EE391

Economic Evaluations of First-Line Non-Small Cell Lung Cancer Therapies: A Systematic Review with Focus on PD-L1 Subgroups

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BACKGROUND

- Lung cancer is the leading cause of cancer-related deaths globally, responsible for 1.8 million deaths in 2020[1,2] with non-small cell lung cancer (NSCLC) accounting for ~85% of all lung cancer cases.[2]
- Over the past decade, immunotherapies have significantly improved survival. Immune checkpoint inhibitors (ICIs) are now central to NSCLC treatment, either alone or in combination with chemotherapy/targeted agents.[3,4]
- PD-L1 expression has emerged as a key biomarker, with higher levels predicting greater ICI benefit.[5]
- As ICIs become standard of care, economic evaluations increasingly stratify by PD-L1 expression to reflect differences in clinical and cost outcomes.[6]
- The aim of this systematic literature review (SLR) is to summarize published cost-effectiveness analyses (CEAs) and budget impact models (BIMs) for first-line advanced/metastatic NSCLC with focus on how economic value differs across PD-L1 subgroups.

METHODS

- Searches were conducted from January 2018 to March 2024 in Embase, MEDLINE, National Health Service Economic Evaluation Database (NHS-EED), EconLit and International Network of Agencies for Health Technology Assessment (INAHTA).
- This was supplemented by searches of congresses, reference lists of relevant SLRs/meta-analysis and HTA submissions.
- The eligibility of studies was defined in terms of the population, intervention, comparators, outcomes, and study design (PICOS) criteria, as presented in **Table 1**.
- Studies reporting CEAs or BIMs of first line therapies in adults with advanced or metastatic NSCLC in North America, Europe and Oceania were included for extraction.

Table 1: PICOs Criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Metastatic/advanced, non-resectable, 1L, NSCLC	Non-metastatic/advanced NSCLC or non-human
Interventions	All	Non-pharmacological interventions or surgery
Outcomes	All/none	None
Study design	Economic evaluations (e.g., cost-effectiveness analyses [CEA], budget impact analyses [BIA])	Any other non-relevant outcome
Language	Cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-minimization analysis, cost-consequence analysis, budget impact analysis and SLRs (for cross-checking only)	Non-systematic reviews, case series, reports, commentaries and editorials

Abbreviations: BIA, budget impact analysis; CEA, cost-effectiveness analyses; NSCLC, non small cell lung cancer; SLR, systematic literature review.

RESULTS

- In total 70 studies reported economic evaluations (60 CEAs, 10 BIMs) [**Figure 1**].
- For the CEAs, model types, geographies, time horizons and discount rates are summarized in **Figure 2**.
- Among the 60 CEAs pembrolizumab-based regimens were the most frequently assessed intervention (n=36, 60%) and chemotherapy (n=46, 76.7%) the most frequently assessed comparator.
- Clinical inputs were mainly from the CheckMate 227, KEYNOTE-024, and KEYNOTE-042 clinical trials.
- Modelled outcomes included costs (total, incremental) and quality adjusted life years (QALYS) or life years (LY) (total, incremental) alongside the calculated ICER.

Figure 1: PRISMA Flow Diagram

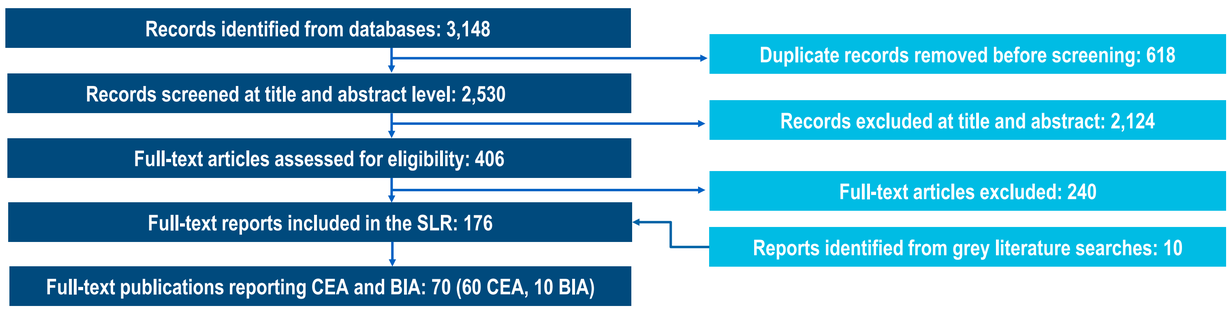
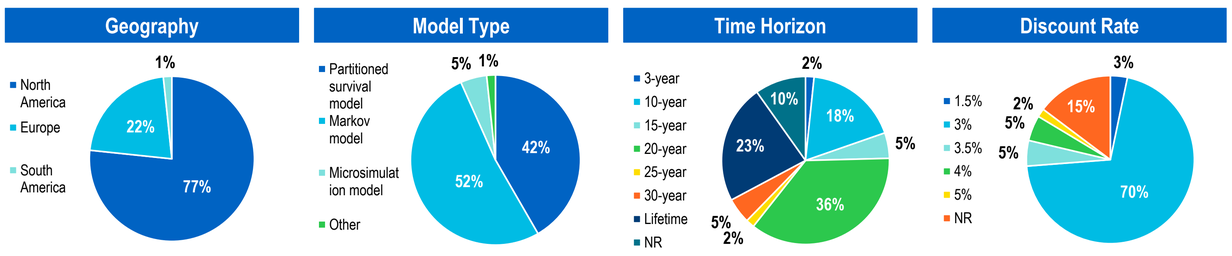


Figure 2: Summary of CEAs (N=60)



PD-L1 Subgroup Reporting

Thirty-seven studies reported results by PD-L1 status, of which 33 reported on a subgroup of PD-L1 ≥50%, 8 on a subgroup of PD-L1 1–49% and 12 on a subgroup of <1%.

A full breakdown is shown in **Table 2** with results by PD-L1 narratively synthesized by intervention:

Atezolizumab-based regimens

- **Monotherapy:** Cost-effective in PD-L1 ≥50% subgroup; ICERs ranged from $54K–$171K/QALY in the US (mostly below the US $150K/QALY WTP threshold). In Spain, atezolizumab was dominant (more effective and less costly) versus chemotherapy.
- **Combination:** Not cost-effective across PD-L1 subgroups; ICERs $528K–$843K/QALY (USA) in PD-L1 ≥50%, 1–49%, and <1% groups.

Cemiplimab-based regimens

- **Monotherapy:** Consistently cost-effective versus chemotherapy in PD-L1 ≥50% subgroup; ICERs $23K–$92K/QALY (USA). Dominant vs pembrolizumab (Spain) and atezolizumab (USA).
- **Combination:** Not cost-effective; ICER of $637K/QALY vs cemiplimab monotherapy (USA).

Nivolumab + Ipilimumab-based regimens

- **Dual immunotherapy:** Mixed cost-effectiveness in <1% subgroup (ICERs $77K–$186K/QALY). For ≥1% subgroup, ICERs $129K–$246K/QALY, often above WTP. In ≥50% subgroup, mostly cost-effective ($107K–$127K/QALY), though one study reported $212K/QALY.
- **Combination:** Addition of chemotherapy not cost-effective; in <1% subgroup, dominated or ICERs >$880K. For ≥1%, ICERs up to $1.1M. In ≥50%, the combination was dominated versus pembrolizumab.

Pembrolizumab-based regimens

- **Monotherapy:** In the PD-L1 <1% subgroup, pembrolizumab was cost-effective in the United States ($112K/QALY) but not in China ($47K/QALY vs a willingness-to-pay threshold of $29K). For patients with PD-L1 expression ≥1% to ≥50%, pembrolizumab was broadly cost-effective in the United States, France, and Switzerland, with ICERs ranging from $47K to $142K/QALY, but it was not cost-effective in the United Kingdom, Ireland, Canada, or China based on local WTP thresholds (as detailed in the footnotes of **Table 2**). In the PD-L1 ≥50% subgroup, several models reported strong cost-effectiveness, with ICERs typically between $47K and $96K/QALY.
- **Combination:** In the United States, the highest ICERs were observed in the PD-L1 <1% ($184K/QALY) and 1–49% ($190K/QALY) subgroups. More favorable results were seen in the PD-L1 ≥50% subgroup, with average ICERs of approximately $124K/QALY. In Argentina, the highest ICER was again reported in the PD-L1 <1% subgroup ($97K/QALY) compared with the 1–49% and ≥50% subgroups.

RESULTS (Continued)

Table 2 Economic Evaluations Reporting Cost-effectiveness by PD-L1 Level (N=37)

Intervention	Comparator	PD-L1 Status	Country (Currency)	ICER Range (Currency/QALY)	Reference
Atezolizumab	Chemotherapy	PD-L1 ≥50%	Spain (EUR)	Dominant	7
		PD-L1 ≥50%	USA (USD)	130,805 – 170,730	8-9
	Pembrolizumab	PD-L1 ≥50%	USA (USD)	54,549 – 115,512	8,10
Atezolizumab + Chemotherapy	Chemotherapy	PD-L1 <1%	USA (USD)	735,111	11
		PD-L1 1–49%	USA (USD)	528,091	11
		PD-L1 ≥50%	USA (USD)	843,183	11
Cemiplimab	Atezolizumab	PD-L1 ≥50%	USA (USD)	Dominant	12
	Chemotherapy	PD-L1 ≥50%	USA (USD)	40,390 – 91,892	13-15
	Pembrolizumab	PD-L1 ≥50%	Spain (EUR)	Dominant	16
		PD-L1 ≥50%	USA (USD)	23,083 – 68,254	12-13
Cemiplimab + Chemotherapy	Cemiplimab	PD-L1 ≥50%	USA (USD)	637,147	17
Chemotherapy	Pembrolizumab + chemotherapy	PD-L1 ≥50%	USA (USD)	154,521	18
	Pembrolizumab	PD-L1 ≥50%	USA (USD)	Weakly dominated	18
Nivolumab + ipilimumab	Chemotherapy	PD-L1 <1%	USA (USD)	77,040 – 185,620	19-23
			USA, China (USD)	NR, cost-effective	24
		PD-L1 ≥1%	USA (USD)	128,948 – 246,584	20-22
			USA, China (USD)	NR, cost-effective	24
			USA (USD)	133,732	19
		PD-L1 1–49%	USA, China (USD)	NR, cost-effective	24
		PD-L1 ≥50%	USA (USD)	126,910 – 212,111	20-21
			USA, China (USD)	NR, cost-effective	24
			USA (USD)	107,404	19
Nivolumab + ipilimumab + chemotherapy	Chemotherapy	PD-L1 <1%	USA (USD)	Dominated	22
		PD-L1 ≥1%	USA (USD)	1,092,784	22
	Nivolumab + ipilimumab	PD-L1 <1%	USA (USD)	881,975	23
	Pembrolizumab	PD-L1 ≥50%	USA (USD)	Dominated	25
Pembrolizumab	Chemotherapy	PD-L1 <1%	China (USD)	46,548	26
			USA (USD)	111,763	26
		PD-L1 ≥1%	UK (GBP)	86,913	27
			USA (USD)	68,061 – 130,155	28-29
		PD-L1 ≥20%	USA (USD)	47,184	29
		PD-L1 1–49%	China (USD)	42,242	26
			USA (USD)	112,088	26
		PD-L1 ≥50%	Canada (CAD)	124,607	30
			China (USD)	65,136	26
			France (EUR)	84,097	31
			Ireland (EUR)	54,237	30
			Switzerland (CHF)	57,403	32
			UK (USD)	81,000	33
			USA (USD)	47,596 – 142,997	8, 23,26,29, 33
			Switzerland (CHF)	68,580	34
	Nivolumab plus ipilimumab	PD-L1 ≥1%	USA (USD)	NR	35
Pembrolizumab + Chemotherapy	Chemotherapy	PD-L1 <1%	Argentina (USD)	97,095	36
			USA (USD)	87,507 – 183,529	37-39
		PD-L1 ≥50%	Argentina (USD)	67,352	36
			France (EUR)	116,606	40
			Switzerland (CHF)	138,266	34
			USA (USD)	99,777 – 171,332	37-39
		PD-L1 1–49%	Argentina (USD)	85,984	36
			USA (USD)	66,837 – 218,159	23, 37-39
	Pembrolizumab	PD-L1 ≥50%	USA (USD)	169,335 – 198,913; Dominant	23, 38, 41
			Switzerland (CHF)	475,299	34
		PD-L1 1–49%	USA (USD)	56,112	42

Note: Common willingness-to-pay (WTP) thresholds reported in the cost-effectiveness analyses (CEAs) included $100,000 to $150,000 per QALY for the United States, $29,196 per QALY for China, €24,000 to €45,000 per QALY for Ireland, CAD 50,000 to 100,000 per QALY for Canada, £50,000 or approximately $42,048 per QALY for the United Kingdom, and €165,000 per QALY for France. Switzerland did not have a formally defined WTP threshold. Incremental cost-effectiveness ratios (ICERs) have been color-coded as follows: green indicates cost-effectiveness relative to the WTP threshold; red indicates not cost-effective; yellow indicates mixed results, with ICERs both above and below the threshold; and grey indicates that no WTP threshold was reported in the source studies. **Abbreviations:** USD = United States Dollar; EUR = Euro; GBP = British Pound Sterling; CHF = Swiss Franc; CAD = Canadian Dollar, NR = Not recorded.

Ten BIMs assessed atezolizumab, cemiplimab, toripalimab, and necitumumab.

- These were conducted across the US (n=6), Italy (n=3), and France (n=1).
- The majority of BIMs used 3–5 year time horizons and assumed 10% market uptake/year.
- PD-L1 levels were not reported in these models.

CONCLUSIONS

- The cost-effectiveness of immunotherapies in NSCLC is strongly influenced by PD-L1 expression level, treatment strategy, and geographic context, as summarized in **Table 3**.
- Monotherapies, particularly cemiplimab and pembrolizumab - were generally cost-effective in PD-L1 ≥50% populations. In contrast, PD-L1 <1% subgroups consistently showed poorer economic value, with ICERs exceeding conventional WTP thresholds across multiple studies.
- Combination regimens were also less cost-effective, particularly outside the ≥50% subgroup. These findings reinforce the importance of PD-L1 stratification in economic evaluations and support tailored decision-making in access and reimbursement.

Table 3 Summary of Cost-Effectiveness by Regimen

Regimens	Most Cost-Effective In	Least Cost-Effective In
Atezolizumab	Monotherapy in PD-L1 ≥50%	Combination with chemotherapy
Cemiplimab	Monotherapy in PD-L1 ≥50%	Combination with chemotherapy
Nivolumab + Ipilimumab	Dual immunotherapy in PD-L1 <1% and ≥50%	Combination with chemotherapy in PD-L1 <50%
Pembrolizumab	Monotherapy in PD-L1 ≥50%	PD-L1 <1% as monotherapy or in combination in countries with low WTP thresholds (e.g., China)

LIMITATIONS

- Despite a robust and transparent methodology, the SLRs had several limitations. The inclusion timeframe (2018–2024) and geographic restrictions – deprioritizing studies from Japan and the Asia Pacific region (n=64) – resulted in the omission of data.
- Some findings were derived from conference abstracts, limiting interpretability. Heterogeneity in study characteristics (e.g., country, sample size, treatment, histology) may have introduced bias.
- Quality of full-text studies (n=41) were assessed using the NICE checklist; most studies had minor limitations, though two had potentially serious issues due to short time horizons. Findings should therefore be interpreted with caution.

SCAN FOR:

- Poster with full reference list.

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Selected references shown; full list available via QR code