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Cost-Effectiveness Analysis of Atezolizumab plus Pemetrexed and Platinum in First-Line Treatment of Non-Squamous Non-Small Cell Lung Cancer in China

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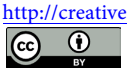

Abstract

Objective: To evaluate the cost-effectiveness of atezolizumab plus pemetrexed and platinum-based (APP) in the first-line treatment of non-squamous non-small cell lung cancer (NSCLC). Methods: A partitioned survival model (PSM) was constructed based on the IMpower132 clinical trial. Total cost, quality-adjusted life years (QALY), and incremental cost-effectiveness ratio (ICER) were the main outputs of the model. Deterministic sensitivity analysis and probabilistic sensitivity analysis were adopted to test the uncertainty of the parameters. Results: The results of the base-case analysis illustrated that compared with PP, the incremental cost of APP was CNY 591040.94, the incremental utility was 0.46 QALY, and the ICER was CNY 1291414.83/QALY. Deterministic sensitivity analysis results illustrated that atezolizumab and other parameters have a greater impact on ICER. Probabilistic sensitivity analysis results show that no matter how each parameter changes, under the willingness to pay threshold of 3-times Chinese per capita GDP, the probability of APP has cost-effectiveness is 0. Conclusion: From the perspective of the Chinese health system, APP is not cost-effective for first-line treatment of non-squamous non-small cell lung cancer without sensitizing EGFR or ALK genetic alterations.

Keywords

Atezolizumab, Non-Small Cell Lung Cancer, Partitioned Survival Model, Cost-Effectiveness Analysis

1. Introduction

Lung cancer is cancer with the highest mortality rate, which can be divided into

small cell lung cancer and non-small cell lung cancer [1]. The non-small cell lung cancer (NSCLC) accounts for up to 85%, and more than half of NSCLC patients have non-squamous histology [2]. The current first-line treatment options for non-squamous non-small cell lung cancer without sensitizing EGFR or ALK genetic alterations include immune checkpoint inhibitors plus pemetrexed and platinum-based chemotherapy. PD-1 inhibitors can effectively improve patients' progression-free survival (PFS) and overall survival (OS) [3] [4].

In China, atezolizumab plus pemetrexed and platinum-based chemotherapy are approved for first-line treatment of non-squamous NSCLC without sensitizing EGFR or ALK genetic alterations in June 2021. According to the IMpower132 clinical trial, APP demonstrated a significant improvement in PFS compared to PP (median = 7.6 vs. 5.2). However, the OS of the two arms was not statistically significant (median = 17.5 vs. 13.6) [5]. The results of PFS and OS were better in the APP than in the PP group.

Compared with the Markov model, the partitioned survival model can directly obtain the number of survivors in each state from the survival curve, avoiding unnecessary model assumptions such as natural mortality, and is closer to the actual survival data, so PSM has been increasingly used in the pharmacoeconomic evaluation of cancer treatment regimens [6]. The cost-effectiveness of first-line treatment of non-squamous NSCLC without sensitizing EGFR or ALK genetic alterations between the APP and PP was compared from the perspective of the Chinese health system.

2. Materials and Methods

2.1. Target Population

The inclusion and exclusion criteria of the target population were derived from the IMpower132 clinical trial [5]. Inclusion Criteria: adults older than or equal to 18 years of age, histologically or cytologically confirmed stage IV non-squamous non-small cell lung cancer; with the measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [7]; Eastern Cooperative Oncology Group performance status of 0 or 1; no previous treatment for metastatic disease. Exclusion criteria: central nervous system metastasis, autoimmune disease, tumors harboring sensitizing mutations in EGFR gene or ALK genetic alterations or received previous immunotherapy.

2.2. Treatment Options

According to the IMpower132 clinical trial, permuted-block randomization with a block size of four was used to allocate patients in a one-to-one ratio to the APP and PP before the start of the clinical trial. APP (292 patients): atezolizumab 1200 mg + carboplatin (AUC = 6) or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2, once every three weeks for four cycles, followed by atezolizumab 1200 mg + pemetrexed 500 mg/m^2. PP (286 patients): carboplatin (AUC = 6) or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2, once every three weeks for four

cycles, followed by continuous treatment with pemetrexed 500 mg/m^2.

2.3. Model Structure

A partitioned survival model was constructed, and it was divided into three mutually exclusive health states (Figure 1): progression-free survival, progressed disease, and death. At the beginning of the simulation, all patients were in PFS state. After a cycle, patients could remain in PFS state or transition to PD or die, while patients in PD could only maintain PD or die [8]. The cycle is 3 weeks. The simulation until 99% of patients died. According to the "China Pharmacoeconomic Evaluation Guidelines 2020" [9], a discount rate of 5% is used and the willing-to-pay threshold (WTP) is three times Chinese per capita GDP in 2021 (CNY 242,928).

2.4. Survival Analysis

The population distribution of each state during the follow-up period can be obtained directly from the OS curve and PFS curve. After the follow-up period is exceeded, the survival function needs to be calculated by the parametric method. First, use GetData2.20 software to take points from the KM curves of the two treatment regimens, and then use R4.0.4 to reconstruct individual data based on the method of Guyot *et al.* [10]. After fitting, the median progression-free survival and median overall survival in the APP were 7.8 months and 17.7 months respectively (median PFS and median OS of clinical trials were 7.6 and 17.5 months), and the PP had a median PFS and median OS were 5.3 and 13.8 months respectively (median PFS and median OS of clinical trials were 5.2 and 13.6 months), the gap was within 0.2 months, and the reproducibility was good. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) combined with visual inspection were used to select the best fitting distribution. The distributions selected for fitting include exponential, gamma, Weibull, log-logistic and lognormal. According to the lowest values of AIC and BIC shown (Table 1), lognormal distribution was selected for the PFS curves of the APP and PP, and Weibull distribution was selected for the OS curves. The parameters are shown in Table 2, and the fitted curves are shown in Figure 2 and Figure 3.

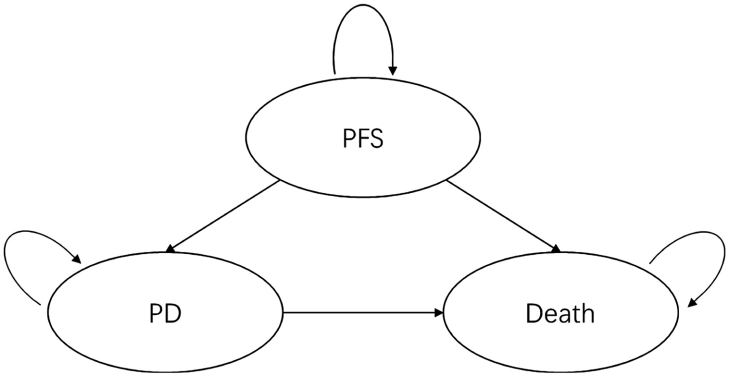

Figure 1. Partitioned survival model health state transitions.

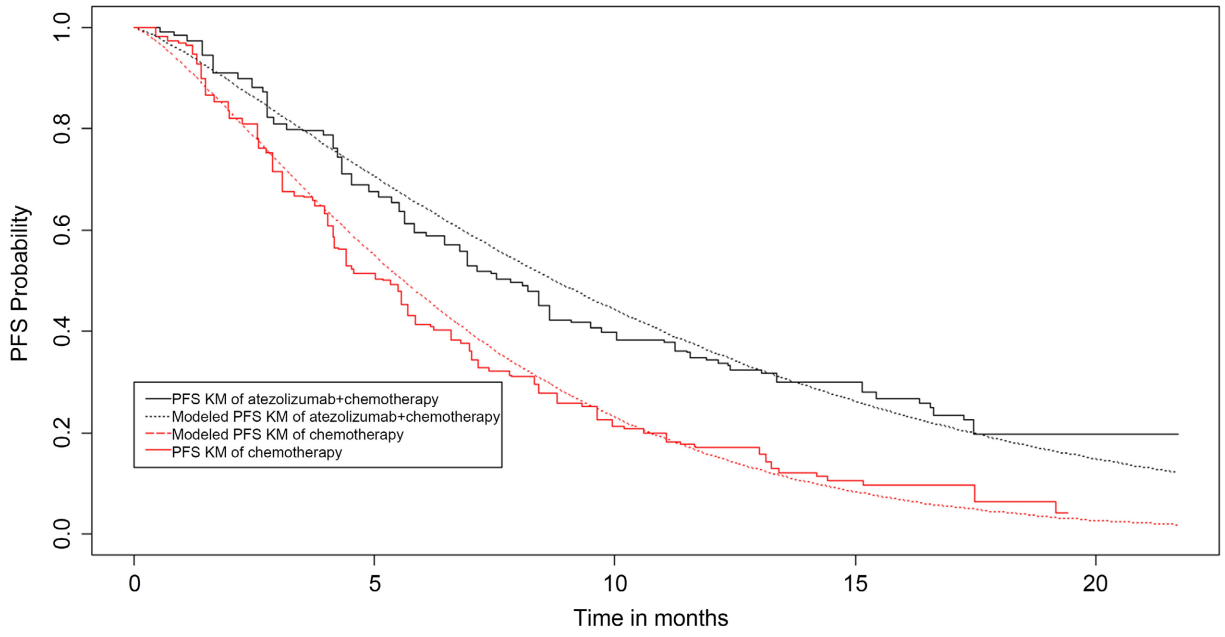

Figure 2. Kaplan-Meier survival curves for progression-free survival.

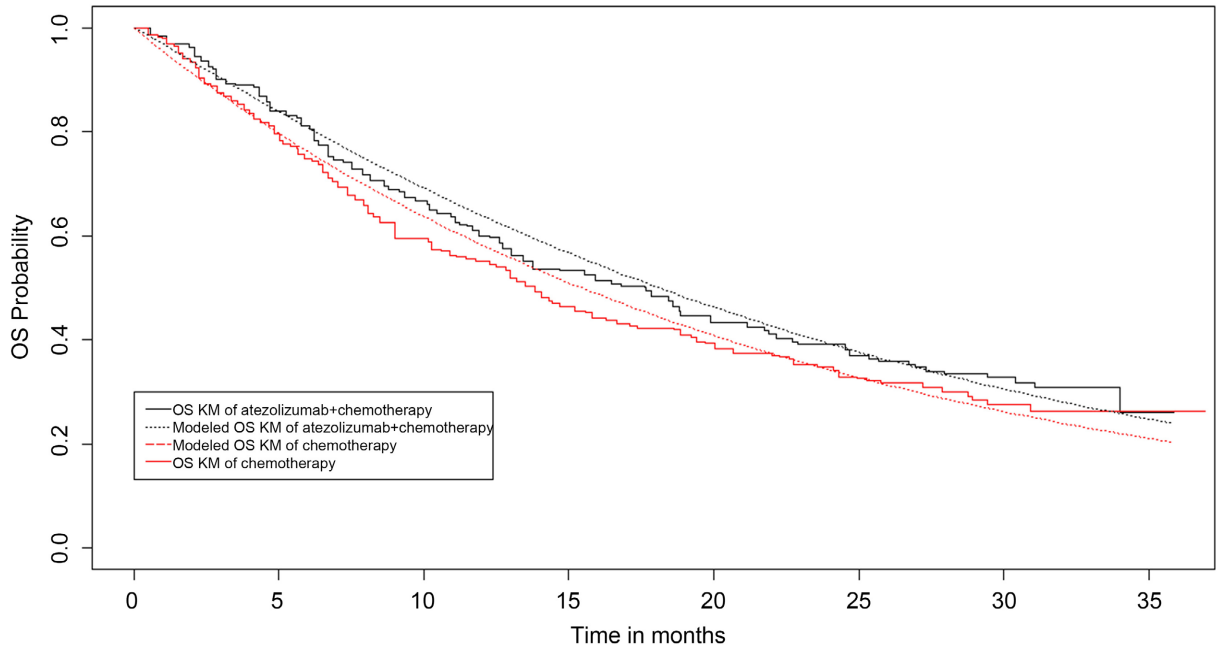

Figure 3. Kaplan-Meier survival curves for overall survival.

Table 1. AIC and BIC of distributions.

AIC/BIC	exponential	gamma	weibull	loglogistic	lognormal
APP-PFS	1471.455/1475.131	1475.116/1464.469	1462.229/1469.582	1444.581/1451.934	1441.049/1448.402
APP-OS	1634.626/1638.302	1634.776/1642.130	1626.037/1633.391	1627.144/1634.498	1635.774/1643.128
PP-PFS	1479.837/1483.493	1451.8561459.168	1458.856/1466.168	1445.236/1452.548	1442.066/1449.378
PP-OS	1619.648/1623.304	1621.497/1628.809	1605.186/1612.498	1608.767/1616.079	1621.613/1628.924

Table 2. Parameters of distributions.

	distributions	parameters
APP-PFS	lognormal	meanlog = 2.0793, sdlog = 1.0230
APP-OS	weibull	$\gamma = 1.06018$, $\lambda = 0.03217$
PP-PFS	lognormal	meanlog = 1.6063, sdlog = 0.9094
PP-OS	weibull	$\gamma = 0.98865$, $\lambda = 0.04634$

2.5. Cost and Utility

2.5.1. Cost

This study was conducted from the perspective of the Chinese health system and only considered direct medical costs. Drug prices are derived from Yaozhi.com (https://www.yaozh.com/). Disease management costs are mainly derived from published literature [11] [12] (**Table 3**). The body surface area of this study was calculated as 1.72 m^2, and the average body weight was 65 kg [13].

2.5.2. Utility

The utility parameters of PFS state and PD state were 0.804 and 0.321, which were based on NSCLC patient populations in China [14] (**Table 4**). In addition, since white patients accounted for 68.5% of the IMpower132 clinical trial, the utility value data of the British population was used for scenario analysis, and the PFS state and PD state utility values were 0.653 and 0.473, respectively [15].

2.5.3. Management Cost of Adverse Events

The IMpower132 clinical trial only reported AEs of Special Interest, so this study used the incidence of adverse events in the Japanese population in the IMpower132 clinical trial by Makoto Nishio *et al.* [16]. Adverse events of Grade 3+ with an incidence of more than 5%, including neutrophil count decreased, anemia, platelet count decreased, and white blood cell count decreased, were included (**Table 5**).

2.6. Subsequent Treatment

According to the "Oncology Society of Chinese Medical Association guideline for clinical diagnosis and treatment of lung cancer (2021 edition)" [18], patients in the APP were treated with docetaxel, and patients in the PP were treated with tislelizumab in subsequent treatment.

2.7. Sensitivity Analysis

One-way deterministic sensitivity analysis (DSA) was performed to evaluate the impact of parameter changes (**Tables 3-5**). The analysis results are presented in the form of a tornado diagram. Through 1000 Monte Carlo simulations, the parameters were subjected to probabilistic sensitivity analysis (PSA), with Beta distribution for utility value and Gamma distribution for cost. And the results of PSA analysis are presented in the form of cost-effectiveness acceptability curves (CEAC).

Table 3. Cost data.

	Unit price (CNY)	Specification	Dosage	DSA	PSA	Remark
Cost of Drugs						
Atezolizumab	32,800	1200 mg	1200 mg/three weeks	±25%	GAMMA	
Pemetrexed	1733.54	500 mg	500 mg/m^2/three weeks	±25%	GAMMA	
Carboplatin	30.35	50 mg	AUC = 6	±25%	GAMMA	
Cisplatin	76	50 mg	75 mg/m^2/three weeks	±25%	GAMMA	
Docetaxel	910	20 mg	75 mg/m^2/three weeks	±25%	GAMMA	
Tislelizumab	2180	100 mg	200 mg/three weeks	±25%	GAMMA	
Cost of Disease Management						
Outpatient clinic	25		every three weeks	±25%	GAMMA	[10]
Blood routine	18		every three weeks	±25%	GAMMA	[11]
Urine routine	26.5		every three weeks	±25%	GAMMA	[11]
Blood chemistry	70		every three weeks	±25%	GAMMA	[11]
Tumor assessment	185		Every 6 weeks for the first 48 weeks, then every 9 weeks	±25%	GAMMA	[11]

Table 4. Utility data.

	utility	DSA	PSA
PFS	0.804	0.536 - 0.840	BETA
PD	0.321	0.031 - 0.473	BETA
death	0		

Table 5. Parameters of adverse events.

	Incidence		Cost data (CNY)	Management mode	DSA	PSA	Remark
	APP	PP					
Neutrophil count decreased	22.9%	19.2%	3080	thiopefilgrastim 6 mg, 1080/6mg * 1	±25%	GAMMA	Jiangsu Hengrui Pharmaceutical
White blood cell count decreased	14.6%	9.6%	3080	thiopefilgrastim 6 mg, 1080/6mg * 1	±25%	GAMMA	Jiangsu Hengrui Pharmaceutical
Anemia	6.3%	13.5%	420	red blood cell suspension 2U, 210/1U	±25%	GAMMA	[17]
Platelet count decreased	8.3%	7.7%	1820	Recombinant Human Interleukin-11,130/1.5mg/day, 14d of treament	±25%	GAMMA	Qilu Pharmaceutical

3. Result

3.1. Base-Case Analysis

The Base-Case analysis results (Table 6) illustrate that compared with PP, the incremental cost of the APP is CNY 597,040.94, the incremental effect is 0.46 QALY, and the ICER is CNY 1,296,414.83/QALY, which is much higher than 3-times Chinese per capita GDP. Therefore, it can be considered that the atezolizumab plus chemotherapy in first-line non-squamous NSCLC is not cost-effective.

3.2. Scenario Analysis

In scenario analysis (Table 7), the ICER is CNY 2,055,935.04/QALY, which is still higher than 3-times Chinese per capita GDP, indicating that the APP is not cost-effective, which is consistent with the base-case results.

3.3. Deterministic Sensitivity Analyses

The results of deterministic sensitivity analysis illustrated that the highest impact on ICER was the price of atezolizumab, the utility value of PD and PFS status, and the discount rate (Figure 4). Even though the reduction in the price of atezolizumab reduces the ICER value to CNY 974,607.54/QALY, it is still higher than 3-times Chinese per capita GDP, so the APP is not cost-effective, which is consistent with the base-case results.

Table 6. The results of base-case analysis.

Treatment Arms	Costs (CNY)	Utility (QALY)
APP	731764.16	1.84
pp	131723.22	1.38
incremental	591040.94	0.46
	ICER	1291414.83

Table 7. The results of scenario analysis.

Treatment Arms	Costs (CNY)	Utility (QALY)
APP	731764.16	1.80
pp	131723.22	1.51
incremental	591040.94	0.29
	ICER	1051935.04

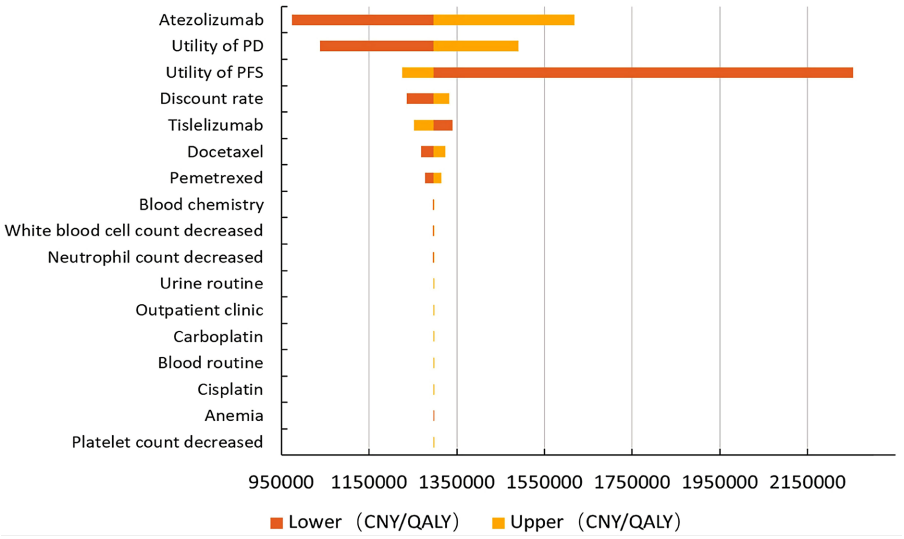

Figure 4. Tornado diagram.

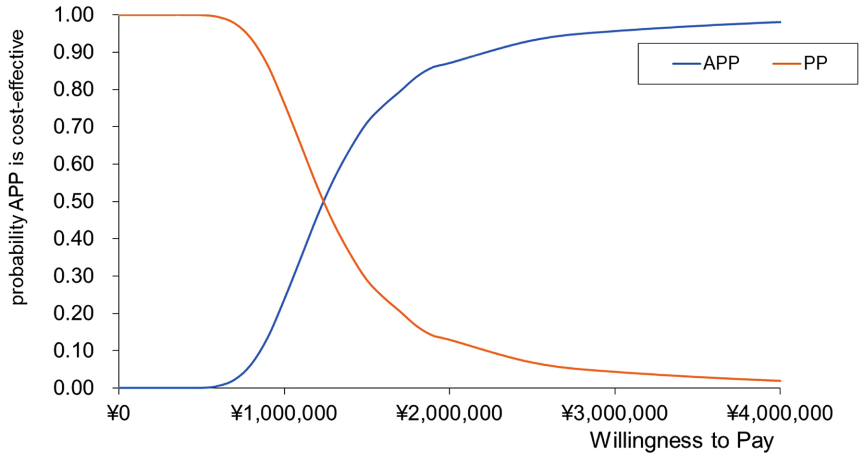

Figure 5. Cost-effectiveness acceptability curve.

3.4. Probabilistic Sensitivity Analysis

As the willingness to pay threshold increases, the probability that the APP is more cost-effective also increases (**Figure 5**). When the willingness to pay threshold is CNY 242,928, which is 3-times Chinese per capita GDP, the probability of the APP being cost-effective is 0. When the willingness to pay threshold is increased to CNY 1,200,000, the probability of the APP being cost-effective is close to 50%. In addition, the results of 1000 Monte Carlo simulations show that the average ICER value is CNY 1286191.31/QALY, indicating that the base-case analysis results are robust.

4. Discussion

Immunotherapy exhibits increasing importance in cancer treatment, but its high cost and financial burden to patients should also be considered when making medical treatment decisions. The results of the study illustrated APP can benefit NSCLC patients by 0.46 QALY, but at the same time, the cost will increase by CNY 597040.94, and the incremental cost-effectiveness is CNY 1296414.83/QALY. The ICER is much higher than 3-times the Chinese per capita GDP. Therefore, the APP is not economical.

With the development of medical insurance negotiations in China, immune checkpoint inhibitors such as camrelizumab and tislelizumab have been included in the medical insurance lists, and the price has been greatly reduced, bringing QALY benefits to patients and reducing the economic burden. Imported drugs have also launched drug donation programs, and the price competition of PD-1 inhibitors has become increasingly fierce. Atezolizumab has also launched a 2 + 3 drug donation. According to this drug donation, the cost of the APP is reduced to CNY 379077.77, and the ICER is reduced to CNY 524077.33/QALY. Although it is still higher than 3-times Chinese per capita GDP, it has reduced a lot of economic burdens compared to not donating medicines.

This study also has certain limitations: First, the patient population of IMpower132 is based on the world, with whites accounting for 68.5% and Asians

accounting for 23.5%, and the utility value and cost data used in this study are all from China. However, the deterministic sensitivity results show that no matter how the value of each parameter changes, ICER is always higher than 3-times Chinese per capita GDP, and the APP is not economical. Second, because the IMpower132 clinical trial did not report the incidence of all-cause adverse events, the incidence of adverse events based on the Japanese population of IMpower132 was employed, which would also cause a certain bias in the research results. Finally, this study made certain assumptions in the Subsequent treatment according to clinical guidelines, which is different from the real-world data. However, the results of deterministic sensitivity analysis and probabilistic sensitivity analysis conducted in this study further corroborate the base-case analysis results: the APP is not cost-effectiveness.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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