Cost-Effectiveness of Durvalumab After Chemoradiotherapy in Unresectable Stage III NSCLC: A US Healthcare Perspective

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ABSTRACT

Background: Durvalumab was approved by the FDA in February 2018 for patients with unresectable stage III NSCLC that has not progressed after platinum-based concurrent chemoradiotherapy (cCRT), and this regimen is the current standard of care. The objective of this study was to examine the cost-effectiveness of durvalumab following cCRT versus cCRT alone in patients with locally advanced, unresectable stage III NSCLC. **Methods:** A 3-state semi-Markov model was used. Modeling was performed in a US healthcare setting from Medicare and commercial payer perspectives over a 30-year time horizon. Clinical efficacy (progression-free and post progression survival) and utility inputs were based on PACIFIC study data (ClinicalTrials.gov identifier: NCT02125461; data cutoff March 22, 2018). Overall survival extrapolation was validated using overall survival data from a later data cutoff (January 31, 2019). The main outcome was the incremental cost-effectiveness ratio (ICER) of durvalumab following cCRT versus cCRT alone, calculated as the difference in total costs between treatment strategies per quality-adjusted life-year (QALY) gained. **Results:** In the base-case analysis, durvalumab following cCRT was cost-effective versus cCRT alone from Medicare and commercial insurance perspectives, with ICERs of \$55,285 and \$61,111, respectively, per QALY gained. Durvalumab was thus considered cost-effective at the \$100,000 willingness-to-pay (WTP) threshold. Sensitivity analyses revealed the model was particularly affected by variables associated with subsequent treatment, although no tested variable increased the ICER above the WTP threshold. Scenario analyses showed the model was most sensitive to assumptions regarding time horizon, treatment effect duration, choice of fitted progression-free survival curve, subsequent immunotherapy treatment duration, and use of a partitioned survival model structure. **Conclusions:** In a US healthcare setting, durvalumab was cost-effective compared with cCRT alone, further supporting the adoption of durvalumab following cCRT as the new standard of care in patients with unresectable stage III NSCLC.

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Background

Lung cancer is the most common cancer worldwide¹ and the second most common in the United States, with an estimated 228,820 new cases predicted for 2020.² Non-small cell lung cancer (NSCLC) is the most common subtype, accounting for 84% of all new US lung cancer diagnoses.³ At diagnosis, approximately 30% of patients with NSCLC have locally advanced stage III disease, many of whom have unresectable tumors.⁴

Historically, the prognosis for patients with locally advanced, unresectable stage III NSCLC has been poor. After platinum-based doublet concurrent chemoradiotherapy (cCRT; the previous standard of care⁵), median progression-free survival (PFS) was approximately 8 months, and 5-year overall survival (OS) rates were approximately 15% to 30%.^{5–8} However, the development of immune checkpoint inhibitors such as durvalumab that target either the PD-1 receptor or its ligand (PD-L1) has revolutionized the outlook for these patients.

Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that binds to PD-L1, blocking its interaction with PD-1 in the tumor microenvironment.^{9–11} This immune “unmasking” enables T cells to recognize tumor cells and eliminate them.^{9–11} In the phase III PACIFIC study (ClinicalTrials.gov identifier: NCT02125461) performed in patients with locally advanced, unresectable stage III NSCLC whose disease had not progressed after cCRT (defined as ≥ 2 overlapping cycles of platinum-based chemoradiotherapy), durvalumab significantly prolonged PFS and OS versus placebo.^{12,13} Median PFS was 16.8 months with durvalumab and 5.6 months with placebo (stratified hazard ratio [HR], 0.52; 95% CI, 0.42–0.65; $P < .001$).¹³ Furthermore, median OS was not reached with durvalumab versus 28.7 months with placebo (stratified HR, 0.68; 95% CI, 0.53–0.87; $P = .0025$).¹²

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In February 2018, the FDA approved durvalumab for patients with unresectable stage III NSCLC that has not progressed after platinum-based cCRT,¹⁴ and durvalumab is now approved in >40 countries. Adjuvant therapy with durvalumab (also known as “consolidation immunotherapy”) after treatment with cCRT in patients with unresectable stage III NSCLC is also recommended in the 2018 (category 2A),¹⁵ 2019 (category 1),¹⁶ and 2020 (category 1) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC.¹⁷ It is therefore important to determine whether durvalumab following cCRT is a cost-effective strategy.

We performed a cost-effectiveness analysis of durvalumab following cCRT versus cCRT alone in patients with locally advanced, unresectable stage III NSCLC, modeled from a US healthcare perspective, using data from the PACIFIC study.¹² The primary objective was to determine the incremental cost-effectiveness ratio (ICER) of durvalumab, expressed as the cost per quality-adjusted life-year (QALY) gained for durvalumab following cCRT versus cCRT alone, using a \$100,000 willingness-to-pay (WTP) threshold.

Methods

Patient Population

Modeling was based on the PACIFIC intention-to-treat population, comprising patients with locally advanced, unresectable stage III NSCLC that had not progressed after platinum-based cCRT. The intention-to-treat population was predominantly male (70% in both the durvalumab and placebo arms) and had a median age of 64 years in each arm and a mean weight of 71.1 kg overall. In the model, this information was used together with US general population mortality data¹⁸ to ensure that at no time point did modeled patients have greater expected survival than members of the general population.

Model Structure

A 3-state semi-Markov model was used to compare the 2 different treatment strategies from Medicare and commercial insurance perspectives. The 3 health states were progression-free, progressed disease, and death (Figure 1).

PFS, time to progression (TTP), and post progression survival (PPS) data from PACIFIC (data cutoff [DCO], March 22, 2018) were used to generate probabilities that patients remained in the same health state or transitioned to a subsequent health state. These probabilities were sufficient to estimate OS at each cycle (Figure 1). Due to the relative immaturity of OS data from the March 22, 2018 DCO and the later January 31, 2019 DCO, too much uncertainty would have been introduced into the model if a partitioned survival approach (using only PFS

Figure 1. Three-state semi-Markov model structure.

Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post progression survival; TTP, time to progression.

and OS data) had been used; this approach was therefore used only for a scenario analysis.

Because PPS was similar between the durvalumab and placebo arms for the first 13 months of the study, with only a slight separation in favor of durvalumab thereafter, PPS data from both arms were pooled, and a conservative assumption was made of no difference in PPS between arms. To extrapolate beyond the trial follow-up period, parametric survival curves were fitted separately to the durvalumab and best supportive care arms using patient-level data from the PACIFIC trial.^{12,13}

All fitted parametric curves were compared and assessed using the following goodness-of-fit criteria:

- Akaike information criterion (AIC) and Bayesian information criterion (BIC) with smaller AIC/BIC values indicating a better statistical fit. In general, models with a difference in AIC and BIC <5 were assumed to be of equal statistical fit.
- A visual inspection of the fitted curves: the fitted parametric survival model curves were overlaid on the Kaplan-Meier curves to assess how closely the modeled curves matched the observed nonparametric survival estimates.

- An external validation process through PACIFIC survival data and the wider clinical literature: the modeled median OS and PFS and the survival probabilities at years 1, 2, 3, and 5 were compared with the reported median and survival estimates from the PACIFIC,¹² START,¹⁹ and RTOG 0167²⁰ trial data.

A time horizon of 30 years was adopted, reflecting a lifetime approach capturing all costs and outcomes. Cycle length was 2 weeks for the first 12 months (to align with durvalumab administration in the PACIFIC trial, whereby patients received treatment until disease progression or for up to 12 months), and 4 weeks thereafter (to decrease computational time).

Efficacy

Effectiveness inputs were based on PACIFIC PFS data from the March 22, 2018 DCO. A sensitivity analysis was

also performed using immature OS data from the January 31, 2019 DCO. PFS was defined as the time from randomization until objective disease progression or death from any cause in the absence of progression.¹² TTP was defined as the time from randomization to progression, censoring death events. PPS was defined as the time from progression to death from any cause. Because PPS was similar between the durvalumab and placebo arms for the first 13 months of the PACIFIC study, with only a slight separation in favor of durvalumab thereafter (supplemental eFigure 1, available with this article at JNCCN.org), PPS data from both treatment arms were pooled.

For each treatment arm, standard parametric distributions (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma) were fitted to the Kaplan-Meier curves for PFS (assessed by blinded independent central review [BICR]), PPS (BICR), and TTP. The best-fitting curves were selected according to the lowest Akaike/Bayesian information criteria and best visual fit. The generalized gamma curve was deemed the best fitting for PFS and TTP, and the log-logistic curve was considered the best fitting for PPS. Because the duration of preprogression treatment effect for durvalumab is unknown, a conservative assumption of no further benefit beyond 60 months was made, after which treatment effect was assumed to be the same as for cCRT alone; this duration was varied in the scenario analyses. PPS was pooled across both arms, and an assumption of no difference was made. Efficacy outputs (ie, QALYs and LYs gained) were assumed to be the same for both Medicare and commercial insurance.

Utility

In the PACIFIC trial, health-related quality of life data were collected using the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire.²¹ In the model, EQ-5D-5L data were converted to US population-based utility values using published algorithms.^{22,23}

Adverse effect (AE)-related disutilities were not considered in the base-case analysis, because the impact of AEs on health-related quality of life was assumed to be accounted for already in patients' health state utilities. There were also only minor differences in AE rates between arms in PACIFIC; thus, their impact on model outcomes was considered only minimal.

Costs

A full breakdown of modeled costs is provided in supplemental eTables 1–5. Unit drug costs were sourced from the Centers for Medicare & Medicaid Services Average Sales Price Drug Pricing Files (October 2018²⁴; “Medicare”) and wholesale acquisition costs from the IBM Micromedex RED BOOK²⁵ (“commercial insurance”). All costs were standardized to 2018 US dollars and, when required, were inflated using the US Bureau of Labor

Statistics Consumer Price Index health inflation indices.²⁶ Drug costs were calculated assuming no vial sharing for durvalumab, consolidation with chemotherapy, or subsequent therapy. Time to treatment discontinuation was used to inform total drug acquisition and treatment administration costs. In PACIFIC, all patients were discontinued from treatment at or before 12 months per protocol; mean times to treatment discontinuation were 7.7 and 6.9 months for durvalumab and placebo, respectively.

Consolidation with chemotherapy was applied as a one-off cost and comprised paclitaxel + carboplatin (4 cycles) or pemetrexed + cisplatin (2 cycles) (supplemental eTable 1). To reflect real-world treatment of unresectable stage III NSCLC in the United States, 36.2% of patients in the cCRT-alone arm were assumed to receive subsequent consolidation with chemotherapy (paclitaxel + carboplatin, 33.9%; pemetrexed + cisplatin, 2.2%).²⁷ However, studies have shown that consolidation with chemotherapy does not improve survival²⁸; thus, it was assumed that these patients incurred no survival advantage.

Costs associated with healthcare resource use (HRU) were estimated retrospectively from the IBM MarketScan Commercial Claims and Encounters Database.²⁹ Patients with unresectable stage III NSCLC who underwent cCRT were identified from the database and observed until 3 months post progression (proxied by initiation of subsequent therapy line). Monthly reimbursed costs for their HRU, including outpatient oncologist visits and radiology scans in the pre and post progression periods, were calculated (supplemental eTable 2).

One line of subsequent (post progression) treatment was accounted for in the model, and included immunotherapy (nivolumab or pembrolizumab, per proportions of patients receiving these as subsequent therapies in the PACIFIC study¹²; supplemental eTable 6), cytotoxic therapy, and radiotherapy (supplemental eTables 3 and 4). For clarity, we note that the NCCN Guidelines for NSCLC do not recommend subsequent immunotherapy after progression on durvalumab or PD-1/PD-L1 inhibitors.¹⁷ Inclusion of further lines was expected to have only a minor impact on model outputs.

The model also included costs associated with grade 3 or 4 AEs occurring in $\geq 2\%$ of patients in either arm of the PACIFIC study (supplemental eTable 5). End-of-life care costs were applied as a one-off cost and assumed to be the same in both arms.

Discounting

Costs and QALYs were discounted at a rate of 3% per annum³⁰; rates of 0% and 5% per annum were explored as scenario analyses.

Sensitivity Analyses

One-way sensitivity analyses investigated the effects of individual model parameters on ICER. Costs and treatment durations were varied using a gamma distribution whereby utilities and the proportions of patients receiving each treatment were varied using a beta distribution, assuming a standard error (SE) of 10% of the base-case value. When data relating to uncertainty were not available, the lower and upper bounds were varied using the 2.5 and 97.5 percentiles, assuming a 10% SE.

A probabilistic sensitivity analysis (PSA) was performed to explore the joint uncertainty of all model parameters and their associated impact on cost-effectiveness, and to quantify the level of confidence in the model outputs. When data were available, variation was based on actual data; when unavailable, a 10% SE was assumed. The PSA was run 1,000 times. The proportion of iterations considered cost-effective was determined and represented via a cost-effectiveness acceptability curve. Details of scenario analyses and model validation are shown in supplemental eAppendix 1.

Results

Base-Case Analysis

Discounted results for durvalumab following cCRT versus cCRT alone are presented in Table 1. Durvalumab following cCRT was associated with an incremental increase of 1.94 LYs and 1.65 QALYs versus cCRT alone. Incremental total costs were \$91,423 for Medicare and \$101,058 for commercial insurance, yielding ICERs of \$55,285 and \$61,111 per QALY gained, respectively, which were both below the \$100,000 WTP threshold.

Durvalumab following cCRT was associated with a greater increase in LYs and QALYs gained in the progression-free state (+2.37 and +2.01, respectively) but fewer LYs and QALYs gained in the progressed-disease state (−0.43 and −0.36, respectively) versus cCRT alone, because fewer patients in the durvalumab arm entered

the post progression state (when durvalumab/placebo therapy was no longer being administered) during the modeled time horizon.

The relatively high drug and administration costs associated with durvalumab were partly offset by lower discounted end-of-life and subsequent therapy costs. Durvalumab was also associated with higher HRU costs because patients spent more time in the progression-free health state. A full breakdown of discounted and undiscounted costs is detailed in supplemental eTables 7 and 8.

One-Way Sensitivity Analyses

From the Medicare perspective, no variable increased the ICER above the \$100,000 WTP threshold, and all variables had only a minor impact (Figure 2A). Variables with the biggest impact on the ICER were the proportion of patients receiving nivolumab subsequent therapy (cCRT-alone arm) and the duration of nivolumab treatment (cCRT-alone arm). Similar results were observed for commercial insurance (Figure 2B).

PSA

Results of the PSA agreed with those of the base-case analysis from both payer perspectives (Table 2). The probability that durvalumab following cCRT was cost-effective versus cCRT alone, with an ICER <\$100,000, was approximately 97.4% for Medicare and 97.3% for commercial insurance (Figure 3).

Scenario Analyses

Alternative assumptions that contributed to model uncertainty included time horizon (\$59,616–\$83,106 for Medicare and \$65,206–\$87,634 for commercial insurance), duration of treatment effect (\$44,529–\$66,114 and \$50,664–\$71,628, respectively), choice of fitted PFS curve (\$42,570–\$60,889 and \$48,768–\$66,562, respectively), duration of subsequent immunotherapy (\$54,810–\$61,606 and \$60,630–\$67,518, respectively), and use of a partitioned survival model (\$58,145 and \$64,016, respectively). However, no scenario increased the ICER above the

Table 1. Discounted Incremental Cost-Effectiveness of Durvalumab (Base-Case Analysis)

	Total				Incremental					
			Cost (USD)				Cost (USD)		ICER (USD/QALY Gained)	
	LYs	QALYs	Medicare	Commercial Insurance	LYs	QALYs	Medicare	Commercial Insurance	Medicare	Commercial Insurance
Durvalumab following cCRT	6.08	5.13	\$206,818	\$244,582	1.94	1.65	\$91,423	\$101,058	\$55,285	\$61,111
cCRT alone	4.14	3.47	\$115,395	\$142,524	—	—	—	—	—	—

Abbreviations: cCRT, concurrent chemoradiotherapy; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

A

B

Figure 2. One-way sensitivity analysis examining the impact of individual model parameters on the ICER of durvalumab following cCRT versus cCRT alone, from (A) Medicare and (B) commercial insurance perspectives. Note: nivolumab use as subsequent treatment was based on post progression therapy from the PACIFIC trial.¹²

Abbreviations: BSC, best supportive care; cCRT, concurrent chemoradiotherapy; freq, frequency; ICER, incremental cost-effectiveness ratio; mono, monotherapy; PFS, progression-free survival; QALY, quality-adjusted life-year.

\$100,000 WTP threshold. Full details of all scenarios are presented in Table 3.

Model Validation

Validation results for modeled PFS and OS data are presented in supplemental eTable 9 and eFigure 2.

Discussion

Durvalumab following cCRT was cost-effective compared with cCRT alone at a WTP threshold of \$100,000 from Medicare (ICER, \$55,285 per QALY gained) and commercial insurance (\$61,111 per QALY gained) perspectives.

The \$100,000 WTP threshold was selected because it was at the lower end of the range recommended by Neumann et al.³¹ However, a threshold of \$150,000 may also be considered acceptable for cancer drugs,³² including NSCLC,³³ meaning the ICER of durvalumab also fell well below the upper theoretical WTP threshold for new oncologic interventions.

Sensitivity analyses showed the robustness of the model results and revealed that the cost-effectiveness of durvalumab was particularly sensitive to use and duration of subsequent (ie, post progression) immunotherapy. In all PSAs, durvalumab following cCRT was

Table 2. Costs, QALYs, and ICERs Generated From Probabilistic Sensitivity and Base-Case Analyses

	Total Costs (USD)		Total QALYs		ICER (USD/QALY Gained)	
	PSA	Base-Case Analysis	PSA	Base-Case Analysis	PSA	Base-Case Analysis
Medicare						
Durvalumab following cCRT	\$206,633	\$206,818	5.15	5.13	—	—
cCRT alone	\$114,331	\$115,395	3.49	3.47	—	—
Incremental (95% CI)	\$92,301 (\$91,795–\$92,807)	\$91,423	1.66 (1.64–1.69)	1.65	\$55,573 (\$54,186–\$56,960)	\$55,285
Commercial insurance						
Durvalumab following cCRT	\$244,014	\$244,582	5.14	5.13	—	—
cCRT alone	\$142,607	\$143,524	3.48	3.47	—	—
Incremental (95% CI)	\$101,408 (\$100,781–\$102,035)	\$101,058	1.66 (1.64–1.69)	1.65	\$61,041 (\$60,022–\$62,060)	\$61,111

Abbreviations: cCRT, concurrent chemoradiotherapy; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

cost-effective compared with cCRT alone, and scenario analyses showed that the model was most sensitive to assumptions regarding time horizon, duration of durvalumab treatment effect, choice of fitted PFS curve, use of a partitioned survival model structure, and duration of subsequent immunotherapy. However, the ICER of durvalumab remained below \$100,000 in all 3 scenarios (3, 6, and 12 months of subsequent immunotherapy). Although we acknowledge that the NCCN Guidelines for NSCLC do not recommend subsequent immunotherapy after progression on durvalumab or PD-1/PD-L1 inhibitors,¹⁷ this sensitivity analysis directly addresses potential bias toward durvalumab and instead endeavors to better reflect real-world clinical care.

Despite durvalumab being associated with lower incremental costs, shorter time horizon and duration

of treatment effect increased the ICER because fewer incremental LYs/QALYs were gained in these scenarios. Likewise, the ICER changed when using the alternative partitioned-survival model, whereby the ICER increased to \$58,145 to \$64,106. This was because of the reduction in incremental LYs/QALYs accrued, which may be explained by the fact that, as of the March 22, 2018 DCO, the PFS curve had plateaued, suggesting long-term benefits from cCRT and/or durvalumab. However, there were too few deaths to produce a plateau in the OS curve. Consequently, the extrapolated PFS and OS curves crossed each other, which is theoretically implausible. Because the partitioned-survival model relies on direct extrapolation of these curves, their crossing will have biased results.

Results from our base-case analysis agree with those published by Criss et al,³⁴ who used a decision

Figure 3. Cost-effectiveness acceptability curves for the durvalumab following cCRT and cCRT-alone arms generated from the probabilistic sensitivity analysis (1,000 iterations) from (A) Medicare and (B) commercial insurance perspectives.

Abbreviations: cCRT, concurrent chemoradiotherapy; WTP, willingness to pay.

Table 3. Scenario Analyses From Medicare and Commercial Insurance Perspectives

Scenario	Medicare				Commercial Insurance			
	Incremental Costs (USD)	Incremental QALYs	Incremental LYs	ICER (USD)	Incremental Costs (USD)	Incremental QALYs	Incremental LYs	ICER (USD)
Time horizon								
10 y	\$81,288	0.98	1.14	\$83,106	\$85,717	0.98	1.14	\$87,634
20 y	\$88,409	1.48	1.74	\$59,616	\$96,700	1.48	1.74	\$65,206
Discount rate								
0%	\$99,639	2.23	2.62	\$44,699	\$113,720	2.23	2.62	\$51,015
5%	\$87,849	1.39	1.63	\$63,124	\$95,464	1.39	1.63	\$68,596
Mean age at baseline								
50 y	\$91,428	1.76	2.06	\$51,994	\$101,761	1.76	2.06	\$57,871
64 y	\$91,359	1.63	1.91	\$55,909	\$100,858	1.63	1.91	\$61,722
65 y	\$91,284	1.61	1.89	\$56,542	\$100,647	1.61	1.89	\$62,342
70 y	\$90,563	1.49	1.74	\$60,869	\$99,037	1.49	1.74	\$66,564
75 y	\$89,157	1.30	1.52	\$68,472	\$96,315	1.30	1.52	\$73,969
Sex distribution								
50% male	\$91,461	1.66	1.95	\$54,986	\$101,162	1.66	1.95	\$60,818
100% male	\$91,363	1.64	1.92	\$55,731	\$100,899	1.64	1.92	\$61,548
100% female	\$91,538	1.69	1.98	\$54,285	\$101,396	1.69	1.98	\$60,130
Mean body weight								
50 kg	\$55,839	1.65	1.94	\$33,767	\$67,248	1.65	1.94	\$40,666
65 kg	\$81,899	1.65	1.94	\$49,525	\$92,008	1.65	1.94	\$55,639
75 kg	\$101,819	1.65	1.94	\$61,572	\$110,936	1.65	1.94	\$67,084
Duration of treatment effect								
Ends at 36 mo	\$90,085	1.36	1.60	\$66,114	\$97,598	1.36	1.60	\$71,628
Ends at 48 mo	\$90,854	1.53	1.79	\$59,438	\$99,576	1.53	1.79	\$65,144
Full treatment effect	\$93,030	2.09	2.45	\$44,529	\$105,847	2.09	2.45	\$50,664
PFS survival curves options								
PFS Gompertz curve	\$95,658	2.25	2.63	\$42,570	\$109,584	2.25	2.63	\$48,768
START trial ¹⁹ PFS from 36 mo	\$90,666	1.49	1.74	\$60,889	\$9,114	1.49	1.74	\$66,562
RTOG trial ²⁰ PFS from 36 mo	\$91,447	1.49	1.74	\$55,441	\$101,049	1.49	1.74	\$61,263
PPS survival curves options								
PPS exponential curve	\$91,910	1.75	2.05	\$52,603	\$102,108	1.75	2.05	\$58,439
PPS generalized gamma curve	\$91,669	1.70	1.99	\$53,879	\$101,591	1.70	1.99	\$59,710
PPS Weibull curve	\$91,924	1.75	2.05	\$52,526	\$102,139	1.75	2.05	\$58,363
No GP mortality considered	\$91,424	1.77	2.08	\$51,570	\$101,846	1.77	2.08	\$57,449
Vial sharing								
For durvalumab	\$90,772	1.65	1.94	\$54,891	\$100,439	1.65	1.94	\$60,737
For consolidation with chemotherapy	\$90,989	1.65	1.94	\$55,023	\$100,694	1.65	1.94	\$60,891
For subsequent therapy	\$91,567	1.65	1.94	\$55,372	\$101,196	1.65	1.94	\$61,195
Mean duration of subsequent immunotherapy								
3 mo	\$101,876	1.65	1.94	\$61,606	\$111,653	1.65	1.94	\$67,518
6 mo	\$98,130	1.65	1.94	\$59,341	\$107,855	1.65	1.94	\$65,222
12 mo	\$90,638	1.65	1.94	\$54,810	\$100,262	1.65	1.94	\$60,630

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Table 3. Scenario Analyses From Medicare and Commercial Insurance Perspectives (cont.)

Scenario	Medicare				Commercial Insurance			
	Incremental Costs (USD)	Incremental QALYs	Incremental LYs	ICER (USD)	Incremental Costs (USD)	Incremental QALYs	Incremental LYs	ICER (USD)
Alternative utility models ¹²								
PACIFIC progression mixed effects model	\$91,423	1.64	1.94	\$55,770	\$101,058	1.64	1.94	\$61,648
PACIFIC time to death mixed effects model	\$91,423	1.64	1.94	\$55,654	\$101,058	1.64	1.94	\$61,519
PACIFIC mean utility by progression	\$91,423	1.68	1.94	\$54,483	\$101,058	1.68	1.94	\$60,224
PACIFIC mean utility by time to death	\$91,423	1.67	1.94	\$54,606	\$101,058	1.67	1.94	\$60,361
Inclusion of disutility associated with AEs and age decrement								
Utility age decrement	\$91,423	1.77	1.94	\$51,738	\$101,058	1.77	1.94	\$57,190
AE disutility	\$91,423	1.65	1.94	\$55,283	\$101,058	1.65	1.94	\$61,109
Consolidation with chemotherapy								
No consolidation in the cCRT-alone arm	\$93,139	1.65	1.94	\$56,323	\$103,206	1.65	1.94	\$62,410
Alternative modeling approach								
Partitioned survival model structure	\$91,355	1.57	1.84	\$58,145	\$100,581	1.57	1.84	\$64,016

Abbreviations: AE, adverse effect; cCRT, concurrent chemoradiotherapy; GP, general population; ICER, incremental cost-effectiveness ratio; LY, life-year; PFS, progression-free survival; PPS, post progression survival; QALY, quality-adjusted life-year.

analytic microsimulation model to determine the cost-effectiveness and potential budgetary impacts of durvalumab following cCRT in patients with NSCLC. Among 2 million simulated patients, the ICER of durvalumab following cCRT versus cCRT alone was \$67,421 per QALY, showing cost-effectiveness at the \$100,000 WTP threshold.³⁴ The investigators concluded that giving patients durvalumab earlier in the treatment course, when the goal of treatment is to prolong survival, potentially with curative intent, and before patients develop metastatic disease, would provide a cost-effective means of prolonging survival.³⁴ However, a number of key differences between our analysis and that of Criss et al³⁴ should be noted. First, durvalumab data (PFS) in the Criss model were based on less-mature PFS data from the first data readout, and OS data were unavailable,³⁴ whereas the data used in our analysis were from the more recent data readout of the PACIFIC trial with approximately 2 years' longer follow-up. Second, we were able to use the actual average sales pricing for durvalumab because the treatment is now in use, whereas Criss et al³⁴ used an estimate for this. Third, we were able to include second-line immunotherapy in our model, although we acknowledge that despite subsequent immunotherapy not being included in the original model by Criss et al,^{34,35} when added in a later analysis, durvalumab remained cost-effective, with an ICER of \$79,609 per QALY. Therefore, our analysis builds on the work of Criss et al³⁵ to provide a more robust estimate of the costs associated with durvalumab consolidation therapy, given current clinical practice patterns.

Economic evaluations are central to the process by which payers in countries such as Australia, Canada, and members of the European Union assess the value of new interventions.³⁶ In the United States, moves toward adopting value-based frameworks have begun to emerge, primarily due to escalating healthcare costs, particularly in cancer care.^{37–39} As the level of importance placed on drug value has increased in the United States, institutions and medical professional societies have responded, developing new frameworks to assess the value of novel interventions. In oncology, these include the ASCO Value Framework Net Health Benefit score,⁴⁰ NCCN Evidence Blocks,⁴¹ NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework),⁴² ESMO Magnitude of Clinical Benefit Scale,⁴³ Institute for Clinical and Economic Review Value Assessment Framework,⁴⁴ and Memorial Sloan Kettering Cancer Center Drug Abacus.⁴⁵ In addition to evaluating the efficacy and safety of an intervention, these frameworks account for other factors underlying value, such as evidence quality, impact on quality of life, and cost-effectiveness.^{38,39} Consistent with the goal of these frameworks to evaluate the value of oncologic treatments, our study found durvalumab following cCRT to be cost-effective compared with cCRT alone in patients with unresectable stage III NSCLC, showing the long-term value of durvalumab in this setting.

The main limitation of the state-transition model used in our analysis was that PFS, TTP, and PPS data were immature; therefore, these curves had to be extrapolated, resulting in model uncertainty (although

extrapolated data were validated clinically). However, the state-transition model offers several advantages over models used more frequently in oncology cost-effectiveness analyses, such as partitioned-survival models, in which survival curves for PFS and OS are fitted completely independently from each other. As described earlier, if PFS and OS data are of different maturity, the more mature endpoint may exhibit trends different from those of the less-mature endpoint, potentially producing contradictory results when the survival curves are combined. This effect is accentuated when a long survival tail is expected, such as in stage III NSCLC, in which 9.4% to 11.6% of patients remain alive and progression-free at 5 years after CRT.⁷

Conclusions

Our findings show that in a US healthcare setting, durvalumab following cCRT is cost-effective compared with cCRT alone, supporting the adoption of this regimen as the new standard of care in unresectable stage III NSCLC.

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Supplemental online content for:

Cost-Effectiveness of Durvalumab After Chemoradiotherapy in Unresectable Stage III NSCLC: A US Healthcare Perspective

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eAppendix 1: Supplementary Methods

eFigure 1: Post Progression Survival During the PACIFIC Study

eFigure 2: Validation of Modeled PFS and OS Using PACIFIC, START, and RTOG 0617 Trial Data

eTable 1: Drug Costs for Consolidation With Chemotherapy

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eAppendix 1. Supplementary Methods

Scenario Analyses

Scenario analyses were conducted using variations in key model setting and assumptions, including time horizon, discount rate, mean age at baseline, sex distribution, mean body weight, duration of treatment effect, choice of fitted progression-free survival (PFS) and post progression survival curves, vial sharing, mean duration of subsequent immunotherapy, alternative utility models, inclusion of disutilities associated with adverse effects and age decrement, and use of a standard partitioned survival model structure (whereby extrapolated overall survival curves were used instead of PFS curves to estimate the proportions of patients in the progressed disease and death states).

Model Validation

Quality checks of the original and US-adapted models were performed, including face validity and third-party validation of the data sources and calculations used. To assess the plausibility of fitted curves, modeled PFS and overall survival were also validated externally using data from the PACIFIC,^{1,2} START,³ and RTOG 0617^{4,5} trials.

eFigure 1. Post progression survival during the PACIFIC study.
Abbreviation: cCRT, concurrent chemoradiotherapy.

eFigure 2. Validation of modeled (A) PFS and (B) OS using PACIFIC,^{1,2} START,³ and RTOG 0617^{4,5} trial data.
Abbreviations: cCRT, concurrent chemoradiotherapy; OS, overall survival; PFS, progression-free survival.

eTable 1. Drug Costs for Consolidation With Chemotherapy

Drug	Frequency/Dosing ⁶	Drug Unit Cost (USD)	
		Medicare ⁶	Commercial Insurance ⁷
Durvalumab, 120 mg	10 mg/kg q2wk	\$73.78 (10 mg)	\$841.18 (120 mg)
Carboplatin, 150 mg ^a	AUC 5 q3wk	\$9.53	\$14.83
Cisplatin, 50 mg	75 mg/m ² q3wk	\$8.78	\$18.05
Pemetrexed, 100 mg	500 mg/m ² q3wk	\$682.17	\$676.52

Abbreviations: AUC, area under the curve; GFR, glomerular filtration rate; NICE, National Institute for Health and Care Excellence.

^aCarboplatin is dosed on an AUC basis. To calculate the dose required for a specific patient to get to a specific AUC, serum creatinine and GFR data are required. This information was not available from the PACIFIC study report; therefore, the estimated dose of carboplatin was taken from previous NICE technology appraisals, which included carboplatin-containing regimens. The NICE technology appraisal guidance document [TA181] estimated that a target AUC of 5 would result in a dose of 500 mg.⁸ Document [TA347] estimated that a target AUC of 5 would result in a dose of 750 mg.⁹ The dose of 500 mg was selected in the base-case analysis as a conservative assumption. The same linear relationship was assumed for both AUC 2 and 6.

eTable 2. Healthcare Resource Use Unit Costs (USD)

Resource	Medicare ⁶	Commercial Insurance ^{a,7}
Outpatient oncologist visit	\$138.56	\$203.11
Chest radiograph	\$36.29	\$60.65
CT scan (chest)	\$238.53	\$472.50
CT scan (other)	\$261.19	\$512.89
Electrocardiogram	\$28.24	\$35.36
PET scan	\$953.12	\$1,762.46
General practitioner surgery visit	\$91.05	\$140.44
End-of-life care ^b	\$66,204.85 ^{a,10}	\$69,848.67 ¹¹

Costs associated with healthcare resource use were calculated using the IBM MarketScan Commercial Claims and Encounters database. In this database, a total of 115,499 patients were identified as having non-small cell lung cancer between July 1, 2012, and June 30, 2017 (and no other cancer following their lung cancer diagnosis). For these patients, claims that had a CPT code for the resource of interest were extracted. Paid costs on these claims were averaged to provide a unit cost for each resource of interest.

^aClaims were from 2017 therefore these costs were inflated to 2018 USD (Medicare costs were already in 2018 USD and therefore did not need to be inflated).

^bEnd-of-life care included all hospital utilization and spending within the last 6 months of life. This value was applied for patients who did not receive hospice care, but did include nursing home costs.

eTable 3. Subsequent (Post Progression) Treatment Costs

Drug	Required Dose ¹²	Price Per Vial/Pack (USD)	
		Medicare ⁶	Commercial Insurance ⁷
Durvalumab (120 mg)	10 mg/kg q2wk	\$73.78 (10 mg)	\$841.18 (120 mg)
Pembrolizumab (100 mg)	200 mg every 21 days	\$4,935.10	\$4,719.40
Paclitaxel (30 mg) +	200 mg/m ² weekly plus an additional 2 cycles are given	\$4.08	\$10.50
Carboplatin (150 mg)	AUC 2 + AUC 6 for additional 2 cycles	\$9.53	\$14.83
Gemcitabine (1,000 mg) +	1,000 mg/m ²	\$37.17	\$63.90
Carboplatin (150 mg)	AUC 6	\$9.53	\$14.83
Gemcitabine (1,000 mg) +	1,250 mg/m ²	\$37.17	\$63.90
Cisplatin (50 mg)	75 mg/m ²	\$8.78	\$18.05
Pemetrexed (100 mg) +	500 mg/m ²	\$682.17	\$676.52
Cisplatin (50 mg)	75 mg/m ²	\$8.78	\$18.05
Pemetrexed (100 mg) +	500 mg/m ²	\$682.17	\$676.52
Carboplatin (150 mg)	AUC 5	\$9.53	\$14.83
Cisplatin (50 mg) +	50 mg/m ²	\$8.78	\$18.05
Etoposide (100 mg)	50 mg/m ²	\$7.28	\$9.37
Cisplatin (50 mg) +	100 mg/m ²	\$8.78	\$18.05
Vinblastine (10 mg)	5 mg/m ²	\$37.86	\$43.07
Nivolumab (100 mg)	240 mg q2wk or 480 mg q4wk	\$2,754.10	\$2,622.00
Docetaxel (20 mg)	75 mg/m ²	\$30.18	\$61.88
Erlotinib (25 mg × 30 tablets)	150 mg/d	\$2,720.39	\$2,720.39
Vinorelbine (50 mg)	27.5 mg/m ²	\$88.23	\$85.00
Crizotinib (250 mg × 60 capsules)	250 mg/d	\$16,055.81	\$16,055.81
Afatinib (40 mg × 30 tablets)	40 mg/d	\$8,154.77	\$8,154.77
Gemcitabine (1,000 mg)	1,000 mg/m ²	\$37.17	\$63.90
Carboplatin (150 mg)	AUC 5	\$9.53	\$14.83
Cisplatin (50 mg)	75 mg/m ²	\$8.78	\$18.05
Paclitaxel (30 mg)	200 mg/m ²	\$4.08	\$10.50
Radiotherapy (total) ^a		\$2,089.11	\$2,089.11

Abbreviations: ASTRO, American Society for Radiation Oncology; AUC, area under the curve.

^aRadiotherapy costs were calculated as a one-off cost in the model. It was assumed that patients received 14 radiation sessions as subsequent/post progression treatment, with one therapeutic treatment planning session prior to commencing treatment and one complex treatment session on a megavoltage machine. These frequencies were based on ASTRO evidence-based guidelines for palliative thoracic radiotherapy in non-small cell lung cancer.¹³

eTable 4. Radiotherapy Costs^a

	Frequency ¹⁴	Cost (USD)	CPT Code ^b
Therapeutic radiotherapy planning, simple	1	\$73.08	77261
Radiotherapy delivery, ≥1 MeV, simple	14	\$127.79	7740
Deliver a fraction of complex treatment on a megavoltage machine	1	\$226.97	77412

^aRadiotherapy costs were calculated as a one-off cost in the model. It was assumed that patients received 14 radiotherapy sessions as subsequent/post progression treatment, with one therapeutic treatment planning session prior to commencing treatment and one complex treatment session on a megavoltage machine. These frequencies were based on American Society for Radiation Oncology evidence-based guidelines for palliative thoracic radiotherapy in non-small cell lung cancer.¹³

^bPer the American Medical Association.¹⁵

eTable 5. AE Frequency, Disutility, and Costs

Grade 3/4 AEs ≥2% in Either Arm ^a	AEs		Disutility	Cost ^c (USD)	DRG Code
	Durvalumab Following cCRT (n)	cCRT Alone (n)			
Anemia	16	9	−0.070 ^b	\$7,696.56	808, 809, 810
Dyspnea	8	6	−0.085 ^{c,16}	\$3,951.00	204
Pneumonia	28	18	−0.0735 ¹⁷	\$7,728.00	193
Pneumonitis	13	8	−0.05 ^d	\$7,728.00	193

Abbreviations: AE, adverse effect; cCRT, concurrent chemoradiotherapy; DRG, diagnosis-related group.

^aData cutoff March 22, 2018.

^bFrom Herbst et al¹⁸ (KEYNOTE-010), as referenced in the National Institute for Health and Care Excellence technology appraisal guidance [TA428].¹⁹

^cFrom Nafees et al,¹⁷ as referenced in the National Institute for Health and Care Excellence technology appraisal guidance [TA411].²⁰

^dAssumed to be the same as pneumonia.

eTable 6. Distribution of Subsequent Therapies Among Patients in the PACIFIC^{1,2} Trial

Subsequent Treatment	Durvalumab	Best Supportive Care
Immunotherapies		
Nivolumab	14%	29%
Pembrolizumab	3%	5%
Durvalumab	4%	
Non-immunotherapies		
Docetaxel	19%	9%
Erlotinib	4%	8%
Vinorelbine	6%	5%
Crizotinib	2%	3%
Afatinib	5%	2%
Gemcitabine	19%	13%
Carboplatin monotherapy	33%	26%
Cisplatin monotherapy	8%	8%
Pemetrexed monotherapy	21%	17%
Radiotherapy	38%	37%
Watchful waiting/no treatment	10%	16%

eTable 7. Discounted Costs (USD) From Medicare and Commercial Insurance Perspectives

	Durvalumab Following cCRT		cCRT Alone		Incremental Cost	
	Medicare	Commercial Insurance	Medicare	Commercial Insurance	Medicare	Commercial Insurance
Drugs	\$92,549.20	\$87,933.32	\$1,210.35	\$1,346.18	\$91,338.85	\$86,587.14
Drug administration	\$4,171.35	\$6,612.57	\$505.66	\$801.59	\$3,665.69	\$5,810.98
Resource use	\$43,364.91	\$79,483.20	\$28,460.85	\$52,036.00	\$14,904.06	\$27,447.20
Terminal care	\$54,296.73	\$57,285.15	\$58,585.22	\$61,809.67	−\$4,288.49	−\$4,524.52
Subsequent therapy (non-immunotherapy)	\$5,962.44	\$6,703.58	\$6,682.49	\$7,320.42	−\$720.06	−\$616.84
Subsequent nivolumab	\$4,321.57	\$4,381.15	\$17,183.03	\$17,419.93	−\$12,861.47	−\$13,038.78
Subsequent pembrolizumab	\$608.17	\$615.25	\$1,945.65	\$1,968.29	−\$1,337.48	−\$1,353.04
Subsequent durvalumab	\$913.18	\$936.71	\$0.00	\$0.00	\$913.18	\$936.71
Adverse effects	\$630.72	\$630.72	\$821.57	\$821.57	−\$190.85	−\$190.85
Total	\$206,818.27	\$244,581.66	\$115,394.82	\$143,523.65	\$91,423.45	\$101,058.01

Abbreviation: cCRT, concurrent chemoradiotherapy.

eTable 8. Undiscounted Costs (USD) From Medicare and Commercial Insurance Perspectives

	Durvalumab Following cCRT		cCRT Alone		Incremental Cost	
	Medicare	Commercial Insurance	Medicare	Commercial Insurance	Medicare	Commercial Insurance
Drugs	\$92,549.20	\$87,933.32	\$1,210.35	\$1,346.18	\$91,338.85	\$86,587.14
Drug administration	\$4,171.35	\$6,612.57	\$505.66	\$801.59	\$3,665.69	\$5,810.98
Resource use	\$53,745.28	\$98,516.18	\$33,770.06	\$61,745.84	\$19,975.22	\$36,770.34
Terminal care	\$63,870.60	\$67,385.95	\$65,046.90	\$68,626.99	−\$1,176.29	−\$1,241.03
Subsequent therapy (non-immunotherapy)	\$6,267.25	\$7,046.28	\$6,830.38	\$7,482.42	−\$563.13	−\$436.14
Subsequent nivolumab	\$4,542.49	\$4,605.12	\$17,563.30	\$17,805.43	−\$13,020.80	−\$13,200.32
Subsequent pembrolizumab	\$639.26	\$646.70	\$1,988.71	\$2,011.85	−\$1,349.44	−\$1,365.15
Subsequent durvalumab	\$959.86	\$984.60	\$0.00	\$0.00	\$959.86	\$984.60
Adverse effects	\$630.73	\$630.73	\$821.57	\$821.57	−\$190.84	−\$190.84
Total	\$227,376.03	\$274,361.45	\$127,736.91	\$160,641.88	\$99,639.12	\$113,719.57

Abbreviation: cCRT, concurrent chemoradiotherapy.

eTable 9. Validation of Modeled PFS and OS Data Using PACIFIC,^{1,2} START,³ and RTOG 0617^{4,5} Trial Data

Curve	Median (mo)	1-Year (%)	2-Year (%)	3-Year (%)	5-Year (%)
PFS					
Durvalumab following cCRT					
Modeled	16.6	56.6	44.3	38.0	31.2
PACIFIC	17.2	55.5	44.9	37.6	NA
cCRT alone					
Modeled	6.4	34.7	21.9	16.4	11.3
PACIFIC	5.6	34.4	24.3	16.9	NA
START	8.3	42.0	25.0	20.0	14.6
RTOG 0617	11.5	50.1	29.6	24.6	18.4
OS					
Durvalumab following cCRT					
Modeled	45.1	84.3	67.5	56.1	43.0
PACIFIC	46.8	83.1	66.3	57.0	NA
cCRT alone					
Modeled	27.6	77.4	55.3	41.3	26.5
PACIFIC	28.7	74.6	55.3	43.5	NA
START	25.6	73.9	45.9	36.9	19.9
RTOG 0617	28.7	80.5	58.3	44.8	32.1

Abbreviations: cCRT, concurrent chemoradiotherapy; NA, not applicable; OS, overall survival; PFS, progression-free survival.

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