Supplementary appendix 1 The selection of survival models

The digitized KM plots of ramucirumab-erlotinib and placebo-erlotinib were fitted with four commonly used parametric survival models, including Weibull, exponential, log-logistic and log-normal distributions. Then, based on statistical goodness-of-fit test [Bayesian information criterion (BIC) and Akaike's information criterion (AIC)], visual fit and clinical rationality, we chose the optimal fit for our model

OS Fit

As for the OS Kaplan-Meier curves of ramucirumab-erlotinib and placebo-erlotinib , the visual fits of four parametric survival models were showed in Figure1-1,1-2, and the statistical fits [Bayesian information criterion (BIC) and Akaike's information criterion (AIC)] were displayed in Table1-1. The visual fits of the OS curves showed that these four distributions had a similar fit. Among these four distributions, based on the statistic fits, the exponential distribution may be appropriate for OS as it provided the lowest AIC and BIC . Therefore, the exponential distribution was applied in our analysis.

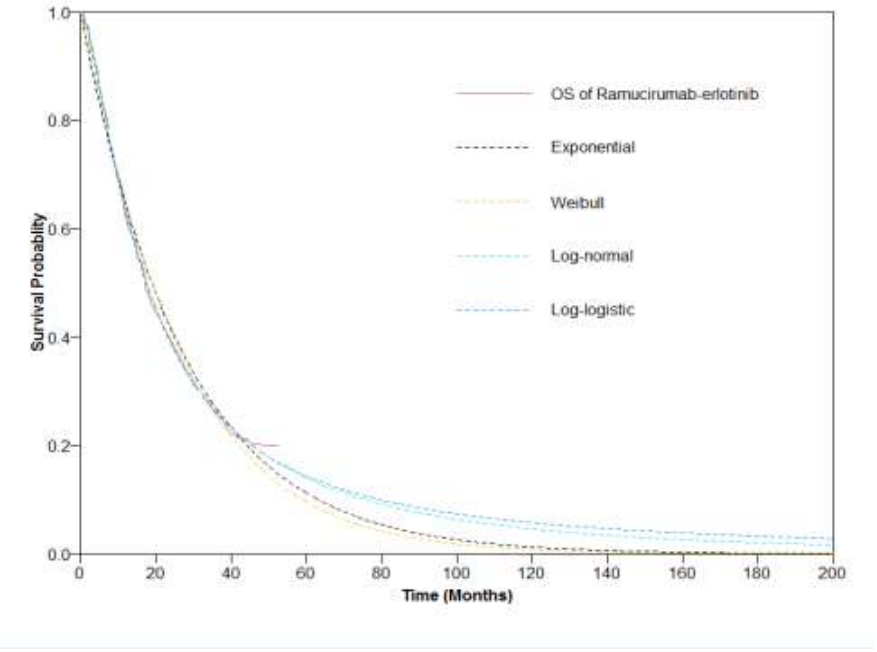

Figure 1-1 Ramucirumab-erlotinib OS fitted and extrapolation

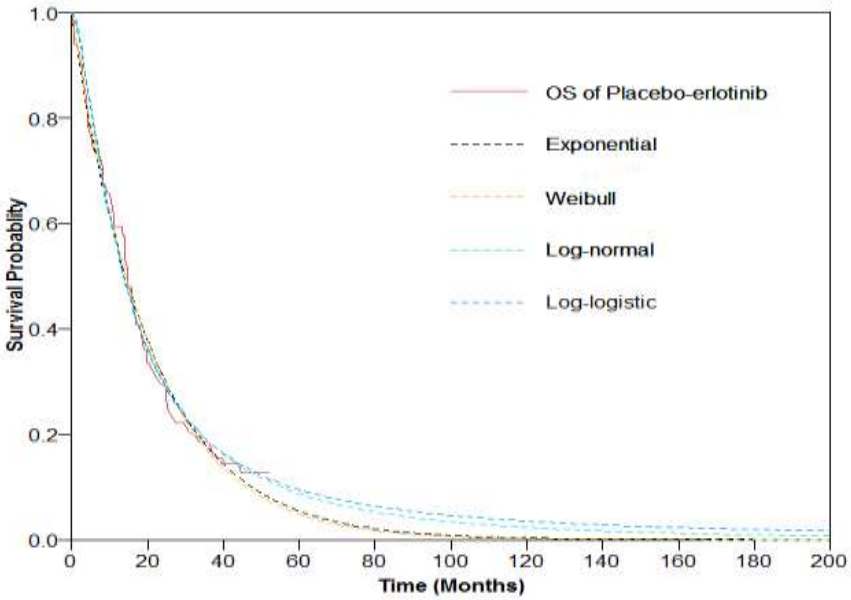

Figure 1-2 placebo-erlotinib OS fitted and extrapolation

Table 1-1 Parametric survival distributions fitted for OS data

Parametric Model	Ramucirumab-erlotinib		Placebo-erlotinib	
	AIC	BIC	AIC	BIC
Exponential	-1189.4673	-1182.3769	-852.1392	-845.3339
Weibull	-599.5989	-590.9278	-471.8127	-463.7113
Log-normal	-893.3327	-884.6616	-435.6913	-427.5898
Log-logistic	-218.6475	-208.0120	-450.9015	-442.8001

PFS Fit

As for the PFS Kaplan-Meier curves of ramucirumab-erlotinib and placebo-erlotinib, the visual fits of four parametric survival models were showed in Figure1-3,1-4, and the statistical fits [Bayesian information criterion (BIC) and Akaike's information criterion (AIC)] were displayed in Table1-2. Based on the statistic goodness-of-fit tests, for ramucirumab-erlotinib arm, the exponential distribution had the lowest BIC and AIC, while for placebo-erlotinib arm, the log-logistic distribution had the lowest BIC and AIC. However, the visual fits of the PFS curves for placebo-erlotinib showed that log-logistic distribution produced the highest extended tail which meant PFS of placebo-erlotinib would be overestimated in long term. Meanwhile, the AIC and BIC of exponential distribution was slightly higher than that of log-normal distribution. Considering that the distribution used for fit both arm should be as consistent as possible. Therefore, exponential distribution was chosen for PFS for both arms.

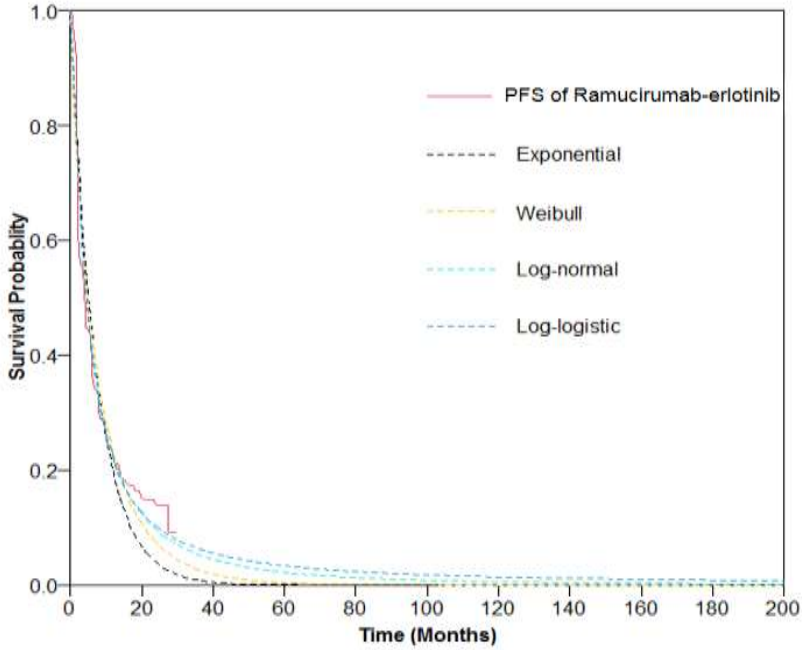

Figure 1-3 Ramucirumab-erlotinib PFS fitted and extrapolation

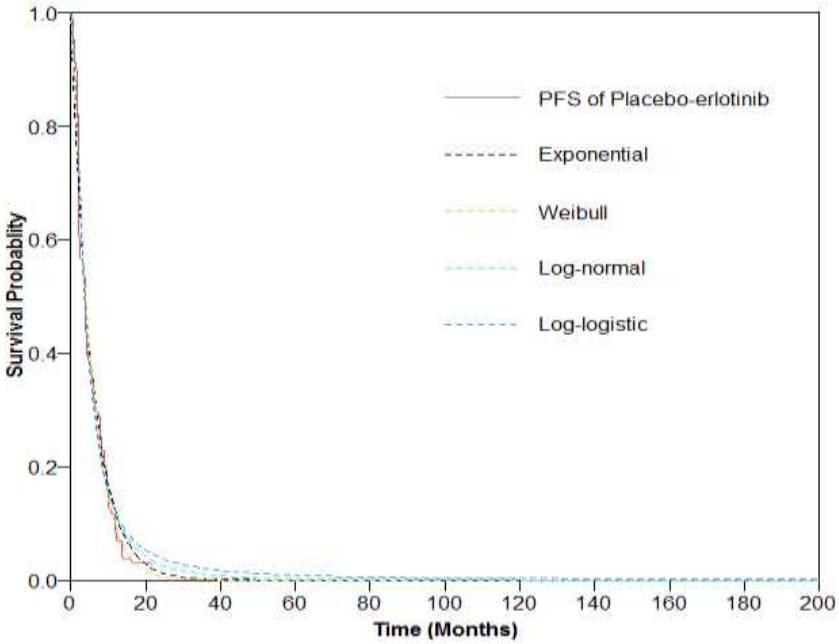

Figure 1-4 Placebo-erlotinib PFS fitted and extrapolation

Table 1-2 Parametric survival distributions fitted for PFS data

Parametric Model	Ramucirumab-erlotinib		Placebo-erlotinib	
	AIC	BIC	AIC	BIC
Exponential	-709.3980	-701.7226	-1329.2980	-1320.9713
Weibull	-407.1952	-397.9324	-571.1492	-561.8496
Log-normal	-502.6582	-493.3954	-608.2321	-598.9325
Log-logistic	-507.3551	-498.0923	-1569.6438	-1557.1539

Supplementary appendix 2 The total costs of ramucirumab and erlotinib for each strategy

According to the protocol of phase III RELAY trial, patients randomly received either intravenous ramucirumab (10mg/kg per 2 weeks) and oral erlotinib (150mg/day), or placebo and erlotinib. Before the next ramucirumab and placebo administration, the patient's biochemical markers and physical status (bone marrow reserve, bilirubin level and whether recovered from adverse events (AEs) were used to guide dose adjustments. Ramucirumab and erlotinib could be delay for a few days (0 to 42 days) to recoved from AEs, and dose reduction of ramucirumab and erlotinib were allowed if a dose reduction criterion was met. Per protocol, all administration had to be stopped for Response Evaluation Criteria In Solid Tumors (RECIST) progression, or unacceptable toxicity or withdrawal of consent, non-compliance, or investigator decision. Therefore, in order to improve estimates accuracy of our model, the total costs of ramucirumab and erlotinib for each strategy were adjusted according to the median relative dose intensity reported in RELA**Y** trial. Adjusted dose of ramucirumab and erlotinib for each strategy in Markov model were list in Table 2.

Table 2 Adjusted dose and adjusted duration of therapy cycle in Markov model

	Ramucirumab-Erlotinib		Placebo-Erlotinib	
	Ramucirumab	Erlotinib	Placebo	Erlotinib
In RELAY trial				
Median relative dose intensity, %	94.9	92.3	97.7	96.3
In Markov model				
Mean relative dose per cycle, mg	617	1938	/	2022

Supplementary appendix 3 The base case results based on whether National Reimbursement Drug List (NRDL) negotiation was available for erlotinib and ramucirumab

The unit cost of erlotinib was estimated based on the average retail price in China. In order to find a reasonable price of erlotinib in the base-case analysis, we weighted the latest retail price of erlotinib

from different manufacturers and specifications by their market shares to obtain the average retail prices. Then, using the average retail prices, we calculated the unit cost of erlotinib according to clinical usage and dosage in phase III RELAY trial. When the National Reimbursement Drug List (NRDL) negotiation became unavailable for erlotinib, the unit cost of erlotinib without discount ($385.3) was used in this analysis. The model shows that the ramucirumab plus erlotinib strategy provided an additional 4.21 QALYs with incremental $195,237 costs, compared with placebo plus erlotinib strategy, which yielded an ICERs of $46,336 per QALY. The results suggest that the NRDL negotiation for erlotinib price has little influence on our primary analyses results.

When the National Reimbursement Drug List (NRDL) negotiation became available for ramucirumab, the unit cost of ramucirumab with56.7% discount ($43.5) was used in this analysis. The model shows that the ramucirumab plus erlotinib strategy provided an additional 4.21 QALYs with incremental $195,237 costs, compared with placebo plus erlotinib strategy, which yielded an ICERs of $28,841 per QALY. The ICERs was far below the willingness-to-pay (WTP) threshold value set for general regions ($30,363/QALY) and affluent regions($70,353/QALY) in the current analysis. The results suggest that negotiating ramucirumab might be an effective way to make ramucirumab less costly and more widely used in China. Base-case results of different erlotinib and ramucirumab prices were listed in Table 3.

Table 3 Base case results based on whether NRDL negotiation was available for erlotinib and ramucirumab

Item	**NRDL negotiation available for ramucirumab**			**NRDLnegotiation unavailable for erlotinib**		
	Ramucirumab-erlotinib	**Placebo-erlotinib**	**Difference**	**Ramucirumab-erlotinib**	**Placebo-erlotinib**	**Difference**
Mean QALYs						
PFS state	2.32	0.63	1.69	2.32	0.63	1.69
PS state	2.90	0.38	2.52	2.90	0.38	2.52
Total	5.22	1.01	4.21	5.22	1.01	4.21
Cost ($)						
PFS state	213,577	2,930	210,647	498,146	8,033	490,113
PS state	74,962	10,429	64,533	74,962	10,429	64,533
Dead state	474	826	-352	474	826	-352

Total	289,013	14,185	274,828	573,582	19,288	554,294
ICER ($)			65,227			131,554

PFS: progression-free survival, PS: progression survival; ICER, incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

Supplementary appendix 4 The results of the probabilistic sensitivity analyses

The probabilistic sensitivity analyses (PSA) were carried by varying all parameters simultaneously, except for specific parameters such as ramucirumab cost (10mg/kg per unit) and erlotinib cost (2100 mg per unit), etc, therefore, to test the influence of uncertainty in the model parameters on the ICERs.

Table 4 The results of the probabilistic sensitivity analyses

Parameter	**Variable range**	**ICER for Ramucirumab-erlotinib vs Placebo-erlotinib**	
		Low value	**High value**
Costs ($)			
Ramucirumab(10mg/kg per unit)	43.5 to 100.5	65226.85	128302.29
Erlotinib(2100 mg per unit)	115.6 to 385.3	128302.29	131554.68
Routine follow-up per unit	27.8 to 46.3	128179.30	128424.75
Subsequent therapy per unit	462.0 to 648.9	127029.19	129497.47
Best supportive care per unit	105.8 to 529.1	124094.94	139035.99
Terminal phase per unit	1527.9 to 1977.7	128291.51	128312.98
Hypertension per event	11.6 to 14.2	128302.03	128302.55
Diarrhea per event	4.14 to 6.22	128302.24	128302.34
Risk for SAEs			
Diarrhea in ramucirumab arm	0.058 to 0.086	128213.85	128385.95
Diarrhea in placebo arm	0.1 to 0.16	128060.34	128159.21
Hypertension in ramucirumab arm	0.188 to 0.282	128125.48	128477.39
Hypertension in placebo arm	0.042 to 0.064	128291.07	128314.22
Rash in ramucirumab arm	0.0070 to 0.011	128284.95	128318.80
Rash in placebo arm	0.018 to 0.026	128293.83	128311.76
Vomiting in ramucirumab arm	0.0070 to 0.011	128280.39	128323.14
Vomtiong in placebo arm	0.0030 to 0.0050	128300.72	128306.38

Fatigue in ramucirumab arm	0.011 to 0.017	128288.76	128323.52
Neutropenia in ramucirumab arm	0.022 to 0.032	128213.38	128386.16
Neutropenia in placebo arm	0.0070 to 0.011	128292.63	128310.93
Health utility values			
PFS state	0.652 to 0.978	122801.27	134319.28
PS state	0.257 to 0.385	114621.00	145692.29
PFS plus diarrhea	0.597 to 0.895	127394.86	129222.74
PFS plus hypertension	0.618 to 0.928	125320.08	131429.90
PFS plus rash	0.576 to 0.846	128266.81	128342.87
PFS plus nausea/vomiting	0.556 to 0.834	128204.91	128399.83
PFS plus fatigue	0.6 to 0.9	128124.41	128480.67
PFS plus neutropenia	0.497 to 0.745	128029.05	128576.71
Discount rate(%)	0.0 to 0.08	108160.85	159964.08
Patient weight(kg)	52.0 to 78.0	106064.97	150539.62