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Cost-effectiveness analysis of nivolumab for the treatment of squamous cell carcinoma of the head and neck in the United States

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ABSTRACT

Aim: To assess the cost-effectiveness of nivolumab monotherapy for recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the US.

Methods: We constructed a cohort-based partitioned survival model for three health states (progression-free, progressed disease, and death). Using overall survival and progression-free survival data from the nivolumab and investigator's choice (IC) arms of the CheckMate 141 study, the proportion of patients in each health state was estimated by parametric modeling over a 25-year period. Cost, utility, adverse event, and disease management data inputs were obtained from relevant literature and applied to patients in each health state. A scenario analysis was conducted assuming increased uptake of subsequent immunotherapies. A one-way deterministic sensitivity analysis assessed the impact of variation in multiple parameters. A probabilistic sensitivity analysis in which probabilistic distributions were applied to each input during 1,000 model iterations was also conducted.

Results: Total costs incurred were higher with nivolumab ($101,552) than with IC ($38,067). Nivolumab was associated with a higher number of life-years (LY; 1.21) and quality-adjusted life-years (QALYs; 0.89), compared with IC (0.68 and 0.42, respectively). The incremental cost-effectiveness ratio for nivolumab compared with IC was $134,438 per QALY, and this remained qualitatively similar when increased uptake of subsequent immunotherapies was assumed ($129,603 per QALY). Sensitivity analyses supported these findings.

Conclusion: These results suggest that, at a willingness-to-pay threshold of $150,000 per QALY, nivolumab is a cost-effective option for therapy of SCCHN in the US.

Keywords: CheckMate 141 study; Cost-effectiveness; Nivolumab; Quality-adjusted life-years; Recurrent/metastatic; Sensitivity analyses; Squamous cell carcinoma of the head and neck; Treatment options

Running head: COST-EFFECTIVENESS ANALYSIS OF NIVOLUMAB FOR TREATING SCCHN IN THE US

JEL classification codes: I10; I00; I11

INTRODUCTION

Head and neck cancers (inclusive of neoplasms of the oral cavity, pharynx, larynx, sinuses, and salivary gland) are major causes of cancer-related mortality in the US, with approximately 65,410 new cases and 14,620 deaths annually[1]; an estimated 90% of all cases are squamous cell carcinoma of the head and neck (SCCHN)[2]. The economic burden of recurrent/metastatic (R/M) SCCHN in the US is considerable, with estimated 6-month attributable costs of $20,000–60,000 per patient[3]. Approximately three-quarters of patients diagnosed with SCCHN present with locoregionally advanced disease[4]; despite curative treatment (generally with chemoradiotherapy and/or surgery), a substantial proportion of these patients will experience recurrence, progression or metastases.

In patients with R/M SCCHN, the addition of cetuximab to platinum-based chemotherapy in combination with fluorouracil (5-FU) as first-line therapy improves survival[5], and until recently this regimen remained the standard of care first-line therapy in this setting[6,7]. More recently, programmed death receptor-1 (PD-1) antibodies such as pembrolizumab and nivolumab have been investigated in this clinical setting. These immune checkpoint inhibitors inhibit the programmed cell death 1 ligand (PD-L1)-mediated evasion of T-cell cytotoxicity exhibited by many tumor types[8]. The US Food and Drug Administration (FDA) recently approved pembrolizumab for first-line therapy of R/M SCCHN, either as monotherapy (in patients whose tumors express PD-L1), or in combination with platinum-based chemotherapy and 5-FU[9], based on observations of efficacy and safety from the KEYNOTE-048 trial[10].

In the second-line setting, pembrolizumab and nivolumab have demonstrated clinical efficacy and safety as therapy for SCCHN[11,12]. The randomized, open-label, phase III CheckMate 141 trial compared nivolumab with investigator's choice (IC; methotrexate, docetaxel, or cetuximab) in patients with R/M SCCHN who had progressed after platinum-based chemotherapy, and reported that patients receiving nivolumab had a significantly longer overall survival (OS) (7.5 months) compared with those receiving IC (5.1 months), and 1-year survival was higher in the nivolumab group (36% vs 17%)[12]. Based on these findings, in November 2016 the FDA approved nivolumab for the treatment of R/M SCCHN with disease progression on or after platinum-based therapy[13].

Given the high costs of these novel therapies[14], rigorous cost-effectiveness analysis is crucial for payers to optimize healthcare spending. A recent cost-effectiveness analysis from a US healthcare system perspective assessed nivolumab for R/M SCCHN compared with other approved therapies (methotrexate, docetaxel, or cetuximab) and reported that nivolumab was cost-effective above a willingness-to-pay (WTP) threshold of $150,000[15]; as only 15-month of published outcomes data were available at that time, the analysis used a time horizon of only 3 years. Guidance from the National Institute for Health and Care Excellence (NICE) recommends that cost-effectiveness evaluations should consider a "lifetime horizon" for patients[16]. Longer-term outcomes data have now been reported for CheckMate 141[17] , and the 2-year survival rate of 17% in patients receiving nivolumab suggests that a 3-year time horizon may underestimate the value of nivolumab treatment over a longer period. Another analysis using a 30-year time horizon reported that nivolumab had an ICER of $294,400 compared with IC[18]. Although that analysis used disease transition probabilities from CheckMate 141, corresponding utility values for progression-free (PF) and progressed

disease (PD) were unavailable at that time and were instead derived from two different non-immunotherapy trials, with identical utilities applied to both the nivolumab and IC arms. Treatment-specific utility values from CheckMate 141 are now available for nivolumab and IC, and more accurately reflect the outcomes associated with each treatment. We assessed the incremental cost-utility of nivolumab for therapy of R/M SCCHN with disease progression on or after platinum-based therapy from a US healthcare system perspective, compared with the CheckMate 141 IC arm.

METHODS

Design and structure

A cohort-based partitioned survival model was developed consisting of three mutually exclusive health states, representing the relevant primary stages of disease in R/M SCCHN: PF, PD, and death (Figure 1). All patients were assumed to be PF at the start of the analysis. The proportion of patients in each health state was estimated by parametric modeling of OS and progression-free survival (PFS) data from the nivolumab and IC arms of CheckMate 141. Consistent with the design of CheckMate 141, the three individual agents comprising the IC arm were considered as an aggregate unit.

The process for fitting parametric survival curves to patient-level data was based on methodological guidance from the NICE Decision Support Unit, which advises that, if possible, the same parametric survival model should be selected when fitting independent parametric models to two arms for comparison when the proportional hazards assumption is not valid, as was the case for OS and PFS from CheckMate 141[16]. Akaike and Bayesian

Information Criterion goodness-of-fit statistics were used to identify the best-fitting survival models.

Model inputs

Incidence of adverse events (AEs) with nivolumab and IC were calculated using CheckMate 141 data reporting any grade 3, 4, or 5 AEs (i.e., AEs defined as severe, life-threatening/disabling, or causing death, respectively, according to "Common Terminology for Adverse Events v5.0")[19] with an incidence of at least 5% in the nivolumab and IC arms[20] (Supplementary Table 1). Treatment-specific utilities for PF and PD health states were generated by applying a US population preference-weighting algorithm[21] to 3-level EuroQol 5-dimension health questionnaire (EQ-5D-3L)[22] data collected in CheckMate 141 (Bristol-Myers Squibb, data on file; OR NIVO 094, 2017) (Supplementary Table 2). As AEs were expected to occur within the first treatment cycle, disutility of AEs was applied to the PF health state, based on values obtained by systematic literature review (Supplementary Table 3).

Cost input parameters applied to the model included those related to drug acquisition and administration, monitoring, disease management, treatment of AEs, and subsequent treatments (Supplementary Table 4–9). When a patient was assumed to have died, an end-of-life care cost of $10,528.07 was applied (based on reported costs for renal cell carcinoma, as no published SCCHN-specific costs were identified)[23]. Cost data for IC used in this analysis represented a mean of the individual agents used in the IC arm of CheckMate 141.

The base case analysis assumed that all treatments were administered until disease progression, in line with their respective FDA-approved prescribing information. The base case analysis also assumed that 0.6% of patients receiving IC would subsequently receive immunotherapy (based on observations from CheckMate 141). An annual discount rate of 3% was applied to all costs and outcomes.

Outcomes

Health state (PF, PD or death) occupancy was evaluated at 4-week intervals over the hypothetical 25-year duration of the model. Total healthcare costs and health outcomes were calculated by combining the cost, medical resource use, and utilities (EQ-5D-3L) assigned to each health state (PF and PD). Health outcomes included life-years (LYs) and quality-adjusted life-years (QALYs). Total costs represented the sum of costs for disease management, treatment acquisition, treatment monitoring, treatment of AEs, and subsequent treatments, and are reported in 2017 US$ per patient.

Scenario and sensitivity analyses

To better reflect evolving clinical practice and increasing use of immunotherapies, a "scenario analysis" was conducted assuming that 30% of patients receiving IC would subsequently receive immunotherapy. As it is possible that the disutilities associated with AEs may partly drive the lower utilities observed with IC treatment compared with nivolumab, a second scenario analysis removed the disutilities associated with AEs from the model, to account for the possibility of AE disutilities being double-counted during IC therapy. One-way deterministic sensitivity analyses (DSA) were conducted assessing variation in the multiple parameters. Individual parameters used in the base case scenario

were replaced with estimated low (minimum) and high (maximum) values for sensitivity analyses; the range used was based on ± standard error for utility values, and ± 20% for all other inputs. To evaluate the impact of uncertainty on the estimated cost-effectiveness, a probabilistic sensitivity analysis (PSA) was conducted using probabilistic distribution of input values during 1,000 model iterations. PSA input values were estimated from multivariate normal distribution (for OS and PFS), gamma distribution (for disease management costs, acquisition costs, administration costs, monitoring costs, AE costs, other costs, and disutility of AEs), and beta distribution (for utility weights).

RESULTS

After preliminary evaluation of OS and PFS data from CheckMate 141, neither met the assumption of proportional hazards. The most appropriate models were log normal (for OS) and generalized gamma (for PFS); these were therefore selected for use in the base case analysis. Parametric extrapolation of OS in patients receiving nivolumab was externally validated against 5-year survival data from the squamous non-small cell lung cancer cohort from the phase 1b, open-label CheckMate 003 study and found to be reliable (Supplementary Table 10).

Base case analysis

Total costs incurred with nivolumab ($101,552) and IC ($38,067) were largely driven by treatment acquisition costs ($75,981 and $14,599, respectively) and disease management costs ($20,816 and $16,316, respectively) (Table 1). Nivolumab was associated with a higher number of QALYs (0.89) and LY (1.21), compared with IC (0.42 and 0.68, respectively). Incremental cost-effectiveness ratios (ICERs) indicated that the cost per additional QALY

with nivolumab was $134,438 compared with IC in the base case scenario (Table 2). The ICER for life-years gained with nivolumab was $118,455 per life-year. When the probability of patients receiving immunotherapies (nivolumab or pembrolizumab) in subsequent lines of therapy was increased in the IC arm (to reflect improved access to these treatments after their approval), total costs for IC increased. Consequently, the ICER for nivolumab versus IC decreased slightly, but all ICERs remained qualitatively similar to the base case (i.e., the ICER for nivolumab was $129,603 per QALY and $114,194 per life-year, compared with IC). An additional scenario analysis in which AE-related disutilities were removed from the model yielded a cost per QALY of $141,806, consistent with the base case findings.

Deterministic sensitivity analyses

A tornado plot representing DSA for nivolumab compared with IC is presented as Figure 2. The ICER for nivolumab versus IC did not change substantially with variation in individual parameters. ICERs were generally influenced most strongly by variation in discount rate on outcomes and costs, and health state utility values for nivolumab.

Probabilistic sensitivity analyses

The results of the PSA for 1,000 model iterations are presented in Table 3. These results supported the findings from the base case analysis, with the ICER for nivolumab ($137,927) considered cost-effective compared with IC at a WTP threshold of $150,000. A scatter plot of individual model iterations during the PSA is presented in Supplementary Figure 1. At a WTP threshold of $150,000, 62.2% of PSA model iterations were deemed cost-effective; a cost-effectiveness acceptability curve describing this is presented in Supplementary Figure 2.

DISCUSSION

The findings from the base case analysis in our model suggest that, at the $150,000 per QALY threshold generally considered acceptable in the US[24], nivolumab would be cost-effective compared with IC (consisting of methotrexate, docetaxel, or cetuximab). PSA results were similar to the base case analysis, and found that the majority (>60%) of model iterations estimated the ICER to be less than $150,000. One-way DSA demonstrated that variations in discount for costs and outcomes, and utility values for PD and PF, had the highest impact on resultant ICER estimates. When increased use of immunotherapies subsequent to IC therapy was assumed, in keeping with contemporaneous clinical observations, the incremental costs between nivolumab and IC decreased slightly. Consequently, the ICER for nivolumab was less than $130,000 per QALY versus IC in this scenario.

Existing ICER thresholds continue to foment debate in the face of rising costs associated with novel therapies[25], and vary greatly across countries in both their magnitude and the way they are applied[26]. The WTP threshold of $150,000 generally used in the US follows World Health Organization recommendations that the upper limit for cost-effectiveness of an intervention should be considered to be approximately three times gross domestic product per capita[24]. However, ICERs for oncology treatments are more than double those of non-oncology treatments[27], and recent oncology-specific studies have suggested that the "true" threshold should be considered to be above $150,000: surveys from academic oncologists[28] and observational analyses of patient behaviors[29] suggest that a threshold as

high as $250,000 may be acceptable, particularly in the metastatic setting. Given the spiraling costs of healthcare in the US, which are approximately double that of other high income countries per capita, optimization of healthcare resources is increasingly important.[30] Initiatives such as the ASCO framework[31] have attempted to provide objective guidance for assessing the cost-effectiveness of therapies but may not reflect affordability or additional "value" of treatments (such as novel mechanisms of action, providing treatment options when few are currently available, or therapies for rare or high-morbidity conditions)[32,33].

To the authors' knowledge, two other analyses have used CheckMate 141 data to estimate the cost-effectiveness of nivolumab as therapy of R/M SCCHN from a US healthcare system perspective. Our findings broadly concur with those of Ward et al, who reported that nivolumab was cost-effective at a WTP threshold of $150,000 compared with IC[15]. However, our model extends over a more appropriate time horizon (25 years) and is therefore more likely to capture the "lifetime" perspective of patients receiving nivolumab in US clinical practice. A further economic analysis reported that nivolumab would not be cost-effective at currently accepted thresholds[18]. That study used a longer-term time horizon (30 years), but drew utility values from older, non-immunotherapy trials, and applied identical utility values for PF and PD to both nivolumab and IC arms. Both of these studies excluded the likelihood of subsequent therapy in patients with progressed disease after platinum-based therapy. Following the approval of immunotherapies, patients now have improved treatment options following disease progression.

From a non-US approach, one analysis from the perspective of Canadian healthcare payers reported that the ICER for nivolumab compared with docetaxel was CAD $144,000, above the conventional WTP threshold of CAD $100,000 suggested by the authors[34]. However, by comparing nivolumab with docetaxel alone, these observations are unlikely to reflect US clinical practice. A further analysis from the perspective of the Swiss healthcare system assessed the cost-effectiveness of nivolumab compared with IC using a Markov model, and estimated that the ICER for nivolumab would be CHF 102,957, just above the authors' proposed WTP threshold of CHF 100,000[35]. It should be noted that both of these analyses used a 5-year time horizon and are therefore unlikely to represent the "lifetime" perspective for patients with R/M SCCHN. Indeed, in the latter publication, a scenario analysis extending the time horizon to 10 years found nivolumab to be cost-effective, with an estimated ICER of CHF 93,325[35]. This illustrates the importance of considering the long-term benefit of immunotherapies in cost-effectiveness analyses; clinical trials have shown such treatments to be associated with delayed responses and "responder" subpopulations, both of which require sufficient time horizons to become apparent[36].

There are several limitations to this analysis. The probabilities of patients experiencing AEs were based on clinical trial data for only grade 3 or above AEs and AEs occurring in more than 5% of patients. Consequently, the presence of rare or low-grade AEs with nivolumab may be underestimated in the model. However, the contribution of AE treatment to total costs was minimal, and DSA did not identify AE treatment as having a strong influence on the resultant ICERs. Disutility of AEs was not reported in the CheckMate 141 trial; the disutilities used in the present model have therefore been taken from other published literature (as listed in Supplementary Table 3). Lastly, it should be noted that WTP

thresholds are variable and no clear consensus on their implementation or interpretation is presently available; caution should be taken when considering the results from this analysis.

In conclusion, this analysis used survival models informed by data from the CheckMate 141 clinical trial to compare the cost-effectiveness of nivolumab versus IC for therapy of R/M SCCHN. Despite higher treatment costs compared with standard care (IC), nivolumab is associated with a considerable improvement in QALYs and LY gained, and is a cost-effective option for therapy of R/M SCCHN in the US.

TRANSPARENCY

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TABLES AND FIGURES

Figure 1. Schematic representation of partitioned survival model and disease health state transitions.

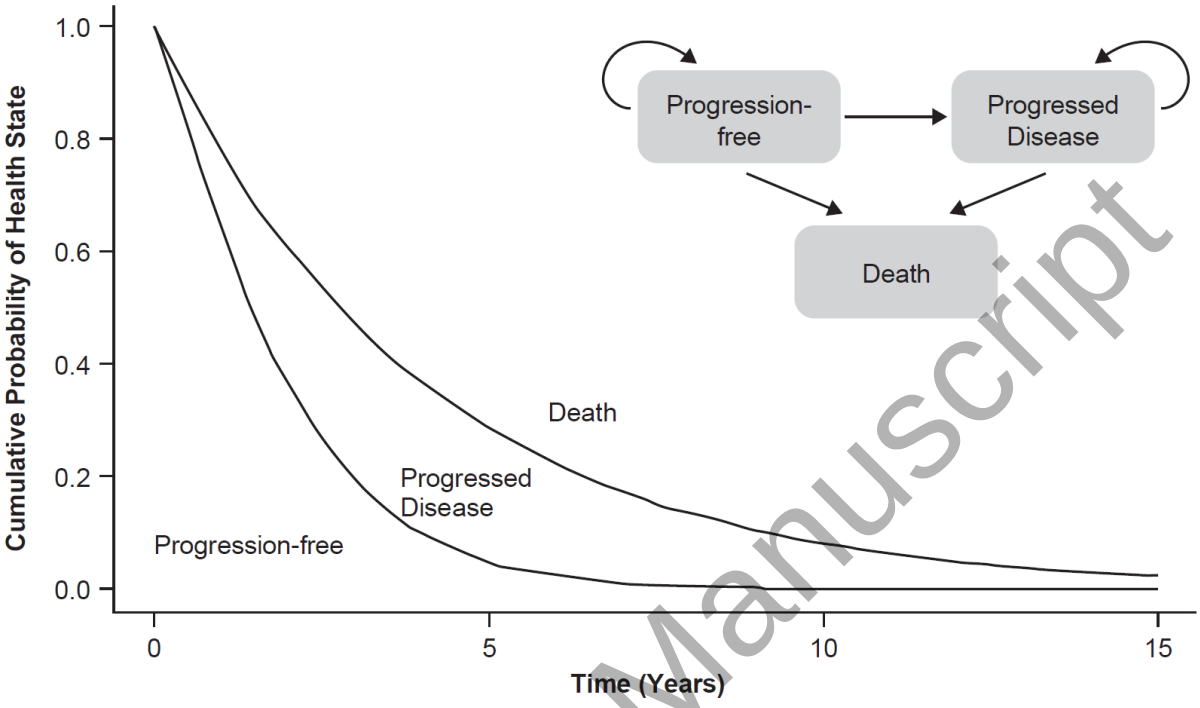
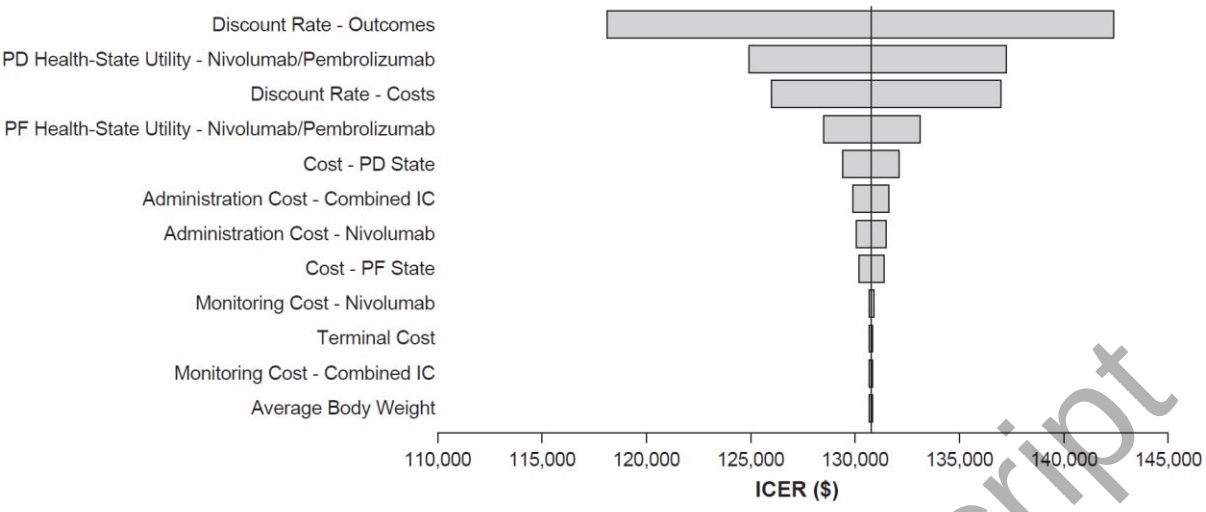


Figure 2. Deterministic sensitivity analysis of ICER response to variability of input parameters for nivolumab vs investigator's choice arm.



ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PF: progression-free.

Range of input variability: ± standard error for utility values; ± 20% for all other inputs values.

Table 1. Absolute value estimates of health outcomes and costs associated with each treatment in the model.

	Health outcomes			Costs ($)						
	AE disutility	LYs	QALYs	Disease management	Treatment acquisition	Treatment administration	Treatment monitoring	AEs	Subsequent treatment	Total
Nivolumab	−0.04	1.21	0.89	20,816	75,981	1,661	275	1,977	842	101,552
Investigator's choice	−0.07	0.68	0.42	16,316	14,599	2,057	72	3,800	1,222	38,067

AEs: adverse events; ICER: incremental cost-effectiveness ratio; LY: life-years; QALYs: quality-adjusted life-years.

All costs are in 2017 US$.

Table 2. Incremental gains with nivolumab vs investigator's choice.

	LYs	QALYs	Costs ($)	Cost per LYG ($)	Cost per QALY ($)
Base case	0.54	0.47	63,485	118,455	134,438
Assuming increased subsequent use of immunotherapies	0.54	0.47	61,202	114,194	129,603
Removing disutilities associated with AEs from the model	0.54	0.45	63,482	118,455	141,806

AEs: adverse events; FDA: US Food and Drug Administration; LY: life-years; LYG: life-years gained; QALYs: quality-adjusted life-years.

All costs are in 2017 US$.

Table 3. Probabilistic sensitivity analysis of health outcomes and costs associated with each treatment in 1,000 model iterations.

	Total costs ($)	Total QALYs	Incremental costs ($) vs IC	Incremental QALYs vs IC	Incremental cost per QALY ($)
IC	37,743	0.421	–	–	–
Nivolumab	102,974	0.894	65,231	0.473	137,927

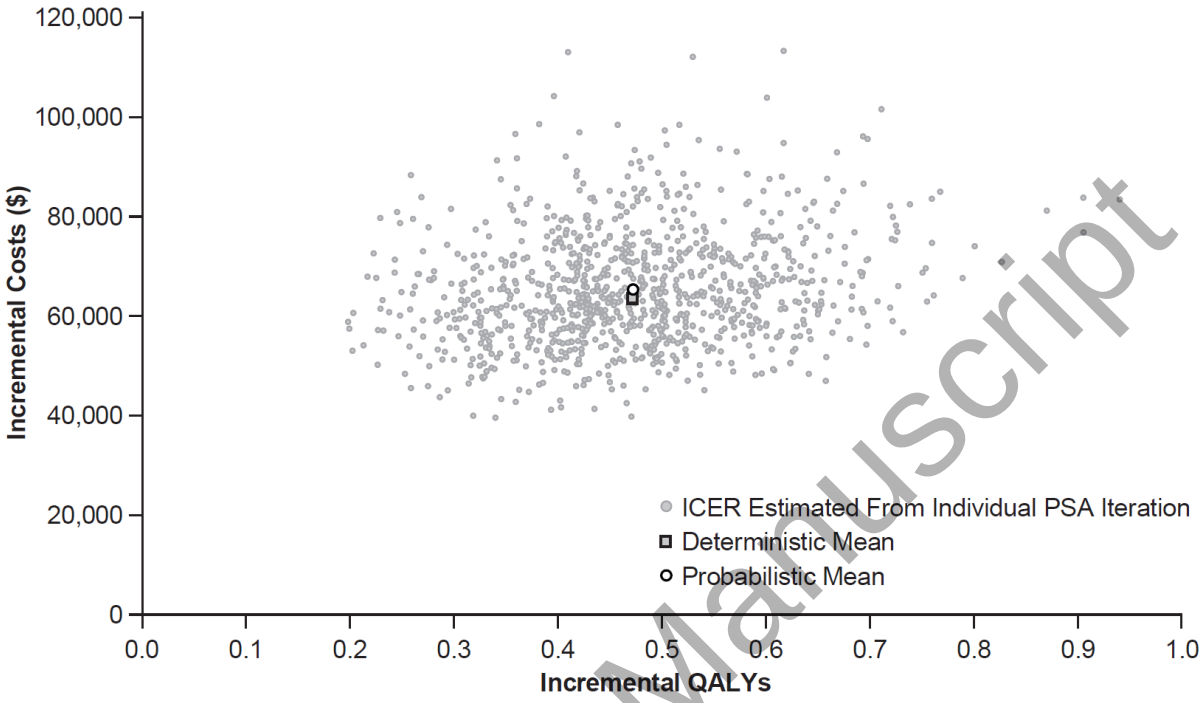
IC: Investigator's choice; QALYs: quality-adjusted life-years.

All costs are in 2017 US$.

62.2% of model iterations had an incremental cost per QALY of less than $150,000.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Scatter plot of incremental cost and QALY gains with nivolumab estimated during each of 1,000 model iterations generated during probabilistic sensitivity analysis

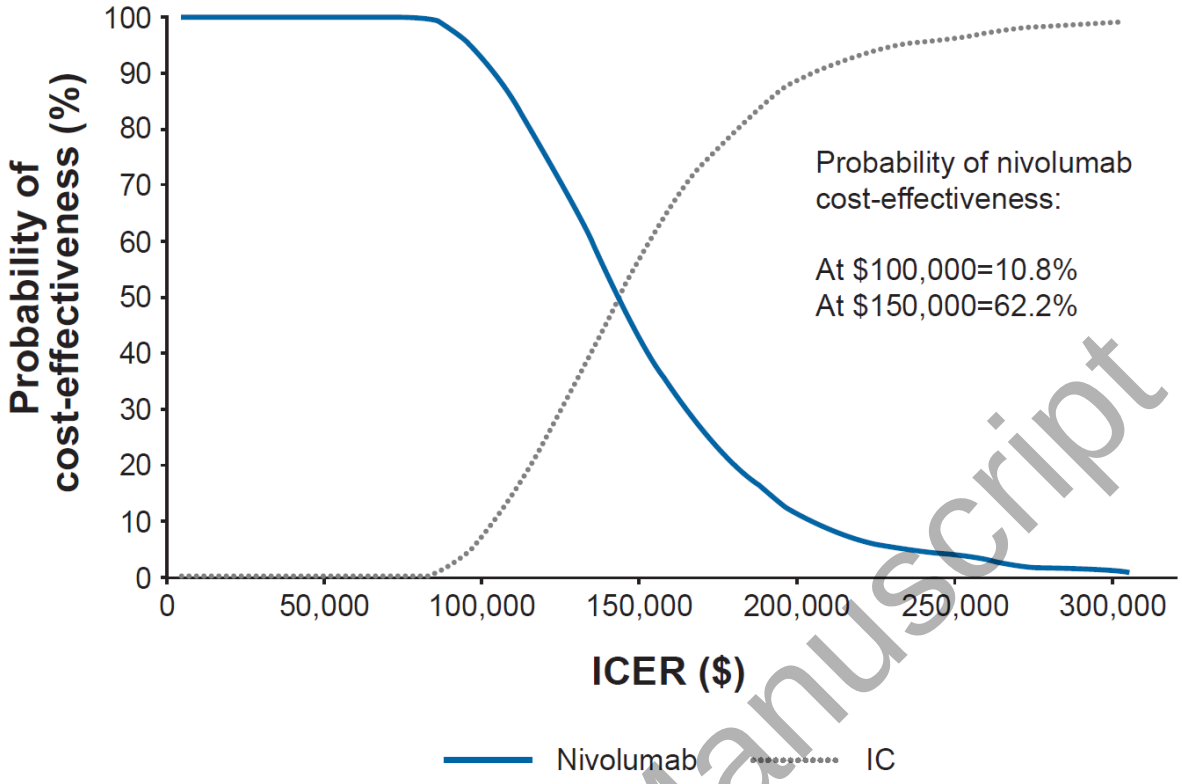


QALY: quality-adjusted life-years.

Deterministic gain with nivolumab: QALY, 0.47; costs, $63,485

Probabilistic gain with nivolumab: QALY, 0.42; costs, $65,231

Supplementary Figure 2. Cost-effectiveness acceptability curve of ICER versus probability of nivolumab being cost-effective versus IC



IC: investigator's choice; ICER: incremental cost-effectiveness ratio.

Supplementary Table 1. Grade 3 or above all-cause adverse events included in the global base case economic model[20].

	Nivolumab	Investigator's choice[a]
Anemia	5.9%	8.1%
Aspartate elevation	–	–
Cancer pain	0.4%	–
Decreased appetite	–	–
Diarrhea	0.8%	2.7%
Dyspnea	5.5%	1.8%
Fatigue	3.4%	6.3%
Febrile neutropenia	–	–
Hyponatremia	4.7%	8.1%
Hypothyroidism	–	–
Leukopenia	0.4%	2.7%
Malignant neoplasm progression	18.6%	22.5%
Mucositis	–	1.8%
Nausea	0.4%	0.9%
Neutropenia	–	7.2%
Peripheral neuropathy	–	–
Pneumonitis	1.3%	–
Rash	–	0.9%
Stomatitis	1.3%	8.1%

Syncope	1.3%	–

[a]Investigator's choice consisted of cetuximab, docetaxel, or methotrexate.

AE: adverse event.

Supplementary Table 2. Health state utility estimates used in model.

	Progression-free	Progressed disease
All patients	0.796 (95% CI: 0.761–1.0) [n = 470]	0.729 (95% CI: 0.700–0.758) [n = 225]
Nivolumab	0.805 (95% CI: 0.786–0.824) [n = 345]	0.746 (95% CI: 0.716–0.775) [n = 172]
Investigator's choice[a]	0.770 (95% CI: 0.708–0.833) [n = 125]	0.676 (95% CI: 0.600–0.752) [n = 53]

[a]Investigator's choice consisted of cetuximab, docetaxel, or methotrexate.

Utility estimates were modeled using a US population preference-weighting algorithm[21], applied to 3-level EuroQol 5-dimension health questionnaire data from CheckMate 141 (Bristol-Myers Squibb, data on file; OR NIVO 094, 2017).

CI: confidence interval

Supplementary Table 3. Disutility associated with adverse events.

Adverse event	Disutility	Source
Anemia	−0.1250	Lloyd A, van Hanswijck de Jonge P, Doyle S, et al. Health state utility scores for cancer-related anaemia through societal and patient valuations. *Value in Health* 2008;11(7)
Aspartate aminotransferase increase	0.0000	Assumption
Cancer pain	−0.0690	Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008;62: 374-80
Decreased appetite	−0.0380	Hudgens S, Briggs A, Tremblay G, et al. Comparison of methods to estimate health state utilities in metastatic breast cancer (MBC). ISPOR 17th Annual European Congress, Amsterdam, The Netherlands, November 2014
Diarrhea	−0.0468	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84
Dyspnea	−0.2900	Grutters JP, Joore MA, Wiegman EM, et al. Treatment-related quality of life in patients surviving non-small cell lung cancer. *Thorax* 2010;65:903-07
Fatigue	−0.0735	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes*

		2008;6:84
Febrile neutropenia	−0.0897	Assumed to be the same as neutropenia
Hyponatremia	−0.1910	Assumed to be the same as hypomagnesemia reflecting a 24% decline in utility (from PF utility); Hannouf MB, Sehgal C, Cao JQ, et al. Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer. *PLoS One* 2012;7:e38557
Hypothyroidism	0.0000	Assumption
Leukopenia	−0.0897	Assumed to be the same as neutropenia
Malignant neoplasm progression	0.0000	Assumption
Mucositis, oral	−0.4410	Assumed to be the same as stomatitis
Nausea	−0.0480	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84
Neutropenia	−0.0897	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84
Peripheral neuropathy	0.0000	Assumption

Pneumonitis	−0.0080	Assumed to be the same as pneumonia; Marti SG, Colantonio L, Bardach A, et al. A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. *Cost Eff Resour Alloc* 2013;11:21
Rash	−0.0325	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non-small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84
Stomatitis	−0.4410	Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. *Curr Oncol* 2013;20:e90-e106
Syncope	0	Assumption

Supplementary Table 4. Drug acquisition costs used in the base case model.

Treatment	Formulation per vial/cap	Vial size or tablets per pack	Unit cost per vial or pack ($)	Dose	Total cost per dose, with vial sharing ($)	Source
Nivolumab	10 mg/mL 10 mg/mL	10 mL 4 mL	2,661.41 1,064.56	3 mg/kg	6,387.38	Medi-Span Price Rx® WAC price
Investigator's choice						
Cetuximab	2 mg/mL	50 mL	621.70	250 mg/m^2		Medi-Span Price Rx® WAC price
Docetaxel	20 mg/mL	1 mL	25.00	30 mg/m^2	957.50	
Methotrexate	1 g/ 40 mL	40 mL	325.13	40 mg/m^2		
Subsequent treatments						
Cisplatin	50 mg/50 mL	50 mL	17.00	100 mg/m^2	NA	Medi-Span Price Rx® WAC price
Fluorouracil	100 g		217.70	9 mg/kg	NA	Medi-Span Price Rx® WAC price; bulk package, wastage not applicable

NA: not applicable (for use without vial sharing); WAC: wholesale acquisition costs.

Supplementary Table 5. Administration costs associated with infusion of treatments.

Treatment	Units per 4 weeks	Unit cost ($)	Source
Nivolumab	2.00	139.61	Nivolumab SPC and 2017 Centers for Medicare and Medicaid Service - Physician Fee Schedule. CPT code: 96413, Chemo IV infusion (1 hour) - Facility price, National Payment Amount
Investigator's choice			
Cetuximab	4	139.61	2017 Centers for Medicare and Medicaid Service - Physician Fee Schedule. CPT code: 96413, Chemo IV infusion (1 hour) - Facility price, National Payment Amount
Docetaxel	1.33		
Methotrexate	4		
Subsequent treatments			
Cisplatin	1.33	139.61	2017 Centers for Medicare and Medicaid Service - Physician Fee Schedule. CPT code: 96413, Chemo IV infusion (1 hour) - Facility price, National Payment Amount
Fluorouracil	8 doses every 42 days		

CPT: Common Procedure Terminology; IV: intravenous.

Supplementary Table 6. Subsequent treatments used in base case model.

	Nivolumab	Investigator's choice
Proportion of patients receiving subsequent treatment (%)	29.6	32.2
Duration of treatment (months)	2.33	2.33
Frequency of treatments (%)		
Nivolumab	0.7	0.6
Cetuximab	7.7	6.1
Docetaxel	3.4	2.4
Methotrexate	5.7	4.3
Paclitaxel	6.4	3.6
Pembrolizumab	0.3	4.9
Cisplatin (carboplatin / cisplatin)	4.0	5.5
5-Fluorouracil	1.3	4.9
Best supportive care	70.4	67.8
Total cost of subsequent treatment per patient ($)	2,948.28	3,867.60

[a]Investigator's choice consisted of cetuximab, docetaxel, or methotrexate.

Values based on CheckMate 141 observations (Bristol-Myers Squibb, data on file; OR NIVO 174, 2019).

Supplementary Table 7. Monitoring costs associated with nivolumab and investigator's choice.

	Test	Units required per 4 weeks	Unit cost ($)	4-week cost ($)	Source
Nivolumab	Hepatic enzymes	1	11.21		2017 Medicare Laboratory Fee Schedule, CPT code 80076
	Renal function	1	11.91	46.17	2017 Medicare Laboratory Fee Schedule, CPT code 80069
	Thyroid test	1	23.05		2017 Medicare Laboratory Fee Schedule, CPT code 84443
Investigator's choice[a]	Weighted average of individual costs for cetuximab, docetaxel and methotrexate			19.64	
Cetuximab	Complete metabolic panel	1	14.49	14.49	2017 Medicare Laboratory Fee Schedule, CPT code 80053
Docetaxel	CBC	1	10.66	10.66	2017 Medicare Laboratory Fee Schedule, CPT code 85025

	CBC	1	10.66		2017 Medicare Laboratory Fee Schedule, CPT code 85025
Methotrexate	Hepatic enzymes	1	11.21	33.78	2017 Medicare Laboratory Fee Schedule, CPT code 80076
	Renal function	1	11.91		2017 Medicare Laboratory Fee Schedule, CPT code 80069
Subsequent therapies					
Cisplatin	CBC	4	10.66	53.85	2017 Medicare Laboratory Fee Schedule, CPT code 85025
	Hepatic enzymes	1	11.21		2017 Medicare Laboratory Fee Schedule, CPT code 80076
Fluorouracil	CBC	8 per 42 day cycle	10.66	63.96	2017 Medicare Laboratory Fee Schedule, CPT code 85025

[a]Investigator's choice consisted of cetuximab, docetaxel, or methotrexate.

"Units required" based on respective label guidance.

CBC: complete blood count; CMS: Center for Medicare and Medicaid Services; CPT: Common Procedure Terminology.

Supplementary Table 8. Disease management costs for the progression-free and progressed disease health states.

	Unit cost ($)	Units per 4 weeks[a]		Source for unit cost
		PF	PD	
Office visit	79.67	4.1613	7.79	CMS – Physician Fee Schedule. CPT code: 99214, National payment amount
Fiber optic examination	125.39	0.0022	0.0002	CMS – Physician Fee Schedule. CPT codes 43191, 43193, 43197, 43198, 43200, 43202, 43235, and 43239. Unweighted average of national payment amounts
Magnetic resonance imaging	781.80	0.002	0.0012	CMS – Physician Fee Schedule. CPT codes 70511, 70553, 70540, 70543, and 70549. Unweighted average of national payment amounts
Computerized tomography scan	386.16	0.0588	0.0171	CMS – Physician Fee Schedule. CPT codes 70486, 70487, 70450, 70470, 70490, 70491, 71250, 70491, and 71275. Unweighted average of national payment amounts
Positron emission tomography	2,716.84	0.0329	0.0036	CMS – Physician Fee Schedule. CPT codes 78811, 78812, 78813, 78814, 78815, and 78816. Unweighted average of national

				payment amounts
Percutaneous endoscopic gastrostomy	210.02	0.0042	0.0091	CMS – Physician Fee Schedule. CPT codes 49440, 49441, 49446, 49450, 49451, 43246, 44372, 44373, 43653, and 43760. Unweighted average of national payment amounts (range: 48 to 594)
Surgical procedure	21,748.47	0.0018	0.0012	HCUP NIS. Weighted average of DRGs 129 and 130, Medicare costs
Home health organization	80.03	0.0414	0.0294	Assumption that home health care is speech and language therapy. CMS – Physician Fee Schedule. CPT codes 92507. National payment amounts
Physical therapy/ rehabilitation	31.77	0.0224	0.0034	CMS – Physician Fee Schedule. CPT codes 97110 and 97140. Unweighted average of national payment amounts
Orthopedic/ reconstruction/ ambulatory surgery	21,748.47	0.0075	0.0003	HCUP NIS. Weighted average of DRGs 129 and 130, Medicare costs
Psychiatry/ counseling/ psychology	89.30	0.001	0.0046	CMS – Physician Fee Schedule. CPT codes 90832, 90833, 90834, 90836, 90837, and 90838. Unweighted average of national payment amounts)

Dental specialist	79.67	0.001	0.0008	Assumption. CMS – Physician Fee Schedule. CPT code: 99214, National payment amount
Pain management	79.67	0.0002	0.0001	Assumption. CMS – Physician Fee Schedule. CPT code: 99214, National payment amount
Audiology	33.38	0	0	CMS – Physician Fee Schedule. CPT code: 92557, National payment amount
Optometry/ ophthalmology	81.47	0	0	CMS – Physician Fee Schedule. CPT code: 92014, National payment amount
Total cost per 4 weeks:		$652.81	$675.45	

CMS: Centers for Medicare and Medicaid Services; CPT: Common Procedure Terminology; CT: computed tomography; DRG: diagnosis related group; HCUP NIS: health care utilization project's Nationwide Inpatient Sample; PD: progressed disease, PF: progression-free.

[a]Rates of resource use in PF and PD based on CheckMate 141 observations (Bristol-Myers Squibb, data on file; OR NIVO 055, 2017).

Supplementary Table 9. Cost of adverse events.

	Unit cost (2014 $)	Unit cost (2017 $)
Anemia	7,066	7,689
Aspartate	6,102	6,641
Cancer pain	8,907	9,693
Decreased appetite	14,010	15,246
Diarrhea	7,041	7,662
Dyspnea	6,058	6,593
Fatigue	6,616	7,200
Febrile neutropenia	11,480	12,493
Hyponatremia	6,541	7,119
Hypothyroidism	9,501	10,339
Leukopenia	9,487	10,324
Malignant neoplasm progression	0	0
Mucositis	9,504	10,343
Nausea	5,749	6,256
Neutropenia	11,480	12,493
Peripheral neuropathy	9,601	10,448
Pneumonitis	13,329	14,506
Rash	5,301	5,768
Stomatitis	9,504	10,343
Syncope	6,751	7,346

Costs identified from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample 2014[37], adjusted to 2017 values.

Supplementary Table 10. External validation of long-term parametric survival model using data from the phase 1b, open-label CheckMate 003 study.

		Proportion of patients surviving at each timepoint (%)									Median OS (months)	Mean OS (months)
		6 months	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years		
Base case	Nivolumab	55.9	32.9	16.5	10.0	6.7	4.7	1.4	0.6	0.3	6.7	15.4
	IC	46.9	19.2	5.7	2.3	1.1	0.6	0.1	0.0	0.0	5.1	8.2
CheckMate 141	Nivolumab	56.5	34	15.8	N/A	N/A	N/A	N/A	N/A	N/A	7.7	N/A
	IC	43.0	19.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.1	N/A
CheckMate 003	Nivolumab	N/A	41	24	20	16	16	N/A	N/A	N/A	N/A	N/A

IC: investigator's choice; N/A: not applicable; OS: overall survival