Analysis of the Potential Cost Utility of the Addition of Rituximab to Standard Chemotherapy in Adults with Aggressive B Cell Non-Hodgkin Lymphoma in Uganda

Camille E. Puronen

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Committee:

Joseph B. Babigumira

Lotte M.G. Steuten

Program Authorized to Offer Degree:

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University of Washington

Abstract

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Camille E. Puronen

Chair of the Supervisory Committee:

Joseph B. Babigumira

Department of Global Health

Background: Rituximab is a monoclonal antibody that confers a survival benefit in adults with aggressive B cell Non-Hodgkin Lymphoma (B-NHL), and has been shown to be cost-effective in in high-income settings. Rituximab is not widely available in Uganda and other low-income countries due to cost. This is an evaluation of the potential cost-utility of the addition of rituximab (R-CHOP) to standard first-line chemotherapy (CHOP) for adults with aggressive B-NHL. Methods: A Markov model was developed to evaluate R-CHOP vs CHOP in adults with aggressive B-NHL treated at the Uganda Cancer Institute (UCI) over a lifetime horizon, from the perspective of the Uganda Ministry of Health. Main outcomes were disability-adjusted life-years (DALYs) averted and the incremental cost effectiveness ratio (ICER). A 3% discount rate was applied. Sensitivity analyses were performed to evaluate uncertainty. Results: The addition of rituximab to CHOP increased life-years (LYs) by 0.32 years (1.96 years with R-CHOP vs 1.62 years with CHOP) and decreased DALYs by 0.05 (0.32 with R-CHOP vs 0.26 with CHOP). The

incremental cost of adding rituximab to CHOP was $3,153 per patient. The ICER comparing R-CHOP vs. CHOP was $9,313 per LY gained and $60,719 per DALY averted. Conclusions: Compared to a cost-effectiveness threshold of 3 times GDP per capita ($1,812 for Uganda in 2019 USD), rituximab is not cost-effective in this setting. As rituximab has been shown to improve to outcomes in adults with aggressive B-NHL, the Ugandan Ministry of Health may wish to further evaluate pricing options.

Background

Cancer is one of the leading causes of death and disability in sub-Saharan Africa. Hematologic malignancies (leukemia, lymphoma, and multiple myeloma) account for nearly 10% of the overall cancer burden. GLOBOCAN 2018 estimates the incidence of B-NHL in Uganda at 5.4 per 100,000, making it the 7th most common cancer diagnosis[1].

Aggressive B-NHL includes diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma, and so-called "gray zone" lymphoma, with pathologic features of both DLBCL and Burkitt. Aggressive B-NHL can be sporadic or immunodeficiency (i.e. HIV) related. DLBCL is the most common histologic subtype of B-NHL, accounting for approximately 30 percent of patients with B-NHL[2]. Survival without treatment is less than one year[3].

In 1993, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) became standard-of-care due to good efficacy with less toxicity than previous combinations[4]. The addition of

rituximab, an anti-CD20 monoclonal antibody, in 1997 resulted in an approximately 10 to 15 percent overall increase in survival with minimal increase in toxicity[5,6].

While B-NHL patients in high-resource settings have experienced improved survival, the clinical outcome for the majority of patients with B-NHL in low-income countries is not as encouraging. Treatment outcomes in Uganda are inferior to those reported in wealthier countries largely due to the limited availability of chemotherapy, difficulty in administering frequent or prolonged intravenous infusions, and scarcity of supportive care measures (such as myeloid growth factors or transfusion services)[7,8]. Furthermore, limited financial resources (individual and national) prevent many patients from completing a full course of chemotherapy in a timely fashion, resulting in higher rates of relapse[9].

Until now, utilization of rituximab in low-income countries has been severely restricted due to high cost and long infusion times (2-6 hours). The relatively recent development of subcutaneous rituximab[10-13], as well as the recent entry of biosimilars into the market[14], may facilitate its use in low and middle income countries (LMICs) where prolonged intravenous infusions are challenging.

Prior studies conducted in North America and Europe have demonstrated that the addition of intravenous rituximab to standard chemotherapy (CHOP) in the treatment of aggressive B-NHL is cost-effective[15-20]. Despite higher initial cost of therapy, use of rituximab-containing regimens is associated with lower relapse rates and therefore less salvage therapy[18]. A prior study in Europe estimated that R-CHOP had a cost-utility ratio of $19,297 per quality-adjusted life-year

(QALY) gained[19]. A large part of the cost offset was related to longer remissions and decreased downstream need for salvage chemotherapy regimens. However, this effectiveness decreased with increasing age. A real-world analysis from Canada determined that the addition of rituximab to CHOP was cost-effective in 79% of patients younger than 60, but only 15% of those 60 and above[15]. In countries such as Uganda, where B-NHL patients tend to present at a younger age and often with more aggressive disease[21-23], rituximab may result in significantly improved outcomes. A clinical trial of subcutaneous rituximab combined with standard chemotherapy in aggressive B-NHL is currently underway at the Uganda Cancer Institute (UCI).

What follows is a cost-utility analysis of the cost and outcomes impact of adding rituximab to CHOP in Uganda. The results of this analysis may contribute to clinical and public health policy maker discussions on B-NHL management in Uganda and other low-income countries.

Methods

Markov Model

A Markov model of a hypothetical cohort of Ugandan adults presenting to the UCI with a new diagnosis of aggressive B-NHL was developed. The model compared standard treatment (6 cycles of CHOP) to standard treatment plus rituximab (6 cycles of R-CHOP). Aggressive B-NHL was defined as any aggressive lymphoma of B cell origin that was not classified as Burkitt lymphoma at the time of diagnosis. Indolent B cell lymphomas (such as follicular lymphoma) were not included.

The Markov model simulated transition from initial diagnosis and treatment of aggressive B-NHL through 5 states: treatment, two response states (complete response [CR], and non-CR), recurrence, and death (figure 1). Response states were modeled as CR or non-CR, which included partial response (PR), stable disease (SD), and progressive disease (PD). A 1-year cycle time was used, with a lifetime event horizon. Patients entered the model at age 40, the median age of diagnosis of aggressive B-NHL among adults in sub-Saharan Africa based on current estimates[22]. Input parameters are listed in table 1.

Transition probabilities

Estimates on the incidence of lymphoma, age at incidence, and survival were obtained from the Global Burden of Disease Study (GBD)[24-26]. Given the lack of primary data on B-NHL response and relapse rates in Uganda, transition probabilities were extrapolated from US and European longitudinal studies[16,17,27-30]. Background mortality rates were obtained from WHO life-tables for Uganda[31].

Disability-Adjusted Life Years (DALYs)

The total number of DALYs attributable to aggressive B-NHL were calculated by adding the years of life lost (YLL) due to ill health, disability or early death to the years lived with disability (YLD). Years of life lost (YLL) with standard chemotherapy was calculated by subtracting the estimated age at death on standard chemotherapy from the standard life expectancy in Uganda then multiplied by the estimated annual number of cases of aggressive B-NHL in Uganda. Years lived with disability (YLD) was calculated by multiplying the estimated duration of illness with

and without treatment by the disability weight for B-NHL and the incident number of cases. Disability weights were obtained from the IHME 2017 database[32].

Costs

Cost data was obtained from an analysis of budget data from the concurrent clinical trial of subcutaneous rituximab plus CHOP in B-NHL at the UCI (table 1). Costs included initial treatment, surveillance costs for those who responded, and salvage therapy for those who did not respond or who recurred after initial response. For salvage chemotherapy, only the most common salvage regimen used at the UCI was modeled. Surveillance costs for those who achieved response consist of blood tests and visits with a hematologist 4-6 times a year. The base year for the cost analysis was 2019 USD.

The ICER was calculated in terms of cost per DALY averted and years of life gained (YLG) from the perspective of the Ministry of Health. A discount rate of 3% was applied to both costs and outcomes. The threshold for cost-effectiveness was based on GDP per capita, consistent with the WHO-CHOICE framework, in which an ICER (in USD/DALY averted) of less than three times the GDP ($1,812 in 2019 USD) is considered cost-effective[33,34].

Sensitivity Analysis

Sensitivity analyses were performed to determine which variables had the greatest impact on outcomes and costs. Ninety-five percent confidence intervals were used when available, and +/- 50 percent for costs and +/- 20 percent for other variables were used otherwise. Univariate sensitivity analyses were performed to determine which variables had the greatest impact on

ICER. Probabilistic sensitivity analyses was performed using 1,000 Monte Carlo simulations to evaluate for uncertainty. A beta distribution was assumed for outcomes, while a gamma distribution was assumed for costs. Data analysis was performed using Microsoft Excel.

Results

Results for both discounted and undiscounted analyses are presented in table 2 for comparison; however this discussion is based on discounted results, consistent with the 2nd Panel on Cost-Effectiveness in Health Care and Medicine[35]. Based on a discounted analysis, the addition of rituximab to standard CHOP chemotherapy for aggressive B-NHL in Uganda resulted in an increase of 0.34 life years (1.96 years with R-CHOP vs 1.62 years with CHOP alone), and a decrease of 0.05 DALYs (0.26 with R-CHOP vs 0.32 with CHOP). The incremental cost of adding rituximab to CHOP in the model is $3,153 per patient. This results in an ICER of $9,313 per YLG, and $60,719 per DALY averted.

Univariate sensitivity analyses demonstrated that cost of rituximab and response to first-line treatment had the greatest effect on ICER in terms of both YLG (figure 2) and DALYs averted (figure 3). Probabilistic sensitivity analysis revealed a significant amount of uncertainty in outcomes, reflected in the wide "east-west" distribution of Monte Carlo simulations in the scatter plot (figure 4). Nevertheless, the bulk of the distribution is in the northeast quadrant of the CE plane, corresponding with improved outcomes at increased cost.

Discussion

Compared to a WHO-CHOICE cost-effectiveness threshold of 3 times GDP per capita ($1,812 per DALY averted), rituximab is not cost-effective for the management of aggressive B-NHL in Uganda in terms of YLG or DALYs averted. In high-income countries, where both GDP and willingness-to-pay are higher, rituximab is cost-effective, despite a much higher price point. To meet the threshold for cost-effectiveness in Uganda, rituximab would need to be priced at roughly USD $19 or less per 500 mg dose, at current exchange rates (figure 5).

The univariate sensitivity analyses demonstrated that outcomes early in the treatment course have a significant impact on the ICER for both DALY and YLG. This is analogous to data from high-income countries where patients achieving early response without early relapse typically have improved survival over those who do not respond to first-line therapy or who suffer early relapse[28,36]. If a patient achieves a CR after initial therapy, the odds of relapse and death are lower, and the odds of response to salvage therapy are higher, than that of a patient who achieves PR/SD/PD after first-line therapy. Similarly, patients who are refractory to first-line chemotherapy often have lower response rates to subsequent salvage regimens[27,28,36]. However, this analysis is limited by the lack of primary data on outcomes of aggressive B-NHL in Uganda, including response rates after first-line chemotherapy, relapse after CR, and mortality rate stratified by presence or lack of CR. Transition probabilities were therefore based on data from the original rituximab studies performed in the US, Canada and Europe, which may not accurately reflect outcomes in Uganda or similar settings. The ongoing clinical trial of subcutaneous rituximab in Uganda will provide more accurate data on incidence, response,

relapse and mortality rates; cost-utility analysis may be revisited upon its completion to revise estimates.

Although there is significant variability in the management of relapsed/refractory lymphoma, both in Uganda and in high-income countries, the sensitivity analyses revealed that this has little impact on overall outcomes or cost, as the prognosis in relapsed or refractory cases is often poor regardless of setting or management. This is confirmed by the probabilistic sensitivity analysis, which demonstrates a high degree of uncertainty with regard to outcomes and response rates and communicates the significant amount of disability associated with diagnosis and treatment of aggressive NHL.

The improvement in overall survival predicted by this model is lower than the survival benefit seen with R-CHOP vs CHOP in Europe and the US[5,29,37] but consistent with lower relative rates of survival observed in other malignancies (for example, breast) in low-income countries when compared to higher-income countries[38,39]. A cost-effectiveness analysis of rituximab in DLBCL in China resulted in an ICER of $60,805 per QALY[40]. This is partly related to higher stage at presentation and limited availability of optimal treatment and follow-up regimens including supportive management[39]. In addition, diagnostic hematopathology is limited in Uganda (as in other areas of sub-Saharan Africa)[41,42], which may result in misclassification or uncertainty as to the subtype of an aggressive NHL (Burkitt vs DLBCL vs gray-zone lymphoma, etc).

While this analysis used cost and outcome data for intravenous rituximab, subcutaneous rituximab (if similarly priced) may achieve higher cost-effectiveness in settings like Uganda due

to its simpler administration. Subcutaneous rituximab requires less durable medical equipment such as IV pumps and tubing and personnel time involved with monitoring and may confer overall cost savings due to increased availability of infusion center chairs for use by other patients. However, given that it is a relatively new introduction to the market, subcutaneous rituximab is likely to remain more expensive than intravenous rituximab for the duration of its patent protection.

The reduced price of rituximab, recently negotiated between Roche and the Ugandan Ministry of Health (USD $357 per 500 mg at current exchange rates), was used for the analysis. Nevertheless, at well above the cost effectiveness threshold of 3 times the GDP, this price remains well out of reach for most Ugandans. In addition, although costs are controlled in the clinical trial, the price and availability of standard chemotherapy, supportive care, and salvage regimens can vary widely. Lower-priced biosimilars to rituximab may soon be available; however many biosimilars have been associated with only modest reductions in cost[43]. The subcutaneous formulation of rituximab, which is being evaluated in the concurrent clinical trial, is unlikely to be available as a biosimilar. Furthermore, using a cost-effectiveness threshold of 3 times the GDP per DALY averted to guide rituximab pricing may still leave rituximab out of reach for most Ugandans. Recent WHO publications have suggested the use of more nuanced decision analysis frameworks, particularly ones that are context-specific, and take into consideration not just value for money spent but affordability, budget impact, fairness, and feasibility[44].

Value-based differential pricing (VBDP) may provide an option for increasing access to drugs like rituximab. Under a VBDP model, each country or payor evaluates whether the ICER of a drug meets their willingness to pay threshold, often based on income or GDP. However, the VBDP model is susceptible to regional and global trade practices[45]. Bans on parallel trade of pharmaceuticals may be difficult to enforce, particularly in low-income countries, which may lead pharmaceutical companies to avoid entering into VBDP contracts for fear of illicit exportation to neighboring countries. Furthermore, this model is most applicable in countries with a single payor who is responsible for the bulk of drug expenditure. In Uganda, like many LMICs, rituximab and many other drugs are currently available on a self-pay basis alone. Effective value-based pricing in this setting would depend on well-informed patients and providers who are able to accurately and objectively assess cost versus benefit, a challenge for cancer patients in any setting, particularly when information is limited or inaccessible and stakes are high[46]. Based on previous data that even small user fees can deter poor patients, countries are unlikely to achieve widespread access to rituximab and similar agents without subsidizing them. In the future, regions like East Africa may consider a bloc approach similar to that employed by the European Union, which results in consistent pricing of drugs across the bloc, despite differences in GDP among member states[45].

Conclusion

In conclusion, this analysis found that the addition of rituximab to first-line CHOP therapy in adults with aggressive non-Hodgkin lymphoma in Uganda is not cost-effective at current pricing. However, given the improvement in clinical outcomes associated with rituximab in aggressive

B-NHL, the Ugandan Ministry of Health may consider further negotiations with the manufacturer for alternative prices or access initiatives, or exploring biosimilar drugs as they become available.

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Tables and Figures

Figure 1: Markov Model

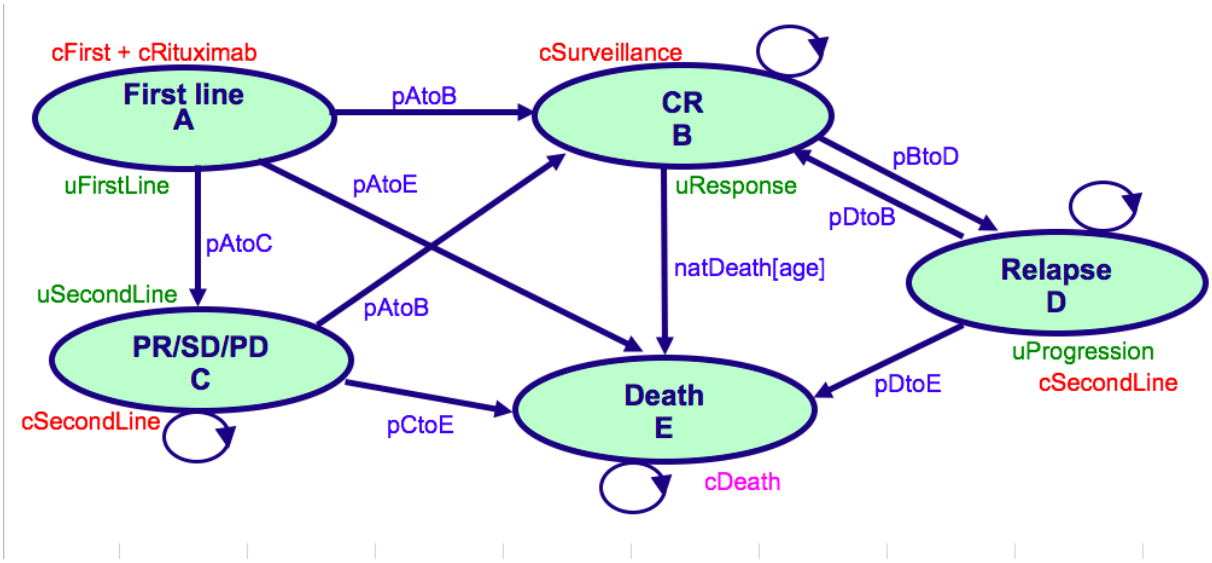


Table 1: Input parameters

Transition probabilities	CHOP	R-CHOP	Ref
Probability of CR after first line	0.713	0.87	17,29,30
Probability of PR/PD/SD after first line	0.279	0.122	17,29
Probability of treatment-related death during first line	0.008	0.008	16,29,30

Probability of relapse after first CR	0.36	0.243	[16,29,30]
Probability of CR after PR/PD/SD	0.13	0.288	[16,29]
Probability of death after initial PR/SD/PD	0.8	0.712	[29,30]
Probability of second CR after relapse	0.05	0.05	[29,30]
Probability of death after relapse	0.9	0.9	[16,27-29]
Background mortality	**Probability**		**Ref**
Age 40-44	0.04		[31]
Age 45-49	0.046		[31]
Age 50-54	0.059		[31]
Age 55-59	0.072		[31]
Age 60-64	0.103		[31]
Age 65-69	0.152		[31]
Costs	**USD**		
First Line Therapy (per 6 cycles)	$5,518.00		Clinical trial
Surveillance	$650.00		Clinical trial
Salvage chemotherapy (per 6 cycles)	$2,000.00		Clinical trial
Rituximab (per 6 cycles)	$3,188.00		UCI
End of Life Care	$200.00		Clinical trial
DALY adjustments			
First Line Treatment	0.288		[32]
Response	0.049		[32]
Recurrence	0.451		[32]
Salvage Treatment	0.54		[32]
Microcosting Data (from associated clinical trial)	**Cost per unit (USD)**	**Number**	**Total cost (USD)**
Supplies			
Powder free gloves	0.20	20	4
Chemotherapy gloves	0.30	20	6
Bone marrow needles	10.00	1	10
LP kits	30.00	1	30
Chemotherapy gowns	2.50	6	15
Chemotherapy bags 200mL	2.00	20	40
Chemotherapy giving sets (tubes)	1.00	20	20
Bandages	0.05	10	1

Sharps containers	10.00	1	10
Alcohol Swabs	0.10	50	5
Vacutainer	0.30	30	9
Vacutainer Safety-Lok blood collection set	1.00	10	10
Prefilled formalin containers	2.00	1	2
Trucut biopsy needles	10.00	1	10
Diagnostics			
X-rays	15.00	1	15
US	15.00	1	15
Echocardiography	60.00	1	60
Bone marrow analysis	45.00	1	45
CT scan	100	1	100
Consultants			
Surgery	400	1	400
Pathology	200	1	200
Hematology	300	8	2,400
Drugs			
Chemotherapy (CHOP)	100	6	600
Anti-emetics	10.00	6	60
Allopurinol	4.00	6	24
Antibiotics	2	10	20
Labs			
Biopsy with FFPR + Slides (15) Prep	38	1	38
Serum Creat	9	10	85
AST/ALT	16	10	160
Tot. Bilirubin	8	10	80
Albumin	8	10	80
LDH	10	10	100
Electrolytes	36	10	355
Uric Acid	8	2	16
HIV Serology	15	1	15
CD4/8	12	1	12
HIV VL	65	1	65
HBV Serology	12	1	12

Hepatitis B viral loads (PCR)	10.00	1	10
Pregnancy	7	1	7
CBC w/Diff	10	20	200
BUN	9	10	90
Rapid malaria test	2.00	1	2

Table 2: Results of cost-utility analysis

	Cost	**Life-Years Gained**	**DALYs averted**
Discounted at 3% per year:			
CHOP	$7,635	1.62	0.32
R-CHOP	$10,788	1.96	0.26
Difference	$3,153	0.34	0.05
ICER		$9,313	$60,719
Undiscounted:			
CHOP	$11,881	3.01	0.59
R-CHOP	$16,133	4.27	0.61
Difference	$4,252	1.26	0.02
ICER		$3,368	$284,926

Figure 2: One-way sensitivity analysis of ICER per LYG

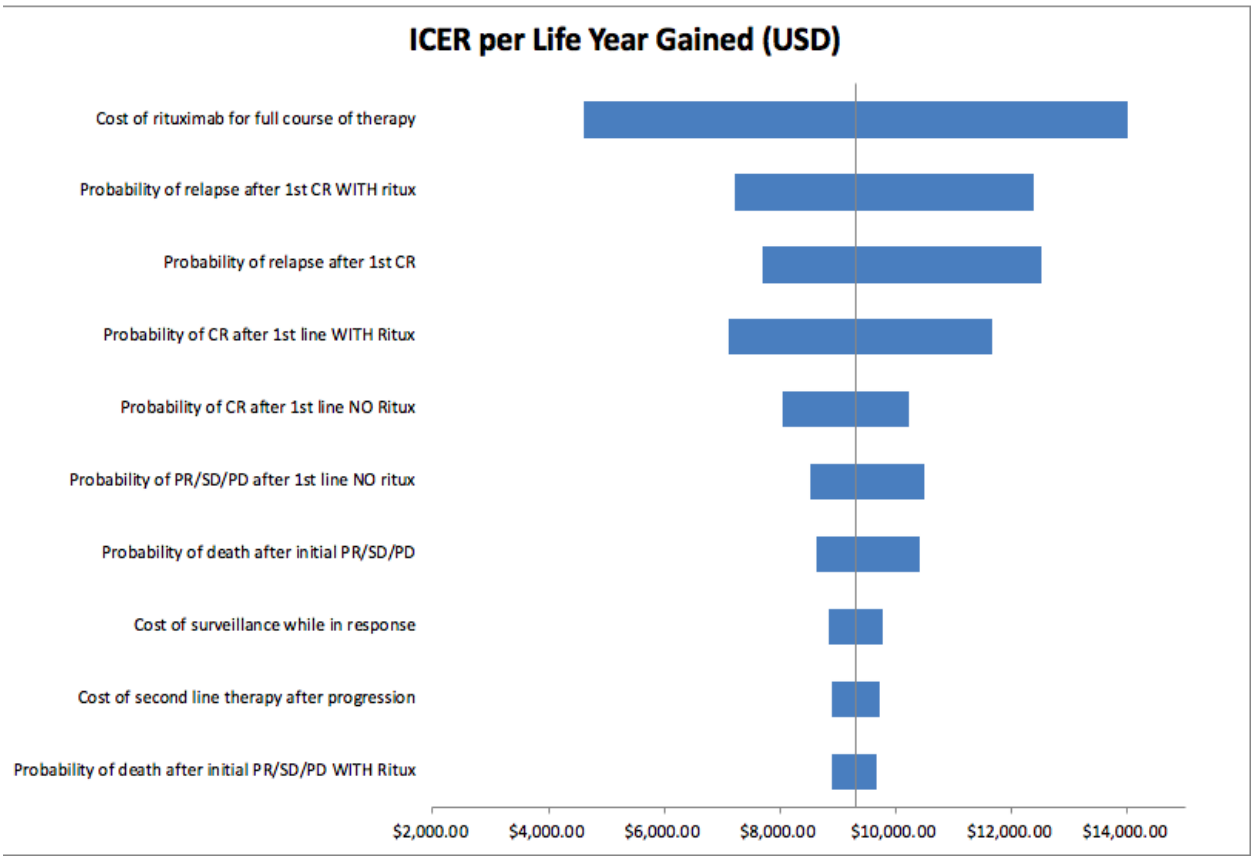


Figure 3: One-way sensitivity analysis of ICER per DALY averted

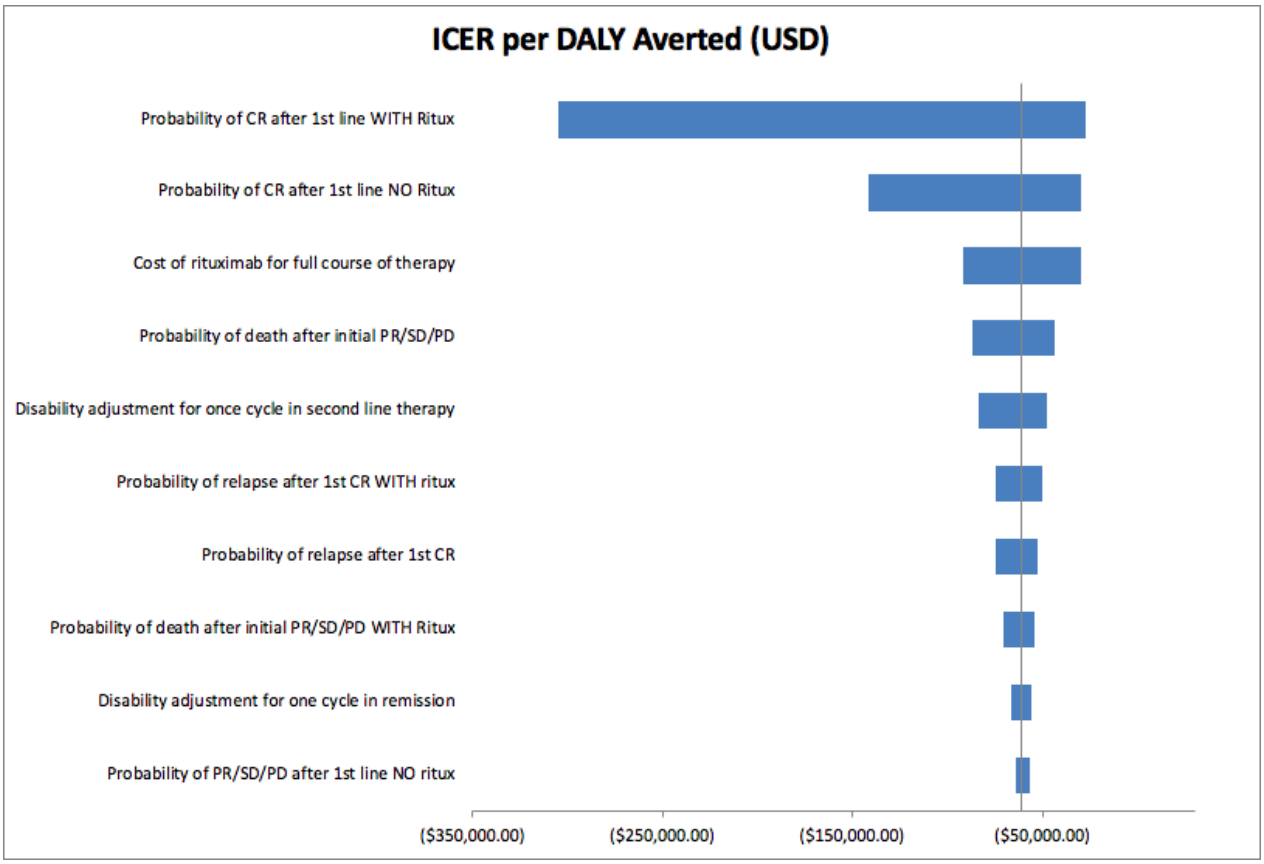
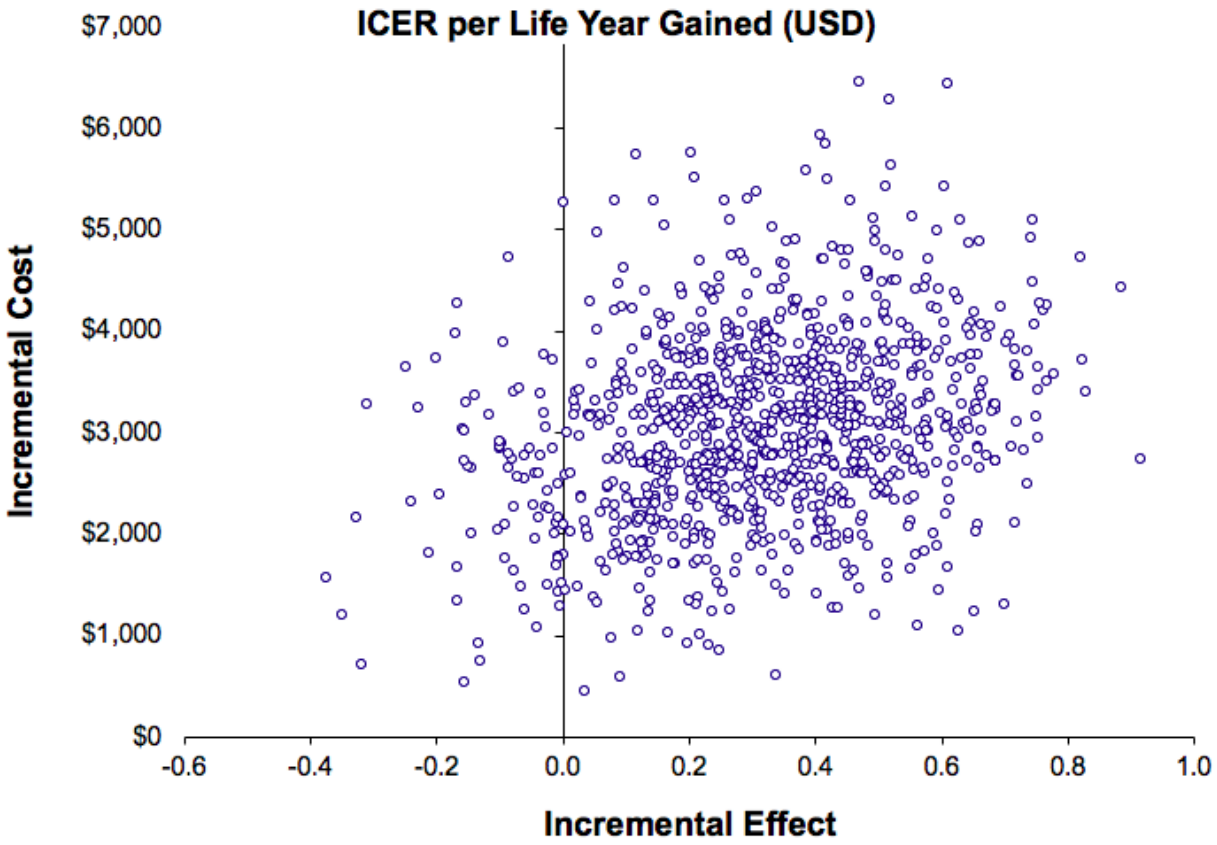


Figure 4: Probabilistic Sensitivity Analysis Scatter Plots


ICER per Life Year Gained (USD)
Incremental Cost
$7,000
$6,000
$5,000
$4,000
$3,000
$2,000
$1,000
$0
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Incremental Effect

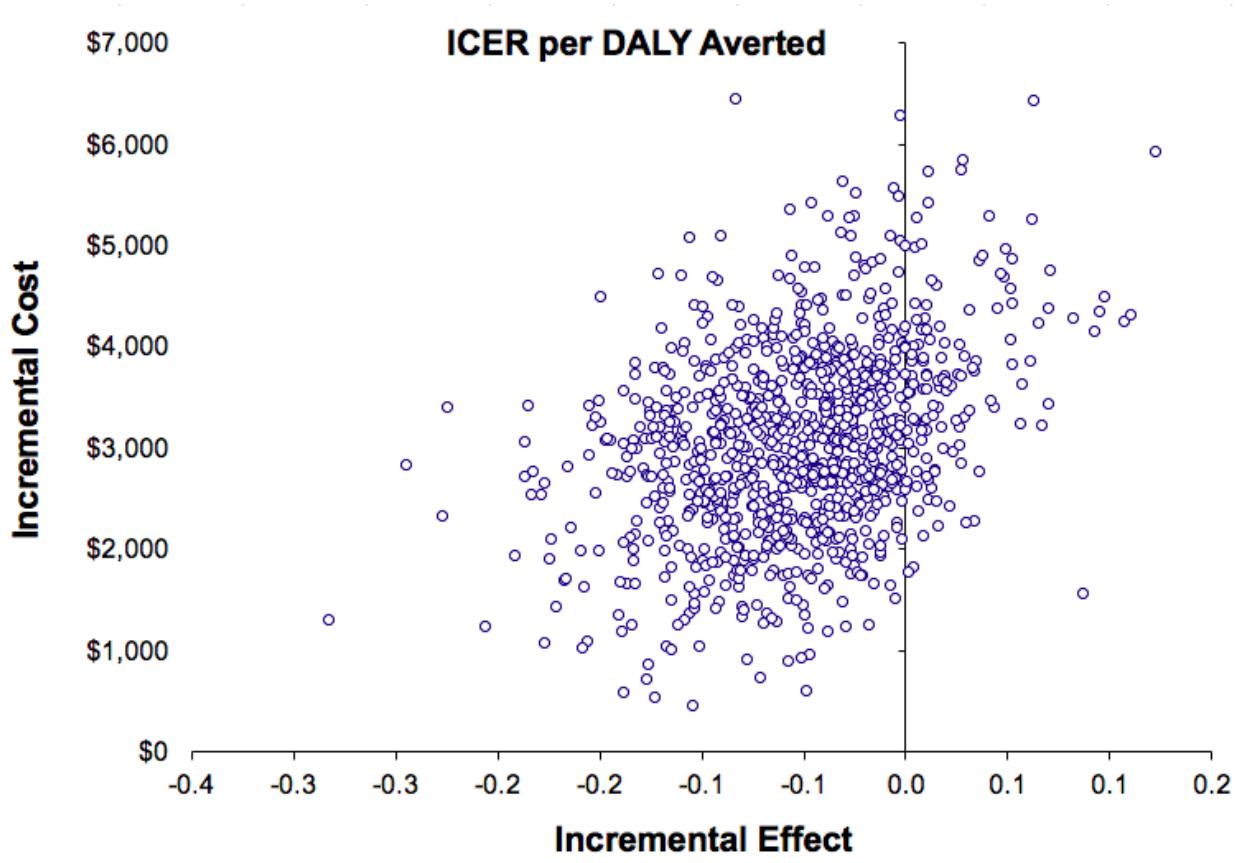
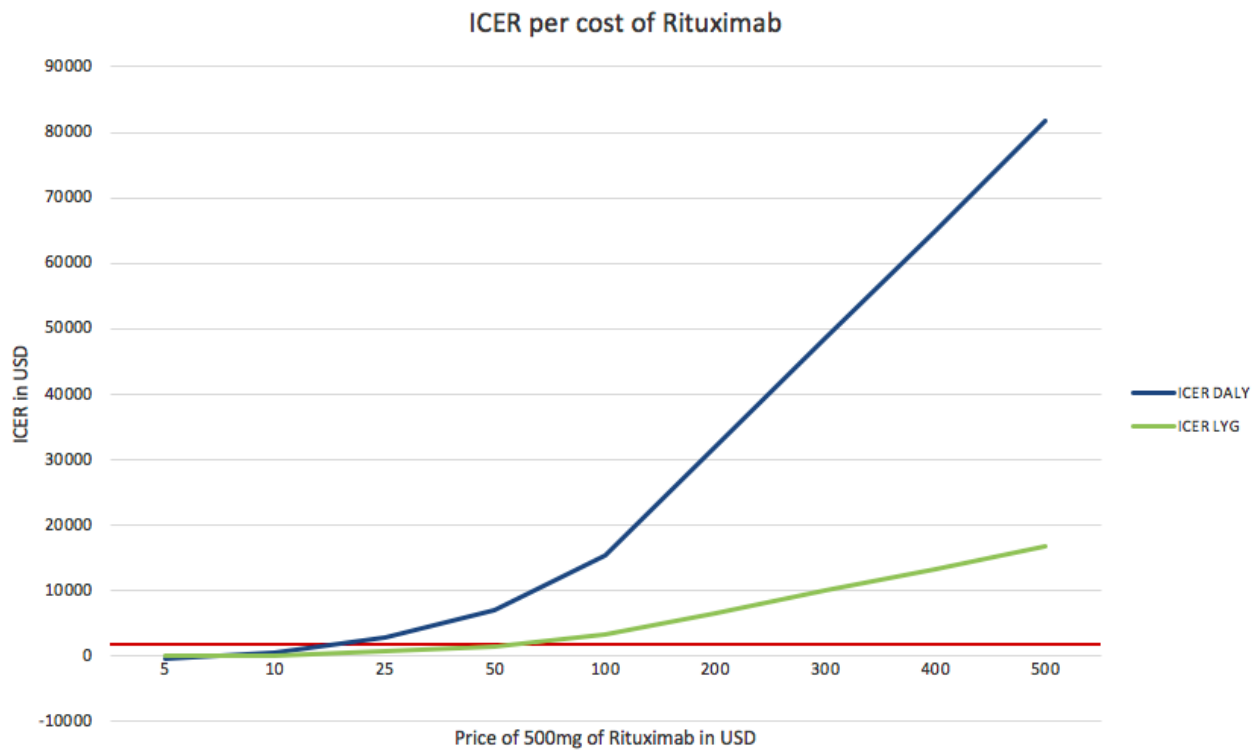


Figure 5: Estimate of ICER based on price of Rituximab



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