SYSTEMATIC REVIEW

Cost-Effectiveness Analyses, Costs and Resource Use, and Health-Related Quality of Life in Patients with Follicular or Marginal Zone Lymphoma: Systematic Reviews

Neerav Monga[1] · Jamie Garside[2] · Binu Gurung[3] · Joan Quigley[3] · Peter O'Donovan[3] · Christoph Tapprich[4] · Loretta Nastoupil[5] · Catherine Thieblemont[6] · Christina Loefgren[7]

Abstract

Background Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are types of indolent non-Hodgkin lymphoma (NHL) that develop in the B lymphocytes (also known as B cells).

Objective The aim of this study was to conduct a comprehensive review of studies relating to cost effectiveness, costs and resource use, and health-related quality of life (HRQoL) in patients with FL or MZL.

Methods Three separate systematic reviews were conducted to identify all published evidence on cost effectiveness, costs and resource use, and HRQoL between 2007 and March 2017 using the MEDLINE®, MEDLINE in-process, E-pubs ahead of print (Ovid SP®), Embase (Ovid SP®), NHS EED, and EconLit databases. Select congress proceedings were also searched. Two systematic reviewers independently reviewed titles, abstracts, and full papers against eligibility criteria. Relevant data were extracted into bespoke data extraction templates (DETs) by a single systematic reviewer; these data were then validated for accuracy by a second reviewer against clean copies of the relevant publications.

Results A total of 25 cost-effectiveness studies (24 in FL; 1 in FL and MZL) met the eligibility criteria. Markov models were the most utilised cost-effectiveness model. US FL studies reported an incremental cost-effectiveness ratio (ICER) of $28,565/QALY for first-line rituximab–cyclophosphamide, vincristine, and prednisone (R-CVP) versus CVP, and $43,000/QALY for second-line obinutuzumab plus bendamustine (G + B) followed by G maintenance versus B. In the UK, ICERs were £1529–10,834/quality-adjusted life-year (QALY) for first-line rituximab + chemotherapy versus chemotherapy, £27,988/QALY for second-line G + B + G-maintenance versus B, and £62,653/QALY for second-line idelalisib versus chemotherapy and/or rituximab. Five costs/resource use and four HRQoL studies were identified in FL, and none in MZL. US mean lifetime costs in first-line patients ranged from $108,000 (rituximab) to $130,300 (rituximab–cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone [CHOP]), and from £2185 (watch-and-wait) to £17,054 (chemotherapy) in the UK. In a multinational study, more rituximab-refractory patients receiving G + B + G-maintenance reported a meaningful improvement in total FACT-Lym scores compared with patients receiving B. In the UK, total FACT-Lym scores were meaningfully higher for newly diagnosed patients compared with patients with progression (136.04 vs. 109.7).

Conclusions and Relevance We found a small body of evidence of quality of life, and potentially cost-effective treatment options for FL; however, no evidence was reported on MZL specifically. The significant data gaps in knowledge in these diseases demonstrate a marked need for further studies.

✉ Neerav Monga
nmonga@its.jnj.com

Extended author information available on the last page of the article

1 Introduction

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are types of indolent non-Hodgkin lymphoma (NHL) that develop in the B lymphocytes (also known as B cells) [1]. Initial treatment of indolent NHL often achieves tumour response and is successful. However, high rates of disease relapse result in repeated courses of chemotherapy characterised by shorter response periods between each relapse [2].

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Key Points for Decision Makers

The addition of rituximab to chemotherapy-based therapies, as well as rituximab maintenance, improved clinical outcomes in a cost-effective way.

Disease progression may be a driver of healthcare resource use, cost, and patient health-related quality of life, however further research is required to confirm this.

Despite treatments being available for patients with follicular lymphoma and marginal zone lymphoma, there is still an unmet need to slow disease progression and improve quality of life for patients.

With limited therapeutic options, novel treatments and combinations of novel treatments for FL and MZL have the potential to improve patient outcomes; however, to the authors' knowledge, there has never been a systematic review to identify the current cost-effectiveness evidence base for such regimens. Such a review would be necessary to not only consider the costs and benefits regimens may bring but also to understand the evolution in economic modelling in this area.

This study aims to describe the economic and health burden in patients with FL or MZL. The combined reporting of relevant economic and health outcomes appraisals (i.e. cost-effectiveness analyses [CEAs] and cost-utility analyses [CUAs]) can provide clinical insights and greater understanding of current evidence to improve overall efficiency in the decision-making process. Combined, the three systematic literature reviews (SLRs) summarise pertinent economic and burden information to help aid health care decision making.

2 Methods

Three separate SLRs were conducted to examine cost-effectiveness models, cost/resource use, and health-related quality of life (HRQoL) associated with treatments for FL and MZL. These SLRs followed validated methodologies [3–5] consistent with those outlined in the existing literature [6]. Eligibility criteria included adult patients with FL or MZL, treated with pharmacological interventions, palliative care (for cost/resource use), and no treatment (for cost/resource use and HRQoL), and study designs specific to the SLR, such as economic modelling publications, or reporting costs/HRQoL data. Full eligibility criteria are provided in electronic supplementary Table 1.

All searches for published studies were conducted on 9 March 2017, from 2007 to 8 March 2017, using the MEDLINE®, MEDLINE in-process, E-pubs ahead of print (Ovid SP®), Embase (Ovid SP®), NHS EED, and EconLit databases.

Search strategies were developed using published and tested search filters for economic and HRQoL studies, as well as combined free text and controlled vocabulary terms (Medical Subject Headings in MEDLINE and Emtree terms in Embase) for the population of interest. A single search strategy was used to identify studies of economic models and costs/resource use, and a separate search was conducted for HRQoL study identification. Relevant conference proceedings from 2015 to 2016 were also searched. Additional searches performed included website of health technology assessment (HTA) bodies using the HTA database (via OVID), Tufts Cost-Effectiveness Analysis registry, National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefit Advisory Committee. Full details of the PICO framework, inclusion/exclusion criteria, and full search strategy are provided in electronic supplementary Tables 1, 2 and 3.

Two systematic reviewers (BG and PO'D) independently reviewed titles, abstracts, and full papers against the eligibility criteria. Relevant data (including study design, methods, outcomes, conclusions) were extracted into bespoke DETs by a single systematic reviewer (PO'D); these data were then validated for accuracy by a second reviewer (BG) against clean copies of the relevant publications. Journal websites were cross-checked for errata and supplementary materials. An additional third reviewer (JQ) was used to resolve disagreements when needed. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams for cost-effectiveness models, costs and resource use, and HRQoL studies are shown in electronic supplementary Fig. 9

3 Results

3.1 Cost-Effectiveness Models/Analyses

A total of 25 studies reporting on cost effectiveness were included in the review (Tables 1, 2, 3). Cost-effectiveness comparisons were reported using CUAs and CEAs in 14 studies. CUA alone was conducted in eight studies, CEA alone was conducted in two studies, and cost-minimisation analysis (CMA) was conducted separately in one study. Models and analyses were developed in the context of the UK (seven studies), USA (five studies), Canada (four studies), Australia (three studies), and Finland (two studies). There was one study each conducted in Russia, The Netherlands, Spain, and Sweden. The most commonly reported

Table 1 Cost-effectiveness studies examining first-line treatments with or without maintenance

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LY	QALY	ICER (cost per QALY/LY)
Papaioannou et al., 2012 [AG model] [9]	UK	FL	M39021 (IPD) [40]	CVP	–	2010; GBP	30,793	9.86	5.99	–
				R-CVP	CVP		38,183	11.5	6.95	7720/QALY
				CHOP	–		34,983	11.55	6.84	–
				R-CHOP	CHOP		40,708	12.4	7.37	10,834/QALY
				MCP	–		36,103	11.45	6.79	–
				R-MCP	MCP		41,370	12.35	7.36	9316/QALY
Papaioannou et al., 2012 [Roche R first-line NICE MS model] [9]	UK	FL	M39021 (IPD) [40] and three RCTs (FL2000 [41], OSHO-39 [42], GLSG-2000) [43]	R-CVP	CVP	–; GBP	–	–	–	1529/QALY [using patient-level data]
				R-CVP	CVP		–	–	–	5611/QALY [using ordinary least squares regression]
				R-CHOP	CHOP		–	–	–	5758/QALY
				R-MCP	MCP		–	–	–	4861/QALY
				R-CHVP+IFNα	CHVP+IFNα		–	–	–	9251/QALY
Ray et al., 2010 [8]	UK	FL	M39021 [40] and three RCTs (FL2000 [44], OSHO-39 [42], GLSG-2000) [43]	R-CVP	CVP	2008; GBP	28,582	7.764	5.392	8613/QALY; 7473/LY
				CVP	–		20,708	6.71	4.748	–
				R-CHOP	CHOP		29,794	8.842	6.335	10,676/QALY; 9294/LY
				CHOP	–		20,922	7.887	5.504	–
				R-MCP	MCP		29,725	9.312	6.747	7455/QALY; 6503/LY
				MCP	–		20,900	7.954	5.563	–
				R-CHVP+IFNα	R-CHVP+IFNα		33,513	8.428	5.966	8498/QALY; 7370/LY
				CHVP+IFNα	–		29,621	7.9	5.508	–
Hornberger et al., 2008 [11]	US	FL	M39021 [45]	R-CVP	CVP	2006; USD	105,607	13.68	5.85	17,504/LY; 28,565/QALY
				CVP	–		79,168	12.17	4.93	–
Prica et al., 2015 [10]	Canada	FL	StiL [46], PRIMA [47], and EORTC 20981 [48]	R+R maintenance	R	2012; CAD	67,489	7.89	6.28	62,360/QALY
				R	–		59,953	7.82	6.16	–
				Watch-and-wait	R		75,895	7.4	5.71	Dominated by R induction
Sabater et al., 2016 [22]	Spain	FL	StiL [46]	BR	R-CHOP	2013; EUR	68,357	12.86	9.63	BR-dominant
				R-CHOP	–		69,528	12.62	9.23	–
Griffiths et al., 2012 [26][c]	US	FL	SEER Medicare registry	R-CHOP/R-CVP	CHOP/CVP	2009; USD	111,815[d]	–	–	382,642/LY after 2 years; 193,859/LY after 3 years; 102,142/LY after 4 years of observation
				CHOP/CVP	–		80,826[d]	–	–	–

Table 1 (continued)

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LY	QALY	ICER (cost per QALY/LY)
Aw et al., 2016 [49]	Canada	FL	–	BR	R-CHOP	2016; CAD	–	–	–	27,398/QALY
		MZL	–	BR	R-CHOP		–	–	–	10,012/QALY

AG Assessment Group, *BR* bendamustine and rituximab, *CAD* Canadian dollars, *CHVP* cyclophosphamide, etoposide, doxorubicin and prednisone, *CVP* cyclophosphamide, vincristine and prednisone, *EORTC* European Organisation for Research and Treatment of Cancer, *EUR* Euro, *GBP* Great Britain pounds, *FL* follicular lymphoma, *ICER* incremental cost-effectiveness ratio, *IFN* interferon, *IPD* individual patient data, *LY* life-year, *MCP* mitoxantrone, chlorambucil, and prednisone, *MS* manufacturer's submission, *MZL* marginal zone lymphoma, *NICE* National Institute of Health and Care Excellence, *QALY* quality-adjusted life-year, *R* rituximab, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *RCTs* randomised controlled trials, *SEER* Surveillance, Epidemiology, and End Results, *USD* United States dollars

[a]Reference of trial(s) provided where reported

[b]Total costs refer to the total cost of the intervention, not the incremental costs

[c]Incremental survival reported in the R group: 0.05 after 2 years, 0.11 after 3 years, 0.18 after 4 years of observation

[d]Unadjusted cumulative costs

regimens were rituximab (R) based, either in monotherapy (12 studies either as first/second-line or maintenance) or as combination with cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone (CHOP; nine studies either as first/second-line or maintenance). Other treatments investigated included bendamustine (B), CHEP (cyclophosphamide, etoposide, doxorubicin and prednisone), CVP (cyclophosphamide, vincristine and prednisone), cyclophosphamide (CTX), idelalisib (IDEL), interferon (IFN)-α, MCP (mitoxantrone, chlorambucil and prednisone), and obinutuzumab (G). Electronic supplementary Table 8 summarises the general study characteristics utilising cost-effectiveness models/analyses.

3.2 Model/Analysis Design Overview

The cost effectiveness of first-line treatments was evaluated in eight studies (seven for FL, one for FL and MZL) [7–13], and nine studies reported cost-effectiveness of maintenance treatment [14–21]. Six studies were found to report cost effectiveness of treatments for relapsed/refractory (R/R) FL, while only three studies reported cost-effectiveness evidence for refractory FL. A Markov modelling approach, mainly depicting a three-state disease model (progression-free, progressive disease and death), was used in the majority of cost-effectiveness publications [8, 11, 18, 20–25]. Other analysis types used included cohort-based analysis [26], probabilistic decision analytic model [9], transitional state model [19], and a partitioned survival model [27]. No relevant structural differences were observed in the included models over the 10-year period this review encompassed. Time horizons ranged between 5 and 30 years, and cycle life ranged from 1 to 6 months. One abstract described differences in routes of treatment administration (subcutaneous vs. intravenous RR), but model characteristics were not described [7].

3.3 Model/Analyses Results

3.3.1 First-Line Treatment

First-line treatment model results are presented in Table 1. R + chemotherapy was cost effective in comparison with chemotherapy for the treatment of FL, as reported in UK-based studies. In particular, R-CVP versus CVP was projected to have an incremental cost-effectiveness ratio (ICER) ranging between £1529/quality-adjusted life-year (QALY) gained and £8613/QALY gained (Great Britain pounds [GBP]; 2008) [8]. R-CHOP versus CHOP was projected to have an ICER ranging between £5758/QALY gained [9] and £10,834/QALY gained (GBP; 2010) [9]. R-MCP versus MCP was projected to have an ICER ranging between £4861/QALY gained [9] and £9316/QALY gained (GBP; 2010) [9].

Table 2 Cost-effectiveness studies examining maintenance treatments

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LYs	QALYs	ICER (cost per QALY/LY)
In the first-line setting										
Roche R maintenance NICE MS, 2010 [14]	UK	FL	PRIMA [47]	R maintenance	Observation	2008/9; GBP	85,402	10.288	8.376	15,978/QALY
		FL		Observation	–		66,721	9.017	7.207	–
Hornberger et al., 2012 [15]	US	FL	PRIMA [47]	R maintenance	Observation	–; USD	183,963	9.51	7.85	34,842/QALY; 31,934/LY
				Observation	–		145,418	8.3	6.74	–
Mervin ISPOR, 2016 [16]	Australia	FL	PRIMA [47] and EORTC 20981 [48]	R maintenance	No treatment	–; AUD	–	–	–	74,989/QALY
Roche R maintenance PBAC, 2014 [17]	Australia	FL	PRIMA [47] and EORTC 20981 [48] and Hainsworth 2005 [50]	R maintenance	Observation	–; AUD	–	–	–	Within the range of 15,000–45,000/QALY[c]
In the R/R setting										
Roche R R/R NICE MS, 2007 [18]	UK	R maintenance	EORTC 20981	R maintenance	Observation	2006; GBP	21,608	5.8694	4.225	7721/QALY; 6885/LY
		Observation		Observation			14,722	4.8693	3.3331	–
Hayslip and Simpson, 2008 [19]	US	R maintenance	EORTC 20981 [51]	R maintenance	Observation	2006; USD	–	–	–	19,522/QALY
Kasteng et al., 2008 [20]	Sweden	R maintenance	EORTC 20981 [51]	R maintenance	Observation	2007; EUR	39,617	5.96	4.29	12,584/QALY; 11,187/LY
		Observation		Observation			28,156	4.94	3.38	–
Blommestein et al., 2014 [21]	Netherlands	R maintenance [Scenario 1[d]]	EORTC 20981 [48, 51] for trial evidence and two registries (PHAROS and HemoBase) for real-work evidence	R maintenance [Scenario 1[d]]	Observation	2012; EUR	56,608	9.39	7.84	12,655/QALY; 11,259/LY
		Observation [Scenario 1]		Observation [Scenario 1]			39,182	7.84	6.46	–
		R maintenance [Scenario 2[d]]		R maintenance [Scenario 2[d]]	Observation		100,424	9.36	7.81	23,821/QALY; 21,202/LY
		Observation [Scenario 2]		Observation [Scenario 2]			67,756	7.81	6.44	–
		R maintenance [Scenario 3[d]]		R maintenance [Scenario 3[d]]	Observation		88,582	10.17	8.65	11,245/QALY; 10,591/LY
		Observation [Scenario 3]		Observation [Scenario 3]			64,846	7.93	6.54	–

Table 2 (continued)

In the first-line and R/R setting

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LYs	QALYs	ICER (cost per QALY/LY)
Roche R maintenance PBAC, 2014 [17]	Australia	R maintenance	PRIMA [47] and EORTC 20981 [48] and Hainsworth 2005 [50]	R maintenance	Observation	–; AUD	–	–	–	Within the range of 15,000–45,000/QALY[c]

AUD Australian dollars, *EORTC* European Organisation for Research and Treatment of Cancer, *EUR* Euro, *GBP* Great Britain pounds, *FL* follicular lymphoma, *ICER* incremental cost-effective ratio, *ISPOR* International Society for Pharmacoeconomics and Outcomes Research, *LY* life-year, *MS* manufacturer's submission, *MZL* marginal zone lymphoma, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *QALY* quality-adjusted life-year, *R* rituximab, *R/R* relapsed/refractory, *USD* United States dollars

[a]Reference of trial(s) provided where reported

[b]Total costs refer to the total cost of the intervention, not the incremental costs

[c]The summary did not specify if this result was for first-line remission or for both the first-line and R/R setting

[d]Scenario 1: effectiveness based on trial efficacy, costs based on trial costs; Scenario 2: effectiveness based on trial efficacy, costs based on matched real-world patients; Scenario 3: effectiveness based on real-world evidence, costs based on matched real-world patients

In Canada, an analysis evaluating first-line therapy with R with or without maintenance (R induction vs. R induction + R maintenance) was projected to have an ICER of $62,360 (Canadian dollars [CAD]; 2012) per QALY gained for FL [10], and R monotherapy was dominant over watch-and-wait for FL [10]. Additionally, B + R versus R-CHOP was projected to have an ICER of $27,398/QALY gained (CAD; 2012) for FL and $10,012/QALY gained (CAD; 2012) for MZL [10].

In the US, R-CVP versus CVP followed a similar trend as the UK, with projected ICERs of $28,565/QALY gained and $17,504/life-year (LY) gained [11]. The projected ICER per LY gained improved annually ($382,642/LY, $193,859/LY and $102,142/LY 2, 3 and 4 years after observation, respectively) for R-CHOP/R-CVP versus CHOP/CVP in the US. The continued accrual of cumulative survival benefit of R throughout the observation periods, and cumulative cost being negligible post first-line treatment, were highlighted to result in a rapid decrease of ICER values over the observed years [26]. In Spanish studies, B + R was dominant over R-CHOP [10].

3.3.2 First-Line Maintenance Treatment

Maintenance treatment results are presented in Table 2. All data reported were for FL patients as no MZL cases were included. R maintenance was compared with watch and wait (or observation) in FL patients. In patients responding to first-line treatment, R maintenance had an ICER of £15,978/QALY gained (GBP; 2008/2009) in the UK [14], $34,842 (US dollars [USD]; year unspecified) in the US [15], and $74,989/QALY gained (Australian dollars [AUD]; year unspecified) in Australia [16]. Another Australian study (Pharmaceutical Benefits Advisory Committee [PBAC] summary) reported an ICER between $15,000 and $45,000/QALY gained, but it was not specified if this was for a first-line or both first-line and R/R setting [28].

3.3.3 Treatment for Relapsed and/or Refractory FL

Treatments for relapsed and/or refractory FL model results are presented in Table 3. All data reported were for FL patients as no MZL cases were included. In the UK, G + B + G maintenance versus R + chemotherapy had an ICER of £27,988/QALY gained, R-CHOP + R maintenance versus CHOP + R maintenance had an ICER of £16,749/QALY gained, and CHOP + R maintenance versus CHOP had an ICER of £9076/QALY gained. G + B + G maintenance versus B had projected ICERs of $62,833/QALY gained in Canada [23], $43,000/QALY gained in the US [29], and $45,000–$75,000 in Australia [28]. In Finland, R-CHOP + R maintenance versus R-CHOP had an ICER of €18,147/QALY gained, R-CHOP + R maintenance versus

Table 3 Cost-effectiveness studies examining treatments with or without maintenance for relapsed and/or refractory follicular lymphoma and other treatment lines

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LY	QALY	ICER (cost per QALY/LY)
Treatments with or without maintenance for R/R FL										
Gilead IDEL SMC, 2015 [52]	UK	Refractory FL	101-09 (DELTA) [53]	IDEL	Chemotherapy and/ or R	GBP[c]	–	–	–	62,653/QALY
Gilead IDEL CADTH MS, 2016 [54]	Canada	Refractory FL	DELTA	IDEL	BSC	CAD[c]	–	–	–	130,435/QALY
Roche R R/R NICE MS, 2007 [18]	UK	R/R FL	EORTC 20981	R-CHOP+R maintenance	CHOP+R maintenance	2006; GBP	28,585	5.7035	4.0906	16,749/QALY
				CHOP+R maintenance	CHOP		22,389	5.2479	3.7207	9076/QALY
				R-CHOP	–		23,054	5.1454	3.626	–
				CHOP	–		16,658	4.5483	3.0892	–
Soini et al., 2011 [25]	Finland	R/R FL	EORTC 20981 [48, 51]	R-CHOP+R maintenance	R-CHOP; CHOP	2008; EUR	68,331	7.25	5.21	18,147/QALY vs. R-CHOP; 14,360/ QALY vs. CHOP 16,380/LY vs. R-CHOP; 13,041/ LY vs. CHOP
				R-CHOP	CHOP		59,521	6.72	4.72	12,123/QALY; 11,049/LY
				CHOP	–		49,562	5.81	3.9	–
Guzauskas et al., ASH, 2016 [29]	US	R/R FL	GADOLIN	G+B+G maintenance	B	2016; USD	114,815	–	–	43,000/QALY
				B	–		62,034	–	–	–
Roche O CADTH MS, 2017 [23]	Canada	R/R FL	GADOLIN	G+B+G maintenance	B	2016; CAD[c]	–	–	–	62,833/QALY
Roche O SMC, 2017 [24]	UK	R/R FL	GADOLIN [55]	G+B+G maintenance vs. R+chemotherapy	R+chemotherapy	GBP[c]	–	–	–	27,988/QALY
Roche O PBAC MS, 2016 [28]	Australia	Refractory FL	GADOLIN [55]	G+B+G maintenance	B (proxy of BSC)	AUD	–	–	–	Within the range of 45,000–75,000/ QALY
Full treatment sequence										
Soini et al., 2012 [56]	Finland	FL	–	R-CHOP+R maintenance→R-COP-BR→BSC	R-CHOP+R maintenance→R-COP-R/COP→BSC	2010; EUR	168,549	11.5	8.8	7382/QALY; 5970/LY
				R-CHOP+R maintenance→R-COP-R/COP→BSC	R-CHOP→R-COP-R/B→BSC		167,124	11.3	8.6	9999/QALY; 8438/ LYs

Table 3 (continued)

Study ID	Country	FL/MZL	Trial used[a]	Intervention	Reference treatment	Cost year; currency	Total costs[b]	LY	QALY	ICER (cost per QALY/LY)
				R-CHOP→R-COP-BR→BSC	R-CHOP→R-COP-R/COP→BSC		154,640	9.8	7.3	8812/QALY; 7194/LY
				R-CHOP→R-COP-R/COP→BSC	–		153,425	9.6	7.2	–
Unclear treatment line										
Kulikov and Rybchenko, ISPOR, 2015 [7]	Russia		–	R SC	–	EUR	58,207	–	–	–
				R IV	–		58,803	–	–	–

AUD Australian dollars, *B* bendamustine, *BR* bendamustine and rituximab, *BSC* best supportive care, *CAD* Canadian dollars, *CADTH* Canadian Agency for Drugs and Technologies in Health, *EORTC* European Organisation for Research and Treatment of Cancer, *EUR* Euro, *G* obinutuzumab, *GBP* Great Britain pounds, *FL* follicular lymphoma, *ICER* incremental cost-effectiveness ratio, *IDEL* idelalisib, *ISPOR* International Society for Pharmacoeconomics and Outcomes Research, *IV* intravenously, *LY* life-year, *MS* manufacturer's submission, *MZL* marginal zone lymphoma, *PBAC* Pharmaceutical Benefits Advisory Committee, *QALY* quality-adjusted life-year, *R* rituximab, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *R-COP* rituximab, cyclophosphamide, vincristine, and prednisone, *R/R* relapsed/refractory, *SC* subcutaneously, *SMC* Scottish Medicines Consortium, *USD* United States dollars

[a] Reference of trial (s) provided where reported

[b] Total costs refer to the total cost of the intervention, not the incremental costs

[c] Assumption about the currency is based on the country in which the submission was made

CHOP had an ICER of €14,360/QALY gained, and R-CHOP versus CHOP had an ICER of €12,123/QALY gained. IDEL versus chemotherapy and/or R had an ICER of £62,653/QALY gained in the UK, while IDEL versus best supportive care had an ICER of $130,435/QALY gained in Canada in patients with refractory FL.

3.3.4 Relapsed/Refractory Maintenance Treatment

For R/R settings in The Netherlands [21], ICERs were calculated for three scenarios looking specifically at R maintenance versus observation. The scenarios were (1) efficacy and costs based on trial data; (2) efficacy based on trial efficacy and costs based on matched real-world patients; and (3) real-world effectiveness based on real-world evidence (RWE) and costs based on matched real-world patients; the ICERs were €11,245, €12,655 and €23,821/QALY gained (EURO; 2012), respectively. The results are presented in Table 2.

3.4 Costs/Resource Use

Three studies and two abstracts in FL met the eligibility criteria for final inclusion. One study assessed patients who received prior treatment [30], while the other four included only treatment-naïve patients [26, 31–33]. Treatment regimens, when reported, all incorporated the use of R in monotherapy or combination. The time horizon ranged from 1 year [30] to a lifetime [32, 33]. Studies were conducted from the health care payer perspective, when reported [30–32, 34].

Table 4 provides direct cost results, with direct drug and non-drug costs further depicted in electronic supplementary Table 5. Two studies [32, 33] reported the total mean cost over a lifetime. The reported lifetime costs from diagnosis until death for patients receiving R-CHOP, R + chemotherapy, and R alone were $108,000 (USD; 2014), $114,800, and $130,300, respectively [32]. UK patients under a watch-and-wait strategy (£2185) and radiotherapy (£4651) were estimated to incur less costs than patients receiving chemotherapy (£17,054) as an initial treatment [33]. Annual total mean costs for patients with disease progression were $30,890, compared with $8704 for patients without disease progression [30]. Indirect costs were not reported in any of the studies. One study [30] concluded that patients with disease progression experience more health care visits (chemotherapy, outpatients and acute care) and laboratory procedures than patients with stable disease.

3.5 Health-Related Quality of Life

HRQoL was evaluated in FL patients in two, multinational, phase III randomised trials [35, 36] and two

Table 4 Direct costs

Study ID (Country)	Treatment status	Time horizon	Patient subgroup	N (%)	Description	Cost year; currency	Mean cost	Median cost	Incremental cost	Cumulative cost	95% CI
Beveridge et al., 2011 [30] (US)	R/R (TE)	12 months	No progression	734	6-month total cost/patient/month	2007; USD	859.98	–	–	–	–
			No progression	734	6-month cost		–	–	–	5226	–
			No progression	734	12-month cost		–	–	–	8704	–
			Progression	268	6-month total cost/patient/month		3527.4	–	–	–	–
			Progression	268	6-month cost					21,621	
			Progression	268	12-month cost					30,890	
Danese et al., 2016 [31] (US)	First-line (TN)	–	R + chemotherapy vs. chemotherapy alone (treated patients)	–	Total cost (6 years)	2013; USD			23,511	–	–
					Total cost (10 years)				28,211	–	–
					Treatment costs					1.74 billion	1.11 billion to 2.57 billion
					Cost difference/male		–	–	28,211	–	–
					Cost difference/female		–	–	28,211	–	–
Griffiths et al., 2012 [26] (US)	First-line (TN)	4 years	R + chemotherapy vs. chemotherapy alone	–	Total cost difference	2009; USD	–	–	–	–	9302 to 28,643
			R + CHOP only vs. CHOP only alone	–	Total cost difference		–	–	–	–	9089 to 32,659
			Chemotherapy alone	367 (33)	Unadjusted IPW cumulative cost		–	–	–	–	74,006 to 88,113
			R + chemotherapy	750 (67)	Unadjusted IPW cumulative cost		–	–	–	–	104,455 to 119,466
Shah et al., ASH 2016 [32] (likely US)	First-line (TN)	Lifetime	R-CHOP; diagnosis until death	485 (44)	Total mean cost diagnosis until death	2014; –	130,300	–	–	–	–
			R + chemotherapy; diagnosis until death	393 (36)	Total mean cost diagnosis until death		114,800	–	–	–	–

Table 4 (continued)

Study ID (Country)	Treatment status	Time horizon	Patient subgroup	N (%)	Description	Cost year; currency	Mean cost	Median cost	Incremental cost	Cumulative cost	95% CI
			R alone; diagnosis until death	217 (20)	Total mean cost diagnosis until death		108,000	–	–	–	–
			R-CHOP; patients living <2 years	–	Mean monthly costs		9100	–	–	–	–
			R + chemotherapy; patients living <2 years	–	Mean monthly costs		7700	–	–	–	–
			R alone; patients living <2 years	–	Mean monthly costs		7900	–	–	–	–
			R-CHOP; patients living >2 years	–	Mean monthly costs in the first year after diagnosis		1600	–	–	–	–
			R + chemotherapy; patients living >2 years	–	Mean monthly costs in the first year after diagnosis		1600	–	–	–	–
			R alone; patients living >2 years	–	Mean monthly costs in the first year after diagnosis		1300	–	–	–	–
			R-CHOP; last year of life	–	Median monthly costs		–	5600	–	–	–
			R + chemotherapy; last year of life	–	Median monthly costs		–	5500	–	–	–
			R alone; last year of life	–	Median monthly costs		–	4800	–	–	–
Wang et al., ISPOR, 2016 [33] (UK)	–	Annual	All FL patients in the UK	Estimated as 64 million	Annual costs of treatment	2013/14; GBP	Approx. 17 million	–	–	–	–
		Lifetime	FL patient	–	Mean cost/ patients from diagnosis to death		10,202	–	–	–	–

Table 4 (continued)

Study ID (Country)	Treatment status	Time horizon	Patient subgroup	N (%)	Description	Cost year; currency	Mean cost	Median cost	Incremental cost	Cumulative cost	95% CI
		–	Initial treatment: chemotherapy	46%	Average cost		17,054	–	–	–	–
		–	Initial treatment: watch-and-wait	42%	Average cost		2185	–	–	–	–
		–	Initial treatment: radiotherapy	12%	Average cost		4651	–	–	–	–

Approx. approximately, *CI* confidence interval, *FL* follicular lymphoma, *GBP* Great Britain pounds, *IPW* inverse probability weighting, *R* rituximab, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *R/R* relapsed/refractory, *TE* treatment-experienced, *TN* treatment-naïve, *USD* United States dollars

population-based studies [37, 38]. Population-based studies were conducted in The Netherlands [37] and the UK [38]. Relevant HRQoL findings were extracted (Table 5) and study characteristics are presented in electronic supplementary Table 7.

FACT-Lym, FACT-Lym-specific subscales, and the FACT-Lym Trial Outcome Index (TOI) were measured at three time points in the GADOLIN trial [35]; day 1 of cycle 5 of induction, 4–6 months post induction, and 8–12 months post induction. Clinically meaningful differences were defined as a ≥ 7-point increase in the total FACT-Lym score, ≥ 3-point increase in the FACT-Lym-specific subscale, and ≥ 6-point increase in the FACT-Lym TOI. At each time point reported, more patients receiving G + B + G maintenance (compared with B-treated patients) had clinically meaningful increases in all three HRQoL scores [35]. However, the authors noted there were no notable differences relating to treatment received in the average scores on the FACT-Lym questionnaire subscales at baseline, during the treatment period, and at follow-up [35].

FACT-Lym and TOI scores were reported for patients being treated with or without chemotherapy in the trial by Pettengell et al. [38]. Five disease states were examined (newly diagnosed active disease, active disease relapsed, partial remission, remission/complete remission, and disease-free) [38]. HRQoL scores were lower in patients who received chemotherapy compared with patients who were not treated with chemotherapy, although statistical significance was not reported. HRQoL scores were high in newly diagnosed active disease states [38]. Scores decreased upon entry into the active disease, relapsed stage, but increased with further disease remission, indicating that patient-reported outcomes differed according to disease state [38].

In the PRIMA [36] trial, patients with non-progressing disease on observation had slightly better quality of life as reported by the EORTC-QLQ-C30 tool compared with those receiving R monotherapy, although statistics were not reported. In the trial by Oerlemans et al. [37], patients on a watch-and-wait treatment regimen experienced significantly and clinically meaningful higher fatigue than the general population, as determined by EORTC-QLC-C30.

4 Discussion

To the authors' knowledge, this is the first SLR performed to date that identifies economic and quality-of-life data for patients with FL or MZL. First, of the 25 included studies, there are several commonalities of note. The majority (18 of the 25 studies) of studies used a three health state Markov model structure with progression-free, progressive disease, and death. A model perspective was reported in 18 of the 25 studies; the majority of these adopted the perspective of

Table 5 Summary of relevant health-related quality of life findings for follicular lymphoma

Study ID	Intervention	Population	Measure	Time point	HRQoL estimate		N	Patients with improvement	
					Mean value	SD		n	%
Cheson et al., GADOLIN [35]	B	R/R FL	FACT-LYM total (≥7-point increase)	Cycle 5 day 1 (induction treatment)	–	–	115	29	25.2
	G+B+G maintenance			Cycle 5 day 1 (induction treatment)	–	–	118	30	25.4
	B			Follow-up 4 and 6 months post end of induction	–	–	58	20	34.5
	G+B+G maintenance			Follow-up 4 and 6 months post end of induction	–	–	78	32	41
	B			Follow-up 8 and 12 months post end of induction	–	–	32	10	31.3
	G+B+G maintenance			Follow-up 8 and 12 months post end of induction	–	–	61	26	42.6
	B		FACT-LYM lymphoma-specific subscale (≥3-point increase)	Cycle 5 day 1 (induction treatment)	–	–	115	39	33.9
	G+B+G maintenance			Cycle 5 day 1 (induction treatment)	–	–	118	47	40.2
	B			Follow-up 4 and 6 months post end of induction	–	–	57	23	40.4
	G+B+G maintenance			Follow-up 4 and 6 months post end of induction	–	–	78	35	44.9
	B			Follow-up 8 and 12 months post end of induction	–	–	32	15	46.9
	G+B+G maintenance			Follow-up 8 and 12 months post end of induction	–	–	61	29	47.5
	B		FACT-LYM TOI[a] (≥6-point increase)	Cycle 5 day 1 (induction treatment)	–	–	115	28	24.3
	G+B+G maintenance			Cycle 5 day 1 (induction treatment)	–	–	118	40	33.9
	B			Follow-up 4 and 6 months post end of induction	–	–	58	17	29.3
	G+B+G maintenance			Follow-up 4 and 6 months post end of induction	–	–	78	32	41
	B			Follow-up 8 and 12 months post end of induction	–	–	32	10	31.3
	G+B+G maintenance			Follow-up 8 and 12 months post end of induction	–	–	61	28	45.9

Table 5 (continued)

Study ID	Intervention	Population	Measure	Time point	HRQoL estimate			Patients with improvement	
					Mean value	SD	N	n	%
Pettengell et al., 2008 [38]	Chemotherapy	–	FACT-LYM total	Baseline (on study entry)	118.26	–	–	–	–
	No chemotherapy	–			132.65	–	–	–	–
	Chemotherapy	–	FACT-LYM TOI[a]		37.02	–	–	–	–
	No chemotherapy	–			42.33	–	–	–	–
	–	Active disease, newly diagnosed	FACT-LYM total	Baseline (on study entry)	136.04	23.22	–	–	–
	–	Active disease, relapsed			109.70	34.9	–	–	–
	–	Partial response			128.81	24.16	–	–	–
	–	Remission/complete response			133.28	23.71	–	–	–
	–	Disease-free			135.26	21.1	–	–	–
	–	Active disease, newly diagnosed	FACT-LYM TOI[a]		92.72	17.59	–	–	–
	–	Active disease, relapsed			73.66	25.12	–	–	–
	–	Partial response			86.93	17.62	–	–	–
	–	Remission/complete response			91.89	18.85	–	–	–
	–	Disease-free			94.83	16.6	–	–	–
Salles et al., PRIMA [47]	Observation	No disease progression	EORTC-QLQ-C30	Baseline	72.6	18.6	–	–	–
	R maintenance	No disease progression			71.6[b]	18.5[b]	–	–	–

B bendamustine, *FL* follicular lymphoma, *G* obinutuzumab, *HRQoL* health-related quality of life, *R/R* relapsed/refractory, *SD* standard deviation, *TOI* Trial Outcome Index

[a]The TOI score sums the physical wellbeing, functional well-being and the specific Lym subscales

[b]$p = 0.54$ between groups; score relates to global health status, other scores also available

a national health care system (14 of the 25 studies). Other studies that specified a perspective utilised a US payer perspective (three studies [15, 19, 26]) or a societal perspective (one study [11]). Clinical trial data were the primary clinical input, with limited RWE data being used; however, given the increasing importance of RWE, and the efforts to collect these data, this will likely change in the future [39]. This could either be real-world cohort analyses (such as in Griffiths et al. [26]) or incorporating RWE data into models (such as in Blommestein et al. [21]). This current research offers a foundation upon which future assessments could be carried out.

In both first-line and R/R populations, R + chemotherapy improved outcomes and QALYs and is cost effective (as per the £30,000/QALY threshold for UK studies). In the first-line FL setting, in the UK, the addition of R to chemotherapy (R-chemo) resulted in a cost per QALY of less than GBP£20,000 compared with chemotherapy alone (Table 3). In all FL studies that investigated maintenance treatments only (only FL studies are reported), in the first-line setting R maintenance was compared with observation, and the impact on the ICER was minimal (several estimates as low as AUD$15,000/QALY). In the R/R FL setting, R-CHOP + R maintenance versus R-CHOP versus CHOP were conducted in UK and Finnish models (electronic supplementary Table 8) and were generally considered to be cost effective. However, in both first-line and R/R disease, further studies analyzing cost effectiveness are needed to strengthen the evidence base in this area.

Disease progression is associated with a substantial economic burden. Of note, one US study included a large sample size and estimated both costs and resource use of patients with R/R FL [30]. The study authors suggest that disease progression is associated with a fourfold increase in annual costs and more medical visits and laboratory procedures than non-progression ($30,890 vs. $8704, respectively), demonstrating that disease progression is a driver of both health care resources and costs for FL for health care systems globally.

Finally, there are limitations of note, both in terms of methods and the evidence identified. It is clear there is a marked dearth of evidence, which makes assessing the cost effectiveness of therapies, or even exploring modelling methodology, difficult. Studies reporting any indirect costs were not found and data on resource use were limited. Additionally, the lack of utility data, particularly in MZL, highlights the need for further research to draw comparisons and guide treatment decision making. There are also several limitations to the three reviews. First, publications that did not separate out FL and MZL were excluded. While there may be some additional papers that can offer further modelling insight, the authors feel this approach is clinically justified. FL and MZL have different etiologies; thus,

patients may require different treatment approaches and can expect different outcomes. Therefore, while further modelling evidence may be available, the results of analyses that pool data on patients with different diseases will not be of importance to decision makers.

Given the limited published data found at the time of our review, there is a need for further research and a continued monitoring of the available evidence base in terms of both modelling strategy and overall cost effectiveness. This review offers the start of an evidence base that, to the authors' knowledge, was not previously available.

5 Conclusions

Overall, the addition of R to chemotherapy-based regimens, as well as R monotherapy, in maintenance improved clinical outcomes in a cost-effective way. Disease progression may be a driver of healthcare resource use, cost and patient HRQoL, however further research is required to confirm this. Despite treatments being available for patients for FL and MZL, there remains an unmet need to slow disease progression, improve quality of life for patients and improve all patient outcomes. Additional pharmacoeconomic analyses would help further our understanding of how best to assess the cost effectiveness of therapies in these disease areas. This in turn would aid healthcare decision making and work towards optimising therapies for patients with FL and MZL, within the constraints faced by healthcare providers.

Compliance with Ethical Standards

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Affiliations

Neerav Monga[1] · Jamie Garside[2] · Binu Gurung[3] · Joan Quigley[3] · Peter O'Donovan[3] · Christoph Tapprich[4] · Loretta Nastoupil[5] · Catherine Thieblemont[6] · Christina Loefgren[7]

1. Global Market Access and Health Policy, Janssen Global Oncology, 19 Green Belt Dr., Toronto, ON M3C 1L9, Canada

2. HEMAR Janssen, High Wycombe, UK

3. ICON Plc, Abingdon, UK

4. Oncology Janssen, Neuss, Germany

5. Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

6. Hemato-Oncology, Hôpital Saint-Louis-APHP, Paris, France

7. Janssen R&D, Raritan, NJ, USA