TITLE: COST-EFFECTIVENESS ANALYSIS OF BENDAMUSTINE PLUS RITUXIMAB AS FIRST-
LINE TREATMENT FOR PATIENTS WITH FOLLICULAR LYMPHOMA.

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ES and IO are employed by PORIB, a consultant company specialized in health economic evaluations.

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AS and ALG have received honoraria from Mundipharma Pharmaceuticals, for advocacy tasks related to the present work.

CONTRIBUTIONS

ES, IO and JMC conceived the model.

ES and IO developed the model and drafted the manuscript.

AR, AS and ALG validated the model structure, provided data related to clinical practice and reviewed and approved final version of manuscript.

ABSTRACT

Background:

To evaluate the cost-utility of rituximab-bendamustine (R-B) compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) as first-line treatment for patients with advanced follicular lymphoma (FL) in Spain.

Methods:

A Markov model was developed to estimate the cost-effectiveness of R-B compared with R-CHOP as first-line treatment, for patients with advanced FL under Spanish National Health System (NHS) perspective. Transitions between health states (progression-free-including induction and maintenance-, first relapse, second relapse and death) were allowed for the patient cohort in 4 weeks-length cycles. Clinical data to extrapolate progression-free survival curves were obtained from randomized trials. Mortality rates and utilities were obtained from the literature. Outcomes were measured as quality-adjusted life-years (QALYs). Total cost (€, 2013) included drug cost (ex-factory prices with mandatory deductions), disease management cost, and adverse event associated costs. Costs and outcomes were discounted at a 3% annual rate. Probabilistic sensitivity analysis was performed through 10,000 Monte Carlo simulations to check model robustness.

Results:

Treatment and administration costs during the induction phase were higher with R-B (€17,671.10) compared to R-CHOP (€11,850.05). At the end of the 25 year period, R-B first line strategy accounted a total cost of €68,357.02 compared to €69,527.79 for R-CHOP.

Health benefits were higher for R-B (10.31 QALYs) than for R-CHOP (9.82 QALYs). In the probabilistic analysis, R-B was a dominant strategy compared to R-CHOP in 50.0% of the simulations.

Conclusion:

First-line therapy with R-B in FL patients was a dominant strategy compared to R-CHOP, showing cost savings and higher health benefits for the Spanish NHS.

KEYWORDS

Bendamustine, Cost effectiveness, Follicular lymphoma, Rituximab

KEY POINTS FOR DECISION MAKERS

- First line treatment with R-B in FL is a strategy associated with higher health benefits than R-CHOP.
- Initiating FL treatment with R-B imply long-term costs savings compared with R-CHOP.

INTRODUCTION

FL is the second most common type of lymphoid cancer in Western Europe [1], representing 22-40% of NHL according to the World Health Organization (WHO) [2].

Despite substantial improvement in survival, FL is usually considered an incurable disease in most of the cases. The disease characteristically responds well to first-line therapy but typically manifests repeated relapses with the need of recurrent therapeutic interventions, with disease-free intervals.

Patients with FL in advanced stages and high-tumour burden usually receive a front-line chemoimmunotherapy, rituximab (R) plus chemotherapy, during the so called induction phase, followed by maintenance therapy with R in patients who achieve at least a partial response after the induction phase, as it is recommended by several Clinical Guidelines. [3,4,5,6,7]

Randomized trials and real world studies have demonstrated that rituximab maintenance (R-maintenance) can prolong time to progressive disease in patients with FL. [8,9] Nevertheless, it has not yet been established which polychemotherapy regimen should be prescribe along with R as induction treatment. [3].

A recent publication showed that regimens based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are associated to better risk/benefit ratio than those based on cyclophosphamide, vincristine and prednisone (CVP) or fludarabine, when combined with R, as first line FL treatment [10].

Bendamustine (B) is an alkylating agent approved by European Medicines Agency (EMA) for treatment of three different haematological malignancies, chronic lymphocytic leukemia, NHL and multiple myeloma [11]. According results of the German Lymphoma Group study [12] combination of R plus bendamustine (R-B) has higher efficacy and is safer than R-CHOP combination during induction phase. An extension of the indication to combined treatment with R in first line FL has been approved by EMA.

The present analysis aim to assess the cost-effectiveness of R-B compared with R-CHOP as first-line treatment for patients with FL in Spain.

MATERIAL AND METHODS

A novel Markov model was developed in Microsoft Excel® 2013 to simulate the long-term evolution for a cohort of 100 patients with FL.

A lifetime horizon equivalent to 25 years, was used, allowing to collect any differences in costs or outcomes between the two strategies compared; R-B (rituximab 375mg/m² on day 1 of each chemo cycle, plus bendamustine 90 mg/m² on days 1 and 2 of a 4-week cycle) and R-CHOP (rituximab 375mg/m² on day 1 of each chemo cycle and cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and vincristine 1.4 mg/m² on day 1, together with prednisone 100 mg/day for 5 days)

The efficiency of first-line R-B therapy was estimated by means of the incremental cost-effectiveness ratio of R-B therapy versus R-CHOP chemotherapy expressed as cost per life year gained (LYG) and cost per additional quality adjusted life year (QALY).

The model was comprised of three main health states: progression-free (PF), disease progression and death. (Figure 1) Both, PFS and progression states, included two sub-health states.

The model cycle length was 4-weeks, fitting with R-B administration. An adjustment was needed to convert R-CHOP chemo cycles (every 3 weeks) to the mentioned model cycle length.

Average patient of the assessed cohort was defined as 58 years aged [13] at model entry, with an average weight of 68 kg, and average body surface of 1.7 m², representing the typical characteristics of Spanish patient population. [14]

The probabilities for the allowed transitions between states were derived from literature. Clinical data were retrieved from two phase III randomized trials, one of them carried out by the German Study group indolent Lymphomas (StiL) which compared R-B with R-CHOP during the induction phase [12], and the other one, the PRIMA trial which assessed maintenance therapy with R [15].

Probability for a second relapse was obtained from a phase III randomized trial in Relapsed/Resistant FL patients [16]. Parametric probabilistic functions (lognormal, weibull, logistic) were fitted to clinical data to extrapolate long-term probabilities (Table1).

Death probabilities were obtained from a large population-based research carried out in US [17]. All follicular lymphoma mortality rates data was used to estimate death probabilities in PFS health state and advanced-stage FL mortality rates for progression state. These death probabilities were updated by the year of diagnosis as it was established in a Joinpoint regression analysis that established that estimated percent change in risk of death decreased by 1.80% per year over the observation period [17]. To implement the increment of death risk associated with age, mortality rates by age data from Spanish National Institute for Statistics [18] was used to fit the death probability by age.

Utility values used to calculate QALYs from the estimated survival were collected from scientific literature, 0.805 for PFS state, and 0.618 for progression state they were obtained through VAS by the EQ-5D questionnaire in 222 patients with FL from UK. [19,20]. The utility values were directly applied to the PFS and PD health states in the model. No utility decrements were associated to adverse event appearance.

The Spanish National Health System perspective was chosen .Following the last published recommendations for performing economic evaluations in Spain [21] a 3% annual discount rate was applied to both, health outcomes and costs.

The simulation begun with the administration of the assessed therapies (R-B or R-CHOP) at PF state (induction phase) up to a maximum of 6 cycles of the correspondent chemotherapy. After these 6 cycles, patients without disease progression transitioned to the maintenance sub-state, where rituximab maintenance (375 mg/m² every 60 days) was continuously administered until death, progression or for 2 years at maximum. In line with available evidence, [15] rituximab maintenance was stopped at the end of the 2 years for survivors patients without disease progression. They remained in the PF state until death or relapse.

The transition to the progression state could imply treatment switch. Chemotherapy patterns for 1st and 2nd relapse, after previous initial treatment with R-B and R-CHOP were defined by an expert panel to reflect usual care. (Table 1. Distribution parameters for clinical data.

Parameters	Value	Distribution	Source of data
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PFSR-B Intercept	4.697	Log-normal	Rummel 2013
PFS R-B shape	1.670	Log-normal	Rummel 2013
PFS R-CHOP Intercept	3.792	Log-normal	Rummel 2013
PFS R-CHOP shape	1.500	Log-normal	Rummel 2013
PFS R Maintanance Intercept	3.884	Log-normal	Salles 2011
PFS R Maintanance shape	1.103	Log-normal	Salles 2011
2nd Relapse probability Intercept	1.574	Log-normal	Van Oers 2010
2nd Relapse probability shape	1.964	Log-normal	Van Oers 2010
PF Death probability intercept	3.330	Log-normal	Swenson 2005
PF Death probability shape	1.918	Log-normal	Swenson 2005
Progression Death probability intercept	2.153	Log-normal	Swenson 2005
Progression Death probability shape	1.440	Log-normal	Swenson 2005

Table 2). An average chemotherapy cost in progression state was calculated for 1st and 2nd relapse which were applied as transitional costs, once a patient suffered the disease progression.

Total cost estimation included pharmaceutical and administration costs for chemo at induction, maintenance, and relapse (1st and 2nd) states, prophylactic premedication cost for R-B and R-CHOP, management cost for adverse event following R-B or R-CHOP therapies and general disease management cost at each health state or sub-state.

Drug costs were calculated based on published ex-factory prices on December 2013 [22] applying the mandatory deduction established by the Royal Decree-Law 8/2010 [23] applicable on December 2013 [24]. The lowest ex-factory prices were chosen for generic drugs. No vial wastage was considered for cost calculations.

Premedication was considered to be prophylactically administered together with each cycle of the assessed therapies. All intravenous medications were assumed to be performed at hospital level in an oncology unit. A unit cost (€252.41) was computed for each hospital visit for drugs administration.

The disease management costs at each health state and adverse event management costs were estimated based on the disaggregate resource consumption provided by a multidisciplinary expert panel. Management at PFS induction phase was considered slightly different from R-B than for R-CHOP.

First cycle management cost after any relapse (1st or 2nd) was assumed to require additional resources than patient management in the following period, therefore, management cost for 1st and 2nd relapse were both split in cost for 1st cycle and cost for subsequent cycles following the first one. (Table 3)

Frequency of grade 3 or 4 for the following adverse events (alopecia, anaemia, arrhythmia, cardiac failure, erythema, stomatitis, leucocytopenia, lymphocytopenia, neutropenia, febrile neutropenia, peripheral neuropathy, allergic reaction, sepsis and thrombocytopenia) was considered and adjusted to estimate risk of each adverse event per R-B or R-CHOP cycle. (Table 4)

An average cost for adverse event management was calculated and computed to each R-B or R-CHOP treatment cycle.

Unitary costs for the health resources identified were obtained from a Spanish national health cost database. [25] All costs were expressed in euros, referred to 2013 year values.

Sensitivity analyses were carried out to check the model robustness. One-way sensitivity analyses (OWSA) were performed testing the following parameters: time horizon, discount rate, utilities and costs. Probabilistic sensitivity analyses (PSA) were performed through 10,000 MonteCarlo simulations. Parametric distributions were applied to the input parameters; gamma for costs, beta for utilities and Dirichlet for relapse treatment patterns (Table 5).

RESULTS

At the end of the 25 years simulation, the first-line treatment with R-B resulted more effective than R-CHOP, yielding 12.86 LYG vs 12.62 LYG. Considering health benefits measured by QALYs treatment with R-B had a higher benefit (9.63 QALYs) than R-CHOP (9.23 LYG).

In deterministic analysis, the first-line treatment with R-B accounted a total cost of €68,357.02 per patient, resulting in a cost saving strategy compared to R-CHOP with a €69,527.79. Analysing costs during the induction phase (treatment, administration and prophylaxis), R-B treatment strategy is associated with higher costs (€17,671.10) compared to R-CHOP (€11,850.05). Cost savings in progressive disease of R-B strategy compared to R-CHOP was -€1,170.77. According with these results, R-B resulted a dominant strategy compared with R-CHOP. Detailed base case results are presented in Table 6.

Robustness of model conclusions was consistent with OWSA results. In all scenarios R-B was the dominant strategy compared to R-CHOP. The inputs with higher influence in results, were relapses management costs, R-B treatment costs and utilities values. A 20% of cost reduction in R-B treatment is associated with € 81,409.64 cost savings. Results of OWSA are shown in Table 7.

PSA results are shown as a cost-effectiveness plane (Figure 2) and as a cost-effectiveness acceptability curve (Figure 3). R-B was a dominant strategy compared to R-CHOP in 50.0%, and cost effective 27.0% of the 10,000 simulations performed.

DISCUSSION

The aim of the treatment of FL is to maximize overall survival, maintain health-related quality of life (HRQoL) and minimize treatment-related morbidity. However, treatment of FL can be often associated to significant toxicity with deleterious impact in health status. For this reason, it is particularly important to consider HRQoL and other patient-reported outcomes) in establishing the suitability of a treatment. Cost-utility analysis was considered to be the best method for conducting the present evaluation because quality of life is integrated and considered through the utilities values. In any case, results were calculated either in terms of cost per QALY gained, either in terms of cost per LYG, allowing us to infer the influence of quality of life in the efficiency ratios.

The efficiency of R-B as first-line therapy has been assessed in other economic evaluations. Comparison between studies is restricted by differences in methodologies used, monetary year values, perspective, patient management and health care system organizations. In terms of health benefits, the present model shows a similar trend as other economic evaluations [26,27].

However, it could be Worthing to mention conclusions from a previous cost-utility analysis which assessed R-B therapy in England and Wales [20]. R-B first-line resulted in a cost-effective strategy compared to R-CHOP for treatment of indolent NHL, and this benefit was mainly due to the better toxicity profile of R-B.

This study is the first evaluation focused on FL which assessed lifetime efficiency of R-B first-line strategy considering a rituximab maintenance for 2 years, as well as up to 2 potential relapses. Taking into account management of relapses rises as the key driver that explains the higher total costs in comparison of other economical evaluation [20,28,29] , and the long-term savings associated with R-B arm.

Limitations

As inherent to most of the economic evaluations, some assumptions have to be taken. The interpretation of the results should consider the potential limitations.

Challenges in cost–effectiveness analysis include the fact that life expectancy for patients with FL exceeds the period of available follow-up data and that treatment pathways are more complex than the model structures frequently used in oncology models.

A strength of the present model is that the progression state is split in two sub-states, in order to include the complexity of the disease evolution as well as the different management over this progression. Despite that it is clear that FL patients could suffer many relapses during the evolution of their disease, in the present model only 2 relapses were considered, due to as much to the need to simplify the patient transition as to the lack of reliable evidence to be used as input for model feeding.

Health related quality of life could be deeply influenced by sociocultural factors.

The lack of utility values especially concerned to Spanish population required the use of values referred to UK population.

However, it was been evidenced, that values for EQ-5D health states in Western European countries (Finland, Germany, The Netherlands, Spain, Sweden and the UK) can be described by a common model. [30] Therefore the UK values assumed in the present model could be extrapolated to Spanish setting. In any case the influence of alternative utility values have been tested in the sensitivity analysis and the conclusions do not change.

Only one utility value was used for PFS state, despite of substate (induction or maintenance phase) in line with published opinion that should be no difference as both group of patients are in remission/full response. [31]

In conclusion, first line therapy with R-B in FL patients was a dominant strategy compared to R-CHOP, showing cost savings and higher health benefits for the Spanish NHS, despite its higher initial treatment cost.”

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TABLES

Table 1. Distribution parameters for clinical data.

Parameters	Value	Distribution	Source of data
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PFS R-B shape	1.670	Log-normal	Rummel 2013
PFS R-CHOP Intercept	3.792	Log-normal	Rummel 2013
PFS R-CHOP shape	1.500	Log-normal	Rummel 2013
PFS R Maintenance Intercept	3.884	Log-normal	Salles 2011
PFS R Maintenance shape	1.103	Log-normal	Salles 2011
2nd Relapse probability Intercept	1.574	Log-normal	Van Oers 2010
2nd Relapse probability shape	1.964	Log-normal	Van Oers 2010
PF Death probability intercept	3.330	Log-normal	Swenson 2005
PF Death probability shape	1.918	Log-normal	Swenson 2005
Progression Death probability intercept	2.153	Log-normal	Swenson 2005
Progression Death probability shape	1.440	Log-normal	Swenson 2005

Table 2 Chemotherapies for relapses treatment

	Posology	Average duration	R-B	R-CHOP
First relapse				
Rituximab	375mg/m ² once a week	4 weeks	15%	15%
R-CHOP	Cyclophosphamide 750 mg/m ² , vincristine 2 mg/m ² , doxorubicin 50 mg/m ² , and prednisone 100mg per day during 5 days	6 cycles	50%	0%
R-CVP	Cyclophosphamide 750 mg/m ² , vincristine 2 mg/m ² , and prednisone 100mg per day during 5 days	7 cycles	20%	15%
R-ESHAP	From 2nd to 5th days etoposide 60 mg/m ² , methylprednisolone 500mg, cisplatin 25mg/m ² and methylprednisolone 500mg	4 cycles	10%	10%
R-B retreatment	Rituximab 375mg/m ² and Bendamustine 90mg/m ² once a cycle	5 cycles	5%	60%
Second relapse				
Rituximab	375mg/m ² once a week	4 weeks	15%	15%
R-CHOP	Cyclophosphamide 750 mg/m ² , vincristine 2 mg/m ² , doxorubicin 50 mg/m ² , and prednisone 100mg per day during 5 days	6 cycles	5%	0%
R-CVP	Cyclophosphamide 750 mg/m ² ,	7 cycles	10%	10%

	vincristine 2 mg/m ² , and prednisone 100mg per day during 5 days			
R-ESHAP	From 2nd to 5th days etoposide 60 mg/m ² , methylprednisolone 500mg, cisplatin 25mg/m ² and methylprednisolone 500mg	4 cycles	5%	5%
R-B retreatment	Rituximab 375mg/m ² and Bendamustine 90mg/m ² once a cycle	5 cycles	15%	15%
Bendamustine	Bendamustine 90mg/m ² once a cycle	5 cycles	10%	10%
R-FC	Fludarabina 25 mg/m ² and Ciclofosfamida 250mg/m ² in 1st and 3 rd days of cycle	6 cycles	10%	15%
Clorambucil	2 mg a day for 5 weeks	5 weeks	10%	10%
Allogeneic transplantation	NA	NA	10%	10%
Autologic transplantation	NA	NA	10%	10%

NA: Not Applicable

Table 3. Unitary costs

	R-B		R-CHOP	
Total drug cost per chemo cycle at induction phase in PF state	€2,961.66		€1,980.41*	
Chemo cost per cycle, including IV administration	€2,750.54		€1,766.63*	
Premedication cost per chemo cycle	€212.12		€213.78*	
Ondasentron	8mg daily for 2 days	100.0%	8mg for 1 day	66.0%
			8mg, three times per day, for 1 day	34.0%
Filgrastim	300mg for 6 days	10.0%	300mg for 6 days	40.0%
Ciprofloxacin	500mg every 12h, for 5 days	20.0%	500mg every 12h, for 5 days	50.0%
Dexamethasone	8m daily for 2 days	35.0%	-	-
Cotrimoxazole (trimethoprim/sulfamethoxazole)	3 tablets (160/800mg) weekly	30.0%	-	-
Total drug cost per cycle at rituximab maintenance phase in PF state	€686,32			
Adverse event (average cost per cycle)	€85.40		€268.15	
Disease management				
PF- induction phase	€242.18		€254.06	
PF- maintenance	€60.82			

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Progression-1 st cycle for 1 st relapse	€1,930.36
Progression-subsequent cycles for 1 st relapse	€1,759.97
Progression-1 st cycle for 2 nd relapse	€2,206.32
Progression-subsequent cycles for 2 nd relapse	€2,143.14

*In the model was adjusted for a 28 days cycle length

Table 4. Adverse events management

Adverse Events	Management cost (€, 2013) per event*	Frequency of grade III or IV events (Rummel 2013)	
		R-B	R-CHOP
Alopecia	€0.00	0%	100%
Anaemia	€818.72	3%	5%
Arrhythmia	€3,328.82	1%	2%
Cardiac failure	€3,970.78	1%	3%
Erythema	€2,289.12	5%	1%
Stomatitis	€886.47	1%	5%
Leucocytopenia	€0.00	37%	72%
Lymphocytopenia	€0.90	74%	43%
Neutropenia	€282.13	23%	55%
Febrile Neutropenia	€2,035.55	6%	14%
Peripheral neuropathy	€92.09	0%	3%
Allergic reaction	€168.35	3%	1%
Sepsis	€10,289.56	0,40%	3%
Thrombocytopenia	€230.65	5%	6%
Average adverse management cost per chemo cycle		€85.40	€268.15

*Estimation based on the desegregate health resource consumption provided by an expert panel

Table 5. Probabilistic distributions parameters.

Parameter	Probability distribution	Parameter α	Parameter β
COSTS			
Prophilaxis R-B	Gamma	1	211.12 €
Prophilaxis R-CHOP	Gamma	1	320.68 €
Adverse events management R-B	Gamma	1	85.46 €
Adverse events management R-CHOP	Gamma	1	268.15 €
PF state (R-B treatment)	Gamma	1	242.18 €
PF state (R-CHOP treatment health state)	Gamma	1	254.06 €
PF state (maintenance)	Gamma	1	60.82 €
Progression state (first relapse, first cycle)	Gamma	1	1,903.36 €
Progression state (first relapse, cycles)	Gamma	1	1,759.97 €
Progression state (second relapse, first cycle)	Gamma	1	2,206.32 €
Progression state (second relapse, cycles)	Gamma	1	2,143.14 €
UTILITIES			
PF state	Beta	88	22
Progression state	Beta	62	38
RELAPSES TREATMENT PATTERN			
First relapse R-B	Dirichlet	$\Pi=(0.15,0.50,0.20,0.10,0.05)$	
First relapse R-CHOP	Dirichlet	$\Pi=(0.15,0.00,0.15,0.10,0.60)$	

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Second relapse R-B	Dirichlet	$\Pi=(0.15,0.05,0.10,0.05,0.15,$ $0.10,0.10,0.10,0.10,0.10)$
Second relapse R-CHOP	Dirichlet	$\Pi=(0.15,0.00,0.10,0.05,0.15,$ $0.10,0.10,0.15,0.10,0.10)$

Table 6. Base case Markov model simulation results

	R-B	R-CHOP	Incremental R-B vs R-CHOP
Total costs (€, 2013)	€68.357,02	€69.527,79	-€1.170,77
Progression-free State			
First-line treatment	€17,671.10	€11,850.05	€5,821.05
First-line maintenance	€1,444.98	€1,013.47	€431.51
Maintenance treatment (Rituximab)	€14,611.22	€14,778.58	-€167.36
Maintenance	€6,749.27	€5,842.20	€907.07
Adverse events management	€509.90	€1,069.67	-€559.77
Progression State			
First relapse Treatment	€6,370.95	€8,207.36	-€1,836.41
First relapse maintenance	€599.42	€740.59	-€141.17
Second relapse Treatment	€4,628.26	€5,974.27	-€1,346.01
Second relapse maintenance	€15,771.93	€20,051.61	-€4,279.68
Health outcomes			
LYG	12.86	12.62	0.24
QALYs	9.63	9.23	0.39
Incremental cost-effectiveness ratio (€/LYG) R-B vs R-CHOP)			R-B Dominant
Incremental cost-utility ratio (€/QALY gained) R-B vs R-CHOP			R-B Dominant

Table 7. One-way sensitivity analysis results

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
Base Case	€68,357.02	12.86	9.63	69,527.79 €	12.62	9.23	-€1.170,77	0.24	0.39	R-B Dominant	R-B Dominant
Sensitivity analysis											
Temporal horizon (15 years)	€62,621.43	10.05	7.55	€62,428.14	9.93	7.32	€ 193.29	0.12	0.23	€ 1,597.68	€ 854.82
Temporal horizon (30 years)	€69,635.75	13.50	10.10	€ 71,114.63	13.23	9.67	-€ 1,478.89	0.27	0.43	R-B Dominant	R-B Dominant
Discount rate (0%)	€68,972.94	13.12	9.82	€ 70,272.72	12.87	9.41	-€ 1,299.78	0.25	0.40	R-B Dominant	R-B Dominant
Discount rate (5%)	€67,956.05	12.70	9.50	€ 69,043.05	12.46	9.12	-€ 1,087.01	0.24	0.38	R-B Dominant	R-B Dominant
R-B treatment costs (-20%)	€65,074.74	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 4,453.05	0.24	0.39	R-B Dominant	R-B Dominant
R-B treatment costs(+20%)	€ 71,639.31	12.86	9.63	€ 69,527.79	12.62	9.23	€ 2,111.51	0.24	0.39	€ 8,695.72	€ 5,383.39
R-CHOP treatment costs (-20%)	€ 68,357.02	12.86	9.63	€ 67,413.62	12.62	9.23	€ 943.40	0.24	0.39	€ 3,885.14	€ 2,405.24

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
R-CHOP treatment costs(+20%)	€ 68,357.02	12.86	9.63	€ 71,641.96	12.62	9.23	-€ 3,284.94	0.24	0.39	R-B Dominant	R-B Dominant
R maintenaince cost(-20%)	€ 65,434.78	12.86	9.63	€ 66,572.08	12.62	9.23	-€ 1,137.30	0.24	0.39	R-B Dominant	R-B Dominant
R maintenaince cost(+20%)	€ 71,279.27	12.86	9.63	€ 72,483.51	12.62	9.23	-€ 1,204.24	0.24	0.39	R-B Dominant	R-B Dominant
Prophilaxis R-B (-20%)	€ 68,105.09	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,422.71	0.24	0.39	R-B Dominant	R-B Dominant
Prophilaxis R-B (+20%)	€ 68,608.96	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 918.83	0.24	0.39	R-B Dominant	R-B Dominant
Prophilaxis R-CHOP (-20%)	€ 68,357.02	12.86	9.63	€ 69,271.95	12.62	9.23	-€ 914.93	0.24	0.39	R-B Dominant	R-B Dominant
Prophilaxis R-CHOP (+20%)	€ 68,357.02	12.86	9.63	€ 69,783.64	12.62	9.23	-€ 1,426.61	0.24	0.39	R-B Dominant	R-B Dominant
1 st Relapse in R-B arm (-20%)	€ 67,082.83	12.86	9.63	€ 67,886.32	12.62	9.23	-€ 803.49	0.24	0.39	R-B Dominant	R-B Dominant
1 st Relapse in R-B arm (+20%)	€ 69,631.21	12.86	9.63	€ 71,169.27	12.62	9.23	-€ 1,538.05	0.24	0.39	R-B Dominant	R-B Dominant

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
1 st Relapse in R-CHOP arm (-20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
1 st Relapse in R-CHOP arm (+20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
2nd Relapse in R-B arm (-20%)	€ 67,431.37	12.86	9.63	€ 68,332.94	12.62	9.23	-€ 901.57	0.24	0.39	R-B Dominant	R-B Dominant
2nd Relapse in R-B arm (+20%)	€ 69,282.68	12.86	9.63	€ 70,722.65	12.62	9.23	-€ 1,439.97	0.24	0.39	R-B Dominant	R-B Dominant
2nd Relapse in R-CHOP arm (-20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
2nd Relapse in R-CHOP arm (+20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
Adverse events R-B arm costs (-20%)	€ 68,255.04	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,272.75	0.24	0.39	R-B Dominant	R-B Dominant
Adverse events R-B costs (+20%)	€ 68,459.00	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,068.79	0.24	0.39	R-B Dominant	R-B Dominant

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
Adverse events R-CHOP costs (-20%)	€ 68,357.02	12.86	9.63	€ 69,313.86	12.62	9.23	-€ 956.84	0.24	0.39	R-B Dominant	R-B Dominant
Adverse events R-CHOP costs (+20%)	€ 68,357.02	12.86	9.63	€ 69,741.73	12.62	9.23	-€ 1,384.70	0.24	0.39	R-B Dominant	R-B Dominant
PF treatment with R-B health state management cost (-20%)	€ 68,068.03	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,459.77	0.24	0.39	R-B Dominant	R-B Dominant
PF treatment with R-B health state management cost (+20%)	€ 68,646.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 881.78	0.24	0.39	R-B Dominant	R-B Dominant
PF treatment with R-CHOP health state management cost (-20%)	€ 68,357.02	12.86	9.63	€ 69,325.10	12.62	9.23	-€ 968.08	0.24	0.39	R-B Dominant	R-B Dominant
PF treatment with R-CHOP health state management cost (+20%)	€ 68,357.02	12.86	9.63	€ 69,730.49	12.62	9.23	-€ 1,373.46	0.24	0.39	R-B Dominant	R-B Dominant
PF maintenance with R	€ 67,007.17	12.86	9.63	€ 68,359.35	12.62	9.23	-€ 1,352.18	0.24	0.39	R-B Dominant	R-B Dominant

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
health state management cost (-20%)											
PF maintenance with R health state management cost (+20%)	€ 69,706.88	12.86	9.63	€ 70,696.23	12.62	9.23	-€ 989.36	0.24	0.39	R-B Dominant	R-B Dominant
First relapse, first cycle management (-20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
First relapse, first cycle management (+20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
First relapse, 2 nd and following cycle management (-20%)	€ 68,237.14	12.86	9.63	€ 69,379.68	12.62	9.23	-€ 1,142.54	0.24	0.39	R-B Dominant	R-B Dominant
First relapse, 2 nd and following cycle management (+20%)	€ 68,476.91	12.86	9.63	€ 69,675.91	12.62	9.23	-€ 1,199.00	0.24	0.39	R-B Dominant	R-B Dominant
Second relapse, first cycle management (-20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant

Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
Second relapse, first cycle management (+20%)	€ 68,357.02	12.86	9.63	€ 69,527.79	12.62	9.23	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
Second relapse, 2 nd and following cycle management (-20%)	€ 65,202.64	12.86	9.63	€ 65,517.47	12.62	9.23	-€ 314.83	0.24	0.39	R-B Dominant	R-B Dominant
Second relapse, 2 nd and following cycle management (+20%)	€ 71,511.41	12.86	9.63	€ 73,538.12	12.62	9.23	-€ 2,026.71	0.24	0.39	R-B Dominant	R-B Dominant
Utilities											
PF treatment (0.70)	€ 68,357.02	12.86	9.58	€ 69,527.79	12.62	9.20	-€ 1,170.77	0.24	0.38	R-B Dominant	R-B Dominant
PF treatment (0.90)	€ 68,357.02	12.86	9.67	€ 69,527.79	12.62	9.26	-€ 1,170.77	0.24	0.41	R-B Dominant	R-B Dominant
PF maintenance (0.70)	€ 68,357.02	12.86	8.73	€ 69,527.79	12.62	8.46	-€ 1,170.77	0.24	0.27	R-B Dominant	R-B Dominant
PF maintenance (0.90)	€ 68,357.02	12.86	10.43	€ 69,527.79	12.62	9.93	-€ 1,170.77	0.24	0.50	R-B Dominant	R-B Dominant
Progression disease, 1 st relapse (0.4)	€ 68,357.02	12.86	9.59	€ 69,527.79	12.62	9.19	-€ 1,170.77	0.24	0.40	R-B Dominant	R-B Dominant

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Model scenario	R-B			R-CHOP			Difference			Cost-effectiveness ratios	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER (€/LYG)	ICER (€/QALYs)
Progression disease, 1 st relapse (0.7)	€ 68,357.02	12.86	9.64	€ 69,527.79	12.62	9.25	-€ 1,170.77	0.24	0.39	R-B Dominant	R-B Dominant
Progression disease, 2 nd relapse (0.4)	€ 68,357.02	12.86	8.81	€ 69,527.79	12.62	8.20	-€ 1,170.77	0.24	0.61	R-B Dominant	R-B Dominant
Progression disease, 2 nd relapse (0.7)	€ 68,357.02	12.86	9.93	€ 69,527.79	12.62	9.62	-€ 1,170.77	0.24	0.31	R-B Dominant	R-B Dominant

FIGURES

Figure 1. Markov diagram