

Economic Evaluations of Immune Checkpoint Inhibitors for Patients with Non-Small Cell Lung Cancer: A Systematic Review

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Objective: This review aimed to assess the quality of available evidence on the economic evaluations of immune checkpoint inhibitors in patients with non-small cell lung cancer (NSCLC) and provide evidence to improve the efficiency of healthcare resources.

Materials and Methods: Literature search was performed using some electronic databases (PubMed, Embase and Cochrane Central Register of Controlled Trials). Final search was performed in December 2019. Study characteristics and results were recorded and compared. The quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklists. We did not elaborate the restrictions on the target population. We included patients with squamous or non-squamous NSCLC and metastatic or advanced cancer.

Results: Of 98 papers considered, 21 were chosen for this review. Most of them are cost-effectiveness analysis. Comparative regimens consisted of either immune checkpoint inhibitor monotherapy, immune checkpoint inhibitor plus chemotherapy, or chemotherapy alone. Fourteen, four, and three studies were about pembrolizumab, nivolumab, and atezolizumab, respectively. The methods mostly used in these studies were modeling and sensitivity analysis. All studies used quality-adjusted life year (QALY) and life years (LY) as outcomes. Most studies were conducted in high-income countries. Based on the willingness to pay threshold, atezolizumab, and pembrolizumab were found to be cost-effective in one and 10 studies, respectively. None of the studies concluded that nivolumab was cost-effective. For quality assessment, all studies fulfilled more than 50% of the CHEERS checklist.

Conclusion: The included studies indicated that pembrolizumab regimens are cost-effective as first-line treatment for patients with NSCLC in developed countries. Nivolumab and atezolizumab are likely to be cost-effective as second-line treatment but not as first-line treatment.

Keywords: non-small cell lung cancer, economic analyses, immune checkpoint inhibitors, systematic review, PD-L1 positive

Introduction

Lung cancer is a heterogeneous group of tumors of more than 50 histomorphological subtypes.¹ Lung cancer remains the most common cancer (11.6% of all cancers) and the leading cause of cancer deaths, with over 1.7 million deaths worldwide in 2018.² Over the past few decades, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the most frequently used diagnostic terms for lung cancer; NSCLC comprises approximately 80–85% of all lung cancers.¹ NSCLC includes squamous cell

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carcinoma, adenocarcinoma, and large cell carcinoma. Cancer cells in non-small cell lung cancer grow and divide more slowly and spread relatively later than those in small cell carcinoma.³ Only a small portion of patients with NSCLC is clinically diagnosed at an early stage (stage I or II); over 60% of patients with lung cancer present with locally advanced or metastatic disease (stage III or IV) at the time of diagnosis, at which point surgical resection may not be an option.¹

The use of advanced molecular profiling to direct targeted therapies has revolutionized the treatment of NSCLC. Although the treatment for this disease has improved with the development of targeted drugs for patients with amenable mutations, only a small proportion of patients has these mutations, and acquired resistance to targeted therapies inevitably occurs.^{4,5} Thus, immunotherapy started to emerge, and targeting the programmed cell death-1 (PD-1) pathway is a promising therapeutic option. The emergence of immunotherapy has expanded the treatment options for patients with NSCLC.⁶ The PD-1 pathway binds PD-1 to its ligands [programmed death-ligand 1 (PD-L1)] on tumor cells and suppresses T cells through a negative feedback loop, leading to evasion of immune responses.⁷ Immunotherapy prevents the combination of PD-1 and PD-L1.⁸

Although immunotherapy is effective for NSCLC, immunotherapeutic drugs are very expensive. The cost-effectiveness of using these drugs for NSCLC remains unclear due to the high cost of them. Immune checkpoint inhibitors for NSCLC include pembrolizumab, nivolumab, atezolizumab, and durvalumab. Several economic evaluations have investigated the costs and consequences of these drugs and reached different conclusions. The cost-effectiveness of these drugs are one of the research hot-spots in different countries. In October 2016, the US Food and Drug Administration (FDA) approved pembrolizumab for first-line treatment of metastatic NSCLC with a PD-L1 tumor proportion score (TPS) $\geq 50\%$ (determined by an FDA-approved test) and without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberration.⁹ In April 2019, the FDA expanded the pembrolizumab monotherapy indication for first-line treatment of patients with locally advanced or metastatic NSCLC with a PD-L1 TPS $\geq 1\%$ based on the data from KEYNOTE-042.¹⁰ However, cost-effectiveness differs among patients with various PD-L1 expression levels. With the improvement of economic level and clinical studies, the research focus and conclusions have also

changed. Hence, the present work aimed to systematic review and assess the quality of the cost-effectiveness data of immune checkpoint inhibitors for NSCLC.

Materials and Methods

A protocol of our systematic review was published in the International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/prospero/>; registration number is CRD42020151578).

Publication Search

The inclusion criteria were as follows: 1) full economic evaluations (cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses) of immune checkpoint inhibitors for patients with NSCLC, 2) immunotherapies compared with chemotherapy or with each other and those used as first- or second-line treatment, 3) the incremental analysis method was used to decide whether the higher cost of the therapeutic regimen relative to the lower plan can bring a satisfactory incremental income, and 4) use of English language in reporting. We excluded articles that focused on diagnostics and adherence, partial economic evaluations, and conference abstract. Two independent researchers (Zheng and Li) carefully searched PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to find economic evaluations of NSCLC that met the inclusion criteria. We searched the databases by using the following search terms: “non-small cell lung cancer,” “cost,” “immunotherapy,” “immune checkpoint inhibitors,” “pembrolizumab,” “nivolumab,” “atezolizumab,” and “durvalumab.” These terms were embellished slightly to meet the subject heading structure of each database.

Quality Assessment and Data Extraction

The two researchers (Zheng and Li) independently performed all quality assessments and data extractions. Any disagreement between the two reviewers was discussed with a third author (Chen). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist¹¹ was used to assess the study quality. The 24-term checklist was created by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and includes the assessment of the following: title and abstract, introduction, methods, results, discussion, and others. According to the CHEERS statement checklist, each “Yes” (fully satisfied), “NS” (partially satisfied), and “No” (not satisfied) are equivalent to 1, 0.5, and 0 points, respectively.

Scores of 19–24, 13–18, 12–17, and below 12 indicate good, medium, poor, and very poor qualities, respectively. Data were extracted following a predesigned table, which includes study details (author, country, and year of publication), baseline characteristics (target population, intervention, comparator, and outcome measure), methods (time horizon, discount, and model based), and results (type of sensitivity analysis and economic evaluation results).

Results

Search Results

Our literature search yielded 98 publications; of which, 68 were retained after excluding duplicates. After we screened the titles and/or abstracts of these publications, 37 were remained. Finally, when we reviewed the full texts, 21 records met our inclusion criteria, 16 of the studies were excluded for the following reasons: not in English language ($n = 3$), not a full report ($n = 5$), review ($n = 5$), and conference abstract ($n = 3$). The flow chart of the literature search is presented in Figure 1.

General Characteristics

The included studies were published between 2016 and 2019. The majority of the studies were conducted in developed countries (USA, UK, France, Canada, Australia, and

Switzerland). Four studies were conducted in China, and one of them was conducted in the Hong Kong region. Fourteen,^{21,22,24–31,34,38–40} four,^{33,35–37} and three^{12,23,32} studies focused on pembrolizumab, nivolumab, and atezolizumab, respectively. No study investigated durvalumab. Almost all the included studies employed cost-effectiveness analysis. Most of them reported the results in terms of cost per quality-adjusted life years (QALYs) and cost per life year (LY) gained. Among these studies, 16^{12,21–31,34,38–40} and 5^{32,33,35–37} were about first- and second-line treatments for NSCLC, respectively. One study¹² had two base cases. We did not make clear restrictions for the target population. We included patients with squamous NSCLC or non-squamous NSCLC and metastatic or advanced cancer. The expression of PD-L1 affects the selection of immune checkpoint inhibitors. Fourteen studies^{21,22,24–31,34,38–40} mentioned positive PD-L1 or high level of PD-L1, whereas one studies³⁶ explored the cost-effectiveness of PD-L1 testing. The other studies were not clearly stated. These studies were mainly based on the following clinical trials: KEYNOTE 024,¹³ KEYNOTE 042,¹⁰ KEYNOTE 189,¹⁴ KEYNOTE 407,¹⁵ KEYNOTE 010,⁵ CheckMate 057,¹⁶ CheckMate 017,¹⁷ CheckMate 078,¹⁸ the OAK trial,¹⁹ and IMpower150.²⁰ The basic characteristics and results of the studies are shown in Tables 1 and 2, respectively.

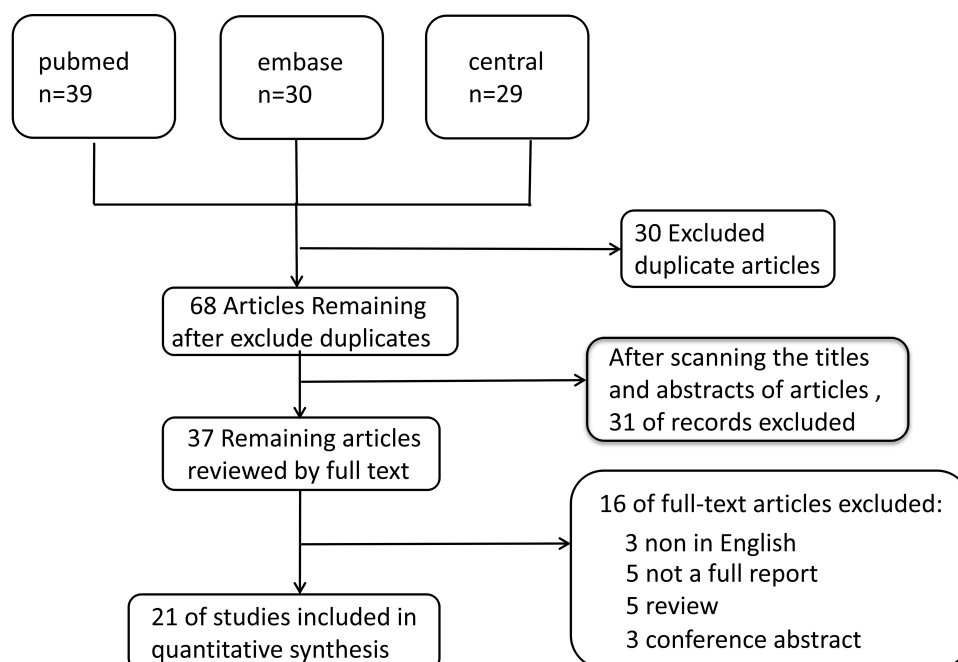


Figure 1 Flow chart of the systematic literature search.

Notes: Our literature search yielded 98 publications, of which, 68 were retained after excluding duplicates. After we screened the titles and/or abstracts of these publications, 37 were remained. Finally, when we reviewed the full texts, 21 records met our inclusion criteria.

Table 1 Characteristics of the Studies

Author	Year	Country	Target Population	Time Horizon	Intervention	Model-Based	Comparator	Discount	Outcome Measure	Perspective	Type of Costs
Huang ²¹	2019	U.S.	Previously untreated advanced or metastatic NSCLC patients whose tumors express PD-L1 (TPS $\geq 1\%$), without an epidermal growth factor receptor sensitizing mutation or an anaplastic lymphoma kinase translocation	20-years	Pembrolizumab	Partitioned-survival model	Platinum-based chemotherapy (pemetrexed + carboplatin and paclitaxel + carboplatin)	3%	LY+QALY	The US third-party public healthcare payers	Direct medical costs
She ²²	2019	U.S.	Previously untreated locally advanced or metastatic NSCLC patients without sensitive epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations and with a PD-L1 TPS $\geq 1\%$.	20-years	Pembrolizumab	Combining a decision tree and the Markov model	Platinum-based chemotherapy	3%	LY+QALY	The United States (US) payer perspective	Direct medical costs
Wan ²³	2019	U.S.	Previously untreated patients with metastatic, nonsquamous NSCLC	Full lifetime	Combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP)	Markov model	Combination of bevacizumab, carboplatin, and paclitaxel (BCP) and carboplatin and paclitaxel (CP)	3%	LY+QALY	The United States (US) payer perspective	Direct medical costs
Weng ²⁴	2019	U.S.	Patients with locally advanced or metastatic NSCLC, previously untreated and without EGFR mutation or ALK translocation.	Full lifetime	Pembrolizumab	Markov model	Platinum-based chemotherapy	3%	QALY	The US health care system perspective	Direct medical costs
Zeng ²⁵	2019	U.S.	A hypothetical US cohort of patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations	20-years	Pembrolizumab + chemotherapy (pemetrexed +platinum)	Markov model	Placebo+chemotherapy (pemetrexed+platinum)	3%	QALY	The US payer perspective	Direct medical costs
Insinga ²⁶	2019	U.S.	Patients are at least 18 years of age have squamous metastatic (stage 4) NSCLC tumor(s) and are eligible for first-line systemic chemotherapy	20-years	Pembrolizumab +chemotherapy (carboplatin and paclitaxel or nab-paclitaxel)	Partitioned-survival model	Chemotherapy alone or pembrolizumab monotherapy	3%	QALY	Third-party healthcare payer	No statement

^a Criss ¹²	2019	U.S.	No statement	No statement	Atezolizumab combination (atezolizumab plus bevacizumab + carboplatin + paclitaxel)	Microsimulation model	Bevacizumab + carboplatin + paclitaxel	3%	QALY	The US health care sector	No statement
Criss ¹²	2019	U.S.	No statement	No statement	Atezolizumab combination (atezolizumab plus bevacizumab + carboplatin + paclitaxel)	Microsimulation model	Pembrolizumab combination (pembrolizumab + carboplatin + pemetrexed)	3%	QALY	The US health care sector	No statement
Insinga ²⁷	2018	U.S.	Patients with non-squamous metastatic (stage 4) NSCLC tumor(s) without sensitizing mutations of EGFR or ALK translocations and are eligible for 1L systemic chemotherapy	20-years	Pembrolizumab + chemotherapy (carboplatin/ cisplatin + pemetrexed)	Partitioned survival model	Carboplatin + pemetrexed or cisplatin + pemetrexed	3%	QALY	A US third-party healthcare payer	No statement
Georgieva ²⁸	2018	US and UK	Previously untreated patients with advanced NSCLC and PD-L1 expression in ≥50% of tumor cells	Full lifetime	Pembrolizumab	Markov model	Platinum doublets chemotherapy		QALY	British National Health System (NHS) perspective, US cost perspective	No statement
Huang ²⁹	2017	U.S.	Adults with metastatic NSCLC expressing high levels of PD-L1	20-years	Pembrolizumab	Partitioned-survival model	Platinum-based chemotherapy	3%	LY+QALY	The US third-party public healthcare	No statement
Huang ³⁰	2016	U.S.	Advanced NSCLC patients who were at least 18 years of age (average age of 62 years) who had experienced disease progression after a platinum-containing systemic therapy	20-years	Pembrolizumab	Partitioned-survival model	Docetaxel	3%	QALY	The US third-party payer healthcare	No statement

(Continued)

Table 1 (Continued).

Author	Year	Country	Target Population	Time Horizon	Intervention	Model-Based	Comparator	Discount	Outcome Measure	Perspective	Type of Costs
Hu ³¹	2018	UK	PD-L1 positive non-small-cell lung cancer patients	Full lifetime	Pembrolizumab	Markov model	Cytotoxic chemotherapy	3.50%	QALY	The UK health care perspective	Direct medical costs
Ondhia ³²	2019	Canada	Canadians with advanced NSCLC who had progressed during or after first-line platinum doublet chemotherapy	10-years	Atezolizumab	Partitioned survival model	Docetaxel and nivolumab	2%	LY+QALY	The Canadian publicly-funded health care system	No statement
Goeree ³³	2016	Canada	Advanced squamous NSCLC patients who have failed one prior platinum doublet-based chemotherapy treatment.	No statement	Nivolumab	Markov model and partitioned-survival model	Docetaxel and erlotinib		LY+QALY	A publicly funded healthcare system	No statement
Chouaid ³⁴	2019	France	Adults, diagnosed with metastatic NSCLC, expressing high levels of PD-L1 (TPS \geq 50%), without EGFR mutations or ALK translocations and naive to systemic chemotherapy treatment for metastatic NSCLC	10-years	Pembrolizumab	Partitioned-survival model	Standard-of-Care (SoC) platinum-based doublets	4%	LY+QALY	Healthcare system perspective	Direct medical costs
Gao ³⁵	2019	Australia	Patients diagnosed with advanced or metastatic squamous NSCLC	6-years	Nivolumab	Markov model and partitioned-survival model	Docetaxel	3%	LY+QALY	The Australian healthcare system perspective	No statement
Matter-Walstra ³⁶	2016	Switzerland	No statement	Lifelong time	Nivolumab	Markov model	Docetaxel		QALY	The Swiss healthcare system perspective	Direct medical costs
Liu ³⁷	2019	China	Stage IIIB or IV or recurrent squamous or non-squamous NSCLC patients progressing on/after one previous platinum-based doublet chemotherapy, and negative for EGFR mutation or ALK translocation	Full lifetime	Nivolumab	Markov model	Docetaxel	3%	LY+QALY	The Chinese healthcare system	Direct medical costs

Zhou ³⁸	2019	China	Patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with different tumor proportion scores (TPS)	10-years	Pembrolizumab	Markov model	Platinum-based chemotherapy (carboplatin, paclitaxel and pemetrexed)	3%	QALY	The Chinese payer perspective	Direct medical costs
Liao ³⁹	2019	China	Patients confirmed stage IV NSCLC with no sensitizing EGFR mutations or ALK translocations, no previous systemic treatments for metastatic disease, and ECOG performance status score of 0 or 1, at least one measurable lesion in line with RECIST	10-years	Pembrolizumab	Markov model	One of the five platinum-based chemotherapy regimens (carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel)	3%	QALY	The Chinese societal perspective	Direct medical costs
Loong ⁴⁰	2019	China (Hong Kong)	Patients with metastatic NSCLC and a PD-L1 TPS≥50%, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations	10-years	Pembrolizumab	Partitioned-survival model	Platinum doublet chemotherapy	3%	LY+QALY	The Hospital Authority in Hong Kong	Direct medical costs

Note: ^aCriss 1 and Criss 2 represent the study had two different base cases.

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-years; NSCLC, non-small cell lung cancer; TPS, tumor proportion score.

Quality of the Identified Studies

We assessed the reporting quality of 21 studies by using the CHEERS checklist. The results are shown in Table 3. The scores ranged between 17 and 22.5 points, and the maximum score was 24 points. Three studies scored below 19, while two scored 17. About half of the studies^{12,22–25,28–31,33,36,38,39} did not provide reasons for their selected decision-analytic model nor report heterogeneity. Most studies^{12,21–28,31–34,37,39,40} did not mention whether there was preference measurement and evaluation. Many studies^{12,22,23,25,26,28,30,31,34,35,37,38,40} did not report currency, price date and conversion. And most studies did not describe how the authors were funded but only mentioned they were funded. Overall, the quality of the included studies is high (Table 3)

Perspective of Analysis

Different opinions or positions in pharmacoeconomic evaluation lead to different results. The studies included in this review indicated the following perspectives: health-care system perspective (n = 9), third-party healthcare payer (n = 9), publicly funded healthcare system (n = 2), and social perspective (n = 1). With different perspectives, the research design, analysis methods, and cost-effectiveness of pharmacoeconomic evaluations differed among various perspectives. Therefore, choosing a research perspective is essential.

Types of Modeling Approaches and Health States

All the studies included used models. The most commonly used models are Markov and partitioned survival (PS) models. One study used a model which was established by combining a decision tree and the Markov approach and one another study used a microsimulation model. Most Markov and PS model-based studies used the same three key health statuses: progression free, progressed disease, and death. The structure of the PS model is similar to that of the Markov model. However, unlike in a Markov model, in which transition probabilities between any two health statuses are needed, PS models directly use the data on the proportions of patients in each health status at each time point.³⁰ Two studies^{33,35} compared the results of using the Markov and PS models because the authors assumed that alternative model structures or modeling approaches are typically not addressed in most economic evaluations. Many papers described good modeling practices, but only a few described how to choose from the many types of

Table 2 Cost-Effectiveness Results

Author	Year	Country	Perspective	Main Outcome	Threshold	ICER
Huang ²¹	2019	U.S.	US third-party public healthcare payers	Pembrolizumab is projected to be cost-effective compared with platinum-based chemotherapy as first-line treatment for advanced non-small-cell lung cancer with PD-L1 tumor proportion score $\geq 1\%$.	\$194,000/QALY	Pembrolizumab vs platinum-based chemotherapy \$130,155/QALY and \$106,617/LY ^a PD-L1 $\geq 50\%$ patients \$111,781/QALY, \$91,063/LY PD-L1 1–49% patients \$161,546/QALY, \$134,227/LY
She ²²	2019	U.S.	The United States (US) payer perspective	Pembrolizumab is a cost-effective strategy compared with platinum-based chemotherapy as first-line treatment in locally advanced or metastatic NSCLC patients with PD-L1 TPS $\geq 50\%$ and without epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, but not in the TPS $\geq 20\%$ and 1% populations.	\$150,000/QALY	Pembrolizumab vs platinum-based chemotherapy PD-L1 $\geq 50\%$ patients \$136,228.82/QALY, \$76,390.48/LY PD-L1 $\geq 20\%$ patients \$160,625.98/QALY, \$90,965.81/LY PD-L1 $\geq 1\%$ patients \$179,530.17/QALY, \$101,763.74/LY
Wan ²³	2019	U.S.	The United States (US) payer perspective	ABCP is estimated to not be cost-effective compared with BCP or CP in the first-line setting for patients with metastatic, nonsquamous NSCLC.	\$100,000/QALY	ABCP vs BCP \$568,967/QALY, \$510,865/LY ABCP vs CP \$516,114/QALY, \$398,657/LY
Weng ²⁴	2019	U.S.	The US health care system perspective	Pembrolizumab is estimated to be cost-effective compared to chemotherapy for previously untreated NSCLC patients with different expression levels of PD-L1.	\$180,000/QALY	Pembrolizumab vs platinum-based chemotherapy PD-L1 $\geq 50\%$ patients \$47,596/QALY PD-L1 $\geq 20\%$ patients \$47,184/QALY PD-L1 $\geq 1\%$ patients \$68,061/QALY
Zeng ²⁵	2019	U.S.	The US payer perspective	Pembrolizumab in addition to chemotherapy provides modest incremental benefit at high incremental cost per QALY for the treatment of previously untreated metastatic NSCLC.	\$150,000/QALY	Pembrolizumab plus chemotherapy vs placebo plus chemotherapy \$194,372/QALY
Insinga ²⁶	2019	U.S.	Third-party healthcare payer	Within all relevant PD-L1 sub-groups, use of pembrolizumab plus chemotherapy can be a cost-effective first-line treatment for eligible metastatic squamous NSCLC patients for whom chemotherapy is currently administered. In the PD-L1 $\geq 50\%$ subgroup, additional follow-up within trials of pembrolizumab plus chemotherapy and pembrolizumab monotherapy are needed to better define cost-effectiveness between these comparators.	\$100,000/QALY	Pembrolizumab plus chemotherapy vs chemotherapy \$86,293/QALY PD-L1 $\geq 50\%$ patients \$99,777/QALY, PD-L1 1–49% patients \$85,986/QALY, PD-L1 $< 1\%$ patients \$87,507/QALY.
Criss ¹²	2019	U.S.	The US health care sector	Atezolizumab combination was not cost-effective compared with bevacizumab, carboplatin, and paclitaxel and provided suboptimal incremental benefit compared with cost vs pembrolizumab combination for first-line treatment.	\$100,000/QALY	ABCP vs BCP \$201,676/QALY BCP vs carboplatin plus pemetrexed \$80,671/QALY pembrolizumab combination dominated ABCP pembrolizumab combination vs BCP \$116,698/QALY pembrolizumab combination vs carboplatin plus pemetrexed \$106,792/QALY

(Continued)

Table 2 (Continued).

Author	Year	Country	Perspective	Main Outcome	Threshold	ICER
Insinga ²⁷	2018	U.S.	A US third-party healthcare payer	Although ICERs vary by subgroup and comparator, results suggest pembrolizumab + chemotherapy yields ICERs near, and in most cases, may be a cost-effective first-line treatment for metastatic non-squamous NSCLC patients.	\$540,000/QALY	Pembrolizumab+chemotherapy vs chemotherapy \$104,823/QALY and \$87,242/LY PD-LI ≥50% patients \$103,402/QALY, PD-LI I–49% patients \$66,837/QALY, PD-LI <1% patients \$183,529/QALY. pembrolizumab +chemotherapy vs pembrolizumab PD-LI ≥50% patients \$147,511/QALY.
Georgieva ²⁸	2018	US and UK	British National Health System (NHS) perspective, US cost perspective	Evidence suggests first-line pembrolizumab for NSCLC may be cost-effective in the US but not the UK, in spite of very similar ICER values in both countries.	The UK \$42,000/QALY the US \$100,000/QALY	Pembrolizumab vs platinum-doublets the UK \$52,000 (\$43,000–69,000)/QALY the US \$49,000 (\$40,000–67,000)/QALY
Huang ²⁹	2017	U.S.	US third-party public healthcare	Pembrolizumab is projected to be a cost-effective option compared with SoC platinum-based chemotherapy as first-line treatment in adults with meta static NSCLC expressing high levels of PD-LI.	No statement	Pembrolizumab vs SoC \$US97621/QALY, \$US78344/LY
Huang ³⁰	2016	U.S.	US third-party payer healthcare	Pembrolizumab improves survival, increases QALYs, and can be considered as a cost-effective option compared to docetaxel in PD-LI positive (TPS ≥50%) pre-treated advanced NSCLC patients in the US.	No statement (3-times GDP per capita)	Pembrolizumab versus docetaxel \$168,619/QALY
Hu ³¹	2018	UK	The UK health care perspective	Pembrolizumab is not cost-effective at its current list price and a discount of 50% or more is required for it to be cost-effective comparing to commonly prescribed chemotherapy.	£50,000/QALY	Pembrolizumab vs chemotherapy £86,913/QALY
Ondhia ³²	2019	Canada	The Canadian publicly-funded health care system	Atezolizumab represents a cost-effective therapeutic option for the treatment of patients with advanced NSCLC who progress after first-line platinum doublet chemotherapy.	No statement	Atezolizumab vs docetaxel \$142,074/QALY, \$103,726/LY atezolizumab dominates nivolumab
Goeree ³³	2016	Canada	A publicly funded healthcare system	Nivolumab was found to involve a trade-off between improved patient survival and QALYs, and increased cost. It was found that the use of a PS or Markov model produced very similar estimates of expected cost, outcomes, and incremental cost-utility.	No statement	From the PS model: nivolumab vs docetaxel \$151,560/QALY nivolumab vs erlotinib \$140,601/QALY from the markov model: nivolumab vs docetaxel \$152,229/QALY nivolumab vs erlotinib \$141,838/QALY
Chouaid ³⁴	2019	France	Healthcare system perspective	Pembrolizumab appears cost-effective versus SoC chemotherapy for first-line treatment of PD-LI-positive (50%) metastatic NSCLC patients.	No statement	Squamous NSCLC: pembrolizumab vs SoC €84,097/QALY, €66,825/LY non-squamous NSCLC: pembrolizumab vs platinum-based chemotherapies with paclitaxel plus bevacizumab €78,729/QALY, €62,846/LY

(Continued)

Table 2 (Continued).

Author	Year	Country	Perspective	Main Outcome	Threshold	ICER
Gao ³⁵	2019	Australia	The Australian healthcare system perspective	The treatment with nivolumab cannot be considered cost-effective. It might be funded publicly by special arrangements given unmet clinical needs for patients.	A\$50,000/QALY	Nivolumab vs docetaxel from the PS model, A\$198,862/QALY, A\$181,623/LY from the markov model, A\$220,029/QALY, A\$193,459/LY
Matter-Walstra ³⁶	2016	Switzerland	The Swiss healthcare system perspective	NIV compared to DOC is not cost-effective for the treatment of non-squamous NSCLC at current prices. Price reduction, or PD-LI testing and selection of patients for NIV based on test positivity, improves cost-effectiveness compared to DOC.	^b CHF100000/QALY	Nivolumab versus docetaxel CHF177478/QALY in PD-LI positive patients CHF124891/QALY
Liu ³⁷	2019	China	The Chinese healthcare system	Nivolumab was unable to be cost-effective versus the standard second-line docetaxel for patients with previously treated advanced NSCLC. When nivolumab is included in the NRDL, and the price of nivolumab discount exceeds 31.6%, nivolumab therapy will be cost-effective in China.	\$28,899/QALY	Nivolumab vs docetaxel \$93,307/QALY, \$74,126/LY
Zhou ³⁸	2019	China	The Chinese payer perspective	Pembrolizumab is not a cost-effective choice compared with standard chemotherapy for patients with locally advanced or metastatic NSCLC, regardless of TPS. Deeper discount of its current price would make pembrolizumab a preferable choice.	\$26,508/QALY	Pembrolizumab vs platinum-based chemotherapy PD-LI≥50% patients \$36,493/QALY PD-LI≥20% patients \$42,311/QALY PD-LI≥1% patients \$39,404/QALY
Liao ³⁹	2019	China	Chinese societal perspective	Pembrolizumab is not likely to be cost-effective in the treatment of PD-LI positive, NSCLC for Chinese patients. Less aggressive pricing may increase accessibility for patients in China.	No statement (three times the Chinese Gross Domestic Product per capita)	\$103,128/QALY
Loong ⁴⁰	2019	China (Hong Kong)	The Hospital Authority in Hong Kong	Pembrolizumab in a BTS to identify patients with NSCLC with PD-LI TPS≥50% can be considered cost-effective as first-line treatment in Hong Kong compared with platinum doublet chemotherapy.	\$130,490/QALY	Pembrolizumab vs platinum doublet chemotherapy \$110,922/QALY, \$89,419/LY

Notes: ^aPD-LI≥50% means that PD-LI expression level is greater than or equal to 50%. ^bCHF means Swiss Franc.

Abbreviations: A, atezolizumab; B, bevacizumab; BTS, biomarker (PD-LI) test-and-treat strategy; C, carboplatin; DOC, docetaxel; GDP, gross domestic product; LY, life-years; P, paclitaxel; PS model, partitioned-survival model; QALY, quality-adjusted life-years; SoC, standard of chemotherapy; TPS, tumor proportion score.

available models. Markov and PS models are the two most common modelling approaches used to estimate long-term costs and effects in cancer research.³³

Ten studies^{21,26,27,29,30,32–35,40} used the PS model. All of them used the parametric models for PFS and OS. The Weibull distributions was most used in PFS. For OS, the lognormal, the log logistic distributions were most used. All models extended the time horizon beyond the observed

data and incorporated an exploration of the impact of choice of particular parametric model. The best-fitting parametric distributions was selected using statistical tests based on the Akaike information criterion and the Bayesian information criterion, combined with visual inspection.

Four studies^{26,27,30,40} mentioned a cohort simulation model, which is equivalent to a Markov model and is

Table 3 CHEERS Score Results

Study	Year	Yes	Ns	No	Total Scores
Huang ²¹	2019	21	3	0	22.5
She ²²	2019	18	6	0	21
Wan ²³	2019	20	4	0	22
Weng ²⁴	2019	20	4	0	22
Zeng ²⁵	2019	16	8	0	20
Insinga ²⁶	2019	19	4	1	21
Criss ¹²	2019	17	6	1	20
Insinga ²⁷	2018	19	5	0	21.5
Georgieva ²⁸	2018	17	5	2	19.5
Huang ²⁹	2017	16	7	1	19.5
Huang ³⁰	2016	13	10	1	18
Hu ³¹	2018	13	8	3	17
Ondhia ³²	2019	18	6	0	21
Goeree ³³	2016	18	4	2	20
Chouaid ³⁴	2019	19	5	0	21.5
Gao ³⁵	2019	17	5	2	19.5
Matter-Walstra ³⁶	2016	15	4	5	17
Liu ³⁷	2019	17	7	0	20.5
Zhou ³⁸	2019	19	4	1	21
Liao ³⁹	2019	16	8	0	20
Loong ⁴⁰	2019	18	6	0	21

Notes: "Yes" indicates sufficiently/correctly described in the study; "No" indicates incorrect or no information regarding the specific topic in the study; "Ns" indicates not sufficiently described in the study.

used as a state-transition model. A cohort simulation model comprises the main health statuses of the disease and response to therapy. These four studies used this model to estimate health outcomes and costs for each regimen in specified patient population. The PS model divides the overall survival time into progression-free survival (PFS) and post-progression survival.

One study²² used a decision tree combined with the Markov model. However, it did not describe why this model was used. A part of the Markov model contains three statuses that are similar to those in the other included studies. Another study¹² used a microsimulation model to estimate the health and cost outcomes of patients. All patients entered the model in the PFS health status and could transition to progressive disease and death, which is similar to the Markov model. Neither studies provided any model framework diagram.

Uncertainty Analysis

All studies had uncertainty analysis (sensitivity analysis). This analysis aims to explore the robustness of a model's outcomes when inputs change. Sensitivity analyses was used for model uncertainty, including multi-way probabilistic

sensitivity analysis (PSA), one-way deterministic sensitivity analysis (DSA), and tornado diagram in 19,^{12,21–31,33–37,39,40} 19,^{12,21–31,33–40} and 18^{12,21–27,29–31,33–37,39,40} studies, respectively. Only one article³² used a scenario analysis to analyze uncertainty and did not use PSA or DSA. Another article²⁸ used PSA but not one-way DSA and did not present a tornado diagram. One study³⁸ only used DSA and did not present a tornado diagram. One-way DSAs were conducted to evaluate the sensitivity of the model to plausible changes in each key model parameter. Among the 19 studies that used DSA, six^{21,26,27,29,30,40} had tornado diagrams and showed that the parameters with the greatest effect on ICER were the extrapolations of PFS or OS RR, extrapolation of ToT for pembrolizumab, and health utility value for patients ≥ 360 days from death. Eight other studies^{22–25,31,33,36,38} also reported that utility values had the largest effect on the ICER results. The price of immune checkpoint inhibitors and body weight also had a high influence. The change in some parameters, ie, median OS in pembrolizumab³¹ and progressive disease,³⁶ also had a considerable influence on the results of some cases. Two-way sensitivity analyses were conducted in one study.³⁹ This analysis varied the utility of non-progression and pembrolizumab price per milligram. The result demonstrated that the increased use of PFS coupled with reductions in pembrolizumab cost resulted in cost-effective strategies.

PSA is conducted to test the robustness of the model with respect to uncertainty in model input parameters. Each study that used PSA had different thresholds and reported different conclusions. In one study,²⁸ the UK and US reached different conclusions. Out of 10 studies in the US, eight were about pembrolizumab and reached the same conclusion. The range of willingness-to-pay (WTP) threshold was \$50,000–200,000/QALY. The economic probability of pembrolizumab slightly differed among studies under the same threshold. When WTP < \$50,000/QALY, the probability of pembrolizumab to be economical is only 15%. If the WTP < \$150,000/QALY, then the economical probability is 85%–95%.^{26,27,29} In China, judging from the current price of pembrolizumab, it was impossible to be economical. If WTP rises to 100,000/QALY, there was 50% economical possibility.³⁹ Nivolumab³⁷ was also not cost-effective in China based on the WTP threshold value in the main regions but was 4.6% cost-effective in affluent regions. Almost all cases achieved cost-effectiveness when the WTP threshold reached > \$320,000. Nivolumab might be economical if

WTP > \$210,000/QALY and \$158,000/QALY in Australia³⁵ and Canada,³³ respectively.

Health Outcome Measure

In many countries, the preferred outcome measure for economic evaluations is QALY, which is a combined information on quality of life and duration. The CHEERS statement proposes an overview of techniques for describing health-related quality of life. Utility was applied to measure the patient's living preference during a particular health status.

In our included studies, several models derived the utilities from the published literature and clinical trials (via EQ-5D-3L instrument). The health utility values in one study²⁸ were obtained in accordance with distributions that were consistent with a UK-based study on health utilities for advanced NSCLC treated with immunotherapy or chemotherapy. One study²² calculated health utilities on the basis of quality-of-life data (QLQ-C30 GHS/QOL) presented in the clinical trial.

Findings of the Studies

Although all studies adopted pharmacoeconomic evaluations of immunosuppressants, their inclusion criteria for populations and study of disease status differed; hence, summarizing and integrating information are slightly difficult. A total of 14,^{21,22,24–31,34,38–40} 4,^{33,35–37} and 3^{12,23,32} studies focused on pembrolizumab, nivolumab, and atezolizumab, respectively. In the studies on pembrolizumab, 13^{21,22,24–29,31,34,38–40} articles focused on the first-line treatment of NSCLC. This drug received the most attention among the immunosuppressants. Some studies compared pembrolizumab with traditional chemotherapy, while some combined it with traditional chemotherapy and then compared their individual effects. All these studies showed that pembrolizumab was highly likely to be cost-effective. However, two Chinese studies^{38,39} indicated that pembrolizumab was not cost-effective under current Chinese pricing. Among the included studies, nine mentioned that pembrolizumab monotherapy should be used in patients who are PD-L1 positive, and the expression of PD-L1 should be $\geq 50\%$.⁹ Four of these eight studies^{29,30,34,40} concluded that pembrolizumab was cost-effective for first-line treatment compared with traditional chemotherapy. By contrast, two studies^{31,39} concluded that under the current threshold conditions of the country, pembrolizumab was not cost-effective. Two more articles^{26,27} considered that pembrolizumab combined

with chemotherapy was more economical. One study²⁸ concluded that pembrolizumab monotherapy was economical in the US but not in the UK. However, the KEYNOTE 042 trial expanded the use of pembrolizumab to PD-L1 $\geq 1\%$. Four studies^{21,22,24,38} were based on this trial. One study³⁸ indicated that pembrolizumab was not cost-effective in China regardless of the expression level of PD-L1. Weng²⁴ and Huang²¹ concluded that pembrolizumab was cost-effective in the US regardless of the expression level of PD-L1. However, in one study,²² pembrolizumab was a cost-effective strategy compared with platinum-based chemotherapy in patients with PD-L1 TPS $\geq 50\%$ but not $\geq 1\%$. Insinga 2019²⁶ compared the effects of traditional chemotherapy, pembrolizumab, and the combination of both. The author found that pembrolizumab combined with chemotherapy was more cost-effective than chemotherapy alone. The comparison between the effect of this combination to that of pembrolizumab was divided into three subgroups: PD-L1 $\geq 50\%$, PD-L1 of 1%–49%, and PD-L1 < 1%. Substantive survival gains on pembrolizumab monotherapy were not observed in the PD-L1 $\geq 50\%$ group compared to those on chemotherapy regimen. For patients with PD-L1 of 1–49%, adding pembrolizumab to carboplatin + paclitaxel/nab-paclitaxel chemotherapy yielded a net increase of 0.98 discounted LYs compared to pembrolizumab monotherapy. For patients with PD-L1 < 1%, life expectancy was projected to be doubled versus chemotherapy. Of the 14 pembrolizumab studies, 13 investigated pembrolizumab as first-line treatment. Of the 13 studies, eight showed that pembrolizumab was more economical than traditional chemotherapy regimens. One study²⁸ included the UK and US perspectives. Pembrolizumab was economical in the US but not in the UK. Four other studies showed that using pembrolizumab was not economical given the country's current threshold. One study³⁰ from the 14 was for included patients who experienced disease progression after undergoing platinum-containing systemic therapy. The results suggested that pembrolizumab improved quality-adjusted expectancy and could be considered a cost-effective option compared with docetaxel for patients with biomarker-identified advanced NSCLC.

Nivolumab was used for second-line treatment in the included studies. Atezolizumab could be used as first- or second-line treatment therapy. Treatment with nivolumab and atezolizumab did not explicitly require high levels of PD-L1 expression. Four studies on nivolumab did not clearly demonstrate this drug to be cost-effective.

Goeree's research³³ showed that a trade-off between improving patient survival and QALYs and increasing costs exist regardless of the cost-effectiveness of nivolumab. In addition, the cost of nivolumab is expected to increase for per patient but also improve LY and QALY outcomes compared with existing SOC (ie, docetaxel and erlotinib). Clinical data of nivolumab in previously treated patients with squamous NSCLC presented a compelling case, that is, nivolumab represents a major advancement in disease management, where few effective treatment options are available and current treatment options are poorly tolerated with moderate efficacy. Three other nivolumab studies showed that the drug was not cost-effective at the current national threshold but could be improved by PD-L1 testing or special funding methods. Ondhia³² concluded that atezolizumab is a cost-effective second-line therapeutic option in Canada for the treatment of patients with advanced NSCLC. However, atezolizumab combination therapy was not cost-effective when used as first-line treatment for NSCLC. Wan²³ and Criss¹² concluded that the combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) is less cost-effective than that of bevacizumab, carboplatin, and paclitaxel (BCP) or carboplatin and paclitaxel (CP) in the first-line treatment of patients with NSCLC. In addition, Criss¹² found that atezolizumab combination provides a suboptimal increased cost benefit compared with pembrolizumab combination for first-line treatment.

Discussion

This comprehensive review examined studies on the cost-effectiveness of immunotherapy for NSCLC. Twenty-one studies were included in our systematic review, and the quality of the studies was assessed using the CHEERS checklists, a well-known and trusted tool. We did not make clear restrictions with regard to the eligibility of the patients. The inclusion criteria were patients with advanced, metastatic, squamous, or non-squamous NSCLC. These studies assessed the comparison of immune checkpoint inhibitors alone with chemotherapy, or comparing immune checkpoint inhibitors in combination with traditional therapies and traditional therapies alone or immune checkpoint inhibitors alone. The models used in these studies were mainly Markov and PS models and included three statuses, namely, progression free, progressive disease, and death, to simulate the disease course. The patients started receiving treatment regimens under progression-free status. QALY was used as an outcome

in all of the analyses. In most situations, a treatment is considered cost-effective when the ICER is below the threshold value.

CEAs were country specific because they included the costs of therapies applicable to each specified country. For each country, the conclusions were not completely consistent because of different clinical practice patterns, health-care systems, cultural and ethical practices,²¹ and thresholds. Georgieva²⁸ found that first-line pembrolizumab is likely to be cost-effective within the US but not in the UK compared with platinum doublets. This difference stemmed from different WTP thresholds (US: \$100,000; UK: \$42,048) as the ICER values of both countries were close to each other in nearly all sensitivity and dependency analyses. In high-income countries, such as the UK, the cost-effectiveness of pembrolizumab must be carefully considered. The contradiction between clinical efficacy and cost is important and must be resolved immediately. Countries need to find ways to lower drug prices for the benefit of more people.

The quality of the reviewed articles was generally good. The quality evaluation scores of most studies were more than 20. However, some studies scored low in measurement and valuation of preference-based outcomes, currency, price date and conversion, choice of model, heterogeneity characteristics, and source of funding. "Source-of-funding" description was among the items most frequently missed. Most studies described their source funding as from a manufacturer but did not describe how the study was funded and the role of the funder. These domain scores further showed that emphasis was given to the design of the studies and interpretation of results. This finding must be further explored to enhance the adherence to methodological standards for economic analysis or to create standards specifically for NSCLC research. Systematic, transparent, and regular assessments of publications and scrutiny of peer-review processes in dominant publication outlets are needed to improve the reporting standards of economic evaluation.

In typical pharmacoeconomic evaluations, almost all analyses were fully or partially funded by the manufacturer. In addition, most analyses clearly indicated the source of funding, and 9 studies were funded by companies. Of them,^{6,21,26,27,29,30,40} were funded by Merck Sharp & Dohme Corp, the other were funded by Hoffmann-La Roche Limited,³² Bristol-Myers Squibb³³ and MSD³⁴ respectively. The results of pharmacoeconomic research supported by the manufacturer are likely to generate

preferences. The data cited would be biased toward the results beneficial to the pharmaceutical companies, and the results may be biased to the side beneficial to them. To improve the efficiency of data obtained for pharmacoeconomic evaluation, we should have the concepts of big data, systematize and standardize data records, strengthen the training of medical personnel about medical records, and provide objective knowledge of drug reactions.

Our review has some limitations. We did not include studies related to durvalumab because no pharmacoeconomic studies on durvalumab met our inclusion criteria. The criterion limiting the articles to those written in English meant that we might have excluded many non-English studies. In addition, selecting only three databases and excluding unpublished studies (gray literature, conference abstracts) created some bias. Thus, the results may be subjected to a slight time lag. Given the small number of long-term economic evaluations, heterogeneity of the study population, differences in interventions and follow up, and huge differences between medical costs and health systems in different countries, the results must be cautiously generalized and utilized for policy-making. These factors are inherent drawbacks in economic evaluation studies. Moreover, further research must be conducted under local conditions.⁴¹

In the NCCN guideline version 3.2019 for NSCLC, single-agent pembrolizumab is the preferred drug regardless of histology for patients with metastatic NSCLC, PD-L1 levels of 50% or more, and negative or unknown test results for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. In our review, pembrolizumab was cost-effective in many developed countries except in the UK. For patients with metastatic non-squamous NSCLC whose PD-L1 levels are less than 50% or unknown, pembrolizumab/carboplatin (or cisplatin)/pemetrexed is the preferred option. One study²⁷ showed that pembrolizumab combination therapy is projected to extend life expectancy and may be a cost-effective first-line treatment for patients with metastatic non-squamous NSCLC. However, another study²⁵ showed that the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC had high incremental cost and modest incremental benefit. Although not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for treatment with PD-1 or PD-L1 inhibitors. Regardless of PD-L1 expression levels, first-line combination therapies with pembrolizumab (or

atezolizumab/bevacizumab)/chemotherapy are the most recommended options for patients with non-squamous NSCLC with negative test results for EGFR mutations and ALK rearrangements. However, atezolizumab combination therapy was found to be not cost-effective in two studies^{12,23} conducted in the US. Pembrolizumab combination represented a better trade-off than atezolizumab combination.¹² Therefore, the benefits and costs must be weighed before choosing atezolizumab combination therapy. Immune checkpoint inhibitors could not be used in patients with NSCLC and EGFR mutation and ALK translocation.

Conclusions

This review indicated that pembrolizumab regimens are cost-effective in patients with NSCLC as first-line treatment in developed countries, especially in the USA. Nivolumab and atezolizumab are likely cost-effective as second-line treatment but not cost-effective as first-line treatment. However, in developing countries, such as China, less aggressive pricing may increase drug accessibility for patients with NSCLC. However, existing economic evaluations are limited by variations in the study design, outcome measure, and population characteristics. Additional research should be performed and include evidence of consistent measurements.

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Disclosure

The authors declare that they have no conflicts of interest.

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