Camrelizumab in patients with advanced non-squamous non-small cell lung cancer: a cost-effective analysis in China

Qian Xie,1 Hanrui Zheng,2 Na Su,2 Qiu Li3


ABSTRACT

Objective Camrelizumab is a selective, humanised, high-affinity IgG4 kappa monoclonal antibody against programmed cell death 1 that shows effective antitumour activity with acceptable toxicity in multiple tumour types. The CameL trial demonstrated that camrelizumab plus chemotherapy (CC) significantly prolonged the median progression-free survival and median overall survival versus chemotherapy alone (CA) in patients with advanced non-squamous non-small cell lung cancer (NSCLC). Our study was conducted to investigate the cost-effectiveness of the two strategies in chemotherapy-naive patients with advanced non-squamous NSCLC.

Design, setting and participants A Markov simulation model was generated based on the CameL trial. The two simulated treatments included CC and CA.

Primary and secondary outcome measures Utility was derived from published literature, and costs were calculated based on those at our hospital in Chengdu, China. Incremental cost-effectiveness ratios (ICERs) were calculated to compare the cost-effectiveness of the two treatment arms.

Results In the overall population, the total costs were $27223.40 and $13740.10 for CC and CA treatment, respectively. The CC treatment produced 1.37 quality-adjusted life years (QALYs), and the CA treatment produced 1.17 QALYs. Hence, patients who were in the CC group spent an additional $13483.30 and generated an increase of 0.20 QALYs, resulting in an ICER of $67416.50 per QALY.

Conclusions For chemotherapy-naive patients with advanced non-squamous NSCLC, CC is not considered a cost-effective treatment versus CA in China when considering a willingness-to-pay threshold of $31 500 per QALY.

Trial registration number NCT03134872

INTRODUCTION

Lung cancer has become one of the leading causes of cancer-related death worldwide and is the most commonly diagnosed cancer in Chinese males.1 2 The most common type of lung cancer is non-small cell lung cancer (NSCLC). More than 30% of patients with NSCLC have locally advanced disease at the time of diagnosis, with a 5-year survival rate of 18%.3 4 The standard of care for patients with advanced NSCLC is mainly platinum-based doublet chemotherapy.5 The treatment paradigm of advanced NSCLC has been changed by immune checkpoint inhibitors (ICIs) in recent years. For example, ipilimumab, a fully human anti-cytotoxic T lymphocyte antigen 4 antibody, and nivolumab, a fully human anti-programmed cell death 1 (PD-1) antibody, are ICIs that result in improved efficacy in patients with NSCLC with few adverse events (AEs).5 6 A significant overall survival (OS) benefit was observed with nivolumab plus ipilimumab compared with chemotherapy as first-line treatment in patients with NSCLC.7 Pembrolizumab, as a first-line monotherapy, improves OS and progression-free survival (PFS) in patients with untreated metastatic NSCLC with programmed death ligand 1 (PD-L1) expression.8

Camrelizumab is a selective, humanised, high-affinity IgG4 kappa monoclonal antibody against PD-1 that shows a great tumour response with acceptable toxicity in multiple tumour types.9 As the outcomes presented in the CameL trial, camrelizumab plus chemotherapy (CC) treatment has shown a clinically significant improvement in PFS versus
chemotherapy alone (CA) treatment in all patients with advanced non-squamous NSCLC without sensitive epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations. \(^{10, 11}\) Camrelizumab successfully entered the Chinese medical insurance catalogue at the end of 2020, and the price was reduced from $3065.02/200 mg to $453.25/200 mg, a decrease of 85\%. Patients can make reimbursement for the drugs included in the medical insurance catalogue in China. Therefore, it is valuable to conduct this study from the perspective of payers in low/middle-income countries with lower willingness-to-pay (WTP) thresholds.

**METHODS**

**Clinical outcomes**

Clinical results were extracted from the CameL trial. \(^{11}\) A total of 412 chemotherapy-naive patients who had histologically confirmed advanced non-squamous NSCLC without sensitive EGFR and ALK alterations were randomly allocated at a 1:1 ratio to the CC group (205) and the CA group (207). Patients in the CC group received intravenous camrelizumab (200 mg) plus carboplatin (area under the curve (AUC), 5 mg/mL per min) and pemetrexed (500 mg/m\(^2\)) on day 1 every 3 weeks, followed by maintenance therapy with camrelizumab plus pemetrexed. Patients in the CA group received intravenous carboplatin (AUC 5 mg/mL per min) and pemetrexed (500 mg/m\(^2\)) on day 1 every 3 weeks, followed by maintenance therapy with pemetrexed alone. The median duration of treatment was 34.1 weeks in the CC group and 19.7 weeks in the CA group. For the first 54 weeks, CT scans were conducted every 6 weeks. Laboratory examinations were performed every 3 weeks. In the overall population, both PFS and OS were significantly prolonged in the CC group compared with the CA group (PFS, 11.3 months vs 8.3 months, \(p=0.0001\); OS, 27.9 months vs 20.5 months).

**Model structure**

A Markov model was conducted in TreeAge Pro software V.2020 (TreeAge Software, Williamstown, Massachusetts, USA) to simulate the disease process, which included three states: PFS, progressive disease (PD) and death. Patients with advanced non-squamous NSCLC were assumed to be in the PFS state until the disease progressed, and then they could either enter the PD state or the death state; however, patients in the PD state could either remain in the same state or enter the death state (figure 1). GetData Graph Digitizer software was used to extract the survival curves from the published CameL trial. Pseudo-individual patient data were generated using the algorithm derived by Hoyle and Henley to minimise the difference between the trial data and our modelled data. The Weibull distributions provided the best fit to the recreated survival data (figure 2). \(^{12}\) Based on the fitted curve, we can estimate the time-dependency transition probability in each cycle using the following formula: \(P(t \rightarrow t+1) = 1 - \exp[\lambda(t) - \lambda(t+1)]\gamma\), where \(t\) equals the current cycle number in the Markov model. \(^{12}\) The cycle length was 1 month, and this model defined the time horizon as 10 years. Health outcomes were measured by quality-adjusted life years (QALYs). We assumed that patients in the two groups received docetaxel after PD based on clinical guidelines. \(^{13}\)

**Costs and utility**

In this analysis, we considered only direct costs, including hospitalisation, costs for drugs, radiology and laboratory tests and treatments for all grades of AEs. The prices of all the drugs were based on the price at our hospital in

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**Figure 1** A Markov structure was built to compare two treatment strategies. PD, progressive disease; PFS, progression-free survival.

**Figure 2** The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial. Weibull distributions were fitted to the two groups. CA, chemotherapy alone; CC, camrelizumab plus chemotherapy; OS, overall survival; PFS, progression-free survival.
Chengdu, China. We assumed a mean body surface area and a body weight of 1.64 m² and 65 kg, respectively. All costs were measured in US dollars based on the exchange rate on 27 December 2020 (US$1=¥6.46). Health utility scores were 0.81, 0.58 and 0 in the PFS state, PD state and death state, respectively. The annual discount rate of 3% was calculated (table 1).

### Sensitivity analysis

One-way probabilistic sensitivity analysis was performed to examine the impact of input factors on the model. Key parameters were used within a range of ±20% to explore their impacts on the incremental cost-effectiveness ratios (ICERs). Treatments were considered cost-effective if the ICER was lower than the WTP threshold. According to the WHO recommendations for cost-effectiveness analysis, the threshold of $31 500 per QALY was defined as three-fold the gross domestic product per capita of China. In addition, probabilistic sensitivity analysis was performed using Monte Carlo simulation, which included 1000 iterations to further address the uncertainty of all the input parameters.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### RESULTS

#### Baseline analysis

In the overall population, the total costs were $27 223.40 and $13 740.10 for CC and CA treatment, respectively. The CC treatment produced 1.37 QALYs, and the CA treatment produced 1.17 QALYs. Hence, patients who were in the CC group spent an additional $13 483.30 and generated an increase of 0.20 QALYs, resulting in an ICER of $67 416.50 per QALY (table 2).

### Sensitivity analyses

The results of the one-way sensitivity analysis are displayed in tornado diagrams (figure 3). The utility of PFS was the most sensitive parameter influencing the results. The second sensitive parameter was the cost of pemetrexed in the CC group, which ranged from $805.35 to $1 208.02, with ICER ranging from $54 115.08 to $84 422.81 per QALY. Changing other parameters, including the cost of camrelizumab, may result in different results but has little impact on the ICER. Thus, considering the current WTP threshold of $31 500, the acceptable curve shows that CC is not cost-effective for chemotherapy-naive patients with advanced non-squamous NSCLC in China (figure 4). All of the scatter points are located above the WTP threshold, implying the same results (figure 5).

### DISCUSSION

The domestic ICI camrelizumab has shown promising tumour response in multiple tumour types with manageable toxicities. In the CameL trial, the incidence of treatment-related AEs of any grade was higher in the CC group than in the CA group. The treatment duration of pemetrexed was longer in the CC group due to longer duration of maintenance therapy, which indicates a better tumour response. Due to the substantial decline in prices...
of camrelizumab, our research was valuable for assessing a cost-effective strategy for chemotherapy-naive patients with advanced non-squamous NSCLC from a Chinese payer perspective.

The combination therapy in the CC group provided incremental benefits at high incremental costs per QALY in our analysis. The probabilistic sensitivity analyses indicated that CC treatment would be cost-effective at a WTP threshold higher than $67,416.50 per QALY, which is nearly twice the current WTP threshold in China. We conducted the subgroup analysis in the PD-L1-positive population. Patients who were in the CC group spent an additional $20,914.18 and generated an increase of 0.29 QALYs, resulting in an ICER of $72,117.86 per QALY, which was also above the WTP threshold. The higher ICERs in the PD-L1-positive population may be associated with increased healthcare costs due to improved PFS that required more expensive treatment.

Several cost-effectiveness studies of other ICIs demonstrated that pembrolizumab monotherapy was cost-effective compared with chemotherapy both in the USA and France; however, it was not cost-effective in the UK or China as the first-line treatment in patients with advanced NSCLC.22–27 For patients with advanced NSCLC, atezolizumab plus bevacizumab and chemotherapy were not cost-effective;8 on the other hand, nivolumab plus ipilimumab was demonstrated to be cost-effective compared with chemotherapy from the US payer perspective.29

Although we conducted our study in China, the results may provide some enlightenment to other countries. The price of domestic pemetrexed was applied in our study and was demonstrated to be the second most sensitive parameter. However, this parameter was not sufficient to change the economic outcomes according to the sensitivity analysis. Recently, the price of imported pemetrexed (ALIMTA) in China has decreased, which is almost the same as that of domestic pemetrexed. Additionally, the chemotherapy drug price will vary due to different body surface areas; however, the sensitivity analysis shows that it has little impact on the ICER. The ICER in our study was far below the WTP value of $150,000 in the USA.30 Due to the much higher WTP threshold, we assumed that the CC treatment is quite possible to be cost-effective in some developed countries. The healthcare system in China was predominantly government funded, which would make it more likely to negotiate lower drug prices with pharmaceutical companies. If the price of pemetrexed will decrease in the future, it may make CC treatment cost-effective in China. Therefore, our analysis is conducive to the rational allocation of health resources, which is crucial to developing countries with relatively limited health resources.

However, there were limitations to our analysis. First, our model was based on a clinical trial, which may not be completely appropriate for real-world patients. The dose of chemotherapy drugs was calculated based on the average body surface in Chinese individuals, which varies in different individuals. Second, the reconstructed survival curves cannot be completely fitted with the actual survival curves due to the inevitable bias when capturing the survival probabilities at each time point through the Plot Digitizer, which will lead to the loss of the corresponding information of the simulated curves. However, the purpose of adjusting the transition probability is to approach the real results to the greatest extent. Although there are some limitations in applying survival analysis to the calculation of Markov model parameters for pharmacoeconomic evaluation, it is still one of the effective and feasible methods to reasonably solve the problem of time dependence of transfer probability in dynamic Markov models, especially the pharmacoeconomic evaluation of cancer. Third, given the lack of utility data in the CameL trial, the utilities of PFS and PD were derived from published literature. Fourth, the regimen of second-line treatment was not mentioned in the CameL trial, so we assumed that all patients accepted docetaxel after PD as recommended in the National Comprehensive Cancer Network (NCCN), which may differ from actual treatment.13 Additionally, reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common immune-related dermatological toxicity of camrelizumab.
CONCLUSIONS

In conclusion, from the Chinese payers’ perspective, CC is not a cost-effective therapy compared with CA in chemotherapy-naive patients with advanced non-squamous NSCLC without sensitive EGFR and ALK alterations at the current WTP of $31 500 per QALY.

Contributors QX wrote the main manuscript text and prepared the two tables and HZ prepared figures 1–5. QL and NS designed the study. QL was in charge of planning, conducting and reporting of the work described in the article and is the guarantor. All authors reviewed the manuscript.

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ORCID iD Qiu Li http://orcid.org/0000-0003-0380-113X

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