



# Copanlisib plus rituximab combination therapy vs. rituximab monotherapy for relapsed indolent non-Hodgkin lymphoma: a cost-effectiveness analysis

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**Background:** In the clinical use of third-line treatment of non-Hodgkin lymphoma (NHL), the combination treatment is increasingly used due to problems such as drug resistance, and while their efficacy has been proven, whether they are economical has become a new issue. A recent trial showed copanlisib plus rituximab combination therapy (CRCT) had better efficacy in the treatment of relapsed indolent NHL (iNHL) compared to rituximab monotherapy (RM). However, the long-term cost and effectiveness of this regimen is not known. We are the first to evaluate the cost effectiveness of CRCT in third-line treatment of relapsed iNHL from the perspective of US payers.

**Methods:** We used a Markov model to evaluate cost and quality-adjusted life years (QALYs) which included a population from CHRONOS-3 with mean age of 62.5 years and total cycle length of 16.3 years. The cycle length was 1 month, adverse reaction rates were from CHRONOS-3, mean body surface area was referenced from published literature, cost values are referenced from published literature and Drugbank, utility values were referenced from the published literature, and the primary endpoint was the incremental cost-effectiveness ratio (ICER). The willingness to pay (WTP) threshold was set at \$150,000 per QALYs, and one-way sensitivity analysis and probabilistic sensitivity analysis were used to verify the robustness of the model. All costs are expressed in 2021 dollars and costs and utilities have been calculated at a discount rate of 3% per year.

**Results:** CRCT and RM obtained 6.53 QALYs and 5.15 QALYs, respectively, and the ICER of CRCT *vs.* RM was \$358,895.2/QALYs. Parameters having the greatest impact on the robustness of the model were the drug cost of copanlisib and the utility value of the progression-free survival (PFS) state. When the WTP threshold was \$150,000, the probability of CRCT and RM being the most cost effective was 0.4% and 99.6% respectively.

**Conclusions:** From a US payer perspective, CRCT is not cost-effective in treating relapsed iNHL at current prices compared to RM. But given its positive clinical efficacy, appropriate price discounts or assistance programs should be considered to make CRCT more affordable to patients with relapsed iNHL.

**Keywords:** Cost-effectiveness; copanlisib; Markov model; indolent non-Hodgkin lymphoma (iNHL)

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## Introduction

Non-Hodgkin lymphoma (NHL) is a disease of the lymphatic system in which tumors form when B cells, T cells, or natural killer (NK) cells grow abnormally. NHL ranks seventh among men and sixth among women among all cancers, and accounts for about 4% of all new cases of cancer in the United States, with a slight overall downward trend (1-3). It is estimated there will be 81,560 new cases of NHL and 20,720 people will die of the disease in 2021, which has a 5-year relative survival rate of 73.2% (4). NHL can be classified according to its growth and spread rate: indolent NHL (iNHL) and aggressive NHL (aNHL), with indolent accounting for about 40% (5-7). Some iNHL will turn into aNHL.

An obvious hallmark of NHL is phosphatidylinositol-3-kinase (PI3K) signaling dysregulation, and blocking the PI3K/protein kinase B (PI3K/AKT) signaling pathway is an effective current treatment (8,9). Copanlisib, a new generation of PI3K inhibitor subsequent to idelalisib (Zydelig<sup>®</sup>), was approved by the Food and Drug Administration (FDA) under the brand name Aliqopa<sup>®</sup> in September 2017 and its monotherapy is recommended in the National Comprehensive Cancer Network (NCCN) guidelines as: "Relapsed/refractory after 2 prior therapies for follicular lymphoma or marginal zone lymphoma" (10-13).

According to the CHRONOS-3 clinical trial published in May 2021 (14), the PI3K inhibitor copanlisib plus rituximab combination therapy (CRCT) for relapsed iNHL of third-line treatment, compared with rituximab monotherapy (RM), showed the progression-free survival (PFS) time was prolonged 7.7 months (21.5 *vs.* 13.8 months), demonstrating its potential to treat NHL. According to a recent report by the National Cancer Institute (15,16), NHL health care costs are expected to reach \$18.6 billion nationwide in 2020, and Caitlin Eichten's study (17) suggests follicular lymphoma (FL) patients treated in the United States alone will spend approximately \$515,884 over their lifetimes. CRCT and RM have been shown to be effective in the treatment of relapsed iNHL, and RM has been shown to be cost-effective in the treatment of NHL (14,18). The effectiveness of idelalisib, a drug similar to copanlisib, in the treatment of relapsed FL is positive, but its safety seems to be considered unacceptable, whereas copanlisib, which has similar efficacy, is safer than idelalisib (19). Knight *et al.* developed a Markov model to assess the cost-effectiveness of rituximab in NHL, and Yu *et al.* developed a partitioned survival model to assess the cost-effectiveness of idelalisib

plus rituximab in chronic lymphocytic leukemia (18,20). Whether the superior efficacy of CRCT as a new treatment option is worth its increased cost, and which of the four populations included in the study is more cost-effective, have been issues of concern to US payers. Previously, no relevant studies were published, therefore, we conducted this study to assess whether CRCT is cost-effective compared with RM in the third-line treatment of relapsed iNHL from the perspective of US payers. We present the following article in accordance with the CHEERS reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1159/rc>).

## Methods

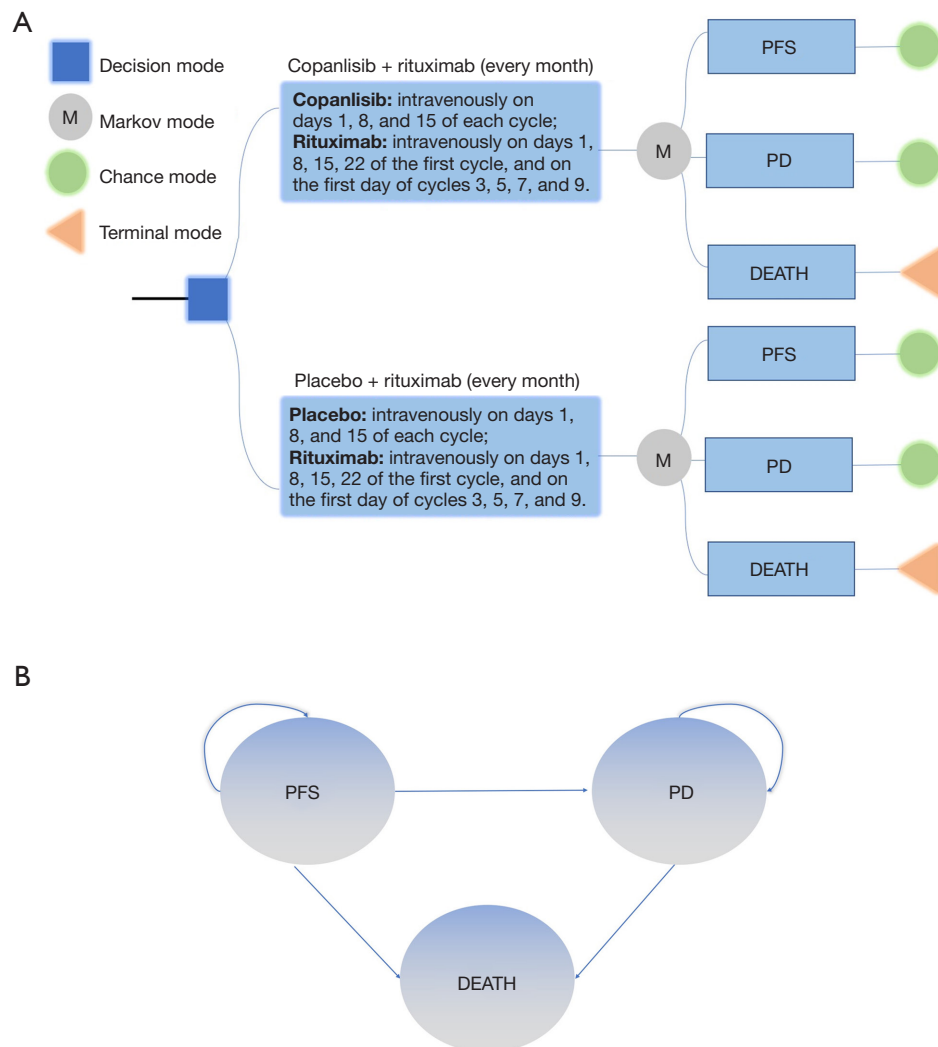
### *Patients and intervention*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Our model was constructed based on relapsed iNHL patients in the CHRONOS-3 clinical trial, where the mean age was 62.5 years. The trial included four subgroups of relapsed iNHL people: FL, small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma-Waldenström macroglobulinaemia (LPL-WM). All patients had relapsed after previous treatment with rituximab or other anti-CD20 monoclonal antibodies. Eligible patients were treated in 2:1 ratio with CRCT *vs.* RM regimens, where copanlisib was administered intravenously on days 1, 8, and 15 of each cycle for 28 days, and rituximab was administered intravenously by 375 mg/m<sup>2</sup> on days 1, 8, 15, and 22 of the first cycle and on the first day of cycles 3, 5, 7, and 9. Patients remained on their respective treatment regimens until disease progression or unacceptable levels of toxicity occurred.

### *Distribution and Markov model*

A three states Markov model, including PFS, progression disease (PD), and death, was built using Microsoft<sup>®</sup> Excel 2019. Cost-effectiveness analysis was also used to explore the economics of the CRCT and RM groups from the perspective of US payers, using incremental cost-effectiveness ratio (ICER) as the primary outcome indicator (*Figure 1A*). Based on the PFS *vs.* overall survival (OS) curves reported in clinical trials, the probability of change over time in the three states of PFS, PD, and death can be obtained (*Figure 1B*). Each model period is 1 month and



**Figure 1** Markov model structure sketch. (A). Markov model used to compare two different regimens for NHLs patients; (B) three transitional health states linked by Markov node. PFS, progression-free survival; PD, progression disease; NHL, non-Hodgkin lymphoma.

the cycle length is 16.3 years. We included the age-specific mortality and the life expectancy in the United States based on US life tables (21,22), and because of the COVID-19, used the 2019 US life expectancy of 78.8 years instead of 2021 data.

### Statistical analysis

#### Data extraction and model fitting

The original patient level data of this clinical trial was not directly available, so we extracted the picture of PFS and OS from the CHRONOS-3 trial, then reconstructed

individual patient data (IPD) using plot digitizer software (GetData Graph Digitizer, version 2.20, <http://www.getdata-graph-digitizer.com/>), and the survival, survHE and survminer packages in R software (version 3.6.3, <https://www.r-project.org/>) were called to obtain several key parameters of the distribution (exponential:  $S_{(t)} = e^{-\lambda t}$ , Gompertz:  $S_{(t)} = e^{-\frac{a}{\beta}(1-e^{-\lambda t})}$ , log-logistic:  $S_{(t)} = [1 + (\lambda t)^\gamma]^{-1}$ , log-normal:  $S_{(t)} = \frac{1}{2} - \frac{1}{2} \operatorname{erf}\left[\frac{\sqrt{2} \ln(t) - \alpha}{2\beta}\right]$ , and Weibull:  $S_{(t)} = e^{-(\lambda t)^\beta}$ ), and then statistical analysis was performed in excel. Selection of the best distribution was based on Akaike information criterion (AIC), Bayesian information criterion (BIC), and goodness of fit ( $R^2$ ), AIC, BIC and  $R^2$  were

calculated using R software, where AIC and BIC were taken as the minimum values. The general cumulative hazard function was  $H_{(t)} = -\ln(S_{(t)})$ , and the general transfer probability function was  $T_{(t)} = 1 - e^{-H_{(t)} - H_{(0)}}$  (23,24).

ICER was the primary outcome metric evaluated, and it was defined as:  $ICER = \frac{Cost_{CRCT} - Cost_{RM}}{Qaly_{CRCT} - Qaly_{RM}}$ , and the willingness to pay (WTP) values of \$100,000, \$150,000, and \$200,000 were used for Monte Carlo simulations, making the main outcome determination at a WTP of \$150,000.

### Cost and utility

Indirect costs are not included in the model, and the direct costs included drug costs, monitoring costs, administration costs, and adverse effects treatment costs. The dose of copanlisib was \$4,300/60 mg (25), and that of rituximab was 375 mg/m<sup>2</sup> and the unit price was \$68.09/10 mg/mL (26), the recommended doses for all drugs are from the CHRONOS-3 trial. We used a 1.91 m<sup>2</sup> average body surface area based on Appukkuttan (25), and in consideration of waste and safety issues, less than 10 mg was treated as 10 mg in the decile position for rituximab dose consumption. Monitoring costs included routine blood examination and biochemical testing every cycle, and computed tomography (CT) or magnetic resonance imaging (MRI) evaluation for tumor screening. Data for both administration and monitoring costs were obtained from a budget impact analysis on copanlisib (25), and end of life costs and best supportive care that patients in PD state will received were also included in the model (27,28). Adverse effects greater than 10%, including hypertension, hyperglycemia, pneumonia, and neutropenia, were taken and treatment costs were cited from the published literature (29,30), and all costs were discounted to 2021 (31).

As the original utility values were not available, we referenced research which had used the EQ-5D scale applied to idelalisib for the treatment of FL in third-line therapy as this had the highest percentage of the population in the CHRONOS-3 clinical trials, and because idelalisib is a PI3K inhibitor. Utility values of 0.805 for the PFS state and 0.618 for the PD state were set as baseline values. We considered the effects of the following grade 3 and 4 adverse events: hyperglycemia, hypertension, pneumonia, and neutropenia, and referenced idelalisib negative utility value to correct the utility value (32). Both the cost and utility value were discounted at an annual rate of 3% and were detailed in *Table 1*.

### Sensitivity analysis

To explore the robustness of the model, Monte Carlo simulations and one-way sensitivity analysis were performed, and in the one-way sensitivity analysis, all parameters taken varies within its  $\pm 20\%$  region due to the fact that most studies used  $\pm 20\%$  as the threshold of variation when 95% confidence intervals were not available. A total of 1,000 Monte Carlo simulations were performed, and all variables changed simultaneously with random probability. The distribution type of each parameter was referenced from Briggs (33). Tornado diagrams (*Figure 2*), cost effectiveness acceptability curves (CEAC) (*Figure 3*), and scatter chart (*Figure 4*) were drawn based on the results of the sensitivity analysis.

### Subgroup analysis

A subgroup analysis was conducted for the four population groups included in the clinical trial to determine if CRCT performed better in a particular subgroup in terms of cost effectiveness. PFS curves of each subgroup and total OS curves reported in the trial were included in the model for analysis.

## Results

### Model validation

According to the evaluation criteria and visual inspection, the log-logistic distribution and the log-normal distribution proved to be the closest to the original graph, specific data, and fitted curve (see *Figure S1* and *Tables S1-S6*). The R<sup>2</sup> for the PFS curve in the CRCT group was 0.97 and for the OS curve in the CRCT group *vs.* RM group was 0.98.

### Base case results

Over the total patient's lifecycle, the total cost in the CRCT group was \$739,998.75 and the total cost in the CM group was \$242,961.95. CRCT compared to the RM, delivered 1.38 more quality-adjusted life years (QALYs) and \$497,036.8 over the patients' lifetime, and the ICER of CRCT was \$358,895.2 each QALY (*Table 2*).

### Subgroup analysis

A subgroup analysis of the population under the four

**Table 1** Base-case parameters, values (range), distribution, and reference

Parameters	Values (95% CI)	Distribution	Ref.
Loglogistic survival model of PFS in CRCT	$\lambda=1/22.673, \gamma=1.513, R^2=0.97$		
Lognormal survival model of PFS in RM	$\lambda=2.5201, \gamma=1.0941, R^2=0.98$		
Lognormal survival model of OS in CRCT	$\lambda=5.357, \gamma=1.846, R^2=0.98$		
Lognormal survival model of OS in RM	$\lambda=4.528, \gamma=1.025, R^2=0.98$		
Probability (%) of hyperglycemia (grade $\geq 3$ )			(14)
Copanlisib plus rituximab	0.56 (range, 0.448–0.672)	$\beta$	
Rituximab	0.08 (range, 0.064–0.096)	$\beta$	
Probability (%) of hypertension (grade $\geq 3$ )			(14)
Copanlisib plus rituximab	0.40 (range, 0.32–0.48)	$\beta$	
Rituximab	0.09 (range, 0.72–0.108)	$\beta$	
Probability (%) of pneumonia (grade $\geq 3$ )			(14)
Copanlisib plus rituximab	0.10 (range, 0.08–0.12)	$\beta$	
Rituximab	0.13 (range, 0.104–0.156)	$\beta$	
Probability (%) of neutropenia (grade $\geq 3$ )			(14)
Copanlisib plus rituximab	0.39 (range, 0.312–0.468)	$\beta$	
Rituximab	0.26 (range, 0.208–0.312)	$\beta$	
Cost (\$)			
Drug cost of rituximab (every cycle)	4,876.95 (range, 3,901.56–5,852.34)	$\gamma$	(26)
Drug cost of copanlisib (every cycle)	13,500 (range, 10,800–16,200)	$\gamma$	(25)
Administration cost of rituximab (every cycle)	855.92 (range, 684.74–1,027.11)	$\gamma$	(25)
Monitor cost (every cycle)	507.11 (range, 405.69–608.53)	$\gamma$	(25)
Best support care	1,380.13 (range, 1,104.10–1,656.16)	$\gamma$	(28)
Care end of life	61,329.39 (range, 49,063.51–73,595.27)	$\gamma$	(27)
Health utility			(32)
Utility of PFS	0.805 (range, 0.644–0.966)	$\gamma$	
Utility of PD	0.618 (range, 0.494–0.742)	$\gamma$	
Mean body surface area	1.91 (range, 1.528–2.292)	Normal	(25)

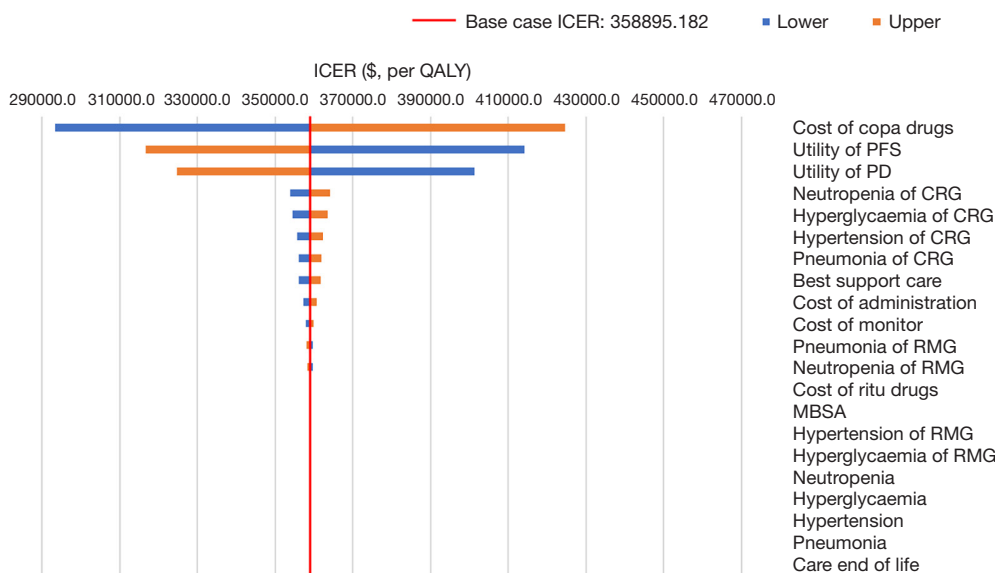
PFS, progression-free survival; CRCT, copanlisib plus rituximab combination therapy; RM, rituximab monotherapy; OS, overall survival; PD, progression disease; CI, confidence interval.

classifications (FL, MZL, SLL, LPL-WM) included in relapsed iNHL showed ICER values of \$360,636, \$348,320.8, \$222,212.4, and \$300,932.7, respectively (Table 2).

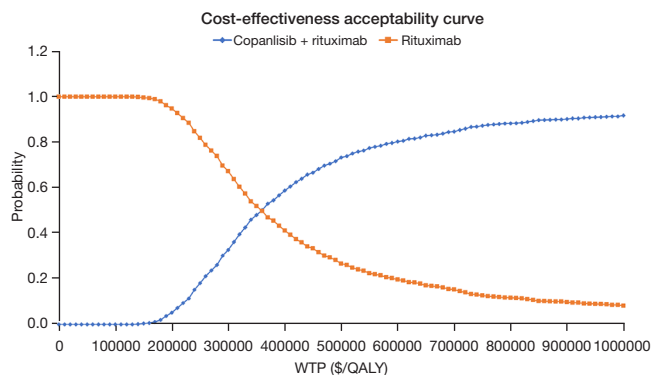
### Sensitivity analysis results

The results of the one-way sensitivity analysis (Figure 2) show the factors having the greatest impact on the robustness

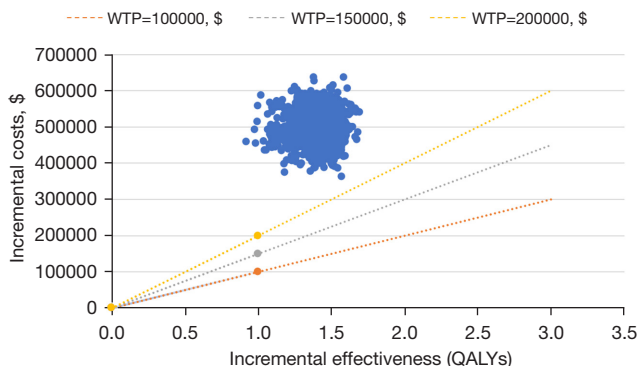
of the model were the drug cost of copanlisib and the utility value of PFS, while others including the utility value of PD and the probability of neutropenia in the CRCT group had moderate influence. Results of the CEAC (Figure 3) show the CRCT group had 0%, 0.4%, and 5.2% probability of being cost-effective compared to the RM group when the WTP were \$100,000, \$150,000, and \$200,000, respectively. The results of 1,000 Monte Carlo simulations showed that 0,



**Figure 2** Tornado diagram summarizing the result of one-way sensitivity analysis. ICER, incremental cost-effectiveness ratio; QALY, quality adjustment life year; copa, copanlisib; PFS, progression-free survival; PD, progression disease; CRG, copanlisib plus rituximab group; RMG, rituximab monotherapy group; ritu, rituximab; MBSA, mean body surface area.



**Figure 3** Cost-effectiveness acceptability curve. WTP, willingness to pay; QALY, quality adjustment life year.



**Figure 4** Scatter plot with three lines stand for the threshold of WTP varying from one to three times per capita GDP of the US. WTP, willingness to pay; QALY, quality adjustment life year.

0, and 0% of the scatter lay below the line when the WTP was \$100,000, \$150,000, and \$200,000, respectively.

**Discussion**

Our study provides the first cost-effectiveness analysis of copanlisib plus rituximab combination for relapsed iNHL using Markov models. Based on the results of the CHRONOS-3 trial, this study showed CRCT was not cost-effective in treating patients with relapsed iNHL compared

to RM over a lifetime at a WTP of \$150,000 in the United States. This finding implies that for the combination therapy to be cost-effective, the price of the regimen would need to be significantly reduced. The results of the one-way sensitivity analysis suggest the most direct and effective way to obtain cost-effectiveness for CRCT at the current WTP threshold (\$150,000) is to reduce the drug price of copanlisib. In addition, the utility of PFS had a strong influence on baseline outcomes. Although the FDA has approved several generic forms of rituximab, this analysis

**Table 2** Base case results and subgroup results

Population	Treatment	Cost (\$)	Incremental cost	QALYs	Incremental QALYs	ICER
All population	CRCT	739,998.8	497,036.8	6.53	1.38	358,895.2
	RM	242,962		5.14		
FL	CRCT	808,222.1	569,536.6	6.58	1.58	360,636
	RM	238,685.5		5.0		
MZL	CRCT	771,018.9	530,326.2	6.58	1.52	348,320.8
	RM	240,692.8		5.06		
SLL	CRCT	578,186	346,667	6.25	1.57	222,212.4
	RM	229,015.2		4.68		
LPL-WM	CRCT	566,803.7	324,372	6.33	1.08	300,932.7
	RM	242,431.8		5.24		

FL, follicular lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; LPL-WM, lymphoplasmacytic lymphoma-Waldenström macroglobulinaemia; CRCT, copanlisib plus rituximab combination therapy; RM, rituximab monotherapy; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

suggests its price has a negligible impact on the robustness of the model. Subgroup analysis showed that among the four populations included in the CHRONOS-3 trial (FL, MZL, SLL, and LPL-WM), the ICER for SLL was the closest group to WTP, suggesting that clinically SLL patients may derive the greatest benefit from the use of CRCT.

There are some published studies on the cost-effectiveness analysis of other PI3K inhibitor classes in NHL patients (20,34). Yu's study (20) reported idelalisib in combination with rituximab for the treatment of chronic lymphocytic leukemia was not cost-effective (ICER of \$242,884/QALY) from the perspective of US payers, and Gilead Sciences Pty Ltd.'s report (34) showed the cost-effectiveness of idelalisib compared with best supportive care was acceptable in the third-line treatment of relapsed indolent FL. However, the Pharmaceutical Benefits Advisory Committee (PBAC) still deferred its marketing application given its safety profile. This suggests copanlisib, which has a better safety profile and more indications (35), would only have to be priced down to an acceptable level to perhaps gain broader acceptance within the US healthcare system. In summary, this study may provide pharmaco-economic data for follow-up studies or policymakers and provide useful evidence for clinicians and patients to choose the best therapy.

There are some limitations in our model. Regarding data usage, due to the unavailability of raw data from clinical

trials, other similar studies were cited for both cost and utility values. In the future, we will update the study if raw data are disclosed and available. In addition, the clinical trial itself has drawbacks, due to the small sample size in the rare iNHL category, namely SLL and LPL-WM. In addition, since disutility values for hyperglycemia were not retrieved, it was assumed to be the same as hypertension, which may introduce some error. Finally, since our study is based on the US payer perspective, the applicability of our results in other countries and regions remains subject to further discussion.

## Conclusions

From a US payer perspective, copanlisib is not cost effective when combined with rituximab for relapsed iNHL at a WTP of \$150,000 unless the price of copanlisib is reduced to 36% of the original price.

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## Footnote

*Reporting Checklist:* The authors have completed the CHEERS reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1159/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-1159/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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