Published in final edited form as:

Am J Hematol. 2010 April ; 85(4): 255–260. doi:10.1002/ajh.21655.

Determinants of the optimal first-line therapy for follicular lymphoma: A decision analysis

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Abstract

Combination immunochemotherapy is the most common approach for initial therapy of patients with advanced-stage follicular lymphoma, but no consensus exists as to the optimal selection or sequence of available regimens. We undertook this decision analysis to systematically evaluate the parameters affecting the choice of early therapy in patients with this disease. We designed a Markov model incorporating the three most commonly utilized regimens (RCVP, RCHOP, and RFlu) in combinations of first- and second-line therapies, with the endpoint of number of quality-adjusted life years (QALYs) until disease progression. Data sources included Phase II and Phase III trials and literature estimates of long-term toxicities and health state utilities. Meta-analytic methods were used to derive the values and ranges of regimen-related parameters. Based on our model, the strategy associated with the greatest number of expected quality-adjusted life years was treatment with RCHOP in first-line therapy followed by treatment with RFlu in second-line therapy (9.00 QALYs). Strategies containing RCVP either in first- or second-line therapy resulted in the lowest number of QALYs (range 6.24–7.71). Sensitivity analysis used to determine the relative contribution of each model parameter identified PFS after first-line therapy and not short-term QOL as the most important factor in prolonging overall quality-adjusted life years. Our results suggest that regimens associated with a longer PFS provide a greater number of total QALYs, despite their short-term toxicities. For patients without contraindications to any of these regimens, use of a more active regimen may maximize overall quality of life.

Introduction

Follicular lymphoma (FL) is considered incurable with currently available therapies, and no chemotherapy agent or combination regimen prior to the introduction of rituximab had been shown to prolong overall survival. As a result, the selection, timing, and sequencing of available therapies have been a matter of continuing debate. In the absence of an overall survival advantage in the prirituximab era, progression-free survival (PFS) and quality of life (QOL) have become the main variables under consideration when choosing initial therapy for patients

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Conflict of interest: Nothing to report.

with this disease [1]. It is not intuitively clear how to maximize QOL, as therapies with greater toxicities, which may decrease QOL, may also provide the longest remission, thus increasing QOL [2]. In addition to efficacy and toxicity, choice may be influenced by planned sequences of future treatments, as initial therapy may influence feasibility of subsequent therapy.

The National LymphoCare Study recently reported that 52% of patients with FL in the US receive immunochemotherapy as initial treatment [3]. The most commonly used regimens include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; 55%), RCVP (rituximab, cyclophosphamide, vincristine, and prednisone; 23%), and RFlu (rituximab- and fludarabine-based chemotherapy; 16%). Use of these regimens is supported by several prospective Phase II and III clinical trials, none of which is directly comparative. We undertook this study to systematically evaluate the parameters informing the choice of early therapy in patients with advanced-stage FL and to determine the relative contribution of each parameter to the selection of initial therapy. Our hypothesis was that PFS would be a more significant determinant of overall quality-adjusted life years than short-term QOL.

The relative importance of each of these issues—PFS, sequence of therapies and QOL—would be difficult, if not impossible, to study in a randomized clinical trial. No such trial is currently ongoing or planned; although the PRIMA study will allow a nonrandomized comparison of RCVP, RCHOP, and RFlu, it is not likely to be adequately powered for this comparison as ~75% of patients received RCHOP [4].

To test our hypothesis, we used decision analysis methodology. Decision analysis is an analytic tool that is used to aid decision making when conditions of uncertainty exist [5]. It approaches a clinical decision situation by identifying the key elements involved in the decision, quantifying these elements using measurable variables, and identifying the choice that maximizes the outcome of interest. This methodology has been widely applied to clinical situations in both benign and malignant hematologic diseases, as in evaluating the choice of early versus delayed allogeneic transplantation for patients with myelodysplasia [6–8].

Methods

Decision strategy and assumptions

The base case was defined as a patient with previously untreated advanced-stage FL (Stage III–IV, WHO grade 1–2) who requires initial treatment with immunochemotherapy and who has no preexisting contraindication to any regimen. The analysis therefore does not apply to patients with Stage I–II FL or patients with WHO Grade 3 FL, for whom well-recognized standards of care do exist (locoregional therapy and anthracycline-based chemotherapy, respectively).

On the basis of the LymphoCare and PRIMA studies, we selected the three most commonly utilized immunochemotherapy regimens (RCVP, RCHOP, and RFlu) as the available choices in our decision. To incorporate the effect of therapy sequence in our model, we allowed a second regimen among those to be utilized at the time of progression from initial therapy, thus arriving at six possible permutations of first- and second-line therapies. Recognizing the paucity of available data for these regimens after multiple (≥ 2) relapses, we limited the model to these two decisions (i.e., six permutations). We therefore defined quality-adjusted time to third-line therapy as the main outcome. This “time-to-event” endpoint is clinically meaningful because tertiary therapy after two failed immunochemotherapy regimens would likely consist of currently less widely utilized or potentially more toxic treatments such as radioimmunotherapy or autologous/allogeneic transplantation, respectively. Rituximab maintenance was not explicitly incorporated in our model, as published clinical trials suggest a benefit following all three chemotherapy regimens [9–11].

Using the decision analysis software package TreeAge Pro 2008 (Williamstown, MA), a Markov model was generated comparing each of the six treatment strategies. In a Markov model, hypothetical cohorts of patients transition over time between clinically relevant health states. In our model (Fig. 1), relevant health states include: (1) receiving treatment (“Rx1” or “Rx2”); (2) in complete or partial remission (“Rem1” or “Rem2”); (3) requiring third-line therapy (“Rx3”); and (4) death. “Rx3” and “death” are terminal states, such that transition out of these states is not possible. When RFlu is part of a treatment strategy, either in first- or second-line therapy, an additional health state representing remission with residual cytopenias is included (not shown in figure for simplicity). Direct transition from any health state to the “dead” state is also possible (not shown in figure for simplicity), to account for the competing risk of death from nonlymphoma-related causes. Transition rates between health states were calculated from the existing literature and by performing a meta-analysis of all published studies. The cycle length for transitions between states was 6 months, which was thought to best reflect the clinical decision-making process.

Histologic transformation to aggressive large cell lymphoma is a significant event for patients with FL and is one of the major causes of death. Although it is thought that the risk of transformation is continuous over time with no plateau [12], it is less clear whether receipt of specific types of therapy can increase or decrease this risk. Additionally, data regarding the influence of prior therapies on the outcome of treatment after transformation are scant. Because of these uncertainties, transformation was not included in the primary decision model but was incorporated into a second exploratory model (Fig. 1). In this model, the “transformed” health state represents the state of having or being treated for histologically transformed lymphoma.

To incorporate adjustments for QOL, time spent in each health state is weighted using utilities. A utility is a number between 0 and 1, which represents the perceived value (to the patient) of a given health state, where 0 represents death and 1 represents perfect health. The utilities for each of the chemotherapy-related health states therefore incorporate the acute decreases in QOL associated with each of these therapies. Values of health state utilities were derived from the existing literature when available or from data regarding comparable health states, as described later.

Data sources for regimen-specific parameters

Data on the overall response rate (ORR), treatment-related mortality (TRM), and PFS for each of the three immunochemotherapy regimens were derived from the existing medical literature by performing a meta-analysis. The ORR was used rather than the complete response (CR) rate because calculation of PFS is based on all responding patients rather than only on patients experiencing a CR. In addition, it is safe to assume that there is no QOL difference between the state of being in complete versus partial response (PR), because patients and doctors generally cannot distinguish these states without the use of imaging. Consequently, we assumed that any difference in the degree of response following each therapy (CR versus PR) should be reflected in the duration of PFS.

Meta-analysis methodology—A literature search of the Medline database as well as abstracts from international meetings identified relevant Phase II and Phase III studies, using the following broad search terms: “follicular lymphoma” [All Fields] or “indolent lymphoma” [All Fields] and Clinical Trial [ptyp]. Additional studies were identified through citations in bibliographies and review articles. Studies were required to contain at least one immunochemotherapy arm (RCVP, RCHOP, or RFlu), with rituximab given either concurrently with chemotherapy or as a single 4-week course at the completion of chemotherapy for all patients regardless of response to chemotherapy alone. Variations of a regimen, including different chemotherapy doses, schedules, or number of rituximab

treatments, were acceptable. Studies that administered maintenance rituximab or consolidation therapy such as autologous stem cell transplant were allowed. Inclusion of other small B-cell lymphoma subtypes such as mantle cell lymphoma was allowed, although if data were reported separately for FL patients they were used preferentially. The patient population was required to be specified as either treatment-naïve (for Rx1) or relapsed/refractory (for Rx2).

Once selected for the meta-analysis, studies of first-line treatment were analyzed separately from studies of relapsed/refractory disease to derive parameter estimates representing first-line and second-line use. ORR, TRM, and PFS for each study were extracted by a single reviewer (R.O.). For studies with multiple publications, the publication with the longest follow-up was used for PFS. An exponential function was used to convert data from Kaplan-Meier curves or median PFS results into the 6-month PFS probability needed to populate the Markov model. Once estimates for each individual study were extracted, these were pooled using a fixed-effects meta-analysis with studies weighted using sample size alone. This approach was chosen because variances and confidence intervals for survival data are not typically available in the published literature, limiting the application of more traditional meta-analysis methods and precluding a formal statistical assessment of heterogeneity across studies. Finally, for each regimen, TRM in second-line therapy was constrained to be equal to or greater than that in first-line therapy; this assumption was made to avoid bias inherent in the high variance associated with small binomial probabilities.

Data sources for other parameters

Transformation—In the largest population-based series of 600 patients, the annual risk of transformation was estimated to be 3% per year, and the median survival after transformation was 1.7 years [13]. In subset analysis, the annual risk of transformation after anthracycline/radiation-based therapy was 1.5%, compared to 3% after alkylator/purine-based therapy. Overall survival after transformation was not different between these groups.

Long-term toxicities—In addition to the short-term side effects associated with immunochemotherapy, such as fatigue, emesis, and alopecia, there are serious long-term side effects that impact patients' QOL and ability to tolerate future therapies, namely cardiac toxicity from anthracyclines and prolonged cytopenias after fludarabine.

The incidence of anthracycline cardiotoxicity was estimated to be 3%, assuming a total dose of 300 mg/m² (equivalent to six cycles of RCHOP) [14,15]. This estimate is consistent with a report of patients with lymphoma treated with anthracycline-containing chemotherapy, in which 1 of 141 patients (0.7%) developed clinically apparent congestive heart failure (95% confidence interval 0.01–3%) [16]. However, a greater proportion of patients will develop subclinical cardiomyopathy of uncertain significance [16]. To be most conservative in this analysis, it was assumed that the health state of anthracycline-induced heart failure would have a utility of 0. The utility of being in remission after RCHOP was therefore decreased by 3% relative to the utility of being in remission after other nonanthracycline therapies.

Although it is a clinically well-recognized phenomenon, little data exist on the incidence of prolonged cytopenias in the months following completion of fludarabine-based therapy. Evidence suggests that CD4+ T lymphocytes may remain depressed for a year or longer, which can increase risk of infection [17]. In this analysis, the probability of any delayed cytopenias was conservatively estimated at 31%, based on a report of delayed neutropenia at 12 weeks after completion of therapy in patients with indolent lymphoid malignancies treated with a common RFlu regimen [18,19]. It was also assumed that 90 and 99% of patients would no longer be cytopenic by 6 and 12 months, respectively.

Competing risks—Nonlymphoma-related competing risk for death was also estimated using the age-adjusted death rate for 2005, which was 798.8 per 100,000 US population, as published by the National Center for Health Statistics [20].

Utilities—Utility values for each of the health states were determined, when possible, from the existing literature. Few utility estimates exist for health states involving FL or other indolent lymphomas, although more estimates exist for aggressive NHL and for Hodgkin's disease. The utilities used in this model were therefore extrapolated from published utilities for similar or related conditions and are listed in Table I [21–24]. The utilities of the chemotherapy health states by definition incorporate all chemotherapy-related short-term toxicities.

Time discount rate—In this analysis, we used the discount rate of 3% per year, which was recommended by the Panel on Cost-Effectiveness in Health and Medicine [25].

Sensitivity analysis

Regimen-specific parameters derived from the meta-analysis (such as ORR and PFS) were varied over the range of values obtained from individual published studies. Toxicity parameters, utilities, competing risks, and time discount rate were varied over a wide range of plausible values based on available literature.

Results

Meta-analysis

Details of the findings from the included studies are provided in Table II. Nine studies were available for RCHOP in first-line therapy [26–34], two for RCHOP in the relapsed/refractory setting [10,35], five for RFlu in first-line therapy [36–40], and five for RFlu in the relapsed/refractory setting [40–44]. Only one study evaluating first-line RCVP met criteria for inclusion in the analysis [45]. There were no studies that evaluated RCVP in the relapsed/refractory setting. To approximate the ORR, TRM, and 6-month PFS for RCVP in second-line therapy, the first-line RCVP parameters were discounted proportionally to the average difference between first-line and relapsed parameters for RCHOP and RFlu. Results of the meta-analysis were used to populate the decision model (Table III).

Markov decision model

To validate the structure of the decision model, survival curves were generated from each decision strategy, using the combined endpoint of time to third-line therapy or death. These curves are consistent with the data derived from the meta-analysis, with a median unadjusted time to the combined endpoint between 6.5 and 10 years. (Fig. 2)

Results of the primary decision model are shown in Table IV. In our model, the strategy associated with the greatest number of expected QALYs was treatment with RCHOP in first-line therapy followed by treatment with RFlu in second-line therapy (9.00 QALYs). RFlu followed by RCHOP provided 8.12 QALYs. Strategies containing RCVP either in first- or second-line therapy resulted in the lowest number of QALYs (range 6.24–7.71).

Our hypothesis was that PFS would be a more significant determinant of overall quality-adjusted life years than short-term decreases in QOL. To determine the relative contribution of PFS and QOL in our model, we performed a number of sensitivity analyses. We first varied the point estimates of treatment-related parameters over the broad range of values from heterogeneous individual studies reported in the literature. We observed that variation in the first-line PFS for RCHOP or RFlu within the range of published values did alter the optimal strategy of the model. To investigate this further, we then performed two-way analysis to

determine the thresholds of PFS that would alter the optimal strategy (Fig. 3). When the median PFS after RCHOP in first-line therapy was <40 months, the optimal decision strategy changed to RFlu followed by RCHOP in second-line therapy. Similarly, when the estimate of PFS after RFlu in first-line therapy was >68 months, the optimal decision strategy changed to RFlu followed by RCHOP in second-line therapy.

To determine whether chemotherapy-related decreases in QOL would influence the optimal strategy, we performed sensitivity analysis on the health state utility values. The model was robust in sensitivity analysis of utility values for any of the health states, with no plausible value for any utility changing the optimal decision strategy identified earlier. The model was also robust to major changes in the incidence of anthracycline cardiotoxicity and the incidence and duration of fludarabine-related cytopenias.

Exploratory analysis incorporating transformation

We designed a second exploratory model incorporating the effects of histologic transformation. In the basic exploratory model, a single probability (3% per year) was used for risk of transformation regardless of prior therapy, and similarly a single probability was used for risk of death after transformation (median survival 1.7 years). The optimal decision strategy remained RCHOP in first-line therapy followed by RFlu in second-line therapy; this strategy generated an expected 8.58 QALYs. (Table IV) Strategies containing RCVP either in first- or second-line therapy provided the lowest number of QALYs (range 6.18–7.58).

Sensitivity analysis was used to determine whether changes in the risk of or outcome after transformation would influence the optimal strategy. The optimal strategy did not change when the risk of transformation after anthracycline was assumed to be either lower or up to two times higher than after nonanthracycline-based treatment. Similarly, the model was insensitive to changes in the median posttransformation survival after prior anthracycline, when this was assumed to be as little as half the median survival after nonanthracycline-based treatment.

Discussion

In this study, we performed a decision analysis to evaluate the most commonly utilized first-line immunochemotherapy options for patients with advanced-stage low-grade FL and to determine the relative contribution of critical parameters to the model-derived optimal treatment approach. Our results suggest that PFS is a more important factor than short-term QOL in maximizing quality-adjusted life years for this patient population. In general, regimens associated with a longer PFS were found to maximize total quality-adjusted life years over the long term, in spite of their greater short-term toxicities. Based on the ranges of values for these parameters that currently exist in the literature, the treatment strategy that provides the highest number of QALYs consists of RCHOP followed by RFlu in the second-line setting. Furthermore, in our model, use of RCVP in either first- or second-line therapy results in a lower number of expected QALYs compared to the other two regimens.

A significant limitation of our study lies in the quality of data available for input into the meta-analysis. Many of the trials examining these chemotherapy regimens in patients with FL have only been published in abstract form. However, practicing clinicians are forced to use these limited data when making daily decisions about patient care. Furthermore, decision analysis methodology can surpass the limitations imposed by available data, by incorporating uncertainty in the model's input and assessing whether the optimal strategy would be affected. In our decision analysis model, large variation in estimates of regimen efficacy did not alter the optimal strategy.

A technical limitation of the meta-analysis is the lack of published information on the variances of PFS data from clinical trials. Thus, our meta-analysis was weighted by sample size rather than variance, and our estimates of first-line PFS are likely imperfect. Furthermore, statistical tests require study-level estimates of variance to generate confidence intervals, perform hypothesis testing, and assess heterogeneity across studies. However, in lieu of statistical testing, we performed highly conservative sensitivity analyses using extreme values for each parameter. The results of our model were robust in the face of such conservative sensitivity analysis.

No trial exists of RCVP in relapsed/refractory patients, and there is only one published study that met our inclusion criteria examining the use of RCVP in the first-line setting. Another large study of CVP for FL was excluded from the meta-analysis because rituximab was only used as maintenance therapy in CVP-responding patients rather than in all patients [9]. This study yielded better outcomes than the RCVP study included in our analysis [45]. However, incorporation of this study into the meta-analysis did not alter any of our findings (data not shown). Additionally, when we moved beyond the range of published trials in our two-way sensitivity analysis, we found that PFS after RCVP would have to be essentially identical to RCHOP to alter the optimal strategy, reinforcing the cardinal importance of PFS in determining total quality-adjusted life years.

We also designed an exploratory model to address the concern of histologic transformation in this patient population and to determine whether inclusion of this phenomenon in our model would alter the relative contribution of PFS and QOL to the optimal strategy. A common concern regarding the use of RCHOP as initial therapy for FL is that, at the time of histologic transformation, anthracycline-based therapy would be unavailable as an option resulting in poor treatment outcomes. However, when transformation was included in the model, the relative contributions of PFS and QOL did not change. Importantly, this finding was robust even when the median posttransformation survival after prior anthracycline was postulated to be half of that achieved after nonanthracycline regimens. Thus, despite a hypothetically worse posttransformation outcome for patients with prior anthracycline treatment, the use of regimens with longer PFS (including RCHOP) still maximize total quality-adjusted life years.

In summary, using decision analysis methodology, we have shown that the most important factor in maximizing quality-adjusted life years in patients with advanced-stage, low-grade FL is the PFS associated with the chosen therapy rather than its short-term effect on QOL. Based on our estimates of PFS and QOL from currently available data, the optimal immunotherapy treatment consists of RCHOP followed by RFlu. Most notably, treatment strategies containing RCVP consistently generated fewer quality-adjusted life years, arguing that regimens associated with fewer short-term toxicities but also lower efficacy may not ultimately maximize quality-adjusted life years in patients who are candidates for more intensive therapy.

Acknowledgments

Contract grant sponsor: National Cancer Institute T32 Training Grant; Contract grant number: NIH T32 CA09679.

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Figure 1.

Markov model schematic diagram. Exploratory model incorporating transformation is indicated by the addition of hatched arrows and the health state of “transformation.” Rx1, first-line therapy; Rx2, second-line therapy; Rx3, third-line therapy; Rem1, first remission; Rem2, second remission. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 2. Model diagnostics and validation. Unadjusted survival curves for each decision strategy were generated using a combined endpoint of third-line therapy or death.

Figure 3.

Two-way sensitivity analysis. Each shaded region represents the combination of median PFS values at which a particular decision strategy is dominant. Axis ranges represent the range of values obtained from individual published studies. "X" indicates the specific PFS values derived from the meta-analysis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

Quality-of-Life Utilities

Health State	Utility value	Literature range for comparable utilities	Range used in sensitivity analysis
Receiving RCHOP	0.70	RCHOP for aggressive NHL: 0.53–0.86	0.53–0.86
Receiving RFlu	0.75	–	0.58–0.91
Receiving RCVP	0.85	–	0.68–0.99
Remission	0.99	Follicular lymphoma in remission, off therapy: 1 Aggressive NHL in remission after RCHOP: 0.97–1 Aggressive NHL in remission after transplant: 0.9–1 MDS: 0.95	0.95–1
Remission with prolonged cytopenias	0.90	CLL with infection: 0.46–0.86 Febrile neutropenia: 0.54–0.73	0.46–0.95

NHL, non-Hodgkin lymphoma; CLL, chronic lymphocyte leukemia; --, not available.

TABLE II

Individual Studies Included in the Meta-Analysis

Study	Publication Format	N	ORR	TRM	PFS
RCVP first-line therapy					
Marcus et al. [45]	Peer-reviewed	162	0.81	0.006	Median 34 months
RCHOP first-line therapy					
Hiddeman et al. [26]	Peer-reviewed	222	0.96	0.01	3-year PFS 75%
Huang et al. [27]	Abstract only	102	0.86	0.01	–
Hensel et al. [28]	Abstract only	69	0.90	0.01	–
Ladetto et al. [29]	Peer-reviewed	68	0.62	0.03	4-year PFS 28%
Ogura et al. arm C [30]	Peer-reviewed	32	0.94	0	Median 34.2 months
Jager et al. [31]	Peer-reviewed	30	1.00	0	5-year PFS 59.4%
Tomita et al. [32]	Peer-reviewed	21	0.76	0	2-year PFS 82%
Niitsu et al. [34]	Peer-reviewed	15	1.00	0	2-year PFS 68.1%
Economopoulos et al. [33]	Peer-reviewed	12 ^a	1.00	0	3-year PFS 60%
RCHOP second-line therapy					
van Oers et al. [10]	Peer-reviewed	234	0.85	0.004	Median 33.1 months
Domingo-Domenech et al. [35]	Peer-reviewed	16	0.88	0	18-month PFS 53%
RF1u first-line therapy					
Vitolo et al. [36]	Abstract only	95	0.84	0	–
Vitolo et al. [37]	Abstract only	80	0.90	0.01	3-year PFS 50%
McLaughlin et al. [38]	Abstract only	76	1.00	0	3-year PFS 77%
Tomas et al. [39]	Abstract only	69	0.97	0.03	–
Tam et al. [40]	Peer-reviewed	7	1.00	0	3-year PFS 100%
RF1u second-line therapy					
Forstpointner et al. [41]	Peer-reviewed	67 ^a	0.96	0.03	Median 3.9 years
Sacchi et al. [42]	Peer-reviewed	54	0.90	0	4-year PFS 60%
Hagemeister et al. [43]	Abstract only	39	0.95	0	2-year PFS 66%
Leo et al. [44]	Peer-reviewed	17	0.88	0	–
Tam et al. [40]	Peer-reviewed	15	0.87	0	3-year PFS 42%

N, number of patients; ORR, overall response rate; TRM, treatment-related mortality; PFS, progression-free survival.

Number of patients with follicular lymphoma.

TABLE III

Overall Response Rate (ORR), Treatment-Related Mortality (TRM), and Median Progression-Free Survival (PFS)

Regimen	ORR	TRM	Median PFS (months)
RCVP, first-line therapy	0.81 (0.64–0.97)	0.006 (0.001–0.03)	34 (25–38)
RCVP, relapsed/refractory ^a	0.7909 (0.63–0.94)	0.006 (0.001–0.03)	25 (20–30)
RCHOP, first-line therapy	0.8944 (0.62–0.99)	0.009 (0.001–0.03)	55 (29–81)
RCHOP, relapsed/refractory	0.8519 (0.85–0.88)	0.009 (0.001–0.03)	31 (19–33)
RFlu, first-line therapy	0.9227 (0.84–0.99)	0.008 (0.001–0.03)	55 (35–101)
RFlu, relapsed/refractory	0.9270 (0.87–0.96)	0.010 (0.001–0.03)	46 (29–67)

Parentheses indicate ranges obtained from individual published studies, which were used in sensitivity analyses. Ranges for all RCVP parameters are $\pm 20\%$.

^aThese parameters were estimated based on those for RCVP in the first-line setting as described in the text.

TABLE IV

Expected Quality-Adjusted Life Years (QALYs) for Each Treatment Strategy

First-line regimen	Second-line regimen	Primary model, not including transformation (expected QALYs)	Exploratory model, including transformation (expected QALYs)
RCVP	RCHOP	6.24	6.18
RCVP	RFlu	7.64	7.43
RCHOP	RCVP	7.38	7.27
RCHOP	RFlu	9.00 ^a	8.58 ^a
RFlu	RCVP	7.71	7.58
RFlu	RCHOP	8.12	7.92

^aDenotes the dominant strategy in each model.