# Cost-effectiveness of programmed cell death ligand 1 testing and tumor mutational burden testing of immune checkpoint inhibitors for advanced non-small cell lung cancer

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*To the Editor*: Worldwide, lung cancer, particularly non-small cell lung cancer (NSCLC), is the leading cause of tumor-related death. Cost-effectiveness analysis show no economic benefits for advanced NSCLC patients over chemotherapy.[1] Furthermore, tests such as programmed cell death ligand 1 (PD-L1) and tumor mutational burden (TMB) tests, evaluated via immunohistochemical methods and next-generation sequencing, respectively, are widely used for screening potential beneficiaries of immune checkpoint inhibitors (ICIs). However, these two methods have different predictive values, making their comprehensive evaluation the focus of the current controversy.

Considering the predictive effect and economic price, we performed a cost-effectiveness analysis of the two ICI biomarkers for advanced NSCLC considering Chinese and US health care systems based on clinical data from the OAK trial (No. NCT02008227) owing to data accessibility. Patients in the OAK study underwent PD-L1 and blood TMB (bTMB) tests simultaneously, allowing comparison of biomarker predictions in a population.[2,3] We hope to provide suggestions for improving precision medicine, providing multi-dimensional benefits to patients, and rationally allocating social medical resources.

A Markov model was used to assess the economic benefits of immunotherapy and its detection methods. Previously treated advanced NSCLC patients in the OAK trial were randomized into the atezolizumab (intravenous, 1200 mg every cycle) or docetaxel group (intravenous, 75 mg/m$^2$ every cycle). Three subgroups, including no-test, PD-L1, and TMB groups, were set; the cut-off value was set as 1% and 16 mutations/megabase (mut)/Mb for PD-L1 and TMB tests, respectively, considering both available data and optimal results. In the Markov model, patients were classified into three mutually exclusive health states: progression-free survival, disease progression (DP), and death. The cycle length was set as 3 weeks; GetData Graph Digitizer, R software, and TreeAge were used to extract data from Kaplan–Meier survival curves, for statistical calculations, and to simulate the decision tree model, respectively. Weibull survival model was used to fit the survival curves; the survival probability at time t and transition probability (pt) at cycle $t_0$ were calculated using the following formula: $p = 1-\mathrm{Exp}\ (-r \times t)$; $pt = 1-\mathrm{Exp}\ (\lambda \times [t_0-u]^{\gamma}\lambda \times t_0^{\gamma})$, where r represents the survival rate, u is the length of the Markov cycle, $\lambda$ is the scale parameter, and $\gamma$ is the shape parameter.

Cost parameters contained costs of drugs (1200 mg atezolizumab: $11,470.01 in China, $11,374.09 in US; 20 mg docetaxel: $97.00 in China, $113.27 in US; PD-L1 tests: $237.70 in China, $244.50 in US; TMB tests: $5675.68 in China, $5800.00 in US; supportive care: $337.50 in China, $146.32 in US; adverse events [AEs]: $507.40 in China, $304.04 in US; and DP state: $2500.00 in China, $5814.00 in US). To calculate the actual costs of different treatment strategies, body surfaces of 1.733 m$^2$ and 1.526 m$^2$ were assumed for men and women, respectively. All-cause AEs of grade 3/4 were included. Costs were derived from local hospitals or published literatures and evaluated in US dollars.[4,5] For utilities, quality-adjusted life years (QALYs) was used to measure treatment strategy effectiveness. The health state utility values were obtained from published literatures, including the utility for atezolizumab (0.7560), docetaxel (0.6520), and DP state (0.4700), and disutility values for various AEs (average: −0.0609).[6]

The primary outcome was the incremental cost-effectiveness ratio (ICER: incremental cost/incremental QALYs); the secondary outcome included average cost-effectiveness ratio (average CE: average cost/average QALYs) and net benefit (willingness-to-pay [WTP] × QALYs-costs) for each group. WTP threshold was set as 3 × the per capital gross domestic product (GDP) in China ($29,307/QALY

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for China and $100,000 for the US). Model stability was measured using one-way sensitivity analysis with ± 30% range of cost parameters and ± 20% range of utility parameters. Probabilistic sensitivity analysis was conducted through Monte Carlo simulation with 1000 iterations with gamma and beta distribution fitting to costs and utilities, respectively.

Cost-effectiveness analyses were performed in three steps. First, according to the current GDP level in China and the US, we compared atezolizumab with docetaxel regarding cost-effectiveness among the no-test, PD-L1, and TMB groups. In China, the ICERs in the no-test, PD-L1, and TMB test groups were $1,554,153/QALY, $1,495,485/QALY, and $1,340,718/QALY, which were similar to those in the US ($1,560,996/QALY, $1,488,871/QALY, and $1,334,338/QALY), respectively. The ICERs were higher than the WTP thresholds, and neither China nor the US benefited economically; thus, atezolizumab was not cost-effective compared with docetaxel considering current GDP. Second, we analyzed the economic benefits of atezolizumab versus docetaxel among different detection methods to identify biomarker efficacies. In the US and China, the PD-L1 and TMB test groups had lower ICERs than the no-test group, suggesting an improvement in economic efficiency. TMB test group ICER was lower than PD-L1 test group ICER, indicating that the TMB test could better achieve cost-effectiveness. The average CE and net benefit were consistent. Finally, to determine which biomarker is advantageous in selecting an atezolizumab advantaged population, we compared their cost-effectiveness in atezolizumab treatment. Compared with the no-test group, the TMB test group achieved economic benefit with a negative incremental cost and an incremental effect of 0.0011 QALYs in both China and the US. Compared with the no-test group, the PD-L1 test group was not cost-effective (ICER of $505,135/QALY in China and $295,962/QALY in the US). The ICER was $886,312/QALY in China and $371,731/QALY in the US, demonstrating that the TMB test obtained more economic benefits than the PD-L1 test [Table 1]. Furthermore, one-way sensitivity analyses showed that chemotherapy had the greatest influence on stability, followed by the DP state. Probabilistic sensitivity analyses demonstrated that if WTP went over $1,500,000, immunotherapy could be cost-effective; tests of biomarkers could slightly shorten the gap.

**Table 1: Results of cost-effectiveness analyses of two immune checkpoint inhibitors for advanced non-small cell lung cancer.**

| Items | QALY | Cost | Average CE | Net benefit | InC | Ineff | ICER |
|---|---|---|---|---|---|---|---|
| Cost-effectiveness of atezolizumab *vs*. docetaxel | | | | | | | |
| China | | | | | | | |
| No test | | | | | | | |
| Atezolizumab | 0.7955 | 150,096.96 | 188,682 | −126,783 | 130,511.72 | 0.0840 | 1,554,153 |
| Docetaxel | 0.7115 | 19,585.24 | 27,526 | 1268 | | | |
| PD-L1 | | | | | | | |
| Atezolizumab | 0.8070 | 155,921.17 | 193,205 | −132,270 | 136,038.84 | 0.0910 | 1,495,485 |
| Docetaxel | 0.7161 | 19,882.33 | 27,766 | 1103 | | | |
| TMB | | | | | | | |
| Atezolizumab | 0.7966 | 146,703.52 | 184,154 | −123,357 | 127,950.17 | 0.0954 | 1,340,718 |
| Docetaxel | 0.7012 | 18,753.35 | 26,745 | 1797 | | | |
| US | | | | | | | |
| No test | | | | | | | |
| Atezolizumab | 0.7955 | 185,514.72 | 233,204 | −105,965 | 131,086.38 | 0.0840 | 1,560,996 |
| Docetaxel | 0.7115 | 54,428.34 | 76,495 | 16,725 | | | |
| PD-L1 | | | | | | | |
| Atezolizumab | 0.8070 | 188,927.17 | 234,103 | −108,224 | 135,437.18 | 0.0910 | 1,488,871 |
| Docetaxel | 0.7161 | 53,489.99 | 74,701 | 18,116 | | | |
| TMB | | | | | | | |
| Atezolizumab | 0.7966 | 185,061.17 | 232,304 | −105,398 | 127,341.28 | 0.0954 | 1,334,338 |
| Docetaxel | 0.7012 | 57,719.88 | 82,316 | 12,400 | | | |
| Cost-effectiveness of atezolizumab among different biomarkers | | | | | | | |
| PD-L1/no test | | | | | | | |
| China | - | - | - | - | 5824.21 | 0.0115 | 505,135 |
| US | - | - | - | - | 3412.45 | 0.0115 | 295,962 |
| TMB/no test | | | | | | | |
| China | - | - | - | - | −3393.44 | 0.0011 | |
| US | - | - | - | - | −453.55 | 0.0011 | |
| PD-L1/TMB | | | | | | | |
| China | - | - | - | - | 9217.65 | 0.0104 | 886,313 |
| US | - | - | - | - | 3866.00 | 0.0104 | 371,731 |

PD-L1: Programmed cell death ligand 1; TMB: Tumor mutation burden; QALY: Quality-adjusted life year; CE: Cost-effective; InC: Incremental cost; Ineff: Incremental effect; ICER: Incremental cost-effectiveness ratio.

Our study has several advantages. First, it is the first cost-effectiveness study to balance the economic benefits of various detection methods in stratifying patients for ICIs. In addition, it was based on the OAK trial, which ensured consistency among subgroups from the study population, treatment options, and statistical methods, which contributed to high comparability. Finally, TMB could be evaluated from tumor tissue (tTMB) and circulating tumor DNA (bTMB), which are highly consistent with a 85.7%–100% and 81.8%–100% ranges of positive and negative percentage agreement, respectively, in the OAK study. bTMB data were used owing to their non-invasiveness and benefit from long-term dynamic monitoring. tTMB and bTMB costs were considered, and no significant difference was observed.

As a limitation, studies demonstrating the synergistic effect of TMB and PD-L1 test should be confirmed with independent predictive variables; thus, they could not replace but complement each other.[7] Considering the high costs of ICIs and biomarker tests, combining the TMB, PD-L1, or other tests for greater economic benefits needs to be further explored and improved. Moreover, owing to data accessibility, we chose the OAK trial for the cost-effectiveness analysis of atezolizumab as an ICI. Following the release of further clinical trials, we will comprehensively analyze clinical data of different ICIs. Additionally, as immunotherapy has entered the era of combination therapy and our cost-effectiveness study focused on a single ICI to eliminate potential factor interference, further research is necessary to verify whether these biomarker detections are cost-effective in combination therapy.

In conclusion, compared with chemotherapy, ICIs were not cost-effective in China and US health care systems. The TMB and PD-L1 tests could improve ICI cost-effectiveness, and relatively, the TMB test was the most economical option.

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## Conflicts of interest

None.

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