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.

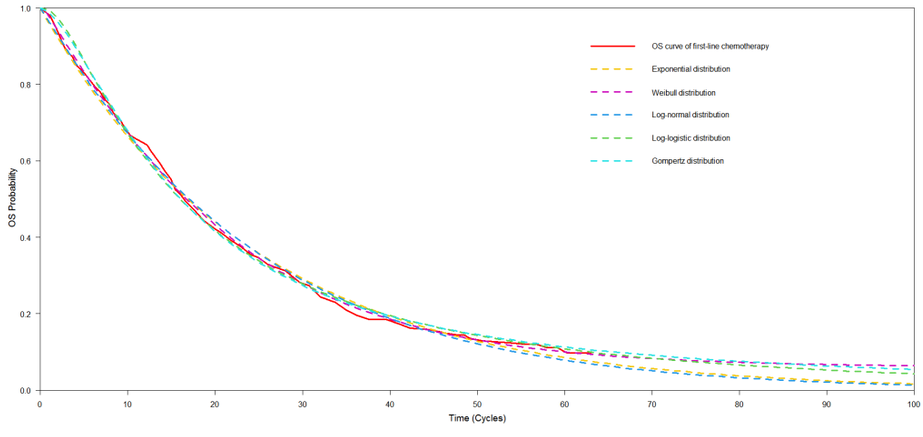

Figure S1 Comparison of statistical fits *vs.* observed OS data for first-line chemotherapy. OS, overall survival.

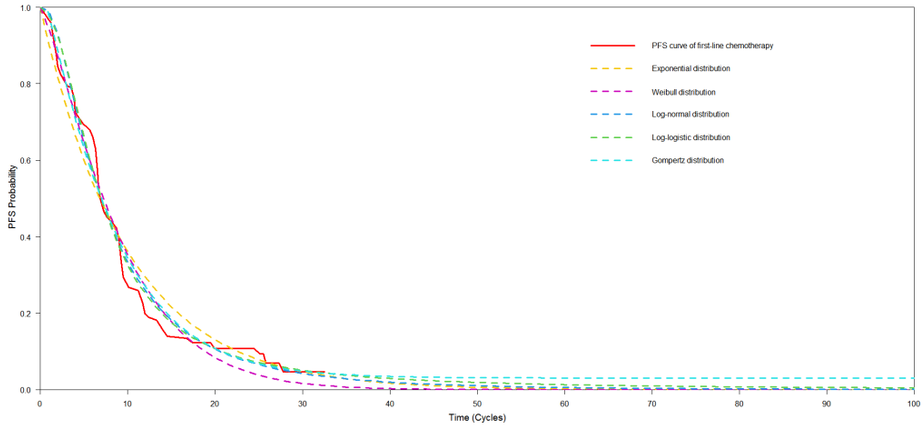

Figure S2 Comparison of statistical fits *vs.* observed PFS data for first-line chemotherapy. PFS, progression-free survival.

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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.

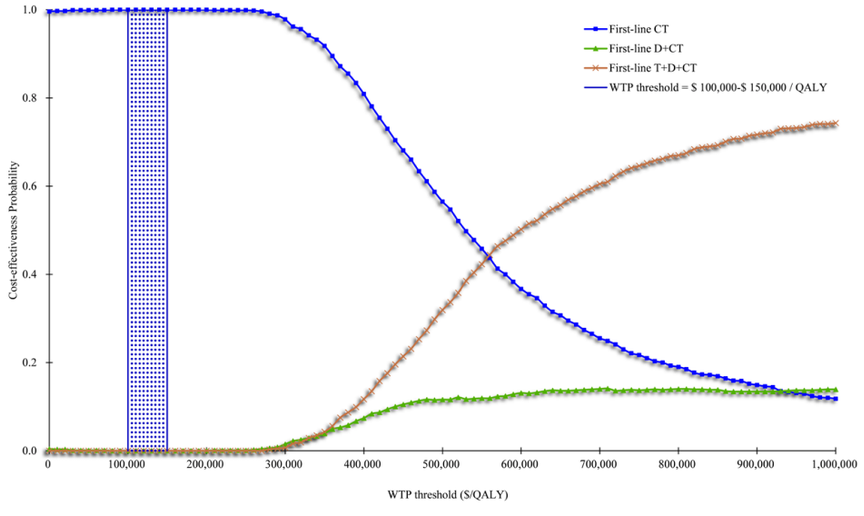

Figure S3 Cost-effectiveness acceptability curves for subgroups with PD-L1 expression <1%. CT, chemotherapy alone; T + D + CT, tremelimumab plus durvalumab and chemotherapy; D + CT, durvalumab plus chemotherapy; WTP, willingness-to-pay; QALY, quality-adjusted life-year.

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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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