BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061592
Article Type:	Original research
Date Submitted by the Author:	10-Feb-2022
Complete List of Authors:	Xie, Qian; Sichuan University West China Hospital Zheng, Hanrui; West China Hospital of Medicine Su, Na; Sichuan University West China Hospital, Pharmacy Li, Qiu; Sichuan University West China Hospital
Keywords:	HEALTH ECONOMICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory tract tumours < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors information

Qian Xie[a], Hanrui Zheng[bc], Na Su[bc*], Qiu Li[d*]

[a] International Medical Center/Ward of General Practice, West China Hospital, Sichuan University, Chengdu, China

[b]Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China

[C]West China School of Pharmacy, Sichuan University, Chengdu, China

[d]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China

∗Correspondence to:

Na Su, Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China West China School of Pharmacy, Sichuan University, Chengdu, China (e-mail: zoya159@163.com)

Qiu Li, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China (e-mail: keythera@126.com, fbqiu9@163.com)

Abstract

Objective Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against programmed cell death 1 (PD-1) that shows effective antitumor activity with acceptable toxicity in multiple tumor types. The CameL trial demonstrated that camrelizumab plus chemotherapy significantly prolonged the median progression-free survival (PFS) and median overall survival (OS) versus chemotherapy alone in patients with advanced non-squamous non-small-cell lung cancer (NSCLC). Because of a rapid cancer burden increase in China, 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 camrelizumab plus chemotherapy (CC) and chemotherapy alone (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 The total costs were $64,874.51 and $13,531.38 for CC and CA treatment, respectively. The CC treatment produced 1.19 quality-adjusted life years (QALYs), and the CA treatment produced 0.96 QALYs. Hence, patients who were in the CC group spent an additional $51,343.44 and generated an increase of 0.23 QALYs, resulting in an ICER of $223,232.35 per QALY. Currently, in China, CC treatment is not cost-effective when considering a willingness-to-pay (WTP) threshold of $28,130 per QALY gained.

Conclusions For chemotherapy-naive patients with advanced non-squamous NSCLC, camrelizumab plus chemotherapy is not considered a cost-effective therapy versus chemotherapy alone in China.

Keywords Cost-effective analysis camrelizumab chemotherapy programmed cell death 1 non-small-cell lung cancer

Strengths and limitations of this study

Given the lack of cost-effectiveness studies on 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. To our knowledge, this is the first study to examine the cost-effectiveness of camrelizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-squamous NSCLC all over the world. However, there were limitations to our analysis. 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. Given the lack of utility data in the CameL trial, the utilities of PFS and PD were derived from published literature, which were demonstrated to indeed affect the results.

Introduction

Lung cancer has become one of the most common cancers, the leading cause of cancer-related death worldwide and 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[3]. 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 (CTLA-

4) antibody, and nivolumab, a fully human anti-programmed cell death 1 (PD-1) antibody, are ICIs that result in few adverse events and improved efficacy in patients with NSCLC[5,6]. The significant overall survival (OS) benefit was observed with nivolumab plus ipilimumab comparing with chemotherapy as first-line treatment in patients with NSCLC[7]. Pembrolizumab, as first-line monotherapy, improves OS and progression-free survival (PFS) in patients with untreated metastatic NSCLC with a programmed death ligand 1 (PD-L1) expressing [8].

Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against PD-1 that shows great tumor response with acceptable toxicity in multiple tumor types[9].

As the outcomes from the CameL trial presented, camrelizumab plus chemotherapy (CC) treatment showing a clinically meaningful and statistically significant improvement in PFS versus chemotherapy alone (CA) in all patients with advanced non-squamous NSCLC without sensitive epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations[10,11]. In practice, given the high price of camrelizumab, whether camrelizumab plus chemotherapy is a cost-effective option in China is unknown. Because of a rapid cancer burden increase in China nowadays, our study was valuable to investigate the cost-effectiveness of CC versus CA in chemotherapy-naive patients with advanced non-squamous NSCLC.

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 and every 12 weeks thereafter. Laboratory examinations were performed every 3 weeks and every month during treatment and 90 days after treatment, respectively. Among the 412 patients, both

PFS and OS were significantly prolonged in the CC group comparing with the CA group (PFS, 11.3 months vs 8.3 months, p=.0001; OS, 27.9 months vs. 20.5 months).

Model structure

A Markov model was used to assess the cost and effectiveness associated with the two treatments from the Chinese payer perspective. The disease process included 3 states: PFS, progressive disease (PD) and death. Patients with advanced non-squamous NSCLC were assumed to be in the PFS state until progression, 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 curve from published OS and PFS curve from the published CameL trial. Pseudo-individual patient data were generated using the algorithm derived by Hoyle et al, while Weibull distributions were fitted to both groups (Figure 2A and 2B). Based on the fitted curve, we can estimate the time- dependency transition probability in each cycle as the following formula: $P(t \rightarrow t+1)=1-\exp[\lambda(t)\gamma - \lambda(t+1)\gamma)]$, where t equals the current cycle number in 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) and were programmed in TreeAge Pro software version 2019 (TreeAge Software LLC, Williamstown, Massachusetts). We assumed that patients in the 2 groups received docetaxel after PD based on clinical guidelines[13].

Costs and utility

In this analysis, we considered only direct costs, including hospitalization, 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 in our hospital in Chengdu, China. We assumed a mean body surface area and a body weight of 1.64 m^2 and 65 kg, respectively[14]. All costs were measured in US dollars (USD) based on the exchange rate on Dec. 27, 2020 (1 USD = 6.46 CHY). Health utility scores were 0.65, 0.47 and 0 in the PFS state, PD state and death state, respectively[15]. The annual discount rate of 3% was calculated (Table 1).

Table 1. Clinical efficacy, baseline input costs and baseline transition probability base on the CameL trial

Parameters	CC group	CA group
Costs per month $		
Camrelizumab	3065.17(3678.20-2452.14)	-
Chemotherapy	1006.68(1208.02-805.35)	805.63(966.76-644.51

Hospitalization	25.81(30.97-20.65)	15.22(18.26-12.18)
Result	CC group	CA group
Cost ($)	64,874.51	13,531.38
Incremental costs	51,343.44	
Effectiveness (†QALYs)	1.19	0.96
Incremental effectiveness	0.23	
†AEs	58.19(69.83-46.55)	63.22(75.87-50.58)
Tests	201.95(242.34-161.56)	166.98(200.37-133.58)
Cost of PFS	4357.80(5229.36-3486.24)	1051.05(1261.26-840.84)
Cost of PD	183.68(220.42-146.95)	249.92(299.91-199.94)
utility		
‡PFS	0.65	0.65
§PD	0.47	0.47
Discount rate, %	3	

†AEs, adverse events; ‡PFS, progression-free survival; §PD, progressive disease

Sensitivity analysis

One-way probabilistic sensitivity analyses were 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 ICERs were lower than the willingness-to-pay (WTP) threshold. According to the WHO recommendations for cost-effectiveness analysis, the threshold of $28,130 per QALY was defined as 3-fold the gross domestic product (GDP) per capita of China[16]. In addition, probabilistic sensitivity analysis was performed using Monte Carlo simulation, which included 1,000 iterations to further address the uncertainty of all the input parameters.

Results

Baseline analysis

The total costs were $64,874.51 and $13,531.38 for CC and CA treatment, respectively. The CC treatment produced 1.19 quality-adjusted life years (QALYs), and the CA treatment produced 0.96 QALYs. Hence, patients who were in the CC group spent an additional $51,343.44 and generated an increase of 0.23 QALYs, resulting in an ICER of $223,232.35 per QALY (Table 2).

Table 2. Results of base-case analysis of CC and CA group

‡ICER ($/QALY)	223,232.35

†QALY, quality-adjusted life year; ‡ICER, Incremental cost-effectiveness ratio.

Sensitivity analyses

The results of the one-way sensitivity analysis are displayed in tornado diagrams (Figure 3). The utility of PD was the most sensitive parameter influencing the results. The second sensitive parameter was the cost of camrelizumab, which ranged from $2,452.14 to $3,678.17 with ICERs ranging from $190,107.80 to $270,060.62 per QALY, which was well above the WTP threshold. Changing other parameters may somehow result in different results but has little impact on the ICER. Thus, considering the current WTP threshold of $28,130, the acceptable curve shows camrelizumab plus chemotherapy 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 clinical benefit from ICIs therapy demonstrated in clinical trials caused great excitement in both oncologists and patients. However, the wide use of these agents results in a rapid increase in health resource consumption, which is of concern to both the health system and patients. 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 110,000 per QALY, which is well above the current WTP threshold in China.

Some cost-effectiveness studies investigated other ICIs, such as pembrolizumab, nivolumab and ipilimumab, as the first-line treatment in advanced NSCLC patients. These studies demonstrated that pembrolizumab monotherapy was more cost-effective than chemotherapy in the US and France; however, it was not cost-effective in the United Kingdom and China[17-22]. For patients with advanced NSCLC, atezolizumab plus bevacizumab and chemotherapy was not a cost-effective option [23], by the other hand, nivolumab plus ipilimumab were demonstrated to be a more cost-effective option than chemotherapy from the US payer perspective [24].

Despite the high price of camrelizumab in China, it still shows promising tumor response in multiple tumor types with manageable toxicities[25-29]. 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 a longer duration of maintenance therapy, which indicates a better tumor response. The median OS in the CC group was estimated to be 27.9 months (95% CI, 21.9−not reached), and the

results might be even more encouraging because only 45% of deaths occurred around the time that the median endpoint was reached. Thus, there is a high likelihood that we may have underestimated the effectiveness of CC treatment.

Given the lack of cost-effectiveness studies on 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. To our knowledge, this is the first study to examine the cost-effectiveness of camrelizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-squamous NSCLC all over the world.

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, given the lack of utility data in the CameL trial, the utilities of PFS and PD were derived from published literature, which were demonstrated to indeed affect the results. Additionally, the regimen of second-line treatment was not mentioned in the CameL trial, so we assumed that patients accepted docetaxel after PD, which was recommended in the NCCN[13]. Reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common immune-related dermatologic toxicity of camrelizumab according to the CameL trial, however, the cost of treating RCCEP was excluded from our study because its effects are mild, reversible, and predictable[29].

Conclusions

In conclusion, from the Chinese payers perspective, camrelizumab plus chemotherapy is not a cost-effective therapy comparing with chemotherapy alone in chemotherapy-naive patients with advanced non-squamous NSCLC at current WTP of $28,130 per QALY.

Declarations

Patient and Public Involvement No patient involved

Authors 'Contributions

Qian Xie wrote the main manuscript text and prepared 2 tables and Hanrui Zheng prepared figures 1-5. Qiu Li and Na Su designed the study. All authors reviewed the manuscript.

Ethical approval Ethical approval is not required for the study

Conflicts of interest The authors have indicated that they have no conflicts of interest.

Acknowledgments None reported.

Funding This study was not supported by any Funds

Availability of data and material The data that supports the findings of this study are presented in this article

Code availability Not applicable

Consent to participate All the authors are consent to participate in the study

Consent for publication All the authors are consent for this article publication

Acknowledgments None reported

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 (6):394-424. doi:10.3322/caac.21492

2. Feng RM, Zong YN, Cao SM, Xu RH (2019) Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 39 (1):22. doi:10.1186/s40880-019-0368-6

3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim Y-C, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M (2017) Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine 377 (20):1919-1929. doi:10.1056/NEJMoa1709937

4. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28 (13):2181-

2190. doi:10.1200/jco.2009.26.2543

5. Paz-Ares L, Brahmer J, Hellmann MD, Reck M, O'Byrne K, Borghaei H, Geese WJ, Lu H, Nathan FE, Ramalingam S (2017) CheckMate 227: a randomized, open-label phase 3 trial of nivolumab nivolumab plus ipilimumab, or nivolumab plus chemotherapy versus chemotherapy in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC). Annals of oncology 28

6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New england journal of medicine 375 (19):1823-1833

7. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, Sakai H, Albert I, Vergnenegre A, Peters S, Syrigos K, Barlesi F, Reck M, Borghaei H, Brahmer JR, O'Byrne KJ, Geese WJ, Bhagavatheeswaran P, Rabindran SK, Kasinathan RS, Nathan FE, Ramalingam SS (2019) Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 381 (21):2020-2031. doi:10.1056/NEJMoa1910231

8. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Jr., Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G (2019) Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 393 (10183):1819-1830. doi:10.1016/s0140-6736(18)32409-7

9. Song Y, Wu J, Chen X, Lin T, Cao J, Liu Y, Zhao Y, Jin J, Huang H, Hu J, Luo J, Zhang L, Xue H, Zhang Q, Wang W, Chen C, Feng J, Zhu J (2019) A single-arm, multicenter, phase II study of camrelizumab in relapsed or refractory classical Hodgkin lymphoma. Clinical Cancer Research 25 (24):7363-7369. doi:http://dx.doi.org/10.1158/1078-0432.CCR-19-1680

10. Wu Y, Huang C, Fan Y, Feng J, Pan H, Jiang L, Yang J, Li X, Liu X, Xiong J, Zhao Y, Cheng Y, Ma R, Wang J, Wang Y, Liu Y, Lin D, Shi W, Lin X (2019) P1.01-61 A Phase II Umbrella Study of Camrelizumab in Different PD-L1 Expression Cohorts in Pre-Treated Advanced/Metastatic Non-Small Cell Lung Cancer. Journal of Thoracic Oncology 14 (10 Supplement):S382-S383. doi:http://dx.doi.org/10.1016/j.jtho.2019.08.776

11. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, Wang Z, Shu Y, Shi J, Hu Y, Wang Q, Cheng Y, Wu F, Chen J, Lin X, Wang Y, Huang J, Cui J, Cao L, Liu Y, Zhang Y, Pan Y, Zhao J, Wang L, Chang J, Chen Q, Ren X, Zhang W, Fan Y, He Z, Fang J, Gu K, Dong X, Zhang T, Shi W, Zou J (2020) Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. doi:10.1016/s2213-2600(20)30365-9

12. Hoyle MW, Henley W (2011) Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol 11:139. doi:10.1186/1471-2288-11-139

13. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients

with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18 (12):2354-2362. doi:10.1200/jco.2000.18.12.2354

14. Wu B, Dong B, Xu Y, Zhang Q, Shen J, Chen H, Xue W (2012) Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. PLoS One 7 (3):e32530. doi:10.1371/journal.pone.0032530

15. Wan N, Zhang TT, Hua SH, Lu ZL, Ji B, Li LX, Lu LQ, Huang WJ, Jiang J, Li J (2020) Cost-effectiveness analysis of pembrolizumab plus chemotherapy with PD-L1 test for the first-line treatment of NSCLC. Cancer Med 9 (5):1683-1693. doi:10.1002/cam4.2793

16. Xin W, Ding H, Fang Q, Zheng X, Tong Y, Xu G, Yang G (2020) Cost-effectiveness of pembrolizumab for treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma in China: an economic analysis based on a randomised, open-label, phase III trial. BMJ Open 10 (12):e038867. doi:10.1136/bmjopen-2020-038867

17. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, Velcheti V (2017) Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics 35 (8):831-844. doi:10.1007/s40273-017-0527-z

18. Tartari F, Santoni M, Burattini L, Mazzanti P, Onofri A, Berardi R (2016) Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges. Cancer Treat Rev 48:20-24. doi:10.1016/j.ctrv.2016.06.002

19. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., de Lima Lopes G, Jr., Haaland B (2018) Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small

cell lung cancer. Lung Cancer 124:248-254. doi:10.1016/j.lungcan.2018.08.018

20. Chouaid C, Bensimon L, Clay E, Millier A, Levy-Bachelot L, Huang M, Levy P (2019) Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Lung Cancer 127:44-52

21. Liao W, Huang J, Hutton D, Li Q (2019) Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ 22 (4):344-349. doi:10.1080/13696998.2019.1570221

22. Zhou K, Jiang C, Li Q (2019) Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores. Lung Cancer 136:98-101. doi:10.1016/j.lungcan.2019.08.028

23. Wan X, Luo X, Tan C, Zeng X, Zhang Y, Peng L (2019) First-line atezolizumab in addition to bevacizumab plus chemotherapy for metastatic, nonsquamous non-small cell lung cancer: A United States-based cost-effectiveness analysis. Cancer 125 (20):3526-3534. doi:10.1002/cncr.32368

24. Hu H, She L, Liao M, Shi Y, Yao L, Ding D, Zhu Y, Zeng S, Carbone DP, Huang J (2020) Cost-Effectiveness Analysis of Nivolumab Plus Ipilimumab vs. Chemotherapy as First-Line Therapy in Advanced Non-Small Cell Lung Cancer. Front Oncol 10:1649. doi:10.3389/fonc.2020.01649

25. Zhang B, Qi L, Xu J, Liu Y, Mu L, Wang X, Bai L, Huang J (2020) Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma. Cancer Communications 40 (12):711-720

26. Shen T, Geng L, Liu Z, Xu J, Lin B, Qian J, Zheng S (2020) Experience With Anti-PD-1 Antibody, Camrelizumab, Monotherapy for Biliary Tract Cancer Patients and Literature Review. Technology in cancer research & treatment 19:1533033820979703

27. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, Chen J, Zhang H, Niu Z, Fan Q, Lin L, Gu K, Liu Y, Ba Y, Miao Z, Jiang X, Zeng M, Chen J, Fu Z, Gan L, Wang J, Zhan X, Liu T, Li Z, Shen L, Shu Y, Zhang T, Yang Q, Zou J, Group ES (2020) Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. The lancet Oncology. 21 (6):832-842

28. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, Fang Y, Duan J, Zhou C, Yang H, Hu Y, Zhou J, Lin X, Wang L, Wang Z, Xu Y, Zhang T, Shi W, Zou J, Wang J (2020) Camrelizumab Plus Apatinib in Extensive-Stage SCLC (PASSION): A Multicenter, Two-Stage, Phase 2 Trial. Journal of Thoracic Oncology

29. Chen Z, Lu X, Koral K (2020) The clinical application of camrelizumab on advanced hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 14 (11):1017-1024. doi:10.1080/17474124.2020.1807939

Figure captions

Figure 1. A Markov structure was built to compare 2 treatment strategies.

Abbreviations: PFS, progression-free survival; PD, progressive disease.

Figure 2. The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial, Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP threshold. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

Figure 5. Dashed line indicates the willingness-to-pay (WTP) threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at current WTP.

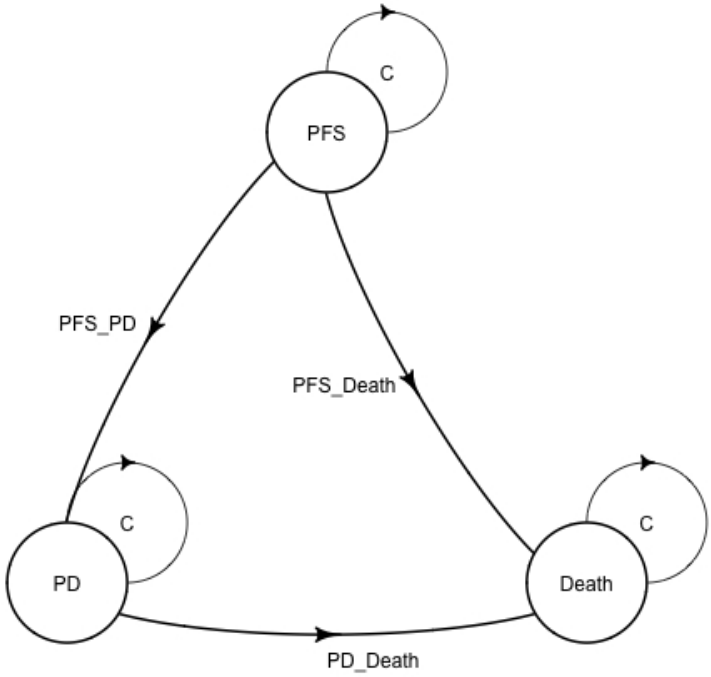


Figure 1. A Markov structure was built to perform the analysis. Abbreviations: PFS, progression-free survival; PD, progressive disease.

211x211mm (72 x 72 DPI)

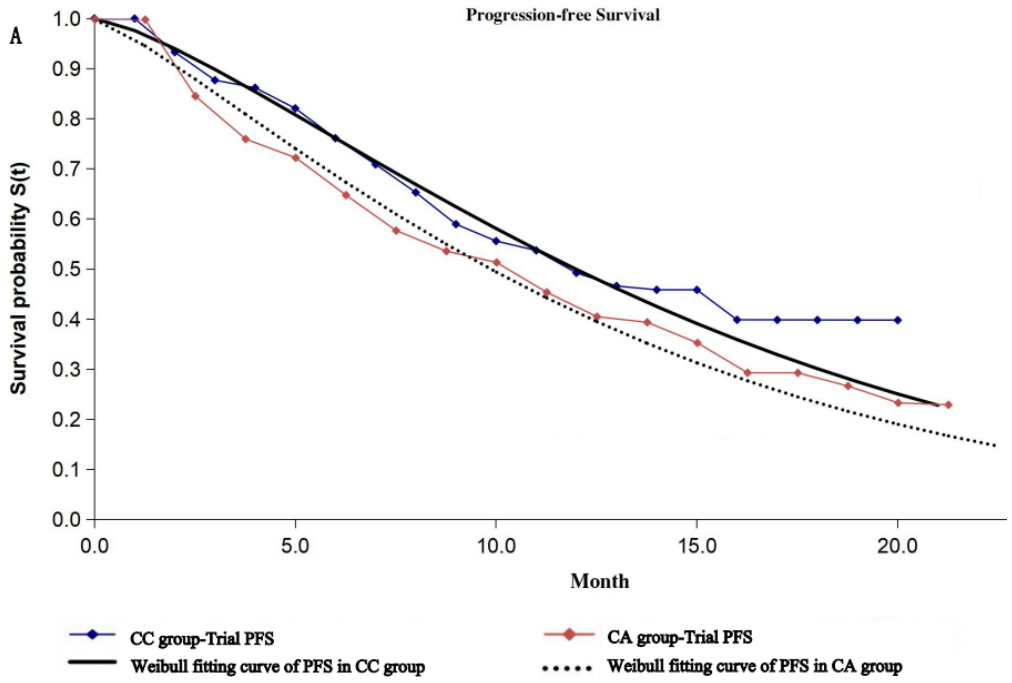


Figure 2. The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial, Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

119x79mm (192 x 192 DPI)

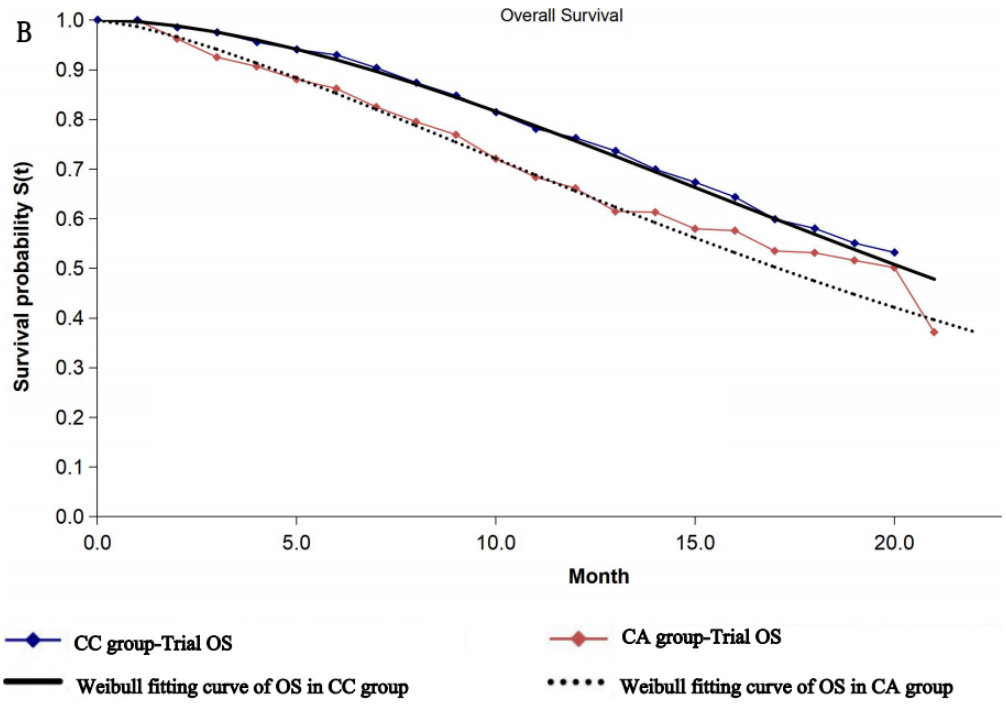


Figure 2. The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial, Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

120x83mm (192 x 192 DPI)

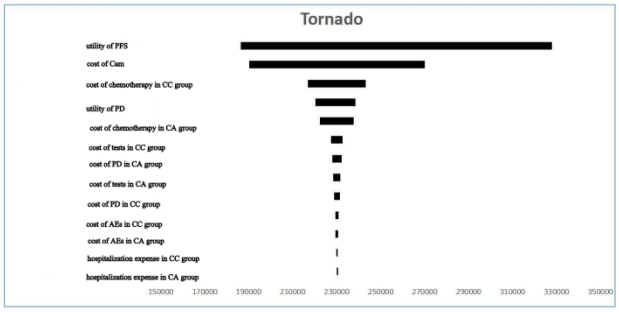


Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

296x209mm (192 x 192 DPI)

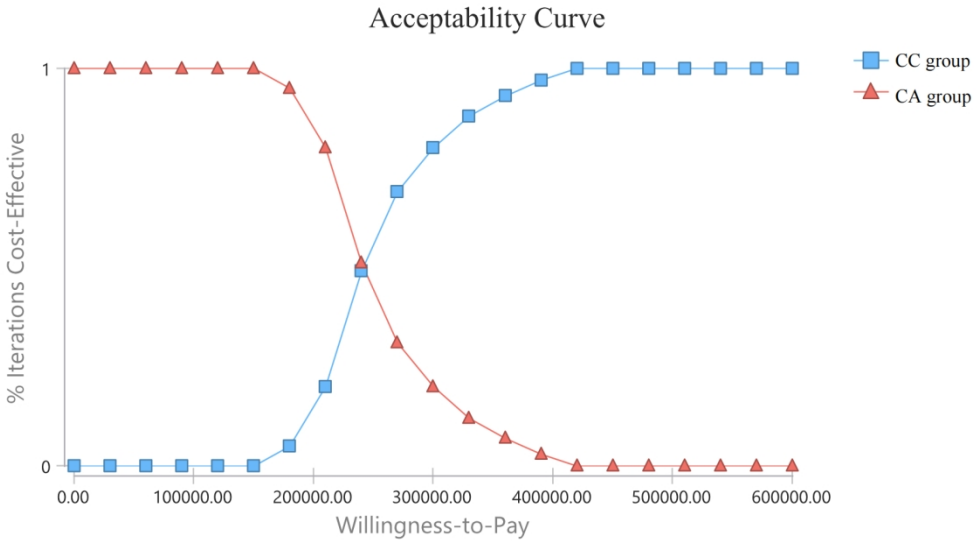


Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP threshold. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

240x135mm (192 x 192 DPI)

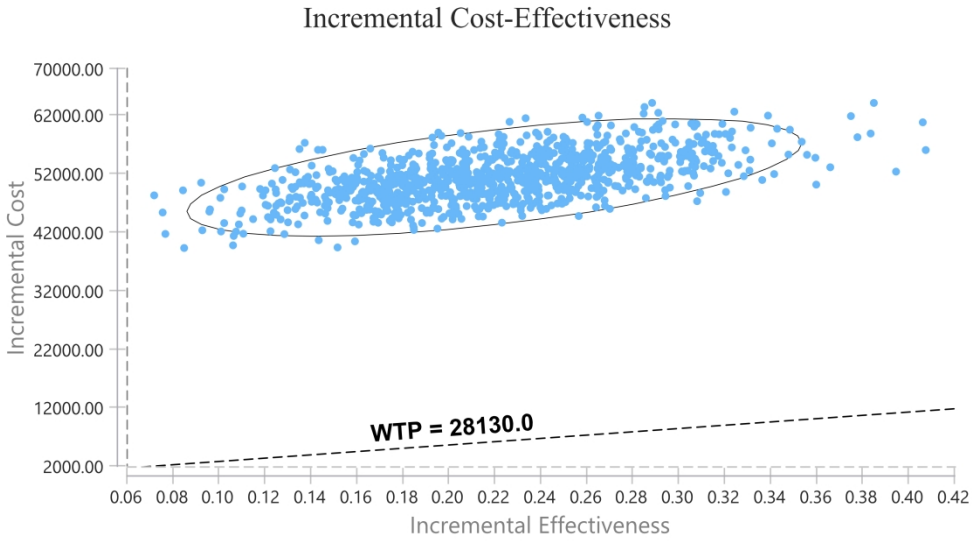


Figure 5. Dashed line indicates the willingness-to-pay (WTP) threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at current WTP.

481x270mm (192 x 192 DPI)

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	page1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	page1
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	page2,3
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	page4
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	page3
Setting and location	6	Provide relevant contextual information that may influence findings.	no
Comparators	7	Describe the interventions or strategies being compared and why chosen.	page3
Perspective	8	State the perspective(s) adopted by the study and why chosen.	page2,3
Time horizon	9	State the time horizon for the study and why appropriate.	page3
Discount rate	10	Report the discount rate(s) and reason chosen.	page5
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	page5
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	page5
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	page4
Measurement and valuation of resources and costs	14	Describe how costs were valued.	page5
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	page4
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	page4
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	page4
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	no
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	no
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	page5
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	page5
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	page4,5
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	page5
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	no
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	no
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	page6,7
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	page8
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	page8

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022;376:e067975.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061592.R1
Article Type:	Original research
Date Submitted by the Author:	10-Jun-2022
Complete List of Authors:	Xie, Qian; Sichuan University West China Hospital Zheng, Hanrui; West China Hospital of Medicine Su, Na; Sichuan University West China Hospital, Pharmacy Li, Qiu; Sichuan University West China Hospital
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health economics, Oncology
Keywords:	HEALTH ECONOMICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory tract tumours < ONCOLOGY, CHEMOTHERAPY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Authors information

Qian Xie[a], Hanrui Zheng[bc], Na Su[bc*], Qiu Li[d*]

[a]International Medical Center/Ward of General Practice, West China Hospital, Sichuan University, Chengdu, China

[b]Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China

[C]West China School of Pharmacy, Sichuan University, Chengdu, China

[d]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China

*Correspondence to:

Na Su, Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China

West China School of Pharmacy, Sichuan University, Chengdu, China (e-mail: zoya159@163.com)

Qiu Li, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China (e-mail: keythera@126.com, fbqiu9@163.com)

Abstract

Objective Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against programmed cell death 1 (PD-1) that shows effective antitumor activity with acceptable toxicity in multiple tumor types. The CameL trial demonstrated that camrelizumab plus chemotherapy significantly prolonged the median progression-free survival (PFS) and median overall survival (OS) versus chemotherapy alone 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 camrelizumab plus chemotherapy (CC) and chemotherapy alone (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 (ICER) was calculated to compare the cost-effectiveness of the two treatment arms.

Results 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 quality-adjusted life years (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.

Conclusions For chemotherapy-naive patients with advanced non-squamous NSCLC, camrelizumab plus chemotherapy is not considered as a cost-effective treatment versus chemotherapy alone in China when considering a willingness-to-pay (WTP) threshold of $31,500 per QALY.

Keywords Cost-effective analysis camrelizumab chemotherapy programmed cell death 1 non-small-cell lung cancer

Strengths and limitations of this study

Our model was based on a clinical trial, which may not be completely appropriate for real-world patients. There are some limitations in applying survival analysis to the calculation of Markov model parameters for pharmacoeconomic evaluation, because the loss of the corresponding information of the simulated curves is inevitable. However, it is still one of the effective and feasible methods to reasonably solve the problem of time dependence of transfer probability in dynamic Markov model, especially the pharmacoeconomic evaluation of cancer. Using a Markov model method for pharmacoeconomic evaluation can not only simplify the complex process of disease occurrence and development but can also provide evidence for the resource allocation problems faced by health decision-makers more efficiently.

Introduction

Lung cancer has become one of the leading cause of cancer-related death worldwide and 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[3]. 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 (CTLA-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[5,6]. The significant overall survival (OS) benefit was observed with nivolumab plus ipilimumab comparing with chemotherapy as first-line treatment in patients with NSCLC[7]. Pembrolizumab, as first-line monotherapy, improves OS and progression-free survival (PFS) in patients with untreated metastatic NSCLC with a programmed death ligand 1 (PD-L1) expression[8].

Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against PD-1 that shows great tumor response with acceptable toxicity in multiple tumor 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 has been successfully entered the Chinese medical insurance catalogue at the end of 2020, and the price was reduced from $3,065.02/ 200mg to $453.25/ 200mg with a decrease of 85%. Patients can make reimbursement for the drugs including in the medical insurance catalogue in China. So, it is valuable to conduct this study from the payers perspective in the low and middle-income countries with lower WTP.

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 were 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 comparing with the CA group (PFS, 11.3 months vs 8.3 months, p=.0001; OS, 27.9 months vs. 20.5 months).

Model structure

A Markov model was conducted in TreeAge Pro software version 2020 (TreeAge Software LLC, Williamstown, Massachusetts) to simulate the disease process which included 3 states: PFS, progressive disease (PD) and death. Patients with advanced non-squamous NSCLC were assumed to be in the PFS state until 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 was generated using the algorithm derived by Hoyle et al to minimize the difference between the trial data and our modeled data. While 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 as the following formula: $P(t \rightarrow t+1)=1-\exp[\lambda(t)\gamma - \lambda(t+1)\gamma)]$, where t equals the current cycle number in 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 2 groups received docetaxel after PD based on clinical guidelines[13].

Costs and utility

In this analysis, we considered only direct costs, including hospitalization, 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 Chengdu, China. We assumed a mean body surface area and a body weight of 1.64 m^2 and 65 kg, respectively[14]. All costs were measured in US dollars (USD) based on the exchange rate on Dec. 27th, 2020 (1 USD = 6.46 CHY). Health utility scores were 0.81, 0.58 and 0 in the PFS state, PD state and death state, respectively[15,16]. The annual discount rate of 3% was calculated (Table 1).

Table 1. Utilities and estimated monthly costs per patient base on the CameL trial

Parameters	CC group	CA group
Costs per month $		
Camrelizumab	3,065.17(3,678.20-2,452.14)	-
pemetrexed	1,012.95(1,215.54-810.36)	805.47(966.56-644.38)
carboplatin	18.29(21.95-14.64)	19.81(23.77-15.85)
Hospitalization	25.81(30.97-20.65)	15.22(18.26-12.18)
†AEs	58.19(69.83-46.55)	63.22(75.87-50.58)
Tests	201.95(242.34-161.56)	166.98(200.37-133.58)
Cost of PD	183.68(220.42-146.95)	249.92(299.91-199.94)
utility		
‡PFS	0.81	0.81
§PD	0.58	0.58
Discount rate, %	3	

†AEs, adverse events; ‡PFS, progression-free survival; §PD, progressive disease

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 (ICER). Treatments were considered cost-effective if the ICER was lower than the willingness-to-pay (WTP) threshold. According to the WHO recommendations for cost-effective analysis, the threshold of $31,500 per QALY was defined as 3-fold the gross domestic product (GDP) per capita of China. In addition, probabilistic sensitivity

analysis was performed using Monte Carlo simulation, which included 1,000 iterations to further address the uncertainty of all the input parameters.

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 quality-adjusted life years (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).

Table 2. Results of base-case analysis of CC and CA group

Result	CC group	CA group
Cost ($)	27,223.40	13,740.10
Incremental costs	13,483.30	
Effectiveness (†QALYs)	1.37	1.17
Incremental effectiveness	0.20	
‡ICER ($/QALY)	67,416.50	

†QALY, quality-adjusted life year; ‡ICER, Incremental cost-effectiveness ratio.

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 CC group, which ranged from $805.35 to $1,208.02 with ICER ranged from $54,115.08 to $84,422.81 per QALY. Changing other parameters including cost of camrelizumab may somehow result in different results but has little impact on the ICER. Thus, considering the current WTP threshold of $31,500, the acceptable curve shows camrelizumab plus chemotherapy 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 ICIs camrelizumab has shown promising tumor response in multiple tumor types with manageable toxicities[17-21]. 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 a longer duration of maintenance therapy, which indicates a better tumor 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. And we conducted the subgroup analysis in the PDL1 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 ICERs of $72,117.86 per QALY, which was also above the WTP threshold. The higher ICERs in the PDL1 positive population may be associated with increased health care costs due to improved PFS that required more expensive treatment.

Several cost-effectiveness studies about other ICIs demonstrated that pembrolizumab monotherapy was cost-effective comparing with chemotherapy both in the US and France; however, it was not cost-effective in the United Kingdom or China, as the first-line treatment in advanced NSCLC patients[22-27]. For patients with advanced NSCLC, atezolizumab plus bevacizumab and chemotherapy was not cost-effective[28], by the other hand, nivolumab plus ipilimumab was demonstrated to be cost-effective comparing with chemotherapy from the US payer perspective [29].

Although we conducted our study in China, the results may give some enlightenment to other countries. The price of domestic pemetrexed was applied in our study, which was demonstrated as the second sensitive parameter. However, this parameter was not sufficient to change the economic outcomes according to the sensitive analysis. And 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 area, however, the sensitive analysis shows it has little impact on the ICER. The ICER in our study was far below the WTP value of $150,000 in the US[30]. Due to 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 descend in the future, it may make the CC treatment cost effective in China. So our analysis is conducive to the rational allocation of health resources, which was 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 model, 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 NCCN, which may differ from actual treatment[13]. Additionally, Reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common immune-related dermatologic toxicity of camrelizumab according to the CameL trial, however, the cost of treating RCCEP was excluded from our study because its effects are mild, reversible, and predictable[21].

Conclusions

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

Declarations

Patient and Public Involvement No patient involved

Authors 'Contributions

Qian Xie wrote the main manuscript text and prepared 2 tables and Hanrui Zheng prepared figures 1-5. Qiu Li and Na Su designed the study. All authors reviewed the manuscript.

Ethical approval Ethical approval is not required for the study

Conflicts of interest The authors have indicated that they have no conflicts of interest.

Acknowledgments None reported.

Funding This study was not supported by any Funds

Availability of data and material The data that supports the findings of this study are presented in this article

Code availability Not applicable

Consent to participate All the authors are consent to participate in the study

Consent for publication All the authors are consent for this article publication

Acknowledgments None reported

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 (6):394-424. doi:10.3322/caac.21492

2. Feng RM, Zong YN, Cao SM, Xu RH (2019) Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 39 (1):22. doi:10.1186/s40880-019-0368-6

3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim Y-C, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M (2017) Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine 377 (20):1919-1929. doi:10.1056/NEJMoa1709937

4. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28 (13):2181-2190. doi:10.1200/jco.2009.26.2543

5. Paz-Ares L, Brahmer J, Hellmann MD, Reck M, O'Byrne K, Borghaei H, Geese WJ, Lu H, Nathan FE, Ramalingam S (2017) CheckMate 227: a randomized, open-label phase 3 trial of nivolumab nivolumab plus ipilimumab, or nivolumab plus chemotherapy versus chemotherapy in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC). Annals of oncology 28

6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New england journal of medicine 375 (19):1823-1833

7. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E,

Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, Sakai H, Albert I, Vergnenegre A, Peters S, Syrigos K, Barlesi F, Reck M, Borghaei H, Brahmer JR, O'Byrne KJ, Geese WJ, Bhagavatheeswaran P, Rabindran SK, Kasinathan RS, Nathan FE, Ramalingam SS (2019) Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 381 (21):2020-2031. doi:10.1056/NEJMoa1910231

8. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Jr., Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G (2019) Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 393 (10183):1819-1830. doi:10.1016/s0140-6736(18)32409-7

9. Song Y, Wu J, Chen X, Lin T, Cao J, Liu Y, Zhao Y, Jin J, Huang H, Hu J, Luo J, Zhang L, Xue H, Zhang Q, Wang W, Chen C, Feng J, Zhu J (2019) A single-arm, multicenter, phase II study of camrelizumab in relapsed or refractory classical Hodgkin lymphoma. Clinical Cancer Research 25 (24):7363-7369. doi:http://dx.doi.org/10.1158/1078-0432.CCR-19-1680

10. Wu Y, Huang C, Fan Y, Feng J, Pan H, Jiang L, Yang J, Li X, Liu X, Xiong J, Zhao Y, Cheng Y, Ma R, Wang J, Wang Y, Liu Y, Lin D, Shi W, Lin X (2019) P1.01-61 A Phase II Umbrella Study of Camrelizumab in Different PD-L1 Expression Cohorts in Pre-Treated Advanced/Metastatic Non-Small Cell Lung Cancer. Journal of Thoracic Oncology 14 (10 Supplement):S382-S383. doi:http://dx.doi.org/10.1016/j.jtho.2019.08.776

11. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, Wang Z, Shu Y, Shi J, Hu Y, Wang Q,

Cheng Y, Wu F, Chen J, Lin X, Wang Y, Huang J, Cui J, Cao L, Liu Y, Zhang Y, Pan Y, Zhao J, Wang L, Chang J, Chen Q, Ren X, Zhang W, Fan Y, He Z, Fang J, Gu K, Dong X, Zhang T, Shi W, Zou J (2020) Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. doi:10.1016/s2213-2600(20)30365-9

12. Hoyle MW, Henley W (2011) Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC medical research methodology 11:139. doi:10.1186/1471-2288-11-139

13. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18 (12):2354-2362. doi:10.1200/jco.2000.18.12.2354

14. Wu B, Dong B, Xu Y, Zhang Q, Shen J, Chen H, Xue W (2012) Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. PLoS One 7 (3):e32530. doi:10.1371/journal.pone.0032530

15. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, Finnern HW, Lungershausen J, Eriksson J, Kim K, Mitchell PL (2013) Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional

patient survey in a real-world setting. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 8 (8):997-1003. doi:10.1097/JTO.0b013e318299243b

16. Shen Y, Wu B, Wang X, Zhu J (2018) Health state utilities in patients with advanced non-small-cell lung cancer in China. Journal of comparative effectiveness research 7 (5):443-452. doi:10.2217/cer-2017-0069

17. Zhang B, Qi L, Xu J, Liu Y, Mu L, Wang X, Bai L, Huang J (2020) Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma. Cancer Communications 40 (12):711-720

18. Shen T, Geng L, Liu Z, Xu J, Lin B, Qian J, Zheng S (2020) Experience With Anti-PD-1 Antibody, Camrelizumab, Monotherapy for Biliary Tract Cancer Patients and Literature Review. Technology in cancer research & treatment 19:1533033820979703

19. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, Chen J, Zhang H, Niu Z, Fan Q, Lin L, Gu K, Liu Y, Ba Y, Miao Z, Jiang X, Zeng M, Chen J, Fu Z, Gan L, Wang J, Zhan X, Liu T, Li Z, Shen L, Shu Y, Zhang T, Yang Q, Zou J, Group ES (2020) Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. The lancet Oncology. 21 (6):832-842

20. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, Fang Y, Duan J, Zhou C, Yang H, Hu Y, Zhou J, Lin X, Wang L, Wang Z, Xu Y, Zhang T, Shi W, Zou J, Wang J (2020) Camrelizumab Plus Apatinib in Extensive-Stage SCLC (PASSION): A Multicenter, Two-Stage, Phase 2 Trial.

Journal of Thoracic Oncology

21. Chen Z, Lu X, Koral K (2020) The clinical application of camrelizumab on advanced hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 14 (11):1017-1024. doi:10.1080/17474124.2020.1807939

22. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, Velcheti V (2017) Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics 35 (8):831-844. doi:10.1007/s40273-017-0527-z

23. Tartari F, Santoni M, Burattini L, Mazzanti P, Onofri A, Berardi R (2016) Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges. Cancer Treat Rev 48:20-24. doi:10.1016/j.ctrv.2016.06.002

24. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., de Lima Lopes G, Jr., Haaland B (2018) Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Lung Cancer 124:248-254. doi:10.1016/j.lungcan.2018.08.018

25. Chouaid C, Bensimon L, Clay E, Millier A, Levy-Bachelot L, Huang M, Levy P (2019) Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Lung Cancer 127:44-52

26. Liao W, Huang J, Hutton D, Li Q (2019) Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ 22 (4):344-349. doi:10.1080/13696998.2019.1570221

27. Zhou K, Jiang C, Li Q (2019) Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores. Lung Cancer 136:98-101. doi:10.1016/j.lungcan.2019.08.028

28. Wan X, Luo X, Tan C, Zeng X, Zhang Y, Peng L (2019) First-line atezolizumab in addition to bevacizumab plus chemotherapy for metastatic, nonsquamous non-small cell lung cancer: A United States-based cost-effectiveness analysis. Cancer 125 (20):3526-3534. doi:10.1002/cncr.32368

29. Hu H, She L, Liao M, Shi Y, Yao L, Ding D, Zhu Y, Zeng S, Carbone DP, Huang J (2020) Cost-Effectiveness Analysis of Nivolumab Plus Ipilimumab vs. Chemotherapy as First-Line Therapy in Advanced Non-Small Cell Lung Cancer. Front Oncol 10:1649. doi:10.3389/fonc.2020.01649

30. Vanness DJ, Lomas J, Ahn H (2021) A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States. Annals of internal medicine 174 (1):25-32. doi:10.7326/m20-1392

Figure captions

Figure 1. A Markov structure was built to compare 2 treatment strategies.

Abbreviations: PFS, progression-free survival; PD, progressive disease.

Figure 2. The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial, Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP threshold. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

Figure 5. Dashed line indicates the willingness-to-pay (WTP) threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at current WTP.

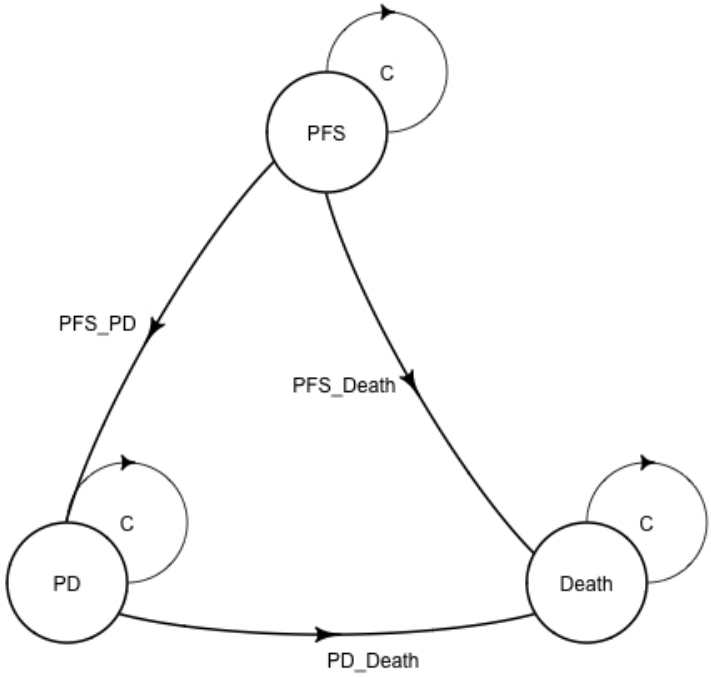
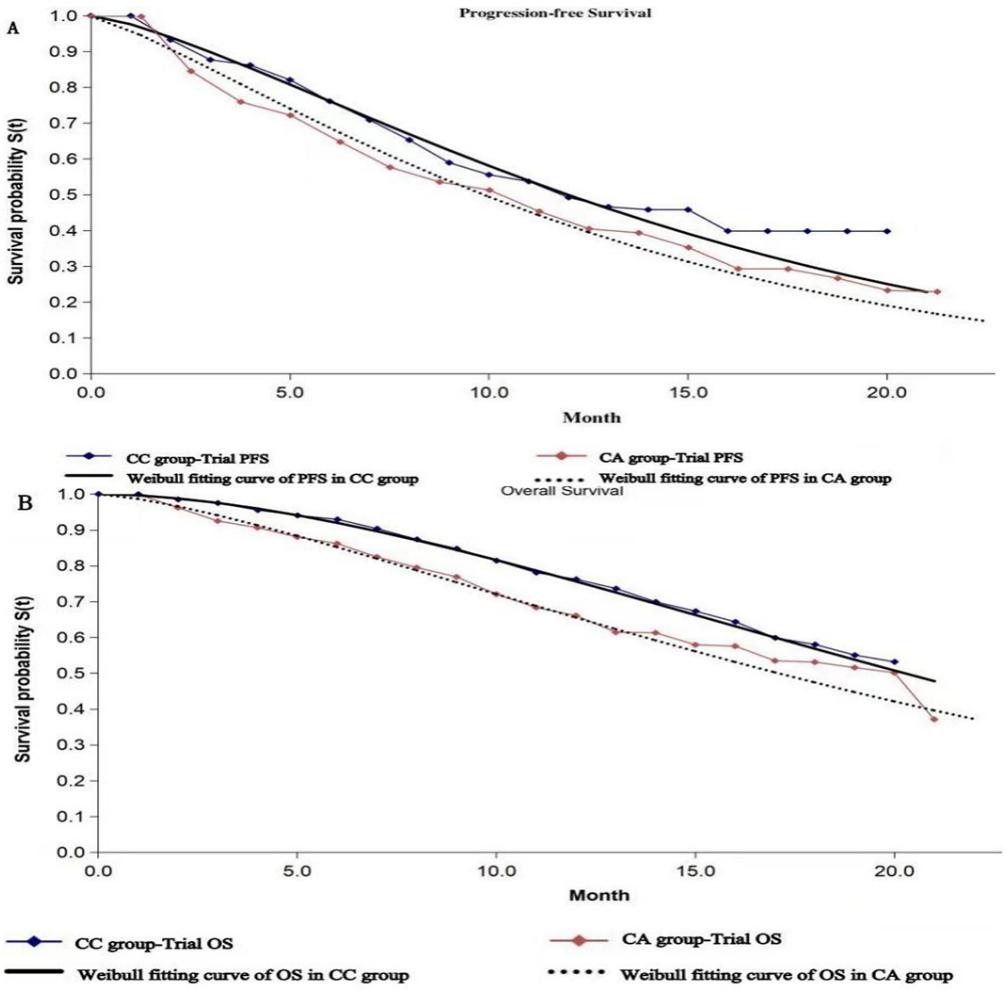


Figure 1. A Markov structure was built to perform the analysis. Abbreviations: PFS, progression-free survival; PD, progressive disease.

211x211mm (72 x 72 DPI)



The original Kaplan-Meier PFS (A) and OS (B) curves from the CameL trial, Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

90x90mm (300 x 300 DPI)

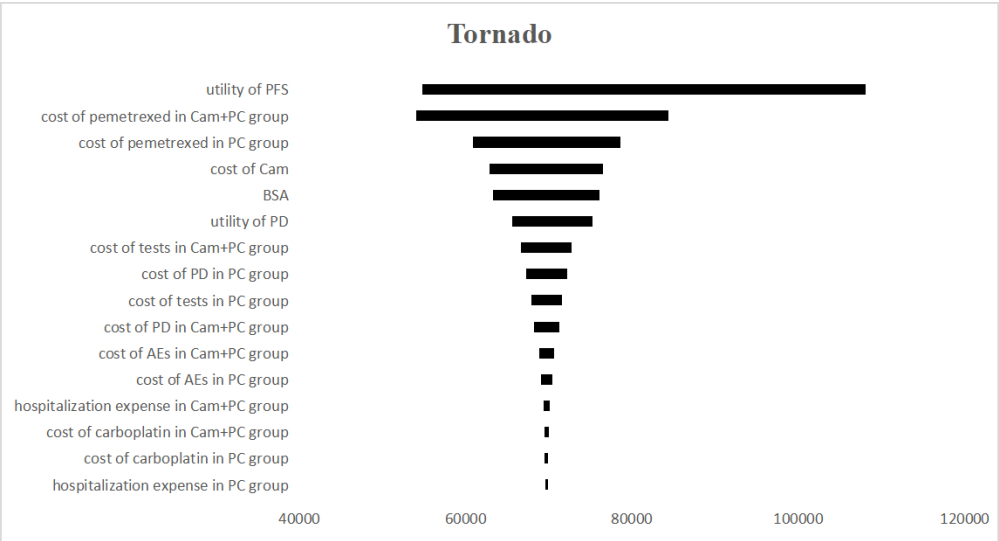


Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

493x266mm (59 x 59 DPI)

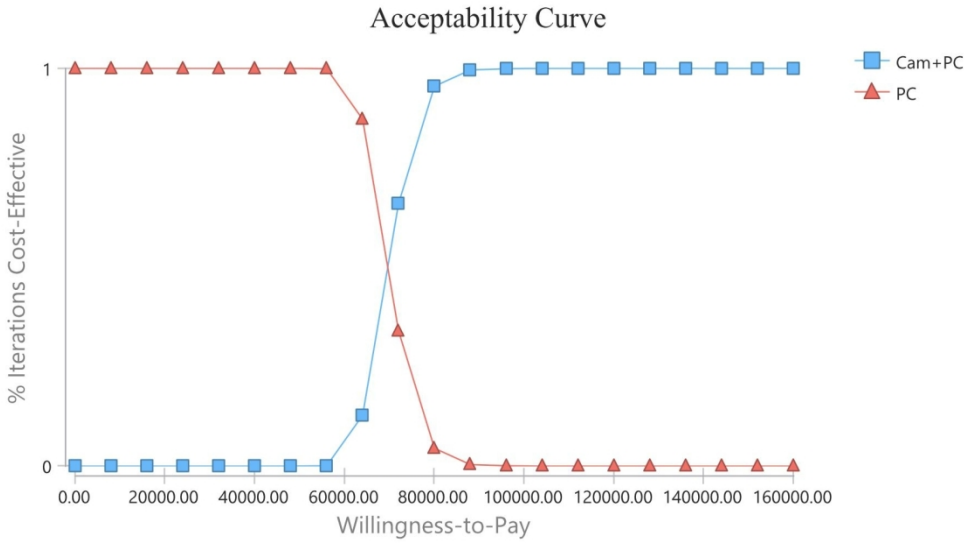


Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP threshold. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

240x135mm (192 x 192 DPI)

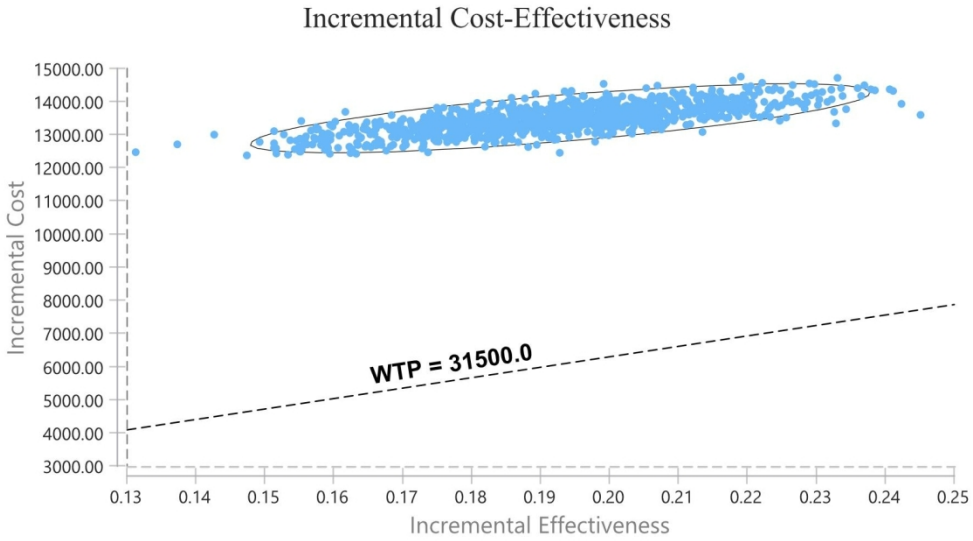


Figure 5. Dashed line indicates the willingness-to-pay (WTP) threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at current WTP.

240x135mm (192 x 192 DPI)

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	page1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	page1
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	page2,3
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	page4
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	page3
Setting and location	6	Provide relevant contextual information that may influence findings.	N/A
Comparators	7	Describe the interventions or strategies being compared and why chosen.	page 3
Perspective	8	State the perspective(s) adopted by the study and why chosen.	page2,3
Time horizon	9	State the time horizon for the study and why appropriate.	page3
Discount rate	10	Report the discount rate(s) and reason chosen.	page5
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	page5
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	page5
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	page4
Measurement and valuation of resources and costs	14	Describe how costs were valued.	page5
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	page4
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	page4
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	page4
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	N/A
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	page5
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	page5
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	page4,5
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	page5
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	N/A
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	N/A
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	page6,7
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	page8
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	page8

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022;376:e067975.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061592.R2
Article Type:	Original research
Date Submitted by the Author:	08-Jul-2022
Complete List of Authors:	Xie, Qian; Sichuan University West China Hospital Zheng, Hanrui; West China Hospital of Medicine Su, Na; Sichuan University West China Hospital, Pharmacy Li, Qiu; Sichuan University West China Hospital
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health economics, Oncology
Keywords:	HEALTH ECONOMICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory tract tumours < ONCOLOGY, CHEMOTHERAPY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Author information

Qian Xie[a], Hanrui Zheng[bc], Na Su[bc*], Qiu Li[d*]

[a]International Medical Center/Ward of General Practice, West China Hospital, Sichuan University, Chengdu, China

[b]Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China

[C]West China School of Pharmacy, Sichuan University, Chengdu, China

[d]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China

*Correspondence to:

Na Su, Department of Clinical Pharmacy, West China Hospital, Sichuan University, Chengdu, China

West China School of Pharmacy, Sichuan University, Chengdu, China (e-mail: zoya159@163.com)

Qiu Li, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China (e-mail: keythera@126.com, fbqiu9@163.com)

Abstract

Objective Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against programmed cell death 1 (PD-1) that shows effective antitumor activity with acceptable toxicity in multiple tumor types. The CameL trial demonstrated that camrelizumab plus chemotherapy significantly prolonged the median progression-free survival (PFS) and median overall survival (OS) versus chemotherapy alone 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 camrelizumab plus chemotherapy (CC) and chemotherapy alone (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 $27,223.40 and $13,740.10 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 $13,483.30 and generated an increase of 0.20 QALYs, resulting in an ICER of $67,416.50 per QALY.

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

Keywords Cost-effective analysis Camrelizumab Chemotherapy Programmed cell death 1 Non-small cell lung cancer

Strengths and limitations of this study

A Markov simulation model was generated based on the published CameL trial.

Survival analysis were applied to the calculation of Markov model parameters for pharmacoeconomic evaluation.

Health outcomes were measured by quality-adjusted life years (QALYs).

Only direct costs including hospitalization, costs for drugs, radiology and laboratory tests and treatments for all grades of AEs were considered.

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.

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[3]. 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 (CTLA-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[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, humanized, high-affinity IgG4 kappa monoclonal antibody against PD-1 that shows a great tumor response with acceptable toxicity in multiple tumor 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 $3,065.02/200 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- and middle-income countries with lower WTP.

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=.0001; OS, 27.9 months vs. 20.5 months).

Model structure

A Markov model was conducted in TreeAge Pro software version 2020 (TreeAge Software LLC, Williamstown, Massachusetts) to simulate the disease process, which included 3 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 et al to minimize 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: $P(t \rightarrow t+1)=1-\exp[\lambda(t)\gamma - \lambda(t+1)\gamma)]$, 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 2 groups received docetaxel after PD based on clinical guidelines[13].

Costs and utility

In this analysis, we considered only direct costs, including hospitalization, 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 Chengdu, China. We assumed a mean body surface area and a body weight of 1.64 m^2 and 65 kg, respectively[14]. All costs were measured in US dollars (USD) based on the exchange rate on Dec. 27th, 2020 (1 USD = 6.46 CHY). Health utility scores were 0.81, 0.58 and 0 in the PFS state, PD state and death state, respectively[15,16]. The annual discount rate of 3% was calculated (Table 1).

Table 1. Utilities and estimated monthly costs per patient based on the CameL trial

Parameters	**CC group**	**CA group**
Costs per month $		
Camrelizumab	3,065.17(3,678.20-2,452.14)	-
pemetrexed	1,012.95(1,215.54-810.36)	805.47(966.56-644.38)
carboplatin	18.29(21.95-14.64)	19.81(23.77-15.85)
Hospitalization	25.81(30.97-20.65)	15.22(18.26-12.18)
†AEs	58.19(69.83-46.55)	63.22(75.87-50.58)
Tests	201.95(242.34-161.56)	166.98(200.37-133.58)
Cost of PD	183.68(220.42-146.95)	249.92(299.91-199.94)
utility		
‡PFS	0.81	0.81
§PD	0.58	0.58
Discount rate, %	3	

†AEs, adverse events; ‡PFS, progression-free survival; §PD, progressive disease

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 willingness-to-pay (WTP) threshold. According to the WHO recommendations for cost-effective analysis, the threshold of $31,500 per QALY was defined as

3-fold the gross domestic product (GDP) per capita of China. In addition, probabilistic sensitivity analysis was performed using Monte Carlo simulation, which included 1,000 iterations to further address the uncertainty of all the input parameters.

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 quality-adjusted life years (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).

Table 2. Results of base-case analysis of the CC and CA groups

Result	CC group	CA group
Cost ($)	27,223.40	13,740.10
Incremental costs	13,483.30	
Effectiveness (†QALYs)	1.37	1.17
Incremental effectiveness	0.20	
‡ICER ($/QALY)	67,416.50	

†QALY, quality-adjusted life year; ‡ICER, incremental cost-effectiveness ratio.

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 camrelizumab plus chemotherapy 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 tumor response in multiple tumor types with manageable toxicities[17-21]. 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 a longer duration of maintenance therapy, which indicates a better tumor 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 PDL1-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 PDL1-positive population may be associated with increased health care 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 US and France; however, it was not cost-effective in the United Kingdom or China as the first-line treatment in advanced NSCLC patients[22-27]. For patients with advanced NSCLC, atezolizumab plus bevacizumab and chemotherapy were not cost-effective[28]; 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 US[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 NCCN, which may differ from actual treatment[13]. Additionally, reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common immune-related dermatologic toxicity of camrelizumab according to the CameL trial; however, the cost of treating RCCEP was excluded from our study because its effects are mild, reversible, and predictable[21].

Conclusions

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

Declarations

Patient and Public Involvement No patient involved

Authors' Contributions

Qian Xie wrote the main manuscript text and prepared 2 tables, and Hanrui Zheng prepared Figures 1-5. Qiu Li and Na Su designed the study. All authors reviewed the manuscript.

Ethical approval Ethical approval is not required for the study.

Conflicts of interest The authors have indicated that they have no conflicts of interest.

Acknowledgements None reported.

Funding This study was not supported by any Funds.

Availability of data and material The data that support the findings of this study are presented in this article.

Code availability Not applicable

Consent to participate All the authors consent to participate in the study.

Consent for publication All the authors are consent for this article publication.

Acknowledgements None reported

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 (6):394-424. doi:10.3322/caac.21492

2. Feng RM, Zong YN, Cao SM, Xu RH (2019) Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 39 (1):22.

doi:10.1186/s40880-019-0368-6

3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim Y-C, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M (2017) Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine 377 (20):1919-1929. doi:10.1056/NEJMoa1709937

4. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28 (13):2181-2190. doi:10.1200/jco.2009.26.2543

5. Paz-Ares L, Brahmer J, Hellmann MD, Reck M, O'Byrne K, Borghaei H, Geese WJ, Lu H, Nathan FE, Ramalingam S (2017) CheckMate 227: a randomized, open-label phase 3 trial of nivolumab nivolumab plus ipilimumab, or nivolumab plus chemotherapy versus chemotherapy in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC). Annals of oncology 28

6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New england journal of medicine 375 (19):1823-1833

7. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, Sakai H, Albert I, Vergnenegre A, Peters S, Syrigos K, Barlesi F, Reck M, Borghaei H, Brahmer JR, O'Byrne KJ, Geese WJ, Bhagavatheeswaran P, Rabindran SK, Kasinathan RS, Nathan FE, Ramalingam SS (2019) Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 381 (21):2020-2031. doi:10.1056/NEJMoa1910231

8. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Jr., Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G (2019) Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 393 (10183):1819-1830. doi:10.1016/s0140-6736(18)32409-7

9. Song Y, Wu J, Chen X, Lin T, Cao J, Liu Y, Zhao Y, Jin J, Huang H, Hu J, Luo J, Zhang L, Xue H, Zhang Q, Wang W, Chen C, Feng J, Zhu J (2019) A single-arm, multicenter, phase II study of camrelizumab in relapsed or refractory classical Hodgkin lymphoma. Clinical Cancer Research 25 (24):7363-7369. doi:http://dx.doi.org/10.1158/1078-0432.CCR-19-1680

10. Wu Y, Huang C, Fan Y, Feng J, Pan H, Jiang L, Yang J, Li X, Liu X, Xiong J, Zhao Y, Cheng Y, Ma R, Wang J, Wang Y, Liu Y, Lin D, Shi W, Lin X (2019) P1.01-61 A Phase II Umbrella Study of Camrelizumab in Different PD-L1 Expression Cohorts in Pre-Treated Advanced/Metastatic Non-Small Cell Lung Cancer. Journal of Thoracic Oncology 14 (10 Supplement):S382-S383. doi:http://dx.doi.org/10.1016/j.jtho.2019.08.776

11. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, Wang Z, Shu Y, Shi J, Hu Y, Wang Q, Cheng Y, Wu F, Chen J, Lin X, Wang Y, Huang J, Cui J, Cao L, Liu Y, Zhang Y, Pan Y, Zhao J, Wang L, Chang J, Chen Q, Ren X, Zhang W, Fan Y, He Z, Fang J, Gu K, Dong X, Zhang T, Shi W, Zou J (2020) Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. doi:10.1016/s2213-2600(20)30365-9

12. Hoyle MW, Henley W (2011) Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC medical research methodology 11:139. doi:10.1186/1471-2288-11-139

13. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18 (12):2354-2362. doi:10.1200/jco.2000.18.12.2354

14. Wu B, Dong B, Xu Y, Zhang Q, Shen J, Chen H, Xue W (2012) Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. PLoS One 7 (3):e32530. doi:10.1371/journal.pone.0032530

15. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, Finnern HW, Lungershausen J, Eriksson J, Kim K, Mitchell PL (2013) Health-related quality of life and

utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 8 (8):997-1003. doi:10.1097/JTO.0b013e318299243b

16. Shen Y, Wu B, Wang X, Zhu J (2018) Health state utilities in patients with advanced non-small-cell lung cancer in China. Journal of comparative effectiveness research 7 (5):443-452. doi:10.2217/cer-2017-0069

17. Zhang B, Qi L, Xu J, Liu Y, Mu L, Wang X, Bai L, Huang J (2020) Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma. Cancer Communications 40 (12):711-720

18. Shen T, Geng L, Liu Z, Xu J, Lin B, Qian J, Zheng S (2020) Experience With Anti-PD-1 Antibody, Camrelizumab, Monotherapy for Biliary Tract Cancer Patients and Literature Review. Technology in cancer research & treatment 19:1533033820979703

19. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, Chen J, Zhang H, Niu Z, Fan Q, Lin L, Gu K, Liu Y, Ba Y, Miao Z, Jiang X, Zeng M, Chen J, Fu Z, Gan L, Wang J, Zhan X, Liu T, Li Z, Shen L, Shu Y, Zhang T, Yang Q, Zou J, Group ES (2020) Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. The lancet Oncology. 21 (6):832-842

20. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, Fang Y, Duan J, Zhou C, Yang H, Hu Y, Zhou J, Lin X, Wang L, Wang Z, Xu Y, Zhang T, Shi W, Zou J, Wang J (2020) Camrelizumab

Plus Apatinib in Extensive-Stage SCLC (PASSION): A Multicenter, Two-Stage, Phase 2 Trial. Journal of Thoracic Oncology

21. Chen Z, Lu X, Koral K (2020) The clinical application of camrelizumab on advanced hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 14 (11):1017-1024. doi:10.1080/17474124.2020.1807939

22. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, Velcheti V (2017) Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics 35 (8):831-844. doi:10.1007/s40273-017-0527-z

23. Tartari F, Santoni M, Burattini L, Mazzanti P, Onofri A, Berardi R (2016) Economic sustainability of anti-PD-1 agents nivolumab and pembrolizumab in cancer patients: Recent insights and future challenges. Cancer Treat Rev 48:20-24. doi:10.1016/j.ctrv.2016.06.002

24. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., de Lima Lopes G, Jr., Haaland B (2018) Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Lung Cancer 124:248-254. doi:10.1016/j.lungcan.2018.08.018

25. Chouaid C, Bensimon L, Clay E, Millier A, Levy-Bachelot L, Huang M, Levy P (2019) Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Lung Cancer 127:44-52

26. Liao W, Huang J, Hutton D, Li Q (2019) Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ

22 (4):344-349. doi:10.1080/13696998.2019.1570221

27. Zhou K, Jiang C, Li Q (2019) Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores. Lung Cancer 136:98-101. doi:10.1016/j.lungcan.2019.08.028

28. Wan X, Luo X, Tan C, Zeng X, Zhang Y, Peng L (2019) First-line atezolizumab in addition to bevacizumab plus chemotherapy for metastatic, nonsquamous non-small cell lung cancer: A United States-based cost-effectiveness analysis. Cancer 125 (20):3526-3534. doi:10.1002/cncr.32368

29. Hu H, She L, Liao M, Shi Y, Yao L, Ding D, Zhu Y, Zeng S, Carbone DP, Huang J (2020) Cost-Effectiveness Analysis of Nivolumab Plus Ipilimumab vs. Chemotherapy as First-Line Therapy in Advanced Non-Small Cell Lung Cancer. Front Oncol 10:1649. doi:10.3389/fonc.2020.01649

30. Vanness DJ, Lomas J, Ahn H (2021) A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States. Annals of internal medicine 174 (1):25-32. doi:10.7326/m20-1392

Figure captions

Figure 1. A Markov structure was built to compare 2 treatment strategies.

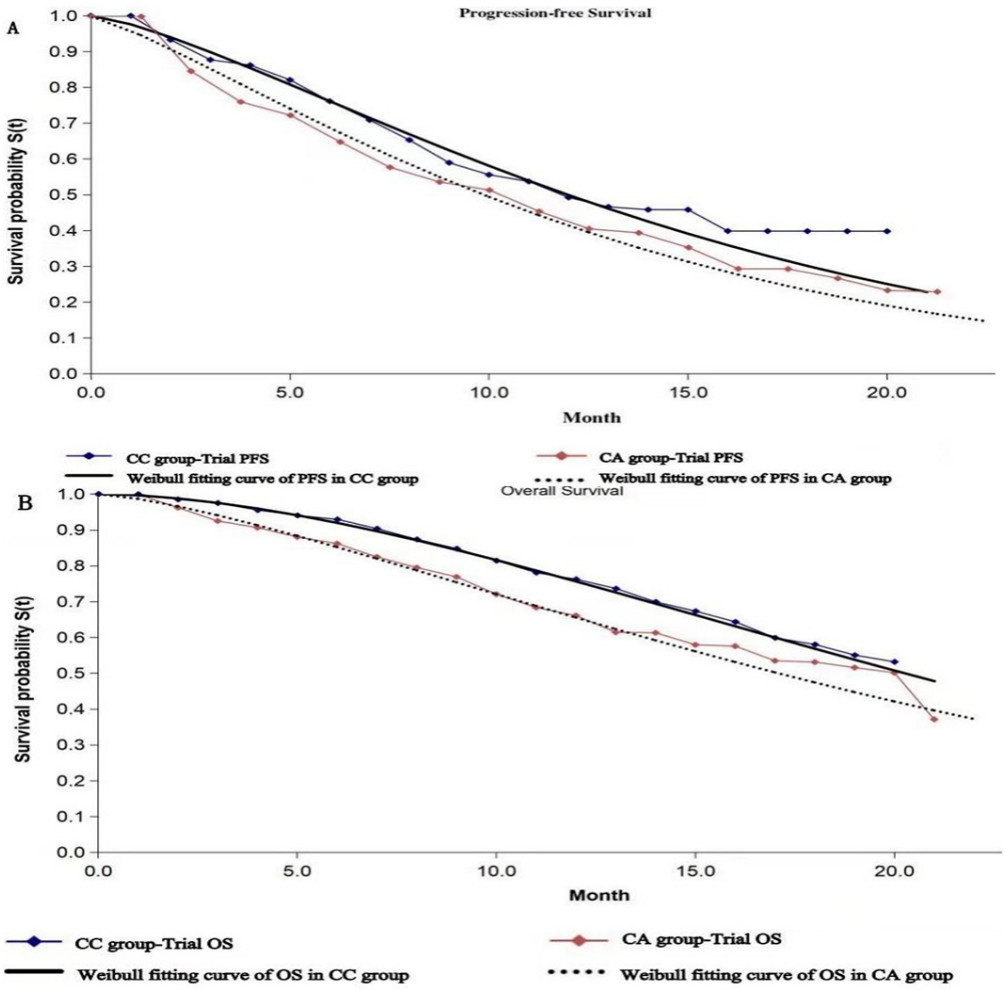
Abbreviations: PFS, progression-free survival; PD, progressive disease.

Figure 2. The original Kaplan–Meier PFS (A) and OS (B) curves from the CameL trial. Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP thresholds. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

Figure 5. The dashed line indicates the WTP threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at the current WTP. Abbreviations: WTP, willingness to pay.



The original Kaplan–Meier PFS (A) and OS (B) curves from the CameL trial. Weibull distributions were fitted to the two groups. Abbreviations: OS, overall survival; PFS, progression-free survival.

90x90mm (300 x 300 DPI)

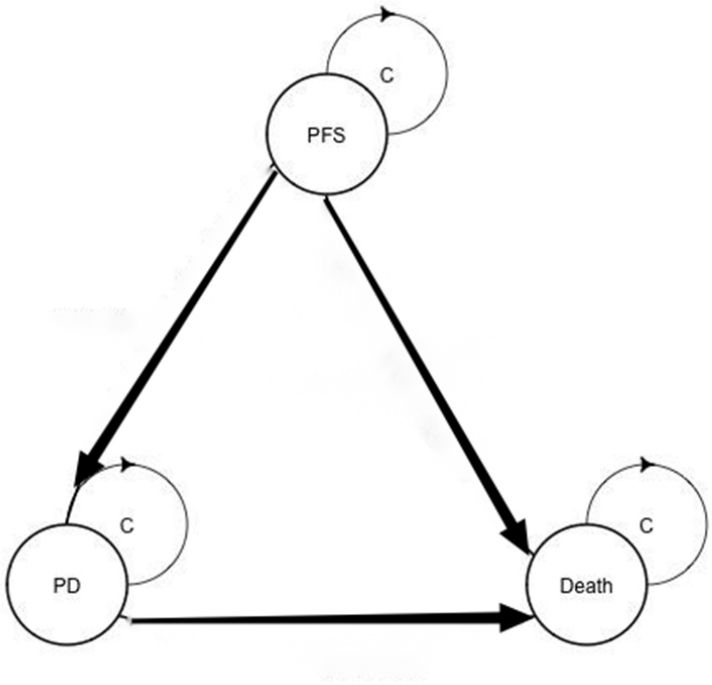


Figure 1. A Markov structure was built to compare 2 treatment strategies.
Abbreviations: PFS, progression-free survival; PD, progressive disease.

89x89mm (280 x 280 DPI)

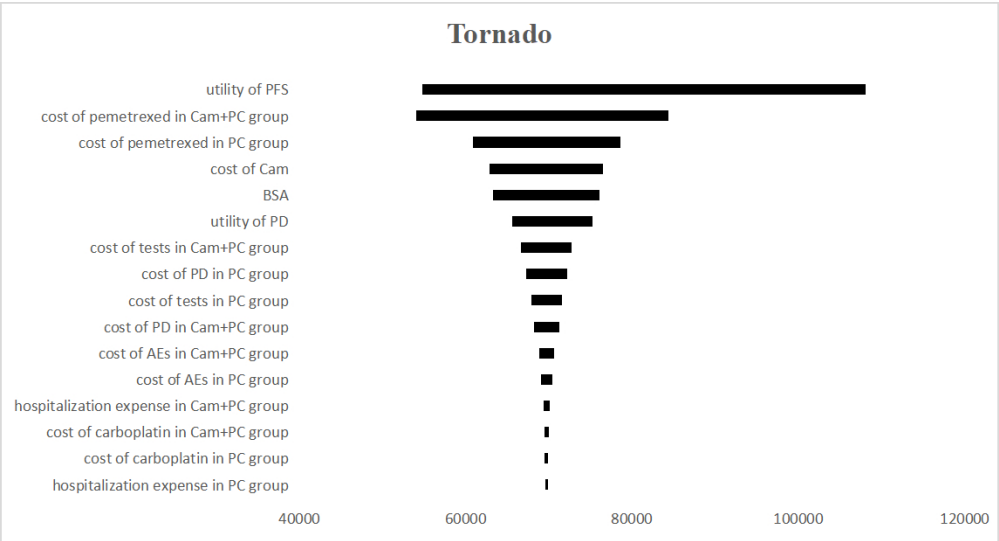


Figure 3. Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

493x266mm (59 x 59 DPI)

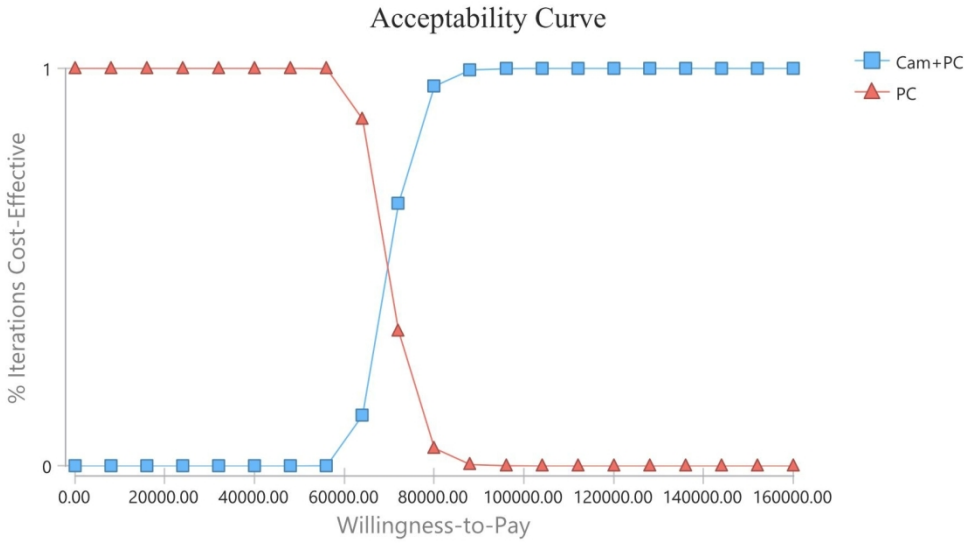


Figure 4. The cost-effectiveness acceptability curve showed the probability at different WTP thresholds. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

240x135mm (192 x 192 DPI)

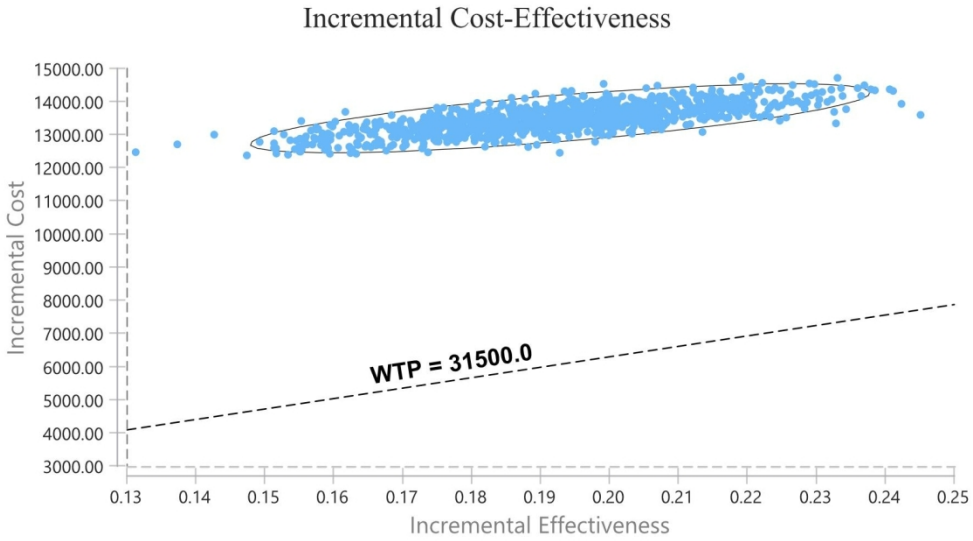


Figure 5. The dashed line indicates the willingness-to-pay (WTP) threshold. All of thescatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at the current WTP. Abbreviations: WTP, willingness to pay.

240x135mm (192 x 192 DPI)

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	page1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	page1
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	page2,3
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	page4
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	page3
Setting and location	6	Provide relevant contextual information that may influence findings.	N/A
Comparators	7	Describe the interventions or strategies being compared and why chosen.	page 3
Perspective	8	State the perspective(s) adopted by the study and why chosen.	page2,3
Time horizon	9	State the time horizon for the study and why appropriate.	page3
Discount rate	10	Report the discount rate(s) and reason chosen.	page5
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	page5
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	page5
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	page4
Measurement and valuation of resources and costs	14	Describe how costs were valued.	page5
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	page4
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	page4
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	page4
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	N/A
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	page5
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	page5
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	page4,5
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	page5
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	N/A
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	N/A
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	page6,7
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	page8
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	page8

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022;376:e067975.