $t_{1/2}$ increased in women compared with men. In addition, the volume of distribution increased by 0.1 L/kg for body weights greater than 75 kg. Although the benefit from addition of rituximab to chemotherapy is similar in younger male and female patients, this does not seem to hold true for older patients, with elderly female patients benefitting more than elderly male patients [52]. Swedish registry data have shown similar patterns, with possibly inadequate dosing in younger female patients, and male patients of all ages [53].

MANUFACTURE OF RITUXIMAB

Rituximab is produced in suspension culture by a Chinese hamster ovary transfectoma containing the TCAE 8 expression vector in a nutrient medium. Process and product impurities such as high molecular weight aggregates are then removed by protein A affinity chromatography and anion exchange chromatography. The purified rituximab is then formulated as an aqueous concentrate for intravenous administration under sterile conditions, in a

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mixture of sodium chloride (9.0 mg/mL), polysorbate 80 (0.7 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and water (solution pH 6.5, rituximab concentration 10 mg/mL), and packaged in 10- or 50-mL borosilicate glass vials. As the vials are designed for single use, no preservatives are added to the formulation. An unopened vial has a shelf life of 30 months when stored at the recommended temperature of 2–8°C.

CLINICAL EFFICACY OF RITUXIMAB

Rituximab in Follicular Lymphoma

The initial regulatory approval of rituximab in 1997 in FL was based on data from a pivotal phase II trial of rituximab monotherapy in 166 patients with relapsed or refractory low-grade NHL. The overall response rate (ORR) in this trial was 48% [complete response (CR) rate 6%], and the median time to progression for the intent-to-treat population was 13.0 months [54]. Several other trials published between 1997 and 2000 showed similar results in relapsed/refractory low-grade NHL, with overall tumor response rates ranging from 38% to 47% after 4 weeks' treatment with rituximab [55–57], and 57% after 8 weeks' treatment [58]. Each of these studies involved between 30 and 70 patients.

More recently, a 74% ORR and a 28% CR rate, with median PFS of 23.5 months and 91.7% OS rate after 7 years of follow-up, were reported in 46 patients with low tumor burden disease after first-line induction therapy with four weekly doses of rituximab at 375 mg/m^2 [59]. Two phase III studies in larger numbers of patients have also shown activity of rituximab monotherapy. Taverna et al. [60] reported a 16.9% CR/unconfirmed CR rate in 261 patients undergoing induction therapy with four doses of rituximab (this study included patients with previously untreated and relapsed/refractory disease). Subsequent short-term (four doses; $n = 82$) or long-term (5 years or less; $n = 83$) rituximab maintenance therapy yielded median event-free survival (EFS) of 3.4 and 5.3 years, respectively ($P = 0.14$). In a trial in patients with

advanced disease receiving four doses of rituximab alone ($n = 156$) or in conjunction with interferon alfa ($n = 157$) [61], there was a 78% ORR to an initial cycle of treatment. Responders who received a second cycle showed CR/unconfirmed CR rates of 21% and 41%, respectively ($P = 0.005$). The median times to treatment failure were 28 and 21.5 months, respectively ($P = 0.302$).

Since then, substantial clinical benefit has been reported in FL patients from the incorporation of rituximab into induction chemotherapy regimens in both the first-line setting [62–70] and in previously treated patients [62, 71].

Induction treatment with rituximab and chemotherapy has been shown to be superior to chemotherapy alone in several large-scale trials (typical treatment duration of 6 months), mainly conducted in previously untreated patients with stage III/IV FL, consistently achieving better results in terms of ORR, CR, time to treatment failure, PFS, and OS (Table 1). A variety of chemotherapy regimens were combined with rituximab therapy in these studies, including CHOP, cyclophosphamide, vincristine, and prednisolone (CVP), and mitoxantrone, chlorambucil, and prednisone (MCP) regimens. On the basis of the body of evidence provided by these studies, rituximab therapy plus chemotherapy has been adopted worldwide as the standard of care for the first-line treatment of patients with FL [10, 22], and the worldwide indications for rituximab are reflective of this.

The use of rituximab maintenance therapy to preserve responses to induction therapy in responding patients, and to further enhance clinical outcomes, has also been demonstrated in previously untreated patients with advanced FL, as demonstrated in the Eastern Cooperative Oncology Group (ECOG) 1496 and PRIMA trials [72–74]. In these two studies, previously untreated patients with advanced FL who had responded to either CVP (ECOG 1496) or one of three rituximab–chemotherapy induction treatment regimens [rituximab plus CVP, R-CHOP, or rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (R-FCM); PRIMA] were randomized to receive rituximab

Table 1 Summary of key studies evaluating rituximab-based immunochemotherapy in patients with previously untreated or relapsed/refractory follicular lymphoma

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
GLLSG Hiddemann et al. [63]	1L (428)	R-CHOP vs CHOP	96% vs 90%[b]	20% vs 17%	TF (median observation time 18 months): 12.6% vs 29.8%[b]	Deaths: 2.7% vs 8.3%[b]
East German Study Group Herold et al. [64]	1L (201)	R-MCP vs MCP	92% vs 75%[b]	50% vs 25%[b]	EFS: NR vs 26 months[b] PFS: NR vs 28.8 months[b] mFU: 47 months	4-year: 87% vs 74%[b]
Marcus et al. [65] Marcus et al. [66]	1L (321)	R-CVP vs CVP	81% vs 57%[b]	41% vs 10%[b]	TTF: 27 months vs 7 months[b] DFS: NR vs 21 months[b] mFU: 30 months	4-year: 83% vs 77%[b]
GELA-GOELAMS FL2000 Salles et al. [67] Bachy et al. [68]	1L (358)	R-CHVP + INF vs CHVP + INF	81% vs 72%[b]	51% vs 39%[b]	EFS: 5.5 years vs 2.8 years[b] 5-year EFS: 53% vs 37%[b] 8-year EFS: 44% vs 28%[b] mFU: 5 and 8.3 years	5-year: 84% vs 79% 8-year: 79% vs 70%
FOLL05 Federico et al. [69]	1L (504)	R-CVP vs R-CHOP vs R-FM	88% vs 93% vs 91%	67% vs 73% vs 72%	3-year TF: 46% vs 62% vs 59% HR 0.62, R-CHOP vs R-CVP[b,c], HR 0.63, R-FM vs R-CVP[b] 3-year PFS: 52% vs 68% vs 63% HR 0.64, R-CHOP vs R-CVP[b,c], HR 0.66, R-FM vs R-CVP[b,c] mFU: 34 months	3-year: 95% (all patients)

Table 1 continued

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
Rummel et al. [70]	1L (514: 420 NHL, including 279 FL; 94 MCL)	R + benda vs R-CHOP	93% vs 91%	40% vs 30%[b]	PFS: 69.5 months vs 31.2 months (HR 0.58) mFU: 45 months	Deaths: 16.5% vs 17.8%
Czuczman et al. [62]	1L and 2L (38)	R-CHOP	100% (1L 100%, R/R 100%)[d]	87% (1L 90%, R/R 78%)[d]	TTP: 82.3 months mFU: NA	
EORTC 20981 van Oers et al. [71]	R/R (465)	R-CHOP vs CHOP	85.1% vs 72.3%[b]	29.5% vs 15.6%[b]	PFS: 33.1 months vs 20.2 months (HR 0.65[b]) mFU: 39.4 months	3-year: 82.5% vs 71.9% (HR 0.74)

All studies were phase III randomized trials except for the study of Czuczman et al. [62], which was a single-arm phase II study

benda bendamustine, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CHVP* cyclophosphamide, doxorubicin, etoposide, and prednisone, *CR* complete response, *CVP* cyclophosphamide, vincristine, and prednisone, *DFS* disease-free survival, *EFS* event-free survival, *EORTC* European Organisation for Research and Treatment of Cancer, *FL* follicular lymphoma, *FM* fludarabine and mitoxantrone, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GLLSG* German Low-Grade Lymphoma Study Group, *GOELAMS* Groupe Ouest Est des Leucémies et Autres Maladies du Sang, *HR* hazard ratio, *INF* interferon, *1L* first line, *2L* second line *MCL* mantle cell lymphoma, *MCP* mitoxantrone, chlorambucil, and prednisone, *mFU* median follow-up, *NA* not available, *NHL* non-Hodgkin lymphoma, *NR* not reached, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *R* rituximab, *R/R* relapsed/refractory, *TF* treatment failure, *TTF* time to treatment failure, *TTP* time to progression

[a] Median values

[b] Statistically significant difference

[c] HR adjusted by Follicular Lymphoma International Prognostic Index 0–2 vs 3–5

[d] Updated values assessed according to International Workshop response criteria

maintenance therapy for 2 years or observation. In the ECOG 1496 study, rituximab maintenance therapy achieved a significantly higher 3-year PFS rate than observation (64% vs 33%; HR 0.4, $P < 0.001$) [72]. OS at 3 years was, however, comparable between the two arms (91% vs 86%; HR 0.6, $P = 0.08$). In the PRIMA trial, the 3-year PFS rate was 74.9% in the rituximab maintenance therapy arm compared with 57.6% for patients randomized to undergo observation (HR 0.55, $P < 0.001$) [73], and long-term follow-up (median of 73 months)

showed that the PFS benefit achieved with rituximab maintenance therapy was maintained after 6 years (59.2% vs 42.7%; HR 0.58, $P < 0.0001$) [74]. Six-year OS in the PRIMA trial was favorable with both rituximab maintenance therapy and observation, and did not differ significantly between the two arms. Neither median PFS nor median OS had been reached in the rituximab maintenance therapy arm at the 6-year follow-up.

The RESORT trial compared the efficacy of rituximab maintenance therapy with rituximab

retreatment in 545 patients with previously untreated FL and a low tumor burden [75]. The study found no difference between groups in terms of the primary end point, time to treatment failure (this outcome measure was defined as a lack of response to rituximab retreatment), time to progression of less than 26 weeks, commencement of alternative treatment, or an inability to complete planned treatment [75]. The lack of a significant benefit of rituximab maintenance therapy over rituximab retreatment may have been because the primary end point favored the retreatment arm or because the study was conducted in patients with low tumor burden, in contrast to the PRIMA study [73, 74], which was conducted in patients requiring treatment.

Similarly, in the relapsed/refractory FL setting, significant improvements in efficacy have been reported with rituximab induction therapy plus chemotherapy and rituximab maintenance therapy compared with standard chemotherapy (Table 2) [71, 76–79]. For example, superior outcomes were reported with R-FCM compared with fludarabine, cyclophosphamide, and mitoxantrone (FCM) in patients with relapsed/refractory FL or MCL enrolled in a phase III study conducted by the German Low-Grade Lymphoma Study Group [76]. In all study patients, the addition of rituximab to FCM induction therapy significantly increased ORR (79% vs 58%; $P = 0.01$), median PFS (16 months vs 10 months; $P = 0.04$), and median OS (not reached vs 24 months; $P < 0.01$) compared with FCM alone [76]. A second randomization, to rituximab maintenance therapy or observation in patients who had responded to induction therapy, showed a significant prolongation of response duration with maintenance treatment (median, not reached vs 17 months; $P < 0.001$) [77]. The phase III European Organisation for Research and Treatment of Cancer 20981 trial included an induction phase during which patients with relapsed/refractory FL were randomized to receive R-CHOP or CHOP, followed by randomization to rituximab maintenance therapy or observation for those patients who responded to induction therapy [71, 78]. The study investigators reported a significant increase in ORR (85% vs 72%;

$P < 0.001$) and PFS (33.1 months vs 20.2 months; HR 0.65, $P < 0.001$), and a trend toward an increase in 3-year OS rate (83% vs 72%; HR 0.74, $P = 0.096$) with R-CHOP compared with CHOP induction therapy. Rituximab maintenance therapy subsequently achieved a significant improvement in median PFS compared with observation (51.5 months vs 14.9 months; HR 0.40, $P < 0.001$); the 5-year OS rate was also greater with rituximab maintenance therapy (74% vs 65%; HR 0.70, $P = 0.07$), but the difference between the two arms did not achieve statistical significance. The investigators cited the unbalanced use of rituximab in postprotocol salvage treatment as a possible reason for this finding [78]. A similar pattern of results was reported in the phase III SAKK 35/98 trial evaluating induction therapy with single-agent rituximab followed by rituximab maintenance therapy or observation (Table 2) [79], further confirming the benefit of rituximab maintenance therapy in patients with relapsed/refractory FL. In a meta-analysis of data from 2315 patients in seven randomized trials, survival was significantly improved with rituximab maintenance therapy compared with observation only (HR 0.79, 95% confidence interval 0.66–0.96) for all categories of patients except those receiving first-line therapy that included rituximab induction therapy [80].

Watchful waiting until disease progression occurs has conventionally been used in FL patients with advanced disease with low tumor burden [81]. The use of rituximab in this setting to delay the need for chemotherapy or radiotherapy was explored in a multinational phase III study in 463 patients who underwent watchful waiting, rituximab induction therapy (375 mg/m^2 weekly for 4 weeks), or rituximab induction therapy followed by 2 years' maintenance therapy [82]. Of the patients in the watchful waiting group, 46% had not needed new treatment at 3 years, compared with 88% in the rituximab maintenance therapy group (HR 0.21, $P < 0.0001$). Significantly more patients in the induction therapy group than in the watchful waiting group (78%) had not needed new treatment at 3 years (HR 0.35, $P < 0.0001$), whereas the proportion not needing new treatment was similar in the

Table 2 Summary of key phase III randomized studies comparing rituximab maintenance therapy with observation after induction therapy in patients with follicular lymphoma

Study reference	Line of therapy and no. of patients	Induction regimen	RMT regimen and duration	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
GLLSG Forstpointner et al. [77]	R/R (176, including 105 FL)	R-FCM vs FCM[b]	R once weekly for 4 weeks at 3 and 6 months	Induction[b]: 95% vs 71%[c]	Induction[b]: 41% vs 23%	RMT vs OBS in FL patients with R-FCM induction therapy; DOR: NR vs 26 months[c]; mOBS: 26 months	–
EORTC 20981 van Oers et al. [71] van Oers et al. [78]	R/R (334)	R-CHOP vs CHOP	R every 3 months (max. 2 years)	Induction (n = 465): 85% vs 72%[c]	Induction (n = 465): 30% vs 16%[c]	RMT vs OBS; PFS: 51.5 months vs 14.9 months (HR 0.40)[c]; mFU: 39.4 months and 6 years	RMT vs OBS; 3-year: 85.1% vs 77.1% (HR 0.52)[c]; 5-year: 74% vs 65% (HR 0.70)
SAKK 35/98 Martinelli et al. [79]	R/R (151 randomized)	R	R at 0, 2, 4, and 6 months after end of induction therapy	–	–	RMT vs OBS; EFS: 24 months vs 13 months[c]; mFU: 9.5 years	RMT vs OBS; Patients died: 32% vs 46% (HR 0.63)
ECOG 1496 Hochster et al. [72]	1L (228)	CVP	R once weekly for 4 weeks every 6 months (2 years)	–	Induction: 12%; Maintenance: 37% RMT vs 21% OBS	RMT vs OBS; 3-year PFS: 64% vs 33%[c]; PFS: 4.3 years vs 1.3 years (HR 0.4)[c]; mFU: 3.7 years	RMT vs OBS; 3-year: 92% vs 86% (HR 0.6)

Table 2 continued

Study reference	Line of therapy and no. of patients	Induction regimen	RMT regimen and duration	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
PRIMA Salles et al. [73] Salles et al. [74]	1L (1018, including 858 confirmed FL)	R + chemotherapy (CVP, CHOP, or FCM)[d]	R once weekly every 8 weeks (2 years)	–	RMT vs OBS in all patients 71.5% vs 52.2%[c]	RMT vs OBS, all patients 3-year PFS: 74.9% vs 57.6% (HR 0.55)[c] 6-year PFS: 59.2% vs 42.7% (HR 0.58)[c] mFU: 36 and 73 months	RMT vs OBS 6-year: 87.4% vs 88.7%

CHOP cyclophosphamide, vincristine, doxorubicin, and prednisone, *CR* complete response, *CVP* cyclophosphamide, vincristine, and prednisone, *DOR* duration of response, *ECOG* Eastern Cooperative Oncology Group, *EFS* event-free survival, *EORTC* European Organisation for Research and Treatment of Cancer, *FCM* fludarabine, cyclophosphamide, and mitoxantrone, *FL* follicular lymphoma, *GLLSG* German Low-Grade Lymphoma Study Group, *HR* hazard ratio, *1L* first line, *mFU* median follow-up, *mOBS* median observation, *NR* not reached, *OBS* observation, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *R* rituximab, *RMT* rituximab maintenance therapy, *R/R* relapsed/refractory

[a] Median values

[b] Result of initial randomized comparison of R-FCM versus FCM in 68 FL patients; all subsequent patients received R-FCM induction therapy before randomization to RMT or OBS

[c] Statistically significant difference

[d] Only patients with a response to induction therapy and having received six or more cycles of R-CVP therapy, or four or more cycles of R-CHOP or R-FCM therapy (including six infusions of R) were eligible for randomization

maintenance therapy and induction therapy groups (HR 0.75, $P = 0.33$). The place of rituximab therapy relative to watchful waiting in FL remains under discussion in the literature [83].

Rituximab in Diffuse Large B-Cell Lymphoma

Rituximab is currently approved in Europe and the USA for previously untreated CD20$^+$ DLBCL in combination with CHOP or other anthracycline-based chemotherapy and is also included in current treatment guidelines in combination with salvage chemotherapy for relapsed/refractory disease [9, 22]. A phase II trial of R-CHOP as first-line treatment in patients with aggressive NHL (67% with DLBCL) was the first study to demonstrate the feasibility and safety of R-CHOP in this population, with an ORR of 94% and 20 of 33 patients (61%) having a CR [84].

Two pivotal phase III randomized trials established R-CHOP therapy as the standard of care for elderly patients with DLBCL [85, 86] (Table 3). In a study conducted by the Groupe d'Etude des Lymphomes de l'Adulte (GELA; LNH98-5), previously untreated elderly patients (aged 60–80 years) with DLBCL were randomized to receive eight cycles of R-CHOP or CHOP therapy [85]. Sixty percent of patients were deemed to be poor risk, with age-adjusted IPI scores of 2 or 3. The CR rate was significantly higher in favor of R-CHOP (76% vs 63%; $P = 0.005$). The proportions of patients with EFS (disease progression or relapse, institution of new treatment, or any-cause death) at 2 years (57% vs 38%; HR 0.58, $P < 0.001$) and OS at 2 years (70% vs 57%; HR 0.64, $P = 0.007$) also favored R-CHOP. In a second phase III study (ECOG 4494/US Intergroup study), DLBCL patients aged 60 years or older were randomized to receive R-CHOP or CHOP, followed by a second randomization for responding patients to rituximab maintenance therapy or observation [86]. The proportion of patients with failure-free survival (FFS; time from randomization to relapse, non-protocol treatment, or death) at 3 years was significantly higher with R-CHOP than with CHOP (53% vs 46%; HR 0.78, $P = 0.04$). In addition, the 2-year FFS rate from the second randomization

was 76% for rituximab maintenance therapy compared with 61% for observation ($P = 0.009$). Subanalyses showed that rituximab maintenance therapy significantly prolonged FFS after CHOP therapy (HR 0.45, $P = 0.0004$) but not after R-CHOP therapy, thus implying that rituximab maintenance therapy after rituximab-based immunochemotherapy does not provide additional clinical benefit in patients aged 60 years or older with DLBCL. No significant differences in OS were reported.

In terms of younger patients, the MabThera International Trial (MInT) Group confirmed the benefit of adding rituximab therapy to CHOP chemotherapy compared with CHOP chemotherapy alone (given for a total of six cycles) in patients aged 18–60 years with previously untreated, good-prognosis DLBCL [87, 88]. R-CHOP therapy was associated with a significant increase in 3-year EFS rate (79% vs 59%; $P < 0.0001$), 3-year PFS rate (85% vs 68%; $P < 0.0001$), and 3-year OS rate (93% vs 84%; $P = 0.0001$) compared with CHOP chemotherapy alone [87] (Table 3). In the R-CHOP and CHOP groups, patients considered to be at low risk (IPI score of 0 and no bulky disease) had significantly longer EFS than those at higher risk (IPI score of 1, bulky disease, or both). Importantly, subsequent follow-up reports from the GELA trial and MInT indicated that the beneficial effect of R-CHOP therapy over CHOP chemotherapy alone was sustained over the longer term in both older patients (GELA trial, 5-year OS rate 58% vs 45%, $P = 0.007$; 10-year OS rate 44% vs 28%, $P < 0.0001$) [89, 90] and younger patients (MInT, 6-year OS rate 90% vs 80%, $P = 0.0004$) [88]. Comparison of rituximab maintenance therapy and observation only in the randomized NHL-13 trial, which enrolled 683 patients with DLBCL who had responded to first-line rituximab therapy plus CHOP-like chemotherapy, showed no difference in the primary end point of EFS after a median follow-up of 45 months [91]; however, PFS was significantly improved in the maintenance therapy arm relative to the observation arm.

Salvage chemotherapy may be an option for patients with DLBCL that is refractory to induction therapy or who subsequently relapse after achieving a CR. As monotherapy,

Table 3 Summary of key studies evaluating rituximab-based immunochemotherapy in patients with previously untreated or relapsed/refractory diffuse large B-cell lymphoma

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
1L: elderly patients						
GELA, LNH98-5 study, phase III Coiffier et al. [85] Feugier et al. [89] Coiffier et al. [90]	1L (399), median age 69 years	R-CHOP vs CHOP, 8 cycles	83% vs 69%	76% vs 63%[b]	2-year EFS: 57% vs 38% (HR 0.58)[b] 5-year PFS: 54% vs 30%[b] 10-year PFS: 37% vs 20%[b] mFU: 24 months, 5 years, NA	2-year: 70% vs 57% (HR 0.64)[b] 5-year: 58% vs 45%[b] 10-year: 44% vs 28%[b]
ECOG 4494/CALGB 9793, phase III Habermann et al. [86]	1L (546), median age 69 years (R-CHOP), 70 years (CHOP)	R-CHOP vs CHOP, 6–8 cycles[c]	77% vs 76%	–	3-year FFS: 53% vs 46% (HR 0.78)[b] mFU: NA	HR 0.83, 95% CI 0.63–1.09
1L: younger patients						
MInT, phase III Pfreundschuh et al. [87] Pfreundschuh et al. [88]	1L (823), median age 47 years	R-CHOP (or R + CHOP-like chemotherapy) vs CHOP (or CHOP-like chemotherapy), 6 cycles	–	86% vs 68%[b]	At mFU of 34 months: 3-year EFS: 79% vs 59%[b] 3-year PFS: 85% vs 68%[b] At mFU of 72 months: 6-year EFS: 74.3% vs 55.8%[b] 6-year PFS: 80.2% vs 63.9%[b]	3-year: 93% vs 84% (at mFU of 34 months)[b] 6-year: 90.1% vs 80.0% (at mFU of 72 months)[b]

Table 3 continued

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
R/R						
Phase III studies						
Gisselbrecht et al. [94]	R/R (396)	R-ICE vs R-DHAP	63.5% vs 62.8%	36.5% vs 39.3% (including CRu)	3-year EFS: 26% vs 35%; 3-year PFS: 31% vs 42%; mFU: 27 months	3-year: 47% vs 51%
Vellenga et al. [93]	R/R (225, including 21 other aNHL)	R-(DHAP-VIM-DHAP) vs DHAP-VIM-DHAP; ASCT	75% vs 54%[b]		2-year PFS: 52% vs 31%[b]; mFU: 31 months	2-year: 59% vs 52%
Phase II studies						
Jermann et al. [95]	R/R (50, including 25 DLBCL, 18 TBCL, 7 MCL)	R-EPOCH	68%	28%	EFS: 11.8 months (MCL 15 months, TBCL 12.4 months, DLBCL 9.7 months); mFU: 33 months	17.9 months
Kewalramani et al. [96]	R/R (36)	R-ICE vs ICE (147 historical controls) + ASCT for responders	78% vs 71%	53% vs 27%[b]	2-year PFS: 54% vs 43% (after ASCT); mFU: NA	2-year: 67% vs 56% (after ASCT)
Mey et al. [97]	R/R (46)	R-DHAP (23) vs DHAP (23); matched-pair analysis of data from 2 phase II trials	74% vs 74%	44% vs 35%	PFS: NR vs 13.0 months; 2-year PFS: 52% vs 50%; mFU: NA	NR vs 31.3 months; 2-year: 57% vs 52%

Table 3 continued

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
Elstrom et al. [98]	R/R (15, including 6 TBCL, 9 DLBCL)	R-DICE + BOR	60%	20%	PFS: 3 months mFU: 26 months	10 months

aNHL aggressive non-Hodgkin lymphoma, *ASCT* autologous stem cell transplantation, *BOR* bortezomib, *CALGB* Cancer and Leukemia Group B *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *CI* confidence interval, *CR* complete response, *CRu* unconfirmed complete response, *DHAP* dexamethasone, cytarabine, and cisplatin, *DICE* dexamethasone, ifosfamide, cisplatin, and etoposide, *DLBCL* diffuse large B-cell lymphoma, *ECOG* Eastern Cooperative Oncology Group, *EFS* event-free survival, *EPOCH* etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, *FFS* failure-free survival, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *HR* hazard ratio, *ICE* ifosfamide, carboplatin, and etoposide, *1L* first-line, *MCL* mantle cell lymphoma, *mFU* median follow-up, *MInT* MabThera International Trial, *NA* not available, *NR* not reached, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *R* rituximab, *R/R* relapsed/refractory, *TBCL* transformed B-cell lymphoma, *VIM* etoposide, ifosfamide, and methotrexate

[a] Median values

[b] Statistically significant difference

[c] Patients underwent a second randomization to R maintenance therapy or observation if they achieved a CR or partial response after the first randomization

rituximab achieved promising response rates in 54 patients, mostly with relapsed/refractory DLBCL, in a phase II study [92]. Subsequently, rituximab was evaluated in combination with a variety of salvage chemotherapy regimens in phase II and phase III studies in this setting, including ifosfamide, carboplatin, and etoposide (ICE), dexamethasone, cytosine arabinoside, and cisplatin (DHAP), and etoposide, ifosfamide, and methotrexate (VIM) regimens (Table 3). In a randomized phase III study, the addition of rituximab therapy to DHAP–VIM–DHAP therapy followed by autologous stem cell transplantation in 225 patients with relapsed or refractory aggressive NHL resulted in a significant improvement in FFS and PFS compared with chemotherapy alone [93]. The second randomized phase III trial, in 396 patients, demonstrated similar efficacy results for rituximab plus ICE and rituximab plus DHAP but did not include a chemotherapy-only arm; the study authors considered that neither regimen offered any benefit over other rituximab-based regimens given before or after autologous stem cell transplantation in previous studies [94]. Other studies in this setting were smaller in scale (50 or fewer patients) and did not include control arms [95–98]; however, the findings from two of these studies suggested potential benefits from the addition of rituximab therapy to chemotherapy when compared with historical data [95, 96] (Table 3).

Rituximab in Chronic Lymphocytic Leukemia

In Europe and the USA, intravenously administered rituximab is approved in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL [11, 23, 29, 30]. Two large phase III randomized studies investigating the concurrent administration of rituximab plus FC (R-FC) compared with FC alone were conducted in patients with CLL [99, 100] (Table 4). Both studies were initiated on the basis of the findings of earlier phase I/II monotherapy and combination chemotherapy studies [101–106]. In the CLL8 trial, R-FC was compared with FC alone in patients with CLL

Table 4 Summary of key studies evaluating rituximab combination therapy in patients with previously untreated or relapsed/refractory chronic lymphocytic leukemia

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
Phase III studies						
CLL8 Hallek et al. [99] Fischer et al. [107]	1L (817), median age 61/61 years (R-FC/FC)	R-FC vs FC, 6 cycles	90% vs 80%[b]	44% vs 22%[b]	mFU: 3.1 years PFS: 51.8 months vs 32.8 months (HR 0.56)[b] 3-year PFS: 65% vs 45%[b] mFU: 5.9 years PFS: 56.8 months vs 32.9 months (HR 0.59)[b] 5-year PFS: 47% vs 26%[b]	3-year: 87% vs 83% (HR 0.67)[b] mFU: 5.9 years NR vs 86.0 months (HR 0.68)[b]
CLL10 Eichhorst et al. [116]	1L fit (561), median age 62/61 years (R-FC/BR)	R-FC vs BR, 6 cycles	95% vs 96%	40% vs 31%[b]	mFU: 37.1 months PFS: 55.2 months vs 41.7 months (HR 1.643)[b] DOR: 52.7 months vs 38.9 months (HR 1.657)[b] EFS: 55.2 months vs 38.5 months (HR 1.626)[b]	3-year: 91% vs 92% (HR 1.034)
REACH Robak et al. [100]	Previously treated (552), median age 63/62 years (R-FC/FC)	R-FC vs FC, 6 cycles	69.9% vs 58.0%[b]	24.3% vs 13.0%[b]	mFU: 25 months PFS: 30.6 months vs 20.6 months (HR 0.65)[b]	NR vs 52 months (HR 0.83)[b]
Phase II studies						
Keating et al. [105]	1L (224), median age 58 years	R-FC, 6 cycles	95%	70%	4-year FFS: 69%	mFU: 2 years. Deaths in 8.9%

Table 4 continued

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
Tam et al. [110]c	1L (300), median age 57 years	R-FC, 6 cycles	95%	72%	mFU: 6 years TTP: 80 months 6-year FFS: 51%	6-year: 77%
Wierda et al. [106]	R/R (177), median age 59 years	R-FC, 6 cycles	73%	25%	mFU: 28 months TTP: 28 months	mFU: 28 months 42 months
Foon et al. [111] Foon et al. [112]	1L (63), median age 58 years	R-FC lite	94%	73%	PFS: 5.8 years 5-year PFS: 66.9%	NR 5-year: 85.5%
GCLLSG Fischer et al. [115]	1L (117), median age 64 years	BR, 6 cycles	88%	23%	mFU: 27 months EFS: 33.9 months PFS: 33.8 months	mFU: 27 months. 90.5% alive
CALGB 9712 Woyach et al. [113]	1L (104), median age 63 years	FR sequentially vs FR concurrently	84% (all FR patients)	–	mFU: 117 months PFS: 42 months 5-year PFS: 28% 10-year PFS: 13%	mFU: 117 months 85 months 5-year: 71%
GCLLSG Fischer et al. [114]	R/R (78), median age 67 year	BR, 6 cycles	59%	9%	mFU: 24 months EFS: 14.7 months PFS: 15.2 months	mFU: 24 months 33.9 months

Table 4 continued

Study reference	Line of therapy and no. of patients	Treatment regimen	ORR	CR	PFS, EFS, or other parameter as indicated[a]	OS
Foà et al. [117]	1L (97), median age 70 years	R-Clb vs Clb, 6 cycles (induction); responders randomized to R or OBS	82.4% (induction) 55.9% R 34.4% OBS	16.5% (induction) 29.4 R 18.7% OBS	3-year PFS: 42.7% 3-year EFS: 38.2% For R: over 3-year PFS 48.6% For OBS: over 3-year PFS 31.8% mFU: 34.2 months (34.9 months in randomized population)	NA
Hillmen et al. [118]	1L (100), median age 70 years	R-Clb, 6 cycles (6 additional cycles in nonresponders)	84%	10%	Median PFS: 23.5 months mFU: 30 months	NR

BR bendamustine and rituximab, *CALGB* Cancer and Leukemia Group B, *Clb* chlorambucil, *CR* complete response, *DOR* duration of response, *EFS* event-free survival, *FC* fludarabine and cyclophosphamide, *FFS* failure-free survival, *FR* fludarabine and rituximab, *GCLLSG* German Chronic Lymphocytic Leukemia Study Group, *HR* hazard ratio, *1L* first line, *mFU* median follow-up, *NA* not available, *NR* not reached, *OBS* observation, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *R* rituximab, *R/R* relapsed/refractory, *TTP* time to progression

[a] Median values

[b] Statistically significant difference

[c] Six-year update of Keating et al. [105] with final results for all study patients (n = 300)

who had not received any prior chemotherapy [99]. Median PFS was significantly prolonged (by 19 months) with R-FC compared with FC (HR 0.56, $P < 0.0001$), with results favoring R-FC for all three Binet stage subgroups. A significant benefit in favor of R-FC over FC was also observed in terms of OS (HR 0.67, $P = 0.012$), and ORR and CR rate ($P < 0.0001$) [99]. In an updated analysis of the CLL8 trial, median PFS with R-FC was almost twice as long as with FC (56.8 months vs 32.9 months; HR 0.59, $P < 0.001$) and median OS was also significantly prolonged (R-FC, not reached; FC, 86.0 months; HR 0.68, $P = 0.001$) [107]. In previously treated patients with CLL in the REACH study, R-FC treatment was associated with a 10-month improvement in median PFS compared with FC (30.6 months vs 20.6 months; HR 0.65, $P < 0.001$) [100]. Consistent with the CLL8 study, improvements in PFS in the R-FC arm were also associated with significant increases in both the ORR and the CR rate. On the basis of the findings from these studies, R-FC became a first-choice treatment for patients with newly diagnosed or relapsed CD20$^+$ CLL. Indeed, R-FC may be able to affect a cure in a subset of CLL patients with favorable genetic profiles: long-term follow-up of patients treated with R-FC in clinical trials has shown that those with mutated *Ig heavy chain variable region gene* status and without the 17p and 11q deletions achieve very long remissions [107–109].

Data from other, mostly phase II studies evaluating rituximab combination therapy in patients with previously untreated and relapsed/refractory CLL have also been published, and are summarized in Table 4. These data are consistent with the results of the CLL8 and REACH studies, and provide further confirmation of the clinical efficacy of R-FC in CLL [105, 106, 110–113]. Promising results have also been reported with the combination of rituximab and bendamustine in a phase II study involving patients with both previously untreated and relapsed/refractory CLL [114, 115]. However, recently published data from the phase III CLL10 trial in 564 previously untreated, fit CLL patients showed that rituximab plus bendamustine was associated with significantly shorter PFS than R-FC (median

41.7 months vs 55.2 months; HR 1.64, $P = 0.0003$) [116]. Although there was a clear difference in PFS between the two study treatments in the overall patient population, subgroup analyses showed that the PFS benefit in the R-FC arm was significant only in younger patients (65 years or younger). Additionally, the tolerability (notably the incidence of severe infections) was better with rituximab plus bendamustine, particularly among patients older than 65 years. Taken together, these findings suggest that although R-FC may be the more effective regimen overall, rituximab plus bendamustine may have a role in the treatment of fit, older patients with CLL.

Another widely used treatment option for less fit patients with CLL is rituximab plus chlorambucil. In two phase II studies in previously untreated patients who received the combination ($n = 85$ and 100), adverse event (AE) profiles were favorable, and ORRs of up to 84% were achieved, with CR rates of 17% and 10% [117, 118].

The potential benefit of rituximab maintenance therapy in CLL has also been explored in a small number of studies, with some encouraging results [119–121]. In a phase II study in previously untreated CLL patients, for example, 4-year PFS and OS rates were 74.8% and 93.7%, respectively, in 67 patients who received rituximab maintenance therapy after responding to R-FCM induction therapy, compared with 69.1% and 90.5%, respectively, for the patient population overall ($n = 81$; treated with R-FCM as induction therapy with or without rituximab maintenance therapy) [120]. Results from the randomized CLL 2007 SA trial of 2 years of rituximab maintenance therapy versus observation following induction therapy with four cycles of R-FC therapy in patients aged 65 years or older included a significant improvement in median PFS (59.3 months vs 49.0 months; HR 0.60, $P = 0.001$). Rituximab maintenance therapy also improved PFS in patients with genetic markers indicative of poorer prognosis, although no difference in 3-year OS was seen, and maintenance treatment was associated with a greater incidence of AEs [121]. In addition, studies are ongoing to determine the efficacy and safety of rituximab in combination with

newer agents such as inhibitors of Bruton's tyrosine kinase and phosphoinositide 3-kinase, as well as inhibitors of the mechanistic target of rapamycin, and BCL2 inhibitors [122–125]. However, approval of these new drugs could be many years away in many countries, and in those with more limited healthcare budgets, the cost of these agents is likely to be prohibitive; for this reason, immunochemotherapy with rituximab combined with FC, bendamustine, or chlorambucil will continue to be a mainstay of patient treatment.

Other B-Cell Malignancies

Encouraging results have also been reported in four studies of rituximab in other B-cell malignancies for which use of the drug is not yet licensed.

In the final report of the randomized IELSG-19 study in 454 patients with extranodal marginal-zone B-cell lymphoma, a combination of rituximab and chlorambucil was associated with significantly longer EFS and PFS than chlorambucil or rituximab alone after a median follow-up of 7.4 years [126]. In a randomized phase III trial of 52 nonfollicular indolent NHL patients with low tumor burden who responded to rituximab induction therapy, those who received 3-monthly rituximab maintenance therapy had a 3.5-fold longer time to treatment failure than those who received retreatment at the time of progression [127]. In two other trials that assessed the addition of rituximab therapy to chemotherapy in highly aggressive lymphoid malignancies, significant increases in EFS relative to chemotherapy alone were seen in 209 patients with CD20$^+$, Philadelphia chromosome-negative acute lymphoblastic leukemia after a median follow-up of 30 months [128], and in 260 patients with previously untreated Burkitt lymphoma after a median follow-up of 38 months [129].

Rituximab has also been shown to improve OS in older patients with MCL, both in the first-line setting when added to induction chemotherapy and when used as maintenance therapy after rituximab therapy plus chemotherapy as induction therapy [130, 131].

Additional B-cell malignancies in which rituximab treatment has been associated with positive outcomes in phase II and phase III clinical trials include Waldenström macroglobulinemia, posttransplant lymphoproliferative disorders, and Hodgkin lymphoma [132–134]. Rituximab is not yet licensed for use in any of these diseases.

Development of Resistance to Rituximab

Although the efficacy of rituximab for the treatment of B-cell hematologic malignancies is well established, some patients do not respond to first-line treatment, and others experience relapse after initial response to therapy [54, 135].

Despite many years of study, the exact mechanisms underlying the development of resistance to rituximab remain unclear. However, given the reliance of rituximab on immune-effector mechanisms for its antitumor efficacy, it has been hypothesized that intrinsic tumor cell alterations and the host immunologic environment may both play a role. There are many postulated in vivo mechanisms of resistance, and these are described in detail elsewhere [136, 137]. In brief, they include inhibition of three of the pathways that are involved in the mechanism of action of rituximab; namely, CDC, ADCC, and apoptosis. Complement depletion, through exhaustion of the store of complement proteins, has been implicated in the development of resistance to rituximab-mediated CDC. Furthermore, host immunologic factors, such as polymorphism of Fcγ receptor IIIa on cytotoxic cells, may affect the sensitivity of tumor cells to ADCC, whereas alterations in apoptotic pathway signaling, through overexpression of antiapoptotic gene products, may facilitate the development of apoptosis resistance in the presence of rituximab [136, 137]. Another possible mechanism of rituximab resistance is loss of the CD20 target antigen, which has been demonstrated in lymphoma cell lines and in biopsy samples from relapsed patients [138, 139]. This phenomenon may occur in several ways, including decreased expression at both the pretranslational level

and the posttranslational level, antigenic modulation (whereby CD20 antibody–antigen complexes are internalized following rituximab binding), or the acquisition of CD20 mutations. Removal of rituximab/CD20 complexes from the B-cell surface by monocytes in a process called "trogocytosis" or "CD20 shaving" has also been reported [140]. In addition, generation of rituximab-resistant clones, the tumor microenvironment, and the PK profile of rituximab may also have a role in the development of rituximab resistance [136, 137].

Patients treated with rituximab may develop an antibody against rituximab, termed "human antichimeric antibody." These patients have the potential to mount allergic reactions when subsequently treated with other antibodies. To date, immune responses against rituximab have been much more common in patients treated for rheumatoid arthritis than in those with other diseases. During clinical trials in patients with B-cell malignancies, up to 2% of patients developed human antichimeric antibody, but no effect of this antibody on the efficacy or safety of rituximab has been demonstrated [29, 30].

Various strategies are being investigated to overcome rituximab resistance. One such approach is the use of adjuncts to inhibit hyperactivated survival/antiapoptotic pathways, which regulate downstream antiapoptotic gene products. Possible candidates include histone deacetylase inhibitors, targeted chemical inhibitors, proteasome inhibitors, selective inhibitors for antiapoptotic gene products, and microRNAs [137]. The combination of rituximab and lenalidomide, an immunomodulatory drug that has been shown to enhance ADCC in in vitro and in vivo leukemia models, has demonstrated efficacy in patients with indolent B-cell lymphomas, DLBCL, and CLL who were rituximab resistant or had previously relapsed following rituximab therapy [141–144]. Another important avenue of research to counter rituximab resistance is the development of novel, next-generation anti-CD20 mAbs with different mechanisms of action. This approach is exemplified by obinutuzumab, a second-generation type II anti-CD20 mAb, which has recently been approved in

combination with bendamustine followed by single-agent maintenance therapy for the treatment of patients with FL who do not respond to or whose disease progresses after treatment with rituximab or a rituximab-containing regimen [145].

SAFETY AND TOLERABILITY OF RITUXIMAB IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Overview of the Safety Profile

With 20 years of postmarketing surveillance experience and more than four million patient exposures, the safety profile of rituximab, both as monotherapy (induction and/or maintenance) and in combination with chemotherapy, in the treatment of patients with B-cell hematologic malignancies is very well defined. Furthermore, in the two decades since the regulatory approval of rituximab, no new or unexpected safety signals have been identified, thus confirming a favorable therapeutic window.

From clinical trial and postmarketing surveillance data from patients with NHL and CLL, infusion-related reactions (IRRs) were identified as the most common adverse drug reactions (ADRs) in patients treated with rituximab as monotherapy or combination therapy [29, 30]. In those studies, IRRs of any grade and type, including cytokine-release syndrome, were observed in 77% of patients. Severe IRRs (grade 3 or 4), including bronchospasm and hypotension, were reported in 12% of patients [29]. Although rare, fatal reactions have occurred within 24 h of drug infusion (most commonly with the first infusion), and it is therefore recommended that patients be closely monitored, and treatment be stopped if there is a severe reaction [30]. Most IRRs occurred during the first rituximab infusion (in the first 1–2 h), and the frequency of reactions typically decreased with subsequent infusions, to less than 1% after eight doses of rituximab [29, 30]. Now that physicians have more experience of

rituximab administration, the management of IRRs has improved, for example, by use of slower infusion rates and by premedication (described later), and IRRs now occur less frequently than during the registration trials.

In addition to IRRs, other common AEs reported in patients treated with rituximab include infections, hematologic AEs, and cardiovascular events. Infections (bacterial and viral) were reported in approximately 30–55% of patients with NHL and in about 30–50% of patients with CLL in clinical trials. Grade 3/4 infections occurred in approximately 4% of patients treated with rituximab as monotherapy in randomized studies, and were more common with rituximab maintenance therapy than with observation [29, 30]. Documented infections in rituximab-treated patients included localized Candida infections, herpes zoster, and cytomegalovirus infections. Rarely, cases of fatal progressive multifocal leukoencephalopathy and severe mucocutaneous reactions, some of which were fatal, have occurred [30]. Hepatitis B reactivation has also been reported, mainly in patients receiving rituximab plus chemotherapy, with outcomes of fulminant hepatitis, hepatic failure, and death in some cases [30]. Among patients with relapsed/refractory CLL, grade 3/4 hepatitis B (reactivation and primary infection) was reported in 2% of patients treated with R-FC compared with 0% of patients treated with FC [29].

Generally mild and reversible cytopenias, including neutropenia, leukopenia, and thrombocytopenia, were reported during treatment with rituximab as monotherapy for 4 weeks in clinical trials, and grade 3/4 events were relatively uncommon, occurring in 4.2% (neutropenia), 1.1% (anemia), and 1.7% (thrombocytopenia) of patients [29]. Compared with observation, patients treated with rituximab as maintenance therapy for up to 2 years experienced a higher incidence of grade 3/4 leukopenia (5% vs 2%) and neutropenia (10% vs 4%) but a similar low incidence of thrombocytopenia (both less than 1%). In clinical studies in NHL and CLL, rituximab therapy plus chemotherapy (CHOP, FC, or CVP) was generally associated with a higher incidence of grade 3/4 leukopenia, neutropenia, and pancytopenia

compared with chemotherapy alone [29, 30]; however, despite the increased incidence of neutropenia, patients treated with rituximab plus chemotherapy were not at higher risk of developing infections compared with patients treated with chemotherapy alone [29]. In studies in previously untreated and relapsed/refractory CLL, prolonged neutropenia (resolving between 24 and 42 days after the last dose) or late-onset neutropenia (resolving later than 42 days after the last dose) was reported more frequently in those receiving R-FC than in those receiving FC alone (up to 25% of R-FC patients) [29, 30].

Cardiovascular events were reported in up to 25% of patients receiving rituximab monotherapy in clinical trials, most commonly hypotension and hypertension [29, 30]. Some cases of grade 3/4 arrhythmias and angina pectoris were also reported during infusion of rituximab. In the maintenance setting, cardiac disorders were reported as serious AEs in 3% of rituximab-treated patients and in less than 1% of untreated patients [29]. In studies evaluating rituximab in combination with chemotherapy, R-CHOP was associated with a higher incidence of grade 3/4 cardiac arrhythmias (mainly tachycardia and atrial flutter/fibrillation) compared with CHOP [29, 30]; however, there was no difference between R-CHOP and CHOP in terms of the incidence of other grade 3/4 cardiac events, including heart failure, myocardial disease, and manifestations of coronary artery disease [29].

Other common AEs reported with rituximab therapy include respiratory system disorders (e.g., dyspnea, cough, and chest pain), gastrointestinal disorders (e.g., nausea, vomiting, and diarrhea), skin and suncutaneous tissue disorders (e.g., pruritus, rash, and urticaria), metabolic disorders (e.g., angioedema and hyperglycemia), and nervous system disorders (e.g., paresthesia, hypoesthesia, and agitation) [29, 30]. In addition, IgG levels are frequently reduced among rituximab-treated patients, with levels below the lower limit of normal reported in approximately 60% of patients with FL receiving rituximab maintenance therapy for 2 years (vs 36% in the observation group) [29].

Safety in Patient Subpopulations

In the current summary of product characteristics for rituximab, brief reference is made to the tolerability profile of rituximab monotherapy in specific patient subpopulations with NHL, including older patients (65 years or older), patients with bulky disease, and patients undergoing retreatment [29]. In older patients, the incidence of ADRs (all grades) and grade 3/4 ADRs is generally similar to that seen in younger patients (younger than 65 years). However, in patients with previously untreated or relapsed/refractory CLL treated with rituximab plus chemotherapy, the incidence and severity of grade 3/4 hematologic AEs and bacterial infections was found to be higher in patients aged 70 years or older than in younger patients [30]. In the monotherapy setting, patients with bulky B-cell lymphomas experienced a higher incidence of grade 3/4 ADRs than those with nonbulky disease (25.6% vs 15.4%), although the incidence of ADRs of any grade was generally similar in the two groups [29]. Retreating patients with further courses of rituximab monotherapy does not appear to affect the drug's tolerability profile, with the proportion of patients experiencing ADRs during later treatment courses being similar to that during initial exposure (both for grade 3/4 ADRs and for ADRs of any grade) [29]. Information on the safety profile of rituximab in children and adolescents is currently scarce, but a randomized phase III trial that is assessing the addition of rituximab therapy to chemotherapy in this subpopulation [146] will help to address this issue.

Management and Prevention Strategies for Rituximab-Associated Adverse Events

Current rituximab patient information provides details of management and prevention strategies for rituximab-associated AEs [29, 30]. Before infusion of rituximab, all patients should receive premedication, comprising an antihistamine and acetaminophen (paracetamol), to minimize the occurrence of cytokine-mediated reactions (flushing, low blood pressure, etc.). In patients with CLL, adequate hydration and administration of uricostatics starting 48 h before infusion of rituximab is recommended to reduce the risk of tumor lysis syndrome. Prednisone (100 mg intravenously) should also be administered shortly before rituximab infusion to decrease the rate and severity of acute infusion reactions and/or cytokine-release syndrome; European prescribing information recommends this for CLL patients with lymphocyte counts greater than 25×10^9/L [29].

In the event of mild-to-moderate IRRs, the infusion rate should be decreased and then increased on symptom abatement. Some physicians use a more rapid infusion (90-min duration) for all infusions after the first dose, and this dosing option is approved in the USA. All patients should undergo screening for hepatitis B, including assessment of hepatitis B surface antigen and hepatitis B core antibody status, before treatment with rituximab because of the possible risk of reactivation of the disease. Consideration should also be given to withholding antihypertensive medicines 12 h before rituximab infusion because of the risk of hypotension.

PHARMACOECONOMIC CONSIDERATIONS

Numerous pharmacoeconomic analyses of rituximab have been conducted in the last 20 years that show rituximab is a cost-effective option compared with reference interventions for the treatment of B-cell hematologic malignancies, with the incremental cost-effectiveness ratios consistently at or below national willingness-to-pay thresholds. Table 5 presents a summary of the key findings from analyses published between 2010 and 2016, specifically evaluating the cost-effectiveness of intravenously administered rituximab for the treatment of FL [147–154], DLBCL [155–157], and CLL [158–161]. These studies were performed in a variety of countries (including several European countries, the USA, Canada, and Australia) from either a payer perspective or a societal perspective. Most of the analyses used Markov models that incorporated outcomes data from

Table 5 Summary of results from pharmacoeconomic analyses published between 2010 and 2016 evaluating the cost-effectiveness of intravenously administered rituximab for the treatment of B-cell hematologic malignancies

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Follicular lymphoma					
Deconinck et al. [147]	R/R, RMT, or OBS after induction therapy (R-CHOP or CHOP)	France (2006, national healthcare system perspective)	Markov model PFS and OS data from EORTC 20981, French official cost data, literature, expert opinion	Direct: drug acquisition, drug administration, treatment of AEs, FU visits (clinical examination, diagnostics), investigations, radiotherapy, routine patient management	RMT vs OBS €71,314 vs €62,251 (lifetime costs) ICER/LYG: €7612 ICER/QALY gained: €8729
Ray et al. [148]	1L, R + chemotherapy (MCP, CVP, CHOP, or CHVP) vs chemotherapy	UK (2008, national healthcare system perspective)	Markov model Event rate data from four phase III clinical trials, life table data, National Health Service references and published literature	Direct: drug acquisition, drug administration, routine patient management and surveillance	R + chemotherapy vs chemotherapy £28,582 to £33,513 vs £20,708 to £29,621 (lifetime costs) ICER/LYG: £6503 (R-MCP), £7473 (R-CVP), £9294 (R-CHOP), £7370 (R-CHVP) ICER/QALY gained: £7455 (R-MCP), £8613 (R-CVP), £10,676 (R-CHOP), £8498 (R-CHVP)

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Soini et al. [149]	R/R, R-CHOP (induction), R-CHOP-R (induction + maintenance), or CHOP	Finland (2008, national healthcare system perspective)	Markov model PFS and OS data from EORTC 20981, official drug cost listings, Finnish case-mix-adjusted national unit costs for healthcare resources	Direct: drug acquisition, drug administration (including traveling), relapse management, routine treatment, treatment of AEs	R-CHOP vs R-CHOP-R vs CHOP €59,521 vs €68,331 vs €49,562 (lifetime costs) ICER/LYG: R-CHOP-R vs R-CHOP €16,380; R-CHOP-R vs CHOP €13,041; R-CHOP vs CHOP €11,049 ICER/QALY gained: R-CHOP-R vs R-CHOP €18,147; R-CHOP-R vs CHOP €14,360; RCHOP vs CHOP €12,123
Griffiths et al. [150]	1L (elderly) R + chemotherapy (CVP, CHOP) vs chemotherapy (CVP, CHOP)	USA (2009, Medicare perspective)	Observational cohort SEER registry data, Medicare claims data	Direct: drug acquisition, cancer care, noncancer care (all total direct costs to Medicare)	R + chemotherapy vs chemotherapy Incremental total cost: $18,695 (costs over 4 years) ICER/LYG: €102,142

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Hornberger et al. [151]	RMT or OBS (after 1L R + chemotherapy)	USA (NA, payer perspective)	Markov model. Event rate data from PRIMA and EORTC 20981, Centers for Disease Control and Prevention data, Centers for Medicare and Medicaid Services data, published literature	Direct: drug acquisition, drug administration, management of AEs, outpatient monitoring, postprogression care	RMT vs OBS. $183,963 vs $145,418 (lifetime costs). ICER/LYG: $31,934. ICER/QALY gained: $34,842
Blommestein et al. [152]	R/R, RMT vs OBS (3 scenarios: trial efficacy + costs, trial efficacy + matched real-world costs, real-world efficacy + costs)	Netherlands (2012, healthcare system perspective)	Markov model. PFS and OS data from EORTC 20981, population-based registries, Netherlands Cancer Registry, literature, national reference list for drug prices	Direct: drug acquisition, hospital inpatient days, day treatment, outpatient days, AEs, postprogression care	RMT vs OBS. Trial efficacy + costs €17,425, trial efficacy + real-world costs €32,668, real-world efficacy + costs €23,736 (lifetime incremental costs). ICER/LYG: trial efficacy + costs €11,259, trial efficacy + real-world costs €21,202, real-world efficacy + costs €10,591. ICER/QALY gained: trial efficacy + costs €12,655, trial efficacy + real-world costs €23,821, real-world efficacy + costs €11,245

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Chen et al. [153]	1L, RMT vs OBS	USA (2013, payer perspective)	Markov models PFS and OS data from PRIMA and ECOG 1496, literature, Medicare physician fee schedule, Centers for Medicare and Medicaid Services database, life table data, expert opinion	Direct: drug acquisition, drug administration, monitoring, blood tests, CT scans, AEs, hospitalization	RMT vs OBS lifetime costs: PRIMA $112,781 vs $68,856; ECOG 1496 $124,406 vs $72,066 ICER/LYG: PRIMA $39,968; ECOG 1496 $37,627 ICER/QALY gained: PRIMA $40,335; ECOG 1496 $37,412
Prica et al. [154]	1L, RIT + RMT vs RIT (only) vs WW	Canada (2012, payer perspective)	Markov model Survival, response and QOL data from clinical trials, cost data from published literature and databases, Statistics Canada life tables	Direct: drug acquisition, cost of patient FU, physician, nursing, pharmacy laboratory, and radiology services, AEs, salvage chemotherapy, palliative care	RIT + RMT vs RIT vs WW $67,489 vs $59,953 vs $75,895 (costs over 30 years) ICER/QALY gained: $62,360 (RMT vs RIT)

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Diffuse large B-cell lymphoma					
Johnston et al. [155]	1L, R-CHOP vs CHOP	Canada (2006, NA)	Observational cohort BCCA Lymphoid Cancer Database, BCCA Provincial Systemic Therapy Drug Database, literature	Direct: drug acquisition, radiotherapy, palliative care, assessment, hospitalization, outpatient care, stem cell transplantation	R-CHOP vs CHOP $46,337 vs $36,765 (age <60 years); $42,892 vs $34,968 (age ≥60 years) (costs over 15 years) ICER/DF-LYG: $11,965 (age <60 years), $4313 (age ≥60 years) ICER/QALY gained: $19,144 (age <60 years), $5853 (age ≥60 years)
Griffiths et al. [156]	1L, R + chemotherapy vs chemotherapy (elderly)	USA (2009, payer perspective)	Observational cohort SEER registry, Medicare claims	Direct: immunochemotherapy, other cancer and noncancer costs (not specified)	R-CHOP vs CHOP Mean cost difference over 4 years $23,097 ICER/LYG: $62,424

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Khor et al. [157]	1L, R-CHOP vs CHOP	Canada (2009, healthcare system perspective)	Observational cohort Population-based administrative healthcare databases, cancer-specific databases, health insurance plan databases for costs	Direct: drug acquisition, hospitalization, laboratory tests, imaging services, emergency department visits, homecare services, rehabilitation, palliative care	R-CHOP vs CHOP $85,293 vs $68,995 (costs over 5 years) ICER/LYG: $61,984 (all patients), $31,789 (age <60 years), $80,601 (age 60–79 years), $110,071 (age ≥80 years)
Chronic lymphocytic leukemia					
Hornberger et al. [158]	1L, R-FC vs FC	USA (NA, payer and societal perspective)	Markov model Event rate data from CLL8, general US population data, Centers for Medicare and Medicaid Services reimbursement data, literature	Direct: drug acquisition, drug administration, AEs, salvage therapy Indirect: caregiver costs, lost work productivity	R-FC vs FC Payer perspective $110,267 vs $83,240 (lifetime costs) ICER/LYG: $12,558 ICER/QALY: $23,530 Societal perspective $205,147 vs $172,565 (lifetime costs) ICER/LYG: $15,140 ICER/QALY: $31,513

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Adena et al. [159]	1L and R/R, R-FC vs FC	Australia (2009, healthcare perspective)	Markov model. Event rate data from CLL8 and REACH, treatment guidelines, expert opinion, literature, Australian prescription data	Direct: drug acquisition, administration, AEs, routine monitoring	R-FC vs FC. $62,365 vs $22,097 (costs over 15 years). ICER/LYG: $36,387. ICER/QALY gained: $42,906
Mandrik et al. [160]	1L and R/R, R-FC vs FC	Ukraine (2014, healthcare system perspective)	Markov model. Event rate data from CLL8 and REACH, literature, clinical guidelines, utility data (UK), resource utilization/costs (Ukraine). Impact of lower life expectancy in Ukraine (1L only) also assessed	Direct: drug costs, hospitalization, AEs, salvage therapy costs	R-FC vs FC. ICER/QALY gained: US$8704 (1L), US$11,056 (R/R), US$13,000 (based on higher mortality of Ukrainian population)

Table 5 continued

Study reference	Setting	Country, year of costing, and perspective	Methodology/data sources	Costs included	Cost-effectiveness
Müller et al. [161]	1L, R-FC vs FC	Germany (2014, payer perspective)	Markov model Event rate data from CLL8, treatment guidelines, hospital/hematologic practice patterns, physicians, fee scale within statutory health insurance scheme, German pharmacy reference sources	Direct: drug acquisition, drug administration, AEs (FU visits, tumor assessments, routine management excluded)	R-FC vs FC €28,384 vs €8118 (costs over 5.9 years) ICER/LYG: €15,773 ICER/QALY gained: €17,979

AE adverse event, *BCCA* British Columbia Cancer Agency, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *CHVP* cyclophosphamide, doxorubicin, etoposide, and prednisone, *CT* computed tomography, *CVP* cyclophosphamide, vincristine, and prednisolone, *DF-LYG* disease-free life year gained, *EORTC* European Organisation for Research and Treatment of Cancer, *FC* fludarabine and cyclophosphamide, *FU* follow-up, *ICER* incremental cost-effectiveness ratio, *1L* first line, *LYG* life year gained, *MCP* mitoxantrone, chlorambucil, and prednisolone, *NA* not available, *OBS* observation, *OS* overall survival, *PFS* progression-free survival, *QALY* quality-adjusted life year, *QOL* quality of life, *R* rituximab, *RIT* rituximab induction therapy, *RMT* rituximab maintenance therapy, *R/R* relapsed/refractory, *SEER* Surveillance, Epidemiology, and End Results *WW* watchful waiting

clinical trials, and a small number were based on real-life data from large observational cohorts.

In FL, rituximab was shown to be cost-effective both as maintenance therapy compared with observation in the first-line [151, 153] and relapsed/refractory [147, 149, 152] settings and as induction therapy combined with chemotherapy compared with chemotherapy alone in previously untreated patients [148, 150]. In DLBCL, rituximab therapy plus chemotherapy was generally found to be cost-effective compared with chemotherapy alone when administered as first-line treatment [155, 157], although results were conflicting as to whether cost-effectiveness increased or decreased with increasing age [155, 157]. In one analysis based on data from a large observational cohort of DLBCL patients in the USA, previously reported cost savings associated with rituximab-related survival benefits in clinical trials were not realized; according to the study authors, this finding was consistent with an ongoing accrual of medical costs associated with multiple comorbidities among elderly cancer survivors treated with rituximab [156]. Cost-effectiveness analyses of rituximab in CLL evaluated rituximab therapy plus chemotherapy versus chemotherapy alone in patients with previously untreated and relapsed/refractory disease [158–161]. In both settings, rituximab therapy plus chemotherapy was considered cost-effective, although in the Ukraine this was considered applicable only under conditions of economic stability, cost-effectiveness threshold growth, or with rituximab price negotiations [160]. In an analysis that evaluated the economic benefit of adding rituximab therapy to FC chemotherapy in CLL in the USA, R-FC was found to be cost-effective from both a payer and a societal perspective [158].

A population analysis of the benefits and costs of rituximab in patients with FL, DLBCL, and CLL in the USA over a 15-year period based on cancer registry data found that almost 280,000 cumulative life years were saved by combining rituximab therapy with chemotherapy, corresponding to a net economic gain of $16.5 billion, when treatment costs were taken into account [162].

CONCLUSION

Since its first approval 20 years ago, the anti-CD20 mAb rituximab has changed the treatment landscape for patients with B-cell hematologic malignancies and established a new standard of care. By prolonging survival in a range of these diseases, rituximab has reduced mortality and improved the clinical prognosis for many patients with B-cell malignancies. Extensive clinical data from the last two decades have confirmed the efficacy of rituximab and allowed its tolerability profile to be clearly defined. On the basis of this evidence, rituximab is now incorporated routinely into treatment regimens for FL, DLBCL, CLL, and MCL: it is designated as a recommended treatment in current clinical practice guidelines for B-cell hematologic malignancies developed by the European Society of Medical Oncology and the US National Comprehensive Cancer Network [9–11, 22, 23], and is included in the WHO Model List of Essential Medicines [24]. The experience with rituximab has confirmed the value of the CD20 protein as an important mechanistic target in the search for new lymphoma treatments. Advances in the design of anti-CD20 antibodies have resulted in the development of new therapies for the treatment of B-cell hematologic malignancies, such as obinutuzumab, which has shown benefit for the treatment of FL, both as first-line treatment and in patients with rituximab-refractory disease, and CLL (see the reviews by Tobinai et al. [163] and Goede et al. [164] for detailed assessments of this agent). Other examples of newer agents include ofatumumab, veltuzumab, and ocrelizumab [165]. Both obinutuzumab and rituximab are important backbones of therapy in this setting for the foreseeable future. Another example of development of a drug that exploits the CD20 pathway is CD20/CD3 antibodies. Furthermore, the introduction of subcutaneously administered rituximab (extensively reviewed by Davies et al. [31]), with its simplified administration schedule, reduced treatment burden for patients, and the potential resource savings for healthcare systems, is likely to further strengthen the position of rituximab

as an essential treatment for symptomatic, advanced B-cell malignancies.

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