Supplementary Online Content

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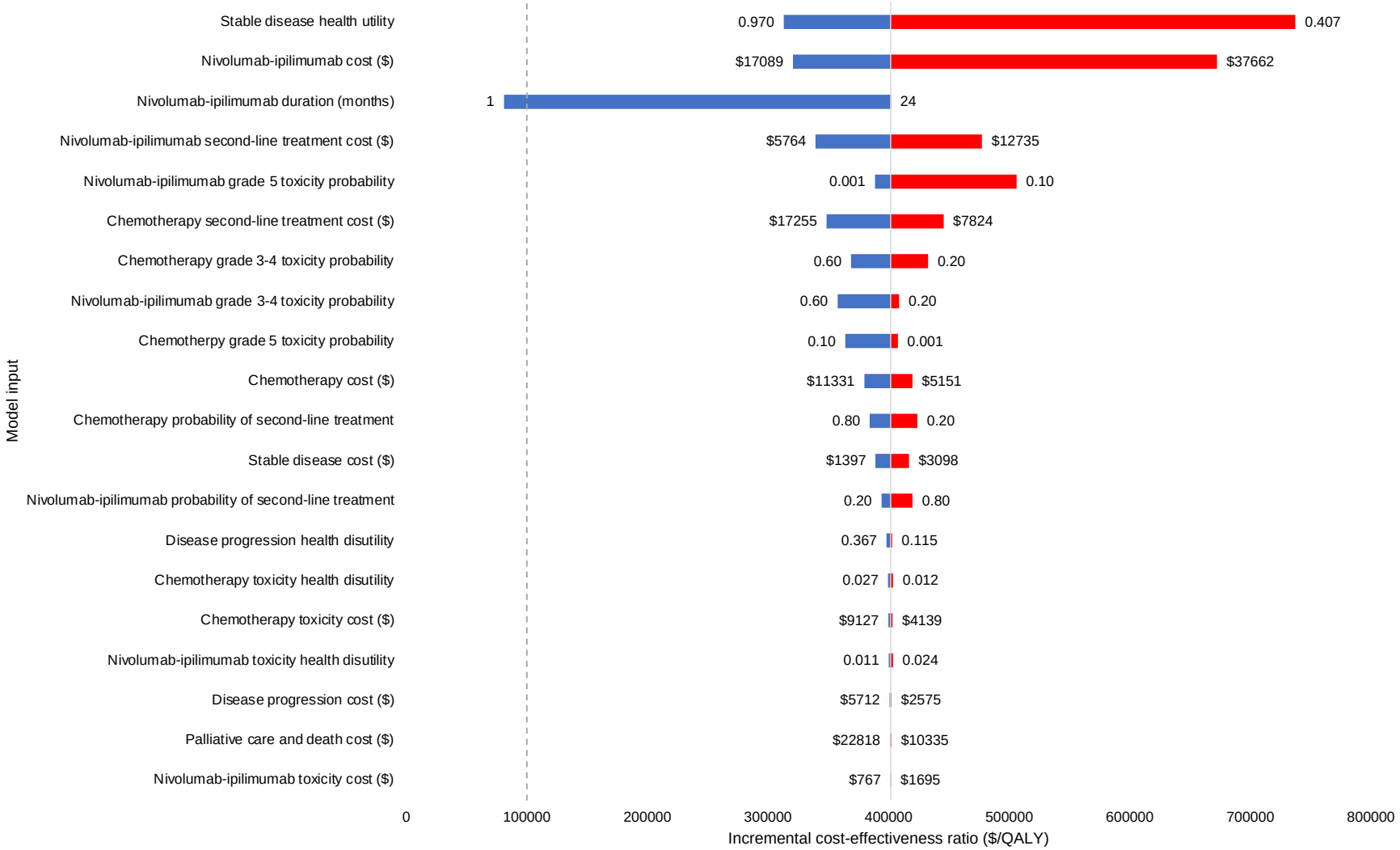
This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Methods for Determining Drug Costs

Per the CheckMate 227 trial, patients in the nivolumab-ipilimumab arm received nivolumab at a dose of 3 mg/kg body weight every two weeks and ipilimumab at a dose of 1 mg/kg body weight every 6 weeks. In the chemotherapy arm, patients received platinum-doublet chemotherapy every three weeks for up to four cycles. The specific chemotherapeutic agents and dosing used in CheckMate 227 varied by tumor histology (squamous versus nonsquamous); therefore, with our costs of chemotherapy, we calculated a weighted average between the two tumor histologic types reported in the trial. With drug cost calculations, we used a body weight of 73kg, based on the male-female proportions in CheckMate 227 using sex-specific body weights[1], and a body surface area of 1.78m^2, based on cancer patient-specific averages[2]. In the sensitivity analysis including maintenance pemetrexed for chemotherapy patients, the cost of maintenance pemetrexed was based on the CheckMate 227 trial's specified dose (500mg/m^2), the proportion of patients with nonsquamous histology, and was assumed to be given every three weeks. Second-line treatment costs[36,37] were calculated as frequency-weighted averages using reported subsequent treatments received by at least 3% of patients for each treatment arm in CheckMate 227. We did not include "targeted therapy" in second-line treatment costs in either arm because those agents were not specified. Drug costs were adjusted to a monthly rate to match the cycle length of our model. Costs of toxicities[38-41], stable disease[41], progression[41], and death[41] were obtained from the literature.

eFigure. Tornado Diagram of 1-Way Sensitivity Analyses



This graph represents the incremental cost-effectiveness ratio (ICER) of nivolumab-ipilimumab compared to chemotherapy in all patients when individually varying the parameters of the base case cost-effectiveness model. The solid vertical line represents the base case analysis ICER ($401,700/QALY) for nivolumab-ipilimumab compared to chemotherapy, and the vertical dashed line represents the willingness-to-pay threshold of $100,000/QALY.

eTable 1. Model Validation

Study End Point	Cost-Effectiveness Model, %	CheckMate 227 Trial, %
Overall Survival (2 year)		
Nivolumab + ipilimumab	40.2	40
Chemotherapy	30.2	30
Progression-Free Survival (2 year)		
Nivolumab + ipilimumab	20.1	20
Chemotherapy	6.4	6
Grade 3-4 Toxicity		
Nivolumab + ipilimumab	32.8	32.8
Chemotherapy	36.0	36.0
Grade 5 Toxicity		
Nivolumab + ipilimumab	1.4	1.4
Chemotherapy	1.1	1.1

This table quantitively compares 2-year overall and progression-free survival rates and grade 3-4 and grade 5 treatment-related toxicities reported in the CheckMate 227 trial with those produced by our model.

eTable 2. Associated Costs of Grade 3 to 4 Treatment-Related Adverse Events

Adverse Event[a]	No. of patients (%)[b]	Costs in 2020 USD[c]	Reference
Nivolumab-ipilimumab			
Fatigue, asthenia	18 (3.1)	1,065.44	Niraula et al[38], 2014
Rash, pruritus	12 (2.1)	272.33	Hornberger et al[39], 2015
Diarrhea	10 (1.7)	169.93	Hornberger et al[39], 2015
Decreased appetite, nausea, vomiting	9 (1.6)	160.13	Hornberger et al[39], 2015
Anemia	8 (1.4)	5,243.47	Smith et al[40], 2002
Weighted average[d]	-	*1,184.81*	
Chemotherapy			
Anemia	66 (11.6)	5,243.47	Smith et al[40], 2002
Neutropenia	54 (9.5)	16,857.15	Hornberger et al[39], 2015
Neutrophil count decreased	36 (6.3)	907.00	Insinga[41], 2019
Decreased appetite, nausea, vomiting	32 (5.6)	160.13	Hornberger et al[39], 2015
Fatigue, asthenia	13 (2.2)	1,065.44	Niraula et al[38], 2014
Diarrhea	4 (0.7)	169.93	Hornberger et al[39], 2015
Weighted average[d]	-	*6,383.72*	

[a]Refers to treatment-related adverse events of any grade that occurred in ≥15% of total patients in the CheckMate 227 trial. Our analysis only included and evaluated grade 3-4 treatment-related adverse events.
[b]Number within treatment arm: nivolumab-ipilimumab (N=576), chemotherapy (N=570).
[c]Cost per one-month cycle.
[d]Calculated as an average cost of toxicity using the weighted frequency of occurrence. This value was used in the base-case model.

eTable 3. Disutility From Grade 3 to 4 Treatment-Related Adverse Events

Adverse Event[a]	Number of patients (%)[b]	Disutility[c]	Reference
Nivolumab-ipilimumab			
Fatigue, asthenia	18 (3.1)	0.024	Nafees et al[43], 2017
Rash, pruritus	12 (2.1)	0.013	Nafees et al[43], 2017
Diarrhea	10 (1.7)	0.018	Nafees et al[43], 2017
Decreased appetite, nausea, vomiting	9 (1.6)	0.017	Nafees et al[43], 2017
Anemia	8 (1.4)	0.006	Freeman et al[42], 2015
Weighted average[d]	-	*0.017*	
Chemotherapy			
Anemia	66 (11.6)	0.006	Freeman et al[42], 2015
Neutropenia	54 (9.5)	0.029	Nafees et al[43], 2017
Neutrophil count decreased	36 (6.3)	0.029	Hornberger et al[39], 2015
Decreased appetite, nausea, vomiting	32 (5.6)	0.017	Nafees et al[43], 2017
Fatigue, asthenia	13 (2.2)	0.024	Nafees et al[43], 2017
Diarrhea	4 (0.7)	0.018	Nafees et al[43], 2017
Weighted average[d]	-	*0.019*	

[a]Refers to treatment-related adverse events of any grade that occurred in ≥15% of total patients in the CheckMate 227 trial. Our analysis only included and evaluated grade 3-4 treatment-related adverse events.
[b]Number within treatment arm: nivolumab-ipilimumab (N=576), chemotherapy (N=570).
[c]Disutility per one-month cycle.
[d]Calculated as an average disutility of toxicity using the weighted frequency of occurrence. This value was used in the base-case model.

eTable 4. Results of 1-Way Sensitivity Analysis

Model	ICER ($/QALY)
Base Case	401,700
Perspective	
Health Care Payer	401,700
Societal	434,400
Duration of nivolumab-ipilimumab treatment	
24 months maximum	401,700
12 months maximum	361,700
4 months maximum[a]	235,200
Continue after disease progression[b]	551,900
Continue after grade 3-4 treatment-related adverse event	467,300
Including maintenance pemetrexed in chemotherapy arm	363,400
Survival Assumptions	
Reduced risk of death from nivolumab-ipilimumab	
27% reduction in risk of death (HR 0.73)[c]	401,700
36% reduction in risk of death (HR 0.64)[d]	249,300
Survival beyond trial range[e]	
All patients alive at 42 months follow SEER survival data for advanced NSCLC	401,700
All patients alive at 42 months follow cured[f] of disease	317,300
Nivolumab-ipilimumab patients alive at 42 months cured[f] of disease[g]	287,800
PD-L1 Expression Level	
All patients	401,700
≥1%	440,100
≥50%	375,700
<1%	332,100

Abbreviations: QALY, quality-adjusted life-year; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.
[a]Median duration of nivolumab-ipilimumab therapy was 4.2 months in CheckMate 227 trial.
[b]Patients remain on nivolumab-ipilimumab for two years per CheckMate 227 protocol.
[c]HR of death in nivolumab-ipilimumab arm compared to chemotherapy in all patients in CheckMate 227 trial. This value was used in base-case model.
[d]Lower end of 95% confidence interval for HR of death in nivolumab-ipilimumab arm compared to chemotherapy in all patients in CheckMate 227 trial.
[e]CheckMate 227 reported survival data through 42 months.
[f]Survival beyond trial range followed US Social Security Administration Actuarial Life Tables[24].
[g]Those on chemotherapy assumed to not be cured of disease, and survival beyond trial range followed SEER data.

eReferences

1. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr.* 2010;91(4):1133S-1137S.
2. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One.* 2010;5(1):e8933.