

# Cost-Effectiveness of Lenalidomide Plus Rituximab Versus Rituximab Monotherapy in Patients with Previously Treated Follicular Lymphoma

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## Research article

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# Abstract

**Background:** Efficacy of lenalidomide plus rituximab (R-LEN) compared to rituximab monotherapy (R-mono) for patients with previously treated follicular lymphoma (FL) was investigated in AUGMENT (NCT01938001). Our aim was to evaluate the cost-effectiveness of R-LEN versus R-mono in this setting from a Dutch perspective.

**Methods:** Cost-effectiveness was assessed through a partitioned survival model with three health states from three perspectives (i.e. societal, healthcare and societal including future non-medical costs). Patient-level data from AUGMENT informed effectiveness parameters (i.e. long-term survival) and health state utilities. Resource use and prices were based on AUGMENT and the literature. Clinical experts validated efficacy input parameters and results. Uncertainty was explored through sensitivity and scenario analyses.

**Results:** R-LEN resulted in 1.7 incremental discounted QALYs. Total incremental discounted costs were 67,161 EUR from a societal perspective, resulting in an incremental cost-effectiveness ratio (ICER) of 40,493 EUR/QALY (healthcare: 37,951 EUR/QALY; societal including future non-medical costs: 49,296 EUR/QALY). Sensitivity analyses indicated some uncertainty in the model results. In some scenarios R-LEN exceed an ICER of 50,000 EUR/QALY.

**Conclusion:** R-LEN was cost-effective at a willingness-to-pay (WTP) threshold of 50,000 EUR/QALY in the base-case analyses. Scenario and sensitivity analyses indicated some level of uncertainty regarding this conclusion, depending on the chosen WTP-threshold and perspective.

## Background

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) in Western Europe and the United States, comprising over 35% of all NHLs and 70% of indolent lymphomas.<sup>1</sup> In the Netherlands, the age-adjusted incidence rate for FL was 2.5 per 100,000 in 2016.<sup>2</sup>

Currently, several treatment options are available for patients who are refractory or relapsed from first-line therapy, none of which are considered curative.<sup>3</sup> For these patients, rituximab,<sup>4</sup> interferon alfa-2b as an add-on to anticancer treatment,<sup>5</sup> ibritumomab tiuxetan,<sup>6</sup> obinutuzumab in combination with bendamustine,<sup>7</sup> and idelalisib<sup>8</sup> were the only approved treatment options by the European Medicines Agency (EMA) until recently. In December 2019, the EMA approved an extension of indication for the immunomodulatory drug lenalidomide.<sup>9</sup> Lenalidomide in combination with rituximab (R-LEN) is since then authorized for adult patients with previously treated FL (Grade 1–3a) in Europe.

The EMA's decision was based on clinical evidence from the recently published phase III AUGMENT study, comparing R-LEN to rituximab plus placebo (R-mono) in previously treated patients with indolent FL or marginal zone lymphoma (MZL).<sup>10</sup> In AUGMENT, R-LEN demonstrated statistically significant superiority in overall survival (OS) and progression-free survival (PFS) over the comparator regimen in the FL subgroup. OS probability at two years, assessed by the independent review committee (IRC) was 95% (95% CI, 90 to 98) for R-LEN and 86% (95% CI, 79 to 91) for R-mono.<sup>10</sup> In addition, R-LEN was found to increase median PFS by approximately 25 months when compared to R-mono (hazard ratio, 0.40; 95% CI, 0.29 to 0.56;  $P < .001$ ).<sup>10</sup> The study also collected health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the 3-level classification system of the EQ-5D questionnaire (EQ-5D-3L).<sup>11,12</sup> Preliminary results of these data suggest no negative impact of R-LEN on patients' HRQoL when compared to R-mono.<sup>13</sup>

While lenalidomide underwent central approval by the EMA, each European member state handles its own reimbursement procedure. In addition to considerations on the safety and efficacy of a new treatment, its cost-effectiveness is a key aspect when making both treatment and reimbursement decisions.<sup>14</sup> Especially when drug prices are relatively high, economic evaluations can provide the necessary information to make informed decisions. Such assessments combine several sources of evidence (i.e. efficacy and costs) to derive conclusions on the cost-effectiveness of a treatment.<sup>15,16</sup> Analyses that also consider

patients' HRQoL are commonly referred to as cost-utility analyses (CUAs). Currently, there is no evidence available on the cost-utility of R-LEN from a societal perspective in a European country.

Therefore, the aim of this study was to evaluate the cost-effectiveness of R-LEN when compared to R-mono in patients with previously treated FL in the Netherlands from a societal perspective. As suggested in the literature, we also present results from a healthcare perspective.<sup>17</sup> While future non-medical costs should be considered when performing CUAs from a societal perspective, not all pharmacoeconomic guidelines explicitly mention their inclusion yet.<sup>18–20</sup> Consequently, the impact of these costs on the results of CUAs remains understudied.<sup>20</sup> For this study, future non-medical costs were considered for a third perspective to fill this gap.<sup>21–23</sup>

## Methods

Patient-level data to inform model efficacy parameters were based on the AUGMENT FL subgroup. A detailed description of the methods can be found in Appendix 1.

We modelled a hypothetical cohort of patients by means of a partitioned survival model.<sup>24</sup> This methodology is commonly used in decision modelling of new interventions in advanced cancers.<sup>24</sup> Our analysis follows the recommendations of the Dutch guideline for conducting economic evaluations in health care (Dutch EE guideline).<sup>25</sup>

The model comprised three states: progression free (PF), progressive disease (PD), and death. The simulation starts with administering either treatment option (R-LEN or R-mono) in the PF state. Simulated patients responding to treatment remained in the PF state and follow-up resource use was considered. In case patients relapsed or were refractory to R-LEN or R-mono, they were assumed to be in the PD state. Modelled patients could die at all times. Figure 1 schematically represents how patients can move through the model over time.

To determine the proportion of patients in each model state, we independently fit a range of parametric models to both PFS and OS in AUGMENT.<sup>26</sup> Consequently, short-term empirical data was extrapolated to a lifetime horizon. The model was adjusted for general population mortality (i.e. extrapolated survival could not exceed this mortality) and a finite treatment effect for R-LEN was assumed (i.e. five years, based on clinical expert opinion). Effects were discounted with 1.5%.<sup>25</sup>

The societal perspective of the base-case analysis included healthcare costs for drugs (acquisition and administration), adverse events (AEs), subsequent treatment, and future medical costs. Prices for drug acquisition were taken from the Dutch drug database (April 2020),<sup>27</sup> and drug administration costs were based on a micro-costing study on intravenous rituximab administration in the Netherlands.<sup>28</sup> The model considered grade 3–4 AEs with more than 5% occurrence as observed in AUGMENT.<sup>10</sup> AE costs and disutilities were based on the literature.<sup>29–31</sup> Subsequent treatment during PD and resource use during all follow-up visits were based on the Dutch clinical practice guideline (CPG) for FL.<sup>32</sup> Prices for these items were taken from the Dutch costing manual.<sup>33</sup>

Additionally, societal costs for travel, productivity losses, and informal care were considered in the model base-case (see Appendix 1 for more detail). Future non-medical costs were included using the iMTA PAID tool (version 3.0).<sup>21–23</sup>

All costs are expressed in 2019 Euros and both prices and costs of earlier years were indexed to 2019 with the pertinent consumer price index.<sup>34</sup> Costs were discounted with 4%.<sup>25</sup>

Effect outcomes include total average life years (LYs) as well as quality-adjusted life years (QALYs) per patient and were validated by clinical experts.

Furthermore, we report total incremental costs and effects as well as the incremental cost-effectiveness ratio (ICER) of R-LEN when compared to R-mono. To determine whether R-LEN is cost-effective the applicable willingness-to-pay (WTP) threshold was estimated using the Burden-of-Disease calculator.<sup>35</sup>

We conducted several scenario analyses with varying efficacy, utility, and cost parameters. Also we tested different assumptions of the treatment effect duration (see Appendix 1). Uncertainty of the model input parameters and estimates was assessed through deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA).

An overview of all parameter (mean) values, their standard error (SE), assumed distributions as well as lower and upper bounds are summarized in Table 1.

Table 1  
Overview of model input parameters

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
Model setting	% discount rate: costs	4.0	NA	NA	NA	NA	Dutch EE guideline <sup>42</sup>	None
	% discount rate: effects	1.5	NA	NA	NA	NA	Dutch EE guideline <sup>42</sup>	None
Patient characteristics	Age, years (mean)	61.18	0.65	Normal	59.89	62.45	AUGMENT study <sup>10</sup>	None
	BSA (mean)	1.85	0.01	Normal	1.82	1.88	AUGMENT study IPD <sup>10</sup>	None
	% female patients	52	NA	Beta	46	58	AUGMENT study IPD <sup>10</sup>	None
Resource use	AE %: neutropenia in R-LEN	0.5	NA	Beta	0.42	0.58	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: leukopenia in R-LEN	0.07	NA	Beta	0.03	0.11	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: anemia in R-LEN	0.05	NA	Beta	0.02	0.09	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).

AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells;

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	AE %: neutropenia in R-mono	0.12	NA	Beta	0.07	0.18	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: leukopenia in R-mono	0.02	NA	Beta	0	0.05	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	AE %: anemia in R-mono	0.01	NA	Beta	0	0.02	AUGEMENT study IPD <sup>10</sup>	Lower and upper bounds were based on the lower and upper bound probabilities of 2.5% and 97.5%, respectively (based on assumed distribution).
	Informal care: probability of receiving (in %)	22	5	Gamma	0	60	iMTA iCARE tool based on HRQoL data in AUGMENT	Upper bound probability was based on Doorduijn et al. (2004) <sup>43</sup>
	Informal care time when receiving (hours per week)	16.00	0.81	Gamma	15.11	18.28	iMTA iCARE tool based on HRQoL data in AUGMENT	None
	Patients returning back to work after first-line therapy (in %)	50	5	Beta	40	60	Arboe et al. <sup>44</sup>	None

AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells;

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
Prices	Drug acquisition: lenalidomide 2.5 mg	226.21	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 5 mg	232.54	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 7.5 mg	238.87	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 10 mg	241.16	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 15 mg	248.99	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: lenalidomide 20 mg	259.18	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses

AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells;

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	Drug acquisition: lenalidomide 25 mg	265.12	NA	NA	NA	NA	G-standaard via Z-index	A 10% and 20% discount for the price of lenalidomide was considered in scenario analyses
	Drug acquisition: rituximab 100 mg (i.v.)	227.46	NA	NA	NA	NA	G-standaard via Z-index	None
	Drug acquisition: rituximab 500 mg (i.v.)	1,137.32	NA	NA	NA	NA	G-standaard via Z-index	None
	Drug acquisition: rituximab 1400 mg (s.c.)	1,680.71	NA	NA	NA	NA	G-standaard via Z-index	None
	Physician specialist (per consultation)	120.64	12.06	Gamma	98.16	145.41	Dutch EE guideline <sup>42</sup>	None
	Follow-up price: CT	188.3	18.83	Gamma	153.21	226.96	Dutch EE guideline <sup>42</sup>	None
	Follow-up price: Outpatient clinic	140.92	14.09	Gamma	114.66	169.85	Dutch EE guideline <sup>42</sup>	None
	Imaging price: abdominal ultrasound	120.9	12.09	Gamma	98.37	145.72	Dutch EE guideline <sup>42</sup>	None
	Lab price: TSH	4.77	0.48	Gamma	3.88	5.75	Dutch EE guideline <sup>42</sup>	None
	Lab price: LDH	1.81	0.18	Gamma	1.47	2.18	Dutch EE guideline <sup>42</sup>	None
	Lab price: WBC	1.80	0.18	Gamma	1.46	2.17	Dutch EE guideline <sup>42</sup>	None
	Lab price: platelets	1.78	0.18	Gamma	1.45	2.15	Dutch EE guideline <sup>42</sup>	None
	Lab price: hemoglobin	1.73	0.17	Gamma	1.41	2.09	Dutch EE guideline <sup>42</sup>	None
	Lab price: creatinine	1.64	0.16	Gamma	1.33	1.98	Dutch EE guideline <sup>42</sup>	None

AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells;

Type	Parameter	Base case value	SE	Distribution	Lower bound	Upper bound	Source	Remark
	Informal care price (per hour)	14.95	1.5	Gamma	12.16	18.02	Dutch EE guideline <sup>42</sup>	None
	Productivity loss price (per hour)	37.08	3.71	Gamma	30.17	44.69	Dutch EE guideline <sup>42</sup>	None
Costs	Drug administration: i.v. therapy	167.82	12.6	Gamma	144.03	193.41	Franken et al. <sup>28</sup>	None
	Drug administration: s.c. therapy	56.54	5.87	Gamma	45.63	68.6	Franken et al. <sup>28</sup>	None
	Travel costs: for i.v. administration	33.39	3.34	Gamma	27.17	40.24	Franken et al. <sup>28</sup>	None
	Travel costs: for s.c. administration	8.2	0.82	Gamma	6.67	9.88	Franken et al. <sup>28</sup>	None
	AE costs: neutropenia	1171.24	530.82	Gamma	373.01	2417.96	Bouwman et al. <sup>29</sup>	None
	AE costs: leukopenia	1171.24	530.82	Gamma	373.01	2417.96	Bouwman et al. <sup>29</sup>	None
	AE costs: anemia	1595.38	479.52	Gamma	798.45	2663.5	Bouwman et al. <sup>29</sup>	None
Utilities and disutilities	Utility: PFS	0.854	0.01	Beta	0.754	0.954	AUGEMENT study IPD <sup>10</sup>	None
	Utility: PD	0.854	0.01	Beta	0.754	0.954	AUGEMENT study IPD <sup>10</sup>	None
	Disutility: neutropenia	0.090	0.02	Beta	0.059	0.120	Nafees et al. <sup>30</sup>	None
	Disutility: leukopenia	0.090	0.02	Beta	0.059	0.120	Assumed to be the same as neutropenia	None
	Disutility: anemia	0.119	0.02	Beta	0.073	0.165	Swinburn et al. <sup>31</sup>	None
AE = adverse event; BSA = Body surface area; CT = computerized tomography scan; EE = economic evaluation; HRQoL = health-related quality of life; IPD = individual patient data; i.v. = intravenous; LDH = lactate dehydrogenase; mg = milligram; NA = not applicable; PD = progressive disease; PFS = progression free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy; s.c. = subcutaneous; SE = standard error; TSH = thyroid stimulating hormone; WBC = white blood cells;								

## Results

### Base-case analysis

### Effectiveness

Based on the statistical goodness-of-fit criteria (see Appendix 2) and clinical expert opinion, we selected the Weibull and the log-normal distribution for the survival extrapolation of PFS and OS until year five, respectively. Thereafter, the hazard ratios between R-LEN and R-mono were kept constant both for PFS and OS extrapolations (see Appendix 1). For the R-LEN arm, the estimated probability of PFS at 5 and 10 years was 27% and 1%, respectively, in the R-LEN group. For patients receiving R-mono, these probabilities were 5% and 0%, meaning that all patients had progressed or died after 10 years. The estimated OS probabilities after R-LEN at 5, 10, 20, and 30 years amounted to 83%, 58%, 33% and 11%, respectively. After R-mono, these probabilities were 67%, 47%, 27%, and 9%, respectively. Empirical and modelled PFS and OS of both groups are depicted in Figs. 2 and 3. The model estimated 12.9 LYs and 10.8 QALYs for R-LEN and 10.9 LYs and 9.1 QALYs for R-mono (discounted results).

## Costs

The presented costs in Table 2 are average, discounted, lifetime costs per patient. Undiscounted costs can be found in Appendix 2.

Table 2 Model results: costs, effects and increments

Perspective		Costs in EUR										Effects	
		Drug acquisition	Drug administration	Adverse events	Subsequent treatment	Follow-up	Informal care	Productivity losses	Future medical (unrelated diseases)	Future non-medical	Total costs	Life years (PFS; PD)	QALYs (PFS; PD)
Societal	R-LEN	57,455	1,096	743	19,990	8,692	28,128	6,123	78,127	NA	200,355	12.9 (3.2; 0)	10.8 (2.8; 8)
	R-mono	6,972	692	176	21,240	7,677	23,952	6,119	65,960	NA	132,789	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
	Increments	50,483	404	567	-1,250	1,015	4,176	4	12,167	NA	67,566	2 (1.5; 0.5)	1.7 (1.3; 0.4)
Healthcare	R-LEN	57,455	957	743	19,805	8,459	NA	NA	78,127	NA	165,547	12.9 (3.2; 0)	10.8 (2.8; 8)
	R-mono	6,972	592	176	21,043	7,479	NA	NA	65,960	NA	102,223	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
	Increments	50,483	365	567	-1,238	980	NA	NA	12,167	NA	63,324	2 (1.5; 0.5)	1.7 (1.3; 0.4)
Societal incl. future non-medical consumption costs	R-LEN	57,455	1,096	743	19,990	8,692	28,128	6,123	78,127	99,588	299,943	12.9 (3.2; 0)	10.8 (2.8; 8)
	R-mono	6,972	692	176	21,240	7,677	23,952	6,119	65,960	84,899	217,687	10.9 (1.7; 9.1)	9.1 (1.5; 7.6)
	Increments	50,483	404	567	-1,250	1,015	4,176	4	12,167	14,689	82,256	2 (1.5; 0.5)	1.7 (1.3; 0.4)

EUR = Euro (currency); PD = progressive disease; PFS = progression free survival; QALYs = quality-adjusted life years; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

Total costs from the base-case societal perspective were 200,355 EUR and 132,789 EUR for R-LEN and R-mono, respectively. Major cost drivers were future medical costs (R-LEN: 78,127 EUR; R-mono: 65,960 EUR), followed by drug acquisition costs for R-LEN (57,455 EUR), and informal care (R-LEN: 28,128 EUR; R-mono: 23,952 EUR). Total healthcare costs were 165,547 EUR and 102,233 EUR for R-LEN and R-mono, respectively. When future non-medical costs were considered in a societal perspective, total costs were 299,943 EUR and 217,687 for R-LEN and R-mono, respectively.

## Incremental cost-effectiveness ratio

Total incremental costs of R-LEN when compared to R-mono were 67,566 EUR from a societal perspective. Incremental costs were highest for drug acquisition (50,483 EUR), followed by incremental future medical costs (12,167 EUR). Only total costs for subsequent treatment regimens were lower for R-LEN when compared to R-mono. This was because modelled patients receiving R-LEN progressed later when compared to patients with R-mono. Consequently, subsequent treatment is administered later and hence the effect of discounting these costs leads to lower costs.

The base-case ICER was 40,493 EUR/QALY (see Table 3). When considering healthcare costs only, the ICER was 37,951 EUR/QALY gained. When future non-medical costs were considered for a societal perspective the ICER increased to 49,296 EUR/QALY gained. In Appendix 2, the ICERs from the undiscounted analysis are presented.

Table 3  
Incremental cost-effectiveness ratios

	Perspective		
	Societal	Healthcare	Societal incl. future non-medical consumption costs
Incremental costs (EUR) per LY gained	33,681	31,567	41,004
Incremental costs (EUR) per QALY gained	40,493	37,951	49,296
EUR = Euro (currency); LY = life years; QALY = quality-adjusted life year			

Based on the disease burden calculator,<sup>35</sup> the most likely WTP-threshold was 50,000 EUR/QALY (51.6%) (see Appendix 2).

#### Deterministic sensitivity analysis

The top ten influential parameters varied in the deterministic sensitivity analysis are summarized in Fig. 4. Increasing the assumed utility value by 0.1 for progression-free disease resulted in the lowest ICER (i.e. 37,116 EUR/QALY), while assuming 60% of patients receiving informal care (instead of 22% in the base-case) resulted in the highest ICER (i.e. 44,816 EUR/QALY).

#### Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are presented in the cost-effectiveness plane (Fig. 5) for the base-case societal perspective (see Appendix 2 for all other perspectives). Assuming a WTP-threshold of 50,000 EUR/QALY gained, the probability of R-LEN being cost-effective was 67%. This probability was 82% when only healthcare costs were considered and 3% when future non-medical costs were included in the societal perspective. The cost-effectiveness acceptability curve in Fig. 6 depicts a range of WTP-thresholds and the probability of R-LEN being cost-effective at each of those for the base-case societal perspective (see Appendix 2 for all other perspectives).

#### Scenario analyses

From the base-case societal perspective, the following three scenarios exceeded the assumed WTP-threshold. First, assuming a treatment effect duration of three years yielded an ICER of 60,496 EUR/QALY gained. With an increase in the duration of the treatment effect, ICERs decreased to 33,354 EUR/QALY gained and 28,691 EUR/QALY gained after seven and ten years of treatment effect, respectively. Assuming no treatment effect waning resulted in the lowest ICER of all scenarios (25,114 EUR/QALY gained).

Second and third, selecting either the Gompertz or Weibull distribution to model OS of R-LEN and R-mono resulted in an ICER of 64,026 EUR/QALY and 53,040 EUR/QALY gained. The results of all scenario analyses can be found in Appendix 2.

## Discussion

### Summary of Results

Our analyses show that R-LEN results in incremental LYs and QALYs gained when compared to R-mono. Simultaneously, R-LEN also results in higher costs when compared to R-mono, regardless of the chosen perspective. Deterministic ICERs of R-LEN versus R-mono ranged from 37,951 EUR/QALY (health care perspective) to 49,296 EUR/QALY gained (societal perspective including non-medical costs).

#### When is R-LEN cost-effective?

To determine whether R-LEN is cost-effective when compared to R-mono, the estimated ICERs need to be compared to the pertinent WTP-threshold. However, based on the disease burden calculator, two WTP-thresholds were nearly equally likely to be applicable. For this analysis we compared the respective ICER to a 50,000 EUR/QALY gained WTP-threshold as this had the

highest probability of being applicable (see Appendix. At this WTP-threshold, R-LEN is cost-effective when compared to R-mono as all deterministic ICERs (i.e. from all perspectives) were below that threshold. However, PSA simulations resulted in some variability in the modelled results (see Fig. 5). The probability of R-LEN being cost-effective from a societal perspective started to increase from 0% at approximately 40,000 EUR/QALY gained to 100% at 62,000 EUR/QALY gained (see Fig. 6).

### Comparison with other studies

While this is the first cost-utility analysis of R-LEN for previously treated FL patients from a societal perspective, R-LEN has been evaluated in the same patient population from a UK healthcare perspective for a single technology appraisal to the NICE.<sup>36</sup> The NICE recommended R-LEN as a treatment option, stating an ICER of 20,156 GBP (approx. 22,976 EUR) per QALY gained when R-LEN was compared to R-CVP.<sup>37</sup> In the committee papers, an ICER of 17,233 GBP (approx. 19,644 EUR) per QALY gained can be found when R-LEN was compared to R-mono.<sup>36</sup> Although the modelled OS estimates between the NICE assessment and our study are comparable, the estimated ICERs deviate. This may be due to several reasons. First, the UK ICERs already include a confidential price discount of lenalidomide. Second, even without such a discount, the UK list price for lenalidomide is less than the Dutch list price. Furthermore, the UK analysis comparing R-LEN to R-mono used different parametric survival models and utility values when compared to our analysis.<sup>36</sup>

Recently, another CUA was published by Zhang et al.<sup>38</sup> The study concluded that R-LEN is not cost-effective with an ICER of 49,849 EUR (58,812 USD) per QALY when compared to R-mono for r/r FL from a Chinese societal perspective. Several methodological aspects between this and our study exist that need to be addressed. First, Zhang et al. did not have patient level data available and therefore extracted survival data from the published Kaplan-Meier curves from the AUGMENT trial. This approach does not allow for stratification by diagnosis, and hence survival data of FL and MZL patients were used together to estimate long-term survival. Second, it was claimed that results were estimated on a lifetime horizon (i.e. until all patients had died). However, the actual time horizon used in the model was 10 years. Consequently, any costs or effects occurring after these 10 years were not captured. Third, Zhang et al. stated that costs were estimated from a societal perspective. Nevertheless, only direct medical costs were considered.

### Assumptions on rituximab

Clinical experts mentioned that rituximab can be given s.c. when it is the only administered drug (as in R-mono) or when the combination drug is either administered s.c. or orally (as in R-LEN). Apart from being more time-efficient for both patients and health care staff, s.c. administration of rituximab in general leads to lower resource use and costs when compared to i.v. administration.<sup>28</sup> Nevertheless, the experts indicated that rituximab is usually administered i.v. since the price of its biosimilar version is lower when compared to the reference product. In contrast to this, Dutch list prices for rituximab and its biosimilars do not differ. Eventual discounts are the result of confidential price negotiations between individual hospitals and the manufacturer. To remain transparent, we adhered to the list prices for rituximab and assumed s.c. administration in both R-LEN and R-mono.

The assumption of s.c. versus i.v. administration for rituximab was tested in scenarios four and five (see Appendix) and did not lead to meaningful changes in the ICER. Assuming a lower price for rituximab (e.g. as a result of using a biosimilar) was not formally tested. However, a price discount for rituximab would affect both R-LEN and R-mono at the same extent and hence changes in the ICER are not expected.

### Strength and weaknesses

In our model, incremental life years were determined by the choice of the parametric survival model to extrapolate empirical trial data and the assumption of the treatment effect waning. Ideally, long-term follow-up data would inform the distribution of patients in each health state (i.e. PF or PD). These data are however not available, and with limited follow-up time in AUGMENT (median = 28.3 months),<sup>10</sup> extrapolation to a longer time horizon was necessary. Therefore, we fit several parametric survival models and consulted clinical experts to validate these long-term estimates.

Our sensitivity analyses show that the choice of a parametric survival function for OS can influence the decision whether R-LEN can be considered cost-effective at a WTP-threshold of 50,000 EUR/QALY gained. Both Gompertz and Weibull distribution resulted in an ICER above that threshold (i.e. 63,581 EUR/QALY and 52,685 EUR/QALY, respectively from a societal perspective). Empirical survival data with a longer follow-up period than in AUGMENT might lead to different results with less uncertainty.

Furthermore, the assumption on the treatment effect duration heavily impacted both the modelled effectiveness and the ICER. Assuming an infinite treatment effect duration for R-LEN resulted in the most favorable ICER of all scenario analyses from a societal perspective (24,983 EUR/QALY), while an effect duration of three years produced the least favorable ICER of 60,181 EUR/QALY gained. Which exact time point to assume for the treatment effect waning is a matter of ongoing discussion, but the NICE committee agreed that a five year horizon was appropriate (with clinical input suggesting a treatment effect lasting between 5 and 10 years).<sup>36</sup> Empirical OS and PFS data of AUGMENT indicate a benefit of R-LEN over R-mono.<sup>10</sup> After trial follow-up there are several possibilities to extrapolate this treatment effect. It can be assumed to either further increase, remain constant, or decrease. Due to the immunomodulatory effect of lenalidomide we considered a constant treatment effect after five years post treatment to be a conservative estimate.

Another important aspect of determining the modelled effectiveness is the utility value for the different model health states (i.e. PF and PD). Based on the analyses of AUGMENT HRQoL data, we found no differences between either treatment option (i.e. R-LEN or R-mono) or health state (i.e. PFS or PD), which was in line with a previous analysis of the same data.<sup>13</sup> No difference in HRQoL between health states seems counterintuitive. For a scenario analysis, we therefore used the study by Wild et al. (2006) with utility values of 0.805 for PF and 0.736 for PD.<sup>39</sup> Although often used in economic evaluations, the reference is only available as a conference abstract with limited information on the methodology or utility values. However, neither the variation of utility values in the DSA nor the scenario with utility values of Wild et al.<sup>39</sup> exceeded an ICER of 50,000 EUR/QALY gained. Further research is needed to determine whether there is indeed no difference in HRQoL between patients who are PF or in PD.

The assumed average starting age of the modelled patient cohort showed to be an influential factor for the estimated ICER (see DSA results). While the mean age of FL patients in AUGMENT was approximately 61 years, clinical experts found this to be a rather young age for previously treated FL patients. Indeed, the median age at FL diagnosis for Dutch patients between 2014 and 2016 in the Netherlands was 64 years (range: 55–72, mean not reported).<sup>2</sup> In the DSA, the influence of assuming different ages at treatment start found that age was indeed one of the most influential parameters for the model results. It needs to be noted that changing the assumed age at treatment start in the model does not lead to different outcomes of the parametric survival estimations. The variations in age mainly influence the remaining time in the model until the lifetime horizon is reached as well as the age-adjusted utility decrements. Only empirical data from a patient cohort with an older average age than in AUGMENT would lead to different outcomes in parametric survival estimations. Such data is however not available for R-LEN versus R-mono.

While we acknowledge the limited use of R-mono in (Dutch) clinical practice, there are currently no clinical data available from a phase III study comparing R-LEN to any other comparator than R-mono in previously treated FL patients. Nevertheless, the cost-effectiveness estimated for R-LEN compared to R-CHOP and R-CVP could be very relevant for clinical and reimbursement decisionmakers. For this purpose reliable evidence needs to be available, however. The modelled effectiveness of R-mono can be seen as a conservative estimate since both R-CHOP and R-CVP are generally considered to be more effective when compared to R-mono.<sup>36</sup> Nevertheless, results of the RELEVANCE trial comparing R-LEN to R-chemo in advanced untreated FL patients suggest similar efficacy results between these treatments.<sup>40</sup> Whether this holds true for later treatment lines needs to be confirmed. Based on the Dutch CPG for FL,<sup>32</sup> total treatment costs of an R-CHOP or R-CVP regimen are approximately 3,000 EUR or 5,800 EUR more expensive than R-mono. It can be hypothesized that most other cost items of R-CHOP and R-CVP will be similar or higher when compared to R-mono. Consequently, a comparison of R-LEN to R-CHOP or R-CVP will lead to lower incremental total costs when compared to R-mono. In case effectiveness outcomes of R-CHOP or R-CVP are similar to R-mono, the ICER of R-LEN when compared to the former two treatment option will be lower than the ICER of this analysis. Real-world evidence, for instance from clinical registries, could shed light on the difference in effectiveness between R-mono and R-CHOP / R-CVP.

As of June 1, 2020 R-LEN is reimbursed under a confidential commercial agreement between the manufacturer and the Ministry of Health in the Netherlands.<sup>41</sup> Details of this confidential agreement (e.g. price discount on lenalidomide) are not taken into account for this evaluation. It can be assumed that a financial discount on the drug price of lenalidomide will result in a more favorable ICER compared to this analysis.

## Conclusions

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.

## Abbreviations

<b>AE</b>	<b>Adverse event</b>
BSA	Body surface area
CI	Confidence interval
CPG	Clinical practice guideline
CT	Computerized tomography scan
CUA	Cost-utility analysis
DSA	Deterministic sensitivity analysis
EE	Economic evaluation
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EUR	Euro (currency)
FL	Follicular lymphoma
GBP	Great British Pound (currency)
HR	Hazard ratio
HRQoL	Health related quality of life
i.v.	intravenously
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
LDH	Lactate dehydrogenase
LY	Life year
mg	milligram
MZL	Marginal zone lymphoma
NA	Not applicable / not available
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
R-LEN	Rituximab plus lenalidomide
R-mono	Rituximab monotherapy
s.c.	subcutaneously
SE	Standard error
TSH	Thyroid stimulating hormone

<b>AE</b>	<b>Adverse event</b>
USD	US Dollar (currency)
vs.	versus
WBC	White blood cells
WTP	Willingness-to-pay

## Declarations

## Ethics approval and consent to participate

Not applicable

## Consent for publication

Not applicable

## Availability of data and material

The data that support the findings of this study are available from Celgene B.V. but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Celgene B.V.

## Competing interests

FW Thielen reports unrestricted grants from Celgene B.V., during the conduct of the study. Also he consulted AstraZeneca on a reimbursement dossier for a treatment and disease indication unrelated to this study. His institution was reimbursed for his time spent on the consultation.

MJ Kersten reports grants and personal fees from Celgene/BMS, grants and personal fees from Roche, during the conduct of the study.

P Kuizenga has nothing to declare.

M Hoogendoorn has nothing to declare.

EFM Posthuma has nothing to declare.

WBC Stevens has nothing to declare.

CA Uyl-de Groot reports unrestricted grants from Celgene B.V., during the conduct of the study.

HM Blommestein reports unrestricted grants from Celgene B.V., during the conduct of the study.

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## Authors' contributions

FW Thielen: Conceptualization, Methodology, Formal analysis, Data Curation, Writing – Original Draft, Visualization

MJ Kersten: Conceptualization, Validation, Writing – Review & Editing

P Kuizenga: Conceptualization, Validation, Writing – Review & Editing

M Hoogendoorn: Conceptualization, Validation, Writing – Review & Editing

EFM Posthuma: Conceptualization, Validation, Writing – Review & Editing

W Stevens: Conceptualization, Validation, Writing – Review & Editing

CA Uyl-de Groot: Conceptualization, Methodology, Validation, Writing – Review & Editing, Supervision

HM Blommestein: Conceptualization, Methodology, Formal analysis, Validation, Writing – Review & Editing

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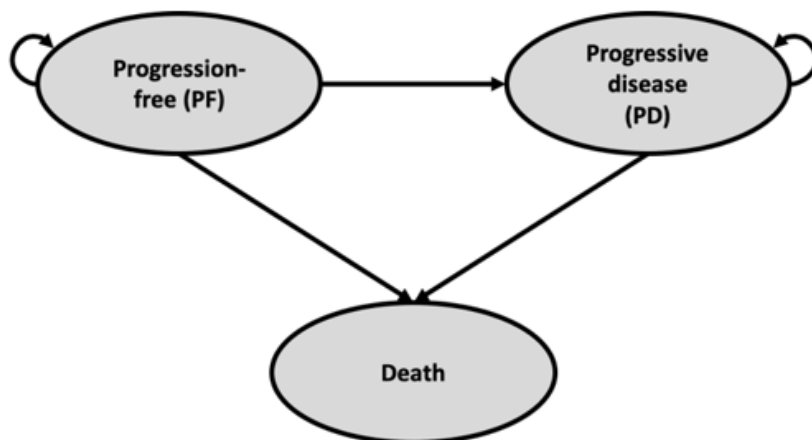
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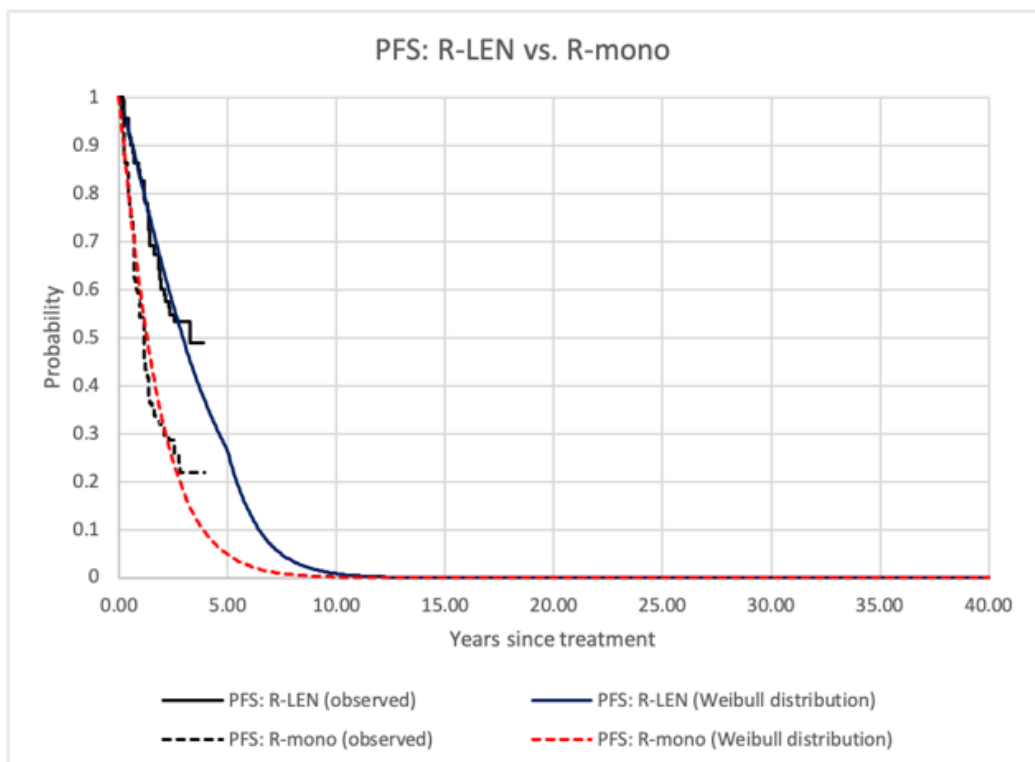
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## Figures



**Figure 1**

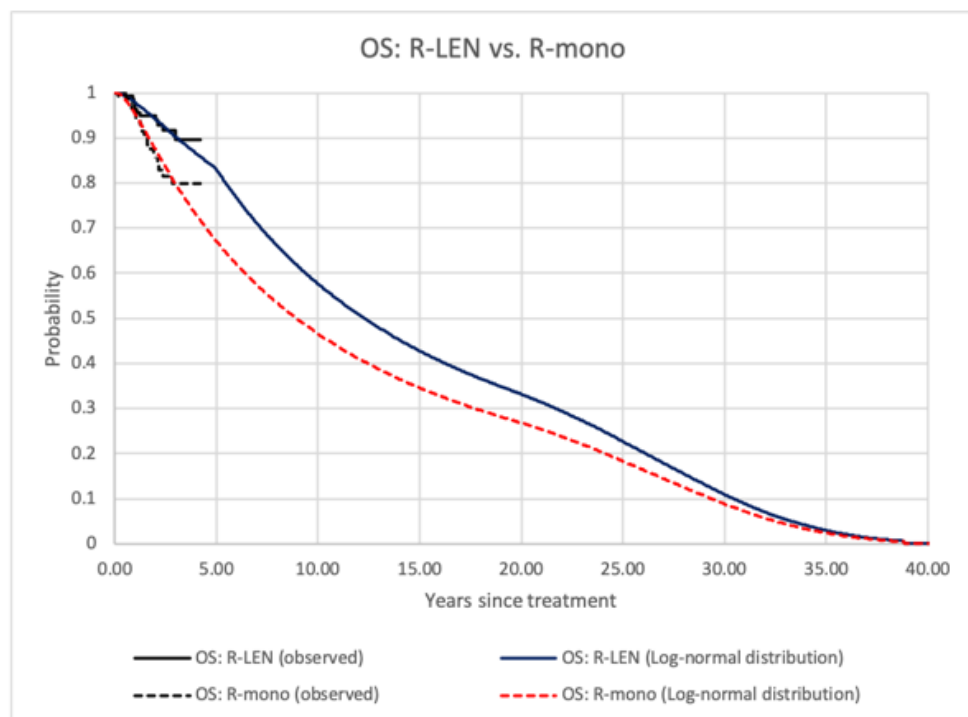
Schematic representation of the de novo model



PFS = progression-free survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

**Figure 2**

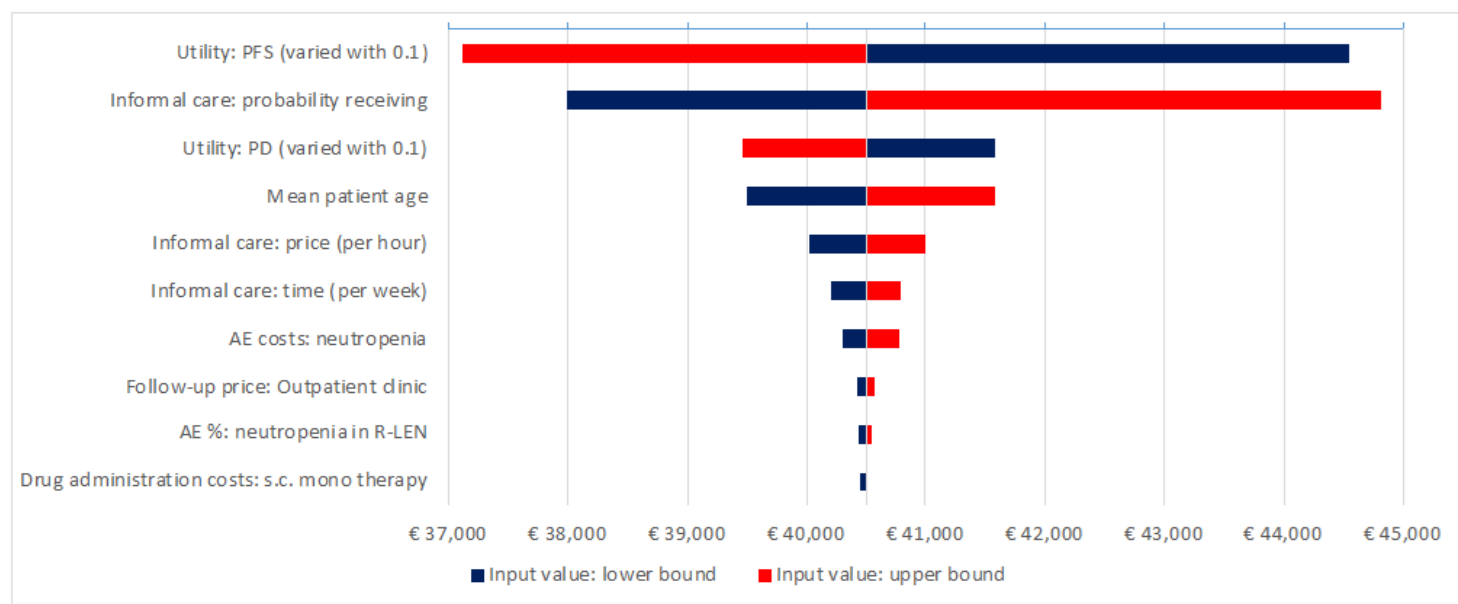
Empirical and extrapolated PFS



OS = overall survival; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

**Figure 3**

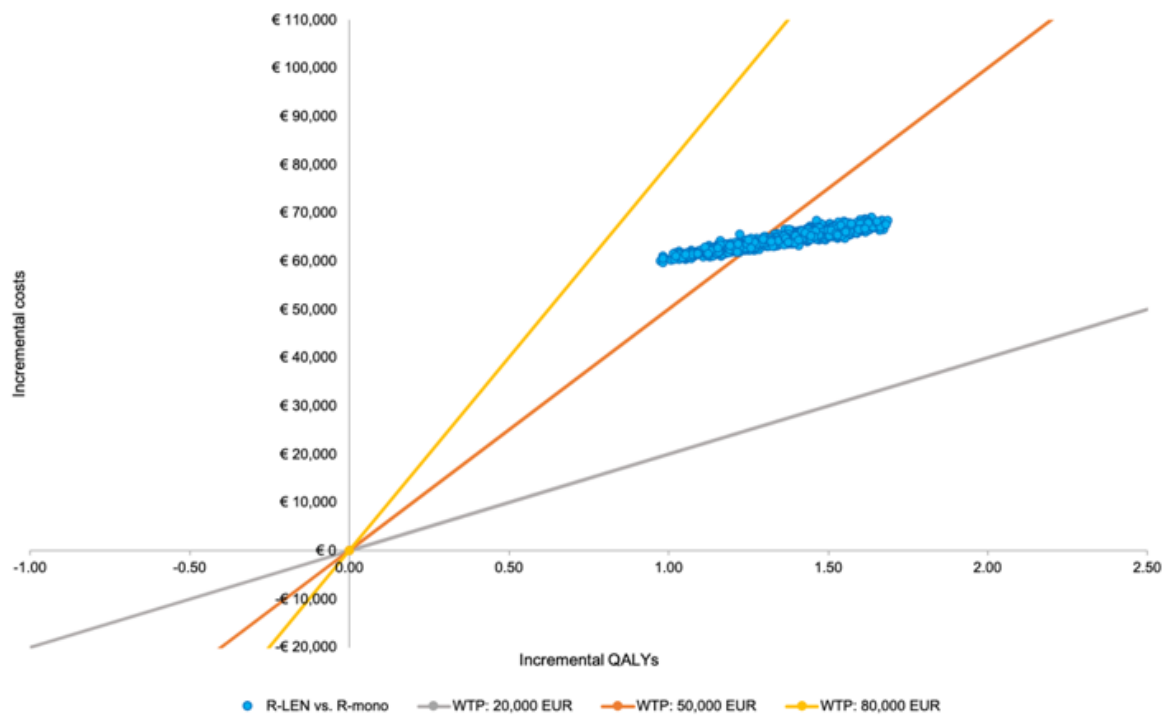
Empirical and extrapolated OS



AE = adverse event; PD = progressive disease; PF = progression-free; R-LEN = rituximab plus lenalidomide

Figure 4

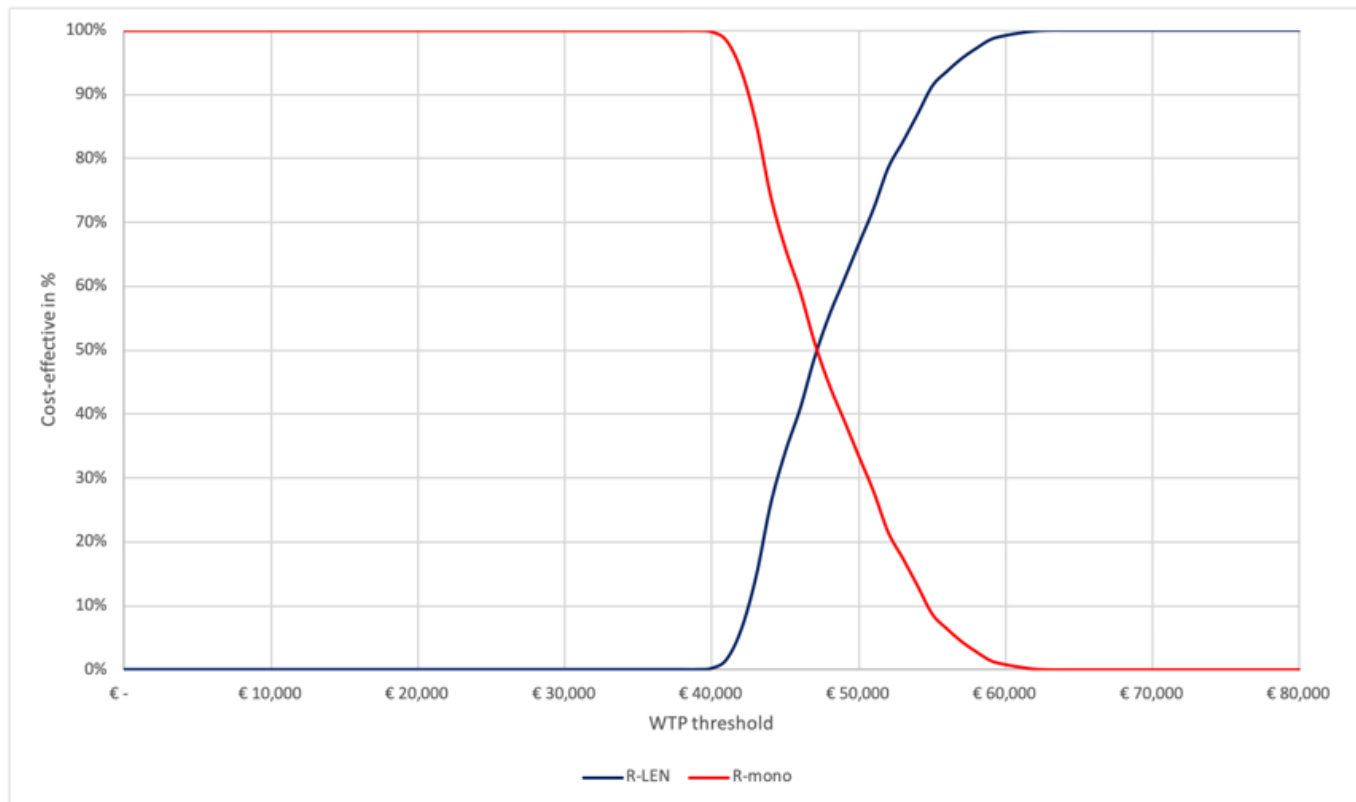
Tornado diagram (societal perspective)



EUR = Euro (currency); QALYs = quality-adjusted life years; WTP = willingness-to-pay

Figure 5

Cost-effectiveness plane (societal perspective)



WTP = willingness-to-pay; R-LEN = rituximab plus lenalidomide; R-mono = rituximab monotherapy

**Figure 6**

Cost-effectiveness acceptability curve (societal perspective)

## Supplementary Files

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