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Rapid Review – Kidney Cancer

First-line Immunotherapy-based Combinations for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis

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Abstract

Context: There have been substantial changes in the management of patients with metastatic renal cell carcinoma (mRCC) over the past decade, with upfront immunotherapy-based combinations replacing targeted therapies. A broad range of combinations have been approved, and comparisons of their efficacy and safety are needed to guide the optimal choice of first-line therapy.

Objective: To perform indirect comparisons of efficacy and safety of first-line immune checkpoint inhibitor (ICI)-based combination therapies for mRCC.

Evidence acquisition: We searched multiple databases and abstracts of major scientific meetings up to February 2021 to identify phase III randomized controlled trials of patients receiving first-line ICI-based combination therapies for mRCC. Progression-free survival (PFS) and overall survival (OS) were the primary endpoints. The secondary endpoints included complete response rates (CRRs), objective response rates (ORRs), grade $\geq$3 treatment-related adverse events (TRAEs), and rates of treatment discontinuation due to adverse events (AEs). Subgroup network meta-analyses were performed based on patients' risk group categories and programmed death ligand 1 (PD-L1) expression status.

Evidence synthesis: Six trials were included in our network meta-analyses comprising 5121 patients. Nivolumab plus cabozantinib had the highest likelihood of providing the maximal OS (P score: 0.7573). Lenvatinib plus pembrolizumab demonstrated the highest likelihood of PFS (P score: 0.9906) and ORR (P score:

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0.9564). CRRs were more likely to be associated with nivolumab plus ipilimumab (P score: 0.8682). In patients with ≥1% PD-L1 expression, the highest likelihood of better PFS was associated with lenvatinib plus pembrolizumab and nivolumab plus ipilimumab. Nivolumab plus ipilimumab was also associated with the lowest rates of grade ≥3 TRAEs; while the highest likelihood of AE-related treatment discontinuation was associated with lenvatinib plus pembrolizumab and nivolumab plus ipilimumab.

Conclusions: Our network meta-analysis suggests that combinations of ICIs and tyrosine kinase inhibitors (TKIs) provide superior PFS, ORR, and OS to ICI-ICI combinations, regardless of the on International mRCC Database Consortium risk group. However, an ICI-ICI combination could be the optimal treatment for tumors with increased PD-L1 expression. The newly introduced ICI-TKI combinations, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab, showed promising activity and are likely to have an important role in the mRCC treatment strategy.

Patient summary: The use of immune checkpoint inhibitor (ICI)-based combinations (ICI plus tyrosine kinase inhibitor and ICI-ICI) improved oncological outcomes of metastatic renal cell carcinoma. Programmed death ligand 1 (PD-L1) expression status could help guide physicians and patients to select the appropriate treatment strategy.

1. Introduction

Renal cell carcinoma (RCC) is annually diagnosed in about 400 000 people worldwide and results in approximately 175 000 deaths [1]. About 35% of patients present initially with advanced or metastatic RCC (mRCC), and of the remaining 65% who present with localized disease, 30% will eventually relapse [2,3].

Systemic first-line treatment for mRCC is rapidly evolving, with multiple approved strategies and new clinical trials underway. In the past decade, there have been major advances in the treatment of mRCC. Mainly the introduction of new immune checkpoint inhibitors (ICIs) has led to a paradigm shift in the management of this disease. Dual checkpoint inhibition with nivolumab and ipilimumab as well as the combination of a PD-(L)-1 ICI and a vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI) were shown to improve response rates, progression-free survival (PFS), and/or overall survival (OS) when compared with sunitinib, the former standard of care [4–6].

No head-to-head trials comparing these novel strategies have been conducted so far. Moreover, no biomarker has yet been made available to facilitate treatment choices. Thus, choosing the best regimen for the individual patient may prove challenging. In a recent network meta-analysis, we compared multiple first-line treatment options for mRCC, including TKIs and ICIs [7]. We reported that pembrolizumab plus axitinib and avelumab plus axitinib seemed to provide the highest likelihood of better OS and PFS, respectively, while nivolumab plus ipilimumab had the most favorable efficacy-tolerability profile. However, updated results of the CheckMate-214, JAVELIN Renal 101, and KEYNOTE-426 trials were recently reported [8–11]. Furthermore, the recent release of the checkmate-9ER trial and the CLEAR trial results has introduced new combinations (nivolumab plus cabozantinib and lenvatinib plus pembrolizumab) that are expected to be important parts of the new mRCC treatment paradigm [12,13]. Therefore, we sought to conduct an updated network meta-analysis with a focus on ICI-based combinations.

2. Evidence acquisition

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42020219094).

2.1. Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for network meta-analysis [14], we systematically searched the PubMed, Web of Science, and Scopus databases to find relevant studies published until February 2021. A PRISMA 2009 checklist was used to describe the methodology of our study. The main search terms were the following: (renal cell carcinoma OR renal cell cancer OR kidney carcinoma OR kidney cancer) AND (metastatic OR advanced) AND (Randomized). All phase III randomized controlled trials regarding first-line ICI-based combinations versus sunitinib in mRCC were retrieved. Furthermore, we also reviewed relevant abstracts presented in major conferences, including the American Society of Clinical Oncology and the European Society for Medical Oncology.

The primary endpoints were OS and PFS; secondary endpoints included objective response rate (ORR), complete response rate (CRR), rates of treatment discontinuation due to adverse events (AEs), and treatment-related adverse events (TRAEs). Subgroup analyses were performed when

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applicable on patients based on International mRCC Database Consortium (IMDC) risk groups and based on programmed death ligand 1 (PD-L1) status. Initial screening was performed independently by two investigators based on the titles and abstracts of the articles to identify ineligible reports. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process. Disagreements were resolved via consensus with a committee of investigators.

2.2. Inclusion and exclusion criteria

Studies were included if these investigated advanced/metastatic clear cell RCC patients (patients) who received ICI-based combination as first-line treatment (intervention) compared with those treated with sunitinib as first-line treatment (comparison) to assess the differential effects on PFS, OS, ORR, CRR, and rates of treatment discontinuation due to AEs and TRAEs (outcome) in phase III randomized studies only. We excluded observational studies, reviews, letters, editorials, replies from authors, case reports, and articles not published in English. In cases of multiple publications on the same cohort, we abstracted the most up to date data for the outcome intended for analysis. References of all papers included were screened for additional studies of interest. We excluded studies that involved patients with a prior history of systemic therapy and if they included interferon or placebo as the control arms. Studies were included only if they involved patients who received sunitinib 50 mg as the control arm.

2.3. Data extraction

Two independent authors extracted the following information from the included articles: first author's name, publication year, period of patient recruitment, number of patients, treatment dosage, age, sex, study design, risk group, histological component of RCC, oncological outcomes, and AE outcomes. Hazard ratios (HRs) and 95% confidence intervals (CIs) associated with OS and PFS were retrieved.

2.4. Risk of bias assessment

Risk of bias (RoB) in the selected studies was assessed by two authors, using the Cochrane Collaboration tool. This tool assesses the selection, performance, detection, attrition, reporting, and other sources of bias (Supplementary Fig. 1). The RoB of each study was assessed independently by two authors. Disagreements were resolved by consultation with the coauthors.

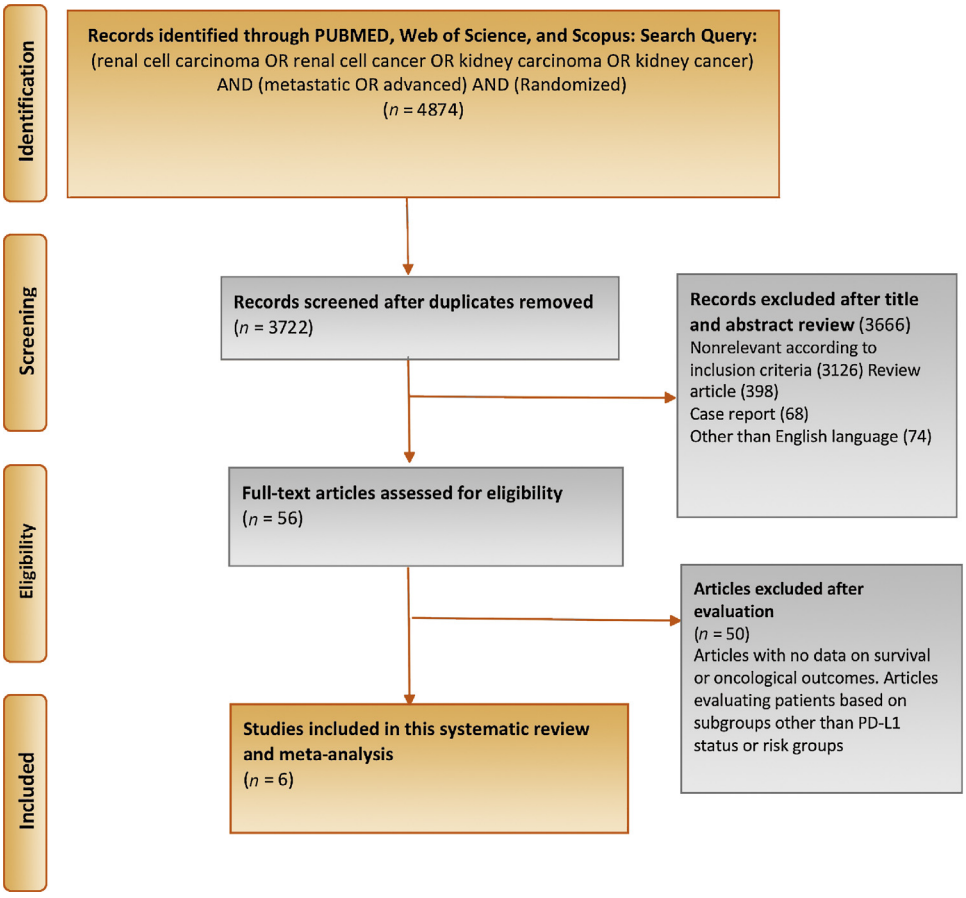

Fig. 1 – Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) diagram. PD-L1 = programmed death ligand 1.

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2.5. Statistical analyses

Network meta-analyses were conducted for each outcome using random- and fixed-effect models for the direct and indirect treatment comparisons with sunitinib as the common comparator arm [15]. In the assessment for OS and PFS, contrast-based analyses were applied with estimated differences in the log HR and the standard error

Table 1 – Characteristics of included phase III randomized control trials of first-line systemic therapy for metastatic renal cell carcinoma

Author	Year	Updated results	Trial	Number of patients (treatment)	Number of patients (control)	Treatment	Control	Patient characteristics
Motzer et al [4]	2018	2020	CheckMate 214	550	546	Nivolumab plus ipilimumab	Sunitinib	Median age (range): treatment 62 (26–85), control 62 (21–85)
								Male (%): treatment 75%, control 72%
								Poor risk group (IMDC; %): treatment 17%, control 16%
								Prior nephrectomy (%): treatment 82%, control 80%
								Patients with ≥1% PD-L1 expression (%): treatment 23%, control 25%
Rini et al [21]	2019	–	IMmotion151	454	461	Atezolizumab plus bevacizumab	Sunitinib	Median age (range): treatment 62 (56–69), control 60 (54–66)
								Male (%): treatment 70%, control 76%
								Poor-risk group (MSKCC; %): treatment 12%, control 12%
								Prior nephrectomy (%): treatment 74%, control 72%
								Patients with ≥1% PD-L1 expression (%): treatment 39%, control 40%
Motzer et al [5]	2019	2020	JAVELIN Renal 101	442	444	Avelumab plus axitinib	Sunitinib	Median age (range): treatment 62 (29–83), control 61 (27–88)
								Male (%): treatment 71.5%, control 77.5%
								Poor-risk group (IMDC; %): treatment 16.3%, control 13.4%
								Prior nephrectomy (%): treatment 79.6%, control 80%
								Patients with ≥1% PD-L1 expression (%): treatment 61.1%, control 65.3%
Rini et al [6]	2019	2020	KEYNOTE-426	432	429	Pembrolizumab plus axitinib	Sunitinib	Median age (range): treatment 62 (30–89), control 61 (26–90)
								Male (%): treatment 71.3%, control 74.6%
								Poor-risk group (IMDC; %): treatment 13%, control 12%
								Prior nephrectomy (%): treatment 82.6%, control 83.4%
								Patients with ≥1% PD-L1 expression (%): treatment 59.3%, control 61.7%
Choueiri et al [12]	2020	–	CheckMate 9ER	323	328	Nivolumab plus cabozantinib	Sunitinib	Median age (range): treatment 62 (29–90), control 61 (28–86)
								Male (%): treatment 77%, control 71%
								Poor-risk group (IMDC; %): treatment 19%, control 21%
								Prior nephrectomy (%): treatment 68.7%, control 71%
								Patients with ≥1% PD-L1 expression (%): treatment 26%, control 25%
Motzer et al [13]	2021	–	CLEAR	355	357	Lenvatinib plus pembrolizumab	Sunitinib	Median age (range): treatment 64 (34–88), control 61 (29–82)
								Male (%): treatment 71.8%, control 77%
								Poor-risk group (IMDC; %): treatment 9.3%, control 10.4%
								Prior nephrectomy (%): treatment 73.8%, control 77%
								Patients with ≥1% PD-L1 expression (%): treatment 30.1%, control 33.3%

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center prognostic risk score; PD-L1 = programmed death ligand 1.

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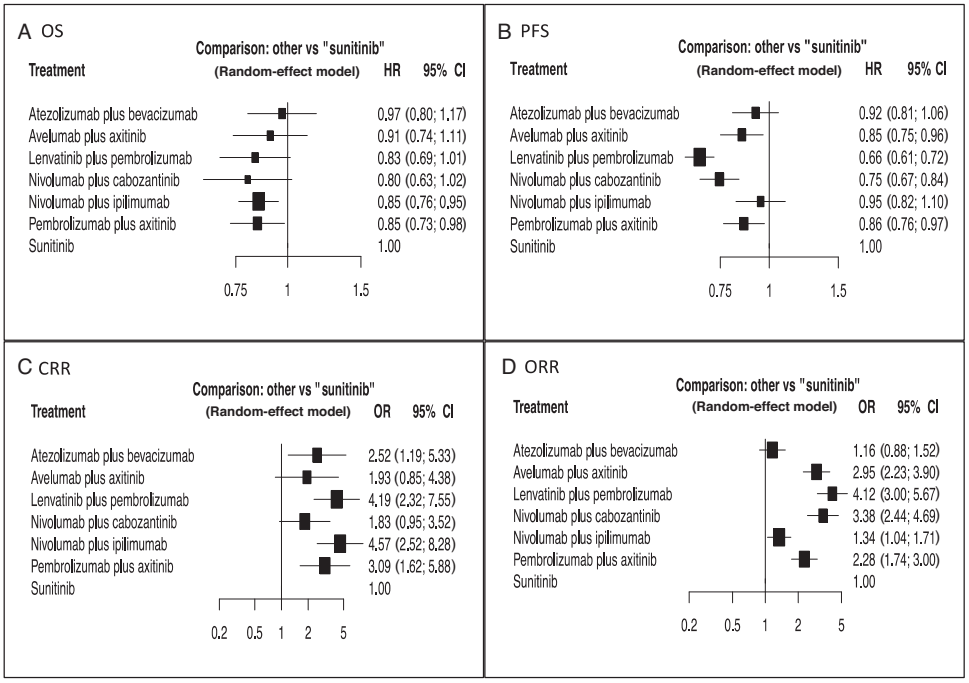

Fig. 2 – Forest plots showing the association of systemic therapy in metastatic renal cell carcinoma with (A) overall survival (OS), (B) progression-free survival (PFS), (C) complete response rate (CRR), and (D) objective response rate (ORR). CI = confidence interval; HR = hazard ratio.

calculated from the published HR and CI [16]. The relative treatment effects were presented as HR and 95% credible interval (CrI) [15]. For the assessment of the ORR, CRR, and AE, arm-based analyses were performed to estimate odds ratios (OR) and 95% CrI from raw data presented in selected manuscripts [15]. Subgroup analyses were performed when applicable on patients based on risk groups (according to the IMDC definitions) [17,18] and based on PD-L1 expression status. The relative treatment rankings were estimated for each outcome using P score, which is considered an analog to the surface under the cumulative ranking curves [19,20]. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of OS, PFS, and AEs. All statistical analyses were performed using R3.6.3 and Stata/MP 14.2 (Stata Corp., College Station, TX, USA); statistical significance was defined as $p < 0.05$.

3. Evidence synthesis

3.1. Results

3.1.1. Characteristics of included trials and patients

The initial literature search identified 4874 publications. A total of 3722 publications were available after removal of duplicate publications. Of these articles, 3666 were excluded after screening the titles and abstracts. Finally, 56 articles were available for full-text review. Based on the selection criteria, six studies comprising 5121 patients were included for the systematic review and network meta-analysis (Fig. 1) [4–6,8,11–13,21,22]. Characteristics of the included studies are provided in Table 1.

3.1.2. Network meta-analysis

The networks of eligible comparisons were graphically represented in network plots in terms of OS (Supplementary Fig. 2A) and PFS (Supplementary Fig. 2B).

3.1.3. Overall survival

For the analysis of OS, a network meta-analysis of seven different agents was conducted. Compared with sunitinib, pembrolizumab plus axitinib and nivolumab plus ipilimumab resulted in significantly improved OS (HR 0.85, 95% CrI 0.73–0.98 and HR 0.85, 95% CrI 0.76–0.95, respectively (Fig. 2A). Based on the analysis of treatment ranking, nivolumab plus cabozantinib had the highest likelihood of providing the maximal OS (P score: 0.7573; Table 2).

3.1.4. Progression-free survival

For the analysis of PFS, a network meta-analysis of seven different agents was conducted. Compared with sunitinib, lenvatinib plus pembrolizumab (HR 0.66, 95% CrI 0.61–0.72), nivolumab plus cabozantinib (HR 0.75, 95% CrI 0.67–0.84), avelumab plus axitinib (HR 0.85, 95% CrI 0.75–0.96), and pembrolizumab plus axitinib (HR 0.86, 95% CrI 0.76–0.97) resulted in significantly improved PFS (Fig. 2B). Based on the analysis of treatment ranking, lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal PFS (P score: 0.9906), followed by nivolumab plus cabozantinib (P score: 0.8216; Table 2).

3.1.5. Complete response rate

For the analysis of CRR, a network meta-analysis of seven different agents was conducted. Compared with sunitinib,

Table 2 – Analysis of treatment ranking in patients with metastatic renal cell carcinoma

	P score (fixed)	P score (random)
Overall survival		
Nivolumab plus cabozantinib	0.7573	0.7573
Lenvatinib plus pembrolizumab	0.6746	0.6746
Pembrolizumab plus axitinib	0.6496	0.6496
Nivolumab plus ipilimumab	0.6358	0.6358
Avelumab plus axitinib	0.4317	0.4317
Atezolizumab plus bevacizumab	0.2444	0.2444
Sunitinib	0.1066	0.1066
Progression-free survival		
Lenvatinib plus pembrolizumab	0.9906	0.9906
Nivolumab plus cabozantinib	0.8216	0.8216
Avelumab plus axitinib	0.5483	0.5483
Pembrolizumab plus axitinib	0.5163	0.5163
Atezolizumab plus bevacizumab	0.3225	0.3225
Nivolumab plus ipilimumab	0.2372	0.2372
Sunitinib	0.0634	0.0634
Complete response rate		
Sunitinib	0.9831	0.9831
Nivolumab plus cabozantinib	0.6881	0.6881
Avelumab plus axitinib	0.6483	0.6483
Atezolizumab plus bevacizumab	0.4983	0.4983
Pembrolizumab plus axitinib	0.3711	0.3711
Lenvatinib plus pembrolizumab	0.1792	0.1792
Nivolumab plus ipilimumab	0.1318	0.1318
Objective response rate		
Sunitinib	0.9745	0.9745
Atezolizumab plus bevacizumab	0.8196	0.8196
Nivolumab plus ipilimumab	0.7054	0.7054
Pembrolizumab plus axitinib	0.4776	0.4776
Avelumab plus axitinib	0.2950	0.2950
Nivolumab plus cabozantinib	0.1842	0.1842
Lenvatinib plus pembrolizumab	0.0436	0.0436
Grade ≥3 adverse events		
Nivolumab plus ipilimumab	0.9433	0.9433
Atezolizumab plus bevacizumab	0.8890	0.8890
Sunitinib	0.5447	0.5447
Avelumab plus axitinib	0.5427	0.5427
Nivolumab plus cabozantinib	0.2815	0.2815
Pembrolizumab plus axitinib	0.2750	0.2750
Lenvatinib plus pembrolizumab	0.0238	0.0238

nivolumab plus ipilimumab (OR 4.75, 95% CrI 2.52–8.28), lenvatinib plus pembrolizumab (OR 4.19, 95% CrI 2.32–7.55), and pembrolizumab plus axitinib (OR 3.09, 95% CrI 1.62–5.88) resulted in significantly higher CRRs (Fig. 2C). Based on the analysis of treatment ranking, it was highly likely that nivolumab plus ipilimumab had the highest CRR (P score: 0.8682), followed by lenvatinib plus pembrolizumab (P score: 0.8208; Table 2).

3.1.6. Objective response rate

For the analysis of ORR, a network meta-analysis of seven different agents was conducted. Compared with sunitinib, lenvatinib plus pembrolizumab, nivolumab plus cabozantinib, avelumab plus axitinib, pembrolizumab plus axitinib, and nivolumab plus ipilimumab resulted in significantly higher ORRs (Fig. 2D). Based on the analysis of treatment ranking, it was highly likely that lenvatinib plus pembrolizumab had the highest ORR (P score: 0.9564), closely followed by nivolumab plus cabozantinib (P score: 0.1394; Table 2).

3.1.7. Treatment-related AEs

Rates of grade ≥3 TRAEs were examined as a measure of treatment toxicity. A network meta-analysis of seven different agents was conducted for the outcome of grade ≥3 TRAEs.

Compared with sunitinib, nivolumab plus ipilimumab and atezolizumab plus bevacizumab were associated with a significantly lower likelihood of toxicity (OR 0.54, 95% CrI 0.42–0.69 and OR 0.58, 95% CrI 0.45–0.76, respectively). The combination of lenvatinib plus pembrolizumab was associated with a significantly higher likelihood of grade ≥3 TRAEs (OR 1.84, 95% CrI 1.28–2.64; Supplementary Fig. 3A). Based on the analysis of treatment ranking, nivolumab plus ipilimumab had the lowest likelihood of grade ≥3 TRAEs (P score: 0. 9433; Table 2).

3.1.8. Treatment discontinuation due to AEs

Rates of treatment discontinuation secondary to AEs were examined as a measure of the toxicity of treatment. A network meta-analysis of seven different agents was conducted. Compared with sunitinib, lenvatinib plus pembrolizumab (OR 3.55, 95% CrI 2.46–5.12), nivolumab plus ipilimumab (OR 2.01, 95% CrI 1.45–2.79), and nivolumab plus cabozantinib (OR 1.84, 95% CrI 1.13–3.0) were associated with a significantly increased likelihood of treatment discontinuation (Supplementary Fig. 3B). Based on the analysis of treatment ranking, lenvatinib plus pembrolizumab had the highest likelihood of treatment discontinuation due to AEs (P score: 0. 9952), followed by nivolumab plus ipilimumab (P score: 0.7684).

3.1.9. Favorable-risk subgroup

Based on the analysis of treatment ranking, in patients with favorable-risk mRCC, avelumab plus axitinib had the highest likelihood of providing the maximal OS (P score: 0.5660), followed by nivolumab plus cabozantinib (P score: 0.5527; Fig. 3A). Based on the analysis of treatment ranking, lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal PFS (P score: 0.9211), followed by nivolumab plus cabozantinib (P score: 0.5967; Fig. 3B and Table 3).

3.1.10. Intermediate/poor-risk subgroup

Based on the analysis of treatment ranking, in patients with intermediate/poor-risk mRCC, lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal OS (P score: 0.8653), followed by nivolumab plus cabozantinib (P score: 0.8352; (Fig. 3C). Treatment ranking analysis for PFS in intermediate/poor-risk mRCC showed that lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal PFS (P score: 0.9755), followed by nivolumab plus cabozantinib (P score: 0.8079; Fig. 3D and Table 3).

3.1.11. PD-L1 expression ≥1%

Based on the analysis of treatment ranking, in patients with ≥1% PD-L1 expression, nivolumab plus ipilimumab had the highest likelihood of providing the maximal OS (P score: 0.8746), followed by pembrolizumab and axitinib (P score: 0.7472; (Fig. 4A and Table 3).

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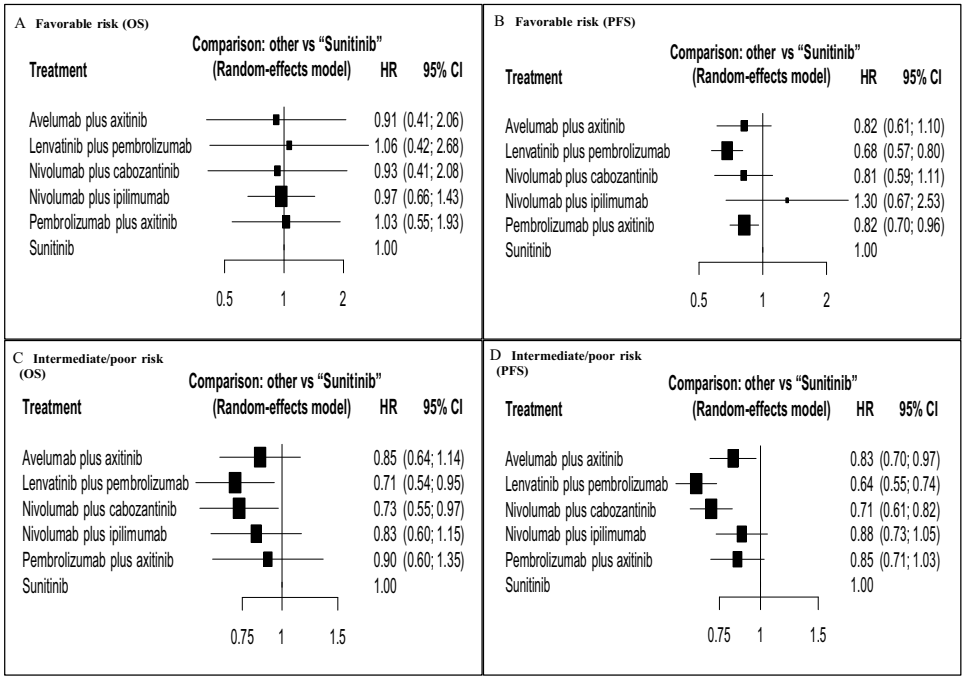

Fig. 3 – Forest plots showing the association of systemic therapy based on International mRCC Database Consortium (IMDC) risk groups: (A) overall survival (OS) and (B) progression-free survival (PFS) in favorable risk group, and (C) OS and (D) PFS in intermediate/poor-risk groups. CI = confidence interval; HR = hazard ratio; mRCC = metastatic renal cell carcinoma.

Based on the analysis of treatment ranking, in patients with ≥1% PD-L1 expression, lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal PFS (P score: 0.8909), followed by nivolumab plus ipilimumab (P score: 0.7606; Fig. 4B and Table 3).

3.1.12. *PD-L1 expression <1%*

Based on the analysis of treatment ranking, in patients with <1% PD-L1 expression, nivolumab plus cabozantinib had the highest likelihood of providing the maximal OS (P score: 0.7449), followed by lenvatinib plus pembrolizumab (P score: 0.7348; Fig. 4C and Table 3). Based on the analysis of treatment ranking, lenvatinib plus pembrolizumab had the highest likelihood of providing the maximal PFS (P score: 0.9704), followed by nivolumab plus cabozantinib (P score: 0.8157; Fig. 4D and Table 3).

3.2. *Discussion*

ICI-based combination therapies (ICI-ICI or ICI-targeted therapy) are now the main first-line treatments for mRCC, and new combinations are emerging. However, it is difficult to provide a comparison between these combinations. Therefore, in our network meta-analysis, we attempted to compare these combinations in different subgroups of patients based on risk group categories and PD-L1 expression status.

Our network meta-analysis demonstrated an overall trend for ICI-TKI combinations providing superior OS and PFS in patients with mRCC, regardless of their IMDC risk group and PD-L1 expression status. Treatment ranking analyses showed that nivolumab plus cabozantinib and lenvatinib plus pembrolizumab had the highest probability of providing better OS and PFS. Combining TKIs with immunotherapies has emerged as an important treatment strategy to enhance tumor responses and improve survival outcomes. The antiangiogenic effects of TKIs have been suggested to enhance the effect of ICIs through working on tumor microenvironment and increasing cytotoxic T-cell activation and T-cell infiltration [23]. On the contrary, adding ICI is also believed to enhance the benefit of TKIs. Indeed, besides being proangiogenic tumors, RCCs are also immunogenic tumors and the immune system is believed to play a significant role in tumor resistance to TKIs. For instance, sunitinib was shown to increase PD-L1 expression in cell lines [24,25].

In contrast to sunitinib and pazopanib, which were associated with excessive toxicity when combined with ICI [26], new combinations were shown to be safe and effective, with manageable AEs [5,6]. Currently approved ICI-TKI combinations for the first-line treatment of mRCC include pembrolizumab plus axitinib, avelumab plus axitinib, and the recently approved combination nivolumab plus cabozantinib. The combination nivolumab plus cabozantinib has shown promising results in a phase III randomized controlled trial (RCT) [12]. Cabozantinib has previously been shown to provide superior OS, PFS, and ORR versus everolimus in a VEGFR-TKI–refractory patient population [27]. Moreover, in the randomized phase II CABOSUN trial, cabozantinib monotherapy improved PFS and ORR when compared with sunitinib. Cabozantinib is a multityrosine kinase inhibitor with activity against VEGFR, MET, AXL,

Table 3 – Analysis of treatment ranking for subgroups of patients with metastatic renal cell carcinoma based on risk groups and PD-L1 expression status

	P score (fixed)	P score (random)
Overall survival (favorable)		
Avelumab plus axitinib	0.5660	0.5660
Nivolumab plus cabozantinib	0.5527	0.5527
Nivolumab plus ipilimumab	0.5209	0.5209
Sunitinib	0.4721	0.4721
Pembrolizumab plus axitinib	0.4539	0.4539
Lenvatinib plus pembrolizumab	0.4343	0.4343
Progression-free survival (favorable)		
Lenvatinib plus pembrolizumab	0.9211	0.9211
Nivolumab plus cabozantinib	0.5967	0.5967
Avelumab plus axitinib	0.5904	0.5904
Pembrolizumab plus axitinib	0.5875	0.5875
Sunitinib	0.1948	0.1948
Nivolumab plus ipilimumab	0.1094	0.1094
Overall survival (poor/intermediate)		
Lenvatinib plus pembrolizumab	0.8653	0.7878
Nivolumab plus cabozantinib	0.8352	0.7406
Nivolumab plus ipilimumab	0.4924	0.5153
Avelumab plus axitinib	0.4411	0.4637
Pembrolizumab plus axitinib	0.3113	0.3705
Sunitinib	0.0547	0.1222
Progression-free survival (poor/intermediate)		
Lenvatinib plus pembrolizumab	0.9755	0.9644
Nivolumab plus cabozantinib	0.8079	0.7940
Avelumab plus axitinib	0.4731	0.4744
Pembrolizumab plus axitinib	0.4071	0.4043
Nivolumab plus ipilimumab	0.3283	0.3362
Sunitinib	0.0079	0.0267
Overall survival (high PD-L1 expression)		
Nivolumab plus ipilimumab	0.8746	0.8746
Pembrolizumab plus axitinib	0.7472	0.7472
Lenvatinib plus pembrolizumab	0.4720	0.4720
Nivolumab plus cabozantinib	0.4368	0.4368
Atezolizumab plus bevacizumab	0.3888	0.3888
Avelumab plus axitinib	0.3744	0.3744
Sunitinib	0.2062	0.2062
Progression-free survival (high PD-L1 expression)		
Lenvatinib plus pembrolizumab	0.8909	0.8909
Nivolumab plus ipilimumab	0.7606	0.7606
Nivolumab plus cabozantinib	0.6931	0.6931
Pembrolizumab plus axitinib	0.4473	0.4473
Avelumab plus axitinib	0.4057	0.4057
Atezolizumab plus bevacizumab	0.2880	0.2880
Sunitinib	0.0146	0.0146
Overall survival (low PD-L1 expression)		
Nivolumab plus cabozantinib	0.7449	0.7449
Lenvatinib plus pembrolizumab	0.7348	0.7348
Pembrolizumab plus axitinib	0.5954	0.5954
Avelumab plus axitinib	0.4235	0.4235
Nivolumab plus ipilimumab	0.4128	0.4128
Sunitinib	0.0886	0.0886
Progression-free survival (low PD-L1 expression)		
Lenvatinib plus pembrolizumab	0.9704	0.9704
Nivolumab plus cabozantinib	0.8157	0.8157
Avelumab plus axitinib	0.4358	0.4358
Pembrolizumab plus axitinib	0.4039	0.4039
Atezolizumab plus bevacizumab	0.3435	0.3435
Nivolumab plus ipilimumab	0.2765	0.2765
Sunitinib	0.2542	0.2542

PD-L1 = programmed death ligand 1.

MER, and TYRO3 [28]. Inhibition of these targets is directed against both the tumor vasculature and the tumor cell; moreover, cabozantinib was shown to provide strong immunomodulatory potency, making it a suitable option for an ICI-TKI combination [28]. The phase III RCT checkmate 9ER compared nivolumab plus cabozantinib with sunitinib, the former standard of care. At a median follow-up of 18 mo, the combination provided better PFS, OS, and tumor

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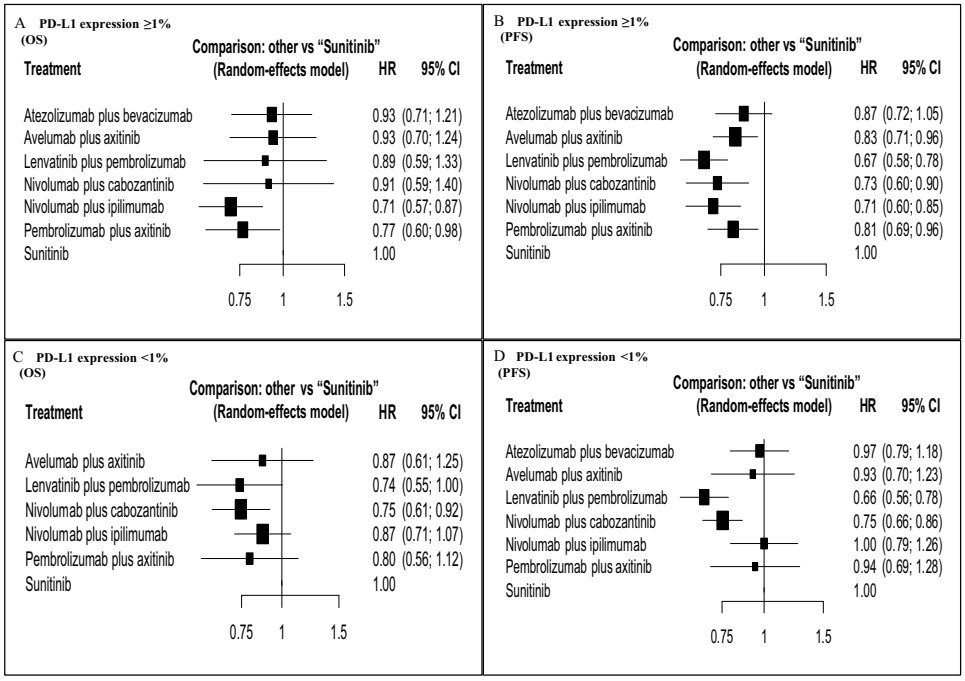

Fig. 4 – Forest plots showing the association of systemic therapy based on PD-L1 status: (A) overall survival (OS) with high PD-L1 expression, (B) progression-free survival (PFS) with high PD-L1 expression, (C) OS with low PD-L1 expression, and (D) PFS with low PD-L1 expression. CI = confidence interval; HR = hazard ratio; PD-L1 = programmed death ligand 1.

response rates [12]. In our network meta-analysis, this combination also demonstrated a high probability of better PFS, OS, and ORR.

The results of this paper support the findings of our previous network meta-analysis, which showed superiority of ICI-TKI combinations in mRCC patients regardless of their tumors PD-L1 expression status. However, to further explore the efficacy of these regimens, we performed subgroup analyses on patients based on the PD-L1 expression status. The combination of the PD-1 inhibitor nivolumab with the CTLA-4 inhibitor ipilimumab is currently the only dual ICI combination that is approved for the first-line setting of patients with mRCC. In the CheckMate-214 phase III trial, nivolumab plus ipilimumab was shown to improve survival in IMDC intermediate- and poor-risk patients, as well as in the intention-to-treat population [4]. These results were maintained in updated analyses [8,9,12,22]. In our study, we demonstrated that nivolumab plus ipilimumab provided the highest likelihood of OS and PFS improvement in patients with high PD-L1 expression. The predictive role of PD-L1 expression has been the focus of research efforts. Although a low or absent PD-L1 expression in tissue obtained from the primary tumor does not preclude response to ICIs, a higher ORR and longer PFS and OS were observed in patients with PD-L1–positive tumors [4,29]. In the CheckMate-214 trial, patients with PD-L1 $\geq$ 1% had a median PFS of 22.8 mo with nivolumab plus ipilimumab versus 5.9 mo with sunitinib. Furthermore, the 18-mo OS was 86% versus 66%, and the ORR was 58% versus 22% for nivolumab plus ipilimumab versus sunitinib [4]. In a recent meta-analysis, Mori et al [30] demonstrated a significantly higher ORR and CRR, and longer PFS in patients with PD-L1–positive mRCC. Moreover, the combination of nivolumab plus ipilimumab provided the highest ORR and the longest PFS in this group of patients.

Despite the clinical benefits of immunotherapy in patients with mRCC, it can be hampered by the occurrence of a unique set of AEs related to excessive immune activation, collectively called immune-related AEs (irAEs). In the analysis of high-grade TRAEs (grade $\geq$3), we found the lowest rates to be associated with nivolumab plus ipilimumab and atezolizumab plus bevacizumab. However, the combination of nivolumab plus ipilimumab and that of lenvatinib plus pembrolizumab were associated with the highest rates of treatment discontinuation secondary to AEs. Although the rates of high-grade TRAEs were used as a measure of toxicity in our analysis, it should be noted that this might not be completely reflective of the safety profile of each regimen as irAEs are mostly of low grade [31].

This study has several limitations. First, although indirect treatment comparison analyses have been used and validated for comparing outcomes from RCTs, this approach falls short of a head-to-head treatment comparison. Thus, well-designed comparative trials are required to validate the findings of this study. Second, this network meta-analysis was based on the reporting quality of the trials that were reviewed and may have been affected by several types of bias, thus limiting the validity of the overall findings. Third, patient characteristics such as prognostic risk categories and the number of patients with high PD-L1 expression may have differed significantly between the studies, limiting the comparability of the trials evaluated, especially limiting the conclusions reached from subgroup

analyses based on these characteristics. Finally, differences in subsequent therapies received across treatment arms may have influenced the OS results. In addition, the presence of conceptual heterogeneity, which could result from analyzing data with different follow-up durations, warrants caution when interpreting the results of this network meta-analysis.

4. Conclusions

In this systematic review and network meta-analysis of first-line systemic therapies for patients with mRCC, based on an indirect comparison of data from phase 3 clinical trials, ICI-TKI combinations demonstrated higher likelihoods of providing better PFS and OS benefits. In addition, the ICI-ICI combination of nivolumab plus ipilimumab appeared to provide higher PFS and OS among patients with high PD-L1 expression. Moreover, the highest rate of CR was associated with nivolumab plus ipilimumab. These findings may provide guidance to clinicians for treatment decisions.

***Author contributions*:** Fahad Quhal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Quhal, Mori, Shariat, Schmidinger.
Acquisition of data: Quhal, Mori.
Analysis and interpretation of data: Quhal, Mori, Mostafaei.
Drafting of the manuscript: Quhal, Mori, Shariat, Schmidinger.
Critical revision of the manuscript for important intellectual content: Bruchbacher, Resch, Mostafaei, Pradere, Schuettfort, Laukhtina, Egawa, Fajkovic, Remzi, Shariat, Schmidinger.
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Appendix A. Supplementary data

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