



Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer

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ABSTRACT

Objectives: A double-blind, placebo-controlled, phase 3 trial has shown atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer could significantly prolong overall survival and progression-free survival than chemotherapy alone. This study aimed to assess the cost-effectiveness of atezolizumab plus chemotherapy as first-line treatment for patients with extensive-stage small-cell lung from an American perspective.

Materials and methods: Basic medical information was derived from the double-blind, placebo-controlled, phase 3 trial (IMpower133, NCT02763579). A Markov model was developed to simulate the process of small-cell lung cancer, including three health states: progression-free survival (PFS), progressive disease (PD), and death. Utilities and costs were obtained from published resources. Sensitivity analyses were applied to explore the impact of essential variables.

Results: Treatment with atezolizumab plus chemotherapy was estimated to increase costs by \$52,881 compared with chemotherapy alone, with a gain of 0.10 quality adjusted life years (QALYs), leading to an incremental cost-effective ratio of \$528,810 per QALY. The cost of PFS state and atezolizumab were the most influential factors to the model.

Conclusion: The combination of atezolizumab, carboplatin and etoposide is not a cost-effective choice in the first-line treatment of extensive-stage SCLC from an American perspective.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. The United States accounts for the third-largest number of new lung cancer cases worldwide. Because of non-specific symptoms, the majority of lung cancers are typically diagnosed at extensive stage. Compared with non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC) has inferior prognosis [1]. Although nearly all SCLC have inactivation or loss of TP53 and RB1, as well as other mutations, the target driven gene is not definitive. This made the development of treatments for SCLC progress slowly. Standard first-line treatment for SCLC has been well established, which consists of platinum chemotherapy and etoposide. Despite its high sensitivity to first-line chemotherapy, most patients relapse within a year. With the development of immunotherapy, researches indicate high mutation rate may contribute to better response to immune-checkpoint inhibitors [2]. Humanized monoclonal antibody against programmed death 1 (PD-1)

have demonstrated promising antitumor activity in patients with pre-treated SCLC [3]. Meanwhile, results of trials evaluating their application in the first-line treatment of advanced NSCLC were promising, which launched a new era for the treatment of NSCLC.

Atezolizumab, a humanized monoclonal anti-programmed death ligand 1 (PD-L1), was firstly approved by the U. S. Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy. Besides, it shown a clinically relevant improvement of overall survival (OS) versus docetaxel in patients with previously treated NSCLC, with well tolerance. Based on the consistent results in a total of 1137 patients with NSCLC, FDA approved atezolizumab for the treatment in this patient population. Recently, a double-blind, placebo-controlled, phase 3 trial (IMpower133) compared atezolizumab plus chemotherapy versus chemotherapy alone in the first-line treatment for patients with extensive-stage SCLC. The results revealed that the combination therapy

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significantly prolong OS (12.3 VS 10.3 months; HR, 0.70; p = 0.007) and progression-free survival (PFS) (5.2 VS 4.3 months; HR, 0.77; p = 0.02) than its competitor. The safety profile of atezolizumab plus chemotherapy was consistent with that previously reported. The last two decades did not witness breakthroughs in the first-line treatment of extensive-stage SCLC until this extremely exciting result was published [4].

Although immunotherapy brings hope for patients with advanced cancer, its expensive cost cannot be ignored, as medical expenditures have become one of the most severe burdens confronting governments and patients. Previous study suggested that immune checkpoint inhibitors could be considered a cost effective choice in advanced NSCLC patients with high level PD-L1 expression [5]. Hence, we are interested to investigate whether the immunotherapy plus chemotherapy is cost-effective compared with chemotherapy alone in the first-line therapy of extensive-stage SCLC from an American perspective.

2. Materials and methods

2.1. Patients

Basic medical information was derived from a double-blind, placebo-controlled, phase 3 trial (IMpower133, NCT02763579) comparing atezolizumab plus chemotherapy versus chemotherapy alone in the first-line treatment for patients with extensive-stage SCLC [4]. A total of 403 patients were randomly assigned to the atezolizumab group (201 patients) or the placebo group (202 patients). For treatment strategy, patients received four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo. The median duration of treatment with atezolizumab was 4.7 months, and the median number of atezolizumab doses received was 7. The median number of doses of chemotherapy was the same in the two groups (median, 4 doses of carboplatin and 12 doses of etoposide). The median dose intensity and total cumulative dose of chemotherapy were similar in the two groups (Table 1).

2.2. Model structure

A Markov model (TreeAge Software) was developed to simulate the disease process of extensive-stage SCLC, which included three health states: progression-free survival (PFS), progressive disease (PD), and

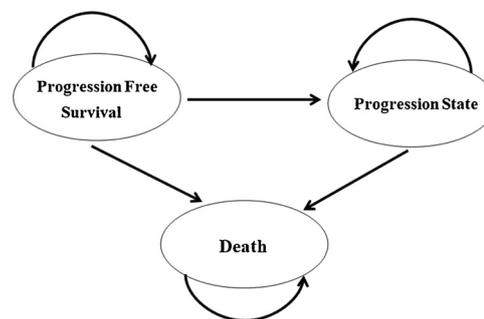


Fig. 1. Markov model for extensive-stage SCLC. A Markov model comprising three health states was built.

death (Fig. 1). Patients entered the model in PFS state and could move to another state on the basis of transition probabilities as well as the transition direction. The Markov cycle was 1 month. Transition probabilities of three states were calculated as follows: $P(1\text{ month}) = 1 - (0.5)^{(1/\text{median time to event})}$, which was derived from the equations: $P = 1 - e^{-R}$ and $R = -\ln[0.5]/(\text{time to event}/\text{number of treatment cycles})$.

2.3. Utilities

Utility values are usually based on EuroQOL-5D (EQ-5D) 3-level utility data collected from patients enrolled in the special trial. New approach to define health state utilities, called time-to-death approach, was well described by Huang et al in metastatic NSCLC [5], which could reflect the decline in cancer patients' quality of life as they approach death. Unfortunately, the phase 3 trial (IMpower133) did not collect the information of quality of life. Thus, utilities of each health states were obtained from previously published studies (0.673 for PFS, 0.473 for PD and 0 for death) [6].

2.4. Measurement of costs

Total costs for the two treatment groups included the cost of drugs, tests and treatments for grade ≥ 3 adverse events (AEs). We adjusted the costs of atezolizumab and chemotherapy drugs based on the IMpower133 trial. Almost half of the patients in two groups received at least one subsequent therapy, including chemotherapy and other anticancer procedures, which were not well specified in original article and the appendix. Thus, we assumed patients receive the standard second-line chemotherapy, topotecan alone. Its dose was based on a random, phase 3 trial [7]. Other medication costs are the wholesale acquisition cost from the Red Book. The estimated monthly costs were shown in Table 1.

2.5. Cost-effectiveness analysis

The cost-effectiveness analysis was carried out from an American perspective. Quality adjusted life years (QALY) gained and an estimate of overall costs were used to evaluate the incremental cost-effectiveness ratio (ICER).

2.6. Sensitivity analysis

One-way sensitivity analysis was performed to explore the potential influences of different parameters, the results of which were shown as a tornado diagram. Monte Carlo simulation of 1000 individuals was performed to figure out uncertainty strategies. According to the guidelines of World Health Organization (WHO) for cost-effective analyses, the threshold of willingness to pay (WTP) was evaluated at \$100,000 per QALY.

Table 1
Clinical efficacy, the most common treatment-emergent AEs and base-case costs.

Variables	Chemotherapy	Aetzolizumab plis Chemotherapy
Efficacy		
median OS (m)	10.3	12.3
median PFS (m)	4.3	5.2
Grade ≥ 3 AEs (%)		
Neutropenia	24.5	23.2
Anemia	12.2	14.1
Decreased neutrophil count	16.8	14.1
Thrombocytopenia	7.7	10.1
Leukopenia	4.1	5.1
Cost per month(\$)		
Aetzolizumab	–	8881
Chemotherapy Drugs	348	342
Grade ≥ 3 AEs	621	955
Total costs for PFS state	969	10,178
Total Costs for PD state	4,020	4,020

OS, overall survival; PFS, progression-free survival. AEs, adverse events; PD, progressive disease.

Table 2
Cost-effectiveness analysis.

Variables	Chemotherapy	Aetzolizumab plus Chemotherapy
Cost (\$)		
PFS state	4,086	52,235
PD state	26,472	31,204
Total costs	30,558	83,439
Incremental costs		52,881
Effectiveness (QALYs)		
PFS state	0.24	0.29
PD state	0.26	0.31
Total effectiveness	0.50	0.60
Incremental effectiveness		0.10
ICER (\$/QALY)		528,810

PFS, progression-free state.

PD, progressive disease.

QALYs, Quality adjusted-life years.

ICER, Incremental cost-effectiveness ratio.

3. Results

3.1. Basic outcomes

From an American perspective, total cost was \$30,558 for chemotherapy group and \$83,439 for the atezolizumab plus chemotherapy group, respectively. The combination treatment provided additional 0.1 QALYs compared with chemotherapy alone. Thus, the ICER was \$528,810 per QALY, which beyond the threshold we set (Table 2). Based on this, we consider atezolizumab plus chemotherapy is not cost effective for extensive-stage SCLC compared with chemotherapy alone in the first-line treatment.

3.2. Sensitivity analysis

In one-way sensitivity analysis, we varied the variables across a range of ± 30%. The results are shown in a tornado diagram (Fig. 2). Costs of PFS state in combination group (cPFS2) and atezolizumab were the most influential factors in our study. In addition, the cost-

effectiveness analysis was sensitive to the cost of PD state in the combination group (cPD2) and the chemotherapy group (cPD1). Utilities also had influence on the model. One-way sensitivity analysis was used to search the optimal price of atezolizumab, the results of which indicated when the price of atezolizumab was set up as nearly \$482 (2ml: 1200 mg), it could be cost-effective.

4. Discussion

The inspiring results of the phase 3 study showed the addition of atezolizumab to chemotherapy significantly prolonged OS and PFS than chemotherapy alone in the first-line treatment for patients with extensive-stage SCLC, which brought great breakthroughs in the first-line treatment of this malignant [4]. We intended to compare cost-effectiveness of atezolizumab plus carboplatin and etopotecan with the standard first-line chemotherapy from an American perspective. According to our analysis, the ICER was \$528,810 per QALY, which beyond the threshold we set (\$100,000 per QALY). AS a result, we did not consider atezolizumab plus chemotherapy is a cost-effective choice compared with chemotherapy alone for patients with extensive-stage SCLC.

Since immunotherapy plays an increasingly important role in the treatments of cancer, clinicians take its amazing efficacy into consideration when making treatment decisions, as well as its high costs. Tumor PD-L1 receptor expression is being studied as a predictive biomarker. A previous study revealed economic benefit of immune checkpoint inhibitors, such as nivolumab and pembrolizumab, was associated with PD-L1 expression in the treatment of NSCLC. High PD-L1 expression improved incremental QALY, which led to an ICER drop [8]. Meanwhile, two studies aiming to evaluate cost-effectiveness of pembrolizumab in the first-line treatment of NSCLC also indicated that whether pembrolizumab with or without chemotherapy, it is projected to be a cost-effective option as first-line treatment for metastatic NSCLC expressing high levels of PD-L1 [5,9]. Unfortunately, the IMpower133 trial did not performed PD-L1 testing owing to the expected high rate of inadequate sample types. And in the phase 1 trial of atezolizumab in extensive-stage SCLC, researchers found it was lack of an association

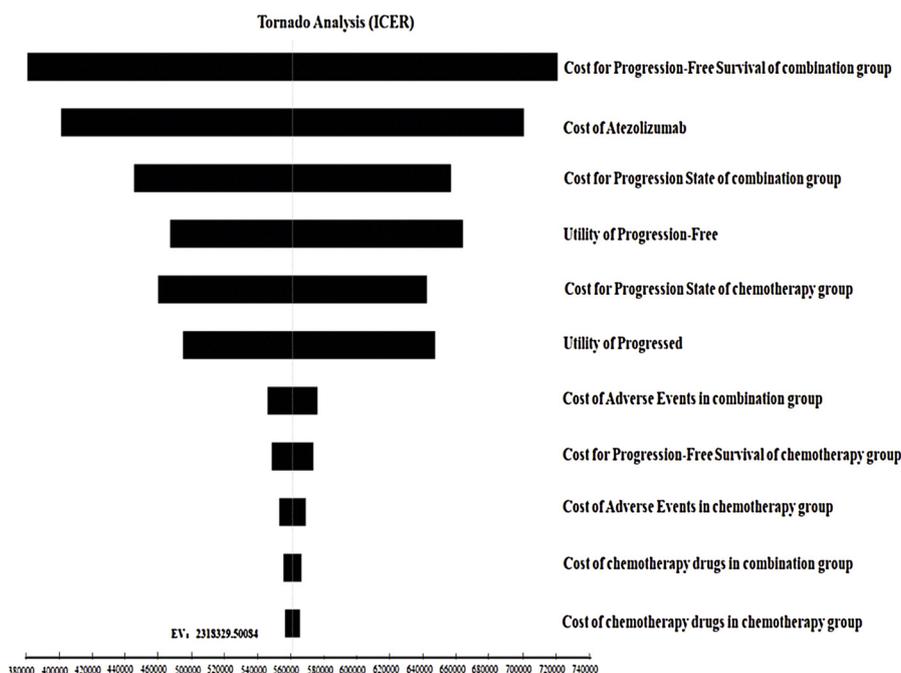


Fig. 2. Tornado diagram of the one-way sensitivity analysis.

Tornado diagram summarized the results of one-way sensitivity analysis to identify model variables. The influential factors were listed descending with the variation of value.

between response and PD-L1 expression.

Noticeably, the threshold that Ralph P et al set was \$180,000/QALY, 3 times of per capita gross domestic product (GDP), since there was no single established ICER threshold for cost-effectiveness in the US [9]. Thus, the ICER they calculated, \$104,823/QALY for the full population, could be considered cost-effective. But if the threshold was set at \$100,000/QALY, which was commonly discussed for the cost-effectiveness in the United States, it may result in a contrary conclusion. Recently, the Institute of Clinical and Economic Review recommended cost effectiveness thresholds are between \$50,000 and \$150,000 per QALY [10]. Despite the range of the thresholds, our results, seems no cost effective in any sense, since the ICER was \$528,810 per QALY, beyond the maximum limit.

One-way sensitivity analysis indicated costs of PFS state in combination group (cPFS2) was the most influential factor in our study, followed by the cost of atezolizumab. Since the price of atezolizumab accounted for about 87% of cPFS2 and the cost of chemotherapy drugs in the combination group had minor effect on the results, we paid more attention to the cost of atezolizumab. The optimal price of atezolizumab we calculated was \$482 (2ml: 1200 mg). It is of great challenge for decision makers think about how to make the promising therapy cost-effective and benefit more candidates. Furthermore, utilities impacted our results, it is essential for researchers to calculate the quality of life, which can help us make more accurate analysis.

Certainly, some limitations in our study should be noted. First, the clinical data were retrospectively collected from a phase 3 trial, which was not patient-level data in clinical practice. For example, four percent of patients in the atezolizumab group and 7.9% of that in the chemotherapy group received immunotherapy and targeted therapy in the subsequent treatment, these may vary the clinical efficacy. Second, costs usually vary between different medical centers or different countries, and this may affect the generalizability of our research. Third, according to our results, the authenticity of utilities is of great importance. As the phase 3 trial did not collect the critical information, they were obtained from previously published literature, which may not be consistent with the real-world.

In conclusion, although atezolizumab plus chemotherapy was the first strategy which overwhelmed the standard chemotherapy in the first-line treatment for extensive-stage SCLC over the past two decades, the results of our study, suggested it is not an optimal strategy from an American cost-effectiveness perspective. Further studies developing a treatment with a great effect but a lower price is still needed. Based on the efficacy of pembrolizumab in advanced SCLC (ASCO 2018 Annual Meeting, Abstract 8506), a phase 3 study assessing the safety and efficacy of pembrolizumab plus standard of care (SOC) chemotherapy (etoposide/platinum) for the participants with newly diagnosed extensive-stage SCLC in the first-line treatment is undergoing (KEYNOTE 604, NCT03066778). In addition, rovalpituzumab tesirine, a DLL3-

targeted antibody-drug conjugate, and alisertib, an orally available selective aurora A kinase inhibitor, also benefited patients with SCLC. We are looking forward to the applications of these novel drugs could bring hope in the treatment of SCLC.

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Conflict of interest

The authors report no conflicts of interest in this work.

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