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*Original Research*

# First-line nivolumab plus chemotherapy *versus* chemotherapy alone for advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma: a cost-effectiveness analysis

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***Abstract***

**Background:** The CheckMate-649 trial compared nivolumab plus chemotherapy (NC) with chemotherapy alone as first-line treatment for advanced gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal adenocarcinoma (EAC) and showed significant benefits to progression-free survival and overall survival. This study evaluated the lifetime cost-effectiveness of NC *versus* chemotherapy alone in patients with GC/GEJC/EAC from the perspective of the US payers.

**Methods:** A 10-year partitioned survival model was constructed to evaluate the cost-effectiveness of NC and chemotherapy alone and measured the health achievements in quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and life-years. Health states and transition probabilities were modeled from the survival data from the CheckMate-649 clinical trial (NCT02872116). Only direct medical costs were considered. One-way and probabilistic sensitivity analyses were conducted to assess the robustness of the results.

**Results:** On comparing the chemotherapy, we found that NC incurred substantial health costs, resulting in ICERs of $240,635.39/QALY, $434,182.32/QALY, and $386,715.63/QALY for the model of patients with programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ⩾5, PD-L1 CPS ⩾1, and all-treated patients, respectively. All ICERs were significantly higher than the willingness-to-pay threshold value of $150,000/QALY. The main influencing factors were the cost of nivolumab, the utility value of the progression-free disease, and the discount rate.

**Conclusion:** Compared with chemotherapy alone, NC may not be a cost-effective option for treating advanced GC, GEJC, and EAC in the United States.

***Keywords:*** chemotherapy, cost-effectiveness analysis, first-line treatment, gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma, nivolumab

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## Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related deaths and the most common cancer, with the fifth and third highest incidence and mortality rates among cancers worldwide.[1] The definition of GC is relatively broad, and a variety of cancers, including gastroesophageal junction cancer (GEJC), which forms at the junction of the stomach and esophagus, can be classified as GC.[2] In the United States, there are approximately 27,500 new cases and 11,000 deaths annually, with a 5-year survival rate of 30% for all stages.[3,4]

Esophageal cancer ranks seventh and sixth in global cancer incidence and mortality.[1] Esophageal cancer mainly consists of squamous cell carcinoma and adenocarcinoma, which account for more than 90% of malignant esophageal tumors.[5] Among them, the incidence of esophageal adenocarcinoma (EAC) is rising faster than any other cancer in the United States. In addition, EAC is usually diagnosed at an advanced stage and has a 5-year survival rate of less than 20%.[6]

GC/GEJC/EAC have similar molecular characteristics and have comparable clinical outcomes with systemic chemotherapy in the advanced setting.[7] Patients with advanced GC/GEJC/EAC have limited treatment options, and NCCN Clinical Practice Guidelines in Oncology recommend fluorouracil plus platinum as systemic chemotherapy. However, the therapeutic effect is still not ideal, leading to tumor recurrence and treatment ineffectiveness in some cases.[8,9] In recent years, immunotherapy has been an emerging approach for treating solid tumors. In particular, immune checkpoint inhibitors (ICIs) have shown promising therapeutic effects on solid tumors, and the possible benefits of combination therapies combining ICIs with other agents are being explored clinically.[10,11]

In the tumor microenvironment, PD-L1 expressed by tumor cells binds to PD-1 expressed by tumor-infiltrating T lymphocytes, allowing tumor cells to evade the immune attack and inducing T cells apoptosis.[11] ICIs can block the interaction between PD-1 and PD-L1 by preventing the binding of PD-L1 and PD-1, and the immune killing ability can then be restored, thereby killing tumor cells.[11]

Nivolumab is a highly potent inhibitor of PD-1 targets.[7] CheckMate-649 is a global multicenter, randomized, open-label phase III clinical trial (NCT02872116).[7] The trial evaluated the efficacy of nivolumab plus chemotherapy (NC) compared to chemotherapy in improving overall survival (OS) and progression-free survival (PFS). The median OS was 13.8 and 11.6 months in the overall population, 14.1 and 11.1 months in patients with PD-L1 CPS $\geqslant$5, and 14.0 and 11.3 months in patients with PD-L1 CPS $\geqslant$1 in the NC and chemotherapy arms, respectively. The median PFS was 7.7 and 6.9 months in the overall population, 7.7 and 6.05 months in patients with PD-L1 CPS $\geqslant$5, and 7.5 and 6.9 months in patients with PD-L1 CPS $\geqslant$1 in the NC and chemotherapy arms, respectively. The results showed that NC significantly improved OS and PFS in patients with advanced GC/GEJC/EAC.

Despite the more extended survival advantage of NC over chemotherapy, its high cost also increases the financial burden on patients' families and society.[12,13] Therefore, as NC is included in the first-line treatment pattern, it is necessary to analyze further the impact of combination chemotherapy with nivolumab on treatment cost-effectiveness. We provided the following articles according to the request of the CHEERS 2022 report list.[14]

## Materials and Methods

### *Population*

*Targeted population.* This study utilized the sample characteristics of the CheckMate-648 clinical trial: patients were aged $\geqslant$18 years (median age 61–62 years) with previously untreated, unresectable advanced or metastatic GC, GEJC, or EAC, regardless of PD-L1 expression. Patients with prior adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy (administered at least 6 months before randomization) were allowed. This study was conducted in the overall population, patients with PD-L1 CPS $\geqslant$5, and patients with PD-L1 CPS $\geqslant$1, respectively.[7]

*Intervention.* Patients received nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) plus chemotherapy [XELOX every 3 weeks (capecitabine 1000 mg/m$^2$ twice daily, days 1–14 and oxaliplatin 130 mg/m$^2$, day 1) or FOLFOX every 2 weeks (leucovorin 400 mg/m$^2$, day 1; fluorouracil 400 mg/m$^2$, day 1 and 1200 mg/m$^2$, days 1–2; and oxaliplatin 85 mg/m$^2$, day 1)] or chemotherapy alone. All treatments were administered intravenously except for oral capecitabine. Treatment continued until disease progression, unacceptable toxic effects, consent withdrawal, or study termination. Patients can be treated with NC for up to 2 years.[7]

### *Model*

*Model approach.* Cost-effectiveness analysis is based on a partitioned survival model, which determines the number and proportion of individuals in each state from the survival curves.[15] It is the method most commonly used by National

Institute for Health and Clinical Excellence currently to evaluate interventions for advanced or metastatic cancer.[15] Survival data were extracted from Kaplan-Meier (K-M) curves of the CheckMate-648 clinical trial using GetData Graph Digitizer software (version 2.26; http://www.getdata-graph-digitizer.com/download.php), which is a software product developed by GetData Pty Ltd, an Australian software development company.[16] According to Guyot *et al.*'s method, the K-M curves were reconstructed by R language software (version 3.5.1) and extrapolated to obtain long-term clinical outcomes.[17] The distribution functions included Exponential, Weibull, Log-Normal, Gamma, and Log-Logistic.[18] The goodness-of-fit was examined using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and visual simulation methods.[19] Lower AIC and BIC values indicate a better fit (The fitting results are shown in Supplemental Figures 1 and 2, and the selected fitting curves and data are shown in Table 1). The area under the OS curve estimated the proportion of patients who survived, and the area under the PFS curve calculated the proportion of patients with progression-free disease (PFD). The space between the OS and PFS curves estimated the proportion of patients with the progressed disease (PD) (The key steps to calculate the transition probability are shown in Supplemental Figure 3).[19] The probability of death for patients with PFD in the model was assumed to be the natural mortality rate.[20]

*Model assumptions.* The median treatment duration for patients receiving first-line NC and chemotherapy alone was 6.5 and 4.9 months, respectively. Therefore, the first-line treatment durations for our model were assumed to be seven and five cycles in the NC and chemotherapy arms, respectively.

All patients received second-line chemotherapy after progression. Second-line chemotherapy regimens were developed based on the recommendations of NCCN Clinical Practice Guidelines in Oncology, systematic treatment information provided by CheckMate-649, and guidance of an oncologist to enhance the validity and reliability of our model.[8,9] Therefore, second-line chemotherapy regimens were assumed to be paclitaxel every 21 days (175 mg/m$^2$, day 1), docetaxel every 21 days (75–100 mg/m$^2$, day 1), or irinotecan monotherapy every 14 days (150–180 mg/m$^2$, day 1); all treatments were administered intravenously.

*Model structure.* This study was based on the data from the CheckMate-649 clinical trial to build a partitioned survival model with TreeAgePro2022, a decision analysis software developed by TreeAge Software, Inc, to obtain total costs and total outputs over the time horizon. The model constructs three mutually exclusive health states: PFD, PD, and death. All patients were initially set to a PFD state, and in each cycle, the patient's status could be maintained or moved to the following health state. Due to the poor prognosis of patients with advanced GC/GEJC/EAC, the 5-year survival rate is less than 20%. The time horizon was set at 10 years, which can fully cover the whole life cycle of the patients. The model cycle was set to 4 weeks, referring to the course of chemotherapy. Based on the CheckMate-649 clinical trial, NC and chemotherapy alone were used as first-line treatment for advanced GC/GEJC/EAC, as shown in Figure 1. Patients in PD status would be treated with irinotecan, paclitaxel, or docetaxel and have an equal chance of receiving them. Sensitivity analysis was performed on the probability of choosing different treatment options after progression to avoid the impact of this assumption on the results. The primary outcomes included total cost, quality-adjusted life-year (QALY), and incremental cost-effectiveness ratio (ICER).

### *Cost input*

Model cost inputs are listed in Table 1. Only direct medical costs were considered in the model, including drug costs, administration costs, management costs of serious adverse events (AEs), and follow-up costs.[21] Drug costs were obtained from the Medicare part B drug average sales price provided by the Centers for Medicare and Medicaid Services, and the administration costs were obtained from the Medicare Physician Fee Schedule.[22,23] Other costs were derived from published literature. Only AEs $\geqslant$3 with an incidence greater than 10% were considered in our study. Management cost of AEs per cycle = incidence rate of AEs $\times$ management cost of AEs. Management costs of AEs were only applied to the first cycle of the model and assumed to occur only once in 1 month. Costs and utilities were discounted using a 3% discount rate.[24]

### *Utility input*

Model inputs concerning utility are listed in Table 1. Health utility values for PFD and PD were derived from published studies.[26] The utility value of PFD was 0.797, derived from EuroQol

**Table 1.** Model parameters and ranges used in the sensitivity analyses.

| Variable | Baseline value | Range | | Reference |
|---|---|---|---|---|
| Overall survival model for overall population | | | | |
| Group NC | Log-logistic: shape = 1.71564, scale = 13.61987 | | | |
| Group chemotherapy | Log-logistic: shape = 1.84576, scale = 11.40354 | | | |
| Progression-free survival model for overall population | | | | |
| Group NC | Log-normal: meanlog = 2.13721, sdlog = 0.9369 | | | |
| Group chemotherapy | Log-normal: meanlog = 1.915121, sdlog = 0.909472 | | | |
| Overall survival model for the patients with PD-L1 CPS ⩾1 | | | | |
| Group NC | Log-logistic: shape = 1.7152, scale = 13.7982 | | | |
| Group chemotherapy | Log-logistic: shape = 1.85335, scale = 11.1739 | | | |
| Progression-free survival model for the patients with PD-L1 CPS ⩾1 | | | | |
| Group NC | Log-logistic: shape = 1.79317, scale = 8.40188 | | | |
| Group chemotherapy | Log-normal: meanlog = 1.890638, sdlog = 0.888063 | | | |
| Overall survival model for the patients with PD-L1 CPS ⩾5 | | | | |
| Group NC | Log-logistic: shape = 1.69429, scale = 14.61612 | | | |
| Group chemotherapy | Log-normal: meanlog = 2.369966, sdlog = 0.940447 | | | |
| Progression-free survival model for the patients with PD-L1 CPS ⩾5 | | | | |
| Group NC | Log-normal: meanlog = 2.16791, sdlog = 1.00472 | | | |
| Group chemotherapy | Log-normal: meanlog = 1.830972, sdlog = 0.937872 | | | |
| Drug cost per mg, US $ | | | | |
| Nivolumab | 29.245 | 23.396 | 35.094 | 22 |
| Oxaliplatin | 0.148 | 0.1184 | 0.1776 | 22 |
| Capecitabine | 0.001686 | 0.0013488 | 0.0020232 | 22 |
| Leucovorin | 0.08884 | 0.071072 | 0.106608 | 22 |
| Fluorouracil | 0.004258 | 0.0034064 | 0.0051096 | 22 |
| Irinotecan | 0.12245 | 0.09796 | 0.14694 | 22 |
| Paclitaxel | 0.124 | 0.0992 | 0.1488 | 22 |
| Docetaxel | 0.459 | 0.3672 | 0.5508 | 22 |
| Drug administration and follow-up, cost per cycle, US $ | | | | |
| Administration iv, first hour | 146.16 | 116.93 | 175.39 | 23 |
| Administration iv, additional hour | 31.04 | 24.83 | 37.25 | 23 |
| Follow-up | 70.37 | 56.30 | 84.45 | 23 |

*(Continued)*

**Table 1.** (Continued)

| Variable | Baseline value | Range | | Reference |
|---|---|---|---|---|
| AEs cost per event, first cycle only, US $ | | | | |
| Neutropenia | 17,181 | 13,744.8 | 20,617.2 | 25 |
| Risks of serious AEs in NC group (grade 3+) | | | | |
| Neutropenia | 0.15 | 0.12 | 0.18 | 7 |
| Risks of serious AEs in chemotherapy group (grade 3+) | | | | |
| Neutropenia | 0.12 | 0.096 | 0.144 | 7 |
| Utility | | | | |
| PFD | 0.797 | 0.6376 | 0.9564 | 26 |
| PD | 0.577 | 0.4616 | 0.6924 | 26 |
| Disutility of serious AEs | | | | |
| Neutropenia | 0.46 | 0.368 | 0.552 | 25 |
| Other parameters | | | | |
| Discount rate | 3% | 0 | 6% | 24 |
| Body area surface/$m^2$ | 1.8 | 1.44 | 2.16 | 25 |

AE, adverse event; CPS, combined positive score; iv, intravenous injection; NC, nivolumab plus chemotherapy; PD, progressed disease; PFD, progression-free disease.

(EQ-5D) responses of the TOGA trial calculated by the Japanese scoring algorithm.[26] The utility value of PD was 0.577, derived from the National Institute for Health and Clinical Excellence.[26] Other utility values were obtained from the published literature. The disutility of AEs per cycle = the disutility of AEs × incidence rate of AEs. The AEs' disutility was applied only to the first cycle of the model and was assumed to occur only once in 1 month.

### *Sensitivity analysis*

One-way sensitivity analysis was used to analyze the influence of different parameters on ICER when they varied within a specific range. Twenty percent fluctuation in cost, utility, the incidence of adverse reactions, and body surface area were used as the range of variation for these parameters. The ranges of variation for other parameters were obtained from the published literature. The results were presented in the figure of the tornado diagram.

Second-order Monte Carlo simulations were used for probabilistic sensitivity analysis to assess the overall robustness of the results. According to the ISPOR-SMDM report, the cost and medical resource utilization parameters were set to Gamma distributions, the incidence rate of AEs and health utility were set to Beta distributions, and body surface area was set to normal distributions.[27] The probabilistic sensitivity analysis was repeated 1000 times. The results were presented as cost-effectiveness acceptability curves and incremental cost-effectiveness scatter plots, representing the probability that each treatment option was cost-effective at the willingness-to-pay (WTP) threshold. The WTP threshold in the United States was set at $150,000, as recommended by Neumann *et al.*[28]

## Results

### *Base-case results*

The results of the base-case analysis are shown in Table 2. The incremental cost of NC was $95,280.39 compared with chemotherapy alone in the overall population, and the incremental effect was 0.25 QALY, leading to the ICER of

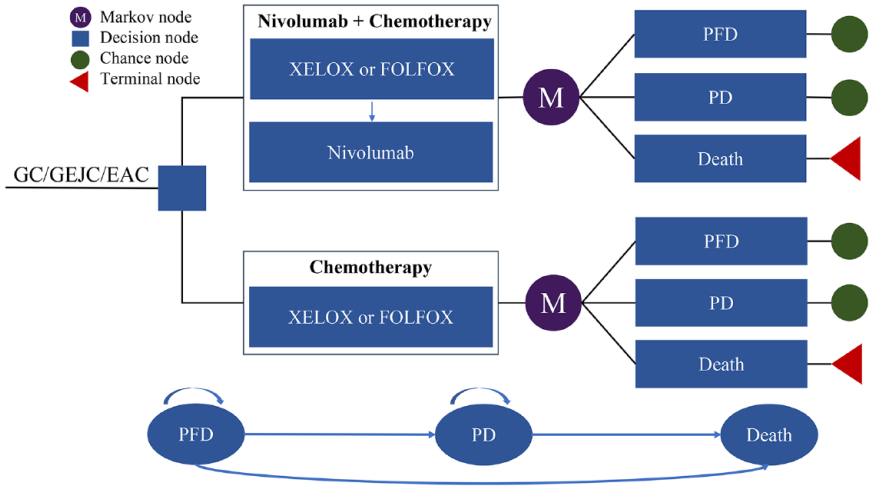


**Figure 1.** Partitioned survival model simulating the results of the CheckMate-649 clinical trial. All patients started in the PFD state and received appropriate treatment. Patients could enter the PFD state and subsequently move to the death state. XELOX: capecitabine 1000 mg/m$^2$ twice daily, days 1–14 and oxaliplatin 130 mg/m$^2$, day 1, every 3 weeks; FOLFOX: leucovorin 400 mg/m$^2$, day 1, fluorouracil 400 mg/m$^2$, day 1 and 1200 mg/m$^2$, days 1–2, and oxaliplatin 85 mg/m$^2$, day 1, every 2 weeks.
EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; PD, progressed disease; PFD, progression-free disease.

$386,715.63/QALY. The incremental cost of NC was $94,841.74 and $93,978.28 compared with the chemotherapy in the patients with PD-L1 CPS ⩾5 and PD-L1 CPS ⩾1, and the incremental effect was 0.39 and 0.22 QALY, leading to the ICER of $240,635.39/QALY and $434182.32/QALY, respectively. All ICERs were significantly higher than the US WTP threshold of $150,000/QALY.

### *Sensitivity analysis*

The results of the one-way sensitivity analysis are shown in Figures 2 to 4. The most influential factors were the cost of nivolumab, the utility value of PFD, and the utility value of PD. Other parameters, including the proportion of XELOX, the incidence rate of AEs, etc., slightly impacted the ICERs. However, none of the variables could reduce the ICER values below the threshold, which was consistent with the base-case results.

The results of the probabilistic sensitivity analysis are shown in Figures 5 to 7 and Supplementary Figures 1 to 3. The cost acceptability curves indicate that at a threshold of $150,000, the probability that NC is a cost-effective option is 0. If the WTP is increased to $250,000, then the probability that NC is economical in the patients with PD-L1 CPS ⩾5 is >50%, while the probability that it is economical in the overall population and in the patients with PD-L1 CPS ⩾1 is 0. The possibility that NC has a cost-effectiveness advantage may increase as WTP improves. However, at present, first-line NC may not be a cost-effective option for advanced GC/GEJC/EAC compared with chemotherapy.

## Discussion

Patients with advanced GC/GEJC/EAC have limited treatment options, poor prognosis, and a low 5-year survival rate.[3,4] The CheckMate-649 clinical trial showed that NC could significantly improve OS and PFS in patients with advanced GC/GEJC/EAC. Based on the CheckMate-649 clinical trial, the FDA approved NC as first-line therapy for advanced GC/GEJC/EAC, regardless of PD-L1 expression status. However, nivolumab is expensive, whether its price reflects the drug's clinical value, the health insurance system will guarantee the drug's cost, and patients will ultimately receive treatment with nivolumab. These questions remain to be determined. Therefore, it is necessary to evaluate the economics of nivolumab use.

Our study shows that first-line NC for patients with advanced GC/GEJC/EAC may not be a cost-effective option from the perspective of third-party payers in the United States. Compared with chemotherapy alone, the ICER values obtained

**Table 2.** The cost and outcome results of the base-case analysis.

| Parameters | Overall population | | PD-L1 CPS ⩾1 | | PD-L1 CPS ⩾5 | |
|---|---|---|---|---|---|---|
| | NC | C | NC | C | NC | C |
| Total cost ($) | 105,714.44 | 10,434.05 | 104,420.67 | 10,442.39 | 104,899.07 | 10,057.33 |
| Incremental costs ($) | 95,280.39 | – | 93,978.28 | – | 94,841.74 | – |
| Total effectiveness (QALYs) | 1.38 | 1.13 | 1.33 | 1.12 | 1.43 | 1.04 |
| Incremental effectiveness (QALYs) | 0.25 | – | 0.22 | – | 0.39 | – |
| ICER ($/QALY) | 386,715.63 | – | 434,182.32 | – | 240,635.39 | – |

C, chemotherapy; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NC, nivolumab plus chemotherapy; QALYs, quality-adjusted life-years.

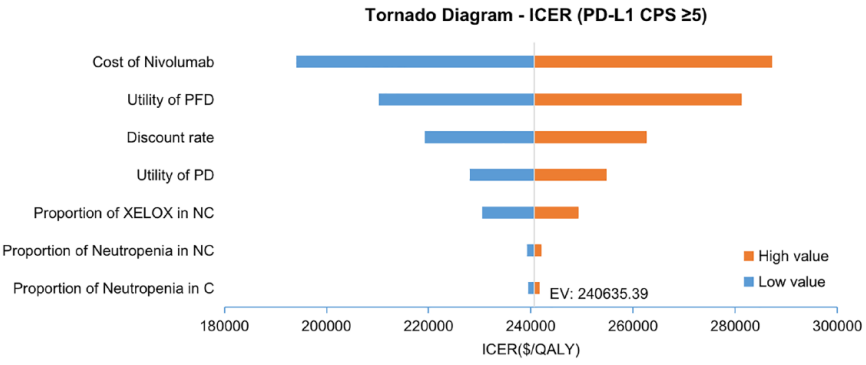


**Figure 2.** One-way sensitivity analysis in patients with PD-L1 CPS ⩾5.
C, chemotherapy; ICER, incremental cost-effectiveness ratio; NC, nivolumab plus chemotherapy; PD, progressed disease; PFD, progression-free disease; QALYs, quality-adjusted life-years; XELOX, capecitabine plus oxaliplatin.

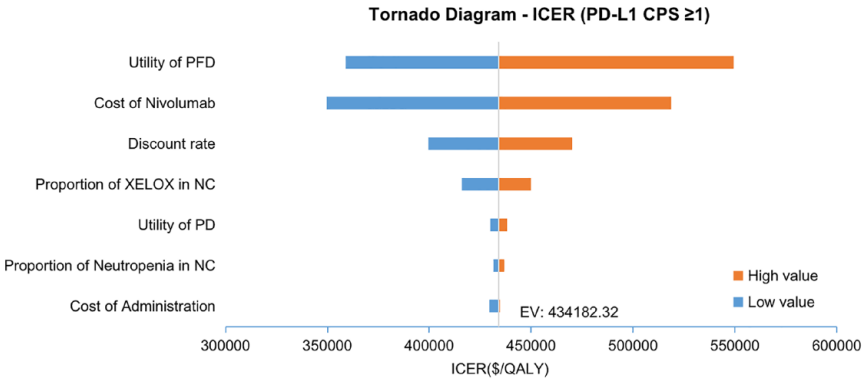


**Figure 3.** One-way sensitivity analysis in patients with PD-L1 CPS ⩾1.
ICER, incremental cost-effectiveness ratio; NC, nivolumab plus chemotherapy; PD, progressed disease; PFD, progression-free disease; QALYs, quality-adjusted life-years; XELOX, capecitabine plus oxaliplatin.

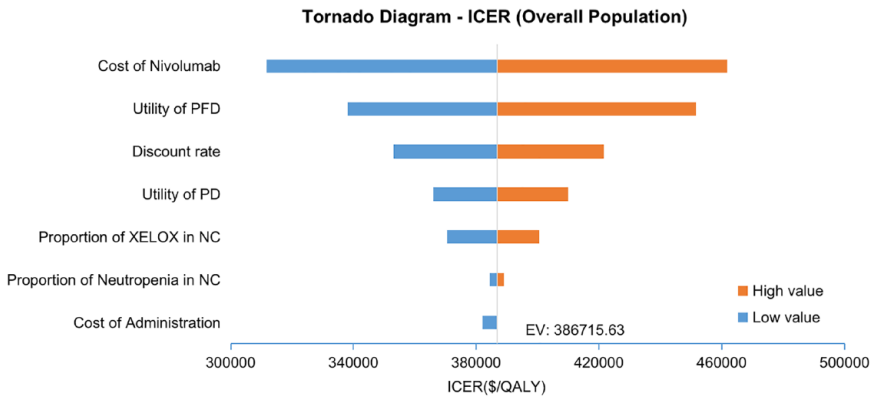


**Figure 4.** One-way sensitivity analysis in the overall population.
ICER, incremental cost-effectiveness ratio; NC, nivolumab plus chemotherapy; PD, progressed disease; PFD, progression-free disease; QALYs, quality-adjusted life-years; XELOX, capecitabine plus oxaliplatin.

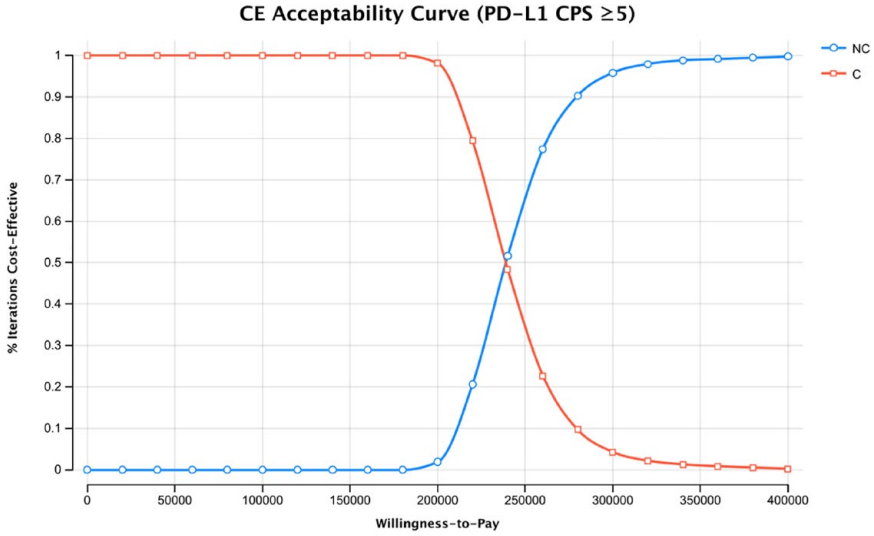


**Figure 5.** The cost-effectiveness acceptability curves of patients with PD-L1 CPS ⩾5.
C, chemotherapy; CE, cost-effective; NC, nivolumab plus chemotherapy.

for NC were significantly higher than the $150,000 WTP threshold in the overall population, the patients with PD-L1 CPS ⩾5, and those with PD-L1 CPS ⩾1. One-way sensitivity analysis showed that the cost of nivolumab, the utility value of PFD, and the utility value of PD significantly impacted the model results but could not reduce ICER below WTP. Probabilistic sensitivity analysis showed that the probability of NC being economical at the US $150,000 WTP threshold was 0. First-line NC for patients with advanced GC/GEJC/EAC does not have a cost-effectiveness advantage compared with chemotherapy.

Our findings are consistent with two recent economic analyses of NC for the treatment of advanced GC/GEJC/EAC.[29,30] Both studies were conducted from the Chinese healthcare system perspective. Jiang *et al.*'s[29] study showed that, compared with chemotherapy alone, ICER produced by NC was $191,266/QALY. Shu *et al.*'s[30] study showed that NC yielded an ICER of $278,658.71/QALY compared to chemotherapy alone. Both ICERs were significantly higher than the WTP threshold in China (triple GDP per capita $37,654/QALY), suggesting that NC is not an economical treatment option for patients

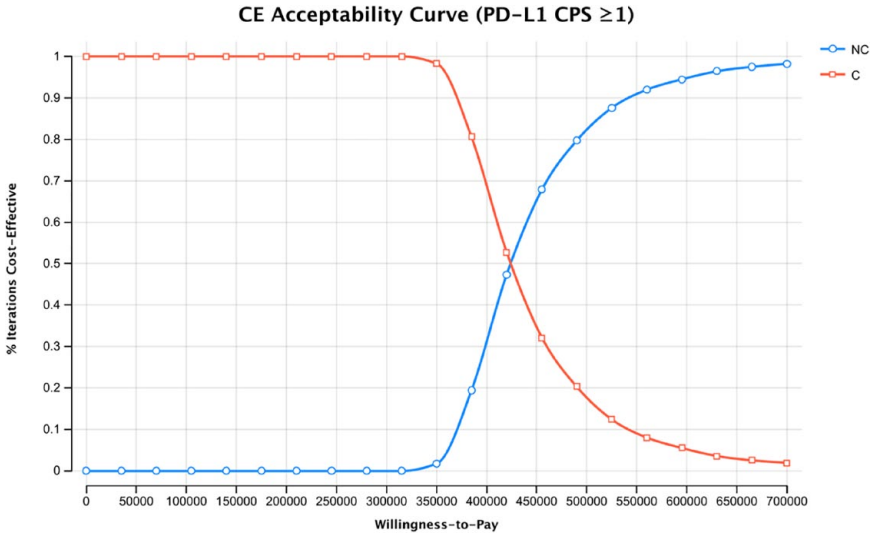


**Figure 6.** The cost-effectiveness acceptability curves of patients with PD-L1 CPS ⩾1.
C, chemotherapy; CE, cost-effective; NC, nivolumab plus chemotherapy.

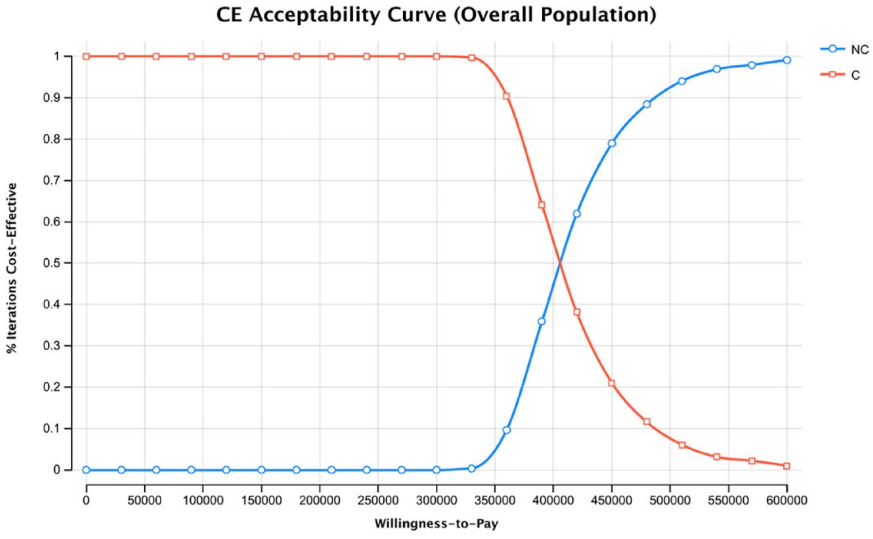


**Figure 7.** The cost-effectiveness acceptability curves for overall population.
C, chemotherapy; CE, cost-effective; NC, nivolumab plus chemotherapy.

with advanced GC/GEJC/EAC compared with chemotherapy alone, which is consistent with our findings. In addition, these studies had some limitations in terms of model and data processing: in Jiang's analysis, the second-line regimen was only paclitaxel monotherapy and did not involve the fitting of the survival model; in Shu's study, the distribution function of survival model were all fitted by Weibull, and the study was only conducted in the patients with PD-L1 CPS ⩾5. Both studies have some limitations.

In addition, patients who discontinue the therapy of NC because of intolerable AEs or for other reasons may continue to show clinical benefit if treatment is continued. There are few studies on immunotherapy combined with chemotherapy as the first-line treatment for advanced GC/GEJC/EAC, and the optimal duration of therapy with nivolumab remains to be investigated.[31]

There are some limitations to our study. First, CheckMate-649 is a multicenter, randomized,

phase III clinical trial comparing NC *versus* chemotherapy alone in advanced GC/GEJC/EAC. This is a large, well-designed clinical trial. But our model depends on the trial's validity and universality, and our study will reflect all deviations in the trial. Second, the utility values were obtained from the published literature in our study. The values of AEs were derived from published studies of small cell lung cancer, and different diseases may affect the results. Third, only AEs ⩾3 were considered in our research, which might have influenced the results. However, the cost of AEs <3 was relatively low, and one-way sensitivity analysis showed that these AEs had little impact on results. Fourth, second-line treatment may use different chemotherapy regimens. We assumed that patients in the PD state would be treated with irinotecan, paclitaxel, or docetaxel according to the NCCN Clinical Practice Guidelines in Oncology and assumed the probability of using all three drugs is equal. However, the situation of patients with advanced GC/GEJC/EAC is more complex and using different treatment regimens may affect the final results.

Although these limitations may limit the applicability of this study, one-way sensitivity analysis showed that the cost of nivolumab, the utility value of PFD and PD, and other parameters were not enough to reduce the ICER value below the threshold, which was consistent with the results of base-case analysis. Therefore, our study can still serve as a valuable reference for doctors and policymakers, reflecting the general clinical treatment of patients with advanced GC/GEJC/EAC.

## Conclusion

From the perspective of a third-party payer in the United States, the ICERs obtained for NC were significantly higher than the $150,000 WTP threshold compared with chemotherapy in the overall population, patients with PD-L1 CPS ⩾5, and patients with PD-L1 CPS ⩾1. At present, first-line NC may not be a cost-effective option for patients with advanced GC/GEJC/EAC.

## Declaration

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contribution(s)*

**Xueqiong Cao:** Software; Writing – original draft.

**Mingming Zhang:** Resources; Writing – original draft.

**Na Li:** Data curation; Resources.

**Bin Zheng:** Writing – review & editing.

**Maobai Liu:** Data curation; Investigation.

**Xiaobing Song:** Formal analysis.

**Hongfu Cai:** Supervision; Visualization.

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### *Competing interests*

The authors declare that there is no conflict of interest.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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## Supplemental material

Supplemental material for this article is available online.

## References

1. Ferlay J, Colombet M, Soerjomataram I, *et al.* Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; 144: 1941–1953.
2. Smyth EC, Nilsson M, Grabsch HI, *et al.* Gastric cancer. *Lancet* 2020; 396: 635–648.
3. Howlader N, Noone AM, Krapcho M, *et al.* SEER cancer statistics review, 1975–2016, https://seer.cancer.gov/archive/csr/1975_2016/ (accessed 7 February, 2022).

4. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66: 7–30.
5. Short MW, Burgers KG and Fry VT. Esophageal cancer. *Am Fam Physician* 2017; 95: 22–28.
6. Zhang HZ, Jin GF and Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer* 2012; 31: 281–286.
7. Janjigian YY, Shitara K, Moehler M, *et al.* First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; 398: 27–40.
8. Ajani JA, D'Amico TA, Bentrem DJ, *et al.* Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022; 20: 167–192.
9. Ajani JA, D'Amico TA, Bentrem DJ, *et al.* Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 855–883.
10. Zavala VA and Kalergis AM. New clinical advances in immunotherapy for the treatment of solid tumours. *Immunology* 2015; 145: 182–201.
11. Tan AC, Bagley SJ, Wen PY, *et al.* Systematic review of combinations of targeted or immunotherapy in advanced solid tumors. *J Immunother Cancer* 2021; 9: e002459.
12. Raut M, Singh G, Hiscock I, *et al.* A systematic literature review of the epidemiology, quality of life, and economic burden, including disease pathways and treatment patterns of relapsed/refractory classical Hodgkin lymphoma. *Expert Rev Hematol* 2022; 15: 607–617.
13. Nesline MK, Knight T, Colman S, *et al.* Economic burden of checkpoint inhibitor immunotherapy for the treatment of non-small cell lung cancer in US clinical practice. *Clin Ther* 2020; 42: 1682–1698.e1687.
14. Husereau D, Drummond M, Augustovski F, *et al.* Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Value Health* 2022; 25: 3–9.
15. Woods BS, Sideris E, Palmer S, *et al.* Partitioned survival and state transition models for healthcare decision making in oncology: where are we now? *Value Health* 2020; 23: 1613–1621.
16. Wan X, Zhang Y, Tan C, *et al.* First-line nivolumab plus ipilimumab vs sunitinib for metastatic renal cell carcinoma: a cost-effectiveness analysis. *JAMA Oncol* 2019; 5: 491–496.
17. Guyot P, Ades AE, Ouwens MJ, *et al.* Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012; 12: 9.
18. Ishak KJ, Kreif N, Benedict A, *et al.* Overview of parametric survival analysis for health-economic applications. *Pharmacoeconomics* 2013; 31: 663–675.
19. Williams C, Lewsey JD, Mackay DF, *et al.* Estimation of survival probabilities for use in cost-effectiveness analyses: a comparison of a multi-state modeling survival analysis approach with partitioned survival and Markov decision-analytic modeling. *Med Decis Making* 2017; 37: 427–439.
20. Arias E and Xu J. United States life tables, 2018. *Natl Vital Stat Rep* 2020; 69: 1–45.
21. Goldstein DA, Chen Q, Ayer T, *et al.* First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis. *J Clin Oncol* 2015; 33: 1112–1118.
22. Centers for Medicare and Medicaid Services. 2022 ASP drug pricing files, https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2022-asp-drug-pricing-files (2022, accessed March 16, 2022).
23. Centers for Disease Control and Prevention. Medicare physician fee schedule, https://www.cms.gov/medicare/medicare-fee-for-service-payment/physicianfeesched?redirect/physicianfeesched (2022, accessed 16 March 2022).
24. Sanders GD, Neumann PJ, Basu A, *et al.* Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA* 2016; 316: 1093–1103.
25. Zhang L, Hang Y, Liu M, *et al.* First-line durvalumab plus platinum-etoposide versus platinum-etoposide for extensive-stage small-cell lung cancer: a cost-effectiveness analysis. *Front Oncol* 2020; 10: 602185.
26. Shiroiwa T, Fukuda T and Shimozuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. *Br J Cancer* 2011; 105: 1273–1278.
27. Briggs AH, Weinstein MC, Fenwick EA, *et al.* Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM

Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making* 2012; 32: 722–732.

28. Neumann PJ, Cohen JT and Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014; 371: 796–797.
29. Jiang Y, Li Y and Wang LXW. Cost-effectiveness analysis of nivolumab plus standard chemotherapy versus chemotherapy alone for the first-line treatment of unresectable advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. *Int J Clin Pharm* 2022; 44: 499–506.
30. Shu Y, Ding Y and Zhang Q. Cost-effectiveness of nivolumab plus chemotherapy vs. chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophagel adenocarcinoma in China. *Front Oncol* 2022; 12: 851522.
31. Emens LA, Ascierto PA, Darcy PK, *et al*. Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape. *Eur J Cancer* 2017; 81: 116–129.