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

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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, Embase (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.

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].
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
| Study ID | Country | FL/MZL | Trial used | Intervention | Reference treatment | Cost year; currency | Total costs<sup>b</sup> | LY | QALY | ICER (cost per QALY/LY) |
|----------|---------|--------|------------|--------------|---------------------|---------------------|---------------------|-----|-----|---------------------|
| Papaioannou et al., 2012 | UK | FL | M39021 (IPD) | 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 | UK | FL | M39021 (IPD) and three RCTs (FL2000 [41], OSHO-39 [42], GLSG-2000) | R-CVP | CVP | –; GBP | – | – | – | 1529/QALY [using patient-level data] |
| | | | | R-MCP | MCP | – | – | – | 5611/QALY [using ordinary least squares regression] |
| | | | | R-CHVP + IFNα | CHVP + IFNα | – | – | – | 9251/QALY |
| Ray et al., 2010 | UK | FL | M39021 and three RCTs (FL2000 [44], OSHO-39 [42], GLSG-2000) | 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 |
| | | | | MCP | – | | 20,922 | 7.887 | 5.504 | – |
| | | | | R-CHVP + IFNα | CHVP + IFNα | – | – | – | 7455/QALY; 6503/LY |
| Hornberger et al., 2008 | US | FL | M39021 | 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 | 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 | 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 | US | FL | SEER Medicare registry | R-CHOP/R-CHOP | CVP | 2009; USD | 111,815<sup>d</sup> | – | – | 382,642/LY after 2 years 193,859/LY after 3 years 102,142/LY after 4 years of observation |
| | | | | CHOP/CVP | – | | 80,826<sup>d</sup> | – | – | – |
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].
| Study ID | Country       | FL/MZL | Trial used<sup>a</sup> | Intervention | Reference treatment | Cost year; currency | Total costs<sup>b</sup> | 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              |
| 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   |
| Mervin ISPOR, 2016 [16] | Australia     | FL     | PRIMA [47] and EORTC 20981 [48] | R maintenance | Observation          | –; AUD              | 145,418                | 8.3    | 6.74  | 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<sup>c</sup> |
| **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 |
| Hayssip and Simpson, 2008 [19] | US            | R maintenance | EORTC 20981 [51] | R maintenance | Observation | – | 14,722 | 4.8693 | 3.3331 | – |
| 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 |
| Blommestein et al., Netherlands 2014 [21] | Netherlands | R maintenance [Scenario 1]<sup>d</sup> | EORTC 20981 [48, 51] for trial evidence and two registries (PHAROS and HemoBase) for real-work evidence | R maintenance [Scenario 1]<sup>d</sup> | Observation | – | 28,156 | 4.94 | 3.38 | – |
| | | R maintenance [Scenario 2]<sup>d</sup> | | | Observation [Scenario 2] | – | 39,182 | 7.84 | 6.46 | – |
| | | R maintenance [Scenario 3]<sup>d</sup> | | | Observation [Scenario 3] | – | 100,424 | 9.36 | 7.81 | 23,821/QALY; 21,202/LY |
| | | Observation [Scenario 3] | | | Observation [Scenario 3] | – | 67,756 | 7.81 | 6.44 | – |
| | | R maintenance [Scenario 3] | | | Observation [Scenario 3] | – | 88,582 | 10.17 | 8.65 | 11,245/QALY; 10,591/LY |
| | | Observation [Scenario 3] | | | Observation [Scenario 3] | – | 64,846 | 7.93 | 6.54 | – |
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 (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].
| Study ID | Country          | FL/MZL | Trial used | Intervention                        | Reference treatment | Cost year; currency | Total costs<sup>b</sup> | LY  | QALY   | ICER (cost per QALY/LY) |
|---------|------------------|--------|------------|-------------------------------------|---------------------|---------------------|------------------------|-----|--------|------------------------|
| Gilead IDEL SMC, 2015 [52] | UK    | Refractory FL | 101-09 (DELTA) | IDEL | Chemotherapy and/or R | GBP<sup>c</sup> | – | – | – | 62,653/QALY |
| Gilead IDEL CADTH MS, 2016 [54] | Canada | Refractory FL | DELTA | IDEL | BSC | CAD<sup>c</sup> | – | – | – | 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 |
| Roche R R/R NICE MS, 2007 [18] | UK    | R/R FL | EORTC 20981 | R-CHOP + R maintenance | CHOP | 2006; GBP | 22,389 | 5.2479 | 3.7207 | 9,470/QALY |
| Roche R R/R NICE MS, 2007 [18] | UK    | R/R FL | EORTC 20981 | R-CHOP + R maintenance | CHOP | 2006; GBP | 23,054 | 5.1454 | 3.626 | – |
| 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 |
| Guzauskas et al., ASH, 2016 [29] | US    | R/R FL | GADOLIN | R-CHOP | CHOP | 2016; USD | 59,521 | 6.72 | 4.72 | 12,123/QALY; 11,049/LY |
| Roche O CADTH MS, 2017 [23] | Canada | R/R FL | GADOLIN | R-CHOP + G maintenance | B | 2016; CAD<sup>c</sup> | 49,562 | 5.81 | 3.9 | – |
| Roche O SMC, 2017 [24] | UK    | R/R FL | GADOLIN [55] | G + B + G maintenance vs. R + chemotherapy | R + chemotherapy | GBP<sup>c</sup> | 62,034 | – | – | 62,833/QALY |
| Roche O PBAC MS, 2016 [28] | Australia | Refractory FL | GADOLIN [55] | G + B + G maintenance | B (proxy of BSC) | AUD | – | – | – | With the range of 45,000–75,000/QALY |
| 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 |
| Roche O PBAC MS, 2016 [28] | Australia | Refractory FL | GADOLIN [55] | R-CHOP + R maintenance → R-COP-R/COP → BSC | R-CHOP + R maintenance → R-COP-R/COP → BSC | 167,124 | 11.3 | 8.6 | 9999/QALY; 8438/LYS |
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
| 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 | – | – | – | – |
| 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 | – | – | 28,211 | – | 1.74 billion to 2.57 billion |
| 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 | – | – | – | – |
| Study ID (Country)       | Treatment status | Time horizon | Patient subgroup | N (%) | Description | 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 | 2013/14; GBP | – | – |                  | – | – |
|                         |                  | Lifetime | FL patient | – | Mean cost/ patients from diagnosis to death | 17 million | 10,202 | – |                  | – | – |
Follicular or Marginal Zone Lymphoma: Economic SLR

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

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.

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

| Study ID          | Intervention | Population | Measure                              | Time point                                      | HRQoL estimate |
|-------------------|--------------|------------|--------------------------------------|-------------------------------------------------|----------------|
|                   |              |            |                                      | Mean value SD N Patients with improvement 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    |
|                   |              |            |                                      | Cycle 5 day 1 (induction treatment)              | 118 30 25.4    |
|                   | G + B + G maintenance |          |                                      | Follow-up 4 and 6 months post end of induction  | 58 20 34.5     |
|                   |              |            | FACT-LYM lymphoma-specific subscale (≥ 3-point increase) | Follow-up 4 and 6 months post end of induction | 78 32 41       |
|                   | G + B + G maintenance |          |                                      | Follow-up 8 and 12 months post end of induction | 32 10 31.3     |
|                   |              |            | FACT-LYM TOI (≥ 6-point increase)   | Follow-up 8 and 12 months post end of induction | 61 26 42.6     |
|                   |              |            |                                      |                                                  |                |
|                   |              |            |                                      |                                                  |                |
|                   |              |            |                                      |                                                  |                |
**Table 5** (continued)

| Study ID                  | Intervention          | Population                  | Measure             | Time point                      | HRQoL estimate     |
|---------------------------|-----------------------|-----------------------------|---------------------|---------------------------------|--------------------|
|                           |                       |                             |                     |                                 | Mean value | SD   | N     | Patients with improvement | n | %    |
|                           |                       |                             |                     |                                 |          |     |       |                             |   |      |
| Pettengell et al., 2008 [38] | Chemotherapy         | –                           | FACT-LYM total     | Baseline (on study entry)       | 118.26    | –    | –     | –                               |   |      |
|                           | No chemotherapy       | –                           | –                   |                                 | 132.65    | –    | –     | –                               |   |      |
|                           | Chemotherapy          | –                           | FACT-LYM TOI        |                                 | 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        |                                 | 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.

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Data Availability Statement The authors declare that the data supporting the findings of this study are available within the article and the supplementary files. All data were identified and assessed from the references listed in the study.
Compliance with Ethical Standards

Conflict of interest Neerav Monga, Jamie Garside, Christina Loefgren, and Christoph Tapprich are employees of Janssen. Loretta Nastoupil and Catherine Thieblement received research support/honoraria from Janssen. Peter O’Donovan, Binu Gurung and Joan Quigley are em-

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