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A SYSTEMATIC REVIEW OF HEALTH ECONOMIC EVALUATIONS OF PD-(L)1 INHIBITORS FOR FIRST-LINE TREATMENT AMONG PATIENTS WITH HIGH PD-L1 EXPRESSION NON-SMALL CELL LUNG CANCER

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ABSTRACT

Objectives: To summarize evidence on the cost-effectiveness of PD-(L)1 inhibitors as first-line therapy in patients with high PD-L1 expression non-small cell lung cancer.

Methods: A systematic review following the PRISMA guidelines was conducted, searching PubMed, Embase, Scopus, and health technology assessment agency websites up to September 24, 2022. Eligible studies evaluated the economic outcomes of PD-(L)1 inhibitors as first-line treatment for high PD-L1 expression non-small cell lung cancer. Study quality was assessed using the CHEERS and QHES checklists

Results: 17 eligible studies were included, mostly from high-income countries (HICs), using model-based analyses from healthcare system or third-party payer perspectives. Pembrolizumab was cost-effective compared to chemotherapy in most HICs, except Singapore, but not against pembrolizumab-platinum combinations in Sweden. In China, its cost-effectiveness was uncertain. Cemiplimab was cost-effective compared to pembrolizumab or chemotherapy in the US. Atezolizumab showed inconsistent results depending on willingness-to-pay (WTP) thresholds in the US and China. Drug price significantly impacted cost-effectiveness results. Quality scores ranged from 18–22.5/28 (CHEERS) and 71.5–92.5/100 (QHES).

Conclusion: Cost-effectiveness of PD-(L)1 inhibitors for the first-line NSCLC treatment varied by country, comparator, model setting, and WTP. Policymakers should use country- and healthcare system-specific economic evaluation to guide their decision-making on resource allocation.

Keywords: Economic evaluation, non-small cell lung cancer, NSCLC, PD-1/PD-L1 inhibitors, systematic review.

1. INTRODUCTION

Lung cancer, or NSCLC, is a malignant disease with a high mortality rate, particularly in advanced stages where treatment options like surgery are limited. Recent treatments like chemotherapy, radiotherapy, and targeted therapies have shown limited advancements, with targeted therapies benefiting only a small subset of patients [1, 2]. Immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 inhibitors, have emerged as promising treatments, significantly improving overall survival (OS) in metastatic NSCLC. However, existing systematic reviews on the pharmacoeconomics of ICIs are limited in scope, often focusing on specific drugs or treatment stages. Therefore, a comprehensive systematic review economic evaluations of PD-1/PD-L1 inhibitors in first-line treatment of NSCLC is needed to better understand their cost-effectiveness.

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Objectives To provide the available evidence on the cost-effectiveness of PD-(L)1 inhibitors as first-line therapy in NSCLC patients with high PD-L1 expression.

2. MATERIALS AND METHOD

2.1. Study design: This systematic review was reported in accordance with PRISMA statements.

2.2. Search strategy:

Searches were conducted on PubMed, Embase, Scopus and health technology assessment (HTA) agency websites (NICE, CADTH) upto September 24, 2022. Search strategy combined terms related to the following topic: (i) Population: NSCLC patients; (ii) Intervention: PD-1 inhibitors include pembrolizumab (Keytruda), nivolumab (Opdivo), cemiplimab (Libtayo), camrelizumab (AiRuiKa)), and PD-L1 inhibitors include atezolizumab (Tecentriq), durvalumab (Imfinzi); and (iii) Study design: economic evaluations, including cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. In addition, previous systematic reviews and reference lists of included studies were reviewed for additional studies meeting criteria. On NICE and CADTH websites, generic drug names were used to locate relevant reports.

Study selection Included studies evaluated the cost-effectiveness of PD-(L)1 inhibitors as first-line therapy in NSCLC patients with high PD-L1 expression, published in English. Exclusions: (i) Full text unavailable, (ii) Non-human studies, (iii) articles not primary research: overviews, systematic reviews, meta-analyses, letters, etc. Studies were managed using Endnote software, where duplicates were removed. Title/abstract, and full-text screenings were independently conducted by two researchers (P.T.T.N and H.N.N). Any discrepancies were resolved through discussion.

Quality assessment Study quality was assessed by two researchers (H.N.N and H.P.T) using the CHEERS and QHES checklists. CHEERS evaluated 28 criteria, covering the title, abstract, introduction, methods, results, and discussion. QHES assessed 16 criteria, with a maximum score of 100.

Data analysis Reported costs were adjusted to 2021 US dollars (USD) using the local currency's inflation rate and the exchange rate.

3. RESULT

3.1. Electronic databases

Search results A total of 766 studies were identified. After removing duplicates, 413 titles and abstracts were screened, with 87 meeting the criteria for full-text review. All full texts were accessible, and 17 studies were included in the systematic review (Figure 1).

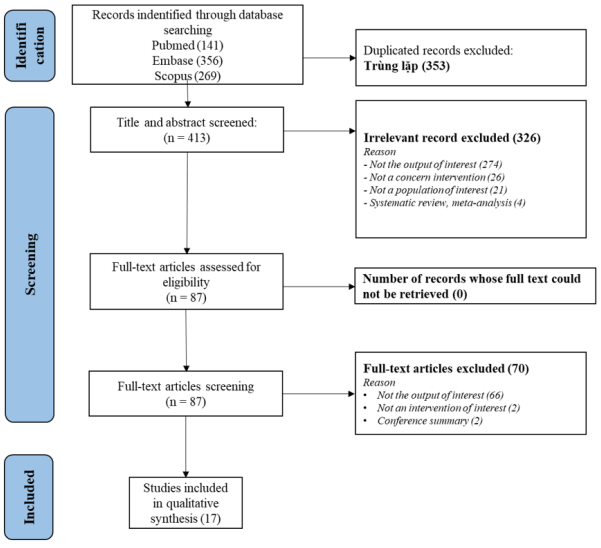

Figure 1. The PRISMA diagram presents the study selection results from electronic databases

Characteristics of the included studies Most studies were conducted in high-income countries (HICs) such as Sweden, Singapore, the US, the UK, and France, with four studies [3-6] in China (a high-middle-income country). Pembrolizumab was evaluated in 12 studies [3, 5, 7-16], atezolizumab in three studies [4, 6, 17] and cemiplimab in two studies [18, 19]. All 17 studies compared interventions to platinum chemotherapy, with three studies [8, 10] and [18] including additional comparisons such as PD-(L)1 monotherapy, combination therapy, or standard-of-care. Most analyses used model-based approaches from a healthcare system or third-party payer perspective. (Figure 2)

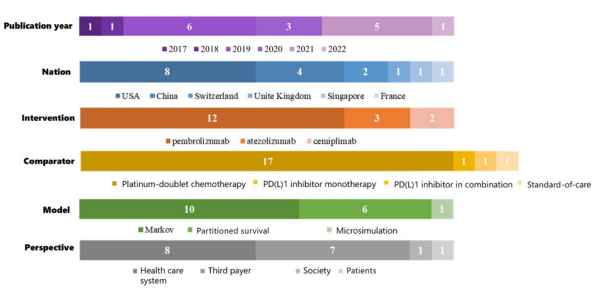

Figure 2. General overview of the included studies

Base-case results All studies [3-10, 12-19] except one [11] evaluated the cost-utility of PD-1/PD-L1 inhibitors for first-line treatment in NSCLC patients with high PD-L1 expression. Pembrolizumab was cost-effective compared to platinum-based chemotherapy in all HICs except Singapore but was not cost-effective compared to pembrolizumab-platinum combinations in Sweden. In China, its cost-effectiveness versus chemotherapy was uncertain. Atezolizumab showed inconsistent cost-effectiveness in the US and China

under different WTP thresholds. Cemiplimab was cost-effective compared to pembrolizumab or platinum-based chemotherapy in the US. The detailed results are presented in Figures 3 and Table 1.

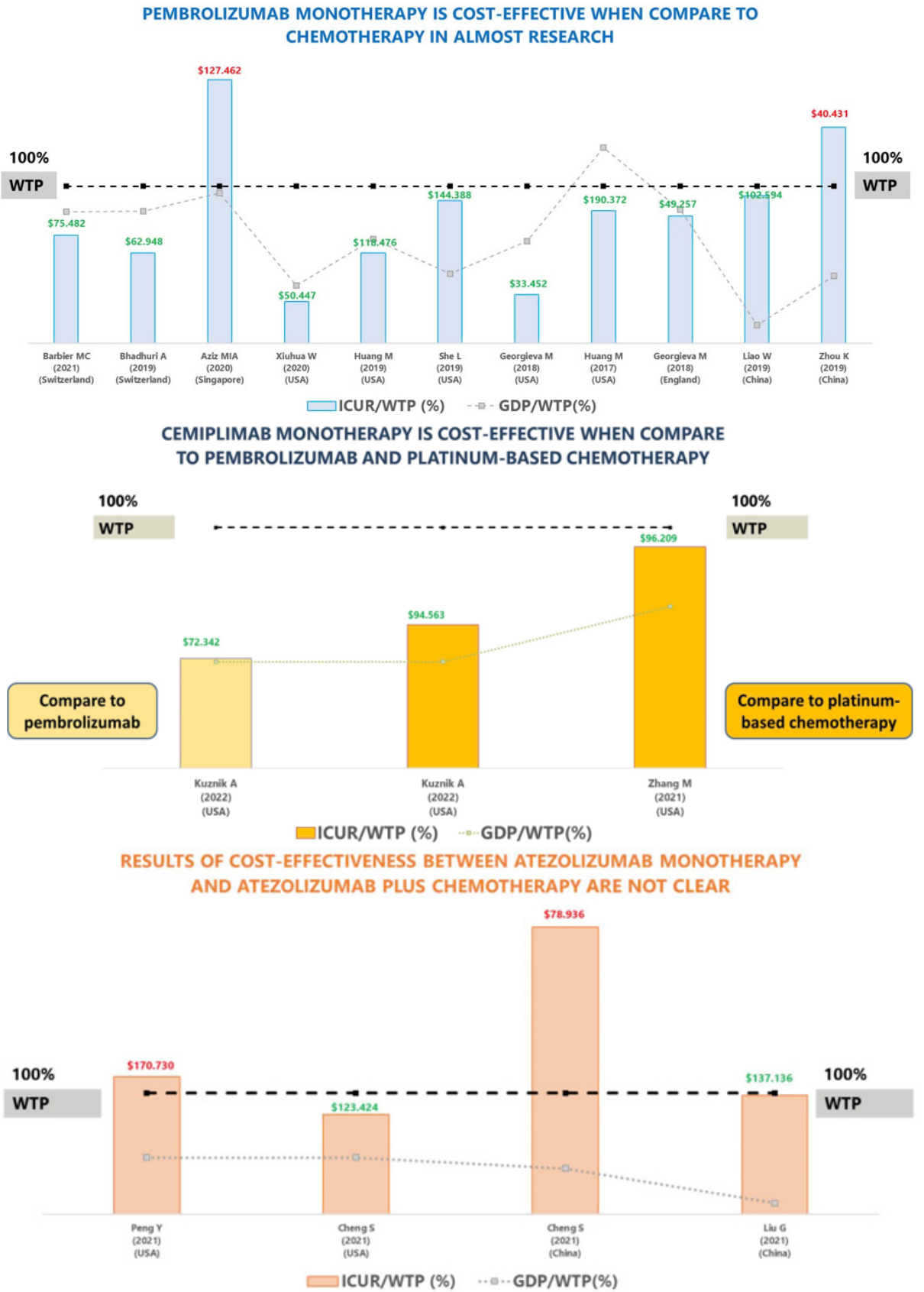

Figure 3. Base-case results of the included studies

Table 1. Base - case results of included studies

	Authors (Year)	Country	Comparison	Δ Cost(*) (USD)	ΔLY	Δ QALY	ICER(*) (USD/LY)	ICUR(*) (USD/QALY)	WTP(*) (USD/QALY)	GDP (2021)	WTP/ GDP	Conclude
Pembrolizumab												
1	Barbier MC (2021)[8]	Swedish	Pem + HTP	-89.256	NA	-0,17	NA	523.125	110.064	91.992	1,20	Cost-effective
			HTP	62.680	NA	0,83	NA	75.482	110.064	91.992	1,20	Cost-effective
2	Bhadhuri A (2019)[9]	Swedish	HTP	84.505	1,69	1,34	49,930	62.948	109.662	91.992	1,19	Cost-effective
3	Aziz MIA (2020)[7]	Singapore	HTP	110.455	1,15	0,87	96,048	127.462	76.009	72.794	1,04	Not cost-effective
4	Xiuhua W (2020)[16]	United States	HTP	57.005	NA	1,13	NA	50.447	190.791	70.249	2,72	Cost-effective
5	Huang M (2019)[13]	United States	HTP	67.367	0,94	0,77	96,517	186.876	105.989 – 205.619	70.249	1,51 – 2,93	Cost-effective
6	She L (2019)[15]	United States	HTP	91.326	1,13	0,63	80,965	118.476	158.984	70.249	2,26	Cost-effective
7	Georgieva M (2018) [12]	United States	HTP	63.667	NA	0,82	NA	144.388	107.910	70.249	1,54	Cost-effective
		England	HTP	94.168	NA	0,82	NA	33.452	60.916	70.249	0,87	Cost-effective
8	Huang M (2017)[14]	United States	HTP	181.230	1,18	0,95	181.230	49.257	56.450 – 225.801	70.249	0,80 – 3,21	Cost-effective
9	Chouaid C (2019)[10]	France	CSC-B(a)	77.161	0,93	0,74	83.123	190.372	211.460	43.659	4,84	Cost-effective
			CSC-B(b)	78.534	1,27	1,02	61.877	104.607	161.705	43.659	3,70	Cost-effective
			GC-B(b)	74.538	1,32	1,02	56.469	77.043	161.705	43.659	3,70	Cost-effective
			PC-B(b)	66.717	0,85	0,68	78.490	73.077	161.705	43.659	3,70	Cost-effective
			PC(b)	58.542	1,03	0,83	56.837	98.113	161.705	43.659	3,70	Cost-effective
			PC-B(b)	-18.592	0,85	0,64	-21.873	70.532	161.705	43.659	3,70	Superior
11	Liao W (2019)[5]	China	HTP	50.617	NA	0,45	NA	-29.051	109.179	12.556	8,70	Cost-effective
12	Zhou K (2019)[3]	China	HTP	72.371	NA	1,79	NA	112.594	29.369	12.556	2,34	Not cost-effective
Atezolizumab												
13	Peng Y (2021)[17]	United States	HTP	224.590	2,08	1,32	54.156	170.730	100.000 – 150.000	70.249	1,42 – 2,14	Not cost-effective

	Authors (Year)	Country	Comparison	Δ Cost(*) (USD)	ΔLY	Δ QALY	ICER(*) (USD/LY)	ICUR(*) (USD/QALY)	WTP(*) (USD/QALY)	GDP (2021)	WTP/ GDP	Conclude
14	Cheng S (2021)[6]	United States	HTP	107.089	1,27	0,87	58.643	123.424	100.000 – 150.000	70.249	1,42 – 2,14	Cost-effective
		China		68.489	1,27	0,87	84.678	78.936	33.210	12.556	2,64	Not cost-effective
15	Liu G (2021)[4]	China	HTP	124.911	2,13	0,91	108.205	137.136	139.598	12.556	11,12	Cost-effective
Cemiplimab												
16	Kuznik A (2022)[18]	United States	Pem	72.235	1,46	1,00	49.456	72.342	105.989 – 158.984	70.249	1,51 – 2,26	Cost-effective
			HTP	168.658	2,63	1,78	64.129	94.563	105.989 – 158.984	70.249	1,51 – 2,26	Cost-effective
17	Zhang M (2021)[19]	United States	HTP	102.825	1,54	1,07	66.769	96.209	104.698	70.249	1,49	Cost-effective

(*)Converted to USD 2021; Classification of patients with ([a]) Charlson Quality Score of 0; ([b]) Charlson Quality Score 1; ([c]) Charlson Quality Score 2; ([d]) Peripheral vascular disease; ([e]) Diabetes; ([f]) Chronic obstructive pulmonary disease; ([g]) Cerebrovascular disease; ([h]) Congestive heart Not cost-effectiveure; Classification of patients with ([I]) Group of people with scabs; (2) Group of patients without scabs; HTTP, platinum valence; GCB, gemcitabine + cisplatin/carboplatin + bevacizumab; PCB, pemetrexed + cisplatin/ carboplatin + bevacizumab; PC, pemetrexed + cisplatin/carboplatin

3.2. Quality assessment:

Regarding quality assessment, the scores of the included studies ranged from 18 to 22.5 out of 28 on the CHEERS checklist and from 71.5 to 92.5 out of 100 on the QHES checklist. (Figure 4)

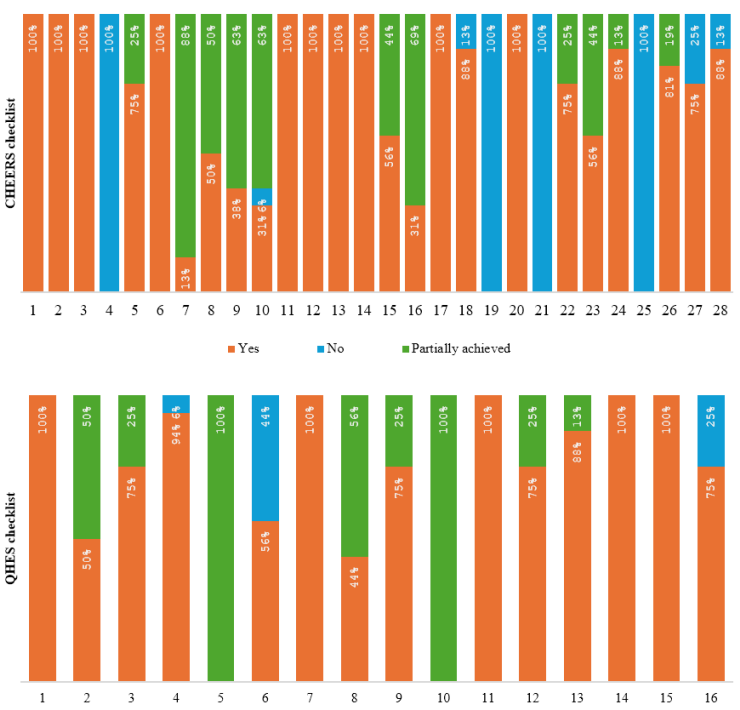

Figure 4. Summary quality assessment results of the included studies

3.3. Health technology assessment Agencies

3.3.1. Search result: Searching the websites of HTA agencies, including NICE and CADTH, we found four reports that meet the inclusion criteria.

Table 2 and Table 3 summarize the results of the reports from NICE and CADTH

3.3.2. HTA Agency in the United Kingdom (NICE): Two reports from NICE met the selection criteria: one for pembrolizumab (2018)[20] and one for atezolizumab (2021)[21].

The pembrolizumab report [20], based on the KEYNOTE-024 trial [22], targeted NSCLC patients with high PD-L1 expression, no EGFR or ALK mutations, and no prior treatment. Pembrolizumab improved overall survival (OS) by over 15 months compared to platinum chemotherapy and was cost-effective, with an ICER ranging from £30,244 to £44,483/QALY. Treatment was limited to 2 years or discontinued earlier for disease progression or unacceptable adverse events. NICE recommended reimbursement for pembrolizumab once a pricing agreement is established.

The report on atezolizumab [21] used a partitioned survival model to compare atezolizumab with pembrolizumab, using indirect analysis from trials IMPOWER110 [23], KEYNOTE-024 [22], and KEYNOTE-042 [24]. Atezolizumab was found to be as effective as pembrolizumab in delaying disease progression and extending lifespan, though ICER values were not reported. NICE recommended reimbursement for atezolizumab under similar conditions, contingent on a pricing agreement.

3.3.3. HTA Agency in Canada (CADTH): Two reports from CADTH aligned with the study criteria: one for pembrolizumab (2017) [25] and one for cemiplimab (2022) [26].

The pembrolizumab report [25], based on the KEYNOTE-024 trial [22] evaluated its cost-effectiveness compared to platinum chemotherapy in NSCLC patients with high PD-L1 levels, no EGFR or ALK mutations, and no prior treatment. Pembrolizumab improved progression-free survival (PFS) by 4.3 months and overall survival (OS) by 14.5 months compared to chemotherapy. However, its ICER exceeded the WTP threshold due to unclear long-term therapeutic efficacy, leading CADTH to recommend reimbursement only if efficacy improves significantly.

In the report for cemiplimab [26] published in June 2022, the study based on the EMPOWER-Lung 1 trial [27], compared cemiplimab with platinum chemotherapy and pembrolizumab in stage IV/IIIB/IIIC NSCLC patients (PD-L1 >50%). Cemiplimab improved PFS by 1.7 months and OS by 7.8 months versus chemotherapy, with an ICER of $26,521/QALY. It was also superior to pembrolizumab in indirect comparisons. CADTH recommended cemiplimab for first-line treatment, limited to a maximum of 108 weeks.

Table 2. Summary of general information of the report on the Health Technology Assessment Agency

No.	HTA Agency	Submission date	Intervention	Comparator	Populations recommended for reimbursement	Recommendation
1	NICE	07/2018	Pembrolizumab monotherapy	Standard of care	Patients with NSCLC have high-grade PD-L1 (PD-L1 >50%), no EGFR and ALK expressions, and have not been previously treated.	NICE recommends when: - Treatment with pembrolizumab only continuously for 2 years or stopping the drug earlier in case of disease progression - Reaching an agreement on the price between the company and the management agency.
2	NICE	06/2021	Atezolizumab monotherapy	Pembrolizumab monotherapy	Patients with NSCLC have high-grade PD-L1 (PD-L1 >50%), no EGFR and ALK expressions, and have not been previously treated.	NICE recommends paying when a price agreement is reached between the company and the regulator.

3	CADTH	08/2017	Pembrolizumab monotherapy	Platinum chemotherapy	Patients with metastatic UTPKTB, with high-grade PD-L1 (PD-L1 >50%), no EGFR and ALK expressions, and no prior treatment.	CADTH recommends payment of pembrolizumab when it improves cost-effectiveness.
4	CADTH	06/2022	Cemiplimab	(1) Platinum chemotherapy (2) Pembrolizumab	Patients with stage IV/IIIB/IIIC have high-grade PD-L1 (PD-L1 >50%), no EGFR, ALK and ROS-1 expressions, and have not been previously treated.	CADTH recommends cemiplimab for up to 108 weeks.

Table 3. The basic characteristics of pharmaceutical economic assessments in the reports of HTA agencies

No.	HTA Agency	Intervention	Perspective	Study design	Model	Health states	Time horizon	ICER (USD/QALY)
1	NICE	Pembrolizumab monotherapy	Third party payers	CUA	The company's economic model	Time to death (days): <30 – ≥360	2 years	30,244 – 44,483£/QALY *(Continuous pembrolizumab treatment only for two years)*
2	NICE	Atezolizumab monotherapy	Third party payers	CUA	Partitioned survival	- Progression -free state - Progressive disease - Death	Life-time	NR
3	CADTH	Pembrolizumab monotherapy	Third party payers	CUA	Partitioned survival	- Progression -free state - Progressive disease - Death	10 years	NR
4	CADTH	Cemiplimab	Canada Health Insurance	CUA	Partitioned survival	- Progression -free state - Progressive disease - Death	Life-time (30 years)	• $26,521/QALY when compared to platinum chemotherapy • More cost-effective than pembrolizumab when compared to chemotherapy

4. DISCUSSION AND CONCLUSTION

PD-1/PD-L1 immune checkpoint inhibitors have demonstrated superior clinical efficacy, but their high cost remains a significant barrier to access. This systematic review evaluated 17 studies, primarily conducted in high- and upper-middle-income countries. All studies employed Markov models or partitioned survival models, with key outcomes measured in ICER/QALYs and ICER/LYs. The included studies were of high quality according to the CHEERS and QHES checklists.

The results showed that pembrolizumab were cost-effective in most high-income countries, but results were inconsistent in China due to lower willingness-to-pay (WTP) thresholds. Atezolizumab showed mixed cost-effectiveness results in countries such as the United States and China, attributed to differences in drug costs and WTP thresholds. Cemiplimab was demonstrated to be cost-effective in both studies conducted in the US, compared to chemotherapy and pembrolizumab. The one-way sensitivity analyses showed that drug price was the most influential parameter on the cost-effective results of pembrolizumab and atezolizumab; for cemiplimab, overall survival (OS) and progression-free survival (PFS) were key drivers of cost-effectiveness.

Reports from Health Technology Assessment (HTA) agencies indicate that PD-1/PD-L1 inhibitors like atezolizumab and pembrolizumab are recommended for reimbursement if pricing agreements are achieved. Pembrolizumab was found to be cost-effective compared to chemotherapy (limited to a maximum of 2 years) according to NICE. However, CADTH recommended pembrolizumab for reimbursement only if there were significant improvements in cost-utility, while cemiplimab was deemed cost-effective compared to both chemotherapy and pembrolizumab, with a treatment duration limited to 108 weeks.

This review aligns with previous studies, showing that pembrolizumab is cost-effective in high-income countries like the United States but not in China or the United Kingdom, due to differences in willingness-to-pay thresholds and drug pricing policies. Cemiplimab demonstrated higher cost-effectiveness in certain contexts. The findings emphasize that economic evaluations of these drugs must align with the specific context of each country. Overall, the systematic review provides policymakers with a comprehensive understanding of the cost-effectiveness of PD-1/PD-L1 therapies and supports decision-making for treatment strategies at the national level.

Recommendations Future economic evaluations of PD-1/PD-L1 inhibitors for NSCLC treatment should be conducted in Vietnam, as the results from existing studies in the review are based in high-income or upper-middle-income countries with differing willingness-to-pay (WTP) thresholds. This will ensure that the specific context of Vietnam is considered in the analyses.

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