Original Article

Tremelimumab and durvalumab with chemotherapy in first-line treatment for metastatic non-small cell lung cancer: a US-based cost-effectiveness analysis

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Background: While the tremelimumab plus durvalumab combined with chemotherapy (T + D + CT) has shown promise in treating epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK) wild-type metastatic non-small cell lung cancer (mNSCLC), particularly in patients with low or no programmed cell death ligand 1 (PD-L1) expression, the economic implications of its high cost remain poorly understood. This study fills a critical gap in knowledge by evaluating the cost-effectiveness of T + D + CT from a US health care perspective, offering valuable insights for clinical and policy decision-making.

Methods: A 10-year Markov model was crafted to track the disease progression, survival, and treatment-related toxicities of a patient cohort with EGFR/ALK wild-type mNSCLC. Transition probabilities were derived from the POSEIDON trial, while health state utilities were obtained from the literature. Cost data, including drug acquisition and administration, subsequent anticancer therapies, and adverse event management were estimated using the Centers for Medicare and Medicaid Services and the Healthcare Cost and Utilization Project databases, with additional costs sourced from current literature. All cost and effectiveness measures were discounted at an annual rate of 3%. The model's robustness was assessed through deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analysis.

Results: T + D + CT compared to chemotherapy alone yielded incremental cost-effectiveness ratios (ICERs) of $370,208 to $691,960 per quality-adjusted life-year (QALY) gained, exceeding the standard willingness-to-pay (WTP) threshold of $100,000 to $150,000 per QALY. Against durvalumab plus chemotherapy, T + D + CT was only cost-effective in all subgroups. DSA results for patients with PD-L1 expression <1% showed that the ICER for first-line T + D + CT remained above the WTP threshold range, even with substantial changes to model inputs. PSA revealed a higher likelihood of T + D + CT being cost-effective as WTP thresholds increased. Scenario analysis confirmed the study's primary findings, with the exception of a scenario where durvalumab was offered at no cost.

Conclusions: The findings suggests that T + D + CT may not be a cost-effectiveness first-line treatment for EGFR/ALK wild-type mNSCLC in the US, given its high ICERs and limited cost-effectiveness in the majority of PD-L1 expression subgroups.

Keywords: Cost-effectiveness; non-small cell lung cancer (NSCLC); programmed cell death ligand 1 (PD-L1); tremelimumab; durvalumab

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Introduction

Lung cancer is the leading cause of cancer-related death in the United States (US), accounting for approximately one-fifth of all cancer deaths (1-3). Non-small cell lung cancer (NSCLC) is the most common type, making up 80–85% of all lung cancer cases (4). Over half of NSCLC patients are diagnosed at an advanced stage (5,6). Immunotherapies targeting the programmed cell death-1 (PD-1) receptor and its ligand (PD-L1) have revolutionized the management of metastatic NSCLC (mNSCLC) over the past decades (7,8). However, anti-PD-(L)1 therapy primarily benefits patients with high levels of tumor PD-L1 expression (9-14), while being less effective in those with low or no PD-L1 expression (15,16). Thus, there is a need for innovative therapeutic strategies to cater this particular patient group.

Durvalumab, a highly selective human IgG1 monoclonal antibody, disrupts PD-L1 interactions with PD-1 and CD80, empowering T cells to target and eliminate tumor cells, showing potential in non-small cell lung cancer when combined with novel agents (17,18). In the phase III POSEIDON trial, durvalumab was assessed in combination with tremelimumab, a novel monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (19). This study investigated the clinical efficacy and safety of adding a limited course of tremelimumab to durvalumab, alongside four cycles of platinum-doublet chemotherapy as the first-line treatment for mNSCLC patients without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangements (19). The four-drug regimen demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone, while maintaining a manageable tolerability profile (19). Furthermore, incorporating the anti-CTLA-4 antibody into first-line PD-L1-containing chemotherapy extended clinical benefits for patients with tumor PD-L1 expression <1%, a subgroup that typically responds poorly to conventional PD-L1 combined chemotherapy. These promising outcomes led to the US Food and Drug Administration (FDA)'s approval of the four-drug regimen for patients with EGFR/ALK wild-type mNSCLC on November 10, 2022 (20).

The dual immunotherapy and chemotherapy combination offer a promising and well-tolerated treatment option for patients with this disease. However, concerns about the treatment's high cost may hinder its widespread adoption. In 2023, an estimated 202,589 new cases of mNSCLC were projected in the US (3,21), with around 65–75% of these cases exhibiting low or negative PD-L1 expression, rendering about 142,000 patients eligible for this treatment. The US healthcare insurance system is complex, with varying levels of physician and pharmaceutical access. By 2021, over half of Americans are privately insured, 8.6% are uninsured, and the rest are covered by public sources like Medicaid, Medicare, or the US military (22). Health insurance plays a pivotal role in determining access to care and health outcomes for cancer patients in the US (23). Given the imperative need for high-quality and affordable medications to improve cancer survival, effective healthcare resource allocation is crucial. Therefore, conducting cost-effectiveness analyses is imperative to ascertain if a novel, albeit costly, treatment regimen provides a clinical benefit at a justifiable cost to inform resource allocation decisions.

Highlight box

Key findings

- Within the $100,000–$150,000 per quality-adjusted life-year willingness-to-pay threshold range in the US healthcare setting, first-line tremelimumab plus durvalumab and chemotherapy (T + D + CT) is not cost-effective for epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK) wild-type metastatic non-small cell lung cancer (mNSCLC) patients, irrespective of their programmed cell death ligand 1 (PD-L1) expression.

What is known and what is new?

- First-line T + D + CT shows significant efficacy in treating EGFR/ALK wild-type mNSCLC, particularly in subgroups with low or no PD-L1 expression. However, its high cost hinders widespread adoption within the US healthcare system.
- The study assessed the cost-effectiveness of first-line T + D + CT for EGFR/ALK wild-type mNSCLC patients across varying PD-L1 expressions.

What is the implication, and what should change now?

- First-line T + D + CT may not offer substantial value for EGFR/ALK wild-type mNSCLC patients. This study aims to serve as a dependable reference for decision-making in US healthcare and clinical practice.

This study aimed to evaluate the cost-effectiveness of tremelimumab with durvalumab, combined with chemotherapy (T + D + CT), as the first-line therapy for patients with EGFR/ALK wild-type mNSCLC from a US healthcare perspective. We present this article in accordance with the CHEERS reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-244/rc) (24).

Methods

Overviews

We developed a Markov model using TreeAge Pro software (version 2022, https://www.treeage.com/) for mathematical modeling and R software (version 4.2.3, http://www.r-project.org) for survival fitting to evaluate the cost-effectiveness of T + D + CT as the first-line therapy for patients with EGFR/ALK wild-type mNSCLC from a US healthcare perspective. The Markov model divides mNSCLC disease progression into distinct health states, with patients transitioning between states at discrete time intervals called cycles. Each state is linked to costs and health outcomes, with transition probabilities guiding movement between states (25). Markov models allow for the simulation of disease progression and treatment effects over time, enabling the evaluation of costs and outcomes associated with different cancer treatment strategies.

The cost-effectiveness model (CEM) considered three competitive strategies based on the POSEIDON trial: (I) T + D + CT; (II) durvalumab plus chemotherapy (D + CT); (III) chemotherapy alone (CT). The model targeted adults mNSCLC patients without sensitizing EGFR mutations or ALK rearrangements and not prior systemic therapy, in line with the POSEIDON trial criteria. Our study exclusively used pre-existing and non-identifiable data for analysis, making it exempt from institutional review board approval (26). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Model structure

The Markov model included three main health states: progression-free disease (PFD), progressed disease (PD), and death. Additionally, a temporary health states called "PFD health state with discontinued first-line therapy" was incorporated to address scenarios where first-line treatment may be discontinued due to unacceptable adverse effects (AEs) before disease progresses (*Figure 1*).

Patients initially started in the PFD health state and were randomly assigned to one of three treatment arms: T + D + CT, D + CT, or CT, based on the POSEIDON trial protocols detailed in Table S1. If patients in the PFS health state experienced AEs-induced first-line treatment discontinuation, they transitioned to the preset temporary health state. Patients who experienced disease progression moved to the PD health state and could receive subsequent anticancer therapy at the investigator's discretion for sustained survival benefits. Additional information on subsequent anticancer therapy can be found in Table S2. Patients in the PD health state without subsequent anticancer therapy were assumed to receive best supportive care (BSC) per the latest National Comprehensive Cancer Network (NCCN) Guidelines, with palliative care recommended before death (27). *Figure 1B* illustrates the possible transitions between these health states.

The CEM integrated clinical efficacy and safety, utility values and costs as inputs, with cumulative costs and quality-adjusted life-years (QALYs) over the modeling period as primary outputs. Incremental cost-effectiveness ratios (ICERs) were calculated to determine the additional costs per each additional QALY and compared to a willingness-to-pay (WTP) threshold to determine the relative cost-effectiveness of different strategies. A 10-year time horizon was chosen to ensure all model patients to reach the terminal health state (death). The model cycle is set at 3 weeks to align with the treatment schedule in the POSEIDON trial, with costs and QALYs discounted at an annual rate of 3% (28).

QALYs

QALY, a common metric in cost-effectiveness analysis, considers both quality of life and life years gained. It is calculated by multiplying health state utilities (ranging from 0 for death to 1 for perfect health), by the time spent in each health state determined by transition probabilities (29).

Transition probabilities between health states were estimated based on the data from the POSEIDON trial, the only study investigating the clinical efficacy and safety of T + D + CT, D + CT and CT in the first-line setting. Survival data for first-line CT were extracted by digitizing Kaplan-Meier (KM) curves from the trial using the GetData Graph Digitizer software (version 2.26; http://www.getdata-graphdigitizer.com/index.php). Goodness-of-fit tests were then conducted to select the optimal survival distribution for these recreated survival data, considering criteria such

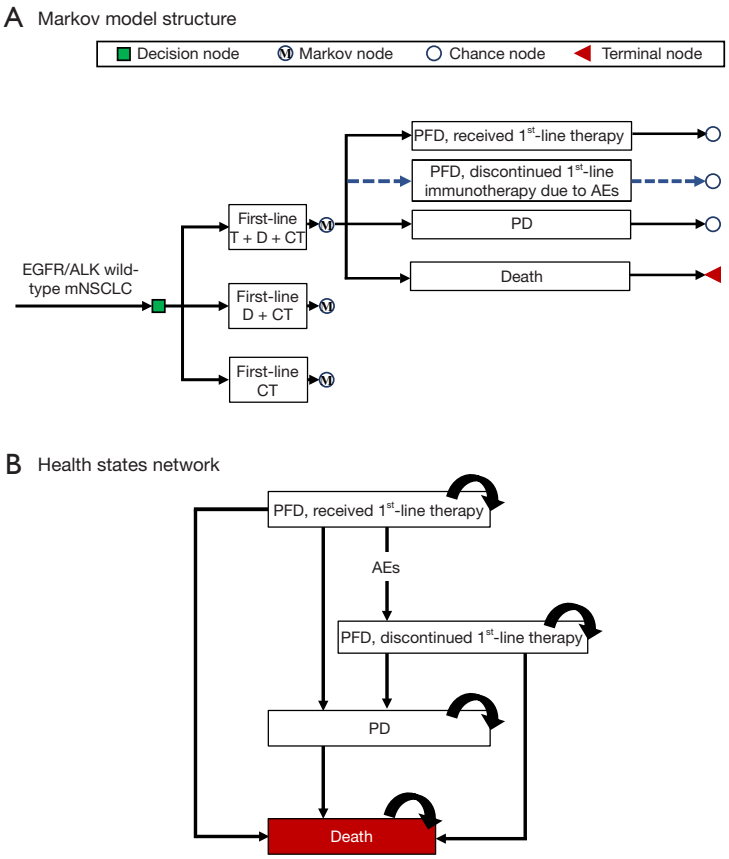


Figure 1 Markov model diagram. (A) Markov model structure used to compare 3 strategies for treating EGFR/ALK wild-type mNSCLC. (B) Health states network showing the possible transitions between 4 health states. mNSCLC, metastatic non-small cell lung cancer; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; PFD, progression-free disease; PD, progressed disease; AEs, adverse events.

as the Akaike information criteria (AIC) and Bayesian information criteria (BIC), as well as graphical evaluation of fits versus observed data. Lower AIC and BIC values, along with greater overlap between the fitted and observed curves, indicated a better fit. Based on the results of the goodness-of-fit tests, the Weibull and log-logistic distributions were chosen to model and extrapolate OS and PFS for first-line CT (see Table S3 and Figures S1,S2). Transition probabilities for first-line T + D + CT and D + CT were estimated using the hazards ratio (HRs) of these two strategies relative to first-line CT, derived from the POSEIDON trial. A specific formula (30) was utilized to estimate the survival rate for these two strategies: $S_{competing\text{-}strategies} = (S_{CT})^{HR}$ (30). In the base-case analysis, HRs stratified by PD-L1 expression were used to provide a comprehensive understanding of the first-line use of T + D + CT for EGFR/ALK wild-type mNSCLC.

Transition probabilities for the temporary health state were estimated using safety data from the POSEIDON trial (Table S4), with the model focusing solely on immunotherapy discontinuation caused by AEs. This decision was made due to the lack of explicit data on the discontinuation of first-line chemotherapy drugs, which are generally cheaper than immunotherapy drugs.

In the absence of health-related quality of life (HRQoL) data from the POSEIDON trial during the analysis, we utilized health utility values sourced from published literature. A health utility score of 0.754 was assigned to the PFD health state, while a score of 0.569 was assigned to the PD health state (31,32). The impact of AEs on HRQoL was assessed by incorporating utility decrements based on a report by the Institute for Clinical and Economic Review (33), as well as estimated episode durations for AEs from Yang *et al.*'s study (34). Further details on AE-related utility decrements can be found in Table S5.

Costs

We analyzed our model from a US healthcare perspective, considering costs such as first-line drug acquisition and administration, subsequent anticancer therapy, AEs and disease management, BSC, and palliative care. Biomarker testing costs were not included in the model, as all patients were assumed to have known PD-L1 expression status. All costs were converted to 2023 US dollars based on the Personal Consumption Expenditures-Health index (35).

Acquisition costs for first-line drugs were estimated using the dosage and schedule provided in Table S1, with average sales prices (ASP) sourced from the Centers for Medicare & Medicaid Services (CMS) (36). Drug administration costs were calculated based on infusion duration and corresponding infusion prices from the CMS Physician Fee Schedule Look-up Tool (37). Drug dosage calculations were based on a mean body surface area of 1.79 m^2 from Criss *et al.*'s economic evaluation, which analyzed data from over 3,500 lung cancer patients treated at Partners Healthcare hospital (38). Additionally, a mean creatinine clearance rate of 70 mL/min for model patients was ascertained from Wan *et al.*'s study (39). In the POSEIDON trial, subsequent anticancer therapies included radiotherapy, immunotherapy, cytotoxic chemotherapy, and targeted therapy (19). As the specific drugs used in subsequent anticancer therapies were not disclosed in the trial, the subsequent regimens were modeled based on the preferred regimens recommended by the latest NCCN Guidelines (27). The costs for subsequent anticancer therapies were calculated and presented in Table S2.

In this CEM, grade 3/4 AE costs were considered. To calculate AE management costs for each arm, unit AE costs were initially obtained from the Healthcare Cost and Utilization Project (HCUP) using Clinical Classification Software Refined (CCSR) diagnosis codes (40). Subsequently, these costs were multiplied by the reported incidence of each AE for each arm and then aggregated to determine the total AE management costs for each arm (refer to Table S6). The medical resources necessary for managing mNSCLC varied depending on the health state, encompassing services such as routine outpatient visits, computed tomography scans, magnetic resonance imaging, ultrasounds, and X-rays. Health state-specific disease management costs were sourced from literature (34), as well as costs for BSC and palliative care (38). Further details can be found in Table S7.

Statistical analysis

In the base-case analysis, we compared the cost-effectiveness of three treatment strategies (T + D + CT, D + CT, and CT) as the first-line treatment of EGFR/ALK wild-type mNSCLC patients. Since there is no specific WTP threshold defined in the US, we used the Institute for Clinical and Economic Review's recommended range ($100,000–150,000 per QALY) as a reference (41). Strategies with ICERs below the preset range were considered cost-effective.

Deterministic sensitivity analyses (DSAs) were undertaken to assess how uncertainty in specific model inputs could affect the cost-effectiveness results. In the DSA, model inputs were individually tested within plausible ranges, including 95% CIs for HRs, 0–5% for discount rate, and ±50% of the baseline values for other inputs (since their 95% CIs were not available). DSA results were presented as tornado diagrams, ranking inputs by their impact on cost-effectiveness results.

To account for multiple input uncertainties, a probabilistic sensitivity analysis (PSA) was performed using 10,000 Monte Carlo simulations. Model inputs were simultaneously sampled from appropriate distributions. Cost-effectiveness acceptability curves (CEACs) were used to visualize the likelihood of achieving cost-effectiveness under different WTPs thresholds. Details of baseline values, ranges for DSA, and distributions for PSA can be found in Table S7.

Scenario analysis was performed to assess the relative cost-effectiveness of the three treatment strategies under varying key model assumptions. A summary of each scenario and its justification for inclusion can be found in Table S8.

Results

Base-case analysis

In patients with EGFR/ALK wild-type mNSCLC, first-line treatment with T + D + CT had varying effects compared to CT alone. In subgroups with PD-L1 expression ≥50%, T + D + CT resulted in the highest increase in LYs of 0.65 (equal to 0.47 QALYs), but incurred the greatest increment medical costs of $173,998 (*Table 1*). On the other hand, in the subgroups with PD-L1 expression <50%, T + D + CT had the smallest increase in LYs of 0.27 (equal to 0.18 QALYs) and the lowest increment medical costs of $124,533 (*Table 1*). In general, the ICREs for first-line T + D + CT ranged from $370,208/QALY to $691,960/QALY,

Table 1 Base-case analysis results

Regimen	PD-L1 expression ≥50%			PD-L1 expression <50%			PD-L1 expression ≥1%			PD-L1 expression <1%		
	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT
Health outcomes												
PFD LYs	1.13	1.04	0.59	0.77	0.72	0.59	0.90	0.89	0.59	0.77	0.61	0.59
PD LYs	0.88	1.02	0.77	0.86	0.72	0.77	0.84	0.79	0.77	0.95	0.76	0.77
Total LYs	2.01	2.06	1.36	1.63	1.44	1.36	1.74	1.68	1.36	1.72	1.37	1.36
PFD QALYs	0.85	0.78	0.44	0.57	0.53	0.44	0.67	0.67	0.44	0.58	0.46	0.44
PD QALYs	0.50	0.58	0.44	0.49	0.41	0.44	0.48	0.45	0.44	0.54	0.43	0.44
Total QALYs	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost outcomes ($)												
Drug acquisition	202,473	147,996	6,642	158,551	111,232	6,642	175,697	132,555	6,642	159,177	97,903	6,642
Drug administration	2,683	2,369	1,333	1,959	1,727	1,333	2,235	2,087	1,333	1,970	1,512	1,333
AE management	9,623	8,543	9,355	9,623	8,543	9,355	9,623	8,543	9,355	9,623	8,543	9,355
Disease management-PFD	11,746	10,835	6,105	7,940	7,423	6,105	9,382	9,322	6,105	7,997	6,301	6,105
Disease management-PD	56,909	66,252	49,936	56,116	46,885	49,936	54,662	51,123	49,936	61,988	49,537	49,936
Subsequent treatment	16,716	19,006	54,311	16,521	13,520	54,311	16,080	14,705	54,311	18,237	14,296	54,311
BSC	3,929	4,296	2,318	3,874	3,040	2,318	3,774	3,315	2,318	4,280	3,212	2,318
Palliative care	3,089	3,081	3,171	3,140	3,162	3,171	3,126	3,133	3,171	3,128	3,169	3,171
Total costs	307,168	262,377	133,171	257,724	195,531	133,171	274,578	224,783	133,171	266,399	184,473	133,171
Incremental results[†]												
Incremental LYs		Dominated	0.65		0.19	0.27		0.06	0.38		0.35	0.36
Incremental QALYs			0.47		0.11	0.18		0.03	0.27		0.23	0.24
Incremental costs			173,998		62,192	124,553		49,795	141,408		81,926	133,229
ICER ($/LY)			267,689		327,327	461,307		829,923	372,125		234,075	370,079
ICER ($/QALY)			370,208		565,382	691,960		1,659,846	523,732		356,201	555,119

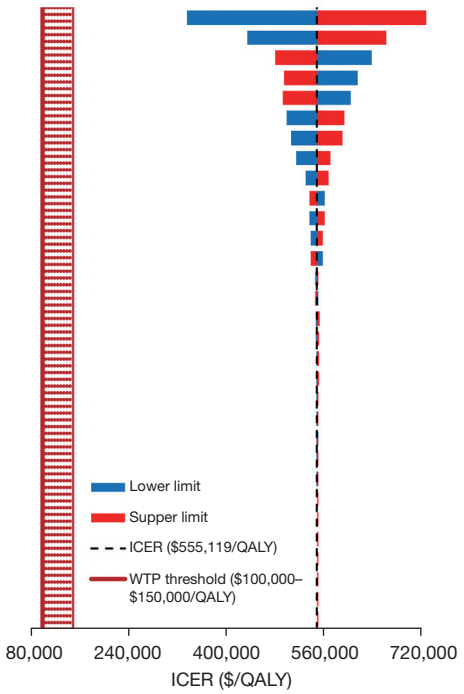
[†], the incremental results in the D + CT column show the comparison between first-line T + D + CT and D + CT, while the incremental results in the CT column show the comparison between first-line T + D + CT and CT. T + D + C, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; PD-L1, programmed cell death ligand 1; PFD, progression-free disease; PD, progressed disease; LYs, life years; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratios; AE, adverse event.

consistently exceeding the recommended range of WTP thresholds recommended ($100,000–$150,000/QALY).

Compared to first-line D + CT, first-line T + D + CT had slightly lower QALY (1.35 *vs.* 1.36 QALY) but higher medical costs ($ 307,168 *vs.* $ 262,377) in the subgroup with PD-L1 expression ≥50%, therefore dominated by first-line D + CT; in other subgroups based on PD-L1 expression, although first-line T + D + CT improved survivals outcomes, its overwhelmingly high medical costs resulted in significantly higher ICER than the predefined range of WTP thresholds.

Sensitivity analysis

Our analysis focused on the cost-effectiveness of first-line T + D + CT in EGFR/ALK wild-type mNSCLC patients with



Mode inputs	Low value	High value	Low ICER	High ICER	Spread
$HR_{OS\ (T+D+CT\ vs.\ CT)}$ in subgroup with PD-L1 expression <1%	0.58	1.00	336,841	728,447	391,606
Durvalumab price/mg ($)	5.89	9.82	435,070	662,654	227,584
Utility for PFD health state	0.566	0.943	480,844	639,081	158,237
Utility for PD health state	0.427	0.711	495,258	615,797	120,539
Cost of subsequent systemic therapy/cycle in first-line CT ($)	3101.63	5169.88	493,321	604,630	111,309
$HR_{PFS\ (T+D+CT\ vs.\ CT)}$ in subgroup with PD-L1 expression <1%	0.59	1.03	499,311	593,680	94,369
Tremelimumab price/mg ($)	102.95	171.59	506,627	591,351	84,723
Discount rate (%)	0	5	515,380	571,542	56,162
Cost of subsequent systemic therapy/cycle in first-line T + D+ CT ($)	833.66	1399.44	530,424	568,222	37,798
$Probability_{3\text{-week}}$ of durvalumab discontinuation in first-line T + D + CT	0.00743	0.01238	536,545	562,370	25,825
Cost of disease management/cycle in PD health state	2867.58	4799.3	536,574	561,664	25,090
AEs management cost in first-line T + D + CT ($)	7217.08	12028.47	539,076	558,902	19,826
AEs management cost in first-line CT ($)	7016.33	11693.89	539,352	558,626	19,275
AEs Disutility in first-line T + D + CT	0.00311	0.00518	546,666	551,349	4,683
AEs Disutility in first-line CT	0.00309	0.00514	546,680	551,318	4,638
BSC cost/cycle	334.43	557.38	546,968	551,010	4,042
Cost of disease management/cycle in PFD health state	458.66	764.43	547,040	550,938	3,898
Pemetrexed price/mg ($)	0.78	1.31	547,908	550,064	2,156
Body surface area ($meters^2$)	1.34	2.24	547,934	550,044	2,110
$Probability_{3\text{-week}}$ of tremelimumab discontinuation in first-line T + D + CT	0.00409	0.00681	548,158	549,760	1,602
Cost of intravenous infusion additional hour	21.35	35.59	548,630	549,348	717
Subsequent radiotherapy cost in first-line CT	792.66	1321.1	548,680	549,298	617
Cost of intravenous infusion 1 hour	99.12	165.2	548,691	549,287	597
Subsequent radiotherapy cost in first-line T + D + CT	583.62	972.69	548,766	549,212	446
Gemcitabine price/mg ($)	0.01	0.02	548,983	549,071	88
Palliative care cost/cycle	4952.33	8253.88	548,946	549,033	87
Paclitaxel price/mg ($)	8.84	14.37	548,961	549,014	53
Carboplatin price/mg ($)	0.04	0.06	548,973	548,999	26
Creatinine clearance rate (mL/min)	52.8	87.8	548,978	549,000	22
Cisplatin price/mg ($)	0.13	0.21	548,981	548,997	16
Proportion of patients receiving carboplatin (%)	0.375	0.625	548,982	548,996	13

Figure 2 Deterministic sensitivity analysis results for first-line T + D + CT *vs.* first-line CT. ICER, incremental cost-effectiveness ratios; WTP, willingness-to-pay; QALY, quality-adjusted life-year; T + D + CT, tremelimumab plus durvalumab and chemotherapy; CT, chemotherapy alone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-L1, programmed cell death ligand 1; PFD, progression-free disease; PD, progressed disease; AE, adverse event; BSC, best supportive care.

PD-L1 expression <1%. We conducted sensitivity analysis specifically for this subgroup. The DSA results revealed that the upper and lower limits of any model inputs did not bring the ICER of first-line T + D + CT below the defined WTP threshold ranges of $100,000–$150,000/QALY compared to first-line D + CT or first-line CT (*Figures 2,3*). The most influential factors on the ICERs were the HR for OS and PFS, utilities (both PFD and PD health states) and the price of durvalumab and tremelimumab, as depicted in the tornado diagrams.

The PSA results revealed that, the likelihood of first-line T + D + CT being cost-effective within the WTP threshold range of $100,000–$150,000/QALY was almost zero when compared to the other treatment strategies (Figure S3). However, as the WTP threshold increased, the probability of first-line T + D + CT becoming cost-effective increased more significantly than that of first-line D + CT.

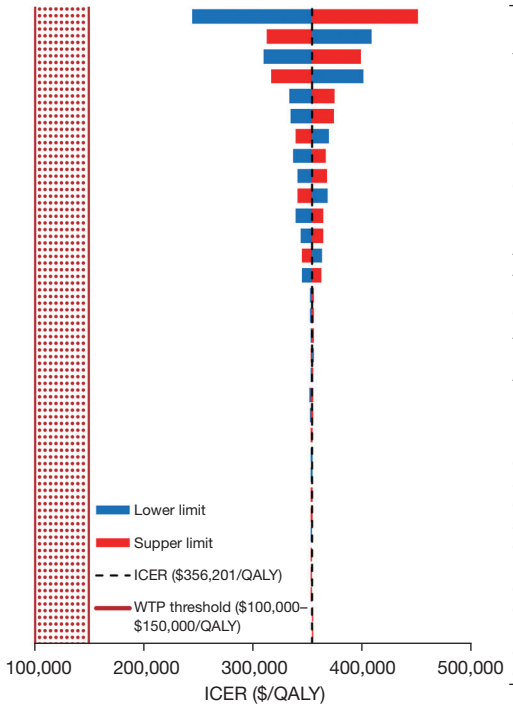
Scenario analysis

The results of the scenario analysis are presented in Table S9. The assumption that durvalumab being free had the most significant impact on model outcomes. In this scenario, first-line T + D + CT was found to be cost-effective compared to first-line CT, with ICERs ranging from $51,028 to 93,983/QALY, falling below the predefined WTP thresholds ranges. When compared to first-line D + CT, the cost-effectiveness results remained consistent with the base-case results.

In other scenarios, there was no significant changes observed in our results, and the ICERs between first-line T + D + CT and first-line D + CT or first-line CT tended to cluster around the base-case value shown in *Table 1*.

Discussion

In our cost-effectiveness analysis, we evaluated the addition of tremelimumab to durvalumab plus platinum-doublet chemotherapy as a first-line treatment for EGFR/ALK wild-type mNSCLC in the US. Our base case analysis revealed that using first-line T + D + CT in the subgroups with PD-L1 expression ≥50% resulted in negative incremental QALYs and higher costs compared to first-line CT, making it cost-ineffective. For other subgroups with different PD-



Mode inputs	Low value	High value	Low ICER	High ICER	Spread
$HR_{OS\ (T+D+CT\ vs.\ CT)}$ in subgroup with PD-L1 expression <1%	0.58	0.84	244,713	450,975	206,262
Utility for PFD health state	0.566	0.943	312,408	408,133	95,726
Tremelimumab price/mg ($)	102.95	171.59	309,611	398,462	88,851
Utility for PD health state	0.427	0.711	316,798	401,196	84,398
Durvalumab price/mg ($)	5.89	9.82	333,308	374,719	41,411
Cost of subsequent systemic therapy/cycle in first-line T + D+ CT ($)	833.66	1399.44	334,567	374,206	39,639
Cost of subsequent systemic therapy/cycle in first-line D + CT ($)	812.67	1354.45	338,870	369,203	30,333
$HR_{PFS\ (T+D+CT\ vs.\ CT)}$ in subgroup with PD-L1 expression <1%	0.59	1.03	336,600	366,369	29,769
Cost of disease management/cycle in PD health state	2867.58	4799.3	340,585	367,769	27,184
$Probability_{3\text{-week}}$ of durvalumab discontinuation in first-line T + D + CT	0.00743	0.01238	340,986	368,069	27,083
Discount rate (%)	0	0.05	338,842	364,226	25,384
AEs management cost in first-line T + D + CT ($)	7217.08	12028.47	343,640	364,432	20,792
AEs management cost in first-line T + CT ($)	6407.18	10678.64	344,807	363,266	18,459
$Probability_{3\text{-week}}$ of durvalumab discontinuation in first-line D + CT	0.00712	0.01186	345,023	362,530	17,506
Cost of disease management/cycle in PFD health state	458.66	764.43	352,204	355,869	3,665
AEs Disutility in first-line T + D + CT	0.00311	0.00518	352,466	355,633	3,167
Pemetrexed price/mg ($)	0.78	1.31	352,662	355,403	2,741
AEs Disutility in first-line D + CT	0.00265	0.00442	352,690	355,398	2,708
BSC cost/cycle	334.43	557.38	352,883	355,190	2,307
Body surface area ($meters^2$)	1.34	2.24	352,955	355,118	2,164
$Probability_{3\text{-week}}$ of tremelimumab discontinuation in first-line T + D + CT	0.00409	0.00681	353,164	354,844	1,680
Cost of intravenous infusion 1 hour	99.12	165.2	353,722	354,351	629
Subsequent radiotherapy cost in first-line D + CT	693.04	1155.07	353,758	354,315	557
Gemcitabine pricelmg ($)	8.84	14.37	353,791	354,316	524
Subsequent radiotherapy cost in first-line T + D + CT	583.62	972.69	353,803	354,270	467
Cost of intravenous infusion additional hour	21.35	35.59	353,856	354,217	360
Palliative care cost/cycle	4952.33	8253.88	353,992	354,081	88
Gemcitabine price/mg ($)	0.01	0.02	354,030	354,037	7
Cisplatin pricelmg ($)	0.13	0.21	354,036	354,037	1
Proportion of patients receiving carboplatin (%)	0.375	0.625	354,036	354,037	1
Carboplatin price/mg ($)	0.04	0.06	354,036	354,037	0
Creatinine clearance rate (mL/min)	52.8	87.8	354,036	354,037	0

Figure 3 Deterministic sensitivity analysis results for first-line T + D + CT *vs.* first-line D + CT. ICER, incremental cost-effectiveness ratios; WTP, willingness-to-pay; QALY, quality-adjusted life-year; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-L1, programmed cell death ligand 1; PFD, progression-free disease; PD, progressed disease; AEs, adverse events; BSC, best supportive care.

L1 expressions, the reported ICERs for first-line T + D + CT (*vs.* D + CT or CT) ranged from $356,201/QALY to $1,659,846/QALY, consistently exceeding the recommended WTP thresholds ($100,000–$150,000/QALY). We concluded that regardless of their PD-L1 expression, first-line T + D + CT did not represent a cost-effective option for patients with EGFR/ALK wild-type mNSCLC.

The robustness of our CEM has been solidly confirmed through the rigorous analysis using both DSA and PSA. DSA revealed that the estimated ICERs were more sensitive to certain model inputs that influence QALYs, such as HRs for OS and PFS, as well as utilities of PFD and PD health states. It is important to note that these inputs, which reflect the efficacy and safety of treatment strategies, are unlikely to be changed through clinical or policy interventions. Alongside these important QALY drivers, the prices of tremelimumab and durvalumab exerted a substantial influence on the ICERs. However, DSA results indicated that varying these two inputs within ±25% of the base-case value did not appear to impact on our findings. Furthermore, scenario analysis revealed that even tremelimumab was assumed to be provided for free, it did not result in first-line T + D + CT being superior to D + CT in patents with different PD-L1 expression. On the other hand, assuming durvalumab was free proved sufficient to make first-line T + D + CT cost-effective compared to CT in all cases. The greater influence of durvalumab's price on determining the cost-effectiveness of first-line T + D + CT, compared to tremelimumab's price, was largely due to its longer treatment duration, resulting in exceptionally high cumulative drug costs.

Despite the demonstrated clinical benefits of combining anti-CTLA-4 antibodies and PD-(L)1 inhibitors in previous clinical trials (42,43), including the recent POSEIDON trial (19), further exploration is needed to assess the cost-effectiveness of dual immunotherapy. This economic evaluation suggested that first-line treatment with T + D + CT did not offer a cost-effectiveness advantage compared to CT. There are two primary reasons for this: firstly, the significant survival improvement observed in the POSEIDON trial did not translate into a substantial extension of QALYs (1.12–1.35 *vs.* 0.88 QALYs) in our

cost-effectiveness analysis due to the limited OS. Secondly, the combination of tremelimumab (an anti-CTLA-4 drug), and durvalumab (an anti-PD-L1 drug), and conventional chemotherapy resulted in a substantial increase in total medical costs. The higher costs of T + D + CT outweighed its marginal QALY advantage, leading to its unfavorable ICERs. However, when considering PD-L1 expression and using first-line CT as a control, the survival benefits of first-line T + D + CT were comparable to D + CT in patients with PD-L1 expression >50% (0.47 and 0.46 additional QALYs) and PD-L1 expression >1% (0.27 and 0.24 QALYs); In patients with PD-L1 expression <50%, particularly those with PD-L1 expression <1%, first-line use of T + D + CT resulted in higher incremental QALYs. Adjusting the prices of key drugs may help achieve cost-effectiveness based on the exceptional clinical efficacy of first-line T + D + CT in patients with PD-L1 <1%.

This study has several notable strengths. First, we utilized comprehensive efficacy and safety data from a phase III, global, randomized trial to establish the CEM. Additionally, various analyses, including DSA, PSA with 10,000 Monte Carlo simulations, and 10 scenario analyses, were conducted to check the robustness of our CEM. Hence, this analysis provides valuable insights for making informed treatment decisions in the mNSCLC patients. Secondly, we extensively investigated the impact of varying safety profiles across three different treatment strategies by integrating first-line immunotherapy discontinuations due to AEs, along with the incidence of AEs, associated costs and disutility in the model. Thirdly, this study represents the first report on the cost-effectiveness of T + D + CT compared to PD-L1-containing chemotherapy or platinum-doublet chemotherapy as the initial treatment regimen for EGFR/ALK wild-type mNSCLC across various PD-L1 expression levels.

This study does have some limitations. Firstly, there is a lack of head-to-head clinical trials comparing T + D + CT with D + CT or CT in subgroups with different PD-L1 expression levels. Therefore, survival fitting techniques were applied to estimate transition probabilities by employing corresponding HRs. However, this approach assumed that the clinical efficacy and safety of first-line CT (as a standard control) were consistent across various subgroups, which may introduce bias into the results. Secondly, this analysis assessed long-term survival for treatment strategies beyond the short follow-up period of the trial, adding further uncertainty to the CEM. Thirdly, there may be heterogeneity in costs from various sources used in the model, but DSA showed that varying cost inputs did not materially alter the main findings of this study. Fourthly, the specific drugs used as subsequent anticancer therapies were not disclosed in the phase III POSEIDON trial. To address this uncertainty, we modeled subsequent therapy drugs based on the latest NCCN Guidelines, although this may not fully represent real-world clinical practice. Sensitivity analysis was conducted by varying the costs and frequency of subsequent anticancer therapy, and it was found that these inputs did not play a decisive role in determining the cost-effectiveness of first-line T + D + C treatment.

Conclusions

From a US health care perspective, first-line T + D + CT is not cost-effective for patients with EGFR/ALK wild-type mNSCLC, regardless of their PD-L1expression. While doublet immunotherapy holds promise in improving mNSCLC treatment, it is crucial to consider whether its clinical benefits justify its high cost.

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Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-244/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-244/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-244/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-244/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our study exclusively used pre-existing

and non-identifiable data for analysis, making it exempt from institutional review board approval.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
3. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
4. Suster DI, Mino-Kenudson M. Molecular Pathology of Primary Non-small Cell Lung Cancer. Arch Med Res 2020;51:784-98.
5. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:339-57.
6. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:358-76.
7. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:586-97.
8. Kang J, Zhang C, Zhong WZ. Neoadjuvant immunotherapy for non-small cell lung cancer: State of the art. Cancer Commun (Lond) 2021;41:287-302.
9. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
10. Mok TSK, Wu YL, Kudaba I, et al. 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 2019;393:1819-30.
11. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol 2021;39:2339-49.
12. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
13. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med 2020;383:1328-39.
14. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 2021;397:592-604.
15. Waterhouse D, Lam J, Betts KA, et al. Real-world outcomes of immunotherapy-based regimens in first-line advanced non-small cell lung cancer. Lung Cancer 2021;156:41-9.
16. Sun JY, Zhang D, Wu S, et al. Resistance to PD-1/PD-L1 blockade cancer immunotherapy: mechanisms, predictive factors, and future perspectives. Biomark Res 2020;8:35.
17. Dempke WCM, Fenchel K, Reuther S, et al. Durvalumab plus novel agents in non-small cell lung cancer-a new COAST on the horizon? Transl Lung Cancer Res 2022;11:697-701.
18. Akkad N, Thomas TS, Luo S, et al. A real-world study of pneumonitis in non-small cell lung cancer patients receiving durvalumab following concurrent chemoradiation. J Thorac Dis 2023;15:6427-35.
19. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol 2023;41:1213-27.
20. US Food and Drug Administration. FDA approves tremelimumab in combination with durvalumab and platinum-based chemotherapy for metastatic non-small cell lung cancer. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-and-platinum-based-chemotherapy-metastatic-non. Accessed 2 January, 2023.
21. American Cancer Society. Key Statistics for Lung Cancer. Available online: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed March 2, 2023.
22. Kaiser Family Foundation. Health insurance coverage of the

total population. Available online: https://www.kff.org/other/state-indicator/total-population. Accessed June 24, 2024.
23. Zhao J, Han X, Nogueira L, et al. Health insurance status and cancer stage at diagnosis and survival in the United States. CA Cancer J Clin 2022;72:542-60.
24. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Pharmacoeconomics 2022;40:601-9.
25. Zhang Z, Liang G, Zhang P, et al. China county-based prostate specific antigen screening for prostate cancer and a cost-effective analysis. Transl Androl Urol 2021;10:3787-99.
26. Lester-Coll NH, Ades S, Yu JB, et al. Cost-effectiveness of Prostate Radiation Therapy for Men With Newly Diagnosed Low-Burden Metastatic Prostate Cancer. JAMA Netw Open 2021;4:e2033787.
27. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Non-small cell lung cancer, Version 3. 2023. Available online: https://www.nccn.org/guidelines/category_1. Accessed September 14, 2023.
28. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;316:1093-103.
29. Mitzman B, Varghese TK Jr, Akerley WL, et al. Surgical-decision making in the setting of unsuspected N2 disease: a cost-effectiveness analysis. J Thorac Dis 2024;16:1063-73.
30. Wu B, Dong B, Xu Y, et al. Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. PLoS One 2012;7:e32530.
31. Nafees B, Lloyd AJ, Dewilde S, et al. Health state utilities in non-small cell lung cancer: An international study. Asia Pac J Clin Oncol 2017;13:e195-203.
32. National Institute for Health and Care Excellence. Nivolumab for advanced non-squamous non-small cell lung cancer after chemotherapy. Available online: https://www.nice.org.uk/guidance/ta713/resources/nivolumab-for-advanced-nonsquamous-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82611131893189. Accessed April 4, 2023.
33. Institute for Clinical and Economic Review. Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks. Available online: https://icer.org/wp-content/uploads/2020/10/MWCEPAC_NSCLC_Final_Evidence_Report_Meeting_Summary_110116.pdf. Accessed March 4, 2023.
34. Yang M, Vioix H, Sachdev R, et al. Cost-Effectiveness of Tepotinib Versus Capmatinib for the Treatment of Adult Patients With Metastatic Non-Small Cell Lung Cancer Harboring Mesenchymal-Epithelial Transition Exon 14 Skipping. Value Health 2023;26:487-97.
35. U.S. Bureau of Economic Analysis. Personal Consumption Expenditures Price Index. Available online: https://www.bea.gov/data/personal-consumption-expenditures-price-index. Accessed March 12, 2023.
36. Centers for Medicare and Medicaid Services. April 2023 ASP Pricing File. Available online: https://www.cms.gov/. Accessed April 16, 2023.
37. Centers for Medicare and Medicaid Services. Physician Fee Schedule Look-Up Tool. Available online: https://www.cms.gov/medicare/physician-fee-schedule/search. Accessed April 21, 2023.
38. Criss SD, Mooradian MJ, Watson TR, et al. Cost-effectiveness of Atezolizumab Combination Therapy for First-Line Treatment of Metastatic Nonsquamous Non-Small Cell Lung Cancer in the United States. JAMA Netw Open 2019;2:e1911952.
39. Wan X, Luo X, Tan C, et al. 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 2019;125:3526-34.
40. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUPnet). Available online: https://datatools.ahrq.gov/hcupnet. Accessed April 22, 2023.
41. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. Available online: https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf. Accessed January 20, 2023.
42. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
43. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:198-211.

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Supplementary

Table S1 Dosage and schedule of first-line regimens

Regimen	Dosage		Infusion time	Schedule	
	Platinum doublet chemotherapy	Proportion		During chemotherapy	Post-chemotherapy
T + D + CT	Tremelimumab, 75 mg		Over 60 minutes on Day 1	Every 3 weeks	Durvalumab + pemetrexed, every 4 weeks[b]; tremelimumab, at week 16[c]
	Durvalumab, 1,500 mg		Over 60 minutes on Day 1		
	Pemetrexed-platinum[a]				
	Pemetrexed, 500 mg/m^2	60.2%	Over 10 minutes on Day 1		
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2		Carboplatin, over 15 minutes one Day 1; cisplatin, over 120 minutes on Day 1		
	Gemcitabine-platinum[a]				
	Gemcitabine, 1,250 mg/m^2	32.5%	Over 30 minutes on Day 1 and 8		
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2		Carboplatin, over 15 minutes one Day 1; cisplatin, over 120 minutes on Day 1		
	Nab-paclitaxel-carboplatin				
	Nab-paclitaxel, 100 mg/m^2	7.3%	Over 30 minutes on Days 1, 8, and 15		
	Carboplatin, AUC 5		Carboplatin, over 15 minutes one Day 1; cisplatin, over 120 minutes on Day 1		
D+CT	Durvalumab, 1,500 mg		The same as above	Every 3 weeks	Durvalumab + pemetrexed, every 4 weeks
	Pemetrexed-platinum[a]				
	Pemetrexed, 500 mg/m^2	59.3%			
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2				
	Gemcitabine-platinum[a]				
	Gemcitabine, 1,250 mg/m^2	32.0%			
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2				
	Nab-paclitaxel-carboplatin				
	Nab-paclitaxel, 100 mg/m^2	8.7%			
	Carboplatin, AUC 5				
CT	Pemetrexed-platinum[a]		The same as above	Every 3 weeks[d]	Pemetrexed, every 4 weeks[e]
	Pemetrexed, 500 mg/m^2	61.3%			
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2				
	Gemcitabine-platinum[a]				
	Gemcitabine, 1,250 mg/m^2	33.6%			
	Carboplatin, AUC 5/cisplatin, 75 mg/m^2				
	Nab-paclitaxel-carboplatin				
	Nab-paclitaxel, 100 mg/m^2	5.1%			
	Carboplatin, AUC 5				

[a], since the POSEIDON Study III did not provide information on the proportion of patients receiving cisplatin or carboplatin in the pemetrexed-platinum and gemcitabine-platinum chemotherapy regimens for each arm, we assume that half of the patients receive cisplatin. [b], non-squamous NSCLC patients who received pemetrexed-platinum chemotherapy also received pemetrexed maintenance therapy. [c], in the tremelimumab + durvalumab + chemotherapy arm, an additional dose of durvalumab + tremelimumab was given at week 16 post-chemotherapy. In there were any dose delays, more than 1 durvalumab + tremelimumab combination dose could be given at and after week 16 post-chemotherapy to ensure that up to 5 combination doses were administered. [d], the chemotherapy arm received a total of 6 doses of chemotherapy. [e], in the chemotherapy arm, pemetrexed maintenance therapy could be given either every 3 weeks or every 4 weeks as per the phase III POSEIDON study. Our model used a uniform 4-week dose schedule for simplicity in calculations. T + D + CT tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; AUC, area under the curve.

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Table S2 Subsequent anticancer therapy used in the model

Regimen		Dosage and schedule[b]	Cost ($)[c]	Proportion (%)		
				T + D + CT	D + CT	CT
Radiotherapy[a]		At least 60 Gy in 2 Gy fractions	5,479.50 (total)[d]	14.2	16.9	19.3
Systemic therapy[a]						
Immunotherapy	Nivolumab	240 mg every 2 weeks	10,767.96 (3-week)[e]	6.5	6.5	33.2
Cytotoxic chemotherapy	Docetaxel	75 mg/m^2 every 3 weeks	61.08 (3-week)[e]	31.7	37.9	36.2
Targeted therapy	Ramucirumab-docetaxel	Ramucirumab,10 mg/kg every 3 weeks; docetaxel, 75 mg/m^2 every 3 weeks	9,462.73 (3-week)[e]	4.1	3.8	5.6
Other systemic therapy	Best supportive care	/	445.90 (3-week)[f]	1.2	0.6	1.8

[a], the systemic therapy regimens were modeled according to the recommended regimens in the latest National Comprehensive Cancer Network Guidelines for non-small cell lung cancer (Version 6.2022), as the specific drugs were not disclosed in the phase III POSEIDON study results. [b], dosage and schedule were determined based on drug instructions provided by the U.S. FDA National Drug Code DataBase. [c], when calculating drug dosages, model patients were assumed to have a body weight of 70.32 kg and a body surface of 1.79 m^2. [d], estimates were made based on the prices associated with radiation treatment delivery available at the Centers for Medicare & Medicaid Services. [e], estimates were made based on the latest average drug sale prices available at the Centers for Medicare & Medicaid Services. [f], sourced from Criss et al.'s study [2019]. T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone.

Table S3 AIC and BIC statistics for first-line chemotherapy

Distribution	OS		PFS	
	AIC	BIC	AIC	BIC
Exponential	−329	−325	−164	−160
Weibull	−335	−328	−190	−184
Lognormal	−310	−304	−202	−196
Loglogistic	−322	−316	−213	−216
Gompertz	−325	−316	−193	−185

OS, overall survival; PFS, progression-free survival; AIC, Akaike information criterion; BIC, Bayesian information criterion.

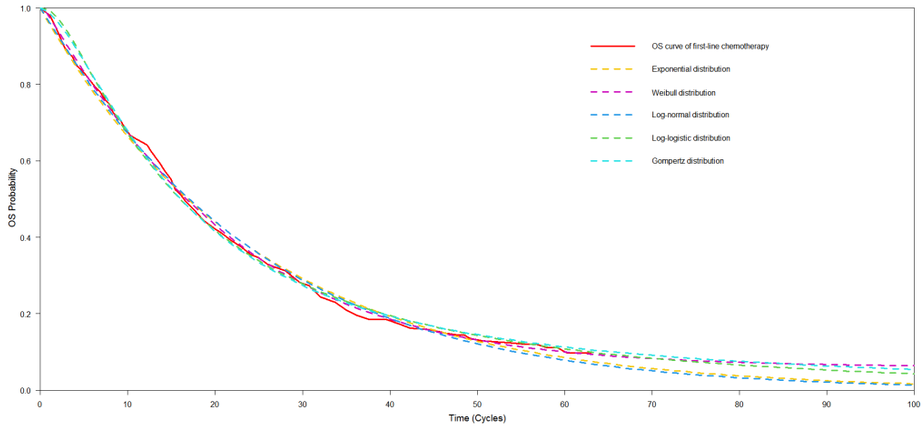

Figure S1 Comparison of statistical fits *vs.* observed OS data for first-line chemotherapy. OS, overall survival.

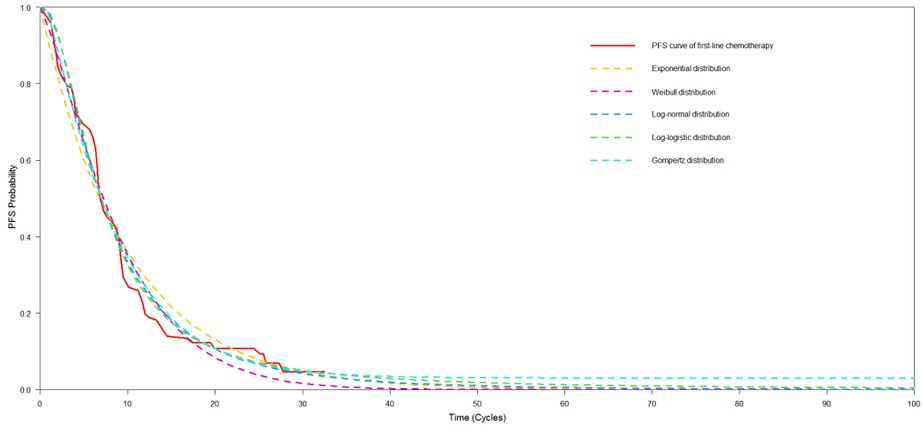

Figure S2 Comparison of statistical fits *vs.* observed PFS data for first-line chemotherapy. PFS, progression-free survival.

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Table S4 3-week probability of first-line immunotherapy discontinuation due to AEs

First-line Regimen	Median OS (months)	Proportion	Instantaneous rate	3-week probabilities[a]
T + D + CT	14.0			
Discontinued tremelimumab		10.36%	0.00547	0.00545
Discontinued durvalumab		18.05%	0.00995	0.00990
D + CT	13.3			
Discontinued durvalumab		16.57%	0.00953	0.00949

[a], the proportion of AEs-related treatment discontinuation during the trial period was converted into a 3-week probability of the event using two successive formulas: first $Rate = -\left[\ln(1 - Proportion)\right]/t$, then $Probability_{3\text{-}week} = 1 - \exp(-Rate)$, where t referred to the median OS in 3-weeks units. T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; OS, overall survival; AEs, adverse events.

Table S5 Derivation of AE-related utility decrements

AEs	Disutilities[a]	Duration (days)[b]	Disutilities decrement
Anemia	0.08973	30.42	0.00748
Nausea	0.04802	30.42	0.00400
Neutropenia	0.08973	30.42	0.00748
Decreased appetite[c]	0.00000	30.42	0.00000
Fatigue	0.07346	30.42	0.00612
Thrombocytopenia	0.08973	30.42	0.00748
Neutrophil count decreased	0.08973	30.42	0.00748
Vomiting	0.04802	30.42	0.00400
ALT increased	0.04680	30.42	0.00390
Diarrhea	0.04680	30.42	0.00390
Constipation	0.04680	30.42	0.00390
Leukopenia	0.08973	30.42	0.00748
Rash	0.03248	30.42	0.00271
AST increased	0.04680	30.42	0.00390
Asthenia	0.07346	30.42	0.00612

[a], sourced from the Institute for Clinical and Economic Review report. [b], sourced from Yang *et al.*'s study (2022). [c], assumptions provided by key opinion leaders consulted in this study. AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table S6 Calculations of cost and disutility for treatment-induced AEs

AEs	Proportion (%)			Cost per event ($)	Disutility
	T + D + CT	D + CT	CT		
Anemia	17.3	15.3	20.4	10,382.06	0.00748
Nausea	1.2	0.3	1.5	8,680.86	0.00400
Neutropenia	16.1	12.6	12.0	21,402.48	0.00748
Decreased appetite	1.5	0.3	1.2	/[a]	0.00000
Fatigue	1.5	2.1	2.1	15,340.80	0.00612
Thrombocytopenia	5.5	4.5	5.1	18,795.54	0.00748
Neutrophil count decreased	7.3	7.2	7.5	21,402.48	0.00748
Vomiting	1.2	0.3	1.2	8,680.86	0.00400
ALT increased	1.2	2.1	2.1	20,941.25	0.00390
Diarrhea	1.5	1.2	1.2	18,795.54	0.00390
Constipation	0.0	0.0	0.6	18,795.54	0.00390
Leukopenia	2.7	2.4	3.6	21,402.48	0.00748
Rash	1.2	0.9	0.0	14,364.87	0.00271
AST increased	0.3	0.9	0.0	20,941.25	0.00390
Asthenia	2.4	0.9	1.5	/[a]	0.00612
Estimated AEs costs and disutility					
AEs cost for first-line T + D + CT, $				9,622.78	
AEs cost for first-line D + CT, $				8,542.91	
AEs cost for first-line CT, $				9,355.11	
AEs disutility for first-line T + D + CT					0.00414
AEs disutility for first-line D + CT					0.00354
AEs disutility for first-line CT					0.00412

[a], according to the key opinion leaders consulted for this study, no further treatment is necessary for decreased appetite and asthenia. AEs, adverse events; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone.

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Table S7 Model inputs

Input	Baseline value	Ranges for DSA	Distribution for PSA	Source
Clinical efficacy				
Survival fits				
OS for first-line CT	Weibull: λ=0.03692; γ=1.03393	N/A	N/A	Parametric survival analyses of POSEIDON data
PFS for first-line CT	loglogistic: θ=0.02001, κ=2.01475	N/A	N/A	
HRs for first-line D+CT *vs* CT				
HR_{OS} in patients with PD-L1 expression ≥50%	0.63	0.45–0.88	LogNormal	POSEIDON trial
HR_{OS} in patients with PD-L1 expression <50%	0.94	0.77–1.14	LogNormal	
HR_{OS} in patients with PD-L1 expression ≥1%	0.79	0.64–0.98	LogNormal	
HR_{OS} in patients with PD-L1 expression <1%	0.99	0.76–1.30	LogNormal	
HR_{PFS} in patients with PD-L1 expression ≥50%	0.61	0.44–0.85	LogNormal	
HR_{PFS} in patients with PD-L1 expression <50%	0.83	0.68–1.02	LogNormal	
HR_{PFS} in patients with PD-L1 expression ≥1%	0.68	0.55–0.86	LogNormal	
HR_{PFS} in patients with PD-L1 expression <1%	0.97	0.73–1.28	LogNormal	
HRs for first-line T + D + CT vs. CT				
HR_{OS} in patients with PD-L1 expression ≥50%	0.65	0.47–0.89	LogNormal	POSEIDON trial
HR_{OS} in patients with PD-L1 expression<50%	0.82	0.67–1.00	LogNormal	
HR_{OS} in patients with PD-L1 expression ≥1%	0.76	0.61–0.95	LogNormal	
HR_{OS} in patients with PD-L1 expression <1%	0.77	0.58–1.00	LogNormal	
HR_{PFS} in patients with PD-L1 expression ≥50%	0.56	0.40–0.78	LogNormal	
HR_{PFS} in patients with PD-L1 expression <50%	0.79	0.64–0.97	LogNormal	
HR_{PFS} in patients with PD-L1 expression ≥1%	0.68	0.54–0.85	LogNormal	
HR_{PFS} in patients with PD-L1 expression <1%	0.78	0.59–1.03	LogNormal	
3-week probability of immunotherapy discontinuation due to AEs				
Discontinuation of tremelimumab in first-line T + D + CT	0.00545	0.00409–0.00681	Beta	Table S5
Discontinuation of durvalumab in first-line T + D + CT	0.00990	0.00743–0.01238	Beta	
Discontinuation of durvalumab in first-line D + CT	0.00949	0.00712–0.01186	Beta	
Health state utilities				
PFD health state	0.754	0.566–0.943	Beta	Nafees *et al.*, 2018
PD health state	0.569	0.427–0.711	Beta	NICE
Disutility				
First-line T + D + CT	0.00414	0.00311–0.00518	Beta	ICER; Yang *et al.*, 2022
First-line D + CT	0.00354	0.00265–0.00442	Beta	
First-line CT	0.00412	0.00309–0.00514	Beta	
Costs ($)				
Drug acquisition and administration cost				
Tremelimumab price/mg	137.27	102.95–171.59	Gamma	CMS,.gov
Durvalumab price/mg	7.86	5.89–9.82	Gamma	
Pemetrexed price/mg	1.05	0.78–1.31	Gamma	
Gemcitabine price/mg	0.02	0.01–0.02	Gamma	
Paclitaxel price/mg	11.78	8.84–14.73	Gamma	
Carboplatin price/mg	0.05	0.04–0.06	Gamma	
Cisplatin price/mg	0.17	0.13–0.21	Gamma	
Intravenous infusion 1 hour	132.16	99.12–165.20	Gamma	
Intravenous infusion additional hour	28.47	21.35–35.59	Gamma	

Table S7 (*continued*)

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Table S7 (*continued*)

Input	Baseline value	Ranges for DSA	Distribution for PSA	Source
Subsequent anticancer therapy costs				
Systemic therapy cost/cycle (first-line T + D + CT)	1,111.55	833.66–1,389.44	Gamma	Table S2
Systemic therapy cost/cycle (first-line D + CT)	1,083.56	812.67–1,354.45	Gamma	
Systemic therapy cost/cycle (first-line CT)	4,135.50	3,101.63–5,169.38	Gamma	
Radiotherapy cost per event (first-line T + D + CT)	778.15	583.62–972.69	Gamma	
Radiotherapy cost per event (first-line D + CT)	924.06	693.04–1,155.07	Gamma	
Radiotherapy cost per event (first-line CT)	1,056.88	792.66–1,321.10	Gamma	
AEs management costs				
First-line T + D + CT	9,622.78	7,217.08–12,028.47	Gamma	HCUPnet
First-line D + CT	8,542.91	6,407.18–10,678.64	Gamma	
First-line CT	9,355.11	7,016.33–11,693.89	Gamma	
Disease management costs				
PFD health state/cycle	611.54	458.66–764.43	Gamma	Yang *et al.*, 2022
PD health state/cycle	3,823.44	2,867.58–4,779.30	Gamma	
BSC cost/cycle	445.90	334.43–557.38	Gamma	Criss *et al.*, 2019
palliative care cost/cycle	6,603.10	4,952.33–8,253.88	Gamma	
Others				
Body surface area (m^2)	1.79	1.34–2.24	Normal	Criss *et al.*, 2019
Creatinine clearance rate (mL/min)	70	52.5–87.5	Normal	Wan *et al.*, 2019
Discount rate (%)	3	0–5	Normal	Sanders *et al.*, 2016
Proportion of patients receiving carboplatin (%)	50	37.5–62.5	Normal	Assumption

DSA, deterministic sensitivity analyses; PSA, probabilistic sensitivity analysis; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; PD-L1, programmed cell death ligand 1; PFD, progression-free disease; PD, progressed disease; NICE, National Institute for Health and Care Excellence; ICER, Institute for Clinical and Economic Review.

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Table S8 Scenario description and rationale

Scenario	Description	Rationale
First-line immunotherapy continued until progression	In this scenario, it was assumed that discontinuation of first-line immunotherapy would occur exclusively upon disease progression. To implement this in the model, the temporary health state reflecting discontinuation of first-line therapy due to unacceptable toxicity was removed	While the base-case analysis considered AEs-induced first-line immunotherapy discontinuation, this scenario aimed to examine the impact on cost-effectiveness results when patients continue receiving first-line immunotherapy until disease progression. This was deemed crucial considering the high costs associated with the immunotherapeutic agents utilized in this study
Tremelimumab was free	In this scenario, the price of tremelimumab was assumed to be free of charge	This scenario intended to investigate the cost-effectiveness of first-line T + D + CT when the price of tremelimumab or durvalumab was set as zero
Durvalumab was free	In this scenario, that the price of durvalumab was assumed to be free of charge	
Included biomarker testing costs	In this scenario, a one-off cost of $2,854.73 was assigned for biomarker testing. This cost was derived from a published study on cost effectiveness	The inclusion of biomarker testing costs was not anticipated to affect the model results since it was applied uniformly across all strategies. However, its potential to significance lies in quantifying the relative contribution of testing to overall treatment costs
Excluded AEs disutilities	In this scenario, it was assumed that the experience of AEs does not have a significant impact on health-related quality of life. This was achieved by setting all AEs-related utility decrements to 0. However, AEs management costs were still taken into account	These two scenarios were designed to investigate how variances in safety profiles of three competing strategies can affect the model results
Excluded AEs costs	In this scenario, it was assumed that the experience of AEs does not have a significant impact on total medical costs. This was achieved by setting all AEs management costs to 0. However, AEs-related utility decrements were still taken into account	
Halved the frequency of subsequent anticancer therapy	In this scenario, it was assumed that there would be a 50% decrease in the frequency of subsequent anticancer therapy compared to the base-case analysis	The base-case analysis utilized the frequency of subsequent anticancer therapy reported in the POSEIDON trial, which may not precisely reflect real-world clinical practice. As a result, these two scenarios aimed to examine the implications of this uncertainty within the model
Increased frequency of follow-up treatment by half	In this scenario, it was assumed that there would be a 50% increase in the frequency of subsequent anticancer therapy compared to the base-case analysis	
5-year time horizon	In this scenario, the cost and health outcomes for each strategy were estimated only for the initial first 5 years	These two scenarios probed the effects of restricting or extending the model horizon on the outcomes
20-year time horizon	In this scenario, the cost and health outcomes for each strategy were estimated over a 20-year time horizon	

T + D + CT, tremelimumab plus durvalumab and chemotherapy; AEs, adverse events.

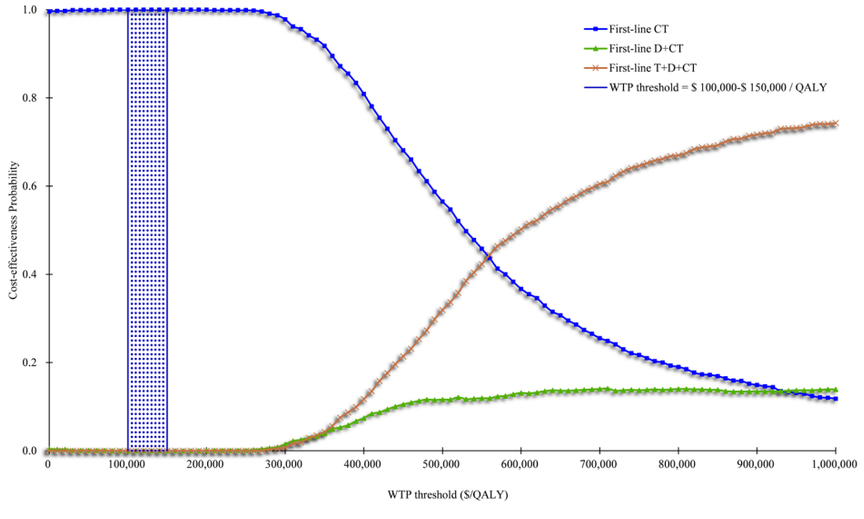

Figure S3 Cost-effectiveness acceptability curves for subgroups with PD-L1 expression <1%. CT, chemotherapy alone; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; WTP, willingness-to-pay; QALY, quality-adjusted life-year.

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Table S9 Scenario analysis results

Scenario	PD-L1 expression ≥50%			PD-L1 expression <50%			PD-L1 expression ≥1%			PD-L1 expression <1%		
	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT	T + D + CT	D + CT	CT
Assumed first-line immunotherapy until progression												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	337,266	290,594	133,171	272,665	208,567	133,171	294,846	245,420	133,171	281,666	193,735	133,171
ICER		Dominated	434,082		544,640	745,420		1,424,929	579,475		379,987	611,898
Tremelimumab was free												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	264,965	262,377	133,171	216,671	195,531	133,171	233,011	224,783	133,171	225,281	184,473	133,171
ICER		Dominated	280,308		179,626	446,206		237,216	357,848		176,348	379,555
Durvalumab was free												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	157,163	124,183	133,171	147,819	91,726	133,171	149,057	100,978	133,171	155,978	93,211	133,171
ICER		Dominated	51,028		476,621	78,278		1,386,087	56,939		271,244	93,983
Included biomarker testing costs												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	310,023	265,232	136,025	260,578	198,386	136,025	277,433	227,638	136,025	269,254	187,328	136,025
ICER		Dominated	370,069		528,442	665,577		1,435,585	506,833		354,036	548,989
Excluded AEs disutilities												
QALY	1.35	1.37	0.88	1.07	0.95	0.88	1.16	1.12	0.88	1.12	0.89	0.88
Cost ($)	307,168	262,377	133,171	257,724	195,531	133,171	274,578	224,783	133,171	266,399	184,473	133,171
ICER		Dominated	370,048		525,742	665,484		1,410,997	506,785		353,114	548,930
Excluded AEs costs												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	297,546	253,834	123,816	248,101	186,989	123,816	264,956	216,240	123,816	256,777	175,930	123,816
ICER		Dominated	369,500		519,267	664,146		1,404,453	505,873		349,370	547,886
Halved the frequency of subsequent anticancer therapy												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	298,810	252,874	106,015	249,463	188,772	106,015	266,538	217,431	106,015	257,281	177,325	106,015
ICER		Dominated	410,050		515,691	766,547		1,415,763	575,347		345,521	623,314
Increased frequency of follow-up treatment by half												
QALY	1.35	1.36	0.88	1.06	0.95	0.88	1.15	1.12	0.88	1.12	0.89	0.88
Cost ($)	315,526	271,880	160,027	265,984	202,291	160,326	282,618	232,135	160,326	275,518	191,621	160,326
ICER		Dominated	330,726		541,193	564,606		1,455,408	438,318		362,552	474,665
5-year time horizon												
QALY	1.25	1.26	0.86	1.02	0.92	0.86	1.10	1.07	0.86	1.07	0.87	0.86
Cost ($)	294,180	249,151	129,732	251,899	192,346	129,732	266,860	218,539	129,732	259,059	181,899	129,732
ICER		Dominated	416,183		588,635	741,726		1,729,728	565,154		386,109	615,078
20-year time horizon												
QALY	1.35	1.37	0.88	1.06	0.95	0.88	1.16	1.12	0.88	1.12	0.89	0.88
Cost ($)	308,092	263,337	133,236	257,938	195,601	133,236	274,935	225,020	133,236	266,730	184,520	133,236
ICER		Dominated	366,730		525,411	662,204		1,415,347	503,801		352,302	545,649

The incremental results in the D + CT column show the comparison between first-line T + D + CT and D + CT, while the incremental results in the CT column show the comparison between first-line T + D + CT and CT. T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; CT, chemotherapy alone; PD-L1, programmed cell death ligand 1; QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratios.

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