Cost-effectiveness analysis of nivolumab plus ipilimumab versus chemotherapy as the first-line treatment for unresectable malignant pleural mesothelioma

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Abstract

Introduction: This study evaluated the cost-effectiveness of nivolumab plus ipilimumab (NI) versus pemetrexed plus cisplatin/carboplatin (C) as the first-line treatment for unresectable malignant pleural mesothelioma (MPM) from the perspective of US payers.

Methods: A 10-year partitioned survival model was constructed using survival and safety data from the CheckMate 743 clinical trial. The output metrics of the model included the patient’s lifetime quality-adjusted life years (QALYs), lifetime costs, and incremental cost-effectiveness ratio (ICER). Only direct medical costs were considered. One-way and probabilistic sensitivity analyses were conducted to assess the robustness of the results.

Results: Among all randomized patients, group NI had an ICER of $475,677/QALY relative to group C. Among patients with epithelioid histology, group NI had an ICER of $760,955/QALY. Among patients with non-epithelioid histology, group NI had an ICER of $418,348/QALY. The ICERs of all three populations exceeded the willingness-to-pay threshold ($150,000). The results of one-way sensitivity analysis revealed that the cost of nivolumab had a great influence on the results. The results of probabilistic sensitivity analysis demonstrated that the possibility of NI being more economical in all randomized patients and in patients with non-epidemiology histology was 0%. In patients with epithelioid histology, the probability that NI had an economic advantage was 0.6%.

Conclusions: From the perspective of US payers, in patients with unresectable MPM, NI has no economic advantage over C.

Keywords: cost-effectiveness, first-line treatment, ipilimumab, malignant pleural mesothelioma, nivolumab

Received: 6 May 2022; revised manuscript accepted: 12 July 2022.
OS) of patients [14.1 months, 95% confidence interval (CI): 12.4–16.3 months versus 18.1 months, 95% CI: 16.8–21.0 months; hazard ratio = 0.73, 95% CI: 0.61–0.87] with the 3-year OS rate (95% CI) of 15.4% (11.5–19.9) versus 23.2% (18.4–28.2).10,11 The NI regimen can significantly improve the health status of patients with unresectable MPM. The NI regimen has been recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology—Malignant Pleural Mesothelioma (Version 1.2022) as the first-line treatment for MPM.12

Although the NI regimen has shown good safety and efficacy, it is expensive; in particular, ipilimumab is priced at $160.7030/mg in the United States.13 The whole course of treatment (one cycle every 6 weeks, with a total treatment time of approximately months) costs approximately $44,800, which is unaffordable for many patients’ families. Our study aims to evaluate the economy of NI versus that of C in the first-line treatment of unresectable MPM from the perspective of US payers.

Materials and methods

Target population and procedures

The population included in this study was consistent with that included in the CheckMate 743 clinical trial. That is, it included eligible patients who were aged 18 years or older with histologically confirmed unresectable MPM that was unamenable to curative therapy (surgery with or without chemotherapy) and an Eastern Cooperative Oncology Group performance status of 0 or 1.10 In accordance with the design of the CheckMate 743 clinical trial, the NI group received intravenous nivolumab (3 mg/kg) every 2 weeks and ipilimumab (1 mg/kg) every 6 weeks. Treatment was continued until disease progression, unacceptable toxicity, or for 2 years. Patients in group C were intravenously injected with cisplatin (75 mg/m²) or carboplatin (area under the concentration time curve of 5 mg/mL per min) and pemetrexed (500 mg/m²) every 3 weeks for up to six cycles.10

Model structure

TreeAge Pro 2022 software was used to build the model and conduct statistical analysis. The model included three mutually exclusive health states: progression-free disease (PFD), progressive disease (PD), and death. All patients were assumed to enter the model in the PFD state and to be able to maintain their designated health state or develop into another health state in each cycle (Figure 1). The probability of the PFD state transition to the death state was assumed to be natural mortality.14,15 The relative 5-year survival rate of patients diagnosed with MPM was 10% or less. Thus, the time horizon of the model was set to 10 years.2 The model period was set to 1 month to facilitate model operation and parameter calculation. The main results of the model output included total cost, quality-adjusted life years (QALY), and incremental cost-effectiveness ratio (ICER). The ICER refers to the additional cost required for each additional QALY. Cost and utility were discounted at the rate of 3%.16 In this study, $150,000 was used as the willingness-to-pay (WTP) threshold.17

Clinical data

The survival data in this study came from the CheckMate 743 clinical trial, which is a multicenter, randomized, open-label, phase III trial. Eligible participants were randomized to receive NI or C (cisplatin or carboplatin). In the economic evaluation of antitumor drugs, performing parameter distribution fitting on the survival curve to obtain the long-term survival data on patients outside the follow-up period of clinical trials is often necessary due to the limited follow-up times of clinical trials and other factors.14 The survival data on each arm were digitally extracted from the survival curves of CheckMate 743 using GetData Graph Digitizer software (version 2.26; http://www.getdata-graph-digitizer.com/download.php). In accordance with Guyot et al.’s method, the Kaplan–Meier survival curves were reconstructed using R software (version 3.5.1) to obtain new survival curves.19 The distribution functions included Weibull, log-logistic, log-normal, Gompertz, exponential, and gamma.19 Akaike information criterion (AIC), Bayesian information criterion (BIC), and visual simulation methods were used to test the goodness of fit, and distribution functions with low AIC and BIC values and good visual simulation were selected as fitting curves for extrapolation to obtain long-term clinical survival outcomes (Supplemental Table A1).

In the CheckMate 743 trial, the authors only performed a graphical analysis on the progression-free survival (PFS) of the all randomized population (NI versus C = 303 versus 302) with a
3-year minimum follow-up. The authors separately compared all randomized patients (NI versus C = 303 versus 302), patients with epithelioid histology (NI versus C = 229 versus 226), and patients with non-epithelioid histology (NI versus C = 74 versus 76) for OS curve analysis. In our study, log-normal distribution and log-logistic distribution were used to fit the PFS curves of groups NI and C, respectively. Weibull distribution, log-logistic distribution, and exponential distribution were applied to fit the OS curves of different populations in group NI, whereas the OS curves of the three different populations in group C were all fitted with log-logistic distribution. We performed internal model validation.\textsuperscript{21} Internal validation demonstrated that the PFS and OS curves were very close to those presented in clinical trials (Supplemental Figures A1–A8). The survival function for each distribution at time $t$ is shown in Supplemental Figure A9. Table 1 presents the key clinical inputs.

\textbf{Cost and utility}

This study was based on the US payer perspective, and we only considered direct medical costs, including drug procurement, follow-up, administration, best supportive care, and adverse events (AEs) management costs. Through the comparison of the AEs of groups NI and C, only three AEs [asthenia (0% versus 4.2%), anemia (0.3% versus 11.3%), and neutropenia (0.7% versus 15.1%)] were included in this study. In reference to the CheckMate 743 clinical trial, first-line treatment was continued until disease progression, unacceptable toxicity, or the prescribed maximum medication time. In accordance with the experimental results, our study considered that the treatment duration of the NI group was 6 months [median = 5.6 months, interquartile range (IQR): 2.0–11.4 months] and that of the C group was 4 months (median = 3.5 month, IQR: 2.7–3.7 months). Moreover, we assumed that the probability of using cisplatin or carboplatin in group C was 0–1. In accordance with the NCCN Guidelines for MPM (version 1.2022),\textsuperscript{12} second-line therapy in the NI arm was pemetrexed (500 mg/m$^2$, intravenously every 3 weeks) plus cisplatin (75 mg/m$^2$) or carboplatin (area under the concentration time curve of 5 mg/mL per min). We assumed the same probability range (0%–100%) for carboplatin and cisplatin. Group
C was treated with nivolumab (3 mg/kg intravenously once every 2 weeks), vinorelbine (25 mg/m² intravenously on days 1 and 8 of a 3-week cycle), or gemcitabine (1000 mg/m² intravenously on days 1 and 8 of a 3-week cycle) monotherapy.²⁸ The probability of second-line treatment with nivolumab in group C patients was 0.40, and under the assumption that the probability of using vinorelbine or gemcitabine was equal (both were equal to 0.30). All patients were assumed to receive second-line treatment until they progressed, and only the costs of drug acquisition and follow-up for second-line treatment were considered. The drug costs were obtained from the average sales price of Medicare part B drugs provided by the Centers for Medicare & Medicaid Services, and the administration costs were obtained from the Medicare Physician Fee Schedule.¹³,²⁵ In reference to the median age in the CheckMate 743 trial, the initial model patients had the following characteristics: age of 69 years, mean body weight of 70 kg, surface area of 1.8 m², and creatinine clearance of 70 mL/min.²⁴,²⁷ Other costs are shown in Table 1.

The utility value represents the health-related quality of life for each health state. The CheckMate 743 trial did not address health utility. Therefore, the utility values and treatment costs for AEs in our model were obtained from other published literature.²³,²⁴,²⁶ We assumed that AEs occurred only in the first cycle. Precise utility scores were not available in the original or previous MPM literature. Therefore, the utility scores in our analysis were referenced to published values for non-small-cell lung cancer (NSCLC)²² under the assumption that the same health status was similar in both groups with 0.706 for the PFS state, 0.565 for the PD state, and 0 for death. All utility values are shown in Table 1.

**Sensitivity analysis**

One-way sensitivity analysis was performed to account for the effect of the parameters on the model by varying one parameter within the ±20% range (the current price of nivolumab and ipilimumab fluctuated downward by 50% as the value range) of its baseline value, whereas the other parameters were fixed. The discount rate was 0%–6%.¹⁶ Probabilistic sensitivity analyses were performed through Monte-Carlo simulation and were repeated 1000 times, and the results were presented in the form of cost-effectiveness acceptability curves and incremental cost-effectiveness scatter plots.

**Results**

**Basic case analysis**

The time horizon was set to 10 years. Combined with the results of the model running, most of the patients died within 10 years, and our model basically simulated the lifelong outcome of the disease. Refer to Table 2 for the basic analysis results. Compared with C, NI could provide higher health benefits to all randomized patients (1.45 QALYs versus 1.19 QALYs), but also had higher total cost ($295,988 versus $168,111). Compared with that of C, the ICER value of NI was $475,677/QALY, which exceeded the threshold of WTP. In patients with epithelioid histology, NI also had higher health effectiveness than C (1.48 QALYs versus 1.34 QALYs) with a higher total cost ($313,857 versus $205,508). Compared with that of C, the ICER value of NI was $760,955/QALY, which exceeded the WTP. Among patients with non-epithelioid histology, the patients in group NI had a longer QALY than those in group C (1.25 QALYs versus 0.79 QALYs) and at the same time, had higher total cost ($268,724 versus $72,783). The ICER value of NI relative to that of C was $418,348/QALY, which also exceeded the WTP threshold.

**Sensitivity analysis**

The patient’s weight, the probability of second-line nivolumab treatment in the group C, and the cost of pemetrexed had a great effect on the results of all randomized patients. The tornado diagram of one-way sensitivity analysis is shown in Figure 2. The probability of second-line treatment with nivolumab in group C, the utility value of PFS status, and the discount rate had great influence on the results of the patients with epithelioid histology. The tornado chart of single-factor sensitivity analysis is shown in Figure 3. The patient’s weight, the utility value of PD status, and the price of nivolumab had a strong effect on the results of the patients with non-epithelioid histology. The tornado plot of univariate sensitivity analysis is shown in Figure 4. The results of the one-way sensitivity analysis of the three populations all revealed that the ICER value could not fall below the WTP threshold no matter how all variables changed individually.
Table 1. Model parameters.

| Variable | Baseline value | Range | Reference |
|----------|----------------|-------|-----------|
| NI: Log-normal PFS survival mode | $\lambda = 1.93843, \gamma = 1.26135$ | – | Peters et al.\[10\] |
| NI: Log-logistic PFS survival mode | $\lambda = 7.53780, \gamma = 2.29427$ | – | Peters et al.\[10\] |
| NI: OS survival mode | | | |
| NI-A: WeibullPH OS survival mode | $\lambda = 0.0241553, \gamma = 1.1284343$ | – | Peters et al.\[10\] |
| NI-E: Log-logistic OS survival mode | $\lambda = 19.01452, \gamma = 1.51241$ | – | Peters et al.\[10\] |
| NI-N: Exponential OS survival mode | $\lambda = 0.0412831$ | – | Peters et al.\[10\] |
| C: OS survival mode | | | |
| C-A: Log-logistic OS survival mode | $\lambda = 14.25065, \gamma = 1.76236$ | – | Peters et al.\[10\] |
| C-E: Log-logistic OS survival mode | $\lambda = 16.70245, \gamma = 1.70694$ | – | Peters et al.\[10\] |
| C-N: Log-logistic OS survival mode | $\lambda = 9.03382, \gamma = 2.15601$ | – | Peters et al.\[10\] |
| NI: Incidence of AEs | | | |
| Asthenia | 0 | – | Peters et al.\[10\] |
| Anemia | 0.003 | 0.0024 | 0.0036 | Peters et al.\[10\] |
| Neutropenia | 0.007 | 0.0056 | 0.0084 | Peters et al.\[10\] |
| C: Incidence of AEs | | | |
| Asthenia | 0.042 | 0.0336 | 0.0504 | Peters et al.\[10\] |
| Anemia | 0.113 | 0.0904 | 0.1356 | Peters et al.\[10\] |
| Neutropenia | 0.151 | 0.1208 | 0.1812 | Peters et al.\[10\] |
| Utility | | | |
| PFS | 0.706 | 0.5648 | 0.8472 | Dansk et al.\[22\] |
| PD | 0.565 | 0.4520 | 0.6780 | Dansk et al.\[22\] |
| Death | 0 | – | – | Dansk et al.\[22\] |
| Asthenia | −0.410 | −0.3280 | −0.4920 | Nafees et al.\[23\] |
| Anemia | −0.073 | −0.0584 | −0.0876 | Wan et al.\[24\] |
| Neutropenia | −0.460 | −0.3680 | −0.5520 | Nafees et al.\[23\] |
| Drug cost per mg, 2022 US$ | | | |
| Nivolumab | 29.2450 | 14.6225 | 29.245 | Centers for Medicare and Medicaid Services\[13\] |
| Ipilimumab | 160.7030 | 80.3515 | 160.703 | Centers for Medicare and Medicaid Services\[13\] |
| Pemetrexed | 7.6037 | 6.08296 | 9.12444 | Centers for Medicare and Medicaid Services\[13\] |

(Continued)
The results of probabilistic sensitivity analysis are presented in the appendix (Supplemental Figure A10–A12). In all randomized patients and in patients with non-epithelioid histology, all points were above the WTP threshold ($150,000) line, indicating that the probability that NI was economical was 0 under this WTP threshold. In patients with epithelioid histology, only six points were below the threshold line of WTP. This result indicated that under this threshold line of WTP, the probability that NI had economic advantages was very low.

The cost-effectiveness acceptability curves of all randomized patients (Figure 5) and patients with non-epithelioid histology (Figure 6) showed that as the WTP threshold increased, the probability that NI was economical increased. However, when the WTP threshold was $150,000, the probability that NI was economical was 0. The cost-effectiveness acceptability curves of patients with epithelioid histology (Figure 7) illustrated that when the WTP fluctuated within the range of $0/QALY to $1,600,000/QALY, the probability that NI was economical increased with the

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**Table 1. (Continued)**

| Variable                  | Baseline value | Range                  | Reference                                                                 |
|---------------------------|----------------|------------------------|---------------------------------------------------------------------------|
|                           |                | Minimum | Maximum             |                                                                           |
| Cisplatin                 | 0.1864         | 0.14912 | 0.22368             | Centers for Medicare and Medicaid Services                                |
| Carboptatin               | 0.0522         | 0.04176 | 0.06264             | Centers for Medicare and Medicaid Services                                |
| Vinorelbine               | 0.8624         | 0.68992 | 1.03488             | Centers for Medicare and Medicaid Services                                |
| Gemcitabine               | 0.0192         | 0.01536 | 0.02304             | Centers for Medicare and Medicaid Services                                |

**Drug administration and follow-up, cost per cycle, 2022 US$**

| Administration IV, first hour | 142.22 | 113.776 | 170.664 | Centers for Medicare and Medicaid Services |
| Administration IV, additional hour | 30.68 | 24.544 | 36.816 | Centers for Medicare and Medicaid Services |
| Outpatient follow-up visit    | 52.33 | 41.864 | 62.796 | Centers for Medicare and Medicaid Services |

**AEs cost per 1-month cycle, 2020 US$**

| AEs                          | Minimum | Maximum | Reference               |
|------------------------------|---------|---------|-------------------------|
| Asthenia                     | 1065.44 | 852.352 | 1278.528                | Courtney et al. |
| Anemia                       | 5243.47 | 4194.776| 6292.164                | Courtney et al. |
| Neutropenia                  | 16,857.15 | 13,485.720 | 20,228.580          | Courtney et al. |
| Body area surface/m²        | 1.8     | 1.44    | 2.16                    | Goulart and Ramsey |
| Weight/kg                    | 70      | 56      | 84                      | Goulart and Ramsey |
| Creatinine clearance/mL/min | 70      | –       | –                       | Goulart and Ramsey |
| Discount rate                | 0.03    | 0       | 0.06                    | Bousmah et al.   |

A, all randomized patients; AEs, adverse events; C, pemetrexed plus cisplatin/carboplatin; E, patients with epithelioid histology; IV, intravenous injection; N, patients with non-epithelioid histology; NI, nivolumab plus ipilimumab; OS, overall survival; PD, progressed disease; PFS, progression-free survival.
Table 2. Cost-effectiveness analysis.

| Strategies                      | Life years | QALYs | Total costs (US$) | ICER (US$/QALY) (NI versus C) |
|--------------------------------|------------|-------|-------------------|-----------------------------|
| In randomized patients          |            |       |                   |                             |
| NI                             | 2.33       | 1.45  | 295,988           | 475,677                     |
| C                              | 1.87       | 1.19  | 168,111           |                             |
| Incremental (NI versus C)      | 0.46       | 0.27  | 127,877           |                             |
| In patients with epithelioid histology |           |       |                   |                             |
| NI                             | 2.38       | 1.48  | 313,857           | 760,955                     |
| C                              | 2.15       | 1.34  | 205,508           |                             |
| Incremental (NI versus C)      | 0.23       | 0.14  | 108,349           |                             |
| In patients with non-epithelioid histology |        |       |                   |                             |
| NI                             | 1.97       | 1.25  | 268,724           | 418,348                     |
| C                              | 1.17       | 0.79  | 72,783            |                             |
| Incremental (NI versus C)      | 0.81       | 0.47  | 195,941           |                             |

C, pemetrexed plus cisplatin/carboplatin; ICER, incremental cost-effectiveness ratio; NI, nivolumab plus ipilimumab; QALYs, quality-adjusted life years.

Figure 2. One-way sensitivity analysis in all randomized patients (A).

C, pemetrexed plus cisplatin/carboplatin; ICER, incremental cost-effectiveness ratio; NI, nivolumab plus ipilimumab; P, probability; PD, progressive disease; PFS, progression-free survival.
Discussion

In contrast to conventional chemotherapy, NI is effective in prolonging survival in patients with epithelioid histology and in patients without epithelioid histology and improves the duration of response (DOR). The median (95% CI) DOR was 11.6 months (8.2–16.8 months) in the NI group versus 6.7 months (5.6–7.1 months) in the chemotherapy group. Among responders, the 3-year DOR rate was 28% versus 0%. Therefore, evaluating the cost-effectiveness of NI is necessary. In this study, we assessed for the first time the cost-effectiveness of NI for the treatment of MPM by building an economic model method and synthesizing the latest evidence.

At present, the economic research on MPM is very limited. In 2017, a Markov model was established to compare the cost-effectiveness of adding bevacizumab versus pemetrexed plus cisplatin from the perspective of Chinese payers. Model calculations showed that using bevacizumab as a part of first-line and maintenance therapy provided an additional 0.112 QALYs at the additional cost of $81,447. That is, compared with chemotherapy alone, the ICER of chemotherapy plus bevacizumab was $727,203/QALY, which was well above the accepted WTP threshold of three times the gross domestic product per capita of China ($23,970 per QALY). 29 Most of the existing economic studies on MPM focused on chemotherapy.30–32 In 2012, Woods et al., on the basis of the results of the EORTC08983 trial, used an indirect comparison method to evaluate the relative efficacy of raltitrexed combined with cisplatin and pemetrexed combined with cisplatin. They concluded that raltitrexed in combination with cisplatin was an economical first-line treatment for patients with MPM. However, no cost-effectiveness studies related to immunotherapy for MPM currently exist. In recent years, tumor immunotherapy has developed rapidly, and many new therapeutic targets have been discovered. However, programmed death 1 (PD-1) and its ligand programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) remain the therapeutic
Figure 4. One-way sensitivity analysis in patients with non-epithelioid histology (N). C, pemetrexed plus cisplatin/carboplatin; ICER, incremental cost-effectiveness ratio; NI, nivolumab plus ipilimumab; P, probability; PD, progressive disease; PFS, progression-free survival.

Figure 5. The cost-effectiveness acceptability curves of all randomized patients [A]. C, pemetrexed plus cisplatin/carboplatin; CE, cost-effective; NI, nivolumab plus ipilimumab.
Figure 6. The cost-effectiveness acceptability curves of patients with non-epithelioid histology (N). C, pemetrexed plus cisplatin/carboplatin; CE, cost-effective; NI, nivolumab plus ipilimumab.

Figure 7. The cost-effectiveness acceptability curves of patients with epithelioid histology (E). C, pemetrexed plus cisplatin/carboplatin; CE, cost-effective; NI, nivolumab plus ipilimumab.
targets that have been most investigated in detail. Immunotherapy has made great progress in the treatment of malignant tumors and is superior to traditional chemotherapy and radiotherapy. However, the drugs that are currently used for immunotherapy, such as ipilimumab, which inhibits CTLA-4, and nivolumab, which inhibits the interaction of PD-1 with PD-L1, are relatively expensive. Therefore, whether immunotherapy has economic advantages over traditional chemotherapy is a major concern of numerous researchers worldwide.

Despite the promising results of the Checkmate 743 trial, our health economics analysis showed that from the US payers’ point of view, the immunotherapy of NI is not a cost-effective alternative to traditional chemotherapy for the first-line treatment of unresectable MPM. Among all randomized patients, group NI had 0.27 QALYs more than group C, resulting in an increase in cost of $127,877 and an ICER of $475,677/QALY. Among patients with epithelioid histology, group NI had 0.14 QALYs more than group C, resulting in an increase in cost of $108,349 and an ICER of $760,955/QALY. Among patients with non-epithelioid histology, group NI had 0.46 QALYs more than group C, resulting in an increase in cost of $195,941 and an ICER of $418,348/QALY. In the three populations, the ICER value was all above the WTP threshold, that is, NI was not cost-effective. However at the same time, patients with epithelioid histology receiving NI therapy had a higher QALY (1.25 versus 1.48) than the patients with non-epithelioid histology. This result indicated that NI therapy has a better effect on patients with epithelioid histology than on those without. However, the ICER of the patients with non-epithelioid histology was approximately half that of the patients with epithelioid histology. This situation indicated that the use of NI therapy in patients with non-epithelioid histology was more economical than in other patients.

The three models established in our study took into account the effect of different second-line treatment drugs on the results. In accordance with the CheckMate 743 trial and NCCN guidelines, we assumed that the patients in the NI group received pemetrexed plus cisplatin/carboplatin for second-line therapy after progression. The probability of receiving nivolumab in group C originated from the CheckMate 743 trial. However, given that the article did not explain the specific chemotherapy plan of this group, we assumed that in addition to nivolumab, the use of vinorelbine and gemcitabine for second-line therapy had the same probability range in accordance with NCCN guidelines. Through one-way sensitivity analysis, we found that in all patients and epithelioid patients, the probability of receiving nivolumab in group C had a great influence on the results. However, no matter how the probability changed within the preset range, the ICER value was always above the WTP threshold, and the NI group showed an absolute cost-effective disadvantage. We suspect that this situation may be related to the higher price of nivolumab than that of other drugs. We directly observed that nivolumab price had a great effect on the outcomes in the non-epithelioid population. This observation verified our conjecture to a certain extent.

The NCCN guidelines did not clearly indicate the use cycle of nivolumab combined with ipilimumab in the treatment of patients with MPM. The specifications of nivolumab issued by the US Food and Drug Administration (FDA) describe the life cycle as follows: in combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression. That is to say, at present, the FDA also has no clear regulations on the use cycle. However, using 2 years as the usage period is obviously incorrect because from the clinical trial, the PFS was far less than 2 years (the CheckMate 743 trial only provided the PFS curves of all patients). This situation would make our calculated cost become significantly higher than the actual cost (the above analysis showed that the price of nivolumab had a great influence on the results). Therefore, in our study, we assumed that the duration of first-line treatment with nivolumab and ipilimumab in the NI group was equal to the median duration in the CheckMate 743 trial, whereas that of second-line treatment with nivolumab and ipilimumab in group C was until the progression of patients with MPM. The same assumption was made for the cycles with pemetrexed plus cisplatin/carboplatin in the NI group.

This study still has certain limitations. First, although the CheckMate 743 trial provided the OS curves of three different populations, it did not provide the PFS curves of the different populations. Therefore, for all three different populations (all randomized patients, patients with
epithelioid histology, and patients with non-epithelioid histology), our study used their respective OS curves but utilized the PFS curve of all random population to fit the survival model. This approach would lead to some bias. Second, only some adverse drug events were included in this study to simplify the model, and the treatment cost data of AEs originated from published relevant literature rather than real-world data. Although this approach may also lead to certain bias, the sensitivity analysis results showed that such parameters had little influence on the results. Moreover, no specific immune-related AEs were included. Although immune-related AEs can lead to serious outcomes in patients, cost has low impact on outcomes. In addition, the conclusion of our study is that the immune group is not economical. Without calculating immune-related AEs, we believe that our results underestimate the economics of the chemotherapy group. That is, calculating immune-related AEs would increase the economy of the results of the chemotherapy group and would not affect the conclusions. Third, the utility value is a key parameter for pharmacoeconomic evaluation. However, given the unavailability of precise utility scores in the original or previous MPM literature, the utility scores in our analysis were taken in reference to the published values for NSCLC.29 Although the results of one-way sensitivity analysis demonstrated that the utility values of PFS status and PD status played an important role in the results, the tornado diagrams showed that no matter how the utility values of PFS status or PD status changed within the preset range, the ICER values were always above the WTP threshold. Fourth, because AE rates and costs were low in both groups, this portion of the cost was not discounted (costs in 2020 US$).

Conclusion
The pharmacoeconomic evaluation carried out in this study conformed with the standard methodological process.18 Despite some limitations, the results obtained have high reliability. That is, when $150,000 was used as the threshold of WTP, immunotherapy (NI) had no economic advantage over traditional chemotherapy (C) in the first-line treatment of unresectable MPM.

Declarations

Consent for publication
All authors participated in this study and approved the final version.

Author contribution(s)
Liu Yang: Software; Writing – original draft.
Xueqiong Cao: Validation; Writing – review & editing.
Na Li: Data curation; Investigation.
Bin Zheng: Formal analysis.
Maobai Liu: Supervision; Visualization.
Hongfu Cai: Methodology; Writing – original draft.

Acknowledgements
We thank all of the people who have contributed to this paper.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by Fujian Provincial Department of Science & Technology (grant no. 2020Y9070, 2018Y9037, and 2021R0053).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All datasets for this study are included in the article as well as in the supplementary material.

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Supplemental materials
Supplemental material for this article is available online.

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