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RESEARCH ARTICLE

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Cost-effectiveness of trastuzumab deruxtecan as a second-line treatment for HER2-mutant advanced non-small cell lung cancer

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ABSTRACT

The study of DESTINY-Lung01 and DESTINY-Lung02 demonstrated the favorable efficacy and optimal dosage of trastuzumab deruxtecan (T-DXd) in managing the human epidermal growth factor receptor 2 (HER2)-mutant non-small cell lung cancer (NSCLC) patients who had received previous treatment. The study sought to assess the cost-effectiveness of T-DXd in both the United States (US) and Chinese healthcare systems. Markov models were developed to evaluate the overall cost, incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALYs), and life years (LYs) of treatment with T-DXd compared with docetaxel, nivolumab, and pyrotinib for patients in the US and China. The level of willingness-to-pay (WTP) in the US and China is 150,000/QALYs and 32,517/QALYs, respectively. Sensitivity analyses were carried out to ensure the precision of the model. T-DXd yielded additional QALYs of 0.63 and 0.06 with an ICER of $338997.84 and $1437258.33 per QALY, respectively, in the US compared to the docetaxel and nivolumab regimens. And T-DXd yielded additional QALYs of 0.63, 0.06, and 0.13 with an ICER of $137959.45, $623805.93, and $515447.12 per QALY, respectively, in China compared to the docetaxel, nivolumab, and pyrotinib regimens. Sensitivity analysis showed that the cost of drugs is the most influential factor. T-DXd provides substantial therapeutic benefit for NSCLC patients with HER2 mutations who have had previous treatment but is not deemed cost-effective in either the US or China when compared to docetaxel, nivolumab, and pyrotinib. Price reduction is perhaps the main way to make T-DXd cost-effective.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) constitutes 85% of all instances of malignant lung tumors.[1] The prognosis for individuals diagnosed with metastatic NSCLC is notably grim, with just 9% of patients managing to survive beyond five years.[2] With the advent of molecular-driven therapy, clinicians are now focusing more on genetic mutations in tumors as part of anti-tumor treatment. Human epidermal growth factor receptor 2 (HER2) mutations are responsible for around 2% – 4% of NSCLC cases, particularly among women, nonsmokers, and younger patients.[3,4] HER2 mutations have a high degree of exclusivity with other oncogenic driver mutations, and the effectiveness of conventional treatment is limited.

Antibody-drug conjugate (ADC), as representative drugs of precision medicine, can specifically target tumor cells and induce cell death, thereby enhancing the delivery of pharmaceuticals to specific tumor cells and reducing off-target events.[5] Trastuzumab deruxtecan (T-DXd), an emerging star in the field of ADCs, has consistently garnered significant acclaim. Based on the findings of the DESTINY-Lung01 trial, T-DXd consistently showed a powerful and enduring ability to suppress tumor growth in patients with HER2 mutant NSCLC that has spread to other parts of the body.[6] According to the findings of the DESTINY-Lung 02 trial, a dosage of 5.4 mg/kg may have a more favorable benefit.[7] The Food and Drug Administration (FDA) granted accelerated clearance to T-DXd in August 2022. This approval is specifically for the adults with metastatic NSCLC with HER2 mutations who have previously been treated systematically. The National Comprehensive Cancer Network (NCCN) guidelines also recommended T-DXd as a follow-up treatment option for patients with metastatic NSCLC with HER2 mutations. Before the approval of T-DXd, the recommended second-line therapy for HER2-mutated NSCLC is the same as that for NSCLC without driver mutations. Docetaxel and nivolumab are the predominant pharmaceuticals in clinical practice based on the clinical trial findings from CheckMate 057.[8] Zhou et al. recent study has verified the favorable efficiency and satisfactory safety of pyrotinib in treating HER2-mutant NSCLC patients who previously received first-line chemotherapy,[9] therefore, the Chinese Society of Clinical Oncology (CSCO) guidelines have endorsed T-DXd and pyrotinib as a recommended option for the treatment of HER2-mutated NSCLC in the second-line setting.

Although T-DXd has achieved satisfactory outcomes in advanced NSCLC with HER2 mutations that have received previous treatment, final clearance of clinical applications

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further examination of treatment costs to accommodate a greater number of eligible patients. Hence, it is imperative to thoroughly balance the cost and efficacy of this innovative therapy. The objective of the study is to assess the cost-effectiveness of T-DXd compared with docetaxel, nivolumab, and pyrotinib for previously treated advanced HER2-mutated NSCLC patients in Asian and American countries, represented by China and the US. It can serve as a valuable resource for making decisions regarding national health insurance and promoting the appropriate use of the drug in clinical settings. This study strictly followed the Comprehensive Health Economic Assessment Reporting Standards (CHEERS) checklist (Supplementary Material 1).[10]

Materials and methods

Patients and treatment

The target patients and intervention measures were obtained from DESTINY-Lung 02, CheckMate 057, NCT02834936 clinical trials.[7–9] Although the study participants were derived from various randomized clinical studies, the inclusion criteria and clinical characteristics of these patients are similar (Table 1). Furthermore, we employed a matched-adjusted indirect comparison (MAIC) method, which aligns the baseline characteristics of different trials through weighted adjustments of the trial data, enabling effective indirect comparisons.[11] Although lacking of formal approval for the treatment of HER2-mutated NSCLC in China, CSCO guidelines have recommended T-DXd and pyrotinib as second-line agents for the treatment of HER2-mutated NSCLC. Based on clinical trials, we evaluated four different treatment strategies: T-DXd monotherapy, docetaxel monotherapy, nivolumab monotherapy, and pyrotinib monotherapy. Eighty-eight patients with HER2 mutations received treatment with T-DXd (5.4 mg/kg every 3 weeks).[7] A total of 287 and 268 advanced NSCLC patients previously treated with chemotherapy were included in the analysis, receiving treatment with nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m2 every 3 weeks), respectively.[8] Sixty patients with HER2 mutations received treatment with pyrotinib (400 mg of pyrotinib orally within 30 minutes after breakfast, with a 21 day cycle).[9] Treatment continues until the disease progresses or unacceptable toxicity occurs, followed by best supportive care (BSC). All patients undergo imaging examinations every six weeks to detect the progression of disease (PD). We included patients from the US and China with an average body surface area of 1.82 and 1.72 m2, respectively.[12,13]

Table 1. Patients baseline characteristics of T-DXd, docetaxel, nivolumab, and pyrotinib trials. T-DXd: trastuzumab deruxtecan.

Characteristic	T-DXd	Docetaxel	Nivolumab	Pyrotinib
Age, median (range), years	60 (29–88)	64 (21–85)	61 (37–85)	57 (40–72)
Sex				
Male	44.0%	62.1%	61.4%	45.0%
Female	66.0%	37.9%	38.6%	55.0%
ECOG performance status score				
0	25.3%	30.9%	26.0%	11.7%
1	74.7%	69.1%	74.0%	88.3%
Region				
Asian	25.3%	2.8%	3.1%	100.0%
Non-Asian	74.7%	97.2%	96.9%	0.0%
Smoking Status				
Former	2.2%	12.4%	12.0%	26.7%
Current	40.7%	71.3%	71.3%	1.6%
Never	57.1%	16.3%	16.6%	71.7%
EGFR mutation Status				
Positive	–	10.1%	14.1%	1.7%
Negative	–	43.4%	58.4%	90.0%
Unknown	–	46.5%	27.5%	8.3%
Previously treatment				
Prior chemotherapy	94.5%	90.1%	91.8%	100.0%
Prior targeted therapy	7.3%	9.9%	8.2%	25.0%
Prior radiotherapy	0.0%	0.0%	0.0%	26.6%
Prior immunotherapy	33.9%	0.0%	0.0%	0.0%

Model construction

TreeAge Pro 2022 software (TreeAge, Williamstown, MA) was used to establish comprehensive Markov models to simulate disease progression in HER2-mutant NSCLC patients receiving different second-line treatments (docetaxel, nivolumab, pyrotinib, and T-DXd). The model assumes three health states: PFS, PD, and death. During the PFS state, all patients received treatment until disease progression, unacceptable adverse events (AEs), or death occurred. In the PD state, due to the lack of effective treatment options, all patients were assumed to receive best supportive care (BSC) until death. Patients transitioned between these health states, with transitions from the progression-free state to the progressive disease state estimated based on PFS survival data and transitions from the progressive disease state to death estimated using overall survival (OS) data. The analysis period was set to 5 years to capture long-term disease management and survival outcomes, with a 3-week cycle length. Transition probabilities between health states were calculated every two cycles. Total costs included medication costs per cycle, costs of managing treatment-related adverse events, laboratory test costs, imaging costs every two cycles, follow-up and management expenses, and costs of best supportive care during the PD state. This study focused on the overall cost, life years (LYs), quality-adjusted life years (QALYs), and incremental cost effectiveness ratio (ICER). The cost-effectiveness of treatment was assessed by using a willingness-to-pay (WTP) threshold of $150,000/QALY in the US[14] and $32,517/QALY (three times GDP per capita) in China.[15] 3% annual discount rate was utilized for the purposes of calculating cost and utility.[16]

Model survival and transition probabilities

The survival curves for PFS and overall survival (OS) were obtained from the DESTINY-Lung02, CheckMate 057, and NCT02834936 trials to evaluate the risk of disease progression associated with each treatment option. Given that NCT02834936 did not report the PFS curve, we utilized the OS curve as an approximate substitute for the PFS curve. Given the short follow-up interval of clinical trials, it is typically required to adjust the parameter distribution of the survival curve to obtain data on the long-term survival of patients beyond the trial's follow-up period. We utilized the GetData

Graph Digitizer software (version 2.22) to extract eight PFS and OS Kaplan-Meier curves to calibrate the parametric survival model, with survival analysis functions including Exponential, Weibull, Gamma, Log-logistic, Gompertz, and Log-normal. The distribution models that best fit the KM curves were determined based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC). (Supplementary materials 2, Table S1, Figure S2)

Cost and utility

In our study, drugs, treatment for serious AEs, managing the disease, regular monitoring and follow-up, and BSC were included to calculate the costs (Supplementary Material 2, Table S2). Drug costs for T-DXd, docetaxel, and nivolumab are from the pharmaceuticals public database for August 2024.[17,18] Due to the lack of officially availability of pyrotinib, we evaluated the cost-effectiveness of T-DXd compared with docetaxel, and nivolumab in the US. The pricing information of T-DXd, docetaxel, nivolumab and pyrotinib in China was sourced from the pharmaceutical official website (https://www.yaozh.com/).[19] Considering the differences in drug prices across various provinces in China, we incorporate the median price into the model for analysis. The costs of other expenses were derived from published studies and have been adjusted to present values based on the discount rate. All expenses are denominated in dollars ($) at an exchange rate of US $1 = 7.28 RMB. We only focused on grade ≥ 3 AEs with in the model. The expenses associated with treatment for serious AEs, managing the disease, monitoring and follow-up, and BSC is based on recent relevant studies.[16,20–27] The dosage of the drugs was calculated based on the assumed weight and surface area of the patient in the US (74 kg and 1.82 m2)[12] and in China (65 kg and 1.72 m2).[13]

In our analysis, we utilized health utility values ranging from 0 (death) to 1 (perfect health) to encompass various health conditions, including PFS, PD, and death status. Due to the absence of reported health utility in the conducted clinical studies, the utility values for various states of NSCLC treatment were obtained by reference to the study conducted by Christos et al,[28] a prospective cross-sectional patient survey set in a real-world context. The characteristics of the population included in the study – such as demographic distribution, age, disease stage, disease status, and comorbidities – closely align with those of the target population. Average health utility was adjusted for the disutility values associated with AEs, as obtained from the published literature.[29–32]

Sensitivity analysis

One-way sensitivity analyses were performed to assess the accuracy of the model and the impact of variable uncertainty on the results.[33] The parameters that affect the results are shown by Tornado diagrams. Subsequently, we performed a probabilistic sensitivity analysis (PSA) by employing 1,000 Monte Carlo simulations to assess the likelihood of cost-effectiveness, as suggested in Hatswell et al. study.[34] The study was based on WTP values from different countries,[35] and the results were presented through acceptability curves and scatter plots.

Scenario analysis

The model additionally incorporates scenario analysis to assess the cost-effectiveness of T-DXd at different prices in both the US and China. This is achieved by varying the price of T-DXd and obtaining the probabilities of cost-effectiveness under different scenarios through PSA. The scatter plots and cost-effectiveness acceptability curves of T-DXd when it is cost-effective in Figure S3 (Supplementary Material 2).

Results

Base-case results

In the US, the total cost for the T-DXd, docetaxel, and nivolumab regimen is $261027.50, $44068.88, and $160419.42, respectively. T-DXd is associated with a 0.63 QALY increase with incremental costs of $216958.62 and a 0.06 QALY increase with incremental costs of $86235.49, yielding an ICER of $338997.84 and $1437258.33 per QALY compared to docetaxel and nivolumab, respectively. Based on the aforementioned findings, it is evident that T-DXd is deemed cost-effective since the ICER per QALY of T-DXd is lower than the $150,000 WTP criteria when compared with nivolumab, while T-DXd is considered not cost-effective for the ICER per QALY of T-DXd exceeds the threshold when compared with docetaxel. In China, the total cost for the T-DXd, docetaxel, nivolumab and pyrotinib regimen is $103049.40, $14755.35, $65621.04 and $36041.27, respectively. T-DXd is associated with a 0.63 QALY increase with incremental costs of $88294.05, a 0.06 QALY increase with incremental costs of $37428.36, and a 0.13 QALY increase with incremental costs of $67008.13, yielding an ICER of $137959.45, $623805.93, and $515447.12 per QALY compared to docetaxel, nivolumab and pyrotinib, respectively. The incremental changes of T-DXd surpass the threshold of $32,517, indicating that T-DXd is not considered cost-effective in China. (Table 2)

Sensitivity analysis

Based on the Tornado diagrams (insert Figure 1a,b and insert Figure 2a,b,c), we find that the model parameters that have the greatest impact on the results in both the US and China are the cost of drugs and the utility of progression-free survival (PFS). In addition, the utility of PD and the cost of managing AEs also have considerable influence on the model. Administrative expenses, imaging and laboratory costs had less impact on results. In reality, variables are not mutually independent; under certain circumstances, a change in one variable may alter the impact of another variable on the outcome. For instance, severe adverse events may reduce the utility value during the PFS period, thereby affecting the cost-effectiveness of the treatment. At the same time, additional medical expenses can increase the overall cost of the treatment regimen, and vice versa.

The probabilistic sensitivity analyses (PSA), presented as scatter plots and cost-effectiveness acceptability curves (insert Figure 3a,b and insert Figure 4a,b), to show that for the entire patients, T-DXd was more effective but more expensive compared to either docetaxel or nivolumab. Based on the WTP standards of $150,000 in the US and $32,517 in China, the cost-effectiveness

Table 2. Results of the base-case. T-DXd: trastuzumab deruxtecan; LY: life year; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

	Outcomes of Survival Models				Incremental Changes		
Treatment	T-DXd	Docetaxel	Nivolumab	Pyrotinib	T-DXd vs Docetaxel	T-DXd vs Nivolumab	T-DXd vs Pyrotinib
US							
Cost	261027.50	44068.88	160419.42	–	216958.62	86235.49	–
LY	1.56	0.72	1.48	–	0.84	0.08	–
QALY	1.16	0.53	1.10	–	0.63	0.06	–
ICER					338997.84	1437258.33	–
China							
Cost	103049.40	14755.35	65621.04	36041.27	88294.05	37428.36	67008.13
LY	1.56	0.72	1.48	1.39	0.84	0.08	0.17
QALY	1.16	0.53	1.10	1.03	0.63	0.06	0.13
ICER					137959.45	623805.93	515447.12

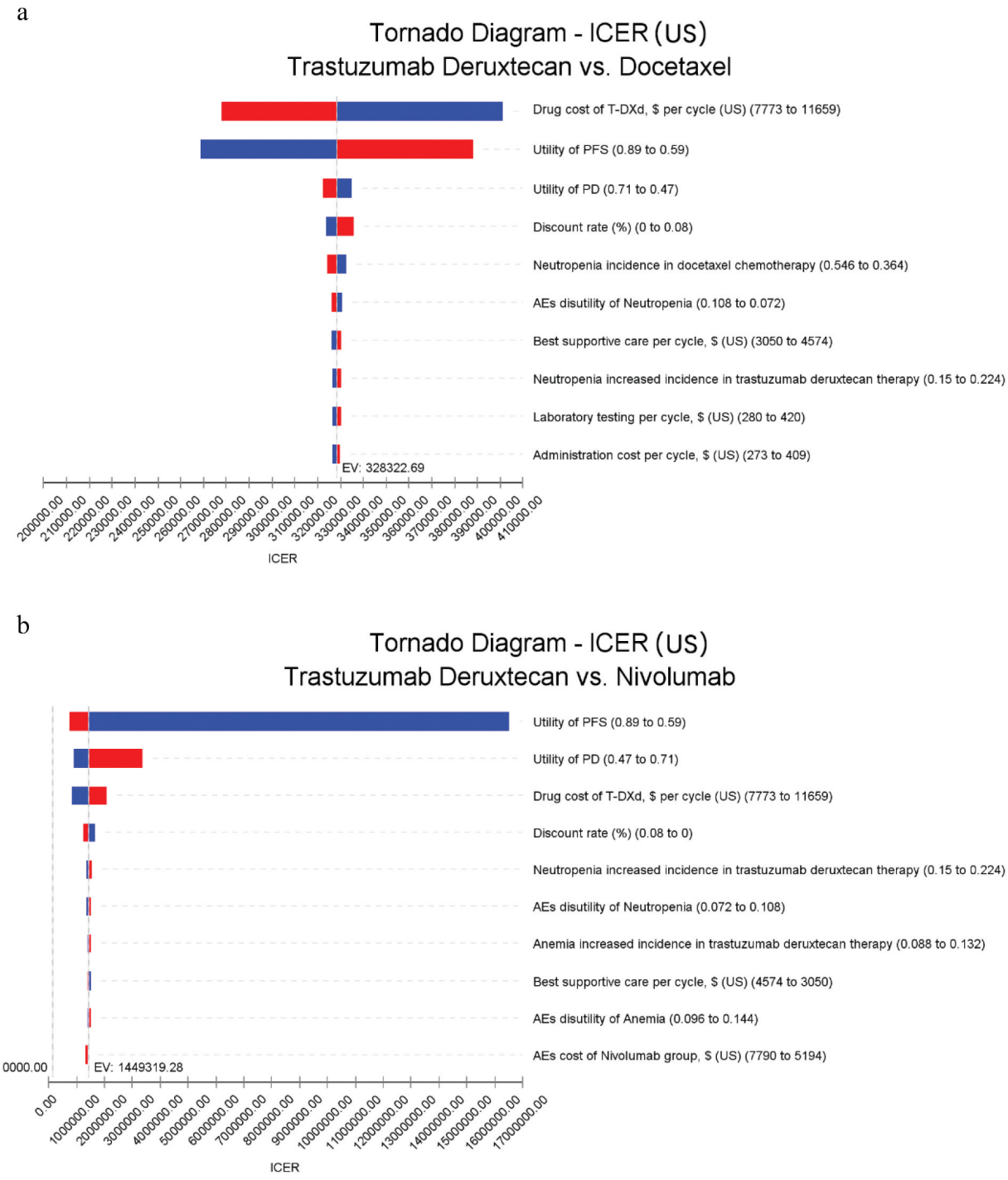

Figure 1. Tornado diagrams for one-way sensitivity analyses of compared to docetaxel and nivolumab in the US. (a) T-DXd versus docetaxel. (b) T-DXd versus nivolumab.

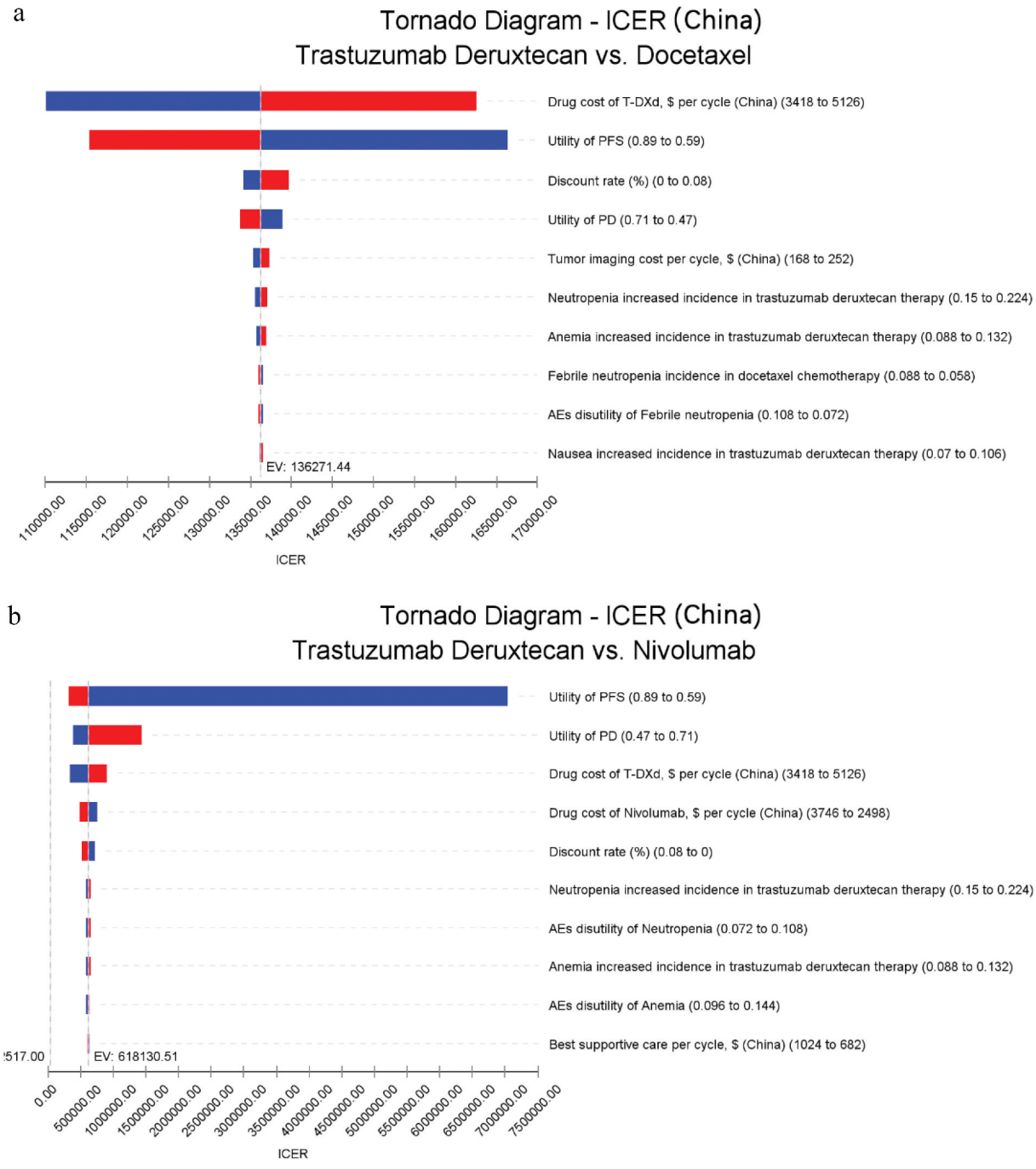

Figure 2. Tornado diagrams for one-way sensitivity analyses of T-DXd compared to docetaxel nivolumab, and pyrotinib in China. (a) T-DXd versus docetaxel. (b) T-DXd versus nivolumab. (c) T-DXd versus pyrotinib.

probability of T-DXd is 0, indicating that it is not cost-effective. This finding is consistent across all PSA results.

Scenario analysis

Considering T-DXd remarkable efficacy but lack of cost-effectiveness, we performed a scenario simulation analysis. The price scenario shows that T-DXd can be considered cost-effective in the US when the cost is reduced by approximately 60%, with a cost-effectiveness probability of 51.7%. In China, cost-effectiveness can be achieved when the cost is reduced by about 80%, and the cost-effectiveness probability is 60.3% (Table 3).

Discussion

Due to the widespread adoption of genetic testing techniques, HER2 has been identified as a carcinogenic alteration associated with lung cancer, accounting for approximately 2–4% of NSCLC.[3,4] The therapeutic effects for HER2-mutated metastatic NSCLC have been frustrating. In breast cancer or gastric

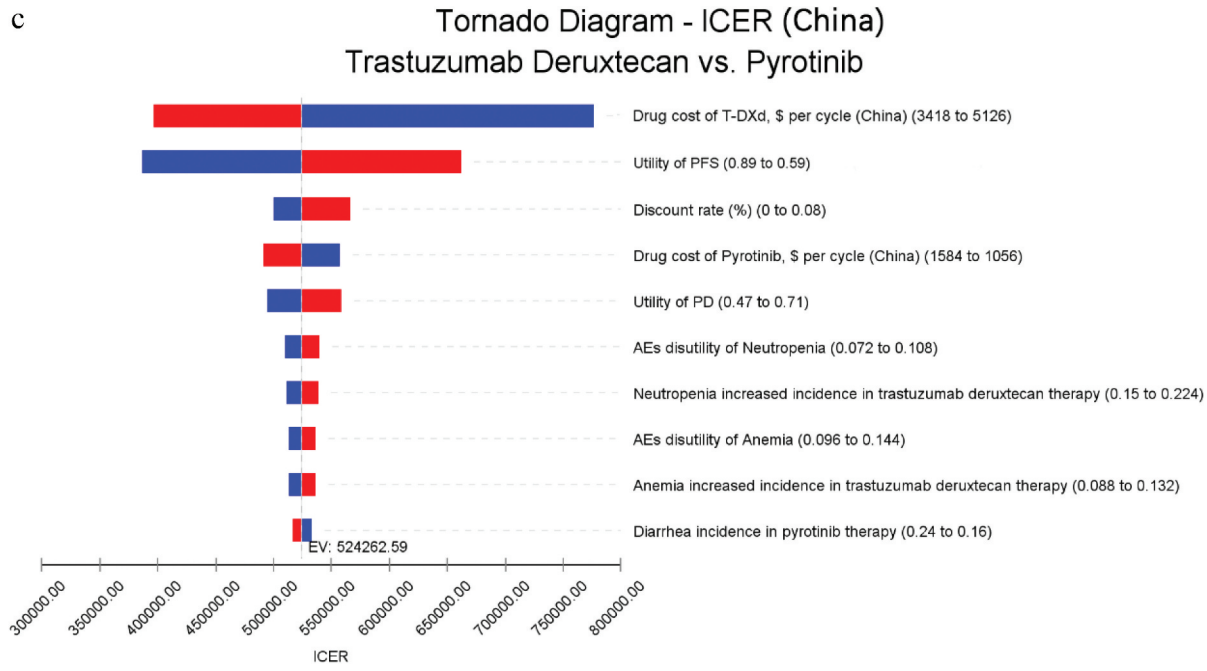

Figure 2. (Continued).

cancer, HER2 overexpression serves as a crucial therapeutic target, with the use of trastuzumab significantly improving patient outcomes and survival rates. In NSCLC, the activation of the HER2 pathway typically occurs through genetic mutations, such as insertions or point mutations, particularly in the kinase domain of HER2. These mutations are closely associated with tumor malignancy, prognosis, and response to treatment.[36,37] Compared with HER2-altered breast cancer and gastric cancer, HER2 mutant NSCLC cannot benefit from classical anti-HER2 drugs such as trastuzumab or trastuzumab emtansine (TDM1). Patients with HER2 mutations often experience chemotherapy resistance and poor response to conventional therapies. Currently, the guidelines for treating HER2-mutated NSCLC align with those for NSCLC without driver gene alterations. T-DXd is the first and only approved treatment option for HER2 mutated metastatic NSCLC patients after standard treatment failure, significantly prolonging their survival.[38] Therefore, the study of HER2 mutations in NSCLC represents a major breakthrough in the field of targeted therapy for NSCLC. Nevertheless, the innovative anti-cancer agents come with a high price tag, imposing a financial strain on both individuals and national healthcare systems. Consequently, to maximize the utilization of scarce resources, conducting economic evaluations of novel therapies and expensive drugs is urgent.

This study carried out a cost-effectiveness analysis of T-DXd for patients with NSCLC harboring HER2 mutations compared with the chemotherapy drug docetaxel, programmed cell death protein 1 (PD-1) inhibitor nivolumab and pan-HER receptor tyrosine kinase inhibitor pyrotinib in the healthcare systems of the US and China. Although the anti-tumor mechanisms of these four drugs are different, the monotherapy regimen of these drugs is currently recommended in the guidelines as an alternative for treating advanced HER-2 mutant NSCLC, so it is reasonable to evaluate the cost-effectiveness of these four drugs. In the US, the ICER of T-DXd is $338997.84 compared to docetaxel and the ICER is $1437258.33 compared to nivolumab in the base-case analysis. This ICER surpasses the value of WTP and hence, T-DXd is judged economically ineffective. National Medical Products Administration (NMPA) granted approval for the inclusion of T-DXd in China in February 2023. The ICER of T-DXd, when compared to docetaxel, nivolumab, and pyrotinib, is $137959.45, $623805.93, and $515447.12, respectively. All of them are beyond the WTP values of $32,517, indicating that T-DXd at the current price is not cost-effective in China.

So far, there has been no comprehensive cost-effectiveness study on T-DXd for advanced NSCLC with HER2 mutations. At present, all economic benefit analyses conducted on T-DXd focused exclusively on breast cancer but there exist divergent perspectives regarding this issue. Shi et al research evaluated the economic benefits of T-DXd and trastuzumab for breast cancer with among American payers, and concluded that T-DXd is an economical alternative to chemotherapy.[39] Jeroen et al research also suggested that T-DXd was cost-effective in Finnish breast cancer patients harboring HER2-mutation.[40] However, according to Zhan et al analysis, T-DXd is considered to have no cost-effectiveness in China.[23] Our findings indicate that T-DXd is not a cost-effective option when compared to the currently recommended second-line treatments for HER2-mutated NSCLC, docetaxel and nivolumab, in either the US or China. This contrasts with the most results observed in the management of HER2-mutated breast cancer. Due to the moderate efficacy of TDM1 in treating HER2-mutated NSCLC, we did not include TDM1 in the study for analysis. Based on the results, T-DXd proved to be the most effective among these drugs, achieving twice as many QALYs as docetaxel. Although it is expensive, it does not mean that we are constrained by its price and give up its additional benefits. The economic foundation of patients greatly affects the formulation of treatment plans. As we analyzed the average

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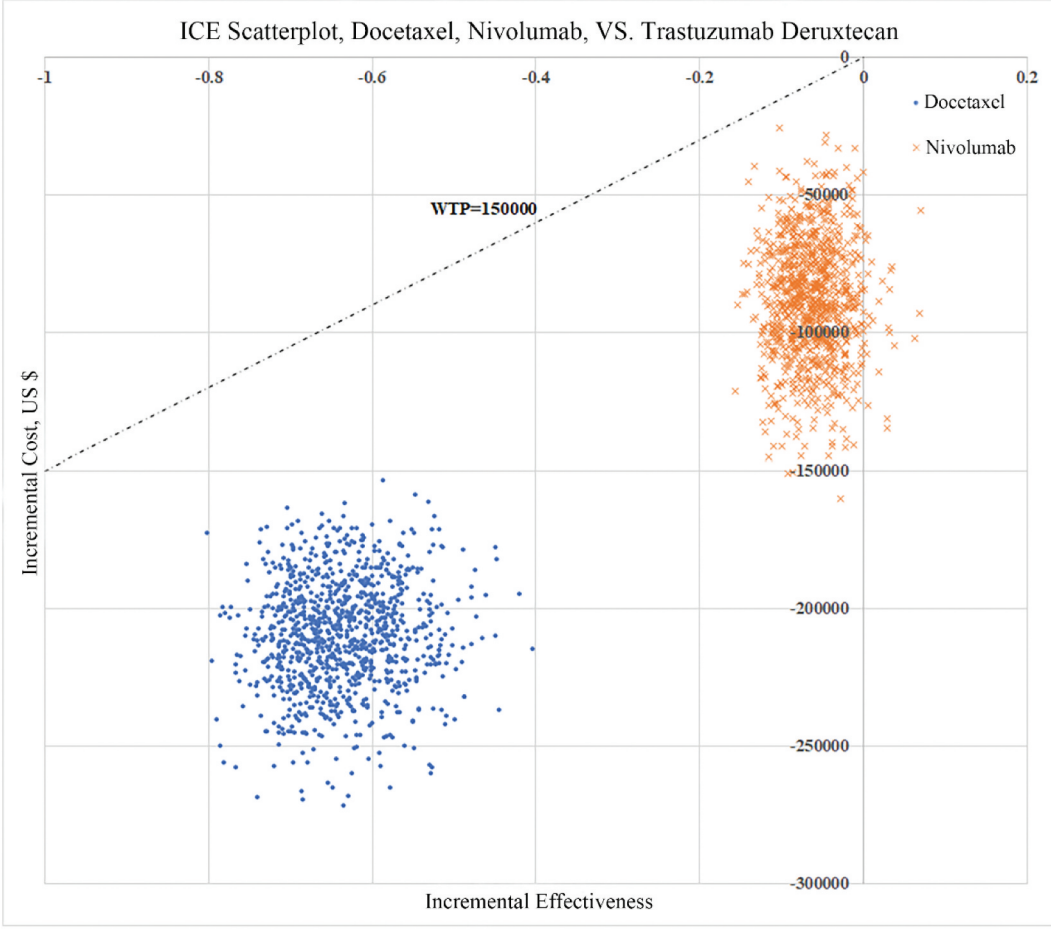

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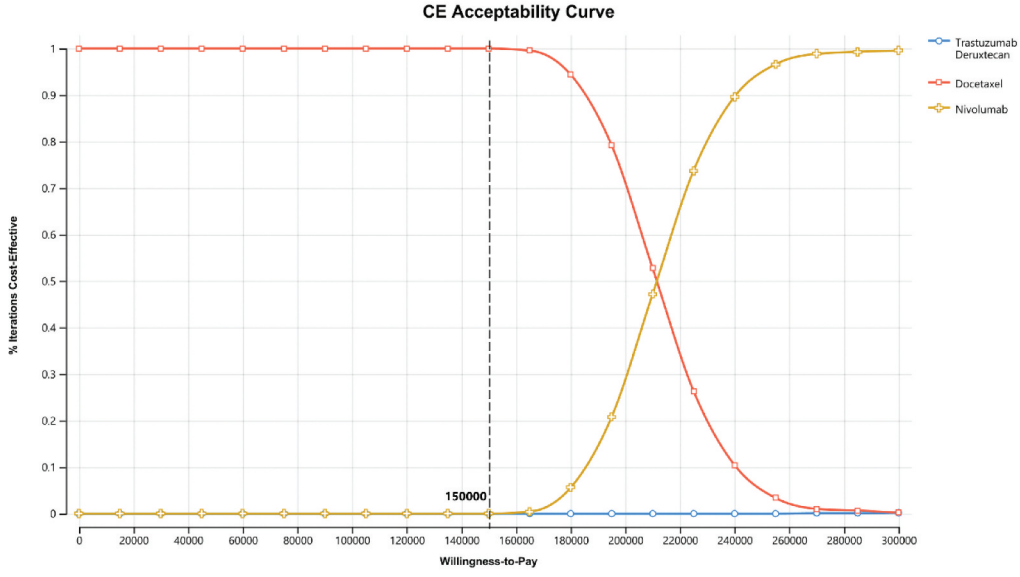

Figure 3. Probabilistic sensitivity analyses (PSA) of T-DXd, docetaxel, and nivolumab in the US. (a) Scatter plot for PSA. (b) The cost-effectiveness acceptability curve for PSA.

WTP of payers in the United States and China, which applies to most patients but not to every patient, decision-making should be individualized.

The commonly used models in pharmacoeconomic analyses are the Markov model and the partitioned survival model (PSM). The Markov model is well-suited for simulating

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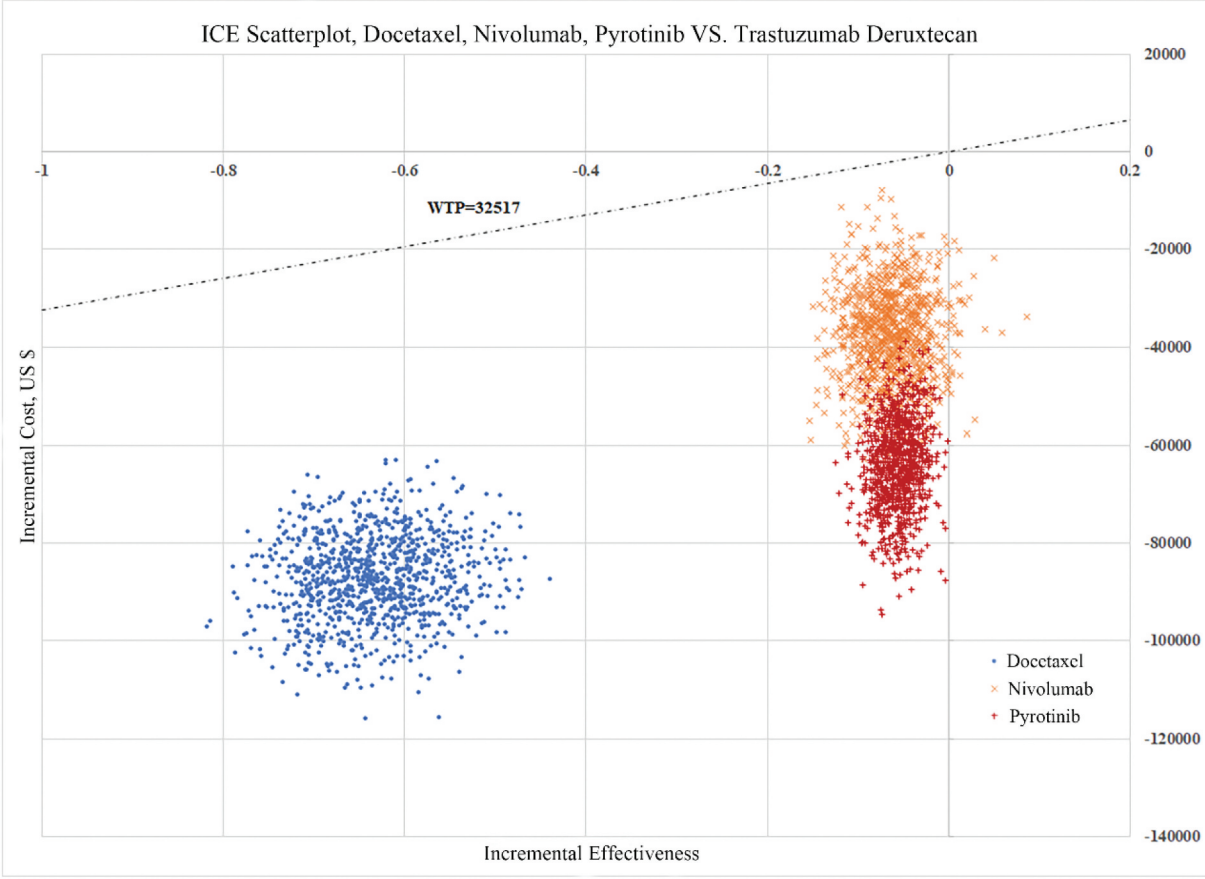

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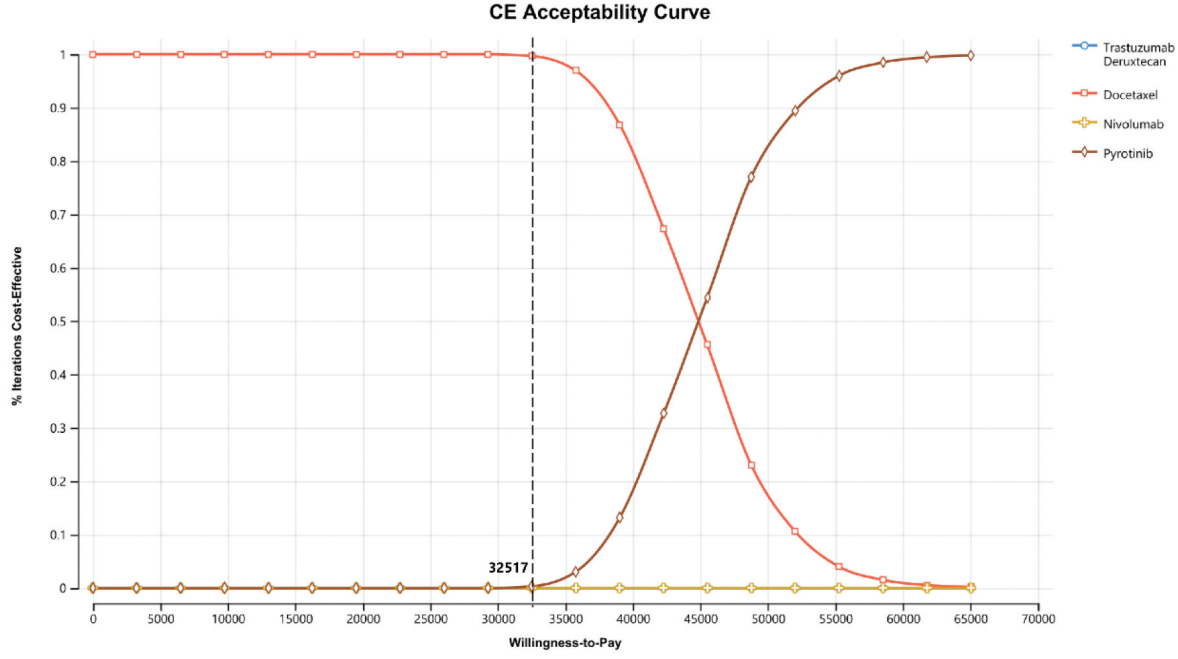

Figure 4. Probabilistic sensitivity analyses (PSA) of T-DXd, docetaxel, nivolumab, and pyrotinib in China. (a) Scatter plot for PSA. (b) The cost-effectiveness acceptability curve for PSA.

disease progression and handling transitions between multiple health states, making it particularly applicable for evaluating chronic diseases or long-term treatment strategies.[41] It is especially effective for assessing long-term outcomes. However, the limitation of the Markov model lies in its reliance on state transition probabilities, which are often

Table 3. Results of scenario analysis. ICER: incremental cost-effectiveness ratio.

Scenario	Cost	Incremental Cost	ICER	Probability of being cost-effective
US				
Base case	261027.50	216958.62	338997.84	0%
80% price of T-DXd	221560.42	177491.56	275831.30	0%
60% price of T-DXd	182093.38	138024.52	214497.45	0.1%
40% price of T-DXd	142626.33	98557.43	153163.49	51.7%
20% price of T-DXd	103159.29	59090.35	91829.56	99.9%
China				
Base case	103049.40	88294.05	137959.45	0%
80% price of T-DXd	86070.49	70476.17	110671.07	0%
60% price of T-DXd	69091.58	53652.96	84252.94	0%
40% price of T-DXd	52112.66	36829.75	57834.92	0.2%
20% price of T-DXd	33133.75	20006.54	31016.90	60.3%

estimated based on assumptions derived from extensive clinical data. This may overlook certain complexities of real-world clinical scenarios, and insufficient data may affect the model's accuracy. In contrast, the PSM focuses on simulating patient survival under different treatment strategies, estimating treatment effects across different time intervals through partitioned survival curves. The advantage of the PSM is that it directly derives treatment effects from survival analyses without requiring assumptions about transition probabilities, providing a more intuitive reflection of the impact of treatment on survival. For diseases where survival is the primary focus, the PSM is highly effective. However, the PSM cannot simulate transitions between multiple health states, making it less suitable for diseases with multi-stage progression, such as cancer.[42] Considering the above, we opted to establish a Markov model to simulate the disease progression of HER2-mutant NSCLC patients receiving different second-line treatments.

In our model, the primary determinant is the expense associated with pharmaceuticals. According to the PSA results of basic case analysis, the probability of T-DXd being cost-effective is 0, regardless of whether in the US or China. In the course of scenario simulation analysis, it was determined that T-DXd was cost-effective when it reduced prices by about 60% and 80% in the US and China, with cost effectiveness probabilities of 51.7% and 60.3%. Of course, the cost-effectiveness of T-DXd can be achieved can be attained by means other than price reduction. For example, shortening the treatment duration while ensuring disease stability can significantly reduce medication costs and minimize adverse events, thereby lowering management expenses. Alternatively, reducing the frequency of outpatient follow-ups can be achieved through online consultations and remote monitoring for health management, thereby cutting outpatient costs. Additionally, employing adjunctive therapies, such as supportive medications like antiemetics and immunosuppressants, can mitigate treatment-related adverse effects and reduce hospitalization expenses associated with such events. Dusetzina et al study suggested that, even after accounting for inflation, the average expense of cancer treatment will experience a substantial rise.[43] Selecting cost-effective medications has become a challenging decision due to the considerably higher prices of new treatments compared to those already available. However, the key approach to resolving the issue is to achieve equilibrium in medicine pricing. At present, the Phase III DESTINY-Lung04 trial of T-DXd as a first-line agent comparing PD-1 inhibitor with chemotherapy is underway, and is expected to become a milestone medication for HER2-mutated NSCLC. Therefore, it is of great significance for the approval of T-DXd for HER2-mutated NSCLC in China and its early inclusion in medical insurance. Utility is considered another important determinant in our model. To mitigate the potential influence of utility values, we undertook an extensive examination of previous studies to broaden the scope of utility values included in the sensitivity analysis. Our investigation indicates that utility values have minimal influence on the results.

Therefore, to ensure the sustainability of the healthcare system, there is an urgent need for policymakers to address cost-related challenges, and there is an urgent need for health care providers to find the balance of effects and benefits of drugs. Our model findings indicate that an increase in PFS and OS is associated with elevated treatment expenses. The exorbitant cost of anti-cancer drugs is a pressing issue in both affluent and moderately prosperous nations. Recently, financial toxicity has gained recognition within the scientific community. It may cause patients to be unable to bear the financial burden and lead to poor prognosis and even discontinuation of treatment. Ensuring patient access to innovative drugs is just as important as minimizing economic toxicity.[44] Hence, to maintain the sustainability of the healthcare system, authorities must promptly tackle cost-related challenges, while healthcare providers must diligently assess the effects and benefits of drugs.

Pharmacoeconomic analysis provides scientific and quantitative data to support drug pricing and reimbursement negotiations, enabling stakeholders to make cost-effective decisions.[45] In drug pricing negotiations, these analyses can demonstrate the reasonableness of drug prices, support rational reimbursement decisions, optimize resource allocation, promote broad coverage of drug indications, and ultimately ensure that patients have access to effective and cost-efficient treatment options. In terms of price negotiations, governments or healthcare insurance agencies may require pharmaceutical companies to reassess their pricing strategies and offer price discounts or other concessions to improve the cost-effectiveness of the drug and enhance its competitiveness. Regarding reimbursement inclusion, scenario analysis suggests that a price reduction could make T-DXd cost-effective, which may facilitate its inclusion in insurance reimbursement plans. As for clinical practice guidelines, unless the drug price is set within an appropriate range, T-DXd may only be recommended for specific patient populations rather than being adopted as a broadly applicable treatment option.

It is important to acknowledge the strengths of this study. This study represents the first attempt to thoroughly assess the cost-effectiveness of T-DXd for advanced NSCLC patients harboring HER2 mutations that have been previously treated.

Second, we expand the applicability of the study by analyzing from the perspective of payers in Asia and America represented by China and the US respectively. Admittedly, there are some limitations to our study. Firstly, including different clinical trials in the study may introduce bias. Although the baseline demographic characteristics of patients in the included trials were similar and weighted adjustments were performed using the MAIC method, differences in disease progression rates and treatment responses may lead to variations in survival curves. Moreover, the limited sample size, differences between experimental settings and real-world clinical practice, and other factors may influence the survival curves and, consequently, the utility values and costs, thereby limiting the generalizability of the data. Secondly, Markov models typically rely on a series of assumptions, which may not fully align with real-world scenarios, potentially affecting the accuracy and robustness of the results. Thirdly, the utility values for PFS and PD were not derived from the exact patient cohort included in the study. Lastly, substantial differences in healthcare resources, treatment costs, patient behavior, and health insurance systems across countries or regions may impact the applicability of pharmacoeconomic findings. Therefore, it is essential to exercise caution when interpreting the results of this study.

Conclusions

T-DXd is currently the most effective drug for the treatment of HER2-mutant NSCLC, but at the current price, it is not cost-effective compared to docetaxel, nivolumab and pyrotinib, either in the US or China. Hence, it is vital to carefully evaluate the therapeutic efficacy of T-DXd in relation to its economic cost prior to making a decision to utilize it.

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Availability of data and materials

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

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