Review

First-line Treatment of Metastatic Renal Cell Carcinoma in the Immuno-oncology Era: Systematic Review and Network Meta-analysis

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Abstract

Combination treatments with immuno-oncology (IO) agents and IO agents plus a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) have been approved for first-line treatment of patients with metastatic renal cell carcinoma (mRCC). No direct comparisons have been performed among these treatment options. We performed a systematic review and network meta-analysis to compare and rank the available regimens for first-line treatment in terms of survival benefit and efficacy. In accordance with the Preferred Reporting Items for Systematic Review statement, a systematic search of reported studies was performed in MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE up to May 31, 2019. Network meta-analysis models were adjusted using the Bayesian method. Four randomized clinical trials, with a total of 3758 patients, met the inclusion criteria. Considering systemic therapy, 1880 patients had received sunitinib and 550, 432, 442, and 454 patients had received ipilimumab plus nivolumab (ipi + nivo), pembrolizumab plus axitinib (pembro + axi), avelumab plus axitinib (avelu + axi), and atezolizumab plus bevacizumab (atezo + bev). No difference was found in overall survival between ipi + nivo and pembro + axi for the intention to treat population (hazard ratio [HR], 1.34; 95% credible interval [CrI], 0.92-1.97). No difference was found in progression-free survival among the treatments. The overall response rate (ORR) was superior with pembro + axi and avelu + axi compared with the ORR with the other treatments (atezo + bev vs. pembro + axi: HR, 0.66; 95% CrI, 0.52-0.84; ipi + nivo vs. pembro + axi: HR, 0.73; 95% CrI, 0.59-0.90; atezo + bev vs. avelu + axi: HR, 0.55; 95% CrI, 0.43-0.71; avelu + axi vs. ipi + nivo: HR, 1.66; 95% CrI, 1.31-2.12), with no differences across them (HR, 1.21; 95% CrI, 0.95-1.53). In the present indirect comparison, for an intention to treat population, we found no survival differences between pembro + axi and ipi + nivo. All treatments showed better progression-free survival compared with sunitinib that was similar among them. The combination of an IO agent (pembrolizumab or avelumab) and axitinib seemed to be the most effective therapy for the ORR.

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Introduction

Globally, the incidence and mortality of renal cell carcinoma (RCC) has corresponded to 403,000 new cases and ~175,000 deaths.[1] However, ~30% to 40% of patients will develop metastatic disease after definitive treatment of localized disease.[2-4] Although for localized disease, surgical resection with curative intent has been the standard approach, for metastatic RCC (mRCC), systemic therapy has been the cornerstone of treatment. In the past 2 decades, systemic therapy has evolved, with significant improvements in overall survival (OS) and quality of life of patients with advanced disease observed.

In the targeted therapy era, patient prognosis can be stratified using the International Metastatic RCC Database Consortium (IMDC) prognostic risk score. Based on the number of adverse prognostic factors, including 6 clinical and laboratory parameters (< 1 year from diagnosis to systemic therapy, Karnofsky performance status < 80%, hemoglobin lower than the normal limit, calcium greater than the normal limit, neutrophil greater than the normal limit and platelets greater than the normal limit), 3 distinct risk groups can be identified. The median OS has been 43.2 months for the favorable risk (FR) group (0 adverse prognostic factors), 22.5 months for the intermediate risk (IR) group (1-2 adverse prognostic factors), and 7.8 months for the poor risk (PR) group (3-6 adverse prognostic factors).[5] However, no predictive biomarkers have been validated for use in clinical practice and the prognostic risk score is still widely used to guide treatment selection.

Until recently, therapies targeting the vascular endothelial growth factor receptor (VEGF), such as sunitinib or pazopanib, were considered the standard first-line systemic treatment of patients with mRCC.[6] However, a new paradigm for the treatment of mRCC has been established after the report of several studies showing the role of the immune system in clear cell RCC biology. Recently, immuno-oncology (IO) therapies, multitarget tyrosine kinase inhibitors (TKIs), and the combination of different mechanisms of action have synergistically increased the clinical benefit (IO plus IO; IO plus TKIs IO plus antiangiogenic antibody; Supplemental Table 1 in the online version). These have demonstrated clinically significant improvements in OS, progression-free survival (PFS), and the overall response rate (ORR) as first-line mRCC treatment and have become the new standard of care.

Although several agents are now available, to the best of our knowledge, no direct comparisons have been performed. In the present analysis, we sought to provide a rational to help in the decision-making process for first-line treatment of mRCC.

Patients and Methods

We evaluated and compared the outcomes after the different treatment options for clear cell mRCC in first-line treatment (International Prospective Register of Systematic Reviews identifier, 152029).

Search Strategy

Using the Preferred Reporting Items for Systematic Review recommendations, a systematic search was performed in electronic databases, including PubMed/MEDLINE, EMBASE, LILACS, ClinicalTrials.gov, and the Cochrane Library.[7,8] The search terms included (Kidney Neoplasms) AND random* AND (sunitinib OR pazopanib OR sorafenib OR cabozantinib OR axitinib OR ipilimumab OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab). The search was completed on May 31, 2019. A supplemental search was performed manually to identify congress abstracts published from the American Society of Clinical Oncology annual meetings, American Society of Clinical Oncology Genitourinary Cancers symposiums, and European Society for Medical Oncology annual meetings from January 2017 to June 2019 (Figure 1). The reference lists of all relevant reports were also reviewed.

The inclusion criteria for the trials were as follows: (1) randomized superiority controlled prospective phase III trials (randomized clinical trials [RCTs]); (2) control arm with sunitinib; (3) first-line treatment setting; (4) clear cell mRCC; and (5) English language.

Endpoints

The primary endpoint assessed within the present analysis was OS, and the secondary endpoints were PFS and the ORR.

Treatment Comparisons

All eligible trials had sunitinib as the control arm, and each trial had evaluated a different treatment in the experimental arm. Therefore, we evaluated the possibility of superior efficacy between the different experimental arms in an intention to treat (ITT) population (Figure 2). For OS, considering that, to date, only 2 trials (CHECKMATE-214 and KEYNOTE-426)[9-12] have reported mature survival data, the indirect comparison was of ipilimumab plus nivolumab (ipi + nivo) versus pembrolizumab plus axitinib (pembro + axi). For PFS and ORR, the following indirect comparisons were performed: (1) ipi + nivo versus pembro + axi; (2) ipi + nivo versus avelumab plus axitinib (avelu + axi); (3) ipi + nivo versus atezolizumab plus bevacizumab (atezo + bev); (4) pembro + axi versus avelu + axi; (5) pembro + axi versus atezo + bev; and (6) avelu + axi versus atezo + bev.

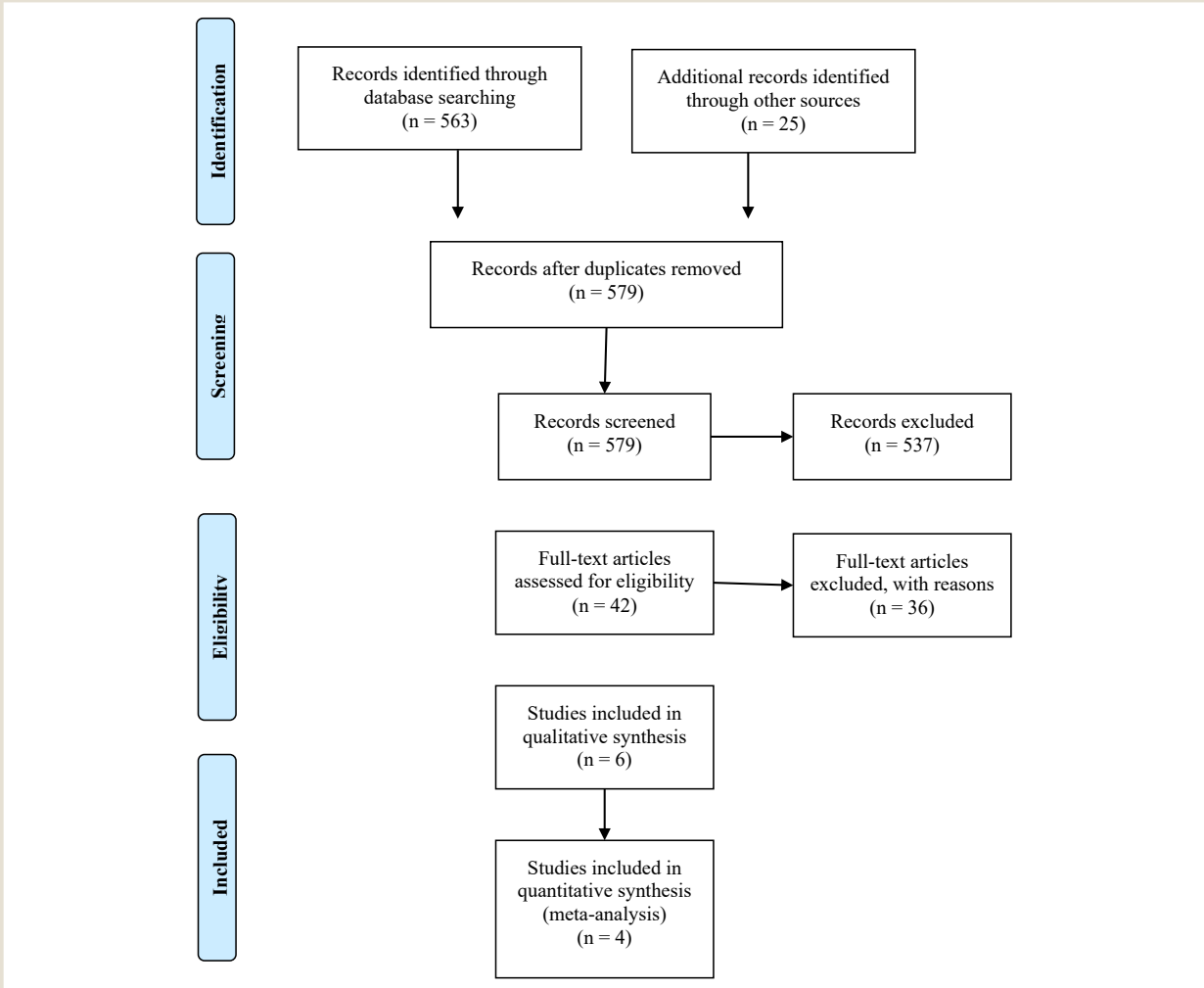
Subgroup Analyses

Exploratory analyses for all endpoints were performed for the subgroups according to the IMDC risk group (ie, FR, IR/PR). For OS, we compared ipi + nivo versus pembro + axi. For PFS and ORR, the analysis was of all experimental treatment regimens versus sunitinib and the following: (1) ipi + nivo versus pembro + axi; (2) ipi + nivo versus avelu + axi; (3) ipi + nivo versus atezo + bev; (4) pembro + axi versus avelu + axi; (5) pembro + axi versus atezo + bev; and (6) avelu + axi versus atezo + bev.

Statistical Analysis

A network meta-analysis was performed using Bayesian mixed treatment comparison models with noninformative prior distributions. Only fixed effect models were adjusted.[13] Network plots were used to illustrate the geometry of the evidence. The results from individual studies were pooled as relative risks (response rates, ORR) for binary data using the raw data provided by the studies. Hazard ratios (HRs) were used for time-to-event outcomes (OS and PFS) using the estimates reported by

Figure 1 Flowchart Showing Literature Search and Trial Selection



the studies. To rank the treatments, we used the surface under the cumulative ranking curve (SUCRA).[13-15] The results are presented as point estimates and 95% credible intervals (CrIs). The analyses were performed using the package GEMTC from R software.[16]

Results

The systematic search identified 4 studies that had met all the inclusion criteria with a total of 3758 patients. We also identified 2 updates of previously selected studies. The systemic therapy was sunitinib for 1880 patients and ipi + nivo, pembro + axi, avelu + axi, and atezo + bev for 550, 432, 442, and 454 patients, respectively. The geometry of the network is illustrated in Figure 2. The pairwise comparisons between the experimental arms and sunitinib were from head-to-head (direct) evidence and the comparisons between the different experimental treatment regimens were from indirect evidence. The characteristics of the eligible trials are summarized in Supplemental Table 2 (in the online version).

ITT Population Analysis

The results of eligible trials for the ITT population are summarized in Table 1.

Figure 2 Network Diagram

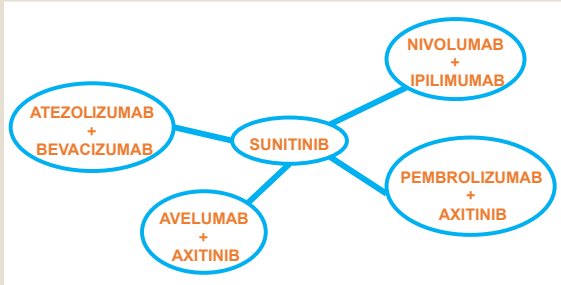


Table 1 Results of Eligible Trials for ITT Population

Trial	Patients, n	Endpoint			Follow-up, mo
		OS, mo	PFS, mo	ORR, %	
CHECK MATE 214[9,10]					30.0
Ipi + Nivo	550	NR	9.7	41	
Sunitinib	546	37.9	9.7	34	
HR; *P* value		0.71; .0003	0.85; .027	.015	
KEYNOTE 426[11,12]					12.8
Pembro + Axi	432	NR	15.1	59.3	
Sunitinib	429	NR	11.1	35.7	
HR; *P* value		0.53; <.0001	0.69; <.001	<.001	
JAVELIN Renal 101[17]					11.6
Avelu + Axi	442	NA	13.8	51.4	
Sunitinib	444	NA	8.4	25.7	
HR; *P* value		0.78; .14	0.69; <.001	NA	
IMmotion 151[18]					12.0
Atezo + Bev	454	33.6	11.2	37	
Sunitinib	461	34.9	8.4	33	
HR; *P* value		0.93; .47	0.83; .021	NA	

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; HR = hazard ratio; Ipi = ipilimumab; NA = not available/not applicable; Nivo = nivolumab; NR = not reached; ORR = overall response rate; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival.

Overall Survival. The survival results for the ITT population were based on 982 patients from CHECKMATE-214 and KEYNOTE-426.[9-12] In an indirect comparison of ipi + nivo and pembro + axi, no significant difference was found in OS between the 2 regimens (HR, 1.34; 95% CrI, 0.92-1.97). Considering the results from the direct comparisons with sunitinib, in the ranking for OS, pembro + axi might be the most effective first-line treatment (SUCRA, 90%). The ranking is detailed in Supplemental Table 3 (in the online version).

PFS and ORR. Considering the indirect comparisons for PFS of all experimental regimens, we found no significant differences. In the direct comparisons with sunitinib, in the ranking for PFS, avelu + axi and pembro + axi might be the most effective first-line treatment (SUCRA, 49% and 48%, respectively).

Regarding the ORR, a significant difference was found for 4 indirect comparisons. Two favored avelu + axi: atezo + bev versus avelu + axi (HR, 0.55; 95% CrI, 0.43-0.71) and avelu + axi versus ipi + nivo (HR, 1.66; 95% CrI, 1.31-2.12). The other 2 favored pembro + axi: atezo + bev versus pembro + axi (HR, 0.66; 95% CrI, 0.52-0.84) and ipi + nivo versus pembro + axi (HR, 0.73; 95% CrI, 0.59-0.90). However, no difference was found for avelu + axi versus pembro + axi (HR, 1.21; 95% CrI, 0.95-1.53). Considering the direct comparisons with sunitinib, for the ORR, avelu + axi might be the most effective first-line treatment (SUCRA, 94%). The PFS and ORR HRs for all comparisons are detailed in Figure 3, and the ranking is detailed in Supplemental Table 5 (in the online version).

Subgroup Analyses for FR

The KEYNOTE-426 and IMmotion-151 trials did not report information on the ORR for the FR population. The results of eligible trials for the FR population are summarized in Table 2.

Overall Survival. The OS results for the FR population are based on 263 patients from CHECKMATE-214 and KEYNOTE-426.[9-12] An indirect comparison of ipi + nivo and pembro + axi showed no significant differences in OS (HR, 1.90; 95% CrI, 0.64-5.77). In the direct comparisons with sunitinib, in the ranking for OS, pembro + axi might be the most effective first-line treatment (SUCRA, 79%). The ranking is detailed in Supplemental Table 4 (in the online version).

PFS and ORR. The indirect comparisons for PFS among all experimental treatment regimens showed a significant difference for only 1 comparison, which favored avelumab + axitinib: avelu + axi versus ipi + nivo (HR, 0.44, 95% CrI, 0.24-0.80). In the direct comparisons with sunitinib, for PFS, avelu + axi might be the most effective first-line treatment (SUCRA, 88%).

For the ORR, a significant difference was found for 1 indirect comparison, which favored avelu + axi: avelu + axi versus ipi + nivo (HR, 2.27; 95% CrI, 1.53-3.44). In the direct comparisons with sunitinib for the ORR, avelu + axi might be the most effective first-line treatment (SUCRA, 100%). The PFS and ORR HRs for all comparisons are detailed in Figure 4A. The ranking is detailed in Supplemental Table 6 (in the online version).

Figure 3 Results of Progression-free Survival (PFS) and Overall Response Rate (ORR) for Intention to Treat (ITT) Population. The Results of Hazard Ratios (HRs) Were Constituted Considering the HR Associated With the Treatment Arm Above and to the Left of the Diagonal Line on HR Associated With the Treatment Arm Below and to the Right of the Same Diagonal Line. For PFS, HR < 1 Indicates a Treatment Results in a Lower Risk of Progression. For ORR, HR > 1 Indicates that a Treatment Results in a Higher Response Rate. Significant HRs Are Highlighted in Bold. Numbers in Parentheses Indicate 95% Credible Intervals

ORR \ PFS	ATEZO + BEV	AVELU + AXI	IPI + NIVO	PEMBRO + AXI	SUN
ATEZO + BEV		1.20 (0.93-1.56)	0.98 (0.78-1.22)	1.20 (0.93-1.55)	**0.83 (0.71-0.98)**
AVELU + AXI	**0.55 (0.43-0.71)**		0.81 (0.63-1.05)	1.00 (0.76-1.33)	**0.69 (0.56-0.85)**
IPI + NIVO	0.91 (0.72-1.16)	**1.66 (1.31-2.12)**		1.23 (0.96-1.57)	**0.85 (0.73-0.99)**
PEMBRO + AXI	**0.66 (0.52-0.84)**	1.21 (0.95-1.53)	**0.73 (0.59-0.90)**		**0.69 (0.57-0.84)**
SUN	1.11 (0.92-1.33)	**2.01 (1.68-2.42)**	**1.21 (1.04-1.41)**	**1.66 (1.44-1.94)**	

Abbreviations: ATEZO = atezolizumab; AVELU = avelumab; AXI = axitinib; BEV = bevacizumab; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; SUN = sunitinib.

Subgroup Analysis for Intermediate and Poor Risk Population

The results of the eligible trials for the IR/PR population are summarized in Table 2.

Overall Survival. The OS results for the IR/PR population were determined from the data from 719 patients from the CHECKMATE-214 and KEYNOTE-426 trials.[9-12] In an indirect comparison of ipi + nivo and pembro + axi, no significant difference was found in OS between them (HR, 1.27; 95% CrI, 0.85-1.89). In the direct comparisons with sunitinib, in the ranking for OS, pembro + axi might be the most effective first-line treatment (SUCRA, 88%). The ranking is detailed in Supplemental Table 4 (in the online version).

PFS and ORR. The indirect comparisons for PFS among all experimental treatments showed no differences among them. In the direct comparisons with sunitinib, in the ranking for PFS, pembro + axi might be the most effective first-line treatment (SUCRA, 54%).

For the ORR, a significant difference was found for only 1 indirect comparison, which favored avelumab + axitinib: avelu + axi versus ipi + nivo (HR, 1.44; 95% CrI, 1.07-1.92). In the direct comparisons with sunitinib, in the ORR ranking, avelu + axi might be the most effective first-line treatment (SUCRA, 75%). The PFS and ORR HRs for all comparisons are detailed in Figure 4B. The ranking is detailed in Supplemental Table 7 (in the online version).

Discussion

The present systematic review and network meta-analysis was focused on systemic therapies for first-line treatment for patients with advanced clear cell RCC.[19,20] Because sunitinib was considered 1 of the standard options for first-line mRCC and was selected as the control arm for most clinical trials in this setting, our analysis included only phase III, superiority RCTs with sunitinib as the control arm. The results of the present network meta-analysis demonstrated no differences in the median OS between ipi + nivo and pembro + axi in the ITT and different prognostic risk groups, although pembro + axi might be the better treatment choice to provide the greatest OS benefit. For PFS, the 2 combinations of IO and axitinib (pembrolizumab or avelumab) were associated with better outcomes than were the other therapies with a greater possibility of providing the longest PFS benefit.

These results are similar to those demonstrated in 2 recent meta-analysis.[21,22] However, our analysis has some differences from these previous analyses. First, we performed an analysis stratified by the IMDC risk classification. Although the result should be interpreted with caution, the comparisons within the specific prognostic groups could lead to a better understanding of the benefits of the available therapeutic options in the first-line setting for the FR and IR/PR subgroups because the prognostic groups are still used to guide treatment selection. In this context, for both FR and IR/PR patients, no differences were found in the OS outcomes between ipi + nivo and pembro + axi. For FR and IR/PR patients, pembro + axi showed a greater possibility of providing the greatest OS benefit; however, for FR patients, sunitinib would be the second treatment option for providing OS benefit. For IR/PR patients, this option would be ipi + nivo. These results are consistent with the reported data from the KEYNOTE-426 trial that pembro + axi improve OS for all risk groups and data from the CHECKMATE-214 trial that ipi + nivo did not demonstrate OS improvement in the subgroup analysis for FR patients but had significantly improved OS compared with sunitinib for the IR/PR patients.[9,11] Regarding

Table 2 Results of Eligible Trials Stratified by IMDC Prognostic Risk Score

Trials	Patients, n	Endpoints		
		OS, mo	PFS, mo	ORR (%)
Favorable risk				
CHECK MATE 214[9,10]				
Ipi + Nivo	125	NR	13.9	39
Sunitinib	124	NR	19.9	50
HR; *P* value		1.22; .443	1.23; .189	.143
KEYNOTE 426[11,12]				
Pembro + Axi	138	NA	NA	NA
Sunitinib	131	NA	NA	NA
HR; *P* value		0.64; NA	0.81; NA	NA
JAVELIN Renal 101[17]				
Avelu + Axi	94	NA	NR	68.1
Sunitinib	96	NA	13.8	37.5
HR; *P* value		NA; NA	0.54; NA	NA
IMmotion 151[18]				
Atezo + Bev	89	NA	NA	NA
Sunitinib	90	NA	NA	NA
HR; *P* value		NA	1.12; NA	NA
Intermediate/poor risk	IR; PR			
CHECK MATE 214[9,10]				
Ipi + Nivo	334; 91	NR	8.2	42
Sunitinib	333; 89	26.6	8.3	29
HR; *P* value		0.66; <.0001	0.77; .001	<.0001
KEYNOTE 426[11,12]				
Pembro + Axi	238; 56	NA	12.6	55.8
Sunitinib	246; 52	NA	8.2	29.5
HR; *P* value		0.52; NA	0.67; NA	NA
JAVELIN Renal 101[17]				
Avelu + Axi	271; 72	NA	13.8; 6.0[a]	51.3; 30.6[a]
Sunitinib	276; 71	NA	8.4; 2.9[a]	25.4; 11.1[a]
HR; *P* value		NA; NA	0.74; 0.57; NA[b]	NA
IMmotion 151[18]				
Avelu + Axi	271; 72	NA	NA	NA
Sunitinib	276; 71	NA	NA	NA
HR; *P* value		NA; NA	0.83; 0.73; NA[b]	NA

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; Ipi = ipilimumab; NA = not available/not applicable; Nivo = nivolumab; NR = not reached; ORR = overall response rate; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival.

[a]PFS for intermediate risk; PFS for poor risk.

[b]HR for intermediate risk; HR for poor risk; *P* value, NA.

PFS, for both FR and IR/PR patients, ipi + nivo would be the less-effective treatment option compared with the other experimental treatments. This result has confirmed the CHECKMATE-214 data, which showed no difference in PFS with ipi + nivo compared with sunitinib for both the ITT population and the patient subgroups stratified by the IMDC risk classification.[9] These data are consistent with previous reports that immunotherapy might present an atypical response pattern (pseudoprogression or response after discontinuation of therapy). Thus, perhaps this is the reason for no PFS benefit with this type of treatment.[23]

The second difference is that the present analysis included the ORR as an endpoint. Thus, for the ITT population, avelu + axi is 94% more likely to provide the greatest ORR benefit. Considering the analysis of ORR using the IMDC risk classification, it was not possible to include atezo + bev treatment because the reported IMMOTION-151 trial did not disclose data for the numerical confidence intervals and *P* values.[18] In addition, for FR patients, considering that the KEYNOTE-426 trial had no available reported data of the ORR for this subgroup of patients, avelu + axi would seem to be the most effective treatment for this subgroup. For IR/PR patients, the most

Figure 4 Results of Progression-free Survival (PFS) and Overall Response Rate (ORR) in (A) Favorable Risk Subgroup and (B) Intermediate Risk/Poor Risk Subgroup. The Results of Hazard Ratios (HRs) Were Constituted Considering the HR Associated With the Treatment Arm Above and to the Left of the Diagonal Line on HR Associated With the Treatment Arm Below and to the Right of the Same Diagonal Line. For PFS, HR < 1 Indicates That a Treatment Results in a Lower Risk of Progression. For ORR, HR > 1 Indicates That a Treatment Results in a Higher Response Rate. Significant HRs Are Highlighted in Bold. Numbers in Parentheses Indicate 95% Credible Intervals

A

ORR \ PFS	AVELU + AXI	IPI + NIVO	PEMBRO + AXI	SUN
AVELU + AXI		**0.44 (0.24-0.80)**	0.67 (0.34-1.30)	**0.54 (0.32-0.91)**
IPI + NIVO	**2.27 (1.53-3.44)**		1.52 (0.90-2.58)	1.23 (0.90-1.69)
PEMBRO + AXI	N/A	N/A		0.81 (0.53-1.24)
SUN	**1.79 (1.37-2.43)**	0.79 (0.60-1.05)	N/A	

B

ORR \ PFS	AVELU + AXI	IPI + NIVO	PEMBRO + AXI	SUN
AVELU + AXI		0.90 (0.68-1.18)	1.03 (0.74-1.43)	**0.69 (0.55-0.86)**
IPI + NIVO	**1.44 (1.07-1.92)**		1.15 (0.86-1.53)	**0.77 (0.66-0.91)**
PEMBRO + AXI	1.11 (0.82-1.51)	0.77 (0.58-1.01)		**0.67 (0.53-0.85)**
SUN	**2.10 (1.68-2.64)**	**1.46 (1.22-1.77)**	**1.89 (1.56-2.34)**	

Abbreviations: ATEZO = atezolizumab; AVELU = avelumab; AXI = axitinib; BEV = bevacizumab; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; SUN = sunitinib.

effective treatment would seem to be both avelu + axi and pembro + axi (75% and 72% possibility, respectively).

Also, cabozantinib, a potent inhibitor of VEGF2, MET, and AXL and 1 of the standard second-line therapies for mRCC, was recently approved in the first-line setting for IR/PR clear cell mRCC. This agent was approved because of the results from a phase II study (CABOSUN) in which cabozantinib was compared with sunitinib in the IR/PR subgroup of patients. Cabozantinib was significantly associated with a longer median PFS (8.2 vs. 5.6 months) and higher response rates. No statistically significant benefits in terms of OS were observed.[24,25] We restricted our analysis to phase III clinical trials to avoid additional biases. However, cabozantinib is an active drug in the treatment-naive population, and these data suggest a favorable efficacy profile compared with sunitinib. Future studies might consider this agent as a better control arm than sunitinib in the first-line setting, and comparisons with the combination therapies presented in the present study are warranted.

Despite the interesting results with these indirect comparisons, our analysis had several limitations. First, we did not analyze the quality of the response rate (eg, complete or partial response) or the duration of response. This point is crucial considering that one of the main features of IO treatment of different types of tumors is the possibility that patients with metastatic disease might have durable responses and long-term OS, as previously demonstrated for patients with mRCC treated with nivolumab in phase I and II trials, with a 3-year OS rate of 41%.[26,27] This durable response seems to be related to patients with a complete response, and in this context, the treatment with the greatest possibility of a complete response was ipi + nivo (Supplemental Table 8 in the online version).[26] The second limitation was that we did not consider biomarkers such as programmed cell death ligand 1 (PD-L1) expression. Although in the CHECKMATE-214 and KEYNOTE-426 trials, PD-L1 expression did not translate into better benefit in the evaluated outcomes, in the JAVELIN RENAL-101 and IMMOTION-151 trials, PD-L1 expression was used to evaluate the primaries endpoints of these trials.[9,11,17,18] Another limitation was that we did not evaluate indirect comparisons of the toxicity profile for each treatment. Because no RCTs have compared these new treatment options head to head, data on the adverse events, tolerability, and safety could be important for deciding among all the available treatments.

Conclusions

We have demonstrated that for both FR and IR/PR patients, no differences were found in the survival outcomes between ipi + nivo and pembro + axi. These findings are reassuring that the treatment choice should consider the physician's choice and experience, the toxicity profile, access, and costs of the treatment regimen, and the patient's clinical condition and choices. However, for all subgroups of patients, pembro + axi is likely to be the better treatment for providing the best OS benefit. In our indirect comparison, ave/pembro + axi seems to be the most effective treatment option for longer PFS and better response rate. These data may assist in the decision-making process and in the design of future clinical trials.

Disclosure

The authors declare that they have no competing interests.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.02.012.

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Supplemental Data

Supplemental Table 1 Actual Therapeutic Agents for First-line mRCC

Drug	Class	Mechanism of Action	Treatment
Cabozatinib	Targeted therapy (TKI)	Multitarget TKI	Monotherapy
Axitinib	Targeted therapy (TKI)	Anti-VEGFR TKI	Combined with IO
Bevacizumab	Targeted therapy	Antiangiogenic antibody	Combined with IO
Ipilimumab	Immune checkpoint inhibitor (IO)	Anti—CTLA-4 antibody	Combined with IO
Nivolumab	Immune checkpoint inhibitor (IO)	Anti—PD-1 antibody	Combined with IO
Pembrolizumab	Immune checkpoint inhibitor (IO)	Anti—PD-1 antibody	Combined with TKI
Avelumab	Immune checkpoint inhibitor (IO)	Anti—PD-L1 antibody	Combined with TKI
Atezolizumab	Immune checkpoint inhibitor (IO)	Anti—PD-L1 antibody	Combined with antiangiogenic antibody

Abbreviations: IO = immuno-oncology (agent); mRCC = metastatic renal cell carcinoma; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Supplemental Table 2 Characteristics of Eligible Trials

Trial	Type	Patients, n	IMDC Risk Group, %	Experimental Treatment	1 Endpoint	2 Endpoint
CHECKMATE 214[9,10]	Phase III	1096	FR, 23; IR, 61; PR, 17	Nivo + Ipi	OS, PFS, ORR—IR/PR	OS, PFS, ORR—ITT
KEYNOTE 426[11,12]	Phase III	861	FR, 31.9; IR, 55.1; PR, 13	Pembro + Axi	OS, PFS—ITT	ORR
JAVELIN Renal 101[17]	Phase III	886	FR, 21.3; IR, 61.3; PR, 16.3	Avelu + Axi	OS, PFS—PD-L1$^+$ patients	PFS, ORR—all patients
IMMOTION 151[25]	Phase III	915	FR, 22; IR, 61.3; PR, 16.7	Atezo + Bev	PFS—PD-L1$^+$ patients; OS—ITT	OS—PD-L1$^+$ patients; PFS, ORR—ITT

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; FR = favorable risk; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; Ipi = ipilimumab; IR = intermediate risk; ITT = intention to treat; Nivo = nivolumab; ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; Pembro = pembrolizumab; PFS = progression-free survival; PR = poor risk.

Supplemental Table 3 Ranking of Overall Survival for ITT Population

Rank	Atezo + Bev, %	Avelu + Axi, %	Ipi + Nivo, %	Pembro + Axi, %	Sunitinib, %
1	0.0	4.0	6.0	90.0[a]	0.0
2	1.0	28.0	63.0[a]	8.0	0.0
3	18.0	48.0[a]	30.0	2.0	2.0
4	57.0[a]	13.0	2.0	0.0	28.0
5	23.0	7.0	0.0	0.0	70.0[a]

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; Ipi = ipilimumab; ITT = intention to treat; Nivo = nivolumab; Pembro = pembrolizumab.
[a]Best result.

Supplemental Table 4 Ranking of Overall Survival for FR and IR/PR Population

OS	Rank	Atezo + Bev, %	Avelu + Axi, %	IPI + Nivo, %	Pembro + Axi, %	Sunitinib, %
FR						
	1	NA	NA	6.0	79.0[a]	15.0
	2	NA	NA	22.0	10.0	68.0[a]
	3	NA	NA	72.0[a]	10.0	18.0
IR/PR						
	1	NA	NA	12.0	88.0[a]	0.0
	2	NA	NA	88.0[a]	12.0	0.0
	3	NA	NA	0.0	0.0	100.0[a]

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; FR = favorable risk; Ipi = ipilimumab; IR = intermediate risk; NA = not applicable/not available; Nivo = nivolumab; OS = overall survival; Pembro = pembrolizumab; PR = poor risk.
[a]Best result.

Supplemental Table 5 Ranking of ORR and PFS for ITT Population

ITT	Rank	Atezo + Bev, %	Avelu + Axi, %	Ipi + Nivo, %	Pembro + Axi, %	Sunitinib, %
ORR						
	1	0.0	94.0[a]	0.0	6.0	0.0
	2	0.0	6.0	0.0	94.0[a]	0.0
	3	22.0	0.0	78.00[a]	0.0	0.0
	4	65.0[a]	0.0	22.00	0.0	13.0
	5	13.0	0.0	1.0	0.0	86.0[a]
PFS						
	1	2.0	49.0[a]	1.0	48.0	0.0
	2	10.0	41.0	6.0	42.0[a]	0.0
	3	47.0[a]	8.0	38.0	7.0	0.0
	4	39.0	2.0	54.0[a]	2.0	3.0
	5	1.0	0.0	2.0	0.0	97.0[a]

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; Ipi = ipilimumab; ITT = intention to treat; Nivo = nivolumab; ORR = overall response rate; Pembro = pembrolizumab; PFS = progression-free survival.
[a]Best result.

Supplemental Table 6 Ranking of ORR and PFS for Favorable Risk Population

FR	Rank	Avelu + Axi, %	Ipi + Nivo, %	Pembro + Axi, %	Sunitinib, %
ORR					
	1	100.0[a]	0.0	NA	0.0
	2	0.0	5.0	NA	95.0[a]
	3	0.0	95.0[a]	NA	5.0
PFS					
	1	88.0[a]	0.0	12.0	0.0
	2	11.0	3.0	71.0[a]	15.0
	3	1.0	11.0	12.0	76.0[a]
	4	0.0	87.0[a]	5.0	8.0

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; FR = favorable risk; Ipi = ipilimumab; NA = not applicable/not available; Nivo = nivolumab; ORR = overall response rate; Pembro = pembrolizumab; PFS = progression-free survival.
[a]Best result.

Supplemental Table 7 Ranking of ORR and PFS for IR/PR Population

IR/PR	Rank	Avelu + Axi, %	Ipi + Nivo, %	Pembro + Axi, %	Sunitinib, %
ORR					
	1	75.0[a]	0.00	25.0	0.00
	2	25.0	3.00	72.0[a]	0.00
	3	0.0	97.0[a]	3.0	0.00
	4	0.0	0.0	0.0	100.0[a]
PFS					
	1	40.0	6.0	54.0[a]	0.0
	2	42.0[a]	26.0	32.0	0.0
	3	18.0	68.0[a]	14.0	0.0
	4	0.0	0.0	0.0	100.0[a]

Abbreviations: Atezo = atezolizumab; Avelu = avelumab; Axi = axitinib; Bev = bevacizumab; Ipi = ipilimumab; IR = intermediate risk; Nivo = nivolumab; ORR = overall response rate; Pembro = pembrolizumab; PFS = progression-free survival; PR = poor risk.
[a]Best result.

Supplemental Table 8 Response Rate for ITT Population

Trial	ORR, %	CR, %	PR, %	SD, %	PD, %
CHECK MATE 214[9,10]					
Ipi + Nivo	41	10.5	30.7	NA	NA
Sunitinib	34	1.8	32.2	NA	NA
KEYNOTE 426[11,12]					
Pembro + Axi	59.3	5.8	53.5	24.5	10.9
Sunitinib	35.7	1.9	33.8	39.4	17
JAVELIN Renal 101[17]					
Avelu + Axi	51.4	3.4	48	29.6	11.5
Sunitinib	25.7	1.8	23.9	45.5	18.7
IMmotion 151[25]					
Atezo + Bev	37	5	31	39	18
Sunitinib	33	2	31	39	19

Abbreviations: CR = complete response; ITT = intention to treat; ORR = overall response rate; NA = not applicable/not available; PD = progressive disease; PR = partial response; SD = stable disease.