First-line treatments for advanced renal-cell carcinoma with immune checkpoint inhibitors: systematic review, network meta-analysis and cost-effectiveness analysis

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Abstract

Background: Immune checkpoint inhibitors (ICIs) are effective for advanced renal-cell carcinoma (aRCC) but can increase costs. This study compares the efficacy, safety and cost-effectiveness of ICIs for newly diagnosed aRCC patients in the first-line setting.

Methods: Trials evaluating ICI regimens as first-line treatment for newly diagnosed aRCC were searched and included. A network meta-analysis (NMA) was conducted, and a cost-effectiveness analysis was performed from the US payer's perspective. The key outcomes were overall survival (OS) and progression-free survival (PFS) in the NMA, and quality-adjusted life years (QALYs), costs and the incremental cost-effectiveness ratio (ICER) in the cost-effectiveness analysis.

Results: Four randomized controlled trials (RCTs) involving 3758 patients receiving first-line ICIs treatment were analyzed. The NMA showed that pembrolizumab plus axitinib was ranked higher than the other three ICI regimens and sunitinib in the overall population. Nivolumab plus ipilimumab and pembrolizumab plus axitinib achieved more health benefits than the other ICI regimens and sunitinib in programmed death ligand 1 (PD-L1)-positive and negative tumors, respectively. Among the four ICI regimens, only the ICERs of nivolumab plus ipilimumab over sunitinib were lower than the willingness-to-pay threshold ($150,000/QALY) in the overall and PD-L1-positive populations, and none of four ICI regimens were lower than $150,000/QALY in PD-L1-negative populations.

Conclusions: The NMA and cost-effectiveness analysis revealed that nivolumab plus ipilimumab is the most favorable first-line treatment for PD-L1-positive aRCC compared with other ICI regimens and sunitinib. Pembrolizumab plus axitinib is likely to be an alternative for PD-L1-negative aRCC due to its more favorable health advantages.

Keywords: cost-effectiveness analysis, immune checkpoint inhibitors, network meta-analysis, renal-cell carcinoma, systematic review

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Introduction

The Global Burden of Disease Study 2017 showed that kidney cancer accounted for 1.40% of the disease burden from all neoplasms.[1] As the most lethal of the common types of kidney cancer, advanced renal-cell carcinoma (aRCC) is diagnosed in approximately 30% of patients due to the generally asymptomatic nature of the disease at onset.[2,3] Over the past decade, targeted agents, such as cabozantinib and sunitinib, have been widely prescribed for treating aRCC. Although notably prolonged survival has been achieved by these targeted agents, aRCC is still incurable, with a median overall survival (OS) of approximately 2 years.[4–6] Therefore, the development of novel agents to treat this advanced disease is necessary.

Immune checkpoint inhibitor (ICI)-based regimens, which could block the programmed cell death 1 (PD-1) pathway or cytotoxic T lymphocyte-associated protein 4 (CTLA-4),[7,8] are emerging as a new therapeutic modality for aRCC because these regimens can improve survival and quality of life. The recent CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials reported that nivolumab plus ipilimumab, pembrolizumab plus axitinib, atezolizumab plus bevacizumab and avelumab plus axitinib could be considered potential alternative first-line treatments for patients with previously untreated aRCC because these drugs are well tolerated and significantly reduce the risk of death in comparison with sunitinib.[9–12] However, no studies have directly compared different ICI regimens with each other, so it is unclear which regimen should be advocated as the first option for most patients. The question of whether the expensive ICIs are balanced by improved health benefits, reduced health resource consumption of later-line treatment, or both, remains unresolved. In addition, the effects of ICI regimens may be mixed in the whole cohort because the efficacy for some patients was not fully realized. We performed a systematic review, network meta-analysis (NMA), and cost-effectiveness analysis to investigate regimens containing ICIs with each other and with sunitinib for the first-line management of aRCC, and constructed a rank order based on efficacy, safety and cost in the US.

Methods

The results were reported following the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions and the consolidated health economic evaluation reporting standards statement (CHEERS) (Supplemental Appendix Tables 1 and 2, respectively).

Study eligibility and selection

The electronic databases including PubMed, EMBASE and the Cochrane Central Register of Controlled Trials were searched to identify eligible randomized controlled trials (RCTs) that compared regimens containing PD-1/programmed death ligand 1 (PD-L1) inhibitors with tyrosine kinase inhibitor (TKI) treatment in the first-line setting. The entry terms for the search included pembrolizumab, atezolizumab, avelumab, durvalumab, nivolumab, PD-1, PD-L1, renal-cell carcinoma, and randomized controlled trial (Supplemental Appendix File 1: supplemental methods of meta-analysis); we searched for studies that were reported in English until 19 March 2019. We also reviewed abstracts presented at the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and the American Association for Cancer Research (AACR). When duplicate trials were found, only the most complete and latest data of the trial were considered. Meeting abstracts without full-text original reports as well as case reports/letters/commentaries and reports not written in the English language were ineligible for this analysis. The inclusion and exclusion criteria are shown in Supplemental Appendix Table 3 of the supplemental methods of the meta-analysis.

Collection of data and assessment of the risk of bias

Two reviewers (JF and YL) independently screened the studies. The extracted data included the study characteristics (author, publication time, design of the trial, number of patients enrolled), patient clinicopathological characteristics (age, histology, PD-L1 level), interventions including PD-1/PD-L1 therapy and the comparator regimen, and the outcome measures [hazard ratios (HRs) for OS and progression-free survival (PFS), and the odds ratio (OR) for adverse drug reactions (ADRs)]. The quality of the trials was evaluated with the Cochrane Collaboration's tool.

Data synthesis and statistical analysis

We produced network plots of comparisons to annotate which regimens had been compared within randomized trials (head-to-head comparisons). Fixed-effects and random-effects models were explored. However, as typically only one trial informed each pair-wise comparison, and hence there were few data to inform the evaluation of heterogeneity between trials, a pragmatic decision was made to use the fixed-effects model; this model was applied to compare the relative efficacy and safety between different regimens by using frequentist methods.[13] Ranking the different treatments in terms of their likelihood of showing the best results was performed using the *p*-value for each outcome, in which higher values represent better success. Statistical analysis was performed using R software (version 3.5.2) with the package 'netmeta'.[14]

Cost-effectiveness analysis

We assessed the most cost-effective first-line regimens containing ICIs in patients with newly diagnosed aRCC from the perspective of the third-party payer in the US. A Markov multistate model with a cycle length of 1 week was adopted (Supplemental Appendix File 2: supplemental methods of the cost-effectiveness analysis). The baseline characteristics of the simulated patients were assumed to be similar to the patients in CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials.[9–12] The expected total costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were estimated over a lifetime horizon (10 years), as in previous economic studies.[15,16] The model inputs of clinical data, cost and utility estimates were collected from the network meta-analysis and published literature (Table 1). To examine the potential drivers of economic outcomes, we performed both one-way and probabilistic sensitivity analyses (PSAs). Subgroup analysis was performed in patients categorized by PD-L1 status. Detailed information about the model development and clinical, cost and health preference inputs are shown in the Supplemental Appendix.

Results

Studies included and the risk of bias

After selecting abstracts and titles, four clinical trials involving 3758 patients were identified (see Supplemental Appendix Table 4 for a summary of the trial characteristics); these patients were treated with nivolumab plus ipilimumab ($n=550$ patients), pembrolizumab plus axitinib ($n=432$ patients), avelumab plus axitinib ($n=442$ patients) and atezolizumab plus bevacizumab ($n=454$ patients) or sunitinib ($n=1334$ patients) as first-line treatment.[9–12]

The risk of bias judgments for the included studies are shown in Supplemental Appendix Figure 2. All four studies were judged to have an unclear risk of bias for sequence generation and allocation concealment and were judged to have a high risk of performance bias. Three studies were judged to have a low risk of bias for blinding of outcome assessment, and all four studies were judged to have a low risk of bias for incomplete outcome data and selective reporting.

Efficacy and safety results

A total of four ICI regimens (atezolizumab plus bevacizumab, avelumab plus axitinib, nivolumab plus ipilimumab and pembrolizumab plus axitinib) and one control regimen (sunitinib) were included in the network (Supplemental Appendix Figure 3). Indirect comparisons demonstrated that both nivolumab plus ipilimumab [HR: 0.63, 95% confidence interval (CI): 0.44–0.9 and HR: 0.45, 95% CI: 0.29–0.7] and pembrolizumab plus axitinib (HR: 0.53, 95% CI: 0.38–0.74 and HR: 0.73, 95% CI: 0.56–0.96) could lead to statistically significant improvements in OS compared with sunitinib treatment in the overall population and PD-L1-positive patients (the definition of positivity is shown in Supplemental Appendix Table 5). The regimens of atezolizumab plus bevacizumab, avelumab plus axitinib and pembrolizumab plus axitinib for the overall population and all four ICI regimens for the population with PD-L1-positive tumors also achieved statistically significant improvements in PFS. The regimens with the highest *p*-value for OS in the overall and PD-L1-positive populations were pembrolizumab plus axitinib (HR: 0.53, 95% CI: 0.38–0.74; $p=0.93$) and nivolumab plus ipilimumab ($p=0.92$), respectively. Among the PD-L1-negative patients, the regimen with the highest *p*-value for OS was pembrolizumab plus axitinib (HR: 0.59, 95% CI: 0.34–1.03; $p=0.86$) followed by nivolumab plus ipilimumab (HR: 0.73, 95% CI: 0.56–0.96; $p=0.69$). No statistically significant differences in PFS and OS were found between the four ICI regimens. The results of indirect comparisons and the *p*-values of the PFS and OS of each regimen are shown in Figures 1 and 2, respectively.

The forest plot revealed that the four ICI regimens had comparable safety profiles concerning any grade ADRs, and nivolumab plus ipilimumab had a lower likelihood of grade ⩾3 ADRs (OR: 0.73, 95% CI: 0.62–0.86) than sunitinib (Supplemental Appendix Figure 4). The regimen with the highest *p*-value for any grade ($p=0.64$) and grade ⩾3 ADRs ($p=0.89$) was nivolumab plus ipilimumab.

Cost-effectiveness results

The base-case predicted mean costs, life years (LYs) and QALYs gained for each strategy are summarized in Table 2. For the overall population,

Table 1. Key model inputs.

Parameters	Values	Reference
Clinical data		
Survival model of sunitinib		Motzer *et al.*[9,10]; Rini *et al.*[12,17]
Log-logistic model for PFS	Shape: 1.3705 (se: 0.0357), scale: 37.5566 (se: 1.2562); AIC: 10134.28	
Log-logistic model for OS	Shape: 1.2800 (se: 0.05), scale: 135.14 (se: 7.02); AIC: 6398.76	
HRs of ICI regimens against sunitinib	See the results of network meta-analysis	
Proportion (%) of receiving active second-line treatment		
Sunitinib	0.57 [Range: 0.52–0.63, distribution: beta (155.2, 117.1)]	Motzer *et al.*[9,10]; Rini *et al.*[12,17]
Avelumab+axitinib	0.43 [Range: 0.33–0.54, distribution: beta (8.7, 11.5)]	Motzer *et al.*[10]
Pembrolizumab+axitinib	0.5 [Range: 0.38–0.63, distribution: beta (7.4, 7.4)]	Rini *et al.*[17]
Nivolumab+ipilimumab	0.39 [Range: 0.29–0.49, distribution: beta (9.3, 14.5)]	Motzer *et al.*[9]
Atezolizumab+bevacizumab#	0.43 [Range: 0.32–0.54, distribution: beta (8.7, 11.5)]	Rini *et al.*[12]
Cost data (US, $)		
Price of sunitinib per 50 mg	602 (Range: 301–602, distribution: fixed)	Red book online
Price of ipilimumab per 50 mg	7324 (Range: 3662–7324, distribution: fixed)	Red book online
Price of nivolumab per 100 mg	2670 (Range: 1335–2670, distribution: fixed)	Red book online
Price of nivolumab per 240 mg	6427 (Range: 3213–6427, distribution: fixed)	Red book online
Price of avelumab per 200 mg	1650 (Range: 825–1650, distribution: fixed)	Red book online
Price of pembrolizumab per 50 mg	2295 (Range: 1148–2295, distribution: fixed)	Red book online
Price of axitinib per 10 mg	525 (Range: 263–525, distribution: fixed)	Red book online
Price of atezolizumab per 1200 mg	9280 (Range: 4640–9280, distribution: fixed)	Red book online
Price of bevacizumab per 100 mg	841 (Range: 420–841, distribution: fixed)	Red book online
Cost of follow-up and monitoring per cycle	422 [Range: 348–496, distribution: gamma (4731, 0.0892)]	Benedict *et al.*[18]
Cost of second-line active treatment per patient	27936 [Range: 26429–29443, distribution: gamma (1015855, 0.0275)]	Perrin *et al.*[19]
Cost of BSC per cycle	1213 [Range: 987–1438, distribution: gamma (4856, 0.2498)]	Henk *et al.*[20]
Cost of terminal per patient	10713 [Range: 8570–12856, distribution: gamma (105029, 0.102)]	Perrin *et al.*[19]; McCrea *et al.*[21]

(Continued)

Table 1. (Continued)

Parameters	Values	Reference
Cost of managing AEs (grade ≥3) per event		
Fatigue	139 [Range: 1–2018, distribution: gamma (44, 3.1871)]	Perrin *et al.*[19]; Hansen *et al.*[22]; Liou *et al.*[23]
Hypertension	202 [Range: 1–6533, distribution: gamma (6, 32.3416)]	Perrin *et al.*[19]; Hansen *et al.*[22]; Liou *et al.*[23]
Anemia	4638 [Range: 3326–5949, distribution: gamma (32164, 0.1442)]	Perrin *et al.*[19]; Hansen *et al.*[22]; Liou *et al.*[23]
Palmar–plantar erythrodysesthesia	119 [Range: 3–1748, distribution: gamma (75, 1.5966)]	Perrin *et al.*[19]; Hansen *et al.*[22]; Liou *et al.*[23]
Thrombocytopenia	4014 [Range: 1716–9391, distribution: gamma (8229, 0.4878)]	Liou *et al.*[23]
Cost of drug administration per unit	292 [Range: 219–365, distribution: gamma (1168, 0.25)]	Sarfaty *et al.*[16]
Health utility scores		
Utility of PFS	0.78 [Range: 0.71–0.85, distribution: beta (106.9, 30.2)]	McCrea *et al.*[21]; Amdahl *et al.*[24]; de Groot *et al.*[25]; Hoyle *et al.*[26]
Utility of PS	0.66 [Range: 0.45–0.82, distribution: beta (16.4, 8.4)]	McCrea *et al.*[21]; Amdahl *et al.*[24]; de Groot *et al.*[25]; Hoyle *et al.*[26]
Disutility due to AEs (grade 1 and 2)	0.01 [Range: 0.01–0.02, distribution: beta (9.4, 933.8)]	Amdahl *et al.*[24]
Disutility due to AEs (grade ≥3)	0.16 [Range: 0.11–0.2, distribution: beta (37.2, 195.1)]	Amdahl *et al.*[24]

#Due to no data reported by the IMmotion 151 at the present time point, an average proportion from the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials was assumed.
AE, adverse event; BSC, best supportive care; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death 1; PFS, progression-free survival; PS, progressed survival.

the mean marginal costs and QALYs of avelumab plus axitinib, pembrolizumab plus axitinib, nivolumab plus ipilimumab and atezolizumab plus bevacizumab *versus* sunitinib were $197,793 and 0.53, $238,651 and 1.19, $121,948 and 0.86, and $81,010 and 0.18, which yielded ICERs of $371,360, $201,027, $141,120 and $448,952 per QALY gained, respectively. For the population with PD-L1-positive and negative tumors, the ICERs of avelumab plus axitinib, pembrolizumab plus axitinib, nivolumab plus ipilimumab and atezolizumab plus bevacizumab *versus* sunitinib were $406,644 and $389,229, $199,084 and $226,595, $92,262 and $180,251 and $245,355 and $500,910 per QALY, respectively. In the fixed dosing of nivolumab, the ICERs of nivolumab plus ipilimumab over sunitinib were $110,838, $71,641

and $138,285 per QALY gained in the overall, PD-L1-positive and PD-L1-negative population, respectively.

The one-way sensitivity analyses found that these results were substantially sensitive to the HRs of OS of ICI regimens against sunitinib (Supplemental Appendix Figure 12). The expected age, median duration for nivolumab treatment in the 2n-line setting and price of the ICI regimen also had considerable impacts on the ICERs. The longer expected survival after immunotherapy led to the smaller ICERs (Supplemental Appendix Figure 13). The other parameters included in the sensitivity analyses, such as the cost and utilities related to ADRs, had minimal impact on the ICER. At a willingness-to-pay threshold of $150,000/QALY,

A. Overall population

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab	1	1.2 (95% CI: 0.93 - 1.56)	1.01 (95% CI: 0.75 - 1.36)	1.2 (95% CI: 0.93 - 1.55)	0.83 (95% CI: 0.71 - 0.98)	0.4
Avelumab + axitinib	0.83 (95% CI: 0.64 - 1.08)	1	0.84 (95% CI: 0.61 - 1.16)	1 (95% CI: 0.76 - 1.32)	0.69 (95% CI: 0.56 - 0.85)	0.82
Nivolumab + ipilimumab	0.99 (95% CI: 0.73 - 1.33)	1.19 (95% CI: 0.86 - 1.64)	1	1.19 (95% CI: 0.87 - 1.63)	0.82 (95% CI: 0.64 - 1.05)	0.44
Pembrolizumab + axitinib	0.83 (95% CI: 0.65 - 1.07)	1 (95% CI: 0.76 - 1.32)	0.84 (95% CI: 0.61 - 1.15)	1	0.69 (95% CI: 0.57 - 0.84)	0.82
Sunitinib	1.2 (95% CI: 1.02 - 1.42)	1.45 (95% CI: 1.18 - 1.77)	1.22 (95% CI: 0.95 - 1.56)	1.45 (95% CI: 1.19 - 1.76)	1	0.02
P-Score	0.4	0.82	0.44	0.82	0.02	

B. Population with PD-L1–positive tumors

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab	1	1.21 (95% CI: 0.84 - 1.75)	1.61 (95% CI: 1.01 - 2.56)	1.19 (95% CI: 0.82 - 1.73)	0.74 (95% CI: 0.57 - 0.96)	0.33
Avelumab+Axitinib	0.82 (95% CI: 0.57 - 1.19)	1	1.33 (95% CI: 0.83 - 2.11)	0.98 (95% CI: 0.68 - 1.43)	0.61 (95% CI: 0.47 - 0.79)	0.62
Nivolumab+ipilimumab	0.62 (95% CI: 0.39 - 0.99)	0.75 (95% CI: 0.47 - 1.2)	1	0.74 (95% CI: 0.46 - 1.18)	0.46 (95% CI: 0.31 - 0.68)	0.94
Pembrolizumab+Axitinib	0.84 (95% CI: 0.58 - 1.22)	1.02 (95% CI: 0.7 - 1.47)	1.35 (95% CI: 0.84 - 2.15)	1	0.62 (95% CI: 0.48 - 0.81)	0.6
Sunitinib	1.35 (95% CI: 1.04 - 1.75)	1.64 (95% CI: 1.26 - 2.13)	2.17 (95% CI: 1.48 - 3.2)	1.61 (95% CI: 1.24 - 2.1)	1	0
P-Score	0.33	0.62	0.94	0.6	0	

C. Population with PD-L1–negative tumors

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab	1	1.11 (95% CI: 0.72 - 1.71)	0.89 (95% CI: 0.65 - 1.21)	1.02 (95% CI: 0.68 - 1.53)	0.89 (95% CI: 0.72 - 1.1)	0.6
Avelumab+Axitinib	0.9 (95% CI: 0.58 - 1.38)	1	0.8 (95% CI: 0.52 - 1.24)	0.92 (95% CI: 0.55 - 1.53)	0.8 (95% CI: 0.55 - 1.16)	0.76
Nivolumab+ipilimumab	1.12 (95% CI: 0.82 - 1.53)	1.25 (95% CI: 0.81 - 1.94)	1	1.15 (95% CI: 0.76 - 1.73)	1 (95% CI: 0.8 - 1.25)	0.29
Pembrolizumab+Axitinib	0.98 (95% CI: 0.65 - 1.46)	1.09 (95% CI: 0.65 - 1.81)	0.87 (95% CI: 0.58 - 1.31)	1	0.87 (95% CI: 0.62 - 1.23)	0.61
Sunitinib	1.12 (95% CI: 0.91 - 1.39)	1.25 (95% CI: 0.86 - 1.82)	1 (95% CI: 0.8 - 1.25)	1.15 (95% CI: 0.82 - 1.62)	1	0.24
P-Score	0.6	0.76	0.29	0.61	0.24	

Figure 1. Hazard ratios (blue cell) and *p*-values (orange cell) of the network meta-analysis of the progression-free survival in the overall population (A), population with PD-L1-positive tumors (B) and population with PD-L1-negative tumors (C).

the cost-effectiveness acceptability curves showed that the probabilities of the avelumab plus axitinib, pembrolizumab plus axitinib and atezolizumab plus bevacizumab strategies being cost-effective were <25% in the overall, PD-L1-positive and PD-L1-negative population except for the nivolumab plus ipilimumab strategy, which were 77.8%, 99.5% and 40.5% compared with sunitinib (Figure 3), respectively.

Discussion
To the best of our knowledge, this is the first evaluation of all currently licensed ICI regimens for patients with untreated aRCC that has explored a *p*-value order for therapy options in terms of efficacy, safety outcomes and overall economic outcomes. Four ICI regimens appear to be superior to the standard sunitinib strategy for improving survival, especially in patients with PD-L1-positive tumors. The findings of the NMAs suggest that both the nivolumab plus ipilimumab and pembrolizumab plus axitinib regimens yielded more survival benefits than the other

ICI regimens and sunitinib in patients with PD-L1-positive and PD-L1-negative tumors, respectively. All four ICI regimens are associated with a comparable risk for ADRs of all grades, and both nivolumab plus ipilimumab and atezolizumab plus bevacizumab were associated with a reduced risk of grade ≥3 ADRs compared with sunitinib. The overall survival advantage of nivolumab plus ipilimumab and pembrolizumab plus axitinib translated into the highest QALYs in PD-L1-positive and PD-L1-negative patients, respectively. However, nivolumab plus ipilimumab is considered to be the most cost-effective alternative only because this regimen has the lowest ICER among all four ICI regimes in the overall, PD-L1-positive and negative patients. The findings in the scenario analyses are comparable with the US setting, which also found that nivolumab plus ipilimumab is the ICI regimen with the lowest ICER in the context of the UK and China (Supplemental Appendix Tables 7 and 8 and Supplemental Appendix Figure 14). Thus, the strengths of this assessment include universal profiles of the present research findings, a critical

A. Overall population

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab	1	1.19 (95% CI: 0.8 - 1.77)	1.48 (95% CI: 0.98 - 2.22)	1.75 (95% CI: 1.19 - 2.59)	0.93 (95% CI: 0.76 - 1.14)	0.25
Avelumab + axitinib	0.84 (95% CI: 0.57 - 1.24)	1	1.24 (95% CI: 0.76 - 2.02)	1.47 (95% CI: 0.92 - 2.36)	0.78 (95% CI: 0.56 - 1.09)	0.5
Nivolumab + ipilimumab	0.68 (95% CI: 0.45 - 1.02)	0.81 (95% CI: 0.5 - 1.32)	1	1.19 (95% CI: 0.73 - 1.93)	0.63 (95% CI: 0.44 - 0.9)	0.75
Pembrolizumab + axitinib	0.57 (95% CI: 0.39 - 0.84)	0.68 (95% CI: 0.42 - 1.09)	0.84 (95% CI: 0.52 - 1.37)	1	0.53 (95% CI: 0.38 - 0.74)	0.93
Sunitinib	1.08 (95% CI: 0.88 - 1.32)	1.28 (95% CI: 0.91 - 1.8)	1.59 (95% CI: 1.12 - 2.26)	1.89 (95% CI: 1.35 - 2.63)	1	0.08
P-Score	0.25	0.5	0.75	0.93	0.08	

B. Population with PD-L1–positive tumors

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab	1	1.02 (95% CI: 0.6 - 1.75)	1.87 (95% CI: 1.08 - 3.22)	1.56 (95% CI: 0.91 - 2.66)	0.84 (95% CI: 0.62 - 1.14)	0.35
Avelumab + axitinib	0.98 (95% CI: 0.57 - 1.67)	1	1.82 (95% CI: 0.97 - 3.42)	1.52 (95% CI: 0.82 - 2.83)	0.82 (95% CI: 0.53 - 1.27)	0.37
Nivolumab + ipilimumab	0.54 (95% CI: 0.31 - 0.92)	0.55 (95% CI: 0.29 - 1.03)	1	0.83 (95% CI: 0.45 - 1.56)	0.45 (95% CI: 0.29 - 0.7)	0.92
Pembrolizumab + axitinib	0.64 (95% CI: 0.38 - 1.1)	0.66 (95% CI: 0.35 - 1.23)	1.2 (95% CI: 0.64 - 2.24)	1	0.54 (95% CI: 0.35 - 0.84)	0.78
Sunitinib	1.19 (95% CI: 0.87 - 1.62)	1.22 (95% CI: 0.78 - 1.9)	2.22 (95% CI: 1.42 - 3.48)	1.85 (95% CI: 1.2 - 2.87)	1	0.08
P-Score	0.35	0.37	0.92	0.78	0.08	

C. Population with PD-L1–negative tumors

	Atezolizumab + bevacizumab	Avelumab + axitinib	Nivolumab + ipilimumab	Pembrolizumab + axitinib	Sunitinib	P-Score
Atezolizumab + bevacizumab*	1	1.19 (95% CI: 0.8 - 1.77)	1.27 (95% CI: 0.91 - 1.78)	1.58 (95% CI: 0.87 - 2.84)	0.93 (95% CI: 0.76 - 1.14)	0.27
Avelumab + axitinib*	0.84 (95% CI: 0.57 - 1.24)	1	1.07 (95% CI: 0.69 - 1.65)	1.32 (95% CI: 0.69 - 2.53)	0.78 (95% CI: 0.56 - 1.09)	0.58
Nivolumab + ipilimumab	0.78 (95% CI: 0.56 - 1.1)	0.94 (95% CI: 0.61 - 1.44)	1	1.24 (95% CI: 0.67 - 2.29)	0.73 (95% CI: 0.56 - 0.96)	0.69
Pembrolizumab + axitinib	0.63 (95% CI: 0.35 - 1.14)	0.76 (95% CI: 0.4 - 1.45)	0.81 (95% CI: 0.44 - 1.5)	1	0.59 (95% CI: 0.34 - 1.03)	0.86
Sunitinib	1.08 (95% CI: 0.88 - 1.32)	1.28 (95% CI: 0.91 - 1.8)	1.37 (95% CI: 1.05 - 1.79)	1.69 (95% CI: 0.97 - 2.95)	1	0.09
P-Score	0.27	0.58	0.69	0.86	0.09	

Figure 2. Hazard ratios (blue cell) and *p*-values (orange cell) of the network meta-analysis of the overall survival in the overall population (A), population with PD-L1-positive tumors (B) and population with PD-L1-negative tumors (C).
*Due to the lack of reported data, we conservatively assumed that the HRs for OS in PD-L1-negative patients were equal to those of the overall population and applied these data in the network meta-analysis.

appraisal of the study quality, a focus on health outcomes, transferability of the findings across different regions and universal assessments that provide comparisons between ICI regimens as well as comparisons of ICI regimens with sunitinib.

Our economic analyses are sensitive to the relative efficacy of ICI regimens; the analysis found that the economic outcomes of the ICI regimens would become more favorable in patients with lower HRs of OS of ICI regimens against sunitinib and would become worse in patients with higher HRs. This finding is consistent with our subgroup analysis that showed that the economic outcomes of ICI regimens in PD-L1-positive patients were better than those in PD-L1-negative patients because the former has a better relative efficacy of ICI treatment. Several studies have found that PD-L1 expression is a poor prognostic factor and is predictive of better treatment responses from both PD-1 and PD-L1 inhibitors in a variety of tumor types, including aRCC.[27,28] Due to the high cost of ICI agents, an early test for the validated biomarkers that predict the prognosis of immunotherapy is vital in the context of cost-efficiency and optimal logistics.

The current evaluation has several potential implications. Our study suggests that, of the presently available ICI regimens, nivolumab plus ipilimumab ranks as the best option for the population with PD-L1-positive tumors after accounting for efficacy, safety and cost. The CheckMate 214 trial showed nivolumab plus ipilimumab had better objective response rates (58% *versus* 37%) and overall survival in (HR 0.45 *versus* 0.73) patients with ≥1% tumor PD-L1 than those with <1%, which is more distinguishable than the other three trials. Therefore, identifying the eligible patients receiving nivolumab plus ipilimumab might be a valuable and rational choice, although the current practice does not recommend checking PD-L1 status in patients with aRCC.[29] It implied that PD-L1-positive tumors might receive nivolumab plus ipilimumab treatment and the rest of the people could receive a regimen containing ICIs

Table 2. Summary of the cost ($) and outcome results in base-case analysis.

Strategy	Cost	Overall LYs	QALYs	ICER*
Overall population				
Sunitinib	291,572	4.03	2.59	NA
Avelumab plus axitinib	489,364	4.80	3.12	371,360
Pembrolizumab plus axitinib	530,223	5.96	3.77	201,027
Nivolumab plus ipilimumab	413,520	5.46	3.45	141,120
Nivolumab plus ipilimumab with a fixed dose#	387,352	5.4566	3.4513	110,838
Atezolizumab plus bevacizumab	372,582	4.26	2.77	448,952
Population with PD-L1-positive tumors				
Sunitinib	262,152	3.48	2.27	NA
Avelumab plus axitinib	455,503	4.08	2.74	406,644
Pembrolizumab plus axitinib	501,747	5.37	3.47	199,084
Nivolumab plus ipilimumab	411,000	5.90	3.88	92,262
Nivolumab plus ipilimumab with a fixed dose#	377,732	5.9043	3.8810	71,641
Atezolizumab plus bevacizumab	356,859	4.00	2.65	245,355
Population with PD-L1-negative tumors				
Sunitinib	309,256	4.37	2.78	NA
Avelumab plus axitinib	499,790	5.14	3.27	389,229
Pembrolizumab plus axitinib	521,157	5.96	3.71	226,595
Nivolumab plus ipilimumab	410,084	5.34	3.34	180,251
Nivolumab plus ipilimumab with a fixed dose#	386,609	5.3389	3.3382	138,285
Atezolizumab plus bevacizumab	391,217	4.59	2.94	500,910

*Incremental cost per QALY (*versus* sunitinib).
#Nivolumab dosing schedule, a single 480 mg iv dose every 4 weeks.
ICER, incremental cost-effectiveness ratio; LY, life year; PD-L1-, programmed death ligand 1; QALY, quality-adjusted life year.

and axitinib after the PD-L1 assay associated with nivolumab plus ipilimumab. These findings suggest that meaningful guidance on the hierarchy of ICI regimens to prolong the survival of patients with aRCC will be necessary, specifically for a therapy hierarchy and contexts under which alternative regimens from within similar classes should be administered (e.g. reserve therapies for those who have a treatment response based on PD-L1 status, specific ADRs or contraindications to the primary regimen). This approach should augment the consumption of this drug class,

benefit patient health, and result in efficient and sustained health resource allocation.

There are several limitations. First, as evidenced in Supplemental Appendix Table 4, pharmaceutical companies have partnered with different PD-L1 assays. Due to the inability consistently to predict response across clinical trials and the limitations of PD-L1 immunohistochemistry staining, the limited role of PD-L1 as a predictive biomarker should be acknowledged in the comparisons across clinical trials. Therefore, the results in
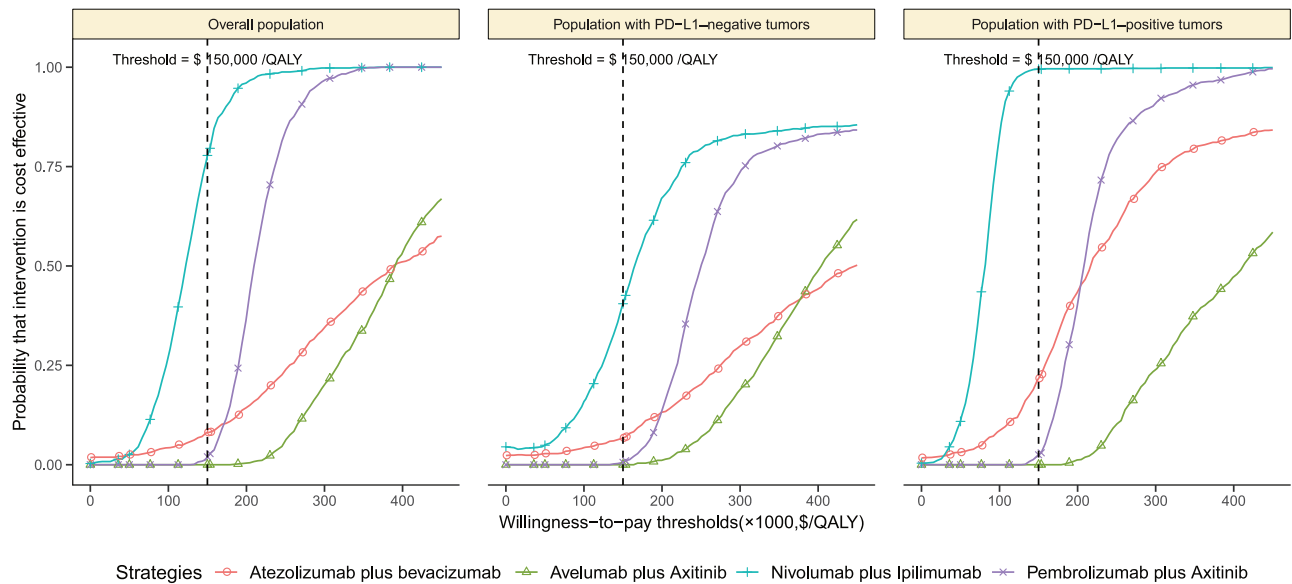
Figure 3. The cost-effectiveness acceptability curves for the avelumab plus axitinib, pembrolizumab plus axitinib, nivolumab plus ipilimumab and atezolizumab plus bevacizumab strategies compared to the sunitinib strategy in the overall population (A), population with PD-L1-negative tumors (B) and population with PD-L1-positive tumors (C).

PD-L1-positive and PD-L1-negative tumors should be carefully interpreted. Second, a NMA approach was adopted for directly comparing between ICI regimens with the assumption that the included studies did not differ in patient characteristics, although no clear evidence of effect modification caused by the patient characteristics was observed (Supplemental Appendix Figure 10). Third, the short-term survival data of each trial were used to project the long-term outcomes in the cost-effectiveness analysis, which informed assumptions about treatment pathways and health state transitions. Third, although the guidelines have recommended cabozantinib to treat aRCC,[30] we did not include it in this analysis because of its non-significant OS compared with sunitinib (HR 0.80, 95% CI 0.53–1.21) and other concerns.[31,32] Fourth, the current analysis conservatively projected the outcomes over a 10-year time horizon. The cost-effectiveness of ICI regimes would become unfavorable when the shorter time horizon was adopted (Supplemental Appendix Figure 13). Nivolumab plus ipilimumab would cost more money than the other three ICI regimes in the first 3 months (Supplemental Appendix Table 9). Fifth, we did not investigate the economic outcomes in other subpopulations, such as the age and International Metastatic Renal Cell Carcinoma Database Consortium risk category. Finally, the analysis does not address the impact of different payment schemes, which is a

much more tangible and relevant issue to most patients and providers, although it is not the focus of this analysis.

Regimens containing ICIs appear to be superior to standard sunitinib treatment in patients with untreated aRCC. Among the four ICI regimens, the combination regimen of nivolumab plus ipilimumab appears to maximize efficacy for those with PD-L1-positive tumors, with more favorable economic outcomes. Although pembrolizumab plus axitinib is likely to be a favorable option for PD-L1-negative patients due to its considerable trend of efficacy, the economic outcome is unlikely to be ideal. Further real-world data may bring new insights with respect to economic outcomes, and it is important to identify patients who may not benefit from ICIs treatment. New studies addressing the limitations of the present analysis may better inform physicians and decision-makers in this clinical context.

Contributors
BW was involved in the design of the study. YS and JF collected the data. YS and JD performed the meta-analysis. BW and YS performed the economic analysis. BW wrote the first draft of the manuscript, which was critically revised by YS, JF, JD and BW. All authors have approved this version for publication. BW is the study guarantor.

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