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Cost-utilities Analysis of Polatuzumab Vedotin Combined with Bendamustine and Rituximab for Relapsed/Refractory Diffuse Large B-cell Lymphoma Which Is Unsuited for Hematopoietic Stem Cell Transplantation

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Abstract: Objectives To evaluate the cost-utilities of Polatuzumab Vedotin (Polivy) combined with bendamustine and rituximab regimen (BR) for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) which is unsuited for hematopoietic stem cell transplantation. Methods From the perspective of the China 's health system, the cost-utilities analysis of BR regimen combined with Polatuzumab Vedotin (Polivy) and BR regimen alone for relapsed/refractory DLBCL which is unsuited for hematopoietic stem cell transplantation was analyzed by using partitioned survival model (PSM). Results Compared with BR regimen alone, BR regimen combined with Polatuzumab Vedotin (Polivy) for relapsed/refractory DLBCL which is unsuited for hematopoietic stem cell transplantation patients can increase 1.1706 QALYs in 15 years, the total cost is increased by 231 117.9 yuan, and the ICUR value is 197 434.7 yuan/QALY. The sensitivity analysis confirmed the robustness of the results. **Conclusion** In the long run, compared with BR alone, BR combined with Polatuzumab Vedotin (Polivy) doesn't have cost-effectiveness advantages for relapsed/refractory DLBCL which is unsuited for hematopoietic stem cell transplantation patients.

Keywords: Polatuzumab Vedotin (Polivy), Relapsed/Refractory diffuse large b-cell lymphoma, Pharmacoeconomic analysis.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 35 %-50 % of adult NHL in China[1]. After first-line treatment, about 30 %-40 % of DLBCL patients have relapsed or refractory (R / R), and 50 % of these R / R patients are not suitable for autologous hematopoietic stem cell transplantation (auto-HSCT) [2][3].Therefore, the prognosis of these patients is poor, and their quality of life and health are also greatly threatened. At present, there is no unified standard of care treatment for R / R DLBCL. The main commonly used treatments are rituximab combined with gemcitabine and oxaliplatin (R-GemOx), bendamustine combined with rituximab (BR) and anti-CD19 chimeric antigen receptor T-cell (CAR-T). The application of Polatuzumab Vedotin (trade name "Youluohua", pola) may provide a new clinical treatment option for patients. In January 2023, based on a multicenter phase II randomized controlled trial (GO29365)[4], the National Medical Products Administration (NMPA) approved the listing of Polatuzumab Vedotin ("Youluohua") in China, mainly for the treatment of diffuse large B-cell lymphoma. One of its approved indications is the combination of BR to treat R / R DLBCL patients who are not suitable for hematopoietic stem cell transplantation. This clinical trial showed that Polatuzumab Vedotin combined with BR can significantly improve the survival benefit of R / R DLBCL patients compared with BR alone. The median overall survival (OS) was extended from 4.7 months to 12.4 months, the median progression-free survival (PFS) was extended from 2 months to 7.5 months, and the objective response rate (ORR) was increased from 25 % to 62.5 %. In terms of safety, both groups exposed similar adverse reactions and the incidence of adverse event above grade 3 was similar[4]. Although the clinical effect of Polatuzumab Vedotin has been proved, there is no study in China to evaluate the economy of Polatuzumab Vedotin combined with BR regimen and BR regimen alone in the treatment of R / R DLBCL. Therefore, based on the cost environment in China, this study intends to analyze the cost-utility of Polatuzumab Vedotin combined with BR regimen (pola_BR) in the treatment of R / R DLBCL which is not suitable for hematopoietic stem cell transplantation from the perspective of medical and health system in China, so as to provide a basis for clinicians to use drugs rationally and provide reference for medical insurance and health-related policy formulation.

2. Material and Method

2.1. Material

This study uses the perspective of the China's health system, which is from the standpoint of health system decision makers, considering the consumption of health resources caused by intervention measure and control measure and the benefits to patients in the medical system. Therefore, costs only consider direct medical costs, excluding direct non-medical costs, indirect costs and hidden costs[5]. The target population was adult R / R DLBCL patients who were not suitable for hematopoietic stem cell transplantation in China. The economics of Polatuzumab Vedotin combined with BR regimen (pola_BR) and BR regimen alone were compared.

2.2. Method

2.2.1. Research Design

In this study, the partitioned survival model was used to simulate the proportion of patients in each cycle under different health states through the overall survival (OS) curve and progression free survival (PFS) survival curve of the study group and the control group, and the partitioned survival model was built by using Excel software. The quality-adjusted life years (QALYs) and treatment costs of Polatuzumab Vedotin combined with BR regimen and BR regimen alone were compared, and the incremental cost-utility ratio (ICUR) index was calculated. The sensitivity analysis of this study includes one-way sensitivity analysis and probability sensitivity analysis. The one-way sensitivity analysis reflects the influence of single uncertainty factor on the results through the tornado diagram. The specific parameters and variation range are shown in Table 2. Among them, for some parameters that cannot obtain the upper and lower limits, such as utility value, incidence of adverse events, etc., ± 20 % of the baseline value is taken as the upper and lower limits; probabilistic sensitivity analysis can simulate the comprehensive influence of the uncertainty of all parameters in the model on the results. It is assumed that the cost parameter in the model obeys the Gamma distribution, the utility value obeys the Beta distribution, and the fitting distribution parameters of the survival function are corrected by the Cholesky decomposition method[6]. And through Monte Carlo simulation, repeated sampling 1 000 times, the simulation results are presented as cost-utility scatter plot and cost-utility acceptable curve.

2.2.2. Model structure

The model includes three states: progression free survival (PFS), progression disease (PD) and death (D). In each cycle, the proportion of patients with PFS states was determined by the area under the PFS curve of the corresponding time, the proportion of patients with PD states was obtained by subtracting the area under the PFS curve from the area under the OS curve, and the proportion of patients with D states was obtained by subtracting the area under the OS curve from 1[7]. The model structure is shown in Fig.1. According to the follow-up period of the treatment plan, the course of treatment and other literature reports, the model cycle of this study was set to 3 weeks (21 days). The time horizon was 15 years to obtain the full impact of the intervention program on patient costs and health outcomes. The patients were in a progression-free state at the time of enrollment. In each cycle of simulation, the patients would exist in a certain state and receive related drug treatment. The treatment pathway and medication regimen of the two regimens were in accordance with the provisions of clinical trials[4]: Patients in the pola_BR group received an intravenous injection of pola once per cycle, each dose was administered at a dose of 1.8 mg / kg, and an intravenous injection of rituximab (R), each dose was administered at a dose of 375 mg / m2 and two intravenous injections of bendamustine (B), each dose was administered at a dose of 90 mg / m2, up to 6 cycles of treatment; the regimen and dose of B and R in the BR group were consistent with those in the pola_BR group, and the patients received up to 6 cycles of treatment. Both groups of patients stopped medication after progress during treatment and did not consider subsequent medication.

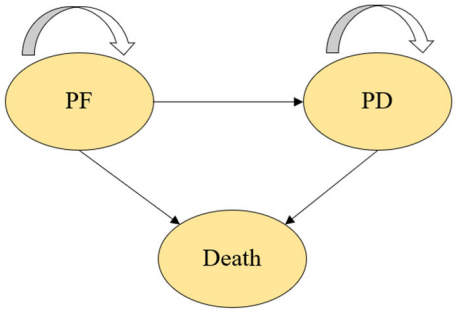

Figure 1. Model structure

2.2.3. Baseline demographic data

The population baseline data of the PSM model as shown in Table 1 includes median patient age, average height, average weight, and average body surface area. Among them, the median patient age was derived from the GO29365 clinical study, and the average height and weight data were derived from the "Chinese Residents Nutrition and Chronic Disease Status Report (2020)", 64.3 kg and 163.85 cm, respectively. The average body surface area was 1.67, which was calculated by the formula: average body surface area (m^2) = 0.0061 × height (cm) + 0.0128 × weight (kg) − 0.1529.

Table 1. Demographic data

Parameters	value
median patient age	67 years old
Average height	163.85cm
Average weight	64.3kg
Average body surface area	1.67m2

2.2.4. Survival analysis

Due to the limited follow-up time of GO29365 clinical research, the long-term efficacy of the target population is difficult to be reflected in the data of clinical trials, so this study will reasonably extrapolate the research results of GO29365. First, GetData Graph Digitizer 2.24 software was used to obtain the original survival data of the patients from the PFS curve and OS curve (Kaplan-Meier analysis, KM curve) of the intervention groups, and then the individual data was reconstructed by the two software packages "survHE" and "ggthemes" in R 4.2.1, and then the six parameter distributions of exponential , gamma , gompertz, weibull, loglogistic and lognormal were used for survival analysis and fitting of two groups of reconstructed individual patient level data[8]. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the optimal fitting distribution is selected, and the minimum AIC and BIC is the optimal fitting distribution.

2.2.5. Cost and utility

Since this study is from the perspective of China 's health system, only direct medical costs are considered, including drug costs, disease management costs, follow-up costs, and adverse event costs. GO29365 study did not publish utility data, so the health utility value of this study comes from the published literature, in which the utility value of PFS state is 0.83, and the utility value of PD state is 0.39[9]. The drug prices of bendamustine and rituximab were derived from the median, maximum and minimum bid prices of drugs in 2022 in the Yaozhi database (https://db.yaozh.com). Polatuzumab Vedotin has just been approved for listing in China at the beginning of this year. At present, there is no price in the database. Therefore, this study uses the approximate price

provided by some pharmacies (CNY 10,400 / 30mg) and converts it into a unit price, that is, CNY 346.67 / mg as the baseline price, and this price is taken as the maximum value of this parameter, and the minimum value is assumed to be 80 % of the baseline price. The drug cost per cycle of pola_BR group and BR group was calculated according to their price, medication regimen, average weight, and average body surface area, which were 52,521.43 yuan and 12,397.84 yuan respectively. The follow-up cost and disease management cost came from the median, maximum and minimum cost of each medical service item in the medical service price of 14 provinces and cities such as Beijing, Dongguan, Hangzhou, Qingdao, Hefei, Guangxi, Hainan and Ya 'an. The follow-up examination items, disease management items and frequency were set according to the GO29365 study. Considering that most of the adverse events below grade 3 do not require additional clinical intervention and data availability, this study only considers adverse events of grade 3 and above with an incidence rate greater than 5 %. According to the results of GO29365 study, the adverse events included in pola_BR group and BR group were mainly neutropenia, thrombocytopenia and anemia. The cost of adverse event treatment came from literature[10]. According to the recommendations of the "Chinese Pharmacoeconomic Evaluation Guide 2020[5]", the cost and utility of this study were discounted at an annual discount rate of 5 %, and 1 time of China 's gross domestic product (GDP, 85,698 yuan[11]) in 2022 was selected as the willingness-to-pay (WTP) threshold. The model parameters and distribution are shown in Table 2.

3. Result

3.1. Result of survival curve fitting

The fitting results of the six parameter distributions showed that the optimal fitting distribution of OS curve and PFS curve in the pola_BR group was Log-normal distribution, and the optimal fitting distribution of OS curve and PFS curve in the BR group was Log-logistic distribution, as shown in Table 3, Table 4, Figure 2 and Figure 3. In the pola_BR group, the median OS and PFS values of the survival curve reconstructed according to the optimal fitting distribution were 12.4 months and 7.38 months, respectively, which were basically consistent with the 12.4 months and 7.5 months in the clinical trial[4]. The median OS value and median PFS value of the survival curve reconstructed according to the optimal fitting distribution in the BR group were 4.76 months and 2 months, respectively, which were basically consistent with 4.7 months and 2 months in the clinical trial[4].

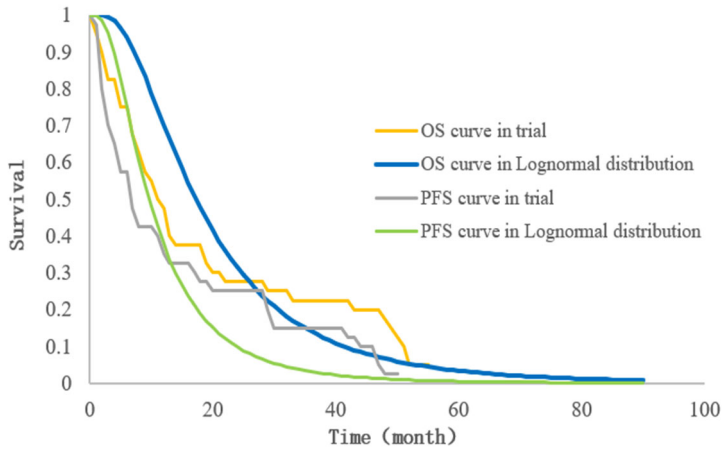

Figure 2. The survival curve of the trial and the fitted survival curve in pola_BR group

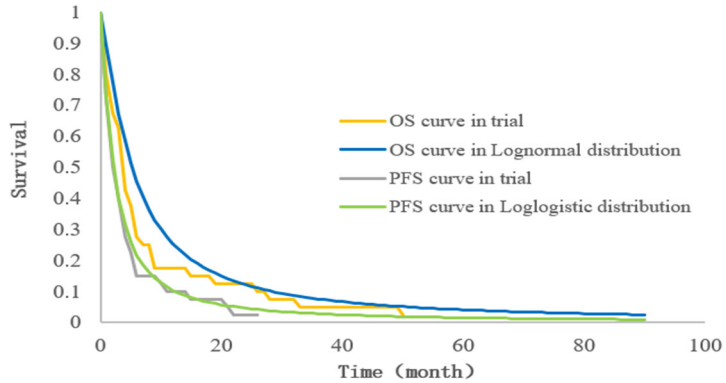

Figure 3. The survival curve of the trial and the fitted survival curve in BR group

3.2. Result of base case

The basic analysis results of the partitioned survival model in this study showed that the treatment cost of the pola_BR group was 274,027.18 yuan, and the quality-adjusted life years (QALYs) obtained was 1.73 in the 15-year simulation period. The treatment cost of the BR group was 42,909.27 yuan, the quality-adjusted life years (QALYs) obtained was 0.56, and the incremental cost-utility ratio (ICUR) calculated from this was 197,434.75 yuan / QALY. Then, under the premise of using 1 times China 's per capita GDP in 2022 (85,698 yuan) as the WTP threshold. The pola_BR group did not have a cost-utility advantage compared to the BR group.

3.3. Result of sensitivity analysis

The tornado diagram of one-way sensitivity analysis (Fig.4) showed that the parameters such as drug cost per cycle in pola_BR group, PFS state utility value, discount rate and drug cost per cycle in BR group had a great influence on the results of cost-utility analysis, but these parameters could not lead to the reversal of base case results. Other parameters, such as follow-up cost, disease management cost, incidence of adverse events and treatment cost, had little effect on ICUR. The cost-utility scatter plot (Figure 5) and the cost-utility acceptable curve (Figure 6) of the probabilistic sensitivity analysis showed that when the WTP is 1 times China 's per capita GDP in 2022, 85,698 yuan / QALY, the probability that the pola_BR group has a cost-utility advantage is 0 %.

Figure 4. Tornado diagram of one-way sensitivity analysis

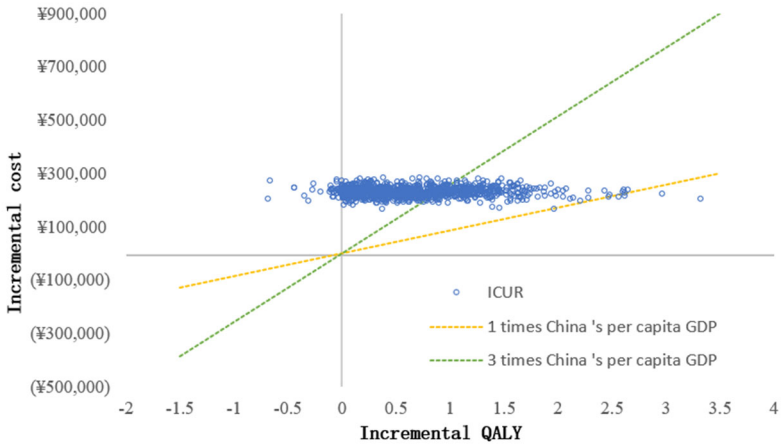

Figure 5. Cost-utility scatter plot

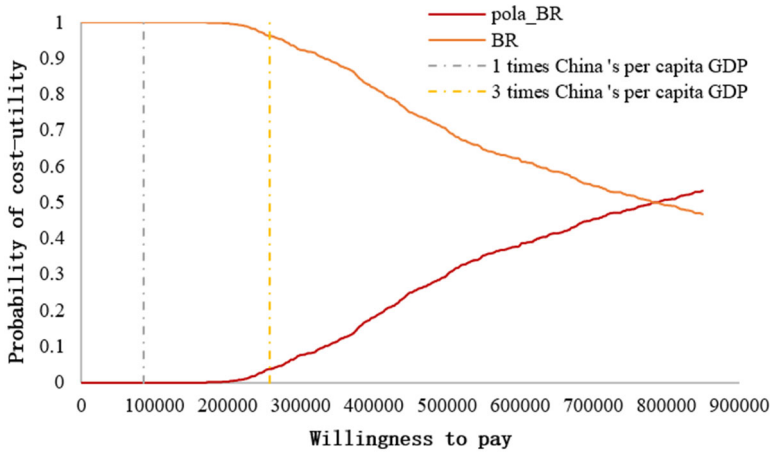

Figure 6. Cost-utility acceptable curve

4. Discussion

Although most of diffuse large B-cell lymphoma patients can be cured, some patients still have refractory or recurrent conditions after receiving first-line treatment, and about half of these patients may not respond to second-line rescue chemotherapy. The effect is not optimistic and is not suitable for the treatment of hematopoietic stem cell transplantation[2][3].Then, after receiving second-line rescue treatment failure, patients will be recommended to choose CAR-T for treatment[1], which may cause patients to face a greater economic burden. Therefore, for patients with R / R DLBCL, a treatment regimen that can significantly improve the survival benefit during rescue treatment is needed. As an antibody-conjugated drug, Polatuzumab Vedotin uses CD79b protein (almost only expresses on B cells) as a targeted antibody, accurately targets to B cells, and then releases drugs, which has a cytotoxic effect on malignant B cells and can inhibit the proliferation and differentiation of B cells to achieve therapeutic effects. Related clinical trials have shown that its efficacy in the treatment of diffuse large B-cell lymphoma is significantly improved compared with the control group[4],[12], and its safety is also within the tolerable range. Therefore, its emergence provides a new choice for clinical experts and patients. Nowadays, in China, medical insurance negotiation has become an important means of adjusting the national medical insurance catalogue, and pharmacoeconomic evaluation provides important evidence for medical insurance negotiation and pricing, which is particularly important in the process of medical insurance access[13]. Especially for exclusive patent innovative drugs with obvious benefits but high prices, it is more necessary to use the method of pharmacoeconomic evaluation to carry out value-based negotiation pricing. Therefore, from the perspective of China 's health system, this study constructed a partitioned survival model based on the international multi-center phase II clinical trial (GO29365) to evaluate the economy of Polatuzumab Vedotin combined with bendamustine and rituximab in R / R DLBCL treatment.

The results of base case showed that compared with the BR group, the incremental cost of patients in the pola_BR group was 231,117.90 yuan, the incremental quality-adjusted life years (QALYs) was 1.17, and the ICUR was 197,434.75 yuan / QALY. That is to say, patients in the pola_BR group need to pay 197,434.75 yuan more for each additional QALY than patients in the BR group, which is more than 1 time the per capita GDP of China in 2022, 85,698 yuan. It shows that it is not economical under this threshold. Since the results of the basic analysis calculated by the baseline price of Polatuzumab Vedotin shows that the study group is not economical under the threshold of 1 times per capita GDP, this study assumes that the maximum price of Polatuzumab Vedotin is the baseline price, while the minimum price is 20 % lower than the baseline price. The results of univariate sensitivity analysis showed that the drug cost of each cycle in pola_BR group, the utility value of PFS status, the discount rate and the cost of each cycle in BR group, had a greater impact on the results of the cost-utility analysis, while the incidence of adverse events, the cost of follow-up testing and other parameters had less impact on the results, and the results would not be reversed within the set parameter range. The results of probability sensitivity analysis show that when WTP is 1 times China 's per capita GDP in 2022, the probability that the pola_BR group has a cost-utility advantage is 0 %. When the WTP is 172,000 yuan / QALY, the possibility of cost-utility advantage in pola_BR group begins; under the threshold of 3 times per capita GDP, the probability of cost-utility advantage in pola_BR group is only 3.8 %; when the probability of cost-utility advantage in pola_BR group reached 50 %, the WTP reached 784,000.

This study also has some limitations: (1) The partitioned survival model depends on the complete report of the survival curve in clinical trials. In the currently published GO29365 study, the OS curve and PFS curve of the two groups of treatment regimens are not yet mature, which may affect the fitting of the survival curve. At the same time, the GO29365 study is a multi-center phase II clinical trial with a small number of patients (40 in each intervention group) and no subgroup analysis for the Asian population. The patient size and the difference in treatment effects between different ethnic groups may affect the results. (2) In this study, the cost of subsequent treatment was not included in the cost calculation, mainly because in reality, the subsequent treatment of patients may be different due to different individual characteristics, which is difficult to determine. In addition, due to the difficulty in obtaining data such as the cost of hematopoietic stem cell transplantation in China, the cost of follow-up after transplantation, the occurrence of infection, and the related treatment costs, this study did not consider the patients receive the hematopoietic stem cell transplantation which patients can be clinically cured after receiving rescue treatment and obtaining great effect , which may underestimate the potential benefits of Polatuzumab Vedotin in this study. Therefore, in the future, it is urgent to evaluate based on the mature subgroup survival analysis data of the Chinese population and explore the choice of subsequent treatment options for the above two groups of patients and the treatment costs before and after hematopoietic stem cell transplantation in the real world. In summary, based on China 's 1 times per capita GDP threshold and treatment environment of China, Polatuzumab Vedotin combined with BR regimen for R/R DLBCL unsuitable for hematopoietic stem cell transplantation has no economic advantage compared with BR regimen alone. At the same time, in the specific decision-making, it is necessary to pay attention to the influence of variables such as the price of Polatuzumab Vedotin, discount rate and PFS state utility value on the results.

Acknowledgment

This study has no found to support.

Table 2. Model parameters and distribution

Parameter	Base value	Minimum value	Maximum value	distribution
Polatuzumab Vedotin price	112.66	90.128	112.66	Gamma
Bendamustine price	398.8	360.3825	572	Gamma
Rituximab price	121,4	958.5667	229 4.44	Gamma
Pola_BR*_cycle drug cost	25,437.11	20,767.68	34 285.93	/
BR#_cycle drug cost	12 397.85	10 336.26	21 246.66	/
bed cost(unit)	33	1	69	Gamma
registration cost(unit)	3	0.5	15	Gamma
intravenous injection cost	9.4	3	15.6	Gamma
imaging detection cost	585.08	420	950	Gamma
blood biochemical test cost	157	89	246	Gamma
routine blood test cost	10.25	5	19	Gamma
routine urinalysis cost	4.33	1	9	Gamma
treatment cost of neutropenia	777.1189	341.3126	2 389.388	Gamma
treatment cost of thrombocytopenia	10 176.07	8 281.855	11 831.21	Gamma
treatment cost of anemia	937.5912	712.7429	1 069.148	Gamma
Utility of PFS	0.83	0.664	0.996	Beta
Utility of PD	0.39	0.312	0.468	Beta
Pola_BR*_incidence of neutropenia	0.325	0.26	0.39	Beta
Pola_BR*_incidence of thrombocytopenia	0.205	0.164	0.246	Beta
Pola_BR*_incidence of anemia	0.126	0.1008	0.1512	Beta
BR#_incidence of neutropenia	0.333	0.2664	0.3996	Beta
BR#_incidence of thrombocytopenia	0.231	0.1848	0.2772	Beta
BR#_incidence of anemia	0.179	0.1432	0.2148	Beta
Discount ratio	**5%**	**0**	**8%**	**Constant**

***: Polatuzumab Vedotin combined with bendamustine and rituximab; #: bendamustine and rituximab**

Table 3. The value and distribution of efficacy

Parameters	Base value	Minimum value	Maximum value	distribution
meanlogPola_BROS	2.849383	2.340376	3.35839	Lognormal
sdlogPola_BROS	1.470204	1.094152	1.975501	Lognormal
lambdaBROS	5.20063	3.337346	8.104212	Log-logistic
gammaBROS	1.296436	0.959249	1.752146	Log-logistic
meanlogPola_BRPFS	2.268081	1.802605	2.733557	Lognormal
sdlogPola_BRPFS	1.420292	1.091311	1.848446	Lognormal
lambdaBRPFS	2.171925	1.423644	3.31351	Log-logistic
gammaBRPFS	1.268828	0.968311	1.662612	Log-logistic

Table4. The AIC and BIC value of survival curve fitting

	KM curve	Exponential	Gamma	Gompertz	Weibull	Loglogistic	Lognormal
AIC	**pola_BROS**	**222.47**	**223.58**	**217.52**	**222.68**	**218.24**	**217.13**
	pola_BRPFS	**239.09**	**239.20**	**232.15**	**237.67**	**231.71**	**230.28**
	BROS	**200.50**	**200.68**	**192.46**	**198.89**	**191.85**	**192.60**
	BRPFS	**191.59**	**190.65**	**183.26**	**188.46**	**182.54**	**182.85**
BIC	**pola_BROS**	**224.16**	**226.96**	**220.90**	**226.06**	**221.62**	**220.51**
	pola_BRPFS	**240.78**	**242.58**	**235.52**	**241.05**	**235.09**	**233.65**
	BROS	**202.19**	**204.06**	**195.84**	**202.27**	**195.23**	**195.98**
	BRPFS	**193.28**	**194.03**	**186.64**	**191.84**	**185.91**	**186.23**

Note : AIC : Akaike Information Criterion ; BIC : Bayesian information criterion ; pola _ BROS : the overall survival curve of the Polatuzumab Vedotin combined with bendamustine and rituximab group ; pola _ BRPFS : progression-free survival curve of the Polatuzumab Vedotin combined with bendamustine and rituximab group ; BROS : overall survival curve of bendamustine and rituximab group ; BRPFS : progression-free survival curve of bendamustine and rituximab group

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