Health Economics Review

RESEARCH

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Trastuzumab plus chemotherapy versus chemotherapy alone in HER2-positive gastric cancer treatment in Iran: a cost-effectiveness analysis

Sara Kaveh[1,2], Nashmil Ghadimi[2], Amirhossein Zarei Alvar[2], Kamran Roudini[3] and Rajabali Daroudi[1,2*]

Abstract

Background Combining Trastuzumab with chemotherapy for HER2-positive gastric cancer shows treatment promise but may raise costs. We aimed to evaluate the cost-effectiveness of combining Trastuzumab with chemotherapy for HER2-positive gastric cancer treatment in Iran.

Methods We employed a partitioned survival model (PSM) to evaluate the cost-effectiveness of trastuzumab plus chemotherapy versus chemotherapy alone. The PSM framework included three distinct health states: progression-free, post-progression, and death. Clinical data, including overall survival and progression-free survival rates, were derived from the ToGA trial, a randomized controlled study. A bottom-up approach was used to calculate costs by considering drug costs, adverse event management costs and other disease management costs separately for the progression-free and post-progression states. The analysis was conducted from the Iranian healthcare system's perspective, considering direct medical costs. We performed a cost-effectiveness analysis to determine the optimal strategy by comparing the incremental cost-effectiveness ratio (ICER) to Iran's cost-effectiveness threshold, set at one to three times the GDP per capita. Additionally, we conducted sensitivity analyses to assess the robustness of our findings.

Results Both FOLFOX-based regimens were strongly dominated. In comparison, the CAPOX regimen cost $2,811.11 for 0.75 QALYs. Adding Trastuzumab to CAPOX increased the cost to $6,128 and improved effectiveness to 0.92 QALYs, resulting in an ICER of $19,089.94 per QALY, which is between 2 and 3 times the GDP per capita in 2022.

Conclusion The addition of trastuzumab to chemotherapy regimens improved clinical outcomes in HER2-positive gastric cancer patients. From an economic perspective, the CAPOX regimen is the most cost-effective option when considering a cost-effectiveness threshold of up to two times Iran's GDP per capita. However, when the threshold increases to three times the GDP per capita, the CAPOX + Trastuzumab regimen becomes the preferred choice. These findings provide valuable insights for healthcare policymakers in Iran.

Keywords Trastuzumab, Gastric neoplasms, Economic evaluation, Cost-effectiveness, Iran

*Correspondence:
Rajabali Daroudi
rdaroudi@sina.tums.ac.ir
[1]National Center for Health Insurance Research, Tehran, Iran
[2]Department of Health Management, Policy & Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Internal Medicine, Hematology and Medical Oncology Ward, Cancer Research Center, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Gastric cancer, also called stomach cancer, poses a significant threat to global health. In 2020, it was the fifth most common malignant tumor worldwide, with approximately 1.1 million new cases and the fourth leading cause of cancer-related mortality, responsible for around 800,000 deaths [1]. This points to its significant contribution to cancer morbidity and mortality at the global scale [2].

Among the different subtypes of gastric cancers, HER2-positive gastric cancer is particularly defined by overexpression of human epidermal growth factor receptor 2 (HER2) protein. Elevated expression of this protein is associated with more aggressive disease and worse prognosis [3]. Trastuzumab, a monoclonal antibody that targets the HER2 protein, has demonstrated promise in the treatment of HER2-positive gastric cancer when used in combination with chemotherapy, revealing prolonged overall survival (OS) and progression-free survival (PFS) rates in clinical trials [4, 5].

In spite of these advantages, the utilization of novel medications like trastuzumab may result in an increase in the financial burden of treatment [6]. The perceived additional benefit of trastuzumab for gastric cancer may vary across countries, as evidenced by the reported range of incremental cost-effectiveness ratios (ICERs). These ratios for trastuzumab have been documented to range from £45,000–50,000 per Quality adjusted life years (QALY) based on a NICE report, to £110,000/QALY in Japan [6, 7]. This variation is consistent with the general observation that the cost-effectiveness of healthcare technologies often differs by country due to factors such as healthcare infrastructure, drug pricing policies, and economic conditions [8]. Cost-effectiveness analysis (CEA) helps ensure that the incremental costs of treatments are justified by their incremental effectiveness, facilitating efficient healthcare resource allocation [9, 10]. This research aims to address the cost-effectiveness of combining trastuzumab with chemotherapy for treating HER2-positive gastric cancer in Iran, in comparison to chemotherapy alone.

Methods

Model structure

We employed a partitioned survival model (PSM) to evaluate the cost-effectiveness of combining trastuzumab with chemotherapy compared to using chemotherapy alone. The method for ascertaining a patient's status within the PSM can be illustrated using a model framework commonly utilized in economic evaluations of treatments for gastric cancer [11]. This model comprises three distinct health states associated with cancer, which do not overlap: progression-free (PF), post-progression (PP), and death. Progression signifies the worsening or spreading of the cancer (Fig. 1). In the PSM, the classification of individuals into health states relies on two survival curves. The first curve, referred to as OS, directly measures the percentage of patients who remain alive over time and represents the duration from model entry to the point of death. Importantly, OS is independently specified from other clinical endpoints and regardless of whether individuals are associated with the PF or PP health states. The PFS curve measures the duration from when a patient enters the model until they transition out of the PF state due to either disease progression or death. It also tracks how patients move into the PF state over time. In the case of the PP health state, the distinction between the OS curve and the PFS curve at each interval indicates the portion of patients who are alive but have not yet experienced disease progression.

In the simulation, all patients enter the PSM in the PF state and encounter the potential risks of disease advancement and mortality. Following disease progression, with the assumption that reverting to a state PFS is not feasible, all patients then face the risk of mortality alone. The simulation was designed with monthly cycles

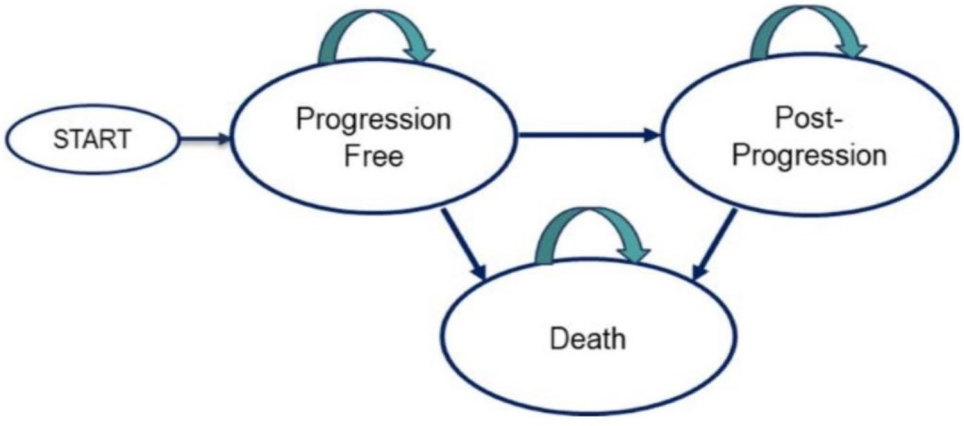

Fig. 1 Transition diagram of the simulation model

over a 5-year time span, during which it is anticipated that each patient will experience mortality. The analyses were conducted considering the Iranian healthcare system's perspective.

Model parameters

Clinical data

In routine practice in Iran, chemotherapy regimens predominantly included FOLFOX (comprising Fluorouracil, Leucovorin, and Oxaliplatin) and CAPOX (consisting of Capecitabine and Oxaliplatin). It is noteworthy that these commonly used chemotherapy regimens differ from those studied in existing research, but they have demonstrated similar effectiveness to guideline-recommended drugs [12, 13]. However, their adverse events (AEs) profiles vary [14]. Consequently, efficacy data were derived from the ToGA study [4], while data regarding the occurrence of AEs were gathered from relevant studies for each treatment arm [15–18].

The primary source of clinical data was the ToGA trial [4]. The ToGA trial was an open-label, multinational, phase 3 randomized controlled study conducted across 24 distinct countries. Participants were assigned randomly in a 1:1 ratio to receive one of two treatment groups. The first group received a chemotherapy regimen comprising capecitabine plus cisplatin or fluorouracil plus cisplatin. The second group received chemotherapy along with intravenous trastuzumab. The chemotherapy regimen was administered in a six-cycle protocol, with each cycle occurring at three-week intervals. Capecitabine was prescribed orally at a dosage of 1000 mg/m^2, taken twice daily for a duration of 14 days, followed by a one-week intermission. Alternatively, Fluorouracil was administered intravenously at a daily dose of 800 mg/m^2 via continuous infusion on days 1 to 5 of each treatment cycle. Cisplatin, administered at a dosage of 80 mg/m^2, was delivered intravenously on day 1 of each cycle. Trastuzumab was initially administered intravenously at a dose of 8 mg/kg on the first day of the initial cycle, followed by subsequent administrations of 6 mg/kg at three-week intervals, until either disease progression, the emergence of intolerable adverse effects, or voluntary withdrawal of consent by the patient. According to the TOGA trial, the median PFS was 6.7 months (95% CI 6–8) for the group receiving trastuzumab plus chemotherapy, compared to 5.5 months (95% CI 5–6) for the chemotherapy alone group (HR 0.71, 95% CI 0.59–0.85; $p=0.0002$). Parameter distributions are listed in Table 1.

Table 1 Parameter for Weibull models fitted to Kaplan-Meier survival curves

Variable		Value
Scale parameter for PFS/OS Weibull distribution	OS_FOLFOX	0.0185
	OS_ trastuzumab	0.0117
	PFS_FOLFOX	0.065
	PFS_ trastuzumab	0.0399
Shape parameter for PFS/OS Weibull distribution	OS_FOLFOX	1.48
	OS_ trastuzumab	1.54
	PFS_FOLFOX	1.44
	PFS trastuzumab	1.438

OS overall survival, PFS: progress free survival

PFS and OS were determined utilizing the Kaplan-Meier methodology, with the observation period extending up to 36 and 34 months for OS and PFS, respectively. Subsequently, the model applied parametric survivor functions tailored to the trial data. It utilized the Weibull distribution within TreeAge Pro Healthcare 2020 software (TreeAge Software, Inc., version 2020, Williamstown, MA) to extend the extrapolation of OS and PFS curves for a duration of up to 60 months.

Utility score

The QALYs were determined by multiplying the length of time an individual remained in a particular health state by the corresponding utility score assigned to that state [19]. As utility values specific to the Iranian gastric cancer population were not accessible, we primarily relied on the utility estimates derived from the conclusive findings of the ToGA trial [4] for each health state in the model. In Table 2, we have provided the utility values corresponding to different health states. In addition, the disutility related to level 3 and 4 AEs were included among the parameters that populated the PSM. In our base case analysis, we calculated that the average disutility attributed to AEs was estimated at 0.15. The percentages for each group are displayed in Table 2.

Costs

All costs were converted from Iranian Rial to US dollars using the 2022 average exchange rate of 1.00 US$ ≈ 252,362 IRR, as officially reported by the World Bank [22]. A bottom-up approach was used to calculate costs by separately considering drug costs, adverse event management, and other disease management for the progression-free and post-progression states. A comprehensive breakdown of all costs included in the model can be found in Table 3. For drug costs, factors such as acquisition price, dosage, treatment duration, and administration costs were considered. The total drug cost per dose was computed based on required dosage and treatment duration, including injection costs, and then the overall monthly drug cost was determined. The average monthly cost of each of the four treatment regimens, encompassing medicine, visits, tests, and imaging, is presented in Table 3. Since the model's cycles were monthly, chemotherapy regimen costs were calculated accordingly.

The dosage regimens and treatment durations were meticulously determined based on the inherent

Table 2 Baseline costs, risks, and utility values included in model

Parameter	VALUE	LOW	HIGH	Distributions	Reference
Costs ($)[a]					[20]
CAPOX	244.97	195.98	293.97	Gamma	
CAPOX + Trastuzumab	713.95	571.16	856.74	Gamma	
FOLFOX	276.57	221.26	331.88	Gamma	
FOLFOX + Trastuzumab	882.28	705.83	1058.74	Gamma	
Costs on main AEs[b]($)					[20]
Hand-foot syndrome	8.05	6.44	9.66	Normal	
Gastrointestinal disorders	1.60	1.28	1.92	Normal	
thrombocytopenia	64.20	51.36	77.03	Normal	
Anemia	6.93	5.55	8.32	Normal	
Neutropenia	9.17	7.34	11.00	Normal	
Costs of states ($)					[20]
PFS[c]	95.62	76.49	114.74	Gamma	
PP[d]	117.62	94.10	141.15	Gamma	
Probability of main AEs (%)					
FOLFOX					[15, 17]
Hand-foot syndrome	0.55	0.44	0.66	Beta	
Gastrointestinal disorders	8.66	6.928	10.392	Beta	
thrombocytopenia	1.43	1.144	1.716	Beta	
Anemia	3.25	2.6	3.9	Beta	
Neutropenia	10.03	8.024	12.036	Beta	
CAPOX					[16–18]
Hand-foot syndrome	2.39	1.912	2.868	Beta	
Gastrointestinal disorders	2.16	1.728	2.592	Beta	
thrombocytopenia	0.91	0.728	1.092	Beta	
Anemia	2.03	1.624	2.436	Beta	
Neutropenia	4.78	3.824	5.736	Beta	
Utility					[21]
PFS	0.81	0.648	0.972	Beta	
PP	0.6	0.480	0.720	Beta	
Disutility					[21]
AE	0.15	0.120	0.180	Beta	
BD[e]	0.079	0.063	0.095	Beta	

(a) Year-2022 US $; local charges, (b) AE: Adverse Events, (c) PFS: Progression Free Survival, (d) PP: Post Progress, (e) BD: Before Death

characteristics of the drugs and available clinical data. Specifically, for trastuzumab administration, an initial dosage of 8 mg/kg is administered in the first cycle. Considering the average patient weight as 65 kg, the first cycle necessitates 520 mg of trastuzumab. Subsequent cycles involve a reduced dosage of 6 mg/kg, corresponding to 390 mg of the drug for patients with the specified weight and clinical conditions.

In the case of 5-Fluorouracil (5FU) treatment, the prescribed dosage aligns with established clinical guidelines, amounting to 400 mg/m2. Consequently, for a patient weighing 65 kg, the bolus dose requires 689 mg, while the maintenance dose necessitates 4134 mg. Thus, each injection of 5FU necessitates a total of 4823 mg of the medication to be administered.

For Oxaliplatin, the prescribed dosage is 130 mg/m2, translating to a requirement of approximately 223.6 milligrams for a patient with a weight of 65 kg. Leucovorin, on the other hand, is administered at a dosage of 400 mg/m2, necessitating 688 milligrams for each chemotherapy cycle for patients with the specified conditions.

In the case of Capecitabine, the prescribed dosage is 850 mg/m2, resulting in a requirement of 1462 milligrams for patients with a body surface area of 1.72 m^2. Since Capecitabine is available in 500 mg tablets, the patient needs 3 tablets, taken twice a day, totaling 6 tablets per day for 14 days. This corresponds to the administration of 84 tablets in each chemotherapy injection cycle.

In this study, the incidence of AEs associated with the CAPOX and FOLFOX regimens was extracted from systematic reviews and relevant meta-analyses. However, when it comes to the combination of these treatment regimens with trastuzumab, there is limited and often low-sample-size research available. This limitation is due to the fact that the most significant clinical trial study

Table 3 Dosing schedules and costs for each patient in a 6-month chemotherapy cycle

Item	CAPOX		Trastuzumab	FOLFOX		
	Oxaliplatin	Capecitabin		Leucovorin	Oxaliplatin	Fluorouracil
Guideline	130 mg/m^2	850 mg/m^2	First = 8 mg/kg, other = 6 mg/kg	400 mg/m^2	85 mg/m^2	400 mg/m^2
Dose per administration[1]	223.6 mg	1462 mg	First: 520 mg Other: 390 mg	688 mg	146.2 mg	Bulus: 689 mg Maintenance dose: 4134 Total = 4823 mg
	Total drug cost for each cycle [2]					
Chemotherapy regimen	CAPOX	CAPOX plus Trastuzumab		FOLFOX plus Trastuzumab		FOLFOX
Total cost for each cycle ($)	1129.45	3583.84		5293.71		1659.42
The monthly cost of prescribing four chemotherapy regimens per patient along with the required measures						
Item				**Private tariff per time ($)**		**Numbers needed in one chemotherapy cycle**
Oncologist visit				6.82		2
Blood tests				15.62		2
CT scan				55.07		1
Cardiologist visit				6.82		2
Echocardiography				21.06		1
Administration of intravenous or arterial chemotherapy with rapid administration technique and infusion method of multiple pre-mixed drugs per cycle up to 8 h.				12.43		2
Preparation of chemotherapy injection solutions (bulky and non-bulky) (cytotoxic drugs compounding)				18.12		2
Average monthly cost				**116.64**		
The average monthly cost of each chemotherapy regimen (including drug costs and other services associated with drug prescription)						
CAPOX	**CAPOX + Trastuzumab**			**FOLFOX**		**FOLFOX + Trastuzumab**
244.97	713.95			276.57		882.28

Dosing was adjusted for a patient with weight 65 kg, height 1.64 m, and BSA of 1.72 m^2

Unused drugs in opened vials were discarded

concerning the combination of trastuzumab with standard chemotherapy (the ToGA trial) primarily focused on the CFC regimen. Since the safety profile of the CFC regimen significantly differs from that of the CAPOX and FOLFOX regimens, the results of the ToGA clinical trial cannot be generalized to the incidence of AEs associated with the CAPOX and FOLFOX regimens.

On the other hand, based on the findings of the ToGA trial and other trials where trastuzumab was added to standard chemotherapy regimens, there were no statistically significant differences in terms of the incidence of AEs between the chemotherapy regimens administered alone and in combination with trastuzumab [4, 21]. Therefore, in this study, we assumed that the incidence of AEs in regimens accompanied by trastuzumab is similar to that of chemotherapy regimens administered alone.

In addition to the costs associated with drug regimens and the management of their AEs, cancer patients incur additional expenses such as hospitalization, care, follow-up visits, and palliative care. These costs were calculated separately for two stages of the disease: PP and PF. Utilization rates and consumption frequencies were extracted from previous studies and medical guidelines, and these were multiplied by the unit cost of each care component, which was obtained from the latest approved tariff schedules [23]. Required interventions in both stages were based on the Gastric Cancer Treatment Guidelines [24] and relevant studies [25], with the likelihood of hospitalization considered equal across both stages, as derived from a study by Hess and colleagues [26]. Since this study reported data in six-month intervals, we recalculated these costs on a monthly basis. Specialist visits, tests, and imaging were determined according to the National Comprehensive Cancer Network (NCCN) Guidelines [24], while palliative interventions for the PP stage were based on the same guidelines and relevant probabilities were sourced from a thesis [25]. The average monthly cost per patient, by stage of the disease, is presented in Table 4, with an estimated cost of $117.62 for the PP stage and $95.62 for the PFS state.

Cost-effectiveness analysis

To determine the optimal strategy, we calculated the ICER. We computed the ICER and subsequently compared it to Iran's cost-effectiveness threshold. This threshold was established by drawing upon data from the statistical center of Iran data for the year 2022, which provided the Gross Domestic Product (GDP) figures. the GDP per capita was estimated to be 6696.8 dollars [27].

Table 4 Average monthly cost of patients in the state progression free state (PFS) and post progression (PP)

Disease state	Cost item	Frequency	Numbers needed in each cycle	Unit cost	Cycle cost	Monthly cost
Progress Free State (PFS)	inpatient	0.56	3	93.79	157.57	26.26
	oncologist visit	1	6	6.82	40.92	6.82
	CT scan	1	5	37.27	186.35	31.06
	Endoscopy	1	2	44.99	89.98	15.00
	Laboratory tests	1	6	16.56	99.36	16.56
	Total					**95.62**
Post progress State (PP)	inpatient	0.63	3	93.79	177.26	29.54
	oncologist visit	1	6	6.82	40.92	6.82
	CT scan	1	5	37.27	186.35	31.06
	Endoscopy	1	2	44.99	89.98	15.00
	Laboratory tests	1	6	16.56	99.36	16.56
	Bypass or Intestinal Obstructive Surgery	0.14	1	113.24	15.85	2.64
	stent	0.7	1	115.50	80.85	13.48
	feeding tube	0.26	1	49.71	12.92	2.15
	Total					**117.62**

Following the guidance of the World Health Organization (WHO), we determined an effective cost threshold that spans from one to three times the GDP [10, 28]. This range was found to encompass 6696.8 to 20090.3 dollars. Both costs and QALYs were discounted at a rate of 5% per year [29]. All phases of the model implementation were carried out using Excel 2016 and TreeAge 2020 software.

Sensitivity analysis

We performed both a deterministic one-way sensitivity analysis (OWSA) and a probabilistic sensitivity analysis (PSA). OWSA was conducted to evaluate the impact of individual parameters on model outcomes by varying one parameter at a time while holding others constant. This helped identify parameters that had the most significant influence on base-case cost-effectiveness results. In the PSA, we utilized probability distributions for key model parameters. Beta distributions were employed for utility values, and Gamma distributions for costs [30]. The PSA was supported by a 1000-iteration Monte Carlo simulation which provided a distribution of the average cost and outcome of the examined treatment regimens. The distribution of average cost and outcome of each treatment regimen were plotted on a cost-effectiveness plane [31]. As recommended by literature [32], whenever the health care programs under comparison are three or more, average instead of incremental cost and outcomes are plotted on the cost-effectiveness plane. In addition, we used cost-effectiveness acceptability frontier to represent the results of the PSA [33].

Results

Base-case analysis

The results of simulating OS and PFS curves, showcased in Figs. 2 and 3, are outlined below. These curves present the OS and PFS curves, originally derived from ToGA study [4] (Kaplan-Meier curve), and then simulated for two treatment scenarios.

As illustrated in Figs. 2 and 3, the use of both chemotherapy and trastuzumab results in better OS compared to using chemotherapy alone. The combined treatment approach leads to a more favorable survival trend when contrasted with using chemotherapy by itself. Furthermore, when combined with trastuzumab, the duration of PFS in the chemotherapy group is significantly longer than when chemotherapy is used as a standalone treatment.

Cost-effectiveness analysis results

The result of cost effectiveness analysis of different chemotherapy regimens is shown in Fig. 4; Table 5. As mentioned in the previous sections, the effectiveness of CAPOX and FOLFOX regimens are the same, but the average cost of CAPOX regimen is lower than FOLFOX regimen. The effectiveness of chemotherapy regimens in combination with trastuzumab is more than chemotherapy alone. Of course, the effectiveness of FOLFOX+TRASTUZUMAB and CAPOX+TRASTUZUMAB regimens are also the same, but the cost of FOLFOX+TRASTUZUMAB regimen is more than the cost of CAPOX+TRASTUZUMAB regimen. As shown in Fig. 4, FOLFOX and FOLFOX+TRASTUZUMAB regimens have been dominated by CAPOX and CAPOX+TRASTUZUMAB regimens, respectively. Because FOLFOX-based regimens have the same effectiveness but cost more than CAPOX-based regimens.

The findings related to the PSA model analysis are presented in Table 5 by different treatment regimens and different disease states. The average value of QALY in a 5-year time horizon is estimated to be 0.75 in

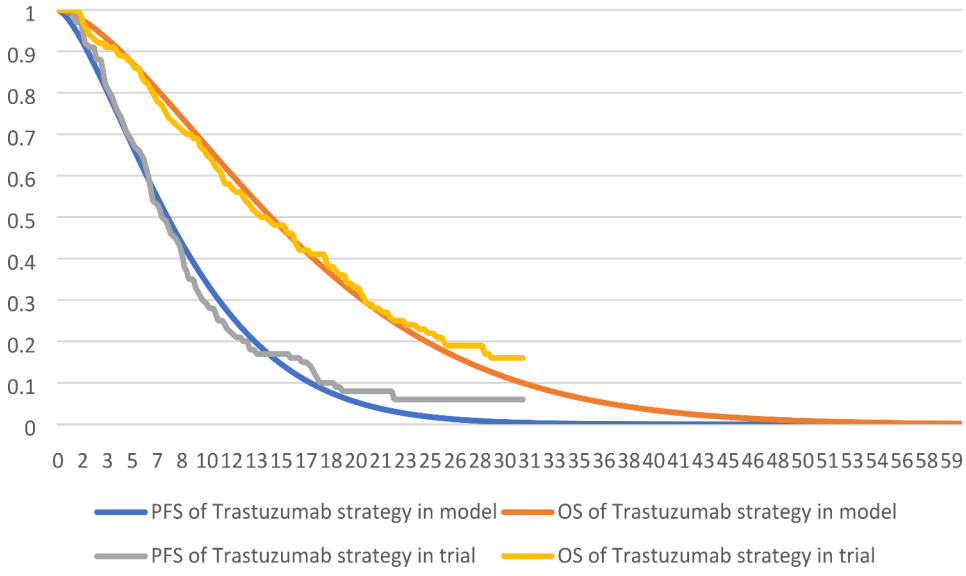

Fig. 2 Modeled OS and PFS curves related to the trastuzumab plus chemotherapy group (times in month)

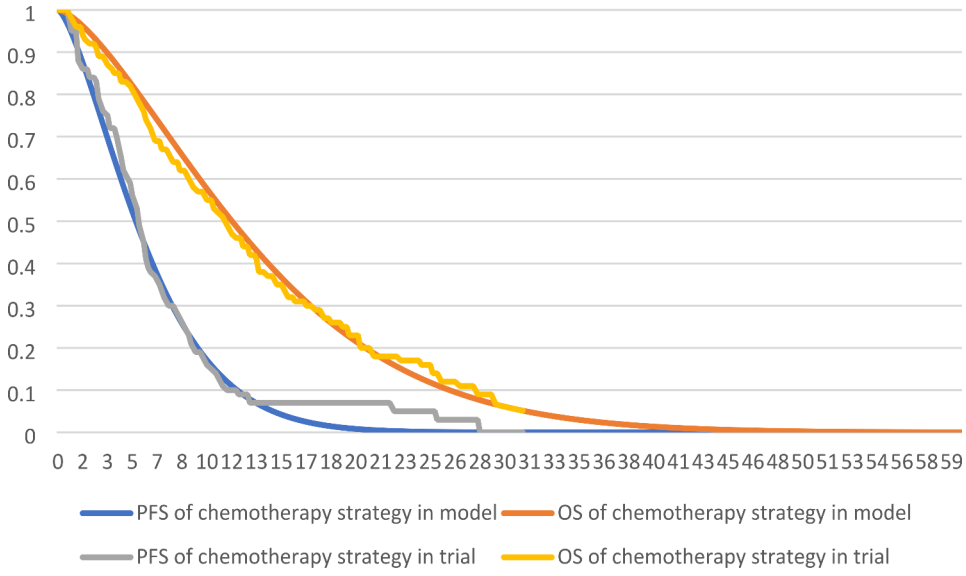

Fig. 3 Modeled OS and PFS curves related to the chemotherapy group (times in month)

chemotherapy regimens alone and 0.92 in chemotherapy regimens combined with trastuzumab. The lowest average cost related to the CAPOX regimen was 2811.11 $ and the highest average cost related to the FOLFOX+TRASTUZUMAB regimen was 7158.83 $.

In Table 6, the ICER of the investigated regimens is reported. Both FOLFOX-based regimens were weakly dominated, with the FOLFOX regimen costing $2,974.14 for 0.75 QALYs and the FOLFOX plus Trastuzumab regimen costing $8,370.67 for 0.92 QALYs. In comparison, the CAPOX regimen cost $2,811.11 for 0.75 QALYs. Once the weakly dominated options were eliminated, the cost-effectiveness analysis compares CAPX vs. Trastuzumab. Adding Trastuzumab to CAPOX increased the cost to $6,128 and improved effectiveness to 0.92 QALYs, resulting in an ICER of 19089.94 $ per QALY, which is between 2 and 3 times the GDP per capita in 2022.

If we consider the cost-effectiveness threshold equal to three times the GDP per capita, the CAPOX+Trastuzumab regimen will be the most cost-effective treatment regimen for patients with HER2-positive advanced gastric cancer. But if the cost-effectiveness threshold is considered less than two times of GDP per capita, the CAPOX regime is the most cost-effective intervention.

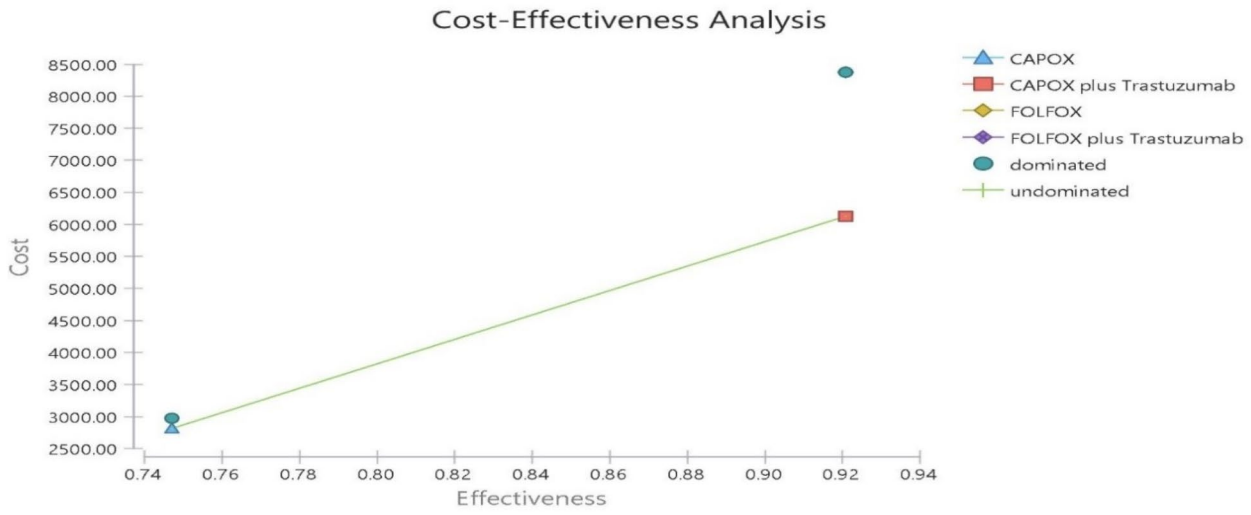

Fig. 4 Base Case cost effectiveness analysis

Table 5 Average cost and QALY of chemotherapy regimens

	STATE	AREA	COST ($)	QALY
FOLFOX				
	Progression-Free State	6.9	1988.15	0.45
	Post-Progression State	6.35	1010.33	0.29
	(Dead)	46.75		
	Total	**60**	**2998.48**	**0.75**
FOLFOX + TRASTUZUMAB				
	Progression-Free State	9	5677.07	0.59
	Post-Progression State	7.25	1481.76	0.33
	(Dead)	43.74		
	Total	**60**	**7158.83**	**0.92**
CAPOX				
	Progression-Free State	6.9	1835.15	0.45
	Post-Progression State	6.35	975.96	0.29
	(Dead)	46.75		
	Total	**60**	**2811.11**	**0.75**
CAPOX + TRASTUZUMAB				
	Progression-Free State	9	4765.34	0.59
	Post-Progression State	7.25	1362.63	0.33
	(Dead)	43.74		
	Total	**60**	**6127.98**	**0.92**

Table 6 Incremental cost-effectiveness ratios for different treatment strategies

Strategy	Cost ($)	Incremental Cost ($)	Effect	Incremental Effect	Incremental cost effectiveness ratio ($)
CAPOX	2811.11	0	0.75	0	0
FOLFOX	2974.14	163.02	0.75	0	Weakly Dominated
CAPOX plus Trastuzumab	6128	3316.88	0.92	0.17	19089.94
FOLFOX plus Trastuzumab	8370.67	2242.67	0.92	0	Weakly Dominated

Sensitivity analyses

Deterministic sensitivity analysis

One-way sensitivity analysis The analysis reveals that variations in the cost of Trastuzumab demonstrate a substantial impact on the ICER, with lower costs yielding a more cost-effective outcome. Similarly, reductions in the utilities of PF and PP contribute to lower ICER values, suggesting enhanced cost-effectiveness. The cost of FOLFOX, percentages for Thrombocytopenia and Neutropenia, and

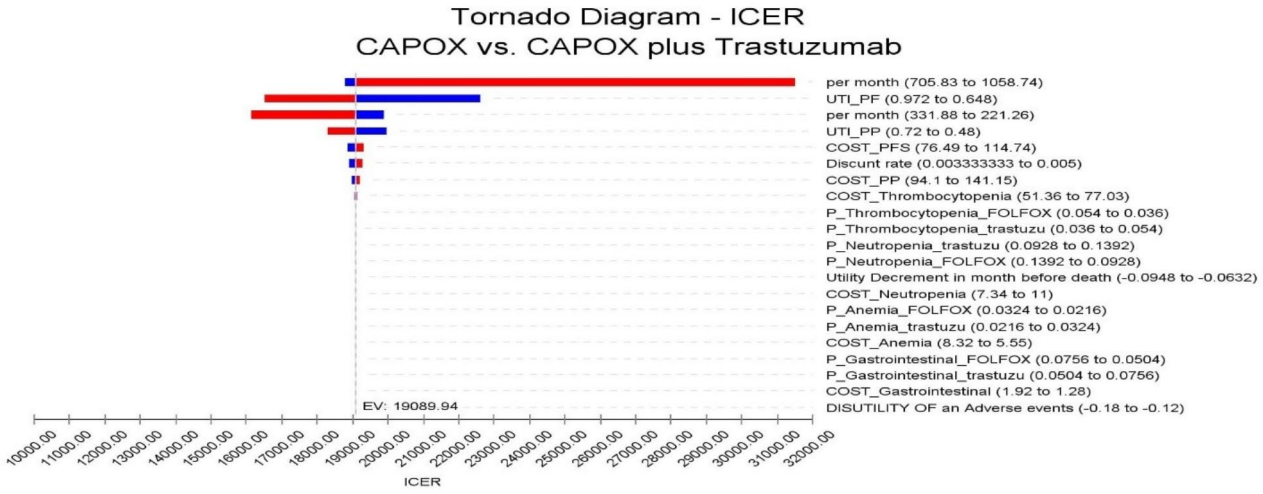

Fig. 5 Tornado diagram for sensitivity analysis of model input variables

Table 7 The results of one-way sensitivity analysis

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High
Cost of Trastuzumab	705.83	1075.93	1058.74	Increase	18797.48058	31508.2107
Utility PFS[1]	0.648	0.81	0.972	Decrease	16516.55064	22613.22765
Cost FOLFOX	221.26	272.47	331.88	Decrease	16118.78074	19900.50217
Utility PP[2]	0.48	0.6	0.72	Decrease	18283.65661	19970.6114
Cost PFS	76.49	95.62	114.74	Increase	18869.15424	19310.60623
Discount rate	0.003	0.004	0.005	Increase	18891.33631	19289.49341
Cost PP	94.1	117.62	141.15	Increase	18986.21833	19193.70165
Cost Thrombocytopenia	51.36	64.2	77.03	Increase	19064.36882	19115.48714
P[3] Thrombocytopenia_FOLFOX	0.036	0.045	0.054	Decrease	19081.07004	19094.37189
P Thrombocytopenia_trastuzumab	0.036	0.045	0.054	Increase	18957.6584	18970.96026
P Neutropenia_trastuzumab	0.0928	0.116	0.1392	Increase	19085.27246	19090.17016
P Neutropenia_FOLFOX	0.0928	0.116	0.1392	Decrease	19087.48909	19092.38679
Disutility BD[4]	-0.0948	-0.079	-0.0632	Increase	19088.12561	19091.75062
Cost Neutropenia	7.34	9.17	11	Increase	19089.49558	19090.3803
P Anemia_FOLFOX	0.0216	0.027	0.0324	Decrease	19093.97429	19094.8358
P Anemia_trastuzumab	0.0216	0.027	0.0324	Increase	19086.95456	19087.81607
Cost Anemia	5.55	6.93	8.32	Decrease	19089.55394	19090.31918
P Gastrointestinal_FOLFOX	0.0504	0.063	0.0756	Decrease	19089.31912	19089.78324
P Gastrointestinal_trastuzumab	0.0504	0.063	0.0756	Increase	19090.1479	19090.61201
Cost Gastrointestinal	1.28	1.6	1.92	Decrease	19089.92689	19089.94899
Disutility AE[5]	-0.18	-0.15	-0.12	Increase	19089.93794	19089.93794

1) PFS: Progression-Free State, 2) PP: Post Progress, 3) P: probability of transition to other states, 4) BD: Before Death, 5) AE: Adverse Event

the discount rate all exhibit predictable influences on the ICER. (Fig. 5; Table 7)

Probabilistic sensitivity analysis

In this study, a probabilistic sensitivity analysis was performed to investigate the impact of the uncertainty of the study parameters on the study findings. Figure 6 shows the distribution of the average cost and effectiveness of the examined treatment regimens. As shown in the graph, in most cases, the FOLFOX+Trastuzumab regimen generally had a higher average cost than the other regimens. Although, in many cases, the average effectiveness of the FOLFOX+Trastuzumab regimen was higher than that of the chemotherapy regimens alone (FOLFOX alone and CAPOX alone), its average effectiveness was similar to that of the CAPOX+Trastuzumab regimen. Additionally, when comparing the two chemotherapy regimens (CAPOX and FOLFOX without Trastuzumab) with each other, in many instances, the two regimens had similar costs and effectiveness.

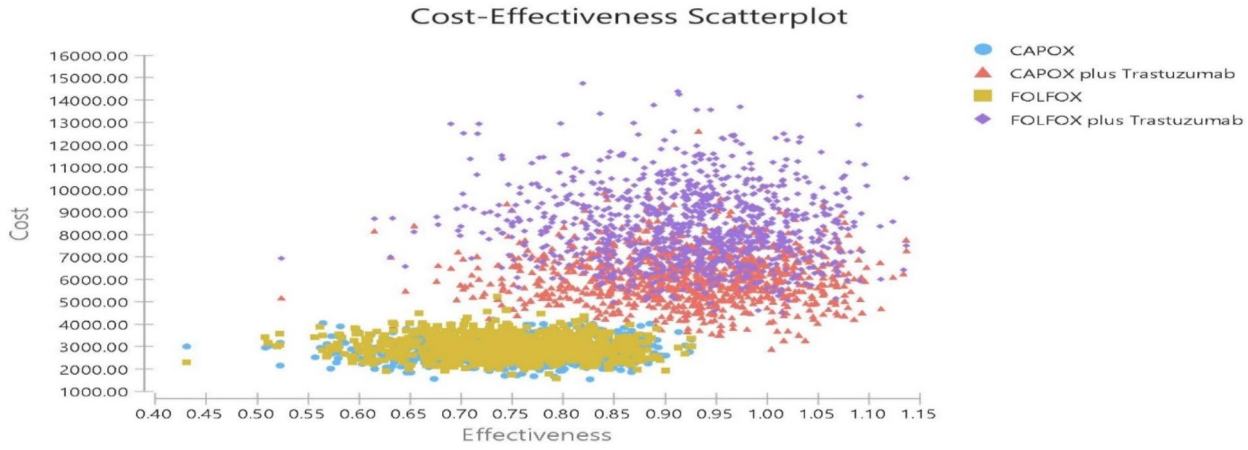

Fig. 6 Cost effectiveness scatter plot for all treatment regimens

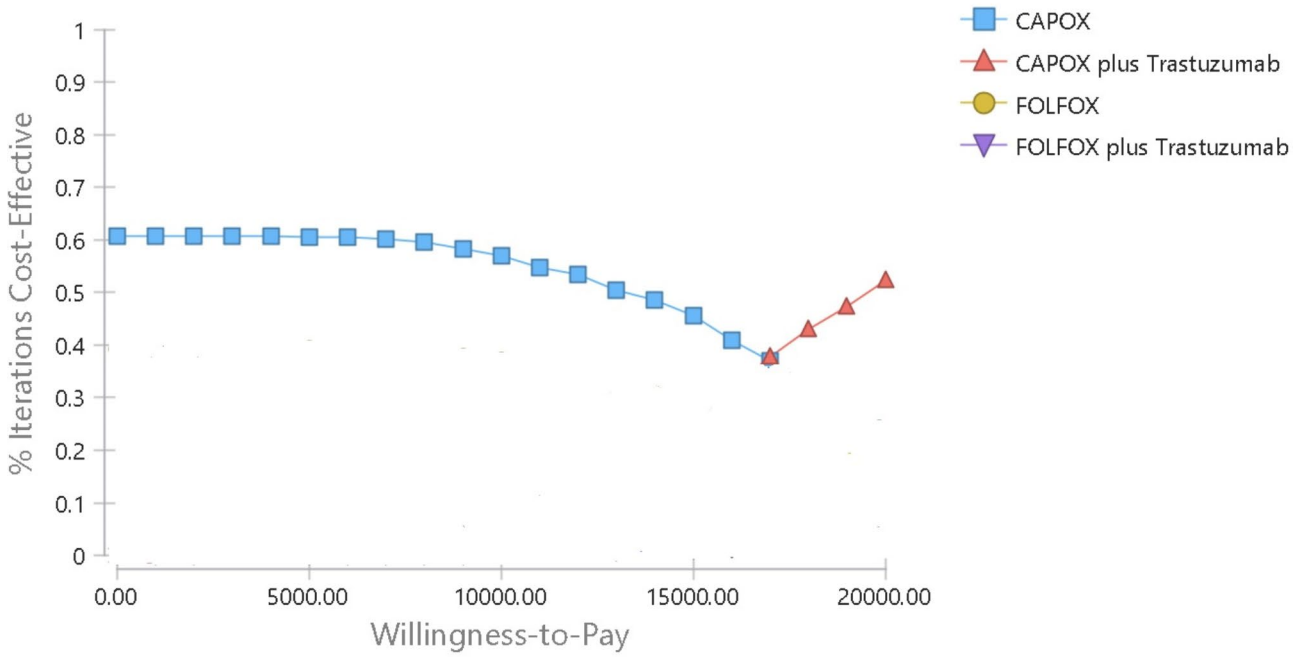

Fig. 7 Cost-effectiveness acceptability frontier of the studied treatment regimens

The Cost-effectiveness acceptability frontier, which plots the probability for each of the alternatives under comparison to be the optimal for different cost-effectiveness threshold values, is presented in Fig. 7.

As shown in Fig. 8, if the cost-effectiveness threshold is one time the GDP per capita in 2022 (about 6697 dollars), the CAPOX regimen shows a 59% probability of being the optimal treatment regimen. If the cost-effectiveness threshold equals to two times the GDP per capita (13,394 dollars), CAPOX regimen will be the optimal chemotherapy with a probability of 50%. Finally, if the cost-effectiveness threshold reaches three times the GDP per capita (20,090 dollars), the probability for CAPOX plus Trastuzumab to be optimal health care programme reaches 50%.

Discussion

Advanced gastric cancer imposes a significant financial and social burden worldwide. Recently, trastuzumab have been emerge as new treatment for advanced gastric cancer. As with other medicines and technologies used for treatment and disease detection, it's crucial to understand the economic implications of using trastuzumab in the treatment of advanced gastric cancer. Especially, in

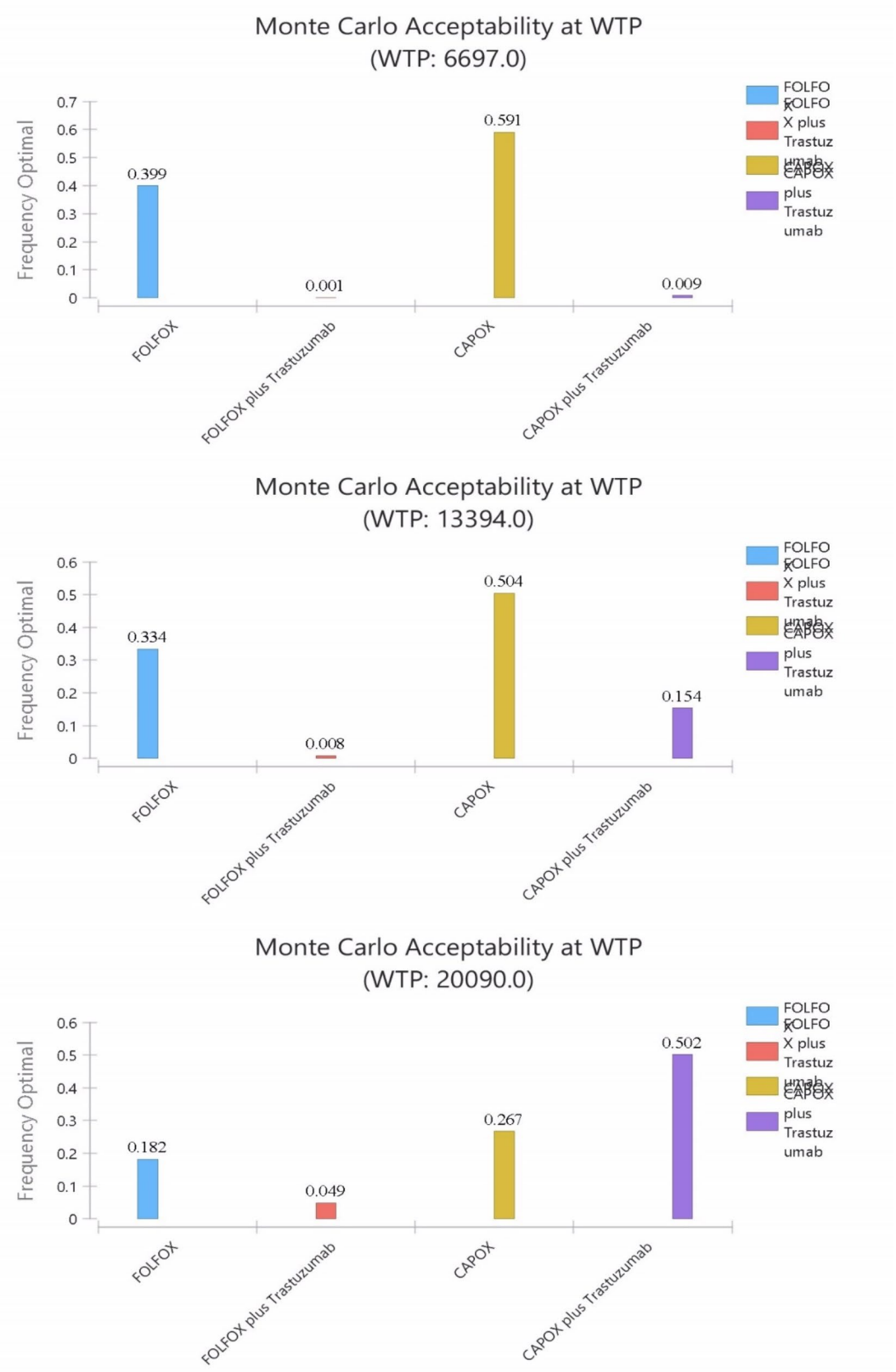

Fig. 8 Monte Carlo Acceptability at different willingness-to-pay thresholds(Strategy Selection Diagram): (**A**)=Threshold equal to one times the GDP per capita, (**B**)=Threshold equal to 2 times the GDP per capita, and (**C**)= Threshold equal to 3 times the GDP per capita.

countries like Iran, where resources are limited. Studies have shown that adding trastuzumab to chemotherapy can improve survival rates for patients with HER2-positive advanced gastric cancer [21]. However, the high cost of this medication remains a major concern.

Our study dives deep into the complex relationship between clinical effectiveness and economic factors in managing HER2-positive advanced gastric cancer, specifically examining how integrating trastuzumab with chemotherapy regimens impacts healthcare in Iran. By meticulously analyzing both the clinical outcomes and economic consequences of different treatment approaches, we aim to provide a comprehensive understanding of the cost-effectiveness of trastuzumab-containing regimens. Our research sheds light on the intricate decision-making process involved in cancer care, highlighting the need for balanced approaches that prioritize both clinical benefits and economic sustainability.

In this study, we compared four chemotherapy regimens in accordance with Iran's guidelines for HER2-positive gastric cancer treatment. These regimens included trastuzumab combined with FOLFOX or CAPOX, as well as FOLFOX and CAPOX alone. Our cost-effectiveness analysis highlights the enhanced cost-effectiveness of chemotherapy regimens when augmented with trastuzumab, in contrast to chemotherapy administered alone. While both CAPOX and FOLFOX regimens exhibit comparable effectiveness, the former emerges as the more economically favorable option due to its lower associated costs. Consequently, CAPOX-based regimens overshadow FOLFOX-based ones, despite their similar efficacy profiles but higher costs. Moreover, when considering a cost-effectiveness threshold set from one to two times Iran's GDP per capita, CAPOX regimen emerged as the most cost-effective option. However, when considering a cost-effectiveness threshold set to three times Iran's GDP per capita, CAPOX plus Trastuzumab regimen will be the most cost-effective option These findings offer valuable insights into the economic considerations surrounding treatment decisions for HER2-positive advanced gastric cancer in Iran.

According to the results of the present study, CAPOX plus Trastuzumab regimen was the most cost-effective regimen with 3 times Iran's GDP per capita as the cost-effectiveness threshold. While this result was not similar with a study conducted in China. They found that combination of Trastuzumab and conventional chemotherapy was not economically justified by an ICER of $251,667.10/QALY gained according to 2010 US dollars [11]. However, the results of a Japanese study in 2011 were in line with ours and revealed that combining Trastuzumab to chemotherapy was a cost-effective option. It is to be noted that the outcomes and cost were note discounted due to limited life expectancy [6]. While in the present study, we discounted both with 5%. This discount rate is proposed for low and middle income countries (LMICs) [34]. The difference in the results between countries can be attributed to varying thresholds and lower GDP in Iran. These discrepancies in thresholds for CEA in healthcare decision-making has a significant effect on considering an intervention to be economically viable. Consequently, they have substantial impact on budget al.location and equity considerations within healthcare systems.

The research has some admitted limitations that offer a more comprehensive understanding of the context: 1. **Assumption of Utility Estimates**: Our analysis is based on utility estimates from the ToGA trial [4] because there are no specific utility values available for the Iranian gastric cancer population. This reliance introduces a potential bias, as assuming these findings apply uniformly to the Iranian context may not be fully accurate.

Another limitation of our study is that we did not conduct a subgroup analysis based on gene expression. The ToGA trial found that the addition of trastuzumab to chemotherapy significantly improved overall survival in patients with advanced gastric cancer or gastro-oesophageal junction cancer, particularly in those with high expression of HER2 protein. Our study assumed similar efficacy among chemotherapy regimens across subgroups, but it is important to note that the effectiveness of trastuzumab increases with higher gene expression. Therefore, the cost-effectiveness of trastuzumab is likely to be more favorable in patients with increased gene expression. Future studies should consider analyzing the cost-effectiveness of trastuzumab in relation to gene expression to optimize treatment decisions and resource allocation. **Limited Generalizability**: - The study was conducted solely from the Iranian healthcare system perspective, thus limiting the applicability of the findings to other healthcare settings with different resource allocations and healthcare structures.

In synthesizing clinical and economic evidence, our study not only informs healthcare policies but also underscores the imperative of optimizing treatment strategies to improve patient outcomes. By bridging the gap between clinical efficacy and economic considerations, we pave the way for evidence-based decision-making that maximizes the value of healthcare investments and enhances the quality of care for patients with HER2-positive advanced gastric cancer in Iran.

In conclusion, our research serves as a testament to the importance of context-specific analyses in guiding healthcare practices and resource allocation decisions. By elucidating the cost-effectiveness of trastuzumab-containing regimens within the Iranian healthcare context, we contribute to advancing the field of cancer care and

pave the way for tailored, patient-centered approaches that prioritize both clinical efficacy and economic sustainability.

Acknowledgements
We extend our heartfelt thanks to all who contributed to this manuscript.

Author contributions
SK: Data collection, interpretation of results, writing - review and editing, final approval of the version to be published. NG: Data collection, writing - review and editing, final approval of the version to be published. AZ: Data collection, final approval of the version to be published. KR: Validation of clinical content, review and editing of the manuscript, final approval of the version to be published. RD: Conceptualization, supervision, critical review of the methodology and model structure, interpretation of results, final approval of the version to be published.

Funding
This work was supported by the Tehran University of Medical Sciences under Grant number [IR.TUMS.MEDICINE.REC.1401.656].

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 3 May 2024 / Accepted: 4 November 2024
Published online: 09 November 2024

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