Systemic therapies for metastatic renal cell carcinoma in the second-line setting
A systematic review and network meta-analysis

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Abstract

Objectives: To perform a systematic review and network meta-analysis to compare the survival benefit and safety profile of current available second-line treatment options of metastatic renal cell carcinomav.

Methods: PubMed, EMBASE, Web of Science, and Cochrane Library were systematically researched for eligible articles which were published before July 20, 2021. Studies comparing overall/progression free survival (OS/PFS), objective response rate (ORR), and/or adverse events (AEs) in patients with metastatic renal cell carcinomav were included.

Results: Nine trials (with 4911 patients) were finally included for final network meta-analysis. Cabozantinib, lenvatinib, and lenvatinib plus everolimus were associated with significantly better PFS, OS, and ORR compared with everolimus, and lenvatinib plus everolimus emerged as the best option. As for grade 3 to 4 AEs, nivolumab showed significantly lower risk of AEs compared with everolimus. Other included treatments were associated with significantly increased risk of AEs. When comprehensively assessed the efficacy and safety of included treatments based on the ranking analysis of PFS, ORR, and grade 3 to 4 AEs, lenvatinib plus everolimus, cabozantinib, and nivolumab showed superior efficacy over other treatments, with relatively lower risk of grade 3 to 4 AEs.

Conclusions: Among all included therapies, Lenvatinib plus everolimus was identified as the most effective treatment approach, with the best PFS, OS, and ORR. nivolumab was associated with decreased incidence of grade 3 to 4 AEs among included treatment therapies. When comprehensively evaluated the efficacy and safety of included treatment options, lenvatinib plus everolimus, cabozantinb, and nivolumab were associated with better survival benefits and lower risk of AEs. Future studies should focus on the direct comparison of different second-line treatment in real-world populations.

Abbreviations: AEs = adverse events, ccRCC = clear cell RCC, CrI = credible interval, FDA = the Food and Drug Administratio, HR = hazard ratio, ICI = immune checkpoint inhibitor, mRCC = metastatic renal cell carcinoma, MSKCC = Memorial Sloan Kettering Cancer Center, NMA = network meta-analysis, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progressive-free survival, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria in Solid Tumors, SUCRA = the surface under the cumulative ranking, TKIs = tyrosine kinase inhibitors.

Keywords: metastatic renal cell carcinoma, network meta-analysis, safety profile, second-line treatment, survival outcomes, systematic review

1. Introduction

Renal cell carcinoma is the most common type of malignant kidney disease, with 76,080 estimated new cases and 13,780 estimated mortalities in 2021 in the United States.[1] Due to its high aggressiveness, 25% to 30% of patients presented with metastatic disease at initial diagnosis, while another 20% of patients with localized diseases experienced recurrence after radical nephrectomy.[2,3] Historically, cytokine therapies (interleukin-2 and interferon-α) were standard systematic therapy for patients with metastatic renal cell carcinoma (mRCC).[4,5] Since the introduction of tyrosine kinase inhibitors (TKIs)

and mammalian target of rapamycin inhibitors, the prognosis of patients with mRCC has been significantly improved.[6–9] After being a decade of standard treatment, the value of TKIs was challenged by the immune checkpoint inhibitors (ICIs)-based therapies (alone or combined with CTLA-4 antibody or TKIs).[10–12] Unfortunately, neither first-line ICI plus TKI nor TKI alone could persistently control the disease, and most patients would progress after 11 to 15 months.[10–13] Thus, the optimal choice of second-line therapy after first-line treatment failure was vital to maximally improve the survival outcomes of mRCC patients.

Currently, several treatments were approved by the Food and Drug Administration (FDA) as the second-line treatment in mRCC patients. Sorafenib was the first TKI drugs that approved by FDA as the second-line treatment in 2005, and everolimus was the first mammalian target of rapamycin inhibitors approved in 2009.[14,15] In the recent years, nivolumab, a programmed-death ligand-1 inhibitor, showed superior efficacy over everolimus in mRCC.[16] Two clinical trials also propelled the new generation of TKIs into the second-line treatment options: METEOR study demonstrated the superior treatment efficacy of cabozantinib over everolimus, and another phase II trial confirmed the survival benefit of lenvatinib and lenvatinib plus everolimus in mRCC patients with first-line TKI failure.[17,18] However, there were limited data directly comparing the efficacy and safety of those agents. Thus, we conducted a systematic review and network meta-analysis (NMA) to compare the survival benefit and safety profile of currently available second-line treatment options of mRCC.

2. Materials and Methods

2.1. Searching strategy

We performed a systematic review and NMA of parallel-group randomized controlled trials (RCTs) which compared at least 2 systematic therapies in the second-line treatment of mRCC patients. Eligible studies were searched using the electronic database (PubMed, EMBASE, Web of Science, and Cochrane Library) from inception to July 20, 2021. We used both subject headings and text-word terms for "metastatic," "renal cell carcinoma," "immunotherapy," "targeted therapy," "systematic therapy," "progression-free survival," "survival," "randomized-controlled trial," and related and exploded terms including MeSH terms in combination with keyword searching. Details of search procedure and strategy were presented in Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/H215. References from review articles, commentaries, editorials, and conference publications were hand-searched and cross-referenced to ensure completeness. Conference abstracts were included where they reported data that were not available from published manuscripts. This study was approved by the ethics committee of Jiangjin District Central Hospital.

2.2. Trial selection criteria

Studies were screened through a systematic literature review. Eligible studies were restricted to RCTs comparing systematic therapies in the second-line treatment of mRCC patients. Only English language publications were considered. Observational studies, retrospective studies, editorials, commentaries, review articles, and case-control studies were excluded. As we focused on the efficacy and safety of systematic therapies in the second-line treatment of mRCC patients, studies in which patients were treatment-naive or previously received more than one systematic therapy were excluded from further analysis.

If there was more than one publication resulting from the same populations and same outcome, we only included the most recent publications for analysis. If there were 2 publications utilizing the same cohort but reporting different outcomes, both studies were included.

2.3. Outcome measurements

The primary outcome was progressive-free survival (PFS), which was defined as the time duration from the initiation of second-line treatment to disease progression, treatment cessation, or end of the second-line treatment. Secondary outcomes were overall survival (OS), objective response ratio (ORR), and rates of grade 3 or 4 adverse events (AEs). ORR was measured using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and treatment-related AEs were evaluated using Common Terminology Criteria for Adverse Events.

2.4. Screening of eligible studies

Title, abstract, and full text of included references were independently screened by 2 investigators. Any disagreement between 2 investigators would be assessed by an independent expert. Titles and abstracts were screened for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion criteria.

2.5. Risk of bias assessment

Risk of bias of included studies was assessed using The Cochrane Collaboration's tool for assessing risk of bias,[19] which included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias.

2.6. Data synthesis

A Bayesian multiple treatment NMA with fixed effects and uninformative priors was performed. When assessing PFS, we applied contrast-based analysis using estimated differences in log hazard ratio (HR) and standard error calculated based on published HR and confidential intervals.[20] The relative treatment effects were reported as HR and 95% credible interval (CrI). For assessing ORR and AEs, odds ratio (OR), and 95%CrI were estimated calculated by the raw data from RCTs. The surface under the cumulative ranking (SUCRA) curve and with a rankogram plot were provided to assess the hierarchy of treatments.[21] The SUCRA value would be 0 when a treatment is certain to be the worst and 1 when it is certain to be the best. Sensitivity analyses were conducted to evaluate the robustness of the results by comparing the outcomes of random-effects model with fixed-effects models with the purpose of heterogeneity and inconsistency checking. All analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria) with the GeMTC package. Statistical significance was set at $P < .05$. All outcomes of this study were documented and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for RCTs.[22]

3. Results

3.1. Literature search results

A total of 7246 references were identified through the systematic search. A total of 5637 publications were available for further assessment after eliminating duplication. After screening the titles and abstracts, a total of 5601 articles were further excluded, and full-text reviews were performed for the remaining 36 articles. Finally, 9 RCTs with 4911 patients were finally included.[15–18,23–27] Flowchart of study search and screening was presented in Figure 1.

Assessment of risk of bias was presented at Figure S1, Supplemental Digital Content 8, http://links.lww.com/MD/H324. All of the ten studies were classified into low risk of bias. Among all trials fitting our eligibility criteria, our final network included 8 studies for further analysis.

3.2. Characteristics of included trials

Table 1 summarized the characteristics of included trials. Among all included RCTs, 8 of them were 2-armed studies, and one study contains 3 arms.[18] All trials except one[18] were phase III RCTs. Two trials[14,15] were placebo-controlled, while the other 8 were compared with active pharmaceuticals.
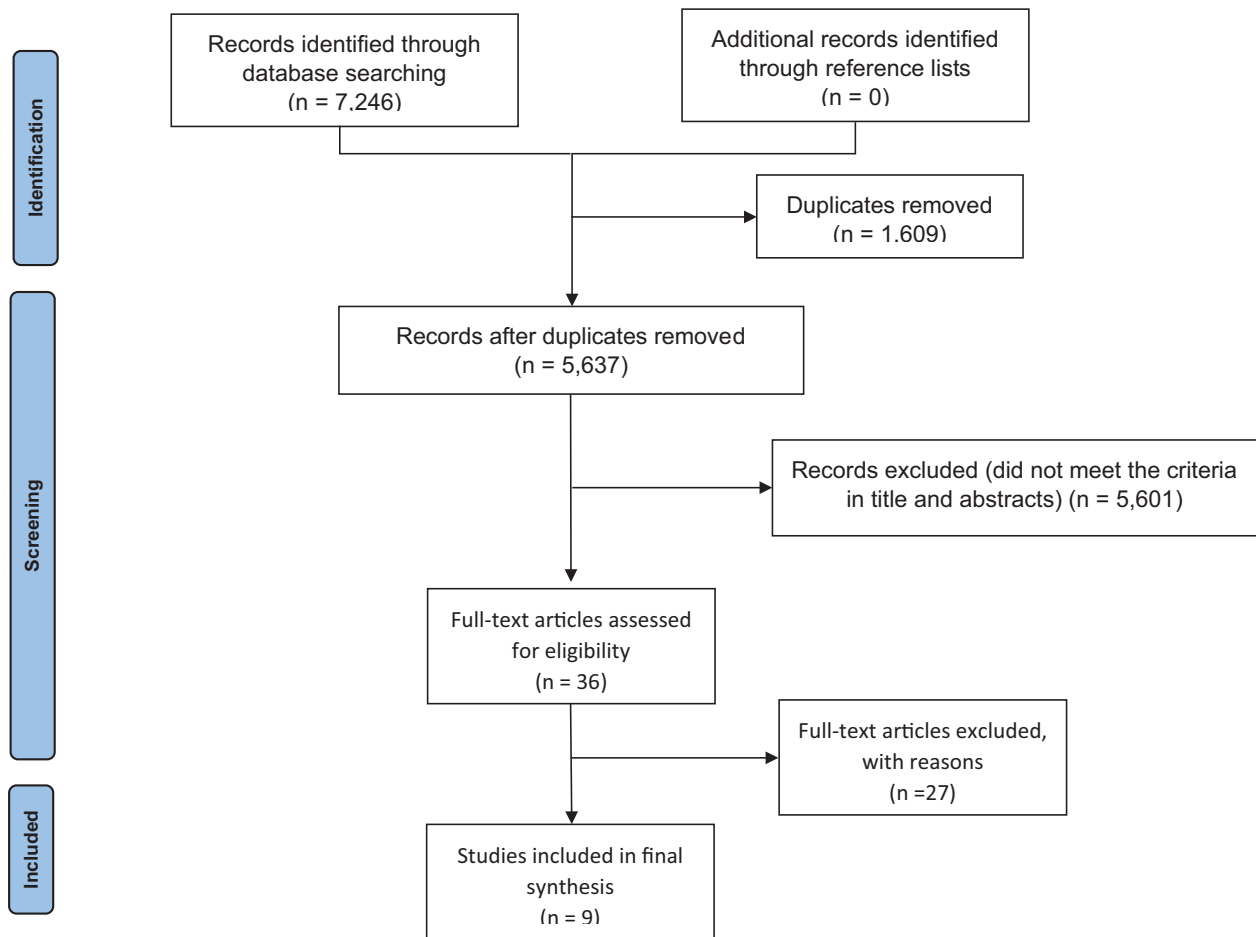
Figure 1. Flow diagram of study identification, screening, eligibility assessment, and inclusion.

Patients in 8 trials[16–18,24–27] predominantly received TKIs as first-line treatment. Two trials[14,15] specifically limited patients to favorable- or intermediate-risk groups of Memorial Sloan Kettering Cancer Center (MSKCC), while patients of other trials were predominantly intermediate or intermediate to poor risk groups of MSKCC. Six studies[14–17,24,25] were double-blind trials, and the other 3[18,26,27] were open-label trials. It is noting that

3.3. Progressive-free survival

NMA for PFS included 8 trials,[14–18,23,24,27] including 3569 patients with ten different treatments (Figure S2A, Supplemental Digital Content 2, http://links.lww.com/MD/H216). Compared to treatment with everolimus, superior PFS was observed in cabozantinib (HR: 0.58, 95% Crl: 0.45–0.75), lenvatinib (HR: 0.61, 95% Crl: 0.38–0.98), and lenvatinib plus everolimus (HR: 0.40, 95% Crl: 0.24–0.67). Other included TKI treatments, including sorafenib, sunitinib, axitinib, temsirolimus, and nivolumab showed comparable PFS with everolimus (Fig. 2A). Based on the outcomes of SUCRA analysis, lenvatinib plus everolimus had the highest probability to have the best PFS (SUCRA = 0.972), followed by cabozantinib (SUCRA = 0.829) and lenvatinib (SUCRA = 0.786) (Fig. 2B). In pairwise comparison, everolimus showed inferior PFS compared with cabozantinib, lenvatinib, lenvatinib plus everolimus, and nivolumab (Table S2, Supplemental Digital Content 3, http://links.lww.com/MD/H217).

3.4. Overall survival

Data of OS were extracted from 8 trials,[14–18,24,25] including 3569 patients with ten different treatments (Figure S2A, Supplemental Digital Content 2, http://links.lww.com/MD/H216). The NMA showed that lenvatinib plus everolimus (HR: 0.77, 95% Crl: 0.59–0.90), cabozantinib (HR: 0.84, 95% Crl: 0.74–0.95), and nivolumab (HR: 0.87, 95% Crl: 0.78–0.97) compared with everolimus (Fig. 3A). Based on the outcomes of SUCRA analysis, lenvatinib plus everolimus had the highest probability to have the best PFS (SUCRA = 0.868), followed by cabozantinib (SUCRA = 0.752) and nivolumab (SUCRA = 0.659) (Fig. 3B). In pairwise comparison, cabozantinib, lenvatinib, lenvatinib plus everolimus, and nivolumab showed superior OS over everolimus (Table S3, Supplemental Digital Content 4, http://links.lww.com/MD/H218).

3.5. Objective response rate

Based on the available data of ORR, the NMA included all 9 trials[15–18,23–27] with 4911 comparing everolimus, axitinib, sorafenib, sunitinib, temsirolimus, lenvatinib, lenvatinib plus everolimus, cabozantinib, nivolumab, and pazopanib (Figure S2B, Supplemental Digital Content 2, http://links.lww.com/MD/H216). Compared with everolimus, nivolumab (OR: 0.16, 95% Crl: 0.09–0.25), cabozantinib (OR: 0.20, 95% Crl: 0.09–0.40), lenvatinib (OR: 0.17, 95% Crl: 0.04–0.62), and lenvatinib plus everolimus (OR: 0.08, 95% Crl: 0.02–0.27) were associated with significantly increased ORR (Fig. 4A). There was no

Table 1

Characteristics of the included studies.

Study	Study design	Intervention	No. of patients	Age (yr)	Prognostic Score (MSKCC)	Previous treatment
1. Escudier et al, 2007 (TARGET)	Phase III Double-blind	Sorafenib Placebo	451 452	58 59	Favorable: 52% Intermediate: 48% Missing data: 0% Favorable: 50% Intermediate: 49% Missing data: 1%	Cytokine-based: 83% Radiotherapy: 27% Nephrectomy: 94% Cytokine-based: 81% Radiotherapy: 24% Nephrectomy: 93%
2. Motzer et al, 2008 (RECORD-1)	Phase III Double-blind	Everolimus Placebo	272 138	61.0 60.0	Favorable: 29% Intermediate: 56% Poor: 15% Favorable: 28% Intermediate: 57% Poor: 15%	Sunitinib only: 46% Sorafenib only: 28% Both sunitinib and sorafenib: 26% Sunitinib only: 43% Sorafenib only: 30% Both sunitinib and sorafenib: 26%
3. Rini et al, 2011 (AXIS)	Phase III Double-blind	Axitinib Sorafenib	361 362	61 61	Favorable: 28% Intermediate: 37% Poor: 33% Missing data: 2% Favorable: 28% Intermediate: 36% Poor: 33% Missing data: 3%	Sunitinib: 54% Cytokines: 35% Bevacizumab: 8% Tesirolimus: 3% Sunitinib: 54% Cytokines: 35% Bevacizumab: 8% Tesirolimus: 3%
4. Hutson et al, 2014 (INTORSE CT)	Phase III Double-blind	Temsirolimus Sorafenib	249 252	60 61	Favorable: 19% Intermediate: 69% Poor: 12% Favorable: 17% Intermediate: 70% Poor: 13%	Sunitinib: 100% Sunitinib: 100%
5. Eichelberg et al, 2015 (SWITCH-I)	Phase III Open label	Sunitinib Sorafenib	182 183	64 65	Favorable: 0.5% Intermediate: 59% Poor: 39% Unknown: 1.1% Missing data: 0 Favorable: 0.5% Intermediate: 51% Poor: 45% Unknown: 2.2% Missing data: 1.1%	Sorafenib: 100% Sorafenib: 100%
6. Motzer et al, 2015 (NCT01136733)	Phase II Open-label	Lenvatinib plus everolimus	51	61	Favorable: 24% Intermediate: 37% Poor: 39%	Axitinib: 2% Bevacizulab: 0 Pazopanib: 18% Sorafenib: 2% Sunitinib: 71% Tivozanib: 6% Other: 2%
		Lenvatinib	52	64	Favorable: 21% Intermediate: 35% Poor: 44%	Axitinib: 4% Bevacizulab: 2% Pazopanib: 25% Sorafenib: 0 Sunitinib: 67% Tivozanib: 2% Other: 0
		Everolimus	50	59	Favorable: 24% Intermediate: 38% Poor: 38%	Axitinib: 0 Bevacizulab: 8% Pazopanib: 26% Sorafenib: 4% Sunitinib: 56% Tivozanib: 4% Other: 2%
7. Choueiri et al, 2015 (METEOR)	Phase III Double-blind	Cabozantinib	330	63	Favorable: 45% Intermediate: 42% Poor: 13%	Sunitinib: 69% Pazopanib: 45% Axitinib: 16% Sorafenib: 6%

(Continued)

Table 1

(Continued)

Study	Study design	Intervention	No. of patients	Age (yr)	Prognostic Score (MSKCC)	Previous treatment
		Everolimus	328	62	Favorable: 46% Intermediate: 41% Poor: 13%	Bevacizulab: 2% Sunitinib: 68% Pazopanib: 42% Axitinib: 17% Sorafenib: 10%
8. Motzer et al, 2015 (CheckMat e025)	Phase III Double-blind	Nivolumab	410	62	Favorable: 35% Intermediate: 49% Poor: 16%	Bevacizulab: 3% Sunitinib: 60% Pazopanib: 29% Axitinib: 12%
		Everolimus	411	62	Favorable: 26% Intermediate: 49% Poor: 15%	Sunitinib: 59% Pazopanib: 32% Axitinib: 12%
9. Retz et al, 2018 (SWITCH II)	Phase III Open-label	Pazopanib	189	68	Favorable: 50% Intermediate: 48% Poor: 2% Missing data: 0	Sorafenib: 100%
		Sorafenib	188	68	Favorable: 48% Intermediate: 47% Poor: 3% Missing data: 2%	Pazopanib: 100%

MSKCC = Memorial Sloan Kettering Cancer Center.
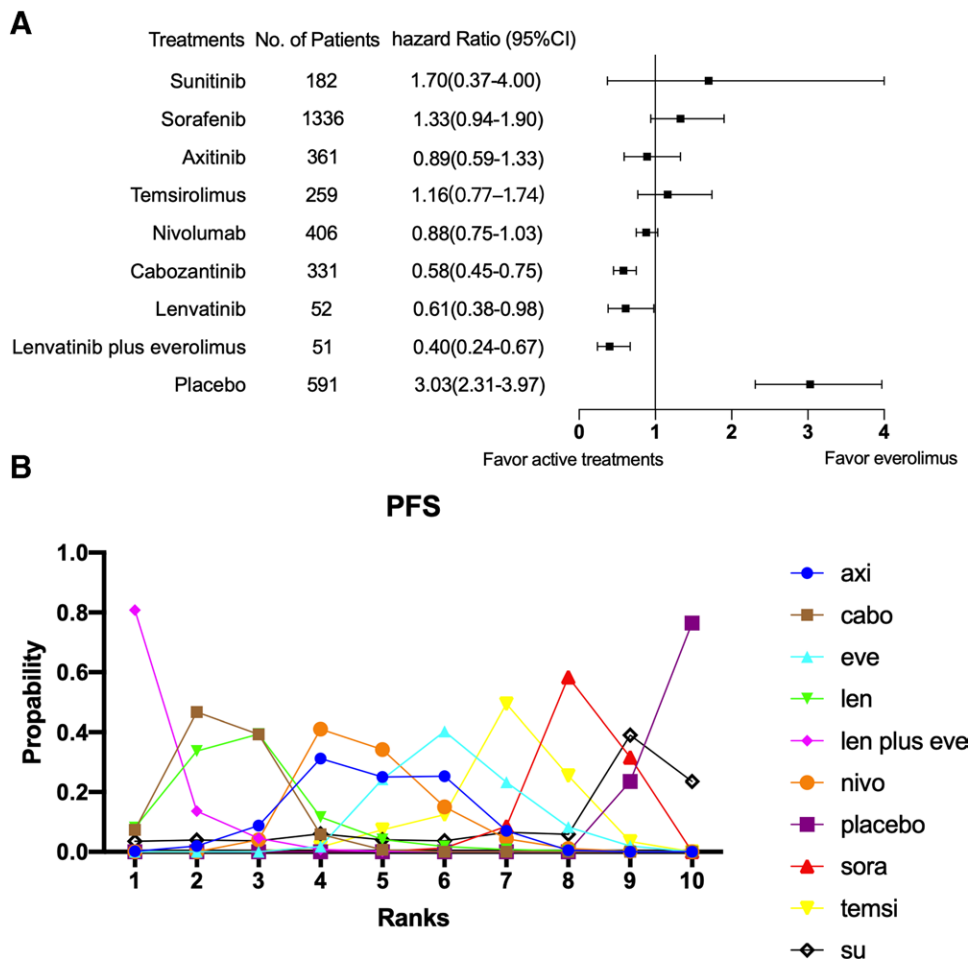
Figure 2. Analysis of PFS: (A) forest plot (compared with everolimus); (B) SUCRA plot. CI = confidential interval, PFS = progressive-free survival, SUCRA = the surface under the cumulative ranking.
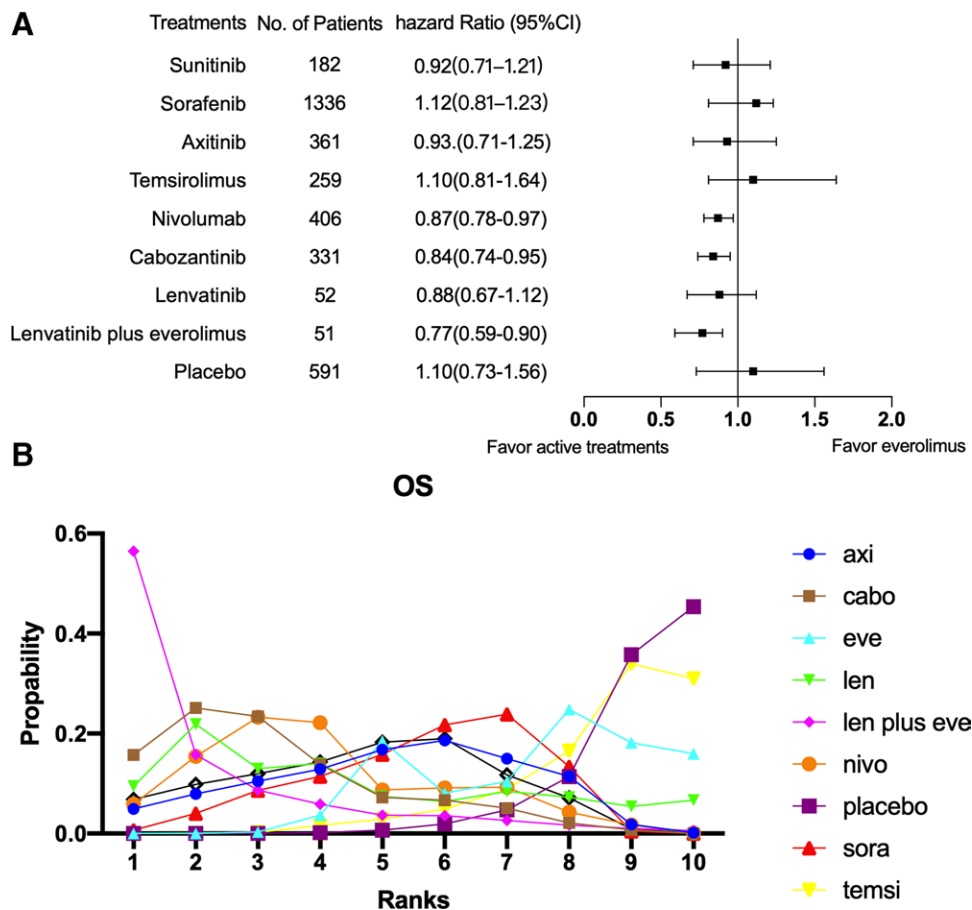
Figure 3. Analysis of OS: (A) forest plot (compared with everolimus); (B) SUCRA plot. CI = confidential interval, OS = overall survival, SUCRA = the surface under the cumulative ranking.

difference for sorafenib, sunitinib, axitinib, temsirolimus, and pazopanib in ORR compared with everolimus. Ranking analysis suggested that lenvatinib plus everolimus had the highest probability to have the best ORR (SUCRA = 0.834) among included treatments (Fig. 4B). Pazopanib (SCURA = 0.698), nivolumab (SCURA = 0.639), lenvatinib (SCURA = 0.595), and cabozantinib (SUCRA = 0.539) had a similar probability of being the second-best treatments. Except for placebo, everolimus was likely to be the lowest choice (SUCRA = 0.177). In pairwise comparison, all included treatments showed superior ORR compared with placebo, except for everolimus (Table S4, Supplemental Digital Content 5, http://links.lww.com/MD/H219).

3.6. Safety

Eight trials[15–18,23,25–27] reported the overall incidence of treatment-related AEs. In this analysis, we focused on the incidence of grade 3 to 4 AEs. Compared with everolimus, sorafenib (OR: 8.01, 95% Crl: 4.40–15.23), temsirolimus (OR: 8.41, 95% Crl: 4.22–17.52), cabozantinib (OR: 1.66, 95% Crl: 1.12–2.27), lenvatinib (OR: 3.85, 95% Crl: 1.66–9.51), lenvatinib plus everolimus (OR: 2.45, 95% Crl: 1.10–5.73), and pazopanib (OR: 5.45, 95% Crl: 2.44–12.57) were associated with significantly increased risk of AEs (Fig. 5A). On the contrary, nivolumab showed significantly lower risk of AEs (OR: 0.40, 95% Crl: 0.29–0.55) compared with everolimus. Based on the outcomes of SUCRA analysis, nivoliumab had the highest chance to have the most favorable safety profile (SUCRA = 1), followed by everolimus (SUCRA = 0.859) and

cabozantinib (SUCRA = 0.633) (Fig. 5B). Pairwise comparison also suggested the superior safety profile of nivolumab, everolimus, and cabozantinib among all included treatments (Table S5, Supplemental Digital Content 6, http://links.lww.com/MD/H220).

3.7. Comprehensive analysis of efficacy and safety

We further comprehensively assessed the efficacy and safety of included treatments based on the ranking analysis of PFS, ORR, and grade 3 to 4 AEs (Fig. 6). Among all included treatments, lenvatinib plus everolimus, cabozantinib, and nivolumab showed superior PFS and ORR, with relatively lower risk of grade 3 to 4 AEs.

3.8. Sensitivity analyses

Sensitivity analysis showed that the results were consistent with the fixed- and random-effect model, showing the robustness of the results (Table S6, Supplemental Digital Content 7, http://links.lww.com/MD/H221). Inconsistency could not be assessed as there were no independent sources of indirect and direct evidence for the same comparison.

4. Discussion

In this study, we performed a systematic review of systematic therapy for mRCC patients in the second-line setting, and then conducted a NMA and indirect comparison of included treatment options. There were several important findings. First, the
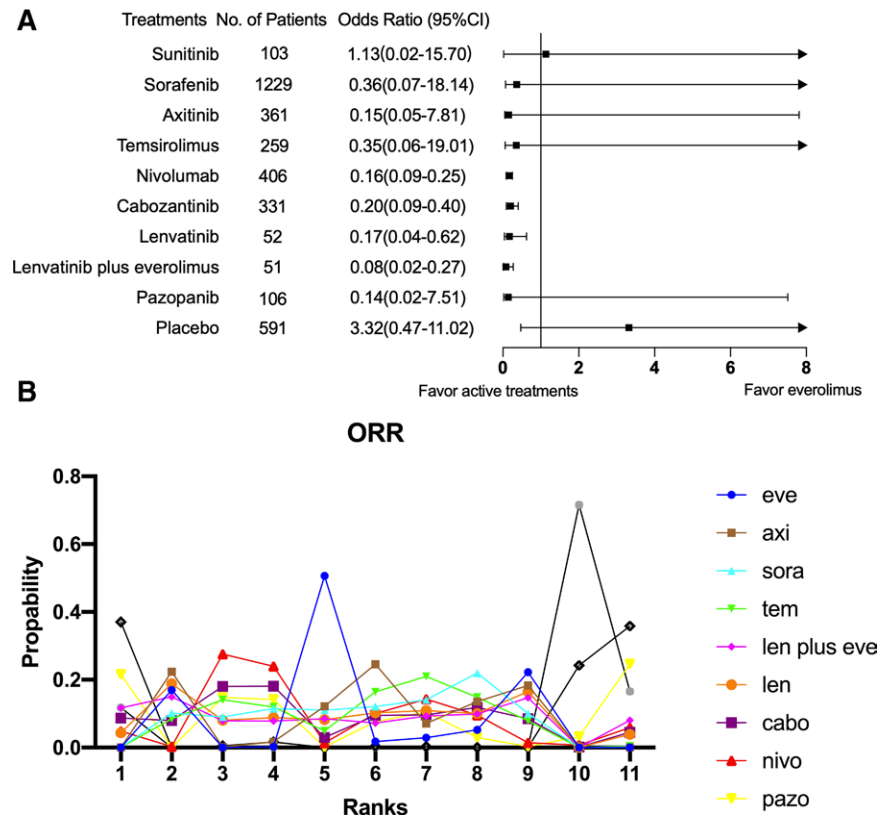
Figure 4. Analysis of ORR: (A) forest plot (compared with everolimus); (B) SUCRA plot. CI = confidential interval, ORR = objective response rate, SUCRA = the surface under the cumulative ranking.
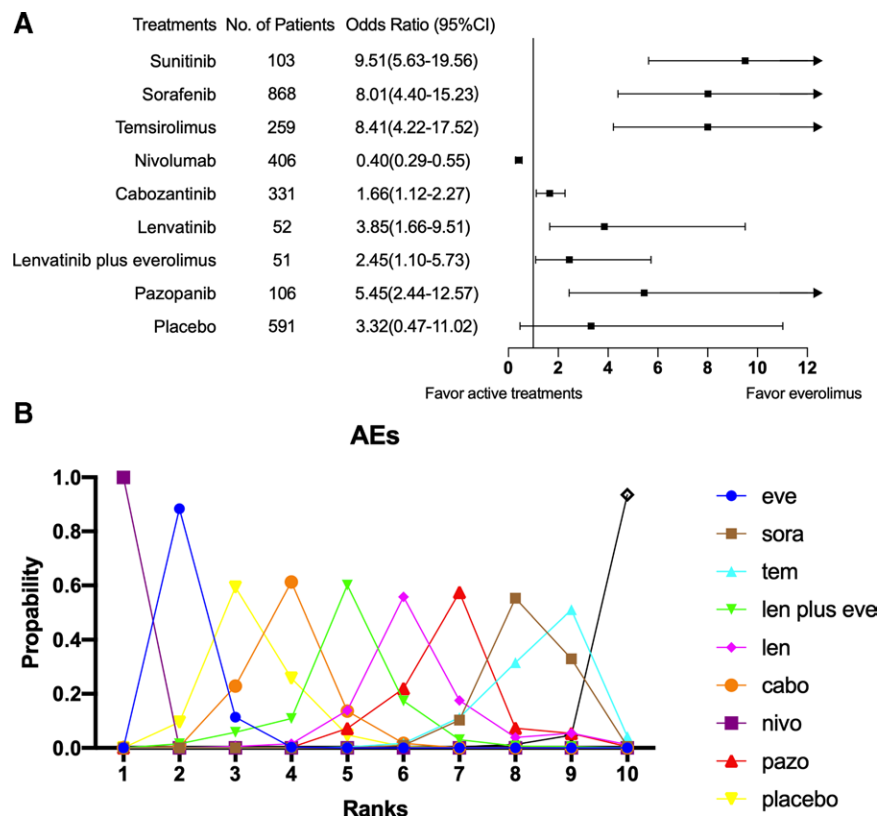
Figure 5. Analysis of AEs: (A) forest plot (compared with everolimus); (B) SUCRA plot. AEs = adverse events, CI = confidential interval, SUCRA = the surface under the cumulative ranking.
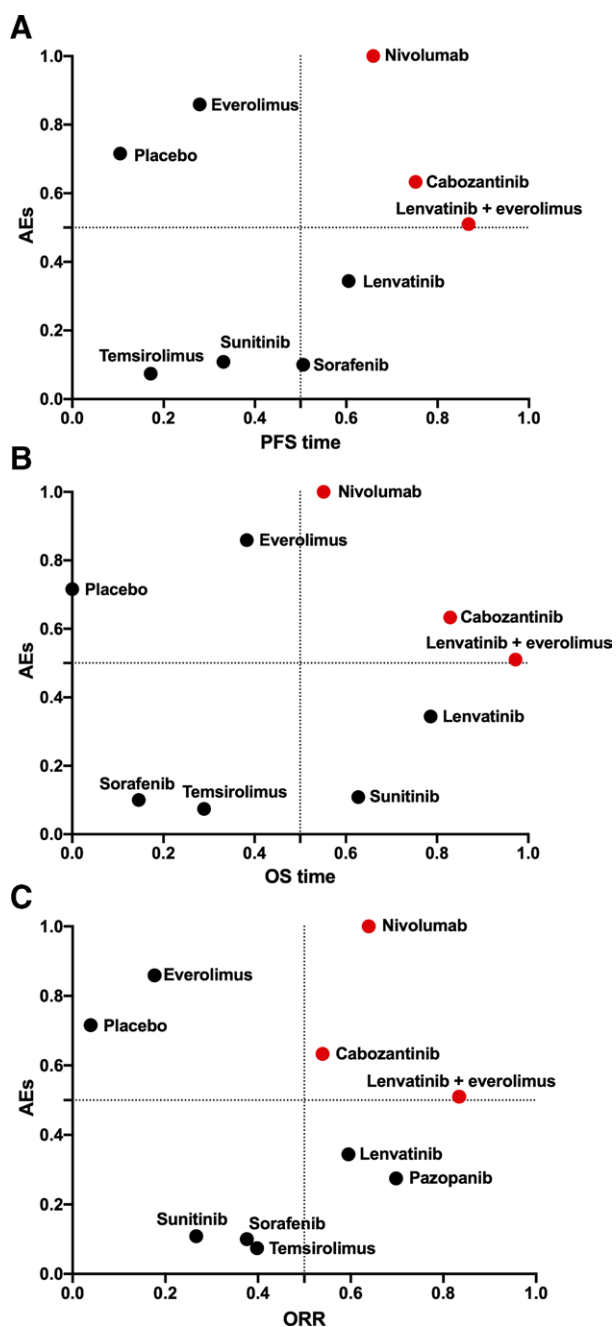
Figure 6. Comprehensive analysis of efficacy and safety: (A) PFS and AEs; (B) OS and AEs; (C) ORR and AEs. AEs = adverse events, ORR = objective response rate, OS = overall survival, PFS = progressive-free survival.

combination of lenvatinib plus everolimus had the highest probability of providing the best PFS and OS benefits, as well as the best ORR in mRCC patients compared with to other second-line treatment options. Second, nivolumab was the only treatment that showed decreased incidence of grade 3 to 4 AEs among included treatment therapies. Other second-line treatment options were associated with higher incidence of grade 3 to 4 AEs compared with everolimus. Third, when comprehensively evaluated the efficacy and safety of included treatment options, we noticed that lenvatinib plus everolimus, cabozantinb, and nivolumab were superior to other included treatments, with relatively improved PFS, OS, and ORR, as well as lower risk of grade 3 to 4 AEs.

Most of the mRCC patients would experience disease progression after 8 to 15 months under current first-line treatment approaches. Thus, sequencing treatments were crucial for further improving survival outcomes of mRCC patients. Sorafenib was the first targeted treatment approved by FDA in 2005 as the sequencing treatment in mRCC patients who progressed after cytokine treatment, with median PFS of 5.5 months.[14] Nivolumab was the first ICIs that applied for the treatment of mRCC patients. CheckMate 025 trial suggested that mRCC patients with previously TKI treatment failure could obtain more survival benefit with nivolumab compared with everolimus, with median PFS of 4.6 months and OS of 25.0 months.[16] Lenvatinib plus everolimus was the first combined therapy for mRCC second-line treatment, and greatly improved survival outcomes compared with everolimus.[18] The median PFS and OS of lenvatinib plus everolimus 14.6 and 25.5 months, with ORR of 43%. Besides, several ongoing trials are focused on the efficacy and safety of immune-based treatment in the second-line setting. In the 2019 ESMO meeting, Lee et al[28] reported the results of the phase II clinical trial of lenvatinib plus pembrolizumab treating mRCC patients who progressed from prior immune checkpoint therapy. With ≥12 of follow-up for 33 patients enrolled, the ORR was 52%, and DCR was 94%, which demonstrated promising antitumor activity of lenvatinib and pembrolizumab combined treatment. Besides, in 2020 ASCO-GU, Msaouel et al[29] reported the results of sitravatinib plus nivolumab in advanced clear cell RCC (ccRCC) patients with previous TKIs treatment failure. In a total of 34 patients, tumor reductions have been noted in 28 patients (82.3%) with objective responses. Median PFS time was 10.5 months. Studies focused on the sequencing therapies would further improve the survival outcomes of mRCC patients.

Former studies systematically reviewed and compared the efficacy of second-line treatment options of mRCC. Wiecek and Karcher[30] indirectly compared the survival benefit of cabozantinib and everolimus, and found that patients treated with cabozantinib exhibited a lower risk of death over nivolumab until the fifth month of treatment, whereas patients on nivolumab had superior efficacy over cabozantinib over 5 months. Amzal et al[31] conducted a systematic review and NMA comparing the survival benefit of PFS and OS of second-line treatment. With 5 trials included, cabozantinib showed significantly prolonged PFS over nivoluimab, axitinib, and sorafenib. Compared to these studies, this NMA completely included the available trials referring to second-line treatment of mRCC, and compared not only the efficacy but also safety profile of included treatments. Our study confirmed the superior efficacy and safety of lenvatinib plus everolimus, nivolumab, and cabozantinib as the second-line treatment of mRCC.

Although interesting outcomes were found in this study, the results must be interpreted appropriately. First, the combination of lenvatinib plus everolimus showed the best efficacy among included treatments. However, the data of this combination are driven from a phase II trial,[18] which is the only phase II trial among included studies. There are only about 50 participants in each arm, which might bring some concerns about the final outcomes. Second, in the TARGET therapy,[14] all the included patients in both arms are in MSKCC favorable- or intermediate-risk groups, and most of them were previously progressed from cytokine-based therapy, which might potentially exaggerate the effect of pazopanib. Third, in CheckMate 025 trial,[16] the efficacy of nivolumab was evaluated by RECIST criteria, which was not quite accurate for assessing tumor shrinkage for immunotherapy. In fact, immune-related RECIST criteria were designed to capture atypical responses seen with immunotherapy. Fourth, in

this study, we used the frequency of grade 3 to 4 AEs to represent the safety of included treatments. However, it might not entirely reflect the treatment-related toxicity. Treatment discontinuation due to adverse events, dose reduction, types of AEs, and treatment-related death were also important for assessing safety profile. Fifth, most included patients in this study were histologically diagnosed with ccRCC. Trials that enrolled non-ccRCC patients were not included in this NMA.[32–35] However, based on the available data, the present results still provide information for clinicians and patients for treatment decisions, as well as perhaps providing clarity for future clinical trial design.

There are several limitations of this NMA. First, based on the available data from, we could only compare the primary outcomes of included treatments. Further meaningful analyses of subgroup efficacy are not applicable. Second, most of included patients in this NMA were progressed from previous TKI treatment. However, currently immune-based therapy is preferred for the first-line treatment of mRCC, which might weaken the findings of this study. Third, several trials of novel second-line treatments in mRCC are one-armed study. Thus, outcomes of these trials were not included in this analysis. Future studies should be focused on the evaluation of novel second-line treatment options, as well as biomarker-driven approach to further improve survival outcomes of mRCC patients.

5. Conclusions

In the present systematic review and NMA, we indirectly compared the efficacy and safety of current available second-line treatment options in mRCC. Lenvatinib plus everolimus was identified as the most effective treatment approach, with the best PFS, OS, and ORR over other included treatments. Regarding safety profile, nivolumab were associated with decreased incidence of grade 3 to 4 AEs among included treatment therapies. When comprehensively evaluated the efficacy and safety of included treatment options, we noticed that lenvatinib plus everolimus, cabozantinib, and nivolumab were superior to other included treatments, with relatively improved PFS, OS, and ORR, as well as lower risk of grade 3 to 4 AEs.

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