Cost-Effectiveness Analysis of Durvalumab Plus Chemotherapy in the First-Line Treatment of Extensive-Stage Small Cell Lung Cancer

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ABSTRACT

Background: In the CASPIAN trial, durvalumab + chemotherapy demonstrated significant improvements in overall survival compared with chemotherapy alone in patients with extensive-stage small cell lung cancer (SCLC). We aimed to assess the cost-effectiveness of durvalumab in patients with extensive-stage SCLC from the US health-care system perspective. **Patients and Methods:** A comprehensive Markov model was adapted to evaluate cost and effectiveness of durvalumab combination versus platinum/etoposide alone in the first-line therapy of extensive-stage SCLC based on data from the CASPIAN study. The main endpoints included total costs, life years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). Model robustness was assessed with sensitivity analysis, and additional subgroup analyses were also performed. **Results:** Durvalumab + chemotherapy therapy resulted in an additional 0.27 LYs and 0.20 QALYs, resulting in an ICER of \$464,711.90 per QALY versus the chemotherapy treatment. The cost of durvalumab has the greatest influence on this model. Subgroup analyses showed that the ICER remained higher than \$150,000/QALY (the willingness-to-pay threshold in the United States) across all patient subgroups. **Conclusions:** Durvalumab in combination with platinum/etoposide is not a cost-effective option in the first-line treatment of patients with extensive-stage SCLC.

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Background

Lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths in the United States.^{1,2} Approximately two-thirds of patients with small cell lung cancer (SCLC) have extensive-stage disease at diagnosis, with a 5-year survival rate of <7%.^{3,4} Etoposide with either cisplatin or carboplatin (platinum/etoposide) was the standard first-line therapy for extensive-stage SCLC for 3 decades.^{5,6} Most patients experience relapse within 6 months of completing initial treatment, despite high rates of response to chemotherapy.^{7,8}

Immunotherapy targeting PD-L1 has demonstrated clinical activity in first-line treatment of extensive-stage SCLC.⁹ Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80.¹⁰ Recently, a randomized, controlled, open-label, phase III trial (CASPIAN) compared durvalumab + chemotherapy versus chemotherapy alone in the first-line treatment of patients with extensive-stage SCLC. The results demonstrated that treatment with durvalumab + platinum/etoposide significantly improved overall survival (OS; hazard ratio [HR], 0.73; 95% CI, 0.59–0.91; $P < .0001$).¹¹ Durvalumab + platinum/etoposide as the first-line treatment option for patients with extensive-stage SCLC was recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for SCLC, Version 2.2020,¹² and was subsequently approved by the FDA in March 2020.¹³

Although the combination of durvalumab + chemotherapy provides clinical benefits, these benefits must be weighed against the financial burden. The current study investigated the economic outcomes of durvalumab + chemotherapy versus chemotherapy alone for patients with previously untreated extensive-stage SCLC in the

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context of the US healthcare system by using the published results of the phase III CASPIAN trial.

Patients and Methods

Model Structure

A comprehensive Markov model with 3 mutually exclusive health states—progression-free survival (PFS), progressive disease (PD), and death—was adapted to evaluate the costs and effectiveness of treatment of extensive-stage SCLC with durvalumab + chemotherapy and chemotherapy alone. All patients were assumed to be treated with durvalumab + chemotherapy or chemotherapy alone in the PFS state until disease progression. When the disease progressed or unacceptable adverse reactions occurred, patients in both groups could receive subsequent comprehensive treatment until death (supplemental eFigure 1, available with this article at JNCCN.org).

We assigned the model cycle as 6 weeks, to fit with the various dosage frequencies of interventions. The time horizon was lifetime. An annual 3% discount rate was adopted both on costs and outcomes.¹⁴ The primary outcome measures of the models included the total costs, life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). Based primarily on results of the CASPIAN trial, the model structure and data were also supplemented by data retrieved from publicly available databases and published literature. The model was constructed via TreeAge Pro 2020 (TreeAge Software, Inc.).

Model Transitions and Survival Estimates

The transition probabilities for both groups were derived from the PFS and OS curves in the CASPIAN trial. We used GetData Graph Digitizer 2.26 to collect data points from the curves for the 2 groups based on the method described by Rini et al,¹⁵ and these data points were then fit into the parametric survival model. The Weibull distribution provided the most appropriate fit to pseudo-individual patient data among the exponential, log-logistic, log-normal, and Gompertz distributions, according to the Akaike information criterion and the Bayesian information criterion, combined with visual inspection.¹⁶ A detailed description of the survival model selection is shown in supplemental eTable 1 and eFigure 2. Detailed parameters of the survival model are shown in Table 1.

Utility Estimates

We used utility to measure patients' health-related quality of life at a particular health state. The mean health utility values for the PFS and PD states, 0.840^{17,18} and 0.473,¹⁹ respectively, were derived from the previously published

literature. The disutility values due to grade 3/4 adverse effects (AEs) were factored during the analysis.^{19,20}

Cost Inputs

This analysis adopted the third-party payer in the United States, which only considered direct medical care costs, including costs of drugs, administration,²¹ AEs (assuming that AEs appeared only once in the PFS and PD states), and laboratory²² and radiographic tests.²³ According to the CASPIAN trial, the durvalumab + chemotherapy group received up to 4 cycles of durvalumab at 1,500 mg and chemotherapy (etoposide at 80–100 mg/m² [administered on days 1–3 of each 21-day cycle] and either carboplatin at an area under the curve [AUC] of 5–6 mg/mL or cisplatin at 75–80 mg/m² [administered on day 1 of each cycle]). After 4 cycles, patients received maintenance treatment with 1,500 mg of durvalumab administered intravenously every 4 weeks. Patients in the platinum/etoposide group could receive an additional 2 cycles of platinum/etoposide (up to 6 cycles total). For chemotherapy dosing, we used a standard AUC of 6 mg/mL/min and assumed male sex, 65 years of age, weight of 70 kg, height of 70 cm, body surface area of 1.84 m², and serum creatinine level of 1 mg/dL.²⁰ Drug prices were based on the Centers for Medicare & Medicaid Services Average Sales Price²⁴ (Table 1). The subsequent therapy received in 2 groups were not well described in the CASPIAN trial. Therefore, we assumed patients received the standard second-line chemotherapy: topotecan alone (1.5 mg/m²/d administered intravenously on days 1–5 every 21 days). Its dose was based on clinical trial data.^{25,26}

Grade 3/4 severe AEs were included in the model, which had notably different probabilities between the arms of the CASPIAN trial. The incidence rates of AEs in the model came from the CASPIAN trial data. The costs of managing AEs per event in the United States were extracted from the published literature.^{27,28} All costs were adjusted to present 2020 US dollars and the US consumer price index was adopted as reference for inflation. Information on these costs is provided in Table 1.

Sensitivity Analysis

A series of sensitivity analyses were performed to evaluate the robustness of the model and the influence of variable uncertainty on the results. The 1-way sensitivity analyses were used to examine the individual effects of this parameter on the ICERs. The values, variation ranges, and distributions of the parameters are shown in Table 1. We also completed probabilistic sensitivity analyses to assess the probability of durvalumab + chemotherapy being cost-effective by performing 10,000 Monte Carlo repetitions.

In addition, subgroup analyses were completed in patients in the forest plot of the CASPIAN trial based on the subgroup-specific HRs according to the approach taken by Hoyle et al.²⁹

Table 1. Model Parameters

Variable	Baseline Value	Range		Reference	Distribution
		Minimum	Maximum		
Weibull survival model of durvalumab + chemotherapy		—	—	11	—
OS	Shape = 1.397873, Scale = 0.033386				
PFS	Shape = 1.30834, Scale = 0.11415				
Weibull survival model of chemotherapy		—	—	11	—
OS	Shape = 1.578908, Scale = 0.030819				
PFS	Shape = 1.91213, Scale = 0.05936				
Utility					
Utility PFS in first-line treatment	0.840	0.672	0.883	16,17	Beta
Utility PD	0.473	0.378	0.568	18	Beta
Disutility due to AEs					
Anemia	−0.073	−0.058	−0.088	18	Beta
Neutropenia	−0.09	−0.072	−0.108	18	Beta
Leucopenia	−0.09	−0.072	−0.088	18	Beta
FN	−0.09	−0.072	−0.088	18	Beta
Thrombocytopenia	−0.650	−0.325	−0.670	19	Beta
Drug cost per cycle					
Durvalumab	\$22,390.80	\$17,912.64	\$26,868.96	23	Gamma
Etoposide	\$1,663.84	\$1,331.07	\$1,996.61	23	Gamma
Carboplatin	\$67.82	\$54.26	\$81.39	23	Gamma
Cisplatin	\$51.78	\$41.42	\$62.13	23	Gamma
Topotecan	\$199.87	\$159.90	\$239.84	23	Gamma
Expenditures on main AEs					
Anemia	\$7,969.56	\$6,375.65	\$9,536.47	27	Gamma
Neutropenia	\$32,995	\$24,746	\$41,244	26	Gamma
Leucopenia	\$32,995	\$24,746	\$41,244	26	Gamma
FN	\$32,995	\$24,746	\$41,244	26	Gamma
Thrombocytopenia	\$5,308.86	\$4,247.09	\$6,370.63	27	Gamma
Administration per cycle	\$139.61	\$111.69	\$167.53	20	Gamma
Tumor imaging per cycle	\$231	\$208	\$254	22	Gamma
Laboratory testing per cycle	\$315	\$252	\$378	21	Gamma
Discount rate	0.03	—	—		—

Abbreviations: AEs, adverse events; FN, febrile neutropenia; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Results

Base Case Results

For the patients with previously untreated extensive-stage SCLC, durvalumab + chemotherapy provided an additional 0.20 QALYs (0.27 LYs) at an incremental cost of \$91,469.96 compared with chemotherapy alone, resulting in an ICER value of \$464,711.90 per QALY (\$345,458.24 per LY) (Table 2).

Sensitivity Analysis

Results of the one-way sensitivity analyses are presented in the tornado diagrams (Figure 1). The greatest influence of variables on the ICER was the cost of durvalumab. Other considerable influential parameters were risk of neutropenia in chemotherapy group, risk of neutropenia in durvalumab group, and utility of PD.

Results of ICER scatterplot (supplemental eFigure 3) and acceptability curves (Figure 2)

Table 2. Baseline Results

Parameters	Durvalumab + Chemotherapy	Chemotherapy
LYs	2.20	1.93
QALYs	1.45	1.25
Total cost, \$	\$164,508.07	\$73,038.11
ICER \$/LY ^a	\$345,458.24	—
ICER \$/QALY ^b	\$464,711.90	—
WTP \$/QALY	\$150,000	—

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

^aCompared with chemotherapy (\$/LY).

^bCompared with chemotherapy (\$/QALY).

demonstrated that the probability of durvalumab + chemotherapy being cost-effective, compared with that of chemotherapy alone was 0% at a WTP threshold of \$150,000. The ICER remained greater than the WTP threshold across all patient subgroups in the subgroup analyses (supplemental eTable 2)

Discussion

In recent years, immune checkpoint inhibitors (ICIs) have shown significant clinical benefits in patients with non-small cell lung cancer (NSCLC) at different stages, and there are also many studies on immunotherapy for refractory or metastatic SCLC.^{9,11,30–34} Although the

results of a study showed that first-line immunotherapy (ipilimumab) + chemotherapy did not significantly improve the OS of patients with extensive-stage SCLC compared with chemotherapy alone,^{34,35} some inspiring results of 2 phase III studies indicated that the addition of atezolizumab or durvalumab to chemotherapy showed promising clinical activity.^{9,11} Considering the expensive cost of ICIs, we conducted the first study to estimate the cost-effectiveness of durvalumab + chemotherapy versus chemotherapy alone as first-line therapy for patients with extensive-stage SCLC.

In our analysis, the base case results indicated that durvalumab + chemotherapy produced an additional 0.20 QALYs compared with chemotherapy alone, and the ICER was \$464,711.90, which was higher than \$150,000/QALY (the WTP threshold in the United States). The acceptability curves also demonstrated that a paucity of certainty was achieved by durvalumab + chemotherapy at the threshold of \$150,000 in the United States. However, this treatment should not be disregarded, because the model outcomes are sensitive to the price of durvalumab in the 1-way sensitivity analyses. The ICER was still greater than \$360,000/QALY regardless of the variation within a certain range of the most sensitive variables, which was not considered to be cost-effective. Subgroup characteristics associated with cost-effectiveness suggest that brain or central nervous system metastases, female sex, current smoker status, and carboplatin use are

Figure 1. Tornado diagram for one-way sensitivity analysis.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; PD, progressive disease; PFS, progression-free survival.

Figure 2. Acceptability curves for the choice of durvalumab + chemotherapy treatment strategies at different WTP thresholds in patients with small cell lung cancer. Abbreviation: WTP, willingness-to-pay.

factors that should be considered to make durvalumab + chemotherapy more cost-effective. However, durvalumab + chemotherapy was not a cost-effective strategy across all patient subgroups.

The IMpower133 trial is another study that demonstrated that first-line treatment with immunotherapy (atezolizumab) + chemotherapy resulted in significantly longer OS and PFS compared with chemotherapy alone for patients with extensive-stage SCLC. Subsequently, the combination of atezolizumab and carboplatin/etoposide was approved by the FDA in this indication and was recommended in NCCN Guidelines for SCLC, Version 1.2019.³⁶ A cost-effectiveness analysis reported by Zhou et al³⁷ suggested that the addition of atezolizumab to carboplatin/etoposide is not a cost-effective choice in the first-line treatment of extensive-stage SCLC from an American perspective, with a gain of 0.10 QALYs and an ICER of \$528,810 per QALY. Our results were in agreement with this finding, and the increased QALYs of durvalumab + chemotherapy (0.20 QALYs) in our study were more significant than those of atezolizumab + chemotherapy. Similarly, immunotherapy combined with chemotherapy was not a cost-effective choice in the cost-effectiveness analysis for NSCLC.^{38,39} The price of ICIs was always the greatest factor affecting the outcomes. A reduction in price of ICIs through trade-off negotiations regarding drug price and coverage may be an appropriate and effective method to improve the cost-effectiveness.

It is a challenge to approve new drugs by solely relying on survival benefits. That is why different economic elements in different regions should be taken into account during drug approval. Meanwhile, physicians and administrators should be aware of the significance of utilizing predictive markers in appropriate patient selection to map out cost-effective strategies aiming to sustain our healthcare systems.

PD-L1 expression has been regarded as a predictive biomarker of response to ICIs. In many pharmacoeconomic studies of NSCLC, it has been found that high PD-L1 expression incrementally improves QALYs, resulting in a decrease in ICER.^{28,40–42} Our previous analysis results attested that first-line treatment with pembrolizumab is a cost-effective strategy compared with platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC and PD-L1 tumor proportion score (TPS) $\geq 50\%$, but not in those with TPS $\geq 20\%$ and $\geq 1\%$.⁴¹ Another predictive biomarker of immunotherapy for lung cancer is high tumor mutational burden (TMB) which had no significant correlation with tumor PD-L1 expression.^{43–45} Similarly, it was found that there was an association between immunotherapy response and PD-L1 expression or TMB in SCLC.^{30,43,46} Unfortunately, the CASPIAN trial did not report the expression of PD-L1 or TMB. The ICER of durvalumab + chemotherapy may be improved by selecting patients according to the expression level of biomarkers. Further study is needed to explore biomarkers such as PD-L1 expression and TMB in order to identify which patients with this heterogeneous disease are likely to experience greater treatment benefits, so that therapy may be tailored to the individual.

This study has several limitations. First, extrapolations of the survival data were based on the short-term survival data from CASPIAN, and the data would change along with long-term follow-up. As more mature data become available, the model will be more stable. For now, it is an inevitable limitation in our model. Second, immunotherapy-related AEs are rare, and the cost of treatment in such cases is rather high. Therefore, more cases of immunotherapy-related AEs would be conducive to more accurate evaluation of AE cost for patients using durvalumab. In addition, the benefits of durvalumab + chemotherapy would be overestimated in this model. Third, due to the lack of complete quality-of-life data to calculate the utility values, we referred to the mean health utility value of NSCLC in PD, and corrected the utility values by considering the disutility values of AEs, and only grade 3/4 AEs were included, which might have led to overestimates or underestimates of the utility values. Finally, the CASPIAN trial did not provide the Kaplan-Meier curve for each subgroup, making it impossible to run the model completely for each subgroup, and the original group balance produced by randomization may not exist in the subgroups; thus, results of the subgroup analyses should be interpreted with caution.

Conclusions

Our findings showed that durvalumab in combination with platinum-etoposide as first-line treatment is not cost-effective compared with chemotherapy alone in patients with extensive-stage SCLC from the US payer standpoint.

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Supplemental online content for:

Cost-Effectiveness Analysis of Durvalumab Plus Chemotherapy in the First-Line Treatment of Extensive-Stage Small Cell Lung Cancer

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eFigure 1: Markov States

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eFigure 1. Markov states, used to illustrate the disease development process of extensive-stage small cell lung cancer.

eFigure 2. Kaplan-Meier curve fitting and extrapolation: **(A)** durvalumab + chemotherapy OS curve; **(B)** chemotherapy OS curve; **(C)** durvalumab + chemotherapy PFS curve; **(D)** chemotherapy PFS curve. Abbreviations: OS, overall survival; PFS, progression-free survival.

eFigure 3. Results of Monte Carlo probabilistic sensitivity analysis showing incremental cost-effectiveness of durvalumab + chemotherapy versus chemotherapy alone.
Abbreviation: WTP, willingness-to-pay.

eTable 1. Summary of Statistical Goodness-of-Fit of Kaplan-Meier Curve in the CASPIAN Trial					
	Exponential	Weibull	Log-Logistic	Log-Normal	Gompertz
Durvalumab + chemotherapy OS curve					
AIC	24.3941	23.8942	23.5959	23.5372	25.072
BIC	26.1667	25.4394	25.1411	25.0823	26.9172
Chemotherapy OS curve					
AIC	27.8527	27.6103	27.0166	26.988	27.9779
BIC	28.5608	28.7264	28.4327	28.4041	29.394
Durvalumab + chemotherapy PFS curve					
AIC	47.8501	47.4231	46.7323	46.9699	49.5817
BIC	49.1581	48.8392	48.1484	48.386	50.9978
Chemotherapy PFS curve					
AIC	53.9253	46.5829	42.3063	44.069	91.0773
BIC	54.8951	47.0678	43.2761	45.0388	92.0471

For the 4 curves listed in the table, the log-logistic and log-normal distribution had the lowest AIC and BIC. Although the AIC and BIC tests are important for determining which models fit the observed data best, they do not tell us how suitable a parametric model is for the time period beyond the final trial follow-up. They described the internal validity of fitted models, but not their external validity. The log-logistic and log-normal distribution produced the longest extended tail in the visual fits of the 4 curves (supplemental eFigure 2), which meant PFS and PFS would be overestimated in long term. Meanwhile, Weibull distributions are flexible and widely used in cancer survival analyses, and the AIC and BIC of Weibull distribution were slightly higher than that of the log-logistic and log-normal distribution. Weibull distribution was chosen for OS and PFS curves.

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

eTable 2. Results of Subgroup Analyses

Subgroup	OS HR (95% CI)	ICER per QALY (95% CI)	Cost-Effectiveness Probability at WTP \$150,000/QALY
Planned platinum			
Carboplatin	0.70 (0.55–0.89)	\$261,779.97 (\$210,877.41–\$344,058.41)	13.2%
Cisplatin	0.88 (0.55–1.41)	\$339,034.60 (\$210,877.41–\$905,637.24)	0.4%
Age, y			
<65	0.74 (0.56–0.98)	\$277,115.05 (\$214,002.97–\$393,978.41)	7.1%
≥65	0.75 (0.54–1.06)	\$281,090.44 (\$207,783.87–\$447,218.16)	5.7%
Sex			
Male	0.76 (0.59–0.97)	\$285,126.12 (\$223,582.69–\$387,967.19)	4.7%
Female	0.63 (0.40–0.98)	\$236,872.54 (\$167,275.47–\$393,978.41)	20.2%
WHO PS score			
0	0.71 (0.48–1.04)	\$265,532.25 (\$189,837.06–\$432,970.80)	11.2%
1	0.76 (0.59–0.99)	\$285,126.12 (\$223,582.69–\$400,120.29)	5.1%
Smoking status			
Smoker	0.72 (0.58–0.91)	\$269,337.73 (\$220,354.49–\$354,394.51)	7.9%
Nonsmoker	0.90 (0.40–2.11)	\$349,177.28 (\$167,275.47–\$433,089.21)	1.1%
Brain or CNS metastases			
Yes	0.69 (0.35–1.31)	\$258,079.25 (\$153,780.71–\$712,811.73)	14.4%
No	0.74 (0.59–0.93)	\$277,115.05 (\$223,582.69–\$365,137.94)	6.2%
AJCC stage at diagnosis			
III	0.92 (0.44–1.98)	\$359,713.53 (\$178,385.71–\$458,893.47)	0.3%
IV	0.73 (0.58–0.91)	\$273,198.08 (\$220,354.49–\$435,394.51)	8.1%
Race			
Asian	0.81 (0.43–1.49)	\$306,278.67 (\$175,578.43–\$1,141,890.97)	3.2%
Non-Asian	0.73 (0.58–0.92)	\$273,198.08 (\$220,354.49–\$359,713.53)	6.4%
Region			
Asia	0.82 (0.43–1.54)	\$310,719.06 (\$175,578.43–\$135,6795.19)	2.9%
Europe	0.72 (0.56–0.92)	\$269,337.73 (\$214,002.97–\$359,713.53)	8.8%
North America and South America	0.72 (0.37–1.44)	\$269,337.73 (\$159,132.32–\$982,779.74)	8.8%

Abbreviations: CNS, central nervous system; ICER, incremental cost-effectiveness ratio; LY, life-year; OS HR, overall survival hazard ratio; PS, performance status; QALY, quality-adjusted life-year; WTP, willingness-to-pay.