

CADTH Health Technology Review

Lenalidomide Plus Rituximab Chemotherapy for Relapsed or Refractory Indolent B-Cell Non- Hodgkin Lymphomas

Authors: Sara D. Khangura, Andrea Ryce

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Abbreviations

AE	adverse event(s)
ASCT	autologous stem cell therapy
CI	confidence interval
CR	complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ERG	Expert Review Group
FL	follicular lymphoma
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IRC	independent review committee
ITT	intention to treat
MZL	marginal zone lymphoma
NHS	National Health Service
NICE	National Institutes for health Care Excellence
NIH	National Institutes of Health
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
R2	lenalidomide + rituximab
R-CHOP	rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone
RCT	randomized controlled trial
R-CVP	rituximab, cyclophosphamide, vincristine, and prednisone
R-LEN	rituximab and lenalidomide
R-mono	rituximab monotherapy
SD	stable disease
SR	systematic review
WTP	willingness to pay

Key Messages

- Data from 2 randomized controlled trials indicated a statistically significant benefit in progression-free survival and overall survival for patients with follicular lymphoma who received R2 as compared to patients who received rituximab plus placebo or R-CHOP.
- The frequency of all types of adverse events in patients receiving R2 as compared to rituximab plus placebo or R-CHOP was comparable, but patients receiving R2 experienced more severe adverse events.
- Two economic analyses concluded that R2 was cost-effective for the treatment of patients with follicular lymphoma as compared to rituximab plus placebo (UK and Dutch contexts).
- Evidence identified in this review was mostly limited to that describing patients with follicular lymphoma.
- Most evidence identified in this review was generated with support and/or funding from a private industry pharmaceutical manufacturer.

Context and Policy Issues

Non-Hodgkin lymphomas (NHL) are a group of more than 30 diseases that affect the lymphatic system in the human body and are categorized as either indolent (low-grade) or aggressive (high-grade).¹ In Canada, NHL is the fifth most common cancer diagnosed in adults, with an increasing incidence being observed over recent decades.² Follicular lymphoma (FL) is the most common indolent B-cell NHL in North America,¹ representing an estimated half of indolent NHLs, with another 15% being marginal zone lymphoma (MZL).³

Most indolent B-cell NHLs are identified in the advanced stages and are incurable⁴; however, due to their slow progression, many can be treated and often result in remission that can last for 10 years, or more.³ For some patients, however, there is no response, or an insufficient response, to initial therapy e.g., it is estimated that approximately 10% of patients living with FL are refractory to initial therapy.⁵ Treatment for indolent B-cell NHL varies based on the features of the disease and patient, but may include observation, radiotherapy, chemotherapy and/or stem cell transplant, according to the Canadian Cancer Society.⁶ In general, chemoimmunotherapy, combining rituximab and cytotoxic chemotherapy (i.e., cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone) — also known as R-CHOP — has become a commonly recommended treatment option in patients with relapsed, indolent B-cell NHL.⁴ However, R-CHOP may not be suitable for frail elderly patients, those with comorbidities or those who have several disease relapses.⁴

Lenalidomide is a novel immunomodulatory agent with unique and promising mechanisms of action in the context of B-cell NHL.^{7,8} Lenalidomide has demonstrated efficacy as monotherapy in patients with B-cell NHL, and preclinical data suggested a potential benefit of combining lenalidomide with rituximab.⁹ Rituximab has also been used as a monotherapy, as well as combined with other agents, demonstrating a benefit to patients with B-cell NHL.^{10,11} The combination of rituximab with lenalidomide (R2) has demonstrated favourable findings early on — in both previously untreated and previously treated indolent B-cell NHL patients — and has been suggested as a possible alternative to chemotherapy.^{9,11,12}

A Health Canada Notice of Compliance does not exist for lenalidomide in patients with NHL, and CADTH's reimbursement review process does not typically review generic drugs. With the

recent approval of some generic lenalidomide products in Canada, the aim of this report is to summarize available evidence on the clinical and cost-effectiveness of lenalidomide plus rituximab (R2) for the treatment of relapsed or refractory indolent B-cell lymphomas.

Research Questions

1. What is the clinical effectiveness of lenalidomide plus rituximab combination chemotherapy (R2) for relapsed or refractory indolent B-cell non-Hodgkin lymphomas?
2. What is the cost-effectiveness of lenalidomide plus rituximab combination chemotherapy (R2) for relapsed or refractory indolent B-cell non-Hodgkin lymphomas?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE and Embase, all via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lenalidomide and rituximab and indolent B-cell non-Hodgkin lymphomas. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and October 7, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2016. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included health technology assessments or systematic reviews.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)¹³ for systematic reviews, the Downs and Black checklist¹⁴ for randomized and non-randomized studies, and the Drummond checklist¹⁵ for economic evaluations. Summary scores were not calculated for

the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 230 citations were identified in the literature search. Following screening of titles and abstracts, 205 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 21 publications were excluded for various reasons, and 5 publications met the eligibility criteria and were included in this report. Eligible publications were 1 health technology assessment (HTA) (including both an eligible systematic review (SR) and an eligible economic evaluation), 3 randomized controlled trial (RCT) reports representing 2 unique studies, and 1 report of an economic evaluation. Appendix 1 presents the PRISMA¹⁶ flow chart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The HTA identified by this review was published in 2020 and incorporated a SR and an economic evaluation. Both the SR and economic evaluation were conducted by an industry

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with any grade of relapsed or refractory indolent B-cell non-Hodgkin lymphomas (i.e., relapsed/refractory follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma and Waldenström macroglobulinemia, MALT lymphoma)
Intervention	Lenalidomide plus rituximab combination (R2) chemotherapy
Comparator	Rituximab single agent therapy or combination chemotherapy other than R2 therapy (i.e., R-CHOP, R-CVP, R-FCM, R-CEOP, R-fludarabine, R-bendamustine)
Outcomes	Q1: Clinical effectiveness (i.e., progression-free survival, overall survival, response rate, duration of response, quality of life); safety (i.e., adverse events of \geq grade 3 and grade 4, serious adverse events, deaths) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-years)
Study designs	Health technology assessments, systematic reviews,, randomized controlled trials, economic evaluations

MALT = mucosa-associated lymphoid tissue; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine (Oncovin), and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; R-FCM = rituximab, fludarabine, cyclophosphamide, mitoxantrone.

sponsor, and submitted for review to an Expert Review Group (ERG) that was commissioned by the National Institute for Health and Clinical Excellence (NICE) in the UK.¹⁷

While the SR included in the HTA reports identifying 5 eligible studies, the analyses in the HTA focus primarily on data from the AUGMENT trial¹⁸ – including the ERG’s critique of the SR, which focuses only on the AUGMENT trial, as the other 4 studies did not contain data of relevance to the scope of the HTA, according to the ERG.¹⁷ Similarly, only the data from the AUGMENT study as summarized in the HTA met the eligibility criteria for this review, and so the summary of the SR is limited to a description of the findings from the AUGMENT trial only.

Of the 3 RCTs identified by this review,¹⁹⁻²¹ 2^{19,20} report on data from the AUGMENT trial.¹⁸ AUGMENT is described by the authors of the studies included in this review as a phase III, multi-centre, double-blind RCT, using intention-to-treat (ITT) analyses.^{19,20} One of these papers was published in 2019 and described the full study population of the AUGMENT RCT,²⁰ while the other was published in 2020 and described a subset of the AUGMENT study patients.¹⁹ The third RCT was published in 2019 and based in a single centre.²¹

The 2 economic evaluations identified by this review conducted cost-effectiveness analyses and used data from the AUGMENT study¹⁸ One study considered 3 perspectives in the analyses (i.e., societal, health care and societal including future non-medical costs), and used a 3-state partitioned model, incorporating a lifetime time horizon and assuming a willingness-to-pay (WTP) threshold of €50,000 per quality-adjusted life-year (QALY).²² The other economic evaluation was incorporated within the HTA included in this report and described analyses conducted both by an industry sponsor and an ERG – the latter of which also prepared and reported on a critical assessment of the industry sponsor’s cost-effectiveness analyses submission.¹⁷ The HTA-based cost-effectiveness analyses considered 2 perspectives (i.e., both National Health Service (NHS) and personal social services perspectives), and the economic model used a 3-state (including progression-free, post-progression and death) partitioned design that incorporated a lifetime time horizon and assumed a WTP threshold of £30,000 per QALY. Both cost-effectiveness analyses conducted sensitivity (probabilistic and deterministic) as well as scenario analyses.

Finally, despite the overlap between the HTA’s findings (i.e., clinical outcomes and cost-effectiveness data generated from the AUGMENT trial) and the search for this review (i.e., 3 primary study reports describing clinical outcomes and cost-effectiveness analyses using AUGMENT trial data^{19,20,22}), we retained all 4 publications as included studies, because each of them reported on some unique findings not described in the other papers. Another important contributing factor in this decision was the large amount of redacted data in the HTA (where indicated as confidential by NICE),¹⁷ rendering a large amount of the data unavailable. Consequently, most of the findings describing clinical effectiveness from the AUGMENT trial were taken from the primary clinical report from AUGMENT that was included in this review.²⁰

Country of Origin

The HTA was conducted for NICE in the UK; consequently, the industry sponsor’s submission (including both the SR and economic evaluation), ERG’s report and other associated documents within HTA report are specific to a UK context.¹⁷ The AUGMENT RCT is described as having been conducted across 97 centres representing 15 countries (not specified).²⁰ The subset of patients from the AUGMENT RCT described in the paper reported by Izutsu and colleagues included only those participants recruited and followed up in Japan.¹⁹ The

single-centre RCT was conducted in China.²¹ The economic evaluations were conducted in the Netherlands²² and the UK,¹⁷ respectively.

No evidence from a Canadian context was identified by this review.

Patient Population

Because the SR from the HTA reported relevant data from the AUGMENT RCT only,¹⁷ details describing the population were taken from the included report describing the primary study.²⁰ Leonard and colleagues describe the AUGMENT RCT, which recruited patients with previously treated FL or MZL, including 358 participants with a median age of 63 years (range 26 to 88).²⁰ The Japanese substudy of the AUGMENT trial reported data on 36 participants with a median age of 61 years (range 44 to 83).¹⁹ The single-centre RCT described 60 patients with FL and a mean age of 49.3 years (SD 10.4) in the intervention group and 51.1 years (SD 10.6) in the control group.²¹ The proportions of participants who were male in the RCT study populations were 50% in the AUGMENT trial,²⁰ 48% in the Japanese sub study of the AUGMENT RCT,¹⁹ and 58% in the single-centre RCT.²¹ Among the AUGMENT trial participants, 82% had FL and 18% had MZL²⁰; whereas, in the Japanese substudy of AUGMENT, 97% of the patients had FL and 3% had MZL.¹⁹ In all 3 RCTs, baseline characteristics were otherwise described as being similar across the intervention and control groups.¹⁹⁻²¹

Both economic evaluations used patient data from the AUGMENT trial.¹⁸ to inform base-case, sensitivity and scenario analyses.^{17,22} The models used in the HTA pooled data across patients with FL and MZL,⁷ whereas, the cost-effectiveness study used only the subset of patients with FL.²²

No evidence was identified by this review describing the use of R2 in patients with lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, or mucosa-associated lymphoid tissue (MALT) lymphoma.

Interventions and Comparators

Because the SR from the HTA reported relevant data from the AUGMENT RCT only,¹⁷ details describing the intervention and comparator from that study were taken from the other included reports describing the primary study.^{19,20} The intervention and comparators were the same in all papers describing clinical effectiveness data from the AUGMENT trial^{17,19,20} i.e., the active intervention arm was R2, comprised of lenalidomide (20 mg or 10 mg) administered once per day on day 1 to day 21 of a 28-day cycle for 12 cycles, combined with rituximab (375 mg/m²) administered intravenously once per week on days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2 to 5.^{19,20} For the comparison arm, AUGMENT used rituximab plus placebo, with no other details described about its administration, other than it was “administered similarly” (p. 1189)²⁰ as the R2 regimen.^{19,20} In the active comparator group, the single-centre RCT used lenalidomide (15 mg) administered orally with rituximab (375 mg/m²) on day 1; cyclophosphamide (750 mg/m²) on day 2; epirubicin (60 mg/m²) on day 2; vincristine (1.4 mg/m²) on day 2, and; prednisone (100 mg) on days 1 to 5, administered intravenously every 21 days for 6 cycles – described by the authors as R-CHOP.²¹ Control arm patients in the single-centre RCT received R-CHOP (without lenalidomide).²¹

The economic evaluations both drew from the AUGMENT trial as well, and so assessed R2 as the intervention of interest i.e., rituximab (375 mg/m²) administered on days 1, 8, 15, and 22 in cycle 1, and on day 1 of every subsequent 28-day cycle, until cycle 5; with lenalidomide (20 mg or 30 mg) per day, administered orally on days 1 to 21 of a 28-day cycle, for a total

of up to 12 cycles.^{17,22} In the cost-effectiveness study, authors used rituximab monotherapy (R-mono) from the AUGMENT RCT as the comparison intervention i.e., rituximab 375 mg/m² administered intravenously on days 1, 8, 15, and 22 in cycle 1, and on day 1 of every subsequent 28-day cycle until cycle 5.²² In the HTA's economic evaluation, the industry sponsor's economic model included R-CHOP and R-CVP as indirect comparators relevant to this review; that is R-CVP included rituximab 375 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² all on day 1; prednisolone 100 mg on day 1 to 5 of a 21-day cycle, for up to 8 cycles. The R-CHOP comparator comprised the same constituents and followed the same protocol, but also included the addition of doxorubicin (50 mg/m²) on day 1 of the 21-day cycle.¹⁷ Notably, as part of its critique of the industry sponsor's economic model, the ERG requested additional cost-effectiveness analyses using R-mono as a comparator; while the findings of these analyses are provided in the HTA, the methods (including the constituents and treatment protocol for R-mono as included in the economic model), were not detailed in the HTA report.

No evidence was identified by this review describing rituximab, fludarabine, cyclophosphamide, mitoxantrone (R-FCM); rituximab, cyclophosphamide, etoposide, vincristine, prednisone (R-CEOP); rituximab with fludarabine (R-fludarabine); rituximab with bendamustine (R-bendamustine), or; rituximab, cyclophosphamide, etoposide, vincristine, prednisone (R-CEOP) as comparators.

Outcomes

The primary and secondary outcomes from the AUGMENT trial are described in detail below (and in Appendix 2) from the primary report of findings that was included in this review²⁰; however, the HTA's SR did provide some information on health-related quality of life (HRQoL) in addition to the primary and secondary outcomes described below,¹⁷ and the available data from that outcome are included in this report. The primary outcome of the AUGMENT trial, as described in both papers included in this review that reported data from it, was progression-free survival (PFS), measured in months.^{19,20} PFS was not otherwise defined in either paper,^{19,20} but is described in a clinical trials registry record for the study as the time at which either disease progression or death is observed (whichever comes first), beginning from randomization.¹⁸ The AUGMENT trial studies also described secondary outcomes data, including overall response rate (ORR), measured in months; complete response (CR), measured by counting numbers of patients (reported by Leonard and colleagues, only); duration of response (DOR), measured in months (reported by Leonard and colleagues, only); overall survival (OS), measured in months; event-free survival (EFS), measured in months, and; safety, measured by observations of adverse events (AEs).^{19,20} Data describing response and progression outcomes for AUGMENT were reviewed by an independent review committee (IRC) and findings were then reported both from study investigators and the IRC; IRC data were favoured over study investigator data for use in this review, as IRC review is recommended by WHO and has shown effectiveness in mitigating biased effect estimates.²³ Patients in the AUGMENT trial are being followed for 5 years for disease progression, subsequent treatment and responses, as well as subsequent malignancies.²⁰ The single-centre RCT measured ORR, defined as including CR, partial response (PR), stable disease (SD) and progressive disease (PD).²¹ Study investigators also measured overall PFS and OS at 1-, 2- and 3-year intervals.²¹ Data on safety outcomes were also collected by measuring and grading observed AE.²¹

The economic evaluations both reported on cost-effectiveness using costs and QALYs,^{17,22} and the cost-effectiveness study also reported on total average life-years (LY) per patient.²²

Both studies presented their findings using incremental cost-effectiveness ratios (ICERs) reporting on the cost per unit of health benefit gained i.e., QALY or LY.^{17,22}

Additional details regarding the characteristics of included studies are provided in Appendix 2

Summary of Critical Appraisal

SR

The SR described in the HTA included in this report demonstrated several strengths and limitations. The most notable limitation was the absence of a detailed description of the methods. For instance, while the SR portion of the HTA included in the industry sponsor's submission makes reference to appendices describing important details about the SR and its methods, these appendices are not included within the HTA document¹⁷ and are therefore unavailable to the reader. Nonetheless, the ERG report summarizes some of key pieces of information necessary for critically appraising the review methods.¹⁷ Using the available information, it was apparent that a comprehensive search of the literature was performed. In addition, duplicate data extraction was completed and risk of bias assessments were performed.¹⁷ The study characteristics were described and the approach to synthesis was explained and justified appropriately.¹⁷ Another strength was the comprehensive critique provided by the ERG of the SR (as well as the entire submission from the industry sponsor) as the third-party assessment provides the reader with helpful insights into the strengths and limitations of the review. Limitations to the SR were also noted, however; neither research question(s) is/are nor a link to a protocol are provided in the report.¹⁷ The study selection process is not described in detail, and the ERG confirms that duplicate study selection was not indicated by the authors of the SR.¹⁷ Because access to the appendix detailing the methods is unavailable, there are many important pieces of information that were absent such as the search strategies are referenced but not available; duplicate critical appraisal is not specified; a study flow (PRISMA) diagram is not provided, and; reasons for excluding ineligible studies are not detailed.¹⁷ Another important limitation of the SR report itself as included in the HTA is the large amount of data that are redacted from the report. Since the SR was conducted by an industry sponsor as part of an HTA, confidentiality requirements necessitated the redaction of some data that are then unavailable to the reader.

RCTs

Strengths and limitations were identified in all 3 RCT reports included in this review.¹⁹⁻²¹ The clarity of reporting was generally very good across all 3 papers, with only minor concerns identified. While the AUGMENT trial was double-blind (according to both Izutsu and colleagues¹⁹ as well as the AUGMENT clinical trials registration record¹⁸) this was not indicated in the paper reported by Leonard and colleagues.²⁰ And while most details were clearly reported in the single-centre RCT report, there were no estimates of random variability included,²¹ which limits the reader's ability to understand the impact of the small sample size of the trial on the effect estimates reported. In addition, no information on the representativeness of the study populations assessed was provided in any of the 3 reports, preventing the reader from considering whether this may pose a threat to external validity. Bias and confounding were generally well accounted for in the AUGMENT trial reports, with a randomized, double-blind design described, appropriate outcome measures and statistical tests, and both survival and ITT analyses performed.^{19,20} The limitations observed in the 2 AUGMENT reports included no clear description of whether the patients were recruited from the same population,^{19,20} as well as an apparent oversight in the paper by Leonard and colleagues, which did not describe all outcomes assessed in the methods section of the

report.²⁰ In the single-centre RCT, some features supporting the internal validity of the study were reported (e.g., patients were randomized to treatment groups, outcome measures and statistical tests were considered appropriate, and survival analyses were included).²¹ However, there were no blinding procedures described,²¹ leaving the reader uncertain as to whether the study may have been open-label; an open-label study design can threaten the internal validity of the study by introducing bias among both the patients, health care providers and investigators, who have awareness of which patient is receiving which treatment regimen. Further, the single-centre RCT did not describe the time period over which patients were recruited; the randomization procedure, or; any information about loss to follow-up.²¹ These oversights in reporting and/or study design can also threaten internal validity by introducing potential confounding, which may compromise the accuracy of the estimates of differences between patient groups in the study. Finally, no mention of sample size was reported, preventing the reader from considering whether the study was sufficiently powered to render valid and reliable results.

Economic Evaluations

In general, both economic evaluations studies demonstrated more strengths than limitations according to the Drummond checklist¹⁵ assessment, providing sufficient information from a robust source of clinical data (i.e., the AUGMENT study¹⁸) for their analyses.^{17,22} Both the study designs and data collection methods were well described in both papers with perspectives and approaches clearly stated and data sources (including justifications for their use) explicitly provided and cited.^{17,22} Similarly, the analysis and interpretation for both economic evaluations were generally clear and comprehensive, with time horizons stated, discount rates provided, sensitivity, scenario and incremental analyses conducted, and conclusions supported by the data generated.^{17,22} Despite the strengths, however, both studies also demonstrated some important limitations e.g., both studies were either funded or conducted by private industry sources, which constitutes a potential conflict of interest and can introduce important sources of bias.^{24,25} The economic evaluation incorporated into the HTA demonstrated some important limitations that were explicated by the ERG which assessed the industry sponsor's model (e.g., the ERG stated its primary concern as the indirect comparison used to inform the model, which they suggest may have inflated the efficacy estimates used for R2).¹⁷ The ERG highlighted several additional concerns,¹⁷ which may be a function – at least to some extent – of the conflict of interest limitation that exists due to the source of funding from private industry.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Lenalidomide Plus Rituximab for Relapsed or Refractory Indolent Non-Hodgkin Lymphoma

As explained above, clinical effectiveness data describing primary and most secondary outcomes from the AUGMENT study as reported in the HTA's SR¹⁷ have been taken from the primary study report included in this review,²⁰ as they were described in more detail and unredacted in the latter. Only HRQoL as described in the HTA's SR is reported here.

PFS

The paper reported by Leonard and colleagues described the median follow-up time of PFS in the AUGMENT RCT as 28.3 months for the overall study population; during which time,

a total of 185 events were observed.²⁰ Median PFS in the R2 arm was 39.4 months (95% CI, 22.9 to not reached), and in the R-placebo arm was 14.1 months (95% CI, 11.4 to 16.7), rendering a hazard ratio (HR) of 0.46 (95% CI, 0.34 to 0.62), which indicates a statistically significant benefit observed in the R² arm ($P < 0.0001$).²⁰ In the subset of patients participating in AUGMENT in Japan, median PFS in the R2 arm was not reached (95% CI, 19.7 to not estimable), and in the placebo arm, was 16.5 (95% CI, 11.3 to 30.6), resulting in a HR of 0.32 (95% CI, 0.11 to 0.96), also favouring the R2 group.¹⁹ Izutsu and colleagues also calculated the estimated probability of PFS at 2 years, rendering an estimate of 69% (95% CI, 40 to 86) for the R2 group and 33% (95% CI, 14 to 55) for the R-placebo group.¹⁹ In their assessment of PFS, Liu and colleagues found no statistical difference between the groups at 1-year of follow-up, observing a statistically significant benefit in favour of lenalidomide plus R-CHOP at both 2- and 3-years follow-up as 23 and 17 patients, respectively, achieved PFS at 2- and 3-years in the lenalidomide plus R-CHOP arm, and 17 and 10 patients at 2- and 3-years, respectively, in the R-CHOP-only arm ($P = 0.031$ at 2-years and $P = 0.035$ at 3-years follow-up).²¹ Overall PFS in the single-centre study was presented using a Kaplan–Meier curve indicating a significant benefit of lenalidomide plus R-CHOP ($P = 0.032$).²¹

OS

Median OS as observed in the overall AUGMENT RCT,²⁰ as well as the subset of patients reported in the Japanese subanalysis¹⁹ was not reached in either the R2 or R-placebo arms. In the single-centre RCT, overall OS favoured the lenalidomide plus R-CHOP group ($P = 0.024$); though, at 1-year of follow-up, no statistical difference between the groups was observed ($P = 0.313$).²¹ Nonetheless, at 2 and 3-years of follow-up, significantly more patients experienced OS in the lenalidomide plus R-CHOP group ($P = 0.021$ at 2-years and $P = 0.030$ at 3-years follow-up).²¹

ORR

In the full study population of the AUGMENT trial, ORR was found to be statistically significantly superior in the R2 group i.e., 79% of patients (95% CI 73 to 85) as compared to the R-placebo group with 59% of patients (95% CI, 52 to 67) ($P < 0.0001$).²⁰ The Japanese substudy reported higher ORR in the R2 group with 94% of patients (95% CI, 73 to 100) as compared to the R-placebo group with 56% of patients (95% CI, 31 to 79), but did not characterize the difference statistically.¹⁹ The single-centre RCT also found a statistically significant benefit for patients receiving lenalidomide plus R-CHOP, with 83.33% of patients achieving ORR as compared to 66.67% in the R-CHOP-only group ($P = 0.027$).²¹

EFS

Median EFS in the AUGMENT trial was 27.6 months (95% CI, 22.1 to not reached) in the R2 arm and 13.9 months (95% CI, 11.4 to 16.7) among patients receiving R-placebo, rendering a HR of 0.51 (95% CI, 0.38 to 0.67) and indicating a statistically significant benefit of treatment with R2 ($P < 0.0001$).²⁰ Similarly, EFS was found to be higher in both the Japanese substudy of AUGMENT i.e., in the R2 arm, EFS was not reached (95% CI 17.2 months to not estimable) and in the R-placebo arm, EFS was 16.5 months (11.3 to 30.6) producing a HR or 0.35 (95% CI, 0.13 to 0.97).¹⁹

DOR

The DOR also favoured treatment with R2 in the AUGMENT trial, with 36.6 months observed (95% CI, 22.9 to not reached) as compared to 21.7 months (95% CI, 12.8 to 27.6) in the R-placebo group (HR 0.53 [95% CI, 0.36 to 0.79] $P = 0.0015$).²⁰ The findings for this outcome in the Japanese sub study were less clear, with the DOR not reached in the R2 group (95% CI,

13.7 to not estimable) as compared to 19.0 months in the R-placebo group (95% CI 2.8 to not estimable) (HR 0.40 [95% CI, 0.13 to 1.25]); though, authors did highlight that this finding does indicate a benefit of R2 as compared to R-placebo.¹⁹

HRQoL

The HTA's SR report explained that HRQoL between the R2 and R-mono groups in the AUGMENT study was comparable with no clinically meaningful difference identified.¹⁷ The report also makes reference to additional detail that was tabulated in an appendix; however, the appendices were not included in the report as published to the NICE website,¹⁷ and so, no additional detail was available.

Safety

Authors of both reports presenting primary data from the AUGMENT trial described a similar number of AEs overall in both patient groups, but a larger proportion of patients overall experienced more severe AEs (i.e., grade III/IV) in the R2 as compared to the R-placebo arm.^{19,20} The most common AEs observed in the R2 arm were neutropenia, diarrhea and constipation, with more variability in the proportions of patients experiencing AEs in the R-placebo arm.^{19,20} On the other hand, the single-centre study reported no statistically significant difference in the proportions of patients experiencing AEs between the lenalidomide plus R-CHOP and R-CHOP-only groups.²¹

Cost-Effectiveness of Lenalidomide Plus Rituximab for Relapsed or Refractory Indolent Non-Hodgkin Lymphoma

While the total costs estimated for R-LEN exceeded those of R-mono from all 3 perspectives considered in the cost-effectiveness study, at a WTP of €50,000, R-LEN was found to be cost-effective as compared to R-mono.²² From the societal perspective, the ICER for the base-case analysis was found to be €40,493; from the health care perspective, it was €37,951, and; from the societal perspective including future non-medical costs, it was €49,296.²² Sensitivity analyses indicated uncertainty; however, estimating that the probability of cost-effectiveness for R-LEN ranged from as low as 3% when including projected future non-medical costs, to as high as 82% when considering health care costs alone. Deterministic sensitivity analyses suggested that the ICERs were most sensitive to changes in the mean age of the patient, variations in the utility value for PFS and PD.²² The economic analysis presented in the HTA redacted much of the relevant comparative data on costs, incremental costs and QALYs due to confidentiality concerning negotiated drug costs for R2; nonetheless, the industry sponsor's analysis resulted in their conclusion that R2 was cost-effective at a WTP threshold of £30,000 as compared to R-CHOP, R-CVP and R-mono with ICERs of £11,471, £16,814 and £22,580 reported, respectively.¹⁷ The HTA's ERG conducted a follow-up analysis for the base case, reporting on ICERs of £15,505 when compared to R-CHOP; £21,759 compared to R-CVP and £27,372 as compared to R-mono. The ERG portion of the HTA report concludes that there remains significant uncertainty around the comparative cost-effectiveness of R2, given indirect comparative data used in the economic modelling, as well as uncertainty around cost estimates and other parameters.¹⁷

Appendix 4 presents the main study findings and authors' conclusions.

Limitations

There was no evidence of particular relevance to Canada identified by this review, limiting the generalizability of the clinical and cost-effectiveness findings to the Canadian context. As well, no evidence was identified describing the use of R2 in patients with lymphoplasmacytic lymphoma, Waldenström macroglobulinemia or MALT lymphoma, limiting the extent to which the findings of this review may be generalized to a broader B-cell NHL patient population, outside of FL.

Of the 5 included publications,^{17,19-22} 4 reported on data from the AUGMENT RCT,^{17,19,20,22} essentially limiting the findings of this review to data from 2 eligible study populations.^{18,21} Clinical effectiveness outcomes were reported from both of the eligible studies; whereas, cost-effectiveness data describing R2 were drawn solely from AUGMENT RCT data.^{17,22} While the AUGMENT trial is a large, international, multi-centre RCT, the limited number of studies identified by this review indicate that additional research may be needed that investigates the clinical and cost-effectiveness of R² for patients with relapsed or refractory, indolent B-cell NHL.

All of the reports identified by this review demonstrated strengths and limitations in the critical appraisal; importantly however, the 4 publications reporting on data from the AUGMENT trial^{17,19,20,22} described research that was either conducted and/or funded by a private industry sponsor, which represents a potential conflict of interest and introduces a risk of bias. The single-centre RCT did not report on its source of funding.²¹

Lastly, the HTA was limited in its description of eligible data; that is, only data from the AUGMENT RCT were eligible for this review. In addition, large portions of the HTA describing key details were not available (e.g., appendices describing the methods of the SR; tabulated HRQoL data, etc). Further, the HTA redacted a large proportion of the data reported, rendering much of the report unusable.

Conclusions and Implications for Decision- or Policy-Making

This review identified 5 eligible publications, including 1 HTA (describing both an SR and an economic evaluation),¹⁷ 3 RCT reports representing 2 unique studies.¹⁹⁻²¹ and 1 additional economic evaluation.²²

Most of the clinical evidence identified favours the use of R2 as compared to other rituximab-containing regimens for the treatment of relapsed or refractory FL.^{17,19-21} While 2 of the studies reporting on clinical effectiveness outcomes were limited by small sample sizes,^{19,21} the data from the full AUGMENT RCT was generated from a larger sample across multiple centres and countries.^{17,20} Nonetheless, it is important to consider that the source of funding for the AUGMENT RCT comes from a private industry sponsor and may introduce the potential for bias from conflict of interest.

Similarly, the economic analyses identified by this review indicate R2 as being cost-effective when compared to other rituximab-containing regimens in both UK and Dutch contexts.^{17,22} Notably, there were multiple uncertainties highlighted in both publications as to factors

that could affect the cost-effectiveness of R2 — particularly the analyses using indirect comparisons — and importantly, the generalizability of these findings to the Canadian context is unknown and potentially limited.

Notably, since the publication of the main findings from the AUGMENT trial,²⁰ both NICE (UK) and FDA (US) have approved the use of R2 for previously treated FL (as well as MZL in the US).^{26,27}

While the findings of this review are generally favourable toward the clinical and cost-effectiveness of R2 for the treatment of relapsed or refractory, indolent B-cell NHL, available evidence remains limited as most evidence describes patients living with FL; has been produced and/or funded by private industry; and none of the evidence is specific to Canadian health care settings, which makes it difficult to draw conclusions on the clinical and cost-effectiveness of R2 for the treatment of relapsed or refractory, indolent NHL. Additional research that considers evidence of the effects of R2 on additional subtypes of relapsed or refractory indolent NHL, as well as that which further mitigates potential conflicts of interest, and describes information of relevance to the Canadian context, will provide broader insights into the clinical and cost-effectiveness of R2 and help stakeholders in decision-making regarding the use of lenalidomide.

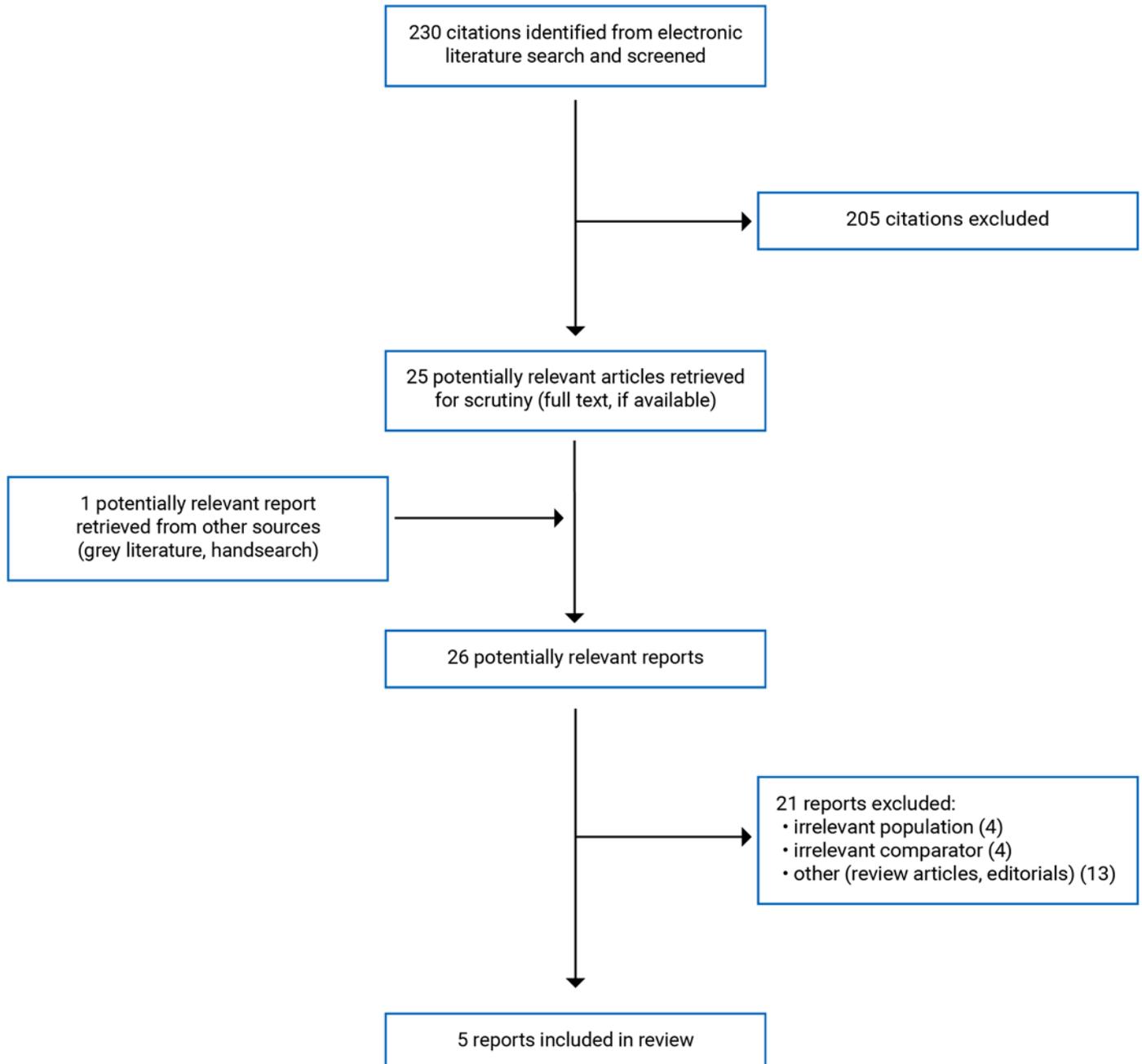
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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study, country, funding source	Study designs, no. of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
NICE 2019 ¹⁷ Country: UK Funding: NICE	PICOS: SRs, RCTs and NRS Eligible for inclusion in this review: 1 RCT included/assessed i.e., the AUGMENT trial ²⁰ – also included in this review due to the lack of available, relevant data in the HTA report	PICOS: Adults with relapsed or refractory FL or MZL Baseline characteristics from the eligible RCT: Randomized to treatment arm, n (%) • R2, 178 (50) • R-mono, 180 (50) Disease, n (%) • FL, 295 (82.4) • MZL, 63 (17.6) Sex, n (%) • Male, 172 (48) Age, n (%) • < 65 yrs, 203 (56.7) • ≥ 65 yrs, 155 (43.3) • ≥ 70 yrs, 91 (25.4) Baseline ECOG score, n (%) • 0, 244 (68.2) • 1, 110 (30.7) • 2, 4 (1.1) Refractory to the last prior regimen, n (%) • Yes, 56 (15.6) • No, 302 (84.4) POD24, n (%) • Yes, 117 (32.7) • No, 240 (67.0)	PICOS interventions of interest: Systemic induction therapies (including R2 among others) PICOS comparator interventions: a list that includes 3 of those eligible for this review i.e., R-CVP, R-CHOP, R-mono Intervention from the eligible RCT: Lenalidomide (10 mg or 20 mg administered orally once per day from days 1 to 21 of a 28-day cycle) with rituximab (R2) (375 mg/m ² , administered IV once per week beginning on day 1 of a 28-day cycle each week in Cycle 1 and on Day 1 of every 28-day Cycle from Cycles 2 through 5) Comparator from the eligible RCT: Rituximab plus placebo (R-mono) (not otherwise detailed/described)	PICOS outcomes of interest: survival, response, duration of treatment, duration of response, quality of life, time to next lymphoma treatment, adverse events Outcomes included in the eligible RCT*: • Progression-free survival (primary end point) • Overall survival • Event-free survival • Overall response rate • Adverse effects of treatment • Health-related quality of life Follow-up: • Until disease progression or unacceptable toxicity *Outcome data were redacted throughout much of the HTA report ¹⁷ ; consequently, most of the findings were summarized in this report from the published report of the AUGMENT study ²⁰ with the exception of health-related quality of life, which appeared only in the HTA report

ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HTA = health technology assessment; ITT = intention-to-treat; IV = IV; m² = metres squared; mg = milligram(s); mo = months; MZL = marginal zone lymphoma; n = number; NICE = National Institutes for health Care Excellence; NR = not reported; NRS = non-randomized study; PICOS = population, intervention, comparator, outcomes, study design (eligibility criteria); POD24 = relapsed within 2 years of initial chemotherapy; R² = lenalidomide + rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine (Oncovin), and prednisone; RCT = randomized controlled trial; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; R-mono = rituximab monotherapy; SR = systematic review; yrs = years.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Izutsu, 2020¹⁹ Japan Funding: Celgene Corp.</p>	<p>Phase III, multi-centre placebo-controlled, double-blind RCT (AUGMENT trial)</p>	<p>Adults with previously treated FL or MZL (N = 36, ITT study subpopulation of Japanese patients from the AUGMENT trial)</p> <p>Randomized to treatment arm, n</p> <ul style="list-style-type: none"> • R2, 36 • R-placebo, 36 <p>Disease, n (%)</p> <ul style="list-style-type: none"> • FL, 35 (97) • MZL, 1 (3) <p>Sex, n (%)</p> <ul style="list-style-type: none"> • Male, 18 (50) <p>Age, median (range)</p> <ul style="list-style-type: none"> • 61 (44-83) <p>Baseline ECOG score, n (%)</p> <ul style="list-style-type: none"> • 0, 33 (92) • 1, 3 (8) • 2, 0 (0) <p>Number of prior systemic therapies, n (%)</p> <ul style="list-style-type: none"> • 1, 15 (42) • 2, 12 (33) • 3, 5 (14) • 4, 4 (11) <p>Refractory to the last prior regimen, n (%)</p> <ul style="list-style-type: none"> • 1 (3) 	<p>Intervention:</p> <p>R2: Lenalidomide 20 mg or 10 mg administered once per day on day 1 to day 21 of a 28-day cycle for 12 cycles with rituximab 375 mg/m² administered IV once per week on days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2 to 5</p> <p>Comparator:</p> <p>R-placebo: administered on the same schedule as R2 (not otherwise described)</p>	<p>Primary outcome*:</p> <ul style="list-style-type: none"> • Progression-free survival (PFS), mo <p>Secondary outcomes*:</p> <ul style="list-style-type: none"> • Overall response rate (ORR), mo • Complete response (CR), n • Duration of response (DOR), mo • Overall survival (OS), mo • Event-free survival (EFS), mo • Safety, adverse events (AEs), n <p>Follow-up:</p> <p>12 treatment cycles or until discontinuation; patients subsequently are being followed up for 5 yrs for</p> <p><i>*Where reported in duplicate, study outcomes assessed by an IRC (as opposed to those assessed by the study investigators) are presented in this report</i></p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Leonard, 2019²⁰ US (lead author) Funding: Celgene Corp.</p>	<p>Phase III, multi-centre (15 countries), placebo-controlled RCT (AUGMENT trial)</p>	<p>Adults with previously treated FL or MZL (N = 358, ITT study population)</p> <p>Disease, n (%)</p> <ul style="list-style-type: none"> • FL, 295 (82.4) • MZL, 63 (17.6) <p>Sex, n (%)</p> <ul style="list-style-type: none"> • Male, 172 (48) <p>Age, median (range)</p> <ul style="list-style-type: none"> • 63 (26 to 88) <p>Baseline ECOG score, n (%)</p> <ul style="list-style-type: none"> • 0, 244 (68.2) • 1, 110 (30.7) • 2, 4 (1.1) <p>Number of prior systemic antilymphoma therapies, n (%)</p> <ul style="list-style-type: none"> • 1, 199 (56) • 2, 73 (20) • 3, 44 (12) • ≥ 4, 42 (12) <p>Prior rituximab therapy, n (%)</p> <ul style="list-style-type: none"> • 56 (16) <p>Refractory to the last regimen, n (%)</p> <ul style="list-style-type: none"> • 302 (84) <p>Randomized to treatment arm, n (%)</p> <ul style="list-style-type: none"> • R2, 178 (50) • R-placebo, 180 (50) 	<p>Intervention:</p> <p>R2: Lenalidomide 20 mg or 10 mg administered orally once per day on day 1 to day 21 of a 28-day cycle for 12 cycles with rituximab 375 mg/m² administered IV once per week on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2 to 5</p> <p>Comparators:</p> <p>R-placebo: Rituximab plus placebo “administered similarly” (p. 1189) – no other detail described</p>	<p>Primary outcome*:</p> <ul style="list-style-type: none"> • Progression-free survival, mo <p>Secondary outcomes*:</p> <ul style="list-style-type: none"> • Overall survival (OS), mo • Event-free survival (EFS), mo • Overall response rate (ORR), n • Safety, adverse events (AEs), n <p>Follow-up:</p> <p>12 treatment cycles or until disease progression, unacceptable toxicity, patient withdrawal; patients subsequently are being followed up for 5 yrs for progression, subsequent therapy and response(s), as well as subsequent malignancy/ies</p> <p><i>*Where reported in duplicate, study outcomes assessed by an IRC (as opposed to those assessed by the study investigators) are presented in this report</i></p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Liu, 2019 ²¹ China Funding: NR	Single-centre RCT	Adults with recurrent FL (N = 60) Randomized to treatment arm, n (%) <ul style="list-style-type: none"> • Lenalidomide with R-CHOP, 30 (50) • R-CHOP, 30 (50) Sex, n (%) <ul style="list-style-type: none"> • Male, 35 (58) • Female 25 (42) Age, mean (SD) <ul style="list-style-type: none"> • Lenalidomide with R-CHOP, 49.3 (10.4) • R-CHOP, 51.1 (10.6) Grading, n (%) <ul style="list-style-type: none"> • Lenalidomide with R-CHOP <ul style="list-style-type: none"> ◦ 1, 6 (20) ◦ 2, 10 (33.33) ◦ 3a, 14 (46.67) • R-CHOP <ul style="list-style-type: none"> ◦ 1, 6 (20) ◦ 2, 9 (30) ◦ 3a, 15 (50) 	Intervention: Lenalidomide 15 mg administered orally with R-CHOP (as described by the study authors) i.e., rituximab 375 mg/m ² on day 1; cyclophosphamide 750 mg/m ² on day 2; epirubicin 60 mg/m ² on day 2; vincristine 1.4 mg/m ² on day 2; prednisone 100 mg on days 1-5, administered intravenously every 21 days for 6 cycles Comparator: R-CHOP (as described by the study authors) i.e., rituximab 375 mg/m ² on day 1; cyclophosphamide 750 mg/m ² on day 2; epirubicin 60 mg/m ² on day 2; vincristine 1.4 mg/m ² on day 2; prednisone 100 mg on days 1-5, administered intravenously every 21 days for 6 cycles	Outcomes: <ul style="list-style-type: none"> • Overall response rate (ORR), n • Complete response (CR) • Partial response (PR) • Stable disease (SD) • Progression disease (PD) • Progression-free survival (PFS) • Overall survival (OS) • Adverse events Follow-up: For ORR, CR, PR, SD, PD: 6 cycles of treatment For PFS, OS: 1 yr, 2 yr, 3 yr

AE = adverse event; CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FL = follicular lymphoma; IRC = independent review committee; IV = IV; m2 = metres squared; mg = milligram(s); mo = month(s); MZL = marginal zone lymphoma; N/n = number; NIH = National Institutes of Health; NR = not reported; NA = not applicable; ORR = overall response rate; OS = overall survival; p. = page; PD = progressive disease; PFS = progression-free survival; POD24 = relapsed within 2 years of initial chemotherapy; PR = partial response; R2 = lenalidomide + rituximab; R-CHOP = rituximab + cyclophosphamide + epirubicin + vincristine + prednisone; R-mono = rituximab monotherapy; R-placebo = rituximab + placebo; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine (Oncovin), and prednisone; RCT = randomized controlled trial; SD = stable disease; yr = year(s).

Table 4: Characteristics of Included Economic Evaluations

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
<p>Thielen, 2021²²</p> <p>Country: Netherlands</p> <p>Funding: Celgene Corp.</p>	<p>Type of analysis: Cost-effectiveness</p> <p>Time horizon: Lifetime</p> <p>Perspective: 3 perspectives considered: societal, health care and societal including future non-medical costs</p>	<p>Adults with previously treated FL (N = 295, data taken from the AUGMENT trial)</p> <p>Sex, % female</p> <ul style="list-style-type: none"> • 52 <p>Age, mean (SD)</p> <ul style="list-style-type: none"> • 61 (11) <p>Body surface area, mean units NR (SD)</p> <ul style="list-style-type: none"> • 1.85 (0.24) <p>History of 1 prior systemic therapy, %</p> <ul style="list-style-type: none"> • 53 	<p>R-LEN:</p> <p>Rituximab 375 mg/m2 administered intravenously/ subcutaneously on days 1, 8, 15, and 22 in cycle 1 and on day 1 of every subsequent 28-day cycle until cycle 5 with lenalidomide</p> <p>20 mg or 30 mg administered orally (frequency NR)</p> <p>R-mono:</p> <p>Rituximab 375 mg/m2 administered intravenously on days 1, 8, 15, and 22 in cycle 1 and on day 1 of every subsequent 28-day cycle until cycle 5.</p>	<p>Three-state partitioned survival model</p> <p>Outcomes:</p> <ul style="list-style-type: none"> • Costs • Life-years (LYs) • QALYs • ICERs (€/LY and €QALY gained) • Costs in 2019 Euros using 4% discount rate for costs and 1.5% discount rate for effects, and; a WTP threshold of €50,000/QALY for the base-case analyses <p>Sensitivity analyses:</p> <ul style="list-style-type: none"> • Deterministic sensitivity analyses: adjustment of P values for model inputs to the upper and lower 25th percentiles of pre-specified distributions (i.e., beta distribution for proportions and utilities; gamma distribution for costs) • Probabilistic sensitivity analyses: using a Monte Carlo simulation with 1000 iterations <p>Scenario analyses:</p> <ul style="list-style-type: none"> • A series of 32 analyses varying model inputs including utilities, drug administration, treatment effect duration, PFS and OS distributions, drug price and average age of treatment initiation 	<p>Clinical data: AUGMENT trial²⁰</p> <p>Cost data: Several published and cited sources (i.e., academic and government) informing estimates for travel, productivity loss and informal care</p> <p>Utility data: AUGMENT study²⁰ and other published, cited academic sources</p>	<p>A 4-week treatment cycle length</p> <p>Potential for use of biosimilars instead of rituximab</p> <p>Subcutaneous administration of rituximab following the first IV dose</p> <p>All patient received 20 mg dose of lenalidomide</p> <p>That clinical effectiveness outcomes were similar/ comparable across the R2 and R-CHOP/R-CVP patient populations</p>

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
NICE 2020 ¹⁷ UK Funding: NICE	Cost-effectiveness analyses (conducted both by the industry sponsor and an Expert Review Group); lifetime time horizon; NHS and Personal Social Services perspective	<p>Previously treated patients with FL and MZL (pooled, from the AUGMENT study)</p> <p>Sex, % female</p> <ul style="list-style-type: none"> • 52 <p>Age, mean (range)</p> <ul style="list-style-type: none"> • 62.5 (26.0 to 88.0) <p>Baseline ECOG score, n (%)</p> <ul style="list-style-type: none"> • 1, 244 (68.2) • 1, 110 (30.7) • 2, 4 (1.1) <p>Refractory to the last regimen, n (%)</p> <ul style="list-style-type: none"> • 56 (15.6) <p>POD24, n (%)</p> <ul style="list-style-type: none"> • 117 (32.7) 	<p>Intervention</p> <p>R2: Lenalidomide 20 mg per day administered orally on days 1 to 21 of a 28-day cycle for up to 12 cycles; rituximab 375 mg/m² per week on days 1, 8, 15, and 22 in cycle 1 and on day 1 of every subsequent 28-day cycle until cycle 5</p> <p>Comparators</p> <p>R-CHOP: Rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² all on day 1; prednisolone 100 mg on days 1 to 5 of a 21-day cycle, for up to 8 cycles</p> <p>R-CVP: Rituximab 375 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² all on day 1; prednisolone 100 mg on day 1 to 5 of a 21-day cycle, for up to 8 cycles</p> <p>R-mono: rituximab plus placebo (not otherwise detailed/described)</p>	<p>Three-state partitioned survival model i.e., PF, PP, death</p> <p>Outcomes:</p> <ul style="list-style-type: none"> • Costs • QALYs • ICERs £/QALY gained) <p>Costs were in British Pounds (£); a 3.5% discount rate was used for utilities and costs, and a WTP threshold of £30,000/QALY was assumed for the base-case analyses</p> <p>Sensitivity analyses:</p> <ul style="list-style-type: none"> • Probabilistic using 1,000 iterations • Deterministic using adjustment of P values for model inputs to the upper and lower bounds of 95% CIs <p>Scenario analyses:</p> <ul style="list-style-type: none"> • Multiple analyses varying model inputs including time horizon, treatment effect estimates, costs, utility values, distributions of data, etc. 	<p>Clinical data</p> <p>AUGMENT study data for R2 data, including PFS and OS; HMRN trial data for R-CHOP and R-CVP comparators</p> <p>Cost data</p> <p>NHS and Personal Social Services data sources</p> <p>Utility data</p> <p>AUGMENT EQ-5D-3L data; published literature for scenario analyses</p>	

AE = adverse event; CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EQ-5D-3L = 3-level EQ-5D questionnaire; FL = follicular lymphoma; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; IRC = independent review committee; IV = IV; LY = life-year(s); m2 = metres squared; mg = milligram(s); mo = month(s); MZL = marginal zone lymphoma; N/n = number; NHS = National Health Service (UK); NICE = National Institutes for health Care Excellence; NIH = National Institutes of Health; NR = not reported; NA = not applicable; ORR = overall response rate; OS = overall survival; PF = progression free; POD24 = defined as relapse within 2 years of initial chemoimmunotherapy; PP = post-progression; POD24 = relapsed within 2 years of initial chemotherapy; QALY = quality-adjusted life-year(s); R2 = lenalidomide + rituximab; QALY = quality-adjusted life-year(s); R-CHOP = rituximab + cyclophosphamide + epirubicin + vincristine + prednisone; R-mono = rituximab monotherapy; R-placebo = rituximab + placebo; RCT = randomized controlled trial; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; SD = standard deviation; WTP = willingness-to-pay; yr = year(s).

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Review using AMSTAR 2¹³

Strengths	Limitations
NICE 2020 ¹⁷	
<p>AMSTAR assessment</p> <p>Search dates and sources are summarized in the ERG report portion of the HTA</p> <p>Data extraction is described as being completed in duplicate and well done by the ERG report</p> <p>Risk of bias assessment was completed and corroborated by the ERG</p> <p>Study characteristics are reported</p> <p>Summary statistics were included in the available data</p> <p>Synthesis methods were appropriate i.e., no quantitative synthesis undertaken</p> <p>SR conducted by private industry (drug manufacturer) and underwent a thorough critique by a third party (i.e., ERG unaffiliated with either the drug manufacturer or NICE/NHS)</p>	<p>AMSTAR assessment</p> <p>Research questions are not explicitly stated/provided</p> <p>Some reference to a protocol is made, but no link to a registration record or protocol document is provided</p> <p>Study selection process is not described</p> <p>No details of methods are provided in the SR portion of the report e.g.,</p> <ul style="list-style-type: none"> • Search strategies are not available in the drug manufacturer's SR report i.e., referenced in an unavailable appendix <p>Duplicate critical appraisal not indicated</p> <p>Study flow diagram not available (i.e., referenced as being included in an appendix that is not available in the HTA document)</p> <p>Excluded studies list not provided</p> <p>Other</p> <p>SR conducted by private industry (drug manufacturer) i.e., conflict of interest</p> <p>A great deal of data were redacted from the report and therefore not useful (though, this limitation does not significantly detract from the current review as the data for AUGMENT were taken from the primary study report that was also included in this review)²⁰⁾</p>

AMSTAR 2 = A Measurement Tool to Assess systematic Reviews 2; ERG = Expert Review Group; HTA = health technology assessment; SR = systematic review.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist¹⁴

Strengths	Limitations
Izutsu, 2020 ¹⁹	
<p>Reporting</p> <ul style="list-style-type: none"> The objective of the study is stated Patient characteristics are clearly described Interventions are clearly described Main outcomes are described in the methods section Main findings are clearly described Estimates of random variability are provided Adverse events were described Actual P values were reported No loss to follow-up is reported <p>Internal Validity (bias)</p> <ul style="list-style-type: none"> Patients and health care workers were blinded to the interventions Main outcome measures were appropriate No evidence of data dredging was apparent Statistical tests used were appropriate Survival analyses were included Compliance with the interventions was described <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> Patients were recruited over the same time period Patients were randomized to treatment groups Randomization was concealed from patients, health care providers, investigators and outcome assessors¹⁸ ITT analyses were undertaken 	<p>External Validity</p> <ul style="list-style-type: none"> No information reported on the representativeness of the patients or health care institutions <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> Unclear whether patients were recruited from the same population <p>Power</p> <ul style="list-style-type: none"> This substudy of the AUGMENT trial was explicitly stated as being underpowered to detect differences in outcomes

Strengths	Limitations
Leonard 2019²⁰	
<p>Reporting</p> <ul style="list-style-type: none"> The objective of the study is stated Patient characteristics are clearly described Interventions are clearly described Main outcomes are described in the methods section Main findings are clearly described Estimates of random variability are provided Adverse events were described Actual P values were reported No loss to follow-up is reported <p>Internal Validity (bias)</p> <ul style="list-style-type: none"> Patients and health care workers were blinded to the interventions Main outcome measures were appropriate Statistical tests used were appropriate Survival analyses were included Compliance with the interventions was described <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> Patients were recruited over the same time period Patients were randomized to treatment groups Randomization was concealed from patients, health care providers, investigators and outcome assessors¹⁸ ITT analyses were undertaken 	<p>Reporting</p> <ul style="list-style-type: none"> A double-blind method was used in the AUGMENT trial,¹⁸ but this was not reported in the paper by Leonard and colleagues <p>External Validity</p> <ul style="list-style-type: none"> No information reported on the representativeness of the patients or health care institutions <p>Internal Validity (bias)</p> <ul style="list-style-type: none"> No significant evidence of data dredging was apparent, but some outcomes (e.g., best response, PR, PD, SD) were reported in the results that were not pre-specified in the methods <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> Unclear whether patients were recruited from the same population <p>Power</p> <ul style="list-style-type: none"> Unclear whether the sample size was sufficient

Strengths	Limitations
Liu 2019 ²¹	
<p>Reporting</p> <ul style="list-style-type: none"> The objective of the study is stated Patient characteristics are clearly described Interventions are clearly described Main outcomes are described in the methods section Main findings are clearly described Adverse events were described Actual P values were reported No loss to follow-up is reported <p>Internal Validity (bias)</p> <ul style="list-style-type: none"> Main outcome measures were appropriate No evidence of data dredging was apparent Statistical tests used were appropriate Survival analyses were included <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> Patients were randomized to treatment groups 	<p>Reporting</p> <ul style="list-style-type: none"> Estimates of random variability are not provided <p>External Validity</p> <ul style="list-style-type: none"> No information reported on the representativeness of the patients or health care institution <p>Internal Validity (bias)</p> <ul style="list-style-type: none"> No information on blinding is reported Compliance with the interventions was not described <p>Internal Validity (confounding)</p> <ul style="list-style-type: none"> The time period over which patients were recruited in not reported The randomization procedure is not described in any detail Loss to follow-up was not described <p>Power</p> <ul style="list-style-type: none"> No information on the impact of the sample size or the power of the study to detect a meaningful difference between groups is provided

ITT = intention-to-treat; PD = progressive disease; PR = partial response; SD = stable disease.

Table 7: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist¹⁵

Strengths	Limitations
Thielen 2021²²	
<p>Study design The research aim and its importance are clearly stated The perspectives and form of economic analysis used are clearly stated and justified Comparator is described</p> <p>Data collection Sources of effect estimates and details of the study design are explicitly provided Outcome measures are explicitly stated Methods and sources describing valuation are reported Productivity changes are described Currency and price data are reported Details and justification for the model used are described</p> <p>Analysis and interpretation Time horizon is stated Discount rate clearly reported Sensitivity and scenario analyses are reported and variables are described Incremental analysis included Findings address the research aim Conclusions follow from the data reported with appropriate caveats included</p>	<p>Study design Rationale for use of the comparator is not explicitly justified</p> <p>Data collection Relevance of productivity changes is not made explicitly clear Quantities of resource use are not reported separately from their costs</p> <p>Analysis and interpretation Choice of discount rate not explicitly justified (but is cited) Choice of variables for sensitivity analyses not explicitly justified</p> <p>Other Funding for the study provided by private industry (drug manufacturer) Absence of long-term data Uncertainty in several of the model parameters</p>

Strengths	Limitations
NICE 2020¹⁷	
<p>Study design The perspectives and form of economic analysis used are clearly stated and justified Some comparators are described and their selection is justified</p> <p>Data collection Sources of effect estimates and details of the study design are explicitly provided Outcome measures are explicitly stated Methods and sources describing valuation are reported Currency and price data are reported Details and justification for the model used are described</p> <p>Analysis and interpretation Time horizon is stated Discount rate clearly reported and cited Sensitivity and scenario analyses are reported and variables are described Incremental analysis included Findings address the research aim Conclusions follow from the data reported with appropriate caveats included</p> <p>Other Original economic model developed by private industry (drug manufacturer) underwent a thorough critique by a third party (i.e., ERG unaffiliated with either the drug manufacturer or NICE/NHS)</p>	<p>Study design The research question and its importance are not made explicit (but may arguably be implicit in the HTA method) One comparator (R-mono) is not described explicitly (as it was included, post hoc, in follow-up analyses only)</p> <p>Data collection Quantities of resource use are not reported separately from their costs</p> <p>Analysis and interpretation The time horizon is criticized by the ERG as having been stated incorrectly Choice of discount rate not explicitly justified (but is cited)</p> <p>Clarity of reporting Many of the findings were redacted from the report Multiple appendices are referred to throughout the report but are not available/accessible Rituximab control arm from the AUGMENT trial is described as R-mono; whereas, the AUGMENT trial control arm is actually R-placebo</p> <p>Additional limitations of relevance to this report identified by the HTA's ERG Partitioned analysis with no state transition model Indirect comparisons may have introduced inaccuracy into the model (e.g., inflated efficacy of R2) Choice of curves for PFS and OS are not best fit and not justified Data describing AEs is inappropriate/missing Utility values likely inaccurate inflating ICERs in favour of R2 Some data describing resources and costs include overestimates that are likely inflating ICERs in favour of R2</p> <p>Other Original economic model developed by drug manufacturer (potential conflict of interest)</p>

ERG = Expert Review Group; HTA = health technology assessment; NHS = National Health Service (UK); NICE = National Institutes for health Care Excellence; R2 = lenalidomide + rituximab; R-mono = rituximab monotherapy; R-placebo = rituximab + placebo.

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Table 8: Summary of Findings of Included Systematic Review

Main study findings	Authors' conclusion
NICE 2020¹⁷	
<p>Data describing PFS, OS, EFS, ORR and AEs were taken from the primary study paper describing the AUGMENT trial (see below)</p> <p>Health-related quality of life</p> <ul style="list-style-type: none"> • Tabulated data not available • Authors reported no clinically meaningful difference found between the treatment groups 	<p>“Clinical-effectiveness evidence shows that, when people take lenalidomide with rituximab, their follicular lymphoma does not progress as quickly as when they take rituximab with chemotherapy. There is also evidence that lenalidomide with rituximab helps people live longer than rituximab with chemotherapy, although it is too early to tell for how much longer.</p> <p>Lenalidomide with rituximab costs more than rituximab with chemotherapy. However, its cost-effectiveness estimate is within the range that NICE normally considers an acceptable use of NHS resources. Therefore, lenalidomide with rituximab is recommended.” (https://www.nice.org.uk/guidance/TA627/chapter/1-Recommendations)</p>

AEs = adverse events; EFS = event-free survival; HTA = health technology assessment; PFS = progression-free survival; ORR = overall response.

Summary of Findings of Included Primary Clinical Studies

Izutsu 2020¹⁹

Main study findings

Primary end point (N = 30)

PFS

- Median PFS (IRC), mo (95% CI)
 - R2
 - NR (19.7 to not estimable [NE])
 - R-placebo
 - 16.5 (11.3 to 30.6)
 - Statistical difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.32 (0.11 to 0.96) (favours R2)
- Probability of PFS at 2 years (IRC), % (95% CI)
 - R2
 - 69 (40 to 86)
 - R-placebo
 - 33 (14 to 55)
 - Statistical difference between groups
 - NR

Secondary end points

ORR, n (% [95% CI])

- R2
 - 17 (94 [73 to 100])
- R-placebo
 - 10 (56 [31 to 79])

CR, n (% [95% CI])

- R2
 - 3 (17 [4 to 41])
- R-placebo
 - 2 (11 [1 to 35])

DOR

- Median DOR, mo (95% CI)
 - R2
 - NR (13.7 to NE)
 - R-placebo
 - 19.0 (2.8 to NE)
 - Statistical difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.40 (0.13 to 1.25)

EFS

- Median EFS, month (95% CI)
 - R2
 - NR (17.2 to NE)
 - R-placebo
 - 16.5 (11.3 to 30.6)
 - Statistical difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.36 (0.13 to 0.97)

OS

- Median OS, month (95% CI)
 - R2
 - NR (NE to NE)
 - R-placebo
 - NR (NE to NE)
 - Statistical difference between groups
 - Hazard ratio (95% CI)

- ◆ NE

Safety

- Adverse events observed in at least 20% of study patients (all grades), n (%)
 - Infusion-related reaction
 - All grades
 - ◆ R2: 13 (72)
 - ◆ R-placebo: 8 (44)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 0 (0)
 - Neutropenia
 - All grades
 - ◆ R2: 11 (61)
 - ◆ R-placebo: 6 (33)
 - Grade 3 or 4
 - ◆ R2: 9 (50)
 - ◆ R-placebo: 3 (17)
 - Constipation
 - All grades
 - ◆ R2: 10 (56)
 - ◆ R-placebo: 2 (11)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
 - Nasopharyngitis
 - All grades
 - ◆ R2: 7 (39)
 - ◆ R-placebo: 5 (28)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
 - Rash
 - All grades
 - ◆ R2: 7 (39)
 - ◆ R-placebo: 3 (17)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 0 (0)
 - Diarrhea
 - All grades

- ◆ R2: 7 (39)
 - ◆ R-placebo: 0 (0)
- Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Decreased lymphocyte count
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 4 (22)
 - Grade 3 or 4
 - ◆ R2: 3 (17)
 - ◆ R-placebo: 2 (11)
- Decreased white blood count
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 5 (28)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 2 (11)
- Leukopenia
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 2 (11)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 0 (0)
- Thrombocytopenia
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 0 (0)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Alanine aminotransferase increased
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 0 (0)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 0 (0)

- Maculopapular rash
 - All grades
 - ◆ R2: 5 (28)
 - ◆ R-placebo: 0 (0)
 - Grade 3 or 4
 - ◆ R2: 1 (6)
 - ◆ R-placebo: 0 (0)
- Peripheral sensory neuropathy
 - All grades
 - ◆ R2: 4 (22)
 - R-placebo: 3 (17)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Decreased blood immunoglobulin
 - All grades
 - ◆ R2: 4 (22)
 - ◆ R-placebo: 1 (6)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)

Authors' conclusion

"R² in Japanese patients from AUGMENT demonstrated superior efficacy compared with R-placebo and reduced the risk of progression by 68% (HR 0.32; 95% CI 0.11–0.96) compared with R-placebo. Median PFS was not reached in the R² group compared with 16.5 months in the R-placebo group." (p. 414)

Leonard 2019²⁰

Main study findings

Primary end point (N = 358 ITT analyses)

PFS (assessed by IRC)

- Median PFS, month (95% CI)
 - R2
 - 39.4 (22.9 to NR)
 - R-placebo
 - 14.1 (11.4 to 16.7)
 - Difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.46 (0.34 to 0.62) (favours R2)
 - P value
 - ◆ < 0.0001 (favours R2)

- Median follow-up (all), month
 - 28.3
- Total events; that is progression or death assessed by IRC before censoring (all), n
 - 185

Secondary end points (N = 358 ITT analyses)

OS

- Median (95% CI), months
 - R2
 - NR (NR to NR)
 - R-placebo
 - NR (NR to NR)
 - Difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.61 (0.33 to 1.13)
 - P value
 - ◆ Not reported
- Probability of OS at 2 years, % (95% CI)
 - R2
 - 93 (87 to 96)
 - R-placebo
 - 87 (81 to 92)
 - Difference between groups
 - Not reported

EFS (assessed by IRC), months

- Median (95% CI)
 - R2
 - 27.6 (22.1 to NR)
 - R-placebo
 - 13.9 (11.4 to 16.7)
 - Statistical difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.51 (0.38 to 0.67)
 - P value
 - ◆ < 0.0001 (favours R2)

ORR, n patients (% [95% CI])

- R2
 - 141 (79 [73 to 85])
- R-placebo

- 107 (59 [52 to 67])
- Difference between groups
 - P value
 - < 0.0001 (favours R2)

DOR, month (95% CI)

- Median (95% CI)
 - R2
 - 36.6 (22.9 to NR)
 - R-placebo
 - 21.7 (12.8 to 27.6)
 - Difference between groups
 - Hazard ratio (95% CI)
 - ◆ 0.53 (0.36 to 0.79)
 - P value
 - ◆ 0.0015 (favours R2)

CR, n patients (% [95% CI])

- R²
 - 57 (32 [25 to 39])
- R-placebo
 - 37 (21 [15 to 27])
- Difference between groups
 - P value
 - 0.0119 (favours R2)

Safety

- Adverse events observed in at least 10% of study patients, n (%)
 - Neutropenia
 - All grades
 - ◆ R2: 102 (58)
 - ◆ R-placebo: 40 (22)
 - Grade 3 or 4
 - ◆ R2: 88 (50)
 - ◆ R-placebo: 23 (13)
 - Diarrhea
 - All grades
 - ◆ R2: 55 (31)
 - ◆ R-placebo: 41 (23)
 - Grade 3 or 4
 - ◆ R2: 5 (3)
 - ◆ R-placebo: 0 (0)

- Constipation
 - All grades
 - ◆ R2: 46 (26)
 - ◆ R-placebo: 25 (14)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Cough
 - All grades
 - ◆ R2: 40 (23)
 - ◆ R-placebo: 31 (17)
 - Grade 3 or 4
 - ◆ R2: 1(1)
 - ◆ R-placebo: 0 (0)
- Fatigue
 - All grades
 - ◆ R2: 38 (22)
 - ◆ R-placebo: 33 (18)
 - Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 1 (1)
- Pyrexia
 - All grades
 - ◆ R2: 37 (21)
 - ◆ R-placebo: 27 (15)
 - Grade 3 or 4
 - ◆ R2: 1 (1)
 - ◆ R-placebo: 3 (2)
- Leukopenia
 - All grades
 - ◆ R2: 36 (20)
 - ◆ R-placebo: 17 (9)
 - Grade 3 or 4
 - ◆ R2: 12 (7)
 - ◆ R-placebo: 3 (2)
- Upper respiratory tract infection
 - All grades
 - ◆ R2: 32 (18)
 - ◆ R-placebo: 23 (13)
 - Grade 3 or 4

- ◆ R2: 2 (1)
 - ◆ R-mono: 4 (2)
- Anemia
 - All grades
 - ◆ R2: 28 (16)
 - ◆ R-placebo: 8 (4)
 - Grade 3 or 4
 - ◆ R2: 8 (5)
 - ◆ R-mono: 1 (1)
- Headache
 - All grades
 - ◆ R2: 26 (15)
 - ◆ R-placebo: 17 (9)
 - Grade 3 or 4
 - ◆ R2: 1 (1)
 - ◆ R-placebo: 0 (0)
- Infusion-related reaction
 - All grades
 - ◆ R2: 26 (15)
 - ◆ R-placebo: 24 (13)
 - Grade 3 or 4
 - ◆ R2: 4 (2)
 - ◆ R-placebo: 0 (0)
- Thrombocytopenia
 - All grades
 - ◆ R2: 26 (15)
 - ◆ R-placebo: 8 (4)
 - Grade 3 or 4
 - ◆ R2: 4 (2)
 - ◆ R-placebo: 2 (1)
- Asthenia
 - All grades
 - ◆ R2: 24 (14)
 - ◆ R-placebo: 19 (11)
 - Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 1 (1)
- Decreased appetite
 - All grades
 - ◆ R2: 23 (13)

- ◆ R-placebo: 11 (6)
- Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 0 (0)
- Muscle spasms
 - All grades
 - ◆ R2: 23 (13)
 - ◆ R-placebo: 9 (5)
 - Grade 3 or 4
 - ◆ R2: 1 (1)
 - ◆ R-placebo: 1 (1)
- Peripheral edema
 - All grades
 - ◆ R2: 23 (13)
 - ◆ R-placebo: 16 (9)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Abdominal pain
 - All grades
 - ◆ R2: 22 (13)
 - ◆ R-placebo: 16 (9)
 - Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 0 (0)
- Pruritis
 - All grades
 - ◆ R2: 21 (12)
 - ◆ R-placebo: 7 (4)
 - Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 0 (0)
- Nausea
 - All grades
 - ◆ R2: 20 (11)
 - ◆ R-placebo: 23 (13)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 1 (1)
- Dyspnea

- All grades
 - ◆ R2: 19 (11)
 - ◆ R-placebo: 8 (4)
- Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 1 (1)
- Rash
 - All grades
 - ◆ R2: 19 (11)
 - ◆ R-placebo: 7 (4)
 - Grade 3 or 4
 - ◆ R2: 2 (1)
 - ◆ R-placebo: 1 (1)
- Tumour flare
 - All grades
 - ◆ R2: 19 (11)
 - ◆ R-placebo: 1 (1)
 - Grade 3 or 4
 - ◆ R2: 1 (1)
 - ◆ R-placebo: 0 (0)
- Alanine aminotransferase increased
 - All grades
 - ◆ R2: 18 (10)
 - ◆ R-placebo: 15 (8)
 - Grade 3 or 4
 - ◆ R2: 3 (2)
 - ◆ R-placebo: 1 (1)
- Influenza
 - All grades
 - ◆ R2: 17 (10)
 - ◆ R-placebo: 8 (4)
 - Grade 3 or 4
 - ◆ R2: 1 (1)
 - ◆ R-placebo: 0 (0)
- Vomiting
 - All grades
 - ◆ R2: 17 (10)
 - ◆ R-placebo: 13 (7)
 - Grade 3 or 4
 - ◆ R2: 0 (0)

- ◆ R-placebo: 0 (0)
- Back pain
 - All grades
 - ◆ R2: 14 (8)
 - ◆ R-placebo: 18 (10)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)
- Nasopharyngitis
 - All grades
 - ◆ R2: 13 (7)
 - ◆ R-placebo: 18 (10)
 - Grade 3 or 4
 - ◆ R2: 0 (0)
 - ◆ R-placebo: 0 (0)

End points not described in the methods, but appearing in the results section

Best response (not otherwise described/defined), n (95% CI)

- PR, n (%)
 - R2
 - 84 (47)
 - R-placebo
 - 70 (39)
 - Difference between groups
 - P value
 - ◆ Not reported
- SD, n (%)
 - R2
 - 22 (12)
 - R-placebo
 - 56 (31)
 - Difference between groups
 - P value
 - ◆ Not reported
- PD/death, n (%)
 - R2
 - 6 (3)
 - R-placebo
 - 15 (8)
 - Difference between groups

- P value
 - ◆ Not reported
- Missing, n (%)
 - R2
 - 9 (5)
 - R-placebo
 - 2 (1)
 - Difference between groups
 - P value
 - ◆ Not reported

Post-hoc subgroup analysis of PFS based on prior treatment

PFS, month (95% CI), prior exposure to rituximab + bendamustine

- R2 (n = 19)
 - NR (20.2 to NR)
- R -placebo (n = 14)
 - 11.1 (3.0 to 30.6)
- Difference between groups
 - Hazard ratio (95% CI)
 - 0.23 (0.06 to 0.85)

PFS, month (95% CI), prior exposure to rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone

- R2 (n = 66)
 - 39.4 (22.1 to NR)
- R-placebo (n = 69)
 - 13.9 (8.7 to 28.0)
- Statistical difference between groups
 - Hazard ratio (95% CI)
 - 0.50 (0.30 to 0.82)

Authors' conclusion

"The magnitude of efficacy differences between the two treatments is clinically meaningful and suggests that lenalidomide plus rituximab should replace rituximab monotherapy as a standard of care for patients with relapsed or refractory indolent NHL." (p. 1197)

Liu 2019²¹

Main study findings

ORR, % patients

- Lenalidomide + R-CHOP
 - 83.33
- R-CHOP
 - 66.67
- Difference between groups

- χ^2
 - 6.193
- P value
 - 0.027

CR, n patients (%)

- Lenalidomide + R-CHOP
 - 15 (50)
- R-CHOP
 - 11 (36.67)

PR, n patients (%)

- Lenalidomide + R-CHOP
 - 10 (33.33)
- R-CHOP
 - 9 (30)

SD, n patients (%)

- Lenalidomide + R-CHOP
 - 6 (20)
- R-CHOP
 - 3 (10)

PD, n patients (%)

- Lenalidomide + R-CHOP
 - 4 (13.33)
- R-CHOP
 - 2 (6.67)

Overall PFS (presented using Kaplan–Meier curve)

- Difference between groups
 - χ^2
 - 5.183
 - P value
 - 0.032

1-year PFS, n patients (%)

- Lenalidomide + R-CHOP
 - 28 (93.33)
- R-CHOP
 - 26 (86.67)
- Difference between groups
 - χ^2

- 0.741

- P value

- 0.389

2-year PFS, n patients (%)

- Lenalidomide + R-CHOP

- 23 (76.67)

- R-CHOP

- 17 (56.67)

- Difference between groups

- χ^2

- 5.279

- P value

- 0.031 (favours intervention)

3-year PFS, n patients (%)

- Lenalidomide + R-CHOP

- 17 (56.67)

- R-CHOP

- 10 (33.33)

- Difference between groups

- χ^2

- 4.986

- P value

- 0.035 (favours intervention)

Overall OS (presented using Kaplan–Meier curve)

- Difference between groups

- χ^2

- 6.576

- P value

- 0.024

1-year OS, n patients (%)

- Lenalidomide + R-CHOP

- 30 (100)

- R-CHOP

- 29 (96.67)

- Difference between groups

- χ^2

- 1.017

- P value

- 0.313

2-year OS, n patients (%)

- Lenalidomide + R-CHOP
 - 26 (86.67)
- R-CHOP
 - 19 (63.33)
- Difference between groups
 - χ^2
 - 6.830
 - P value
 - 0.021 (favours intervention)

3-year OS, n patients (%)

- Lenalidomide + R-CHOP
 - 20 (66.67)
- R-CHOP
 - 14 (46.67)
- Difference between groups
 - χ^2
 - 5.407
 - P value
 - 0.030 (favours intervention)

Adverse events, n (%)

- Neutropenia (grade 3/4)
 - Lenalidomide + R-CHOP
 - 6 (20)
 - R-CHOP
 - 7 (23.33)
 - χ^2
 - 0.600
 - P value
 - 0.438
- Thrombocytopenia (grade 3/4)
 - Lenalidomide + R-CHOP
 - 7 (23.33)
 - R-CHOP
 - 4 (13.33)
 - χ^2
 - 1.200
 - P value

- 0.273
- Rash
 - Lenalidomide + R-CHOP
 - 12 (40)
 - R-CHOP
 - 10 (33.33)
 - χ^2
 - 0.073
 - P value
 - 0.787
- Thrombosis
 - Lenalidomide + R-CHOP
 - 9 (30)
 - R-CHOP
 - 7 (23.33)
 - χ^2
 - 0.073
 - P value
 - 0.787
- Digestive tract reaction
 - Lenalidomide + R-CHOP
 - 7 (23.33)
 - R-CHOP
 - 5 (16.67)
 - χ^2
 - 0.089
 - P value
 - 0.766
- Hepatic impairment
 - Lenalidomide + R-CHOP
 - 6 (20)
 - R-CHOP
 - 4 (13.33)
 - χ^2
 - 0.111
 - P value
 - 0.379

Authors' conclusion

"In conclusion, combined therapy of rituximab and lenalidomide for patients with recurrent FL can not only improve short-term clinical benefit rate, but also effectively controls the progression of disease, prolongs the survival period of patients, and offers good safety. This therapy can be a new option of treatment for recurrent FL." (p. 11713)

Summary of Findings of Included Economic Evaluations

Thielen 2021²²

Main study findings

Total Costs (average, lifetime, undiscounted, per patient), €

Societal perspective

- R-LEN
 - 200,355
- R-mono
 - 132,789

Health care perspective

- R-LEN
 - 165,547
- R-mono
 - 102,223

Societal perspective (including future non-medical costs)

- R-LEN
 - 299,943
- R-mono
 - 217,687

Life-Year

Societal perspective, total, average, per patient (PFS, PD)

- R-LEN
 - 12.9 (3.2, 0)
- R-mono
 - 10.9 (1.7, 9.1)
- ICER (discounted, per life-year gained), €
 - 33,681

Health care perspective, total, average, per patient (PFS, PD)

- R-LEN
 - 12.9 (3.2, 0)
- R-mono
 - 10.9 (1.7, 9.1)

- ICER (discounted, discounted, per life-year gained), €
 - 31,567

Societal perspective (including future non-medical costs), total, average, per patient (PFS, PD)

- R-LEN
 - 12.9 (3.2, 0)
- R-mono
 - 10.9 (1.7, 9.1)
- ICER (discounted, per life-year gained), €
 - 41,004

Quality-adjusted life-year

Societal perspective, total, average, per patient (PFS, PD)

- R-LEN
 - 10.8 (2.8, 8)
- R-mono
 - 9.1 (1.5, 7.6)
- ICER (discounted, per quality-adjusted life-year gained [QALY]), €
 - 40,493

Health care perspective, total, average, per patient (PFS, PD)

- R-LEN
 - 10.8 (2.8, 8)
- R-mono
 - 9.1 (1.5, 7.6)
- ICER (discounted, per QALY gained), €
 - 37,951

Societal perspective (including future non-medical costs), total, average, per patient (PFS, PD)

- R-LEN
 - 10.8 (2.8, 8)
- R-mono
 - 9.1 (1.5, 7.6)
- ICER (discounted, per QALY gained), €
 - 49,296

Sensitivity/scenario analyses

Deterministic (societal perspective)

- ICERs, range (€/QALY)
 - 37,116 to 44,816
- Top 10 influential model parameters (in order of influence on ICER)
 - Age (mean age of patient)

- Utility value of PFS (varied by 0.1)
 - Increase resulted in lowest ICER
- Utility value of PD (varied by 0.1)
- Informal care (price per hour)
- Informal care (probability of receiving)
 - Increase to 60% from 22% assumption in base case resulted in highest ICER
- Informal care (time per week)
- Costs of adverse events (neutropenia)
- Follow-up costs (outpatient clinic)
- % adverse events (neutropenia with R-LEN)
- Drug administration costs
- ICERs per QALY
 - Lowest
 - 37,116
 - Highest
 - 44,816

Probabilistic, probability of cost-effectiveness of R-LEN, %

- Base-case societal perspective (assuming a €50,000 WTP threshold)
 - 67
- Base-case health care costs perspective (assuming a €50,000 WTP threshold) – health care costs only
 - 82
- Base-case societal perspective (assuming a €50,000 WTP threshold) – including future non-medical costs
 - 3

Scenario analyses

- Societal perspective, n cost-effective scenarios/32
 - WTP threshold of €20 thousand
 - 0/32
 - WTP threshold of €50 thousand
 - 29/32
 - WTP threshold of €80 thousand
 - 32/32
- Health care perspective, n cost-effective scenarios/32
 - WTP threshold of €20 thousand
 - 0/32
 - WTP threshold of €50 thousand
 - 29/32
 - WTP threshold of €80 thousand
 - 32/32
- Societal perspective including future non-medical costs, n cost-effective scenarios/32

- WTP threshold of €20 thousand
 - 0/32
- WTP threshold of €50 thousand
 - 24/32
- WTP threshold of €80 thousand
 - 32/32

Authors' conclusion

"Our results show that R-LEN can be considered cost-effective at a WTP threshold of 50,000 EUR/QALY gained from the base-case analysis. Nevertheless, this result is marked by some uncertainty. Long-term efficacy data could validate the model results and reduce this uncertainty. Although more recent and extensive data would be preferred, a further exploration of real-world evidence (e.g., from cancer registries) could be a first step." (p. 11)

NICE 2020¹⁷

Main study findings

Deterministic base-case analysis (manufacturer)

Total costs, £

- NR for any comparisons (i.e., redacted from the HTA report)

Total costs of AEs per treatment, £

- R2 (non-refractory to rituximab)
 - 1,831.71
- R2 (refractory to rituximab)
 - 1773.94
- R-CHOP
 - 3,604.13
- R-CVP
 - 2,753.56
- R-mono
 - 462.41

Incremental costs, £

- NR for any comparisons (i.e., redacted from the HTA report)

Total QALYs

- NR for any comparisons (i.e., redacted from the HTA report)

Incremental QALYs

- NR for any comparisons (i.e., redacted from the HTA report)

ICERs (£/QALY)

- R2 vs. R-CHOP
 - 11,471
- R2 vs. R-CVP

- 16,814
- R2 vs. R-mono
 - 22,580

Deterministic base-case analysis (Expert Review Group)

Total costs, £

- NR for any comparisons (i.e., redacted from the HTA report)

Incremental costs, £

- NR for any comparisons (i.e., redacted from the HTA report)

Total QALYs

- NR for any comparisons (i.e., redacted from the HTA report)

Incremental QALYs

- NR for any comparisons (i.e., redacted from the HTA report)

ICERs (£/QALY)

- R2 vs. R-CHOP
 - 15,505
- R2 vs. R-CVP
 - 21,759
- R2 vs. R-mono
 - 27,372

Incremental and pairwise deterministic base-case analysis (Expert Review Group)

ICER (£/QALY) compared to next relevant alternative

- R-CVP
 - ref
- R-CHOP
 - dominated
- R2
 - 21,759

Sensitivity/scenario analyses

Probabilistic (manufacturer)

- ICERs (£/QALY)
 - R2 vs. R-CHOP
 - 13,443
 - R2 vs. R-CVP
 - 20,896
 - R2 vs. R-mono

- 26,116
- Probability of cost-effectiveness (assuming a £30,000 WTP threshold), %
 - R2 vs. R-CHOP
 - 81.7
 - R2 vs. R-CVP
 - 72.4
 - R2 vs. R-mono
 - 69

Probabilistic (Expert Review Group)

- ICERs (£/QALY)
 - R2 vs. R-CHOP
 - 15,818
 - R2 vs. R-CVP
 - 23,367
 - R2 vs. R-mono
 - 29,010

Deterministic

- R2 vs. R-CHOP
 - ICERs, range (£/QALY)
 - 9,177 to 13,766
 - Top 3 influential model parameters (in order of influence on ICER)
 - Cost of ASCT
 - Subsequent treatment cost post-R-CHOP
 - Proportion of patients w/ASCT post-R-CHOP
- R2 vs. R-CVP
 - ICERs, range (£/QALY)
 - NR to < £30,000
 - Top 3 influential model parameters (in order of influence on ICER)
 - Subsequent treatment cost (post-R-CVP)
 - Resource use cost
 - Administration cost of complex chemotherapy
- R2 vs. R-mono
 - ICERs, range (£/QALY)
 - NR to < £30,000
 - Top 3 influential model parameters (in order of influence on ICER)
 - Subsequent treatment cost (post-R-CVP)
 - Resource use cost
 - Administration cost of complex chemotherapy

Scenario analyses

- R2 vs. R-CHOP, n cost-effective scenarios/ > 80 (assuming a WTP threshold of £30,000)
 - All scenarios/ > 80
- R2 vs. R-CVP, n cost-effective scenarios/ > 80 (assuming a WTP threshold of £30,000)
 - All but 1 scenario (5-year time horizon)/ > 80

Authors' conclusion

"...the uncertainty around the cost effectiveness of R² is substantial, mainly caused by the possible bias introduced by the indirect treatment comparison, which could not be accounted for in the ERG analyses. The ICER for R-CVP is higher and suffers from the same uncertainty. The R-mono analysis is based on a direct comparison, but is also surrounded by substantial uncertainty, as the ICER is rather sensitive to, for instance, the time-point at which treatment waning starts and utilities in the PP health state." (p. 99 of the ERG report; p. 528/890 of the HTA document)

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Review Articles

Narrative reviews, evidence summaries and/or briefings

Shah H, Stephens D, Seymour J, Maddocks K. Incorporating novel targeted and immunotherapeutic agents in treatment of B-Cell lymphomas. *American Society of Clinical Oncology Educational Book*. 2021;41:1-18. [PubMed](#)

Witlox WJA, Grimm SE, Riemsma R, et al. Lenalidomide with Rituximab for Previously Treated Follicular Lymphoma and Marginal Zone Lymphoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics*. 2021 02;39(2):171-180. [PubMed](#)

Blair HA. Lenalidomide: A Review in Previously Treated Follicular Lymphoma. *Drugs*. 2020 Sep;80(13):1337-1344. [PubMed](#)

Flowers CR, Leonard JP, Fowler NH. Lenalidomide in follicular lymphoma. *Blood*. 2020 06 11;135(24):2133-2136. [PubMed](#)

Healthcare Improvement Scotland. Scottish Medicines Consortium. lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg hard capsules (Revlimid®) Celgene Ltd. 04 Sept 2020. <https://www.scottishmedicines.org.uk/media/5465/lenalidomide-revlimid-fl-final-september-2020-for-website.pdf>

NIHR Innovation Observatory. Lenalidomide (Revlimid) + rituximab for relapsed/refractory follicular lymphoma and marginal zone lymphoma. Oct 2017. https://www.io.nihr.ac.uk/wp-content/uploads/migrated_new/13719-Lenalidomide+rituximab-for-follicular-or-marginal-zone-lymphoma.pdf

Additional References

Relevant editorial, commentary, letter to the editor

Barr PM. Augmenting Indolent Lymphoma Treatment Options With the Combination of Lenalidomide and Rituximab. *J Clin Oncol*. 2019 05 10;37(14):1151-1153. [PubMed](#)

No eligible comparative data

Thanarajasingam G, Leonard JP, Witzig TE, et al. Longitudinal Toxicity over Time (ToxT) analysis to evaluate tolerability: a case study of lenalidomide in the CALGB 50401 (Alliance) trial. *The Lancet Haematology*. 2020 Jun;7(6):e490-e497. [PubMed](#)

Non-comparative study

Sacchi S, Marcheselli R, Bari A, et al. Safety and efficacy of lenalidomide in combination with rituximab in recurrent indolent non-follicular lymphoma: final results of a phase II study conducted by the Fondazione Italiana Linfomi. *Haematologica*. 2016 05;101(5):e196-199. [PubMed](#)