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Original Article

Immunotherapy plus chemotherapy in patients with advanced endometrial cancer: a cost-effectiveness analysis

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ABSTRACT

Objective: Pembrolizumab and dostarlimab are immune checkpoint inhibitors that target programmed death receptor 1 (PD-1). Combination anti-PD-1 regimens have been shown to exhibit favorable survival benefits when treating advanced endometrial cancer (EC). Which treatment was preferable will need to be confirmed by a cost-effectiveness comparison between them.
Methods: Based on patient and clinical parameters from RUBY and NRG-GY018 phase III randomized controlled trials, the Markov model with a 20-year time horizon was established to evaluate the cost-effectiveness of dostarlimab plus chemotherapy (DC), pembrolizumab plus chemotherapy (PC), and chemotherapy alone (C) treatment for patients with mismatch repair-proficient microsatellite-stable (pMMR-MSS) and mismatch repair-deficient microsatellite instability-high (dMMR-MSI-H) advanced EC from the American payers' perspective. The main results include total cost, life-years (LYs), quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER) at a $150,000/QALY of willingness-to-pay.
Results: In the pMMR-MSS population, DC, PC, and C produced costs (QALYs) of $99,205 (3.02), $322,530 (3.25), and $421,923 (4.40), resulting in corresponding ICERs of $974,177/QALY (PC vs. C), $234,527/QALY (DC vs. C), $86,671/QALY (DC vs. PC), respectively; In the dMMR-MSI-H population, DC, PC, and C obtained costs (QALYs) of $120,177 (5.73), $691,399 (8.43), and $708,787 (11.26), yielding ICERs of $266,423/QALY (PC vs. C), $135,165/QALY (DC vs. C), $7,866/QALY (DC vs. PC), respectively.
Conclusion: In the US, DC was a more cost-effective treatment than PC for patients with advanced EC irrespective of MMR status. However, compared to C, DC was associated with more cost-effectiveness in the dMMR-MSI-H population.

Keywords: Endometrial Cancer; Immune Checkpoint Inhibitors; Combination Chemotherapy; Mismatch Repair; Cost-effectiveness Analysis

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Availability of Data and Materials
All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Z.Y., L.K., Z.H.; Data curation: Z.H.; Formal analysis: Z.Y., L.K.; Funding acquisition: Z.H.; Investigation: Z.Y., L.K.; Methodology: Z.Y.; Project administration: Z.H.; Resources: Z.H.; Software: Z.H.; Supervision: Z.H.; Validation: Z.Y., L.K., Z.H.; Visualization: Z.Y., L.K., Z.H.; Writing - original draft: Z.Y., L.K., Z.H.; Writing - review & editing: Z.Y., L.K., Z.H.

Synopsis
The Markov model was first established based on RUBY and NRG-GY018 trials. We evaluated the cost-effectiveness of DC, PC, and C for advanced EC based on MMR status. The ICER of DC versus PC or C was $7,866/QALY and $135,165/QALY for dMMR-MSI-H population, respectively.

DC was cost-effective treatment for patients with advanced dMMR-MSI-H EC.

INTRODUCTION

Endometrial cancer (EC) remains the most frequently diagnosed and second deadliest gynecological malignancy in the US, with 66,200 new patients and 13,030 deaths forecast for 2023 alone [1]. While approximately 67% of patients are diagnosed while the disease is in its early stages, 10%–15% are first diagnosed with advanced EC, exhibiting a 5-year survival rate of 15%–17% [2,3]. The specific molecular subtype of a given EV tumor is closely tied to the prognosis of affected patients, with 80% and 30% of patients having mismatch repair-proficient microsatellite-stable (pMMR-MSS) and mismatch repair-deficient microsatellite instability-high (dMMR-MSI-H) tumors [2,4,5]. In patients with recurrent or advanced primary EC, first-line treatment generally consists of carboplatin plus paclitaxel [6]. Even with such treatment, however, patients exhibit a relatively poor overall prognosis, with the GOG0209 (NCT00063999) trial revealing respective median progression-free survival (mPFS) and overall survival (mOS) rates of just 1 and 3 years [7]. There is thus a clear unmet need for novel therapeutic agents and approaches that can achieve significant benefits in EC patients irrespective of their molecular status.

Immune checkpoint inhibitors (ICIs) that blockade the programmed death receptor 1 (PD-1) signaling pathway have emerged as promising options for patients with advanced EC associated with prolonged survival [8-12]. The humanized monoclonal anti-PD-1 antibodies pembrolizumab (Keytruda™; MerckSharpDohme, Rahway, NJ, USA) and dostarlimab (Jemperli™; GlaxoSmithKline, Brentford, UK) have been successfully developed for clinical use [13,14]. Recently, two large phase 3 randomized controlled trials (RCTs) demonstrated significant clinical benefits of PD-1 inhibitors in combination with chemotherapy for advanced EC [11,12]. The phase III RUBY trial (NCT03981796) found that combined dostarlimab plus chemotherapy (DC) treatment was associated with superior progression-free survival (PFS) (pMMR-MSS patients: hazard ratio [HR]=0.76; 95% confidence interval [CI]=0.59–0.98; p<0.001; dMMR-MSI-H patients: HR=0.28; 95% CI=0.16–0.50; p<0.001) and OS (pMMR-MSS patients: HR=0.73; 95% CI=0.52–1.02; dMMR-MSI-H patients: HR=0.30; 95% CI=0.13–0.70; p<0.001) outcomes relative to chemotherapy alone [11]. Another NRG-GY018 trial (NCT03914612) revealed that pembrolizumab plus chemotherapy (PC) treatment was associated with better PFS as compared to chemotherapy (pMMR-MSS population: HR=0.54; 95% CI=0.41–0.71; dMMR-MSI-H population: HR=0.30; 95% CI=0.19–0.48), with similar benefits for patient OS [12]. In light of such efficacy, DC and PC hold promise as an emerging approach to the treatment of patients with advanced EC that is likely to be embraced in updated international guidelines soon.

Given the ever-expanding repertoire of treatment options with promising clinical efficacy profiles, the associated financial costs and the burden they impose on patients and healthcare systems as a whole are an important focus of growing concern. Cost-effectiveness

analyses are vital to providing clinicians, policymakers, and patients with the information necessary to make informed healthcare decisions. As such, the present study was conducted to compare the relative cost-effectiveness of DC, PC, and chemotherapy alone regimens for the treatment of advanced EC from the perspective of payers in the US.

MATERIALS AND METHODS

The Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement was used to guide the design and execution of this study, which was completed in March 2023 [15] (**Table S1**). No institutional review board oversight was required, as this study was based entirely on publically available data.

1. Study population and treatments

While the randomized populations enrolled in the RUBY and NRG-GY018 trials were distinct, they exhibited similar demographic and clinical profiles, thereby enabling the post-hoc comparisons necessary to complete a cost-effectiveness analysis [11,12] (**Table S2**). The eligible hypothetical patient population for the present analysis was comprised of 1,307 advanced, metastatic, or recurrent EC patients, of whom 964 (74%) and 343 (26%) were respectively diagnosed with pMMR-MSS and dMMR-MSI-H disease [11,12]. These patients were randomly assigned to undergo treatment with DC (245 [19%]), PC (405 [31%]), or chemotherapy alone (657 [50%]), of whom 328 (28.0%) and 115 (46.9%), respectively, ultimately exhibited progressive disease (PD) or failed to tolerate the assigned treatment regimens such that they underwent second-line treatment with cisplatin plus doxorubicin, which was selected in light of appropriate guidelines and trial results [6,10,11,16]. The treatment regimens were pembrolizumab (200 mg) and dostarlimab (500 mg) every 3 weeks for the first six cycles, followed by pembrolizumab (400 mg for up to 20 cycles) and dostarlimab (1,000 mg for up to 3 years) every 6 weeks [11,12]; And chemotherapy regimen was carboplatin (area under the curve of 5 mg/mL/min) and paclitaxel (175 mg/m^2) every 3 weeks for the first six cycles [11,12] (**Table S3**). When calculating drug doses, the utilized patient's mean body weight, mean body surface area, and mean serum creatinine values were 70 kg, 1.86 m^2, and 1 mg/dL, respectively [17,18] (**Table 1**). Any patients that did not undergo second-line treatment were assumed to have received the best supportive care (BSC), with terminal care being administered proximal to death [6].

Table 1. Key parameters: clinical data, utility, and cost

Parameters	Baseline value	Range		Reference	Distribution
		Minimum	Maximum		
Clinical data					
Weibull survival model for OS of chemotherapy					
pMMR-MSS population	Scale=0.0062752, Shape=1.4009273	-	-	[11,12]	-
dMMR-MSI-H population	Scale=0.015821, Shape=1.019816	-	-		-
Weibull survival model for PFS of chemotherapy					
pMMR-MSS population	Scale=0.04254, Shape=1.235642	-	-	[11,12]	-
dMMR-MSI-H population	Scale=0.06041, Shape=1.09473	-	-		-
Weibull survival model for OS of dostarlimab plus chemotherapy					
pMMR-MSS population	Scale=0.012645, Shape=1.080963	-	-	[11]	-
dMMR-MSI-H population	Scale=0.02418, Shape=0.58403	-	-		-
Weibull survival model for PFS of dostarlimab plus chemotherapy					
pMMR-MSS Population	Scale=0.07782, Shape=0.88707	-	-	[11]	-
dMMR-MSI-H Population	Scale=0.06473, Shape=0.71997	-	-		-

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Table 1. (Continued) Key parameters: clinical data, utility, and cost

Parameters	Baseline value	Range		Reference	Distribution
		Minimum	Maximum		
Weibull survival model for OS of pembrolizumab plus chemotherapy					
pMMR-MSS Population	Scale=0.005437, Shape=1.405755	-	-	[12]	-
dMMR-MSI-H Population	Scale=0.003074, Shape=1.232086	-	-		-
Weibull survival model for PFS of pembrolizumab plus chemotherapy					
pMMR-MSS population	Scale=0.028099, Shape=1.438687	-	-	[12]	-
dMMR-MSI-H population	Scale=0.045429, Shape=0.696257	-	-		-
Risk for main AEs in chemotherapy group					
Risk of anemia	0.121	0.097	0.145	[11,12]	Beta
Risk of neutropenia	0.118	0.094	0.142	[11,12]	Beta
Risk of neutrophil count decreased	0.054	0.043	0.065	[11,12]	Beta
Risk for main AEs in dostarlimab plus chemotherapy group					
Risk of anemia	0.149	0.119	0.179	[11]	Beta
Risk of neutropenia	0.095	0.076	0.114	[11]	Beta
Risk of neutrophil count decreased	0.083	0.066	0.100	[11]	Beta
Risk of hypertension	0.071	0.057	0.085	[11]	Beta
Risk of white-cell count decreased	0.066	0.053	0.079	[11]	Beta
Risk of lymphocyte count decreased	0.054	0.043	0.065	[11]	Beta
Risk for main AEs in pembrolizumab plus chemotherapy group					
Risk of anemia	0.153	0.122	0.184	[12]	Beta
Risk of neutropenia	0.166	0.133	0.199	[12]	Beta
Proportion of receiving active second-line treatment					
Chemotherapy	0.590	0.472	0.708	[11,12]	Beta
Dostarlimab plus chemotherapy	0.469	0.375	0.563	[11]	Beta
Pembrolizumab plus chemotherapy	0.570	0.456	0.684	[12]	Beta
Utility and disutility					
Utility of PFS	0.817	0.654	0.980	[17]	Beta
Utility of PD	0.779	0.623	0.935	[17]	Beta
Disutility of hypertension	0.010	0.008	0.012	[17]	Beta
Disutility of neutropenia	0.050	0.400	0.600	[17]	Beta
Disutility of anemia	0.073	0.058	0.088	[17]	Beta
Disutility of lymphocyte count decreased	0.090	0.072	0.108	[19]	Beta
Disutility of neutrophil count decreased	0.090	0.072	0.108	[19]	Beta
Disutility of white-cell count decreased	0.090	0.072	0.108	[20]	Beta
Cost, $/cycle					
Pembrolizumab	22,167	17,734	26,600	[21]	Gamma
Dostarlimab	22,392	17,914	26,870	[21]	Gamma
Paclitaxel	110	88	132	[21]	Gamma
Carboplatin	47	38	56	[21]	Gamma
Second-line treatment	350	280	420	[21]	Gamma
AEs in chemotherapy group	5,229	4,183	6,275	[17,19,20]	Gamma
AEs in dostarlimab plus chemotherapy group	5,691	4,553	6,829	[17,19,20]	Gamma
AEs in pembrolizumab plus chemotherapy group	6,340	5,072	7,608	[17,19,20]	Gamma
Administration	299	239	359	[17]	Gamma
MMR testing per patient	488	390	586	[17]	Gamma
Follow-up and monitoring	900	720	1,080	[17]	Gamma
Best supportive care	2,596	2,077	3,115	[17]	Gamma
Terminal care per patient	35,277	28,222	42,332	[17]	Gamma
Body weight (kg)	70	56	84	[17]	Normal
Body surface area (m^2)	1.84	1.47	2.21	[17]	Normal
Discount rate	0.03	0	0.05	[17,19]	Uniform

AE, adverse event; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability-high; MSS, microsatellite-stable; OS, overall survival; PD, progressed disease.; PFS, progression-free survival; pMMR, mismatch repair-proficient.

2. Model establishment and survival outcomes

To simulate disease progression in advanced EC patients, a Markov model was established with three mutually exclusive health states (PFS, PD, and death). This model was then used for comparisons of the relative cost-effectiveness of DC, PC, and chemotherapy alone (**Fig. S1**).

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This model was developed based on the design of the two utilized trials, with 3 weeks per model cycle and an overall time horizon of 20 years after which >99% of patients had died. Survival curves for chemotherapy were reconstructed by summarizing patient data from the two trials (**Fig. S2**). OS and PFS curves were used with this model to assess the advantages of these three therapeutic regimens based on calculated transition probabilities [17], after which fitting was performed for parametric Exponential, Weibull, Gompertz, Log-logistic, and Lognormal survival models [19]. Through a combination of visual assessment, clinical rationality, and Akaike's and Bayesian information criterion results, the Weibull distribution was selected as the model exhibiting the best fit, with appropriate parameters being computed with γ (scale) and λ (shape) [19] (**Fig. S3**, **Table S4**, and **Table 1**). These analyses were completed using the TreeAge Software (TreeAge Pro 2021®), GetData Graph Digitizer (Version 2.26), and the R (v 4.1.1) with 'survHE' and survival' packages.

Primary outcomes for the established model included total costs, life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). A willingness-to-pay (WTP) threshold for payers based in the US of $150,000/QALY was selected as per World Health Organization (WHO) recommendations and prior publications [17]. When adjusting for costs and life expectancies, a 3% annual discount rate was utilized (**Table 1**) [17,19].

3. Utility value and cost inputs

Given that neither of the trials used to develop the present study provided detailed reporting to the global health status-quality of life dimension from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the PFS and PD states were assigned respective utility score values of 0.817 and 0.779 as per a report published previously by Liu et al. [17]. The impact of deteriorating quality of life (QoL) associated with clinical events was assessed based on disutility values multiplied by adverse event (AE) incidence (**Table 1**) [17,19,20].

Direct costs taken into consideration for this analysis included the costs of drugs, costs administration, follow-up, monitoring, MMR testing, BSC, AEs management (Grades 3–4, ≥5% incidence), and terminal care (**Table 1**). The Centers for Medicare & Medicaid Services and American drug price-related websites were used to determine drug costs [21], whereas prior publications were used to determine all other costs included in these analyses [17]. The US Bureau of Labor Statistics CPI calculator was used to adjust all costs to 2022 dollars based on inflation statistics [22].

4. Sensitivity and subgroup analyses

Uncertainty and the effects of particular parameters on the established model were explored through sensitivity analyses in which parameters were varied within 20% from baseline values, as presented using tornado diagrams [23]. Probabilistic sensitivity analyses were performed to determine the odds of a given regimen being cost-effective within the defined range on the cost-effectiveness plane by conducting 10,000 Monte Carlo simulations, with results being presented in the form of scatter plots and acceptability curves [23].

Subgroup analyses were performed for four different subgroups in the dMMR-MSI-H population. HRs for PFS when comparing DC to PC were obtained through indirect comparative analyses of the HRs associated with the target combination regimens (DC to PC vs. chemotherapy; PC vs. chemotherapy) for appropriate subgroups, with other parameters being consistent across the overall patient population. Analyses were performed using the R 'netmeta' package [24].

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5. Ethics approval and consent to participate

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, it does not require the approval of the independent ethics committee.

RESULTS

1. Baseline results

Using the established model with a 20-year time horizon, pMMR-MSS and dMMR-MSI-H advanced EC patients that underwent DC (PC) treatment exhibited survival intervals that were respectively prolonged by 1.76 LYs (0.31 LYs) and 5.52 LYs (2.69 LYs) as compared to those for patients that underwent chemotherapy alone treatment. When taking QoL, DC or PC provided the additional cost of $322,718 ($588,610) and $223,325 ($571,122) with additional 1.38 QALYs (4.36 QALYs) and 0.23 QALYs (2.15 QALYs) compared with chemotherapy alone, respectively, resulting in an ICER of $234,527/QALY ($135,165/QALY) and $974,177/QALY ($266,423/QALY) in the pMMR-MSS (dMMR-MSI-H) population. In addition, ICER of DC versus PC was $86,671/QALY and $7,866/QALY in the pMMR-MSS and dMMR-MSI-H population, respectively (**Table 2**).

2. Sensitivity analysis

The tornado diagrams were derived from the one-way sensitivity analyses between the two different ICI treatment groups in pMMR-MSS and dMMR-MSI-H populations (**Fig. 1**). In the comparison between DC and PC, ICIs prices, the costs of AEs management, and the risk of AEs have a great influence on the ICER results. The effects of other analyzed parameters on ICER values were relatively minor. However, these variable parameters do not change the conclusions significantly to verify the stability of the model.

A cost-effectiveness acceptability curve demonstrated that the cost-effectiveness of DC treatment rises as the WTP threshold is increased (**Fig. 2**). As shown in the associated scatter plot, the cost-effectiveness ratios for DC, PC, and chemotherapy alone in pMMR-MSS (dMMR-MSI-H) population were 0% (0%), 0% (67.1%), and 100% (25.0%) at a WTP threshold of $150,000/QALY (**Fig. S4**). In addition, compared with PC, the probability of cost-effectiveness of DC was 87.9% and 93.3% among pMMR-MSS and dMMR-MSI-H population, respectively (**Fig. S4**).

Table 2. Baseline results

Treatment	Total cost, $	LYs	ICER, $/LY	QALYs	ICER, $/QALY
pMMR-MSS population					
Chemotherapy	99,205	3.84	Reference	3.02	Reference
Pembrolizumab plus chemotherapy	322,530	4.15	736,174	3.25	974,177
Dostarlimab plus chemotherapy	421,923	5.60	183,702*	4.40	234,527*
			68,547†		86,671†
dMMR-MSI-H population					
Chemotherapy	120,177	5.74	Reference	4.50	Reference
Pembrolizumab plus chemotherapy	691,399	8.43	212,996	6.65	266,423
Dostarlimab plus chemotherapy	708,787	11.26	106,694*	8.86	135,165*
			6,144†		7,866†

dMMR, mismatch repair-deficient; ICER, incremental cost-effectiveness ratio; LY, life-year; MSI-H, microsatellite instability-high; MSS, microsatellite-stable; pMMR, mismatch repair-proficient; QALY, quality-adjusted life-year.
*Compared to chemotherapy strategy; †Compared to pembrolizumab plus chemotherapy strategy.

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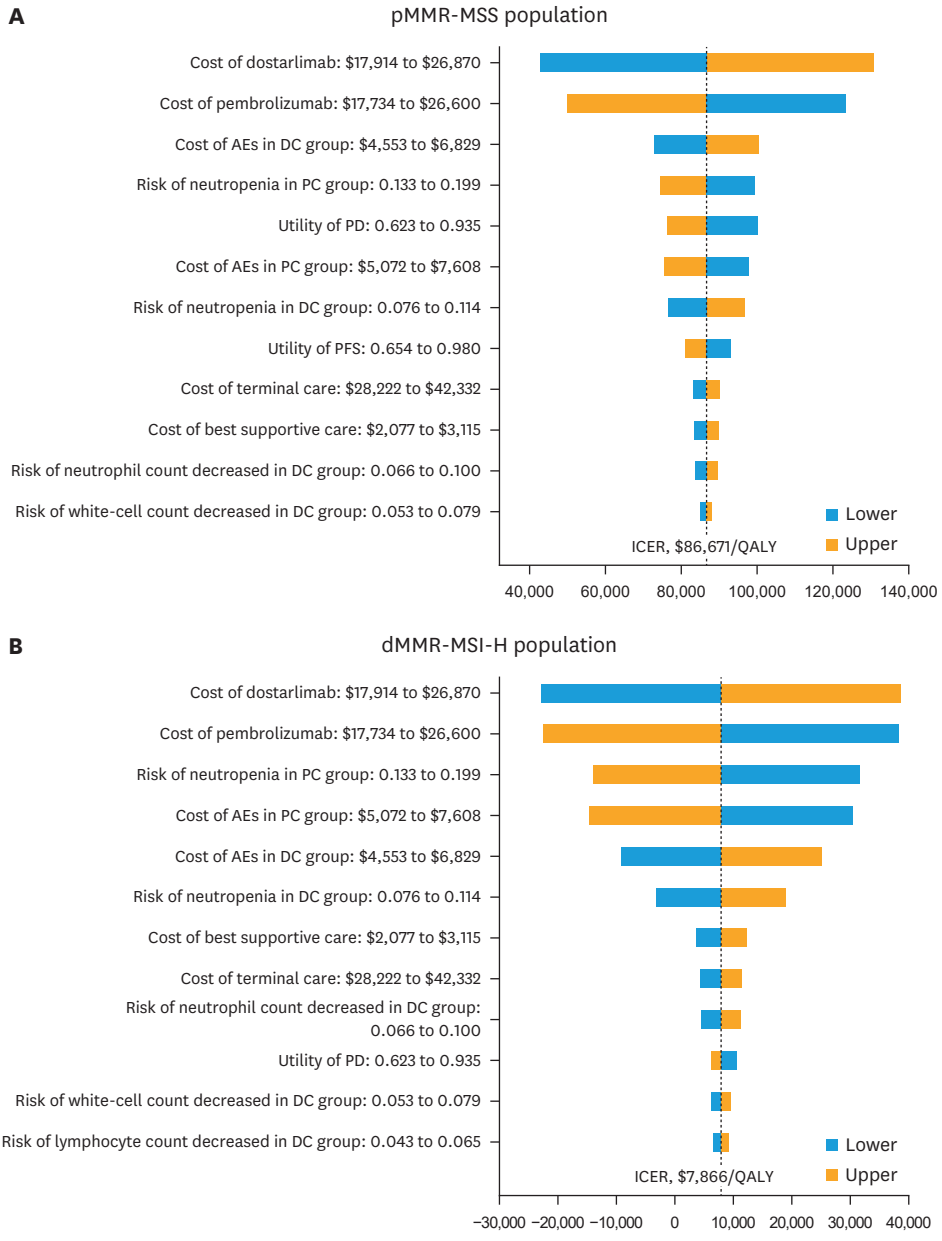

Fig. 1. The one-way sensitivity analyses for DC strategy compared to PC strategy in the pMMR-MSS population (A) and dMMR-MSI-H population (B), respectively.
AE, adverse event; DC, dostarlimab plus chemotherapy; dMMR, mismatch repair-deficient; ICER, incremental cost-effectiveness ratio; MSI-H, microsatellite instability-high; MSS, microsatellite-stable; PC, pembrolizumab plus chemotherapy; PD, progressive disease; PFS, progression-free survival; pMMR, mismatch repair-proficient; QALY, quality-adjusted life-year.

In the four analyzed subgroups, DC treatment was associated with greater odds of a reduction in the risk of death or progression in patients with ≥65 years, prior history of pelvic radiation, and recurrent EC. Other subgroups may choose PC therapy more favorably. Further cost-effectiveness analysis, the ICER values for DC ranged from -$21,968/QALY to $140,174/QALY, with incremental net health benefits (INHBs), INHB from 0.1 to 2.6 QALYs, and a corresponding 77.3% to 96.6% chance of being cost-effective (**Table 3**).

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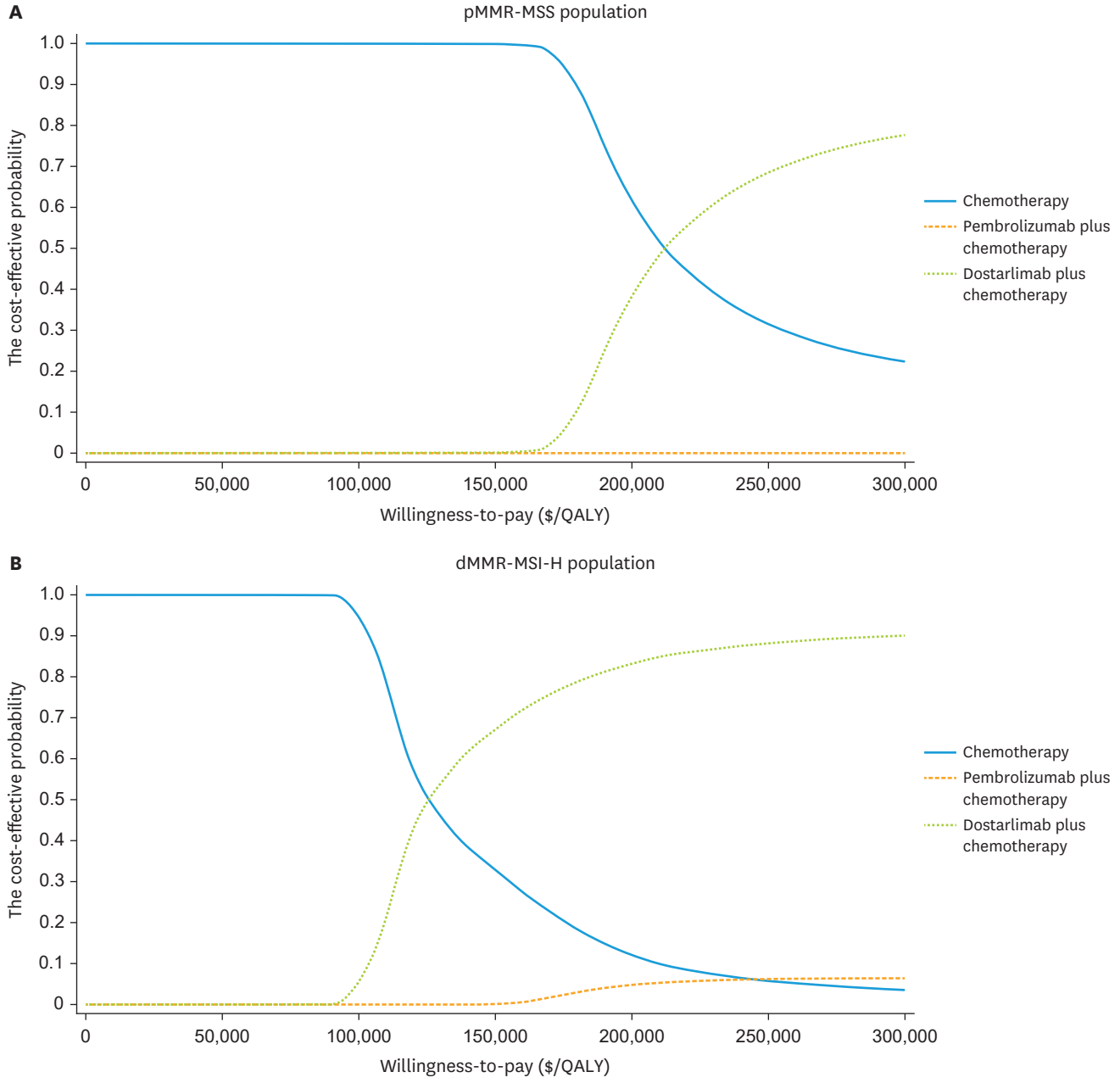

Fig. 2. The cost-effectiveness acceptability curves for dostarlimab plus chemotherapy, pembrolizumab plus chemotherapy, and chemotherapy strategy in the pMMR-MSS population (A) and dMMR-MSI-H population (B), respectively.
dMMR, mismatch repair-deficient; MSI, microsatellite instability; MSS, microsatellite-stable; pMMR, mismatch repair-proficient; QALY, quality-adjusted life-year.

DISCUSSION

Patients with EC treatment and care-related costs in 2020 were estimated at $6.03 billion, and these costs are only continuing to rise in the US [25]. Value-based oncology research is increasingly important in light of rising cancer rates, inherent limitations on the availability of medical resources, and the immense burden that cancer-related medical costs impose. When the emergence of immunotherapeutic treatment options, a growing number of clinical trials have been conducted that offer promising new opportunities for the more effective treatment

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Table 3. Results of subgroup analyses

Subgroup	HR for PFS of DC vs. PC (95% CI)	ICER ($/QALY)	INHB (QALYs), median (range)	Cost-effectiveness probability of dostarlimab plus chemotherapy (%) (WTP of $150,000 per QALY)
Age (yr)				
<65	2.00 (0.69 to 5.80)	−21,968	2.6 (0.8 to 4.3)	96.6
≥65	0.83 (0.31 to 2.26)	77,063	1.0 (−0.1 to 2.8)	91.6
Race				
White	1.12 (0.51 to 2.46)	44,402	1.5 (0.4 to 3.0)	94.4
Other	1.40 (0.18 to 10.90)	18,968	1.9 (−0.6 to 5.0)	93.8
Prior history of pelvic radiation				
Yes	0.43 (0.08 to 2.37)	140,174	0.1 (−0.9 to 2.9)	64.9
No	1.32 (0.54 to 3.21)	25,539	1.8 (0.4 to 3.4)	93.7
Disease status				
Primary advanced	1.08 (0.30 to 3.94)	48,179	1.5 (0.2 to 3.8)	94.4
Recurrent	0.60 (0.23 to 1.55)	110,827	0.5 (−0.4 to 2.1)	77.3

CI, confidence interval; DC, dostarlimab plus chemotherapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefits; PC, pembrolizumab plus chemotherapy; PFS, progression-free survival; QALY, quality-adjusted life-year; WTP, Willingness-to-pay.

of advanced EC, and the introduction of molecular/genomic analysis will help to formulate the most appropriate treatment [26]. Based on the KEYNOTE-146 (NCT02501096) and KEYNOTE-158 (NCT02628067) trials, Barrington et al. [27,28] determined that pembrolizumab or lenvatinib plus pembrolizumab were cost-effective when compared to chemotherapy alone in advanced recurrent dMMR-MSI-H EC patients (ICER, 147,249/QALT or $1.6 million/QALY) in the US, whereas the same was not true for patients with pMMR-MSS disease (ICER, 153,028/QALY). Using data from the KEYNOTE-775 trial, Feng et al. [29] and Zheng et al. [30] similarly determined that lenvatinib plus pembrolizumab was not a cost-effective alternative to chemotherapy when treating advanced pMMR-MSS EC patients (ICER, $413,256.68/QALY and $70,962.09/QALY) from the perspectives of payers in the US or China. In contrast, Liu et al. [17] did find lenvatinib plus pembrolizumab to be a cost-effective treatment option (ICER, $110,401). When comparing various ICI-based regimens, Dioun et al. [31] further determined that second-line pembrolizumab treatment was more cost-effective than dostarlimab treatment in advanced dMMR-MSI-H EC patients. The recent RUBY and NRG-GY018 trials further emphasized the survival benefits that dostarlimab and pembrolizumab treatment can confer on EC patients, emphasizing the need for more data regarding its relative cost-effectiveness to inform future research and the formulation of appropriate international guidelines. The cost-effectiveness of the corresponding immunotherapy combination versus chemotherapy has also been demonstrated in the *Journal of Gynecologic Oncology*. However, there is currently no focus on the comparison between different immunization combination strategies. Accordingly, we herein conducted the first cost-effectiveness analysis specifically comparing PC, DC, and chemotherapy alone in patients with advanced EC from an American payers' perspective, taking patient MRR status into account in these analyses.

While DC was associated with the prolongation of pMMR-MSS patient survival, yielding 1.15 QALYs (1.45 LYs) and 1.38 QALYs (1.76 LYs), the associated costs were also high at $276,286 and $25,719 for an ICER of $86,671/QALY and $234,527/QALY than PC and chemotherapy alone, respectively, which was compared to the WTP threshold of $150,000/QALY. These data thus suggest that DC regimen is more cost-effective than PC when treating patients with advanced pMMR-MSS EC, but not compared with chemotherapy alone. This was largely attributable to the high costs associated with the DC regimen, mainly owing to the costs of managing treatment-related AEs and terminal care. Accordingly, future clinical research should focus on safety profiles and appropriate follow-up to mitigate treatment-related AEs and patient mortality associated with this or similar regimens. In one-way sensitivity analyses,

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ICIs prices were identified as the factor that had the largest impact on model outputs. Pembrolizumab reduced the price by 90% ($5.54/mg) or dostarlimab by 47% ($11.87/mg), which were associated with PC or DC being more cost-effective than chemotherapy alone, respectively. In addition, when the price of pembrolizumab was reduced by 35% ($36.02/mg), PC was a more cost-effective strategy than DC. To render these innovative therapeutics suitable for recommendation under international guidelines, it is thus important that various measures including comprehensive drug procurement efforts and charitable policies be implemented to drive down drug prices. Such price adjustments will ultimately increase the cost-effectiveness of anti-PD-1-based treatment regimens. Changes in other parameters did not impact the conclusions of this study, confirming that the overall model was robust.

ICIs have recently exhibited promising antitumor efficacy and associated improvements in advanced EC patient survival. Molecular and histopathological classification efforts for EC. Emphasize the importance of adequate management of patients with EC, whose improved prognosis and tailored management require new perspectives on prevention and diagnosis [32]. However, are complex, hampering efforts to establish a single regimen that can effectively treat all patients with this devastating form of cancer. Four EC molecular subtypes have been defined to date including DNA POLE (ultra mutated/polymerase ε mutated), MSI-H, pMMR-MSS, and copy number–high (predominantly serous histology), with each being associated with distinct treatment options and prognostic outcomes [33]. Testing for appropriate efficacy-associated biomarkers can thus provide a means of selecting the optimal ICI regimen for a given subset of cancer patients. The majority of EC patients exhibit dMMR-MSI-H disease, with tumors in these individuals harboring a higher mutation load such that they are more likely to respond to ICI treatment [2]. Accordingly, patient MMR status was taken into account when evaluating the cost-effectiveness of these different anti-PD-1-based combination treatment regimens in individuals with advanced EC. Overall, these analyses demonstrated that DC, PC, and chemotherapy alone yielded 8.86 QALYs, 6.65 QALYs, and 4.5 QALYs with the ICER of $266,423 (PC vs. chemotherapy alone), $135,165 (DC vs. chemotherapy alone), and $7,866 (DC vs. PC) for patients with advanced dMMR-MSI-H EC, respectively. These results were in line with the results from the overall EC patient population, suggesting that DC is the most cost-effective approach to treating advanced EC irrespective of patient MMR status. Two recently conducted real-world studies enrolling 1,093 Korean and 124 American patients with advanced gynecologic malignancies reported a 33.3% objective response rate and respective mPFS and mOS intervals of 29 and 30 months in advanced dMMR-MSI-H EC patients [34,35]. Successful outcomes associated with the immunotherapeutic treatment of EC patients underscore the need to better define factors that can predict patient responses to immunotherapy. Selecting the most appropriate treatment options for specific subsets of patients based on available clinical trial evidence and associated cost-effectiveness analyses is vital. Decisionmaking models must therefore be developed that take into account both drug efficacy evaluations and the utilization of available clinical resources to better improve outcomes in particular cancer patient groups.

This study exhibits several notable strengths. For one, this is the first cost-effectiveness analysis we are aware of comparing DC to PC treatment options for advanced EC patients in light of recently published clinical evidence. Dostarlimab and pembrolizumab are emerging therapeutic options with great promise as a tool for EC patient care, having received FDA approval for the treatment of specific EC patient subsets. Despite this fact, economic analyses of these treatment options have remained limited to date. Secondly, given the country-specific differences in medical systems and patient characteristics, this comparison

was specifically conducted from an American payer perspective. As such, these data can serve as a foundation for clinicians, policymakers, and patients in the US seeking to make the most appropriate decisions regarding healthcare-related financial matters. Our results also serve as an objective reference that can inform the approval of DC and PC under international guidelines. Third, the MMR status of patients was taken into consideration for these analyses given its clinical relevance, with economic outcomes being assessed for four relevant patient subgroups. Financial insights for these subsets of patients may help facilitate the selection of the most appropriate treatment regimens. Lastly, all analyses of medical costs performed herein were adjusted based on the most recently available data from the US in 2022, thereby helping to minimize the potential impact of any variations in medical costs on study results.

This study is subject to certain limitations. For one, these analyses are dependent on cross-over comparisons of two large phase III RUBY and NRG-GY018 RCTs given that no corresponding head-to-head comparisons of these treatment options have been conducted to date. While both studies incorporated patient populations with similar characteristics (**Table S2**), the complete elimination of variations between these trial cohorts was not possible. Secondly, full survival outcomes beyond the observation window for the two trials had to be extrapolated based on the Weibull distribution. Even so, owing to the good fit of the model, there was relatively little uncertainty for long-term patient survival. Long-term benefits associated with dostarlimab or PC treatment remain to be addressed. With the availability of additional mature datasets, the validity of the established model to long-term survival can be assessed. Third, detailed QoL information was not reported for the two trials. The disease utility values for the present analysis were thus extracted from a previously published economic model of advanced EC. Even so, these utility values had no impact on the overall model results in sensitivity analyses. Lastly, only grade 3–4 AEs with incidence rates of 5% or greater were included in this analysis, whereas grade 1–2 treatment- and immune-related AEs were excluded, likely causing an underestimation of total costs. However, the limited incidence of these AEs had a relatively small impact on model results.

In summary, the present analysis revealed that DC represents the most cost-effective therapeutic option for patients with advanced dMMR-MSI-H EC at a WTP threshold of $150,000/QALY. However, the health advantages associated with dostarlimab combined with chemotherapy regimens may help to justify its use as an alternative therapy for the pMMR-MSS population. Future analyses assessing survival outcomes will be crucial to identifying those patients with the greatest chance of benefiting from ICI-based treatment. Our results provide a valuable foundation for healthcare decision-making, the associated development of medical reimbursement policies in the US, and the update of international guidelines.

SUPPLEMENTARY MATERIALS

Table S1
The CHEERS 2022 checklist

Table S2
Patient baseline characteristics

Table S3
Drug dose and cost

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Table S4
Summary of statistical goodness-of-fit of K-M curve

Fig. S1
Model structure.

Fig. S2
The replicated Kaplan-Meier curve of chemotherapy alone treatment.

Fig. S3
Kaplan-Meier curve fitting and extrapolation.

Fig. S4
Probability sensitivity analysis scatter plot.

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