A Cost-effectiveness Analysis Comparing Pembrolizumab-Axitinib, Nivolumab-Ipilimumab, and Sunitinib for Treatment of Advanced Renal Cell Carcinoma

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Objectives: The US Food and Drug Administration (FDA) approved nivolumab-ipilimumab and pembrolizumab-axitinib as first-line treatments for metastatic, clear-cell, renal cell carcinoma (mRCC) based on results from CheckMate 214 and KEYNOTE-426. Our objective was to compare the adjusted, lifetime cost-effectiveness between nivolumab-ipilimumab, pembrolizumab-axitinib, and sunitinib for patients with mRCC.

Materials and Methods: A 3-state Markov model was developed comparing nivolumab-ipilimumab and pembrolizumab-axitinib to each other and sunitinib, over a 20-year lifetime horizon from a US medical center perspective. The clinical outcomes of nivolumab-ipilimumab and pembrolizumab-axitinib were compared using matching-adjusted indirect comparison. Costs of drug treatment, adverse events, and utilities associated with different health states and adverse events were determined using national sources and published literature. Our outcome was incremental cost-effectiveness ratio (ICER) using quality-adjusted life years (QALY). One-way and probabilistic sensitivity analyses were conducted.

Results: Nivolumab-ipilimumab was the most cost-effective option in the base case analysis with an ICER of $34,190/QALY compared with sunitinib, while the pembrolizumab-axitinib ICER was dominated by nivolumab-ipilimumab and was not cost-effective (ICER = $12,630,828/QALY) compared with sunitinib. The mean total costs per patient for the nivolumab-ipilimumab and pembrolizumab-axitinib arms were $284,683 and $457,769, respectively, compared with sunitinib at $241,656. QALY was longer for nivolumab-ipilimumab (3.23 QALY) than for adjusted pembrolizumab-axitinib (1.99 QALY), which was longer than sunitinib's (1.98 QALY). These results were most sensitive to treatment cost in both groups, but plausible changes did not alter the conclusions.

Conclusions: The base case scenario indicated that nivolumab-ipilimumab was the most cost-effective treatment option for mRCC compared with pembrolizumab-axitinib and sunitinib.

Key Words: renal cell carcinoma, cost-effectiveness analysis, pembrolizumab, axitinib, nivolumab, ipilimumab, sunitinib, Keytruda, Opdivo, yervoy

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In the United States, an estimated 73,750 new cases of kidney cancer were diagnosed in 2020 with ~14,830 deaths.[1] The most common form is renal cell carcinoma (RCC), with ~70% having the clear-cell subtype, which overexpresses vascular endothelial growth factor (VEGF) receptors.[2,3] One-third of patients present with poor prognosis as metastatic disease becomes resistant to chemo-radiotherapy, requiring combination regimens with enhanced efficacy.[4–6] Sunitinib, a VEGF kinase inhibitor, has been standard of care since 2006.[7] In 2018, nivolumab-ipilimumab, a combination of a programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4 immune checkpoint inhibitors (ICI), was US Food and Drug Administration (FDA)-approved based on the CheckMate 214 trial.[8] In 2019, pembrolizumab-axitinib, a programmed cell death protein 1 ICI and a VEGF kinase inhibitor combination, was FDA-approved based on the KEYNOTE-426 trial.[9]

While cost-effectiveness analyses (CEA) have compared combination and standalone first-line treatments for metastatic renal cell carcinoma (mRCC), there are no direct efficacy trials comparing combination therapies.[10–13] A recently published simulation CEA compared the combination treatments, but did not adjust survival for comparisons across all risks or compare each with sunitinib, which is crucial to help guide clinical decision making.[14–16] The objective of this analysis is to compare the lifetime cost-effectiveness amongst two combination therapies—nivolumab-ipilimumab and pembrolizumab-axitinib—and each with sunitinib in previously untreated, clear-cell mRCC.

MATERIALS AND METHODS

This CEA compared 3 treatment options: (1) nivolumab-ipilimumab, (2) pembrolizumab-axitinib, and (3) sunitinib for mRCC across risk groups to determine the incremental cost-effectiveness ratio (ICER) at the willingness-to-pay (WTP) threshold of $150,000/quality-adjusted life years (QALY).[17]

Model Overview

We constructed a Markov model using TreeAge Pro 2020 software for a base case and two other scenarios using a continuous time stochastic approach (Fig. 1) to simulate a treatment decision from a health system perspective with three different drug regimens and followed patients as they transitioned through three different health states: progression-free, progressed, and death. We used costs in US dollars (USD) annually discounted by 3%, a 1-month cycle length over a 20-year time horizon until death, and half-cycle corrections.[18] The base case model outcome was the ICER using QALY.[17] Each treatment option was compared with the next less costly option as well as to the common comparator sunitinib, using the formula: $(Cost_{RX1}\text{-}Cost_{RX2})/(QALY_{RX1}\text{-}QALY_{Rx2})$ and a WTP threshold of $150,000.[17]

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The authors declare no conflicts of interest.

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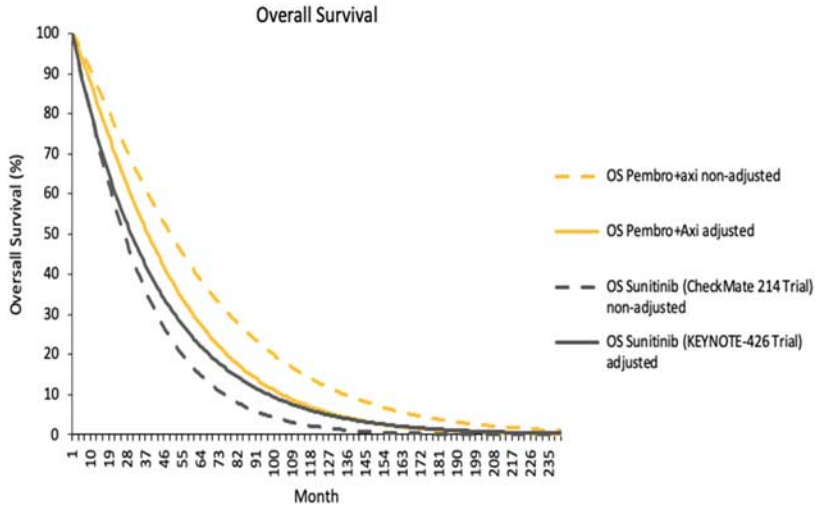

FIGURE 1. Survival outcomes for sunitinib (in both clinical trials), pembrolizumab-axitinib (nonadjusted and adjusted survival outcomes scenarios), and nivolumab-ipilimumab for 20-year time horizon. full color online

Study Population and Treatments

Study Population

The modeled population were at least 18 years old with mRCC, had measurable disease per Respond Evaluation Criteria in Solid Tumors (RECIST) 1.1, a Karnofsky performance status (KPS) of at least 70%, and had no prior systemic therapy for mRCC.

Survival Estimation

Overall survival (OS) and progression-free survival (PFS) from the CheckMate 214 and KEYNOTE-426 clinical trials were used to compare between the treatment groups.

Matching-Adjusted Indirect Survival Comparisons

We assessed inclusion and exclusion criteria for each study, the baseline characteristics of the final patient samples recruited into the trials, and the actual survival curves of the sunitinib treatment arms of each study to determine if adjustments were required to equalize the comparisons. Although the inclusion and exclusion criteria in the two trials were the same, comparison of each treatment group's baseline International Metastatic Renal Cell Carcinoma Database Consortium's (IMDC) prognostic risk demonstrated the nivolumab-ipilimumab trial had a lower proportion of favorable risk patients compared with the pembrolizumab-axitinib trial. This was confirmed by the more favorable survival benefits of the sunitinib treated patients in the pembrolizumab-axitinib trial when compared with the sunitinib survival curves in the nivolumab-ipilimumab study indicating the need for adjustment.

A matching-adjusted indirect comparison was used to control for this difference in risk by standardizing the control and treatment groups based on the ratio of sunitinib survival differences in OS and PFS in the 2 trials.[19] This standardized adjustment to 1 sunitinib comparator also required the same ratio decrease in the PFS and OS outcomes of the pembrolizumab-axitinib group (Fig. 1). To assess the impact of our indirect control method on our ICER results, we analyzed an additional scenario with unadjusted survival for pembrolizumab-axitinib.

Transition Probabilities

To calculate monthly transition probabilities across health states, we extracted monthly PFS and OS probabilities for each treatment from the published Kaplan-Meier curves using a validated graphical digitizer (Engauge Digitizer version 12.1). A statistical modeling program, R studio (Version 1.2.5033), was used to generate and extend the curves.[20] On the basis of the lowest Akaike information criterion, Weibull was chosen as the best-fit parametric curve for each Kaplan-Meier curve and used point estimates to calculate survival probabilities for our Markov model until 240 months, when all patients had entered the terminal health state (Fig. 1).[21]

Cost Inputs

Costs for drugs, adverse events (AE), disease progression, palliative care, and hospitalization costs were adjusted to 2019 USD using the Consumer Price Index. Total drug costs were calculated using wholesale acquisition cost from RED BOOK, based on a standard 70 kg weight, and dosing regimens from CheckMate 214 and KEYNOTE-426 (Table 1).[8,9,22,30–32] On the basis of the package inserts of each treatment and trial protocols, nivolumab and pembrolizumab were assumed to be administered for 2 years, ipilimumab for 3 months, and axitinib and sunitinib to be continued until disease progression or toxicity.[31,32]

Cost of grade 3/4 AE reported by at least 1% of patients were included, were weighted by the percentage of patients experiencing them, and were assumed to last for the median time to resolution of 3.5 weeks (Table 2).[43,44] Costs for AE management included drug treatment, physician consultations while hospitalized, follow-up physician visits, and laboratory and imaging tests used to diagnose and monitor the AE as determined by the study protocol, manufacturer-supplied AE management guides, treatment guidelines, and expert clinical knowledge.

Treatment-associated costs were determined using the Healthcare Cost and Utilization Project (HCUP) data, the Medicare Physician Fee Schedule, and the Clinical Laboratory Fee Schedule.[23–25]

Utility Estimates

Mean health utility scores weighted for each treatment's health state were obtained from published literature. Nivolumab-ipilimumab, pembrolizumab-axitinib, and sunitinib had different utility scores in the "progression-free" health state based on their different treatment protocols (0.78, 0.73, and

TABLE 1. Model Input Parameters, Distributions, and Range

Parameter	Base Case	Range		Source
		Low	High	
Drug costs* ($) (γ distribution)				RED BOOK,[22] ±25%
Nivolumab plus ipilimumab	$21,247.71	$15,935.78	$26,559.64	
Pembrolizumab plus axitinib	$27,166.94	$20,375.21	$33,958.68	
Sunitinib	$12,205.61	$9154.208	$15,257.01	
Total cost of managing adverse events† ($) (γ distribution)				
Nivolumab plus ipilimumab	$1981.03	$1485.773	$2476.29	HCUP[23] ±25%, Medical Fee Book 2019,[24] CLFS 2019[25]
Pembrolizumab plus axitinib	$5554.97	$4166.23	$6943.37	
Sunitinib	$4870.56	$3652.92	$6088.82	
Utilities‡ (β distribution)				
NI—utility of PFS	0.78	0.71	0.85	ranges from literature[26–29]
NI—utility of PD	0.66	0.45	0.82	
PA—utility of PFS	0.73	0.58	0.88	
PA—utility of PD	0.66	0.53	0.79	
Sunitinib—utility of PFS	0.72	0.58	0.86	
Sunitinib—utility of PD	0.66	0.58	0.86	

*Cost for each treatment corresponds to full course treatment per month as indicated in product label.

†Includes costs of outpatient initial visit, follow-up visits, lab draws, provider costs, hospitalization costs as recommended by the manufacturer of each drug, treatment guidelines, and expert opinion.

‡Utilities were derived from published literature.[26–29]

AE indicates adverse event; CLFS, Clinical Laboratory Fee Schedule; HCUP, Healthcare Cost and Utilization Project; NI, nivolumab plus ipilimumab; PA, pembrolizumab plus axitinib; PD, progressed disease; PFS, progression-free survival.

0.72, respectively).[26–29] All treatments had the same utility during disease progression (0.66) (Table 1). The major differences across the 2 treatments are the serious AE involved and resulting utilities. The nivolumab-ipilimumab trial had higher rates of hypertension, palmar-plantar erythrodysesthesia while pembrolizumab-ipilimumab had higher rates of diarrhea,

TABLE 2. Grade 3 to 4 Adverse Event Episodic Cost (2019 USD) and Incidence by Treatment Group

Adverse Event	Estimated Episodic Cost (2019 USD)	Grade 3 to 4 Toxicity Incidence (%)		
		Nivolumab Plus Ipilimumab (%)	Pembrolizumab Plus Axitinib (%)	Sunitinib* (%)
Rash[33]	$8527.87	1.5		
Diarrhea[33]	$8619.67	3.8	9.0	4.9
Nausea[34]	$7583.07	1.5		1.1
Increased lipase level[35]	$8180.84	10.2		6.5
Decreased appetite[34]	$12,486.35	1.3		
Asthenia/fatigue†[36]	$9921.29	4.2	2.8	7.8
Palmar-plantar erythrodysthesia[37]	$7632.49		5.1	6.4
Hyperthyroidism[38]	$12,378.89		1.2	
Hypertension[39]	$9936.27		22.0	17.5
ALT/AST increase†[33]	$8718.85		13.2	3.0
Proteinuria[33]	$5016.67		2.8	1.4
Dyspnea[34]	$7770.45		1.6	1.2
Abdominal pain[34]	$7457.24		1.2	
Weight decreased[34]	$9502.91		3.0	
Vomiting[34]	$7314.65			1.9
Stomatitis[40]	$17,519.50			2.4
Mucosal inflammation[40]	$11,039.55			2.2
Anemia[41]	$8463.96			4.7
Platelet count decreased[42]	$8.63			7.2
Thrombocytopenia[42]	$11,385.44			5.3
Neutropenia[42]	$17,377.51			6.5
Neutrophil count decreased[42]	$8.63			6.8
White-cell count decreased[42]	$8.63			2.8
Back pain[34]	$10,912.46			1.6

Incidence rates for all adverse events were derived from CheckMate 214 and KEYNOTE-426.[8,9]

*Incidence rates for sunitinib were determined by taking an average of the incidence rates between both trials for those adverse events reported in both and taking incidence rates at value for those adverse events that differed between the two trials.

†Adverse events were reported separately but were assumed to be experienced by the same individual, so the event with higher incidence was considered in the cost calculations.

alanine aminotransferase increased, aspartate aminotransferase increased, and neutropenia.[11,12]

Sensitivity Analyses

Several scenario analyses were conducted: (1) a base case QALY analysis including adjusted survival estimates, utility, and mean parameter estimates; (2) an unadjusted survival scenario analysis with utilities and mean parameter estimates; and (3) a life years saved (LYS) adjusted analysis without utilities.[45]

One-way and probabilistic sensitivity analyses were conducted to test the uncertainty in the model. All model inputs were adjusted by a ±25% range for costs and ±20% range for utility (Table 1).

For the probabilistic sensitivity analyses, parameters were sampled using 10,000 Monte Carlo simulations using gamma distributions for costs and beta distributions for utility values, each with a ±25% range (Table 1). Cost-effectiveness acceptability curves demonstrated the probabilities of cost-effectiveness at different WTP thresholds (Fig. 2).

RESULTS

Base Case

Our CEA demonstrates that nivolumab-ipilimumab is the most cost-effective treatment across our three comparisons.

Nivolumab-ipilimumab was the most cost-effective option with an ICER of $34,190/QALY compared with sunitinib. Pembrolizumab-axitinib was not a cost-effective option, dominated by the nivolumab-ipilimumab combination and with an ICER of $12,630,831/QALY compared with sunitinib in the base case analysis.

The mean total costs per patient for the nivolumab-ipilimumab and the pembrolizumab-axitinib options were $284,683 and $457,769, respectively, compared with sunitinib at $241,656 (Table 3). The projected QALY of patients receiving nivolumab-ipilimumab was 3.23, the adjusted base case with pembrolizumab-axitinib was 1.99, and with sunitinib from the nivolumab-ipilimumab study was 1.98. The unadjusted scenario QALY with pembrolizumab-axitinib was 2.44.

Sensitivity Analysis

The univariate sensitivity analyses for the base case scenario demonstrated that the costs of the three different medication regimens had an important influence on the ICER. However, when the estimated ranges of other variables including AE, palliative care, and hospitalization costs were tested at ±25% upper and lower limits, the cost-effectiveness decision of the treatments was unchanged based on the WTP of $150,000/QALY. The average cost of each drug treatment alone per month across the whole treatment period was $15,436, $12,610, and $12,205 for pembrolizumab-axitinib, nivolumab-ipilimumab, and sunitinib, respectively. Total treatment time varies for each combination treatment which affects the CEA cost comparisons. Nivolumab-ipilimumab treatment is recommended for 2 years, while total treatment time for pembrolizumab-axitinib can be longer (until disease progression). Total treatment time for sunitinib is also until disease progression, but its unit cost is lower than the other 2 drugs. The cost of pembrolizumab-axitinib for the first 2 years is $27,247/month while the post-2-year cost of axitinib alone is $14,134/month. Manufacturer guidelines suggest nivolumab-ipilimumab to be given together for the first 3 months and then nivolumab given alone at a cost of $11,377/month for the remaining 21 months until 2 years.

Univariate sensitivity analysis demonstrated that our results were most affected by drug costs, showing that it was necessary to lower the cost of pembrolizumab-axitinib by at least 37% to $11,250 per month to make it cost-effective compared with sunitinib, and by 58% to $6425 per month to make it cost-effective compared with nivolumab-ipilimumab. In contrast, nivolumab-ipilimumab's price could have increased by a maximum of 59% to $20,100 per month and still be cost-effective compared with pembrolizumab-axitinib. As a result, nivolumab-ipilimumab was cost-effective compared with sunitinib or dominated pembrolizumab-axitinib with significantly lower costs and higher quality-adjusted efficacy.

Scenario Analyses

To challenge our model assumptions and ICER results, we performed scenario analyses with 2 other CEA models in addition to our base case scenario; a LYS model with utility

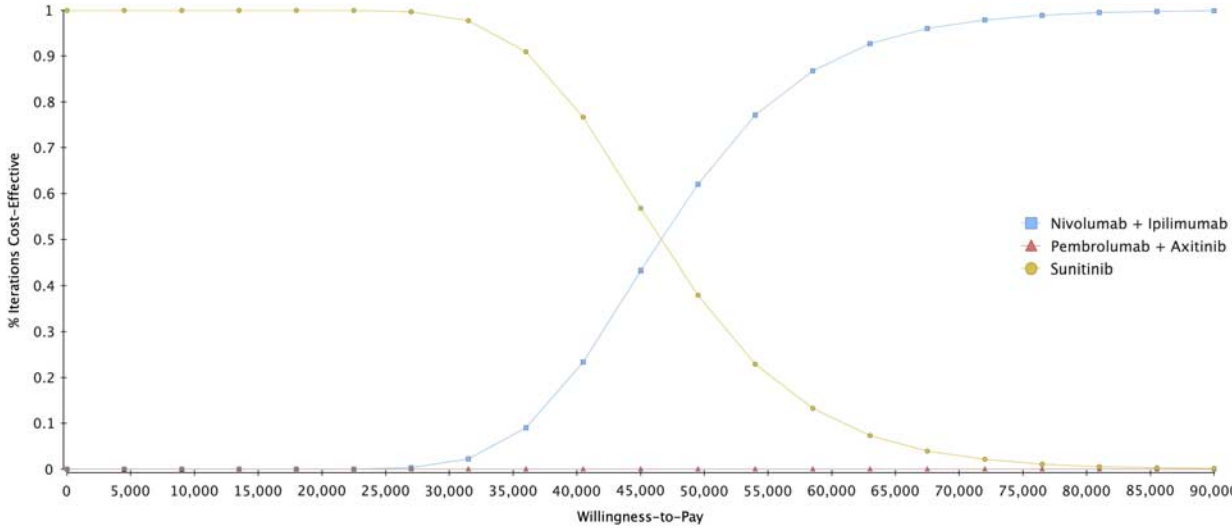

FIGURE 2. Base case acceptability curve for nivolumab-ipilimumab and pembrolizumab-axitinib combination therapy and sunitinib monotherapy from 10,000 Monte Carlo simulations in probabilistic sensitivity analyses. full color online

TABLE 3. Cost-effectiveness Comparing mRCC Treatment of Sunitinib, Nivolumab-ipilimumab, Pembrolizumab-Axitinib for (A) Base Case Scenario (B) Nonadjusted Survival Outcomes Scenario (C) Life Years Saved Scenario

Parameter	Total Cost (2019 USD)	Incremental Cost (2019 USD)	Total Effectiveness	Incremental Effectiveness	ICER
(A) Base case comparisons to the next least cost option					
Sunitinib	$241,656		1.98		
Nivolumab-ipilimumab	$284,683	$43,028	3.23	1.26	$34,190
Pembrolizumab-axitinib	$457,769	$216,113	1.99	−1.24	Dominated by nivolumab-ipilimumab
(A) Base case comparisons -pembrolizumab-axitinib vs. sunitinib					
Sunitinib vs. pembrolizumab-axitinib		$173,085		0.01	$12,620,831
(B) Comparison of nonadjusted survival outcomes scenario to next least cost option					
Sunitinib	$241,656		1.98		
Nivolumab-ipilimumab	$284,683	$43,028	3.23	1.26	$34,190
Pembrolizumab-axitinib	$519,750	$235,067	2.44	−0.79	Dominated by nivolumab-ipilimumab
(B) Comparison of nonadjusted survival outcomes scenario—pembrolizumab-axitinib vs. sunitinib					
Sunitinib vs. pembrolizumab-axitinib		$278,094		0.46	$594,197
(C) Base case comparison of treatments to next least cost option with life years saved scenario					
Sunitinib	$241,656		2.88		
Nivolumab-ipilimumab	$284,683	$43,028	4.60	1.72	$25,095
Pembrolizumab-axitinib	$457,769	$173,086	2.87	−1.73	Dominated by nivolumab-ipilimumab

ICER indicates incremental cost-effectiveness ratio; mRCC, metastatic renal cell carcinoma.

omitted, and an unadjusted survival scenario model to test the validity of our survival adjustments for our cross-trial comparisons.

LYS Scenario

Omitting utility adjustments in our model did not change the comparative ICER decision within our WTP threshold. The base case life expectancy without utility adjustments for nivolumab-ipilimumab was 4.6 LYs, for survival-adjusted pembrolizumab-axitinib was 2.87 LYs, and for sunitinib was 2.88 LYs. Without quality adjustments, the combination of nivolumab-ipilimumab versus sunitinib had an ICER of $25,095/LYs, and the pembrolizumab-axitinib combination was dominated by both the nivolumab-ipilimumab option and the sunitinib treatment option. Therefore, although utility had a strong effect on the ICER of each comparison, it did not have enough effect to alter the conclusion of cost-effectiveness (Table 3).

Unadjusted Scenario

An ICER using unadjusted OS and PFS was calculated, demonstrating that the ICER of both the QALY and LYS pembrolizumab-axitinib scenario comparisons were improved, but still not cost-effective compared with either sunitinib or nivolumab-ipilimumab. The changes in survival did not offset the high costs of pembrolizumab-axitinib (Table 3). The ICER of the unadjusted survival cost-effectiveness scenario comparing pembrolizumab-axitinib versus sunitinib was $594,197/QALY, while the unadjusted survival scenario ICER for nivolumab-ipilimumab versus sunitinib was $34,190/QALY. The unadjusted survival scenario ICER combination treatment comparison still demonstrated that nivolumab-ipilimumab dominated pembrolizumab-axitinib. Again, this scenario showed improvement in the ICER of the pembrolizumab-axitinib combination treatment compared with alternatives, but not enough to change our cost-effectiveness conclusion from the survival-adjusted base case scenario with the accepted WTP for cancer treatments in the United States ($150,000/QALY), confirming our base case model is robust.

The results of the probabilistic sensitivity analyses in the base case scenario are shown in the cost-effectiveness acceptability curves (Fig. 2) and validate initial findings. An increase in WTP thresholds increased the probability for nivolumab-ipilimumab as optimal treatment, whereas the probability for sunitinib decreased. Nivolumab-ipilimumab is associated with the highest probability among the three to be cost-effective above a WTP of $46,000. Pembrolizumab-axitinib fails to be cost-effective at any WTP threshold between 0 and $900,000.

DISCUSSION

To the best of our knowledge, this is the first survival-adjusted CEA comparing combination NCCN recommended first-line treatments including all risk groups for patients with untreated mRCC. Our analysis, using a WTP threshold of $150,000/QALY, demonstrates nivolumab-ipilimumab as the more cost-effective combination treatment compared with pembrolizumab-axitinib with lower costs and better efficacy. Nivolumab-ipilimumab is also a cost-effective treatment option compared with sunitinib, while pembrolizumab-axitinib is not cost-effective or dominated by nivolumab-ipilimumab in any scenario. This result was consistent in the base case analysis where survival was adjusted to better equate the patient samples across clinical trials, and in the analysis scenario with unadjusted survival estimates directly from the trials. The result was also robust across our univariate and probabilistic sensitivity analyses. Our results comparing each combination treatment with sunitinib show a similar ICER to the four single comparison published CEA where nivolumab-ipilimumab or pembrolizumab-axitinib alone is compared with sunitinib.[10–13] Wan et al[13] demonstrated an ICER of $108,363/QALY comparing nivolumab-ipilimumab with sunitinib in a similar population of intermediate- and high-risk patients with mRCC. Wu et al[12] also compared the cost-effectiveness of nivolumab-ipilimumab in mRCC from 3 country perspectives, finding the combination treatment more cost-effective using a Chinese and

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US perspective WTP threshold ($27,351 and $150,000, respectively) but not cost-effective using a UK perspective WTP threshold ($65,000). Reinhorn et al[10] also compared a single drug combination (nivolumab-ipilimumab vs. sunitinib) in first-line intermediate-risk to poor-risk mRCC and determined that the combination treatment is cost-effective with an ICER of $125,739/QALY. Chen et al[11] compared the pembrolizumab-axitinib combination with sunitinib in mRCC in China, concluding the combination treatment was not cost-effective at an ICER of US $178,725, given a WTP threshold of $29,306/QALY. Finally, an additional CEA was recently published comparing pembrolizumab-axitinib and nivolumab-ipilimumab using a microsimulation model and separate analyses for an intermediate-risk/poor-risk group and a favorable-risk group, instead of using an adjusted model across all risk groups as we did.[14] They also concluded that pembrolizumab-axitinib was not cost-effective compared with nivolumab-ipilimumab, despite showing higher QALY. Our approach using adjusted survival estimates for pembrolizumab-axitinib showed that this combination treatment did not show improved QALY over nivolumab-ipilimumab, demonstrating stronger evidence of its lack of efficacy when assessed across all risk groups. Despite the differing approaches that may have contributed to some differences in ICER results, the conclusion that nivolumab-ipilimumab was more cost-effective than pembrolizumab-axitinib and sunitinib is consistent across all studies.

In sensitivity analyses, our model was robust to all variables with no changes in the preferred treatment when parameters for all inputs were varied across their plausible ranges. Our sensitivity analyses demonstrated that one main factor has the biggest impact on the cost-effectiveness of the combination treatments: cost of drug treatment. The overall cost of combination therapy is more expensive than sunitinib alone because of the additive cost of 2 drugs. With an estimated 2-year cost of $292,934 for sunitinib, $302,665 for nivolumab-ipilimumab, and $652,006 for pembrolizumab-axitinib, costs varied greatly for each treatment. Nivolumab-ipilimumab had a cap of 2 years of use in treatment, whereas sunitinib and pembrolizumab-axitinib did not. As a result, this may have led to lower overall drug costs in the 20-year horizon timeline for nivolumab-ipilimumab. Despite costing more than twice that of nivolumab-ipilimumab and sunitinib, pembrolizumab-axitinib did not reflect a proportional efficacy benefit, which led to it not being cost-effective at any WTP threshold below $150,000.[17] Pembrolizumab-axitinib was consistently dominated by these other two treatment groups because of its higher cost and lower efficacy, and would need a price reduction by 37% and 58% to be considered cost-effective compared with sunitinib and nivolumab-ipilimumab, respectively. In the sensitivity analyses of the LYS scenario that excluded utility, the cost-effectiveness conclusions of each treatment remained the same with nivolumab-ipilimumab remaining the recommended therapy.

To estimate the effects of matching-adjusted indirect comparison on the survival outcomes for pembrolizumab-axitinib, the Markov model was run with unadjusted survival estimates for pembrolizumab-axitinib compared with nivolumab-ipilimumab and sunitinib. As a result, pembrolizumab-axitinib QALY increased from 1.99 in the base case to 2.44 in the unadjusted survival outcome scenario, which decreased the ICER from $12,620,831 to $594,197 when compared with sunitinib, but was still dominated by nivolumab-ipilimumab. The only other CEA comparing these two treatments did not use this method, which is standard practice to better make cross-trial comparisons and is a strength of our CEA to more fairly evaluate both combination therapies. In addition, pembrolizumab-axitinib was still above the $150,000 WTP threshold in our unadjusted survival scenario, further supporting the robustness of our analyses.

While the NCCN guidelines (v.2.2020) recommend all three options as first-line treatment for mRCC, there are different recommendations based on prognostic risk categories, favorable and poor/intermediate.[6] For favorable risk, pembrolizumab-axitinib and sunitinib are preferred, whereas for poor/intermediate risk, nivolumab-ipilimumab and pembrolizumab-axitinib are preferred. We highlight that although pembrolizumab-axitinib is recommended as first-line treatment for both the poor/intermediate and favorable risk groups, our study offers a US medical center perspective in which nivolumab-ipilimumab was considered more cost-effective compared with both sunitinib and pembrolizumab-axitinib. Furthermore, the CheckMate 214 and KEYNOTE-426 clinical trial populations had 22% and 31.9% in the favorable risk category, and 87.2% and 68.1% in the poor/intermediate risk category, respectively.[8,9] Our study did not analyze performance of each treatment group within specific prognostic risks as one other CEA did.[14] Instead, we studied their use within the entirety of the mRCC-affected population to understand the impact of each treatment in the overall population. Both CEA approaches drew the same conclusions about treatment efficiency.

Most recently, other trials have demonstrated nivolumab-cabozantinib combination therapy may improve the overall response rate compared with sunitinib in patients with previously untreated mRCC.[46,47] On January 22, 2021, the FDA-approved nivolumab-cabozantinib as first-line treatment for patients with advanced RCC. This new treatment will need to be analyzed for cost-effectiveness compared with the treatments analyzed in our study.[48]

The study of new drug therapies for mRCC provides direction for future CEA to elucidate the cost-effectiveness of potential first-line drug therapies.

Limitations

As with any CEA, there are limitations to our study. The first limitation, which is also the study's main strength, is that 2 different clinical trials were required to compare three treatments for RCC. This indirect comparison was necessary since there is currently no head-to-head clinical trial comparing nivolumab-ipilimumab and pembrolizumab-axitinib. We adjusted the OS and PFS downward for the pembrolizumab-axitinib sample to account for the greater percentage of favorable risk patients in the KEYNOTE-426 study as shown by the comparison of the results for their shared comparator treatment group (sunitinib), adding strength to our study by creating comparable prognostic risk characteristics for the 2 study populations.[9] This adjustment yielded lower OS for KEYNOTE-426 participants (pembrolizumab-axitinib) than the treatment group from CheckMate 214 (nivolumab-ipilimumab) and affected our CEA results.[8,9] However, the unadjusted scenario results in our analysis still showed nivolumab-ipilimumab was more cost-effective compared with pembrolizumab-axitinib. Second, we did not include second-line and third-line treatments in our model and therefore, the costs may not be fully reflective of the total costs of the clinical scenarios. The costs associated with the progression and death health states did not include the cost of any subsequent treatments for mRCC since this data was not available and thus, was outside the scope of our study. Third, there is a lack of data regarding the comparative effectiveness of second-line treatments after failure of initial therapy. Most patients did not complete the clinical trials because of disease progression and study drug toxicity.[8,9] In addition, the administration and duration of secondary treatments is unknown, which may have inadvertently caused inaccuracies in our analyses. If the data was available, it would result in a stronger attestation to our results. However, if the secondary treatments were a reversal of the primary treatments, then this would decrease the difference in costs of the 2 treatments, leading to uncertainties of the resulting effectiveness. It is possible that the effectiveness would

be diminished. Fourth, the CheckMate 214 trial limited nivolumab-ipilimumab treatment-related AE information collected to those AE designated by the manufacturer, which may contribute to the lower incidence and cost of AE reported in that trial.[8] In the sensitivity analysis of our CEA, we varied the costs of AE, doubling those of nivolumab-ipilimumab and decreasing those attributed to pembrolizumab-axitinib by half, and found no change in our cost-effectiveness outcomes.

These limitations contribute to the difficulty of making a clear interpretation for clinical practice despite the current mRCC guidelines separating first-line treatment options by prognostic risk.[6] Our study is based on available clinical trials, which led to the assessment of cost-effectiveness across all risk groups and provides valuable information on the cost-effectiveness of these treatment choices.

CONCLUSION

In this first CEA study directly comparing 2 ICI and targeted therapies using survival adjustment, the base case model indicated that nivolumab-ipilimumab was the most cost-effective treatment option for mRCC compared with pembrolizumab-axitinib and sunitinib. Meanwhile, pembrolizumab-axitinib is not cost-effective compared with nivolumab-ipilimumab or sunitinib for patients with previously untreated mRCC at a WTP threshold value of $150,000/QALY.

While the NCCN guidelines (v.2.2020) recommend all three options as first-line treatment for mRCC, there are different recommendations based on prognostic risk categories, favorable and poor/intermediate.[6] Although pembrolizumab-axitinib is recommended as first-line treatment for both poor/intermediate and favorable risk groups, our findings contribute to clinical decision making from a US payer perspective as nivolumab-ipilimumab was considered more cost-effective compared with both sunitinib and pembrolizumab-axitinib in the overall mRCC-affected population.

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