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REVIEW

First-line therapy for elderly patients with advanced renal cell carcinoma in the immuno-oncology era: a network meta-analysis

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Abstract

Background Tyrosine kinase inhibitors (TKI) or immune checkpoint blockade (ICB), either alone or in combination, confers a significant overall survival (OS) benefit for metastatic RCC in the first-line setting. However, guidance for optimal treatment selection in elderly patients remains limited.

Methods A database search was performed to identify eligible randomized controlled trials (RCTs) evaluating first-line regimens for patients with advanced RCC older than 65 years old. The primary outcomes were progression-free survival (PFS) and OS. Indirect comparisons of available regimens were estimated using a random-effects network meta-analysis.

Results A total of 14 and five RCTs were eligible for PFS and OS analyses. Compared with sunitinib, pembrolizumab plus axitinib (HR 0.68, 95% CI 0.48–0.97) and pembrolizumab plus lenvatinib (HR 0.61, 95% CI 0.4–0.94) were associated with improved OS. Pembrolizumab plus lenvatinib, nivolumab plus cabozantinib, pembrolizumab plus axitinib, and cabozantinib alone each showed improved PFS over sunitinib. Among these, pembrolizumab plus lenvatinib showed better PFS than pembrolizumab plus axitinib (HR 0.58, 95% CI 0.37–0.91), but no PFS difference compared to nivolumab plus cabozantinib (HR 0.63, 95% CI 0.39–1.03) and cabozantinib alone (HR 0.84, 95% CI 0.40–1.77). Network ranking showed pembrolizumab plus lenvatinib provided the favored OS and PFS benefit for elderly patients.

Conclusions The combination of ICB with TKI such as pembrolizumab plus lenvatinib needs to be considered over monotherapy in the elderly population, but further validation using real-world data or prospective trials is necessary to confirm the efficacy and safety of first-line regimens for the geriatric population with advanced RCC.

Keywords Renal cell carcinoma · Immune checkpoint blockade · Geriatric oncology · Immuno-oncology · VEGF inhibitor

Introduction

Since the discovery that angiogenesis pathways play an important role in cellular growth, proliferation, and survival in renal cell carcinoma (RCC), targeting the vascular endothelial growth factor (VEGF) has been the mainstream for advanced RCC [1, 2]. After the development of sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI), many additional molecular-targeted agents were subsequently approved in the first- and later-line settings for patients with advanced RCC [3]. Additionally, some populations of RCC were reported to possess the proinflammatory tumor microenvironment resulting in the expression of immune checkpoints such as programmed death-ligand 1 (PD–L1) conversely, and thus, targeting immune checkpoints such as programmed death protein 1 (PD-1), PD–L1, and cytotoxic T-lymphocyte antigen 4 (CTLA-4) was established as an important strategy to treat advanced RCC [4]. Angiogenesis

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also creates the immunosuppressive tumor environment by recruiting myeloid-derived suppressor cells and regulatory T cells and maturing dendritic cells in the tumor microenvironment [5, 6]. This paved the way for combination VEGF–TKI and immune checkpoint blockade (ICB) regimens to be evaluated in several large prospective clinical trials, each demonstrating higher tumor response rates and significant survival benefits when compared to sunitinib monotherapy, leading to multiple recent approvals in the first-line setting [7, 8]. Changes in the therapeutic landscape simultaneously raised questions such as optimal biomarkers to predict efficacy and mechanisms of primary resistance to these newer VEGF–TKI plus ICB regimens. Several studies have been addressing these questions such as gut microbiota modulation, the usefulness of PD–L1 as a predictive biomarker, and the optimal later-line treatments after failure to the combination of ICB and VEGF–TKI regimens [9–12].

However, the clinical safety and efficacy of ICB and VEGF–TKI regimens for the elderly remain controversial [13, 14]. Although multiple pieces of literature support that the survival benefit of systemic therapy for the geriatric population is similar to that for the younger population, the elderly remain underrepresented in clinical trials due to exclusionary medical comorbidities, barring entry to studies. The updated consensus statement from the International Society of Geriatric Oncology in 2018 concluded that age did not apparently affect the survival outcomes of advanced RCC in the elderly population, but toxicity information among the elderly from larger clinical trials remained scarce [15]. The International Metastatic RCC Database Consortium (IMDC) analysis showed the age of 60 years or older was associated with an increase in treatment discontinuation owing to toxicity related to VEGF–TKIs [16]. These studies were conducted before the era of immunotherapy and were based on data from trials evaluating the safety and efficacy of VEGF–TKIs and mammalian target of rapamycin (mTOR) inhibitors. One meta-analysis from two phase 3 trials evaluating pembrolizumab plus axitinib versus sunitinib (KEYNOTE-426), and avelumab plus axitinib versus sunitinib (JAVELIN Renal 101), concluded that withholding combination therapy by assuming that elderly patients might have an increased incidence of toxicity should be avoided [17]. Since the approval of nivolumab as a second-line agent for advanced RCC in 2015, several ICB regimens either as monotherapy or a part of the combination have been approved; therefore, re-evaluation of therapeutic efficacy and safety for elderly patients with advanced RCC is required.

As no clinical trials focusing on only elderly patients with advanced RCC have been performed, oncologists need to investigate data from clinical trials and consider patients' medical conditions to choose appropriate treatment regimens [15]. Comparison of the efficacy of systemic therapy in the geriatric population among randomized controlled trials (RCTs) is useful for clinical decision-making. Our study aims to compare first-line treatment regimens evaluated in RCTs for elderly patients with advanced RCC using a network meta-analysis.

Material and methods

Data search

To identify all eligible studies, a systematic review was performed using the following databases: PubMed/MEDLINE, Web of Science, Embase, and Scopes. The literature search was performed on December 19, 2021. The search term was selected to find randomized controlled trials evaluating agents for patients with advanced RCC (Supplementary Table 1).

Selection criteria

Inclusion criteria were the published study designed as RCT evaluating at least two different regimens for patients with unresectable and/or metastatic RCC in the first-line setting. Literature should include information on the outcomes of overall survival (OS) and/or progression-free survival (PFS) for patients who were 65 years old or older. Articles such as review, meta-analysis, retrospective studies, single-arm clinical trials, and non-randomized clinical trials were excluded. Studies without sufficient information on survival in the elderly population were also removed from the final analysis. If several articles from one clinical trial contained survival data, the most-updated information was used in network meta-analysis. Two independent and blinded authors (YF and HM) reviewed the search results to select studies based on inclusion criteria. When a consensus was not reached, a third author (BCL) was consulted for final determination. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [18].

Data extraction and risk of bias assessment

The number of patients in the overall and elderly population, therapeutic regimens, year of publication, name of the first author, trial name or the National Clinical Trial number, trial phase, median follow-up months, hazard ratio (HR) with 95% confidence interval (CI) of OS and PFS were extracted from eligible articles. For studies that contained forest plots of OS and PFS subgroup analysis in patients 65 years and older without documented 95% CI in articles, we used the program WebPlotDigitizer to analyze forest plots and

estimate HR and upper and lower 95% CI [19]. Risk of bias in each study was assessed using the Risk of Bias 2 tool [20].

Statistical analysis

HR and its 95% were used to perform a network meta-analysis and compare different regimens as a first-line treatment for elderly patients with advanced RCC. Network meta-analysis was conducted using the "netmeta" 2.1–0 package (R Foundation for Statistical Computing, Vienna, Austria) [21]. A random-effect model was used for analysis given the heterogeneity of the enrolled population in each study. For each outcome, the relative ranking of the different first-line regimens was estimated.

Results

Study selection and characteristics

A database search identified a total of 10,862 records, and after duplicate removal and title and abstract screening, 342 articles were assessed for eligibility in detail. Eventually, 16 articles from 15 RCTs representing more than 2,000 patients were included in the final analysis (Fig. 1) [22–37]. The characteristics of each study are summarized in Table 1. One phase 2 trial and 14 phase 3 trials were included in the meta-analysis. Seven studies contained information on OS and 13 studies possessed information on PFS in the elderly population as a subgroup analysis (Table 1). Supplementary Figure 1 illustrates network plots for OS and PFS. In the network for PFS, 13 RCTs were finally included, but three RCTs comparing bevacizumab plus interferon α (IFN-α) vs IFN-α, and temsirolimus vs IFN-α created an independent network, and therefore, were excluded from the final analysis.

Network meta-analysis of overall survival and progression-free survival

Figure 2A shows forest plots for OS using each regimen as a reference. When compared with sunitinib, pembrolizumab plus axitinib (HR = 0.68, 95% CI: 0.48–0.97) and pembrolizumab plus lenvatinib (HR = 0.61, 95% CI: 0.40–0.94) showed significant improvement in OS. Between these regimens, no statistical difference in OS was observed (HR = 1.11, 95% CI = 0.64–1.95, using pembrolizumab plus lenvatinib as a reference). In comparing the TKI–ICB combinations with dual ICB nivolumab + ipilimumab, no significant OS differences were observed (Pembrolizumab plus lenvatinib: HR 0.71, 95% CI 0.40–1.27; pembrolizumab plus axitinib: HR 0.79, 95% CI 0.47–1.34; avelumab plus axitinib: HR 1.03, 95% CI 0.58–1.85; nivolumab plus cabozantinib: HR 1.03, 95% CI 0.57–1.93, using nivolumab plus ipilimumab as a reference). Networking ranking of OS reveals that pembrolizumab plus lenvatinib has the highest p-score followed by pembrolizumab plus axitinib, nivolumab plus ipilimumab, avelumab plus axitinib, nivolumab plus cabozantinib, and sunitinib in order (Table 2).

Figure 2B illustrates forest plots for PFS comparing different regimens. When compared to sunitinib, pembrolizumab plus axitinib (HR = 0.74, 95% CI: 0.55–0.99), pembrolizumab plus lenvatinib (HR = 0.43, 95% CI: 0.31–0.60), nivolumab plus cabozantinib (HR = 0.68, 95% CI: 0.48–0.97), and cabozantinib monotherapy (HR = 0.51, 95% CI: 0.26–0.99) showed improvement in PFS significantly. Among these treatments, pembrolizumab plus lenvatinib showed a better outcome than pembrolizumab plus axitinib (HR = 0.58, 95% CI: 0.37–0.91), but no differences were observed when compared to nivolumab plus cabozantinib and cabozantinib monotherapy (Fig. 2B and Supplementary Figure 2). Network ranking revealed that pembrolizumab plus lenvatinib was ranked as number one in PFS and several TKI monotherapies were ranked as higher in PFS (Table 2).

Risk of bias assessment

Although all studies included in the network meta-analysis were well-designed RCTs, the overall assessment of risk of bias for all studies was with some concerns as a result of data curation from subgroup analysis in each study. All studies had low risk in the randomization process, but we concluded that the data used in our analysis were with some concerns as the subgroup analysis was not the primary outcome of each RCT. Three studies were conducted as a double-blind RCT, and the rest of the studies were open-label RCTs that resulted in being assessed with some concerns in the measurement of the outcome (Supplementary Figure 3).

Discussion

The present study using data from RCTs demonstrated a comprehensive comparison of the first-line regimens for older patients with advanced RCC and revealed the clinical efficacy of the combination of ICB and VEGF–TKI in this population. Pembrolizumab plus lenvatinib demonstrated the highest comparative efficacy both in OS and PFS, while the other ICB plus VEFG–TKI combinations and dual ICB therapy each individually significantly improved OS compared with sunitinib monotherapy in the elderly population. Therefore, we should not avoid the combination treatment for clinically "fit" elderly patients with advanced RCC. Our study addressed an unmet need regarding the optimal treatment options for older patients with advanced RCC by

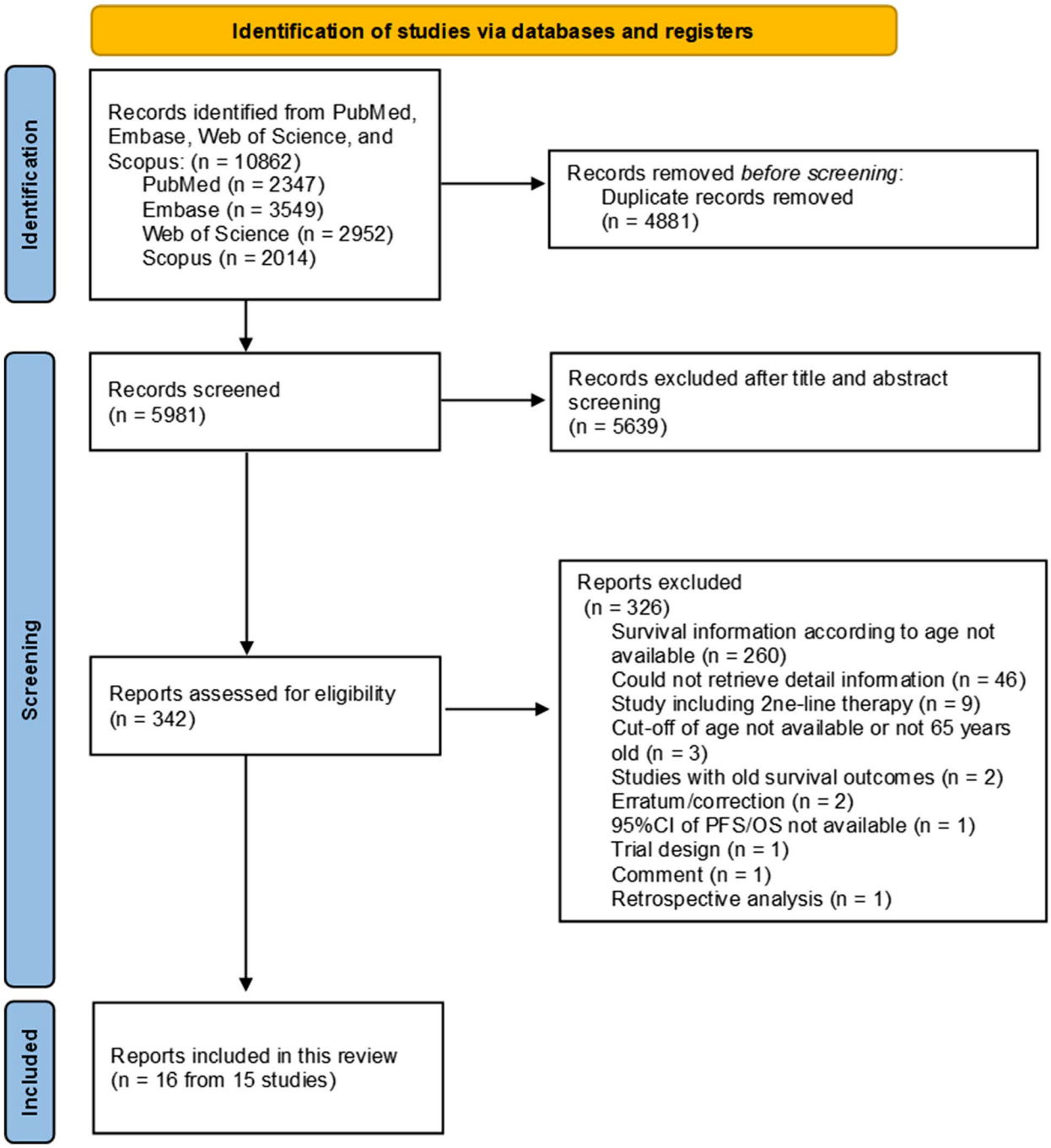

Fig. 1 Flow diagram for identification of relevant studies

indirectly comparing the efficacy of updated available regimens using the network meta-analysis technique.

The definition of the elderly population depends on the context of clinical studies. For example, the World Health Organization (WHO) sets 65 or 70 years old as a cutoff to classify adults as "older" and the Centers for Disease Control and Prevention (CDC) uses 65 years for chronic disease indicators [38, 39]. Although recent clinical trials do not exclude patients simply because of age, the elderly tend to have more comorbidities which sometimes make them ineligible for clinical trials. Focusing on advanced RCC, one recent retrospective study suggested that older patients treated with VEGF–TKI, mTOR inhibitor, or ICB, were more prone to toxicity-related treatment discontinuation and dose reduction, but age did not impact survival outcomes [40]. Another multi-institutional retrospective study from

Table 1 Characteristics of studies included in meta-analyses

Author/Year	Study	P	Treatment	Risk group (*1)	Number of overall patients	Number of older patients	Median follow-up month	OS HR (95% CI)	PFS HR (95% CI)	Ref
Escudier/2007	AVOREN	3	Bev plus IFN-α vs IFN-α	All	325 vs 316	NA (total 239)	13.3 vs 12.8	–	0.77 (0.58–1.03)	[18]
Motzer/2007	NCT00065468	3	Sun vs IFN-α	All	375 vs 375	NA (total 275)	NA	–	0.43 (0.26–0.67)	[28]
Hudes/2007	NCT00083889	3	Tem vs IFN-α	Intermediate & poor	209 vs 207	64 vs 65	NA	1.08 (0.7–1.63)	–	[27]
Escudier/2007	TARGET	3	Sora vs placebo	Favorable & Intermediate	451 vs 452	NA	6.6	–	0.34 (0.22–0.53)	[30]
Escudier/2010	AVOREN	3	Bev plus IFN-α vs IFN-α	All	325 vs 316	NA (total 216)	23 vs 21	1.07 (0.8–1.45)	–	[17]
Sternberg/2010	NCT00334282	3	Paz vs placebo	All	290 vs 145 (155 vs 78: *2)	NA (total 154)	46.2 (*3)	–	0.52 (0.32–0.82)	[32]
Motzer/2013	COMPARZ	3	Paz vs sun	All	557 vs 553	NA	NA	–	1.18 (0.92–1.52)	[23]
Hutson/2013	NCT00920816	3	Axi vs sora	All	192 vs 96	NA	NA	–	0.68 (0.33–1.39)	[29]
Motzer/2013	TIVO-1	3	Tiv vs sora	All	260 vs 257	NA	12 vs 9.5	–	0.69 (0.43–1.10)	[31]
Rini/2014	INTORACT	3	Tem plus bev vs bev plus IFN-α	All	400 vs 391	106 vs 109	NA	–	1.3 (0.9–1.8)	[24]
Motzer/2018	CheckMate 214	3	Niv plus ipi vs sun	Intermediate & poor (*4)	550 vs 546 (425 vs 422: *4)	160 vs 163 (*5)	25.2	0.86 (0.58–1.27) (*5)	–	[20]
George/2019	CABOSUN	2	Cab vs sun	Intermediate & poor	79 vs 78	34 vs 36	25	–	0.51 (0.26–0.97)	[19]
Choueiri/2020	JAVELIN Renal 101	3	Ave plus axi vs sun	All	442 vs 444	171 vs 169	19.3 vs 19.2	0.89 (0.58–1.37)	0.85 (0.63–1.15)	[25]
Powles/2020	KEYNOTE–426	3	Pem plus axi vs sun	All	432 vs 429	172 vs 151	30.6	0.68 (0.48–0.97)	0.74 (0.55–0.99)	[26]
Choueiri/2021	CheckMate 9ER	3	Niv plus cab vs sun	All	323 vs 328	132 vs 118	18.1	0.9 (0.56–1.44)	0.68 (0.48–0.98)	[21]
Motzer/2021	CLEAR (*6)	3	Pem plus len vs sun	All	355 vs 357	161 vs 132	26.6	0.61 (0.4–0.95)	0.43 (0.31–0.61)	[22]

HR of OS and PFS was extracted from subgroup of patients 65 years and older in each study. *1: Studies until 2014 used the Memorial Sloan Kettering Cancer Center risk score and those since 2018 used the International mRCC Database Consortium risk score. "All" means favorable, intermediate, and poor groups. *2: Treatment-naïve patients. This study included patients pretreated with cytokine therapy. *3: Among surviving patients. *4: The CheckMate 214 study included all risk factors in the overall population, but subgroup analysis was based on the IMDC intermediate and poor groups. *5: Age between 65 and 75 was only included. *6: A comparison of lenvatinib plus everolimus vs sunitinib was excluded from the analysis

Ave avelumab; *Axi* axitinib; *Bev* bevacizumab; *Cab* cabozantinib; *HR* hazard ratio; *CI* confidence interval; *IFN-α* Interferon alfa; *IMDC* International mRCC Database Consortium; *Ipi* ipilimumab; *Len* lenvatinib; *Niv* nivolumab; *NA* Not available; *OS* Overall survival; *P* phase; *Paz* pazopanib; *Pem* pembrolizumab; *PFS* Progression-free survival; *Sora* sorafenib; *Sun* sunitinib; *Tem* temsirolimus; *Tiv* tivozanib

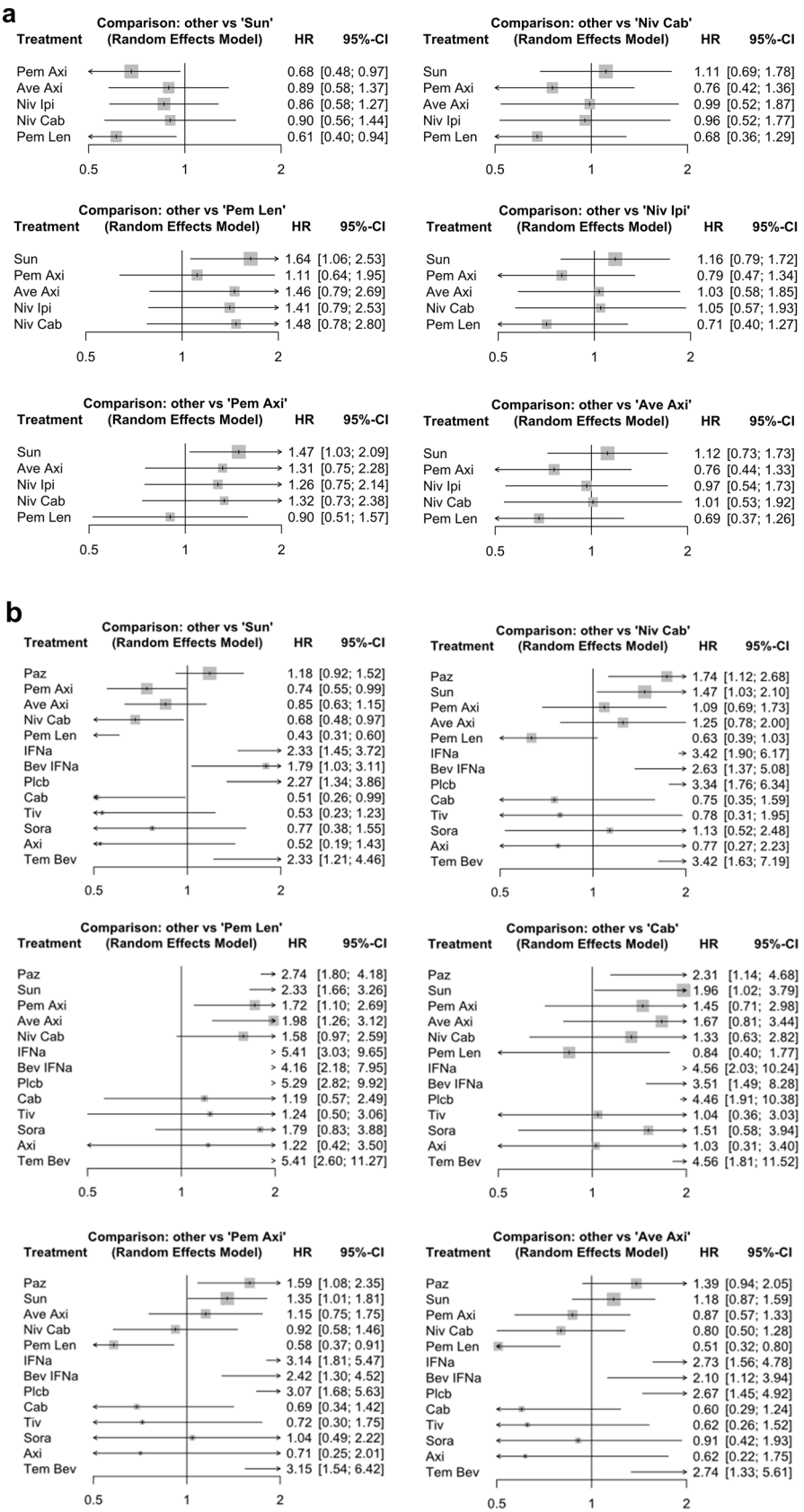

Fig. 2 (A) Forest plots to compare different regimens for overall survival. *Ave* avelumab; *Axi* axitinib; *Cab* cabozantinib; *CI* confidence interval; *HR* hazard ratio; *Ipi* ipilimumab; *Len* lenvatinib; *Niv* nivolumab; *Pem* pembrolizumab; *Sora* sorafenib; *Sun* sunitinib. (B) Selected forest plots to compare different regimens for progression-free survival. *Ave* avelumab; *Axi* axitinib; *Bev* bevacizumab; *Cab* cabozantinib; *CI* confidence interval; *HR* hazard ratio; *IFN-α* Interferon alfa; *Len* lenvatinib; *Niv* nivolumab; *Paz* pazopanib; *Pem* pembrolizumab; *Plcb* placebo; *Sora* sorafenib; *Sun* sunitinib; *Tem* temsirolimus; *Tiv* tivozanib

Table 2 Network ranking of overall survival and progression-free survival

Treatment	HR (95% CI) of OS vs Sun	P-score (random)	Median rank (OS)	HR (95% CI) of PFS vs Sun	P-score (random)	Median rank (PFS)
Pem + Len	0.61 (0.40–0.94)	0.8564	1	0.43 (0.31–0.60)	0.9139	1
Pem + Axi	0.68 (0.48–0.97)	0.7595	2	0.74 (0.55–0.99)	0.6358	6
Niv + Ipi	0.86 (0.58–1.27)	0.4387	3	–	–	–
Ave + Axi	0.89 (0.58–1.37)	0.3908	4	0.85 (0.63–1.15)	0.5411	8
Niv + Cab	0.90 (0.56–1.44)	0.3780	5	0.68 (0.48–0.97)	0.6875	5
Sun (ref)	–	0.1766	6	–	0.4223	9
Cab	–	–	–	0.51 (0.26–0.99)	0.8212	2
Tiv	–	–	–	0.53 (0.23–1.23)	0.8020	3
Axi	–	–	–	0.52 (0.19–1.43)	0.7898	4
Sora	–	–	–	0.77 (0.38–1.55)	0.5795	7
Paz	–	–	–	1.18 (0.92–1.52)	0.3249	10
Bev + IFN-α	–	–	–	1.79 (1.03–3.11)	0.2158	11
Placebo	–	–	–	2.27 (1.34–3.86)	0.1018	12
Tem + Bev	–	–	–	2.33 (1.21–4.46)	0.0850	13
IFN-α	–	–	–	2.33 (1.45–3.72)	0.0793	14

Ave avelumab; *Axi* axitinib; *Bev* bevacizumab; *Cab* cabozantinib; *HR* hazards ratio; *IFN-α* interferon alfa; *Ipi* ipilimumab; *Len* lenvatinib; *Niv* nivolumab; *OS* overall survival; *Paz* pazopanib; *Pem* pembrolizumab; *PFS* progression-free survival; *Ref* reference; *Sora* sorafenib; *Sun* sunitinib; *Tem* temsirolimus; *Tiv* tivozanib

IMDC that evaluated patients (< 70 vs ≧70 years old) receiving ICB either as monotherapy, dual therapy, or in combination with VEGF–TKI, revealed no significant differences in OS, time-to-treatment failure, and time-to-next treatment between younger and older patients [41]. These studies suggest that conventional treatment for advanced RCC does not cause survival differences between younger and older patients in the real-world setting. However, aging appears to alter a single step of anti-tumor response, and immunosenescence, a process of immune dysfunction related to aging, could potentially affect the efficacy and safety of ICB theoretically. It is controversial whether immunosenescence either promotes or regulates cancer progression, and therefore further studies focusing on host immune status in the elderly population with advanced RCC are needed [42, 43]. Although a comparison of the toxicity profiles among each therapy was not made, our study compared the efficacy of available regimens and provides clinical guidance for oncologists when determining treatments for older patients with advanced RCC.

A previous network meta-analysis demonstrated better survival outcomes with nivolumab plus ipilimumab than VEGF–TKI monotherapy in 65 years or older RCC patients, which was consistent with the result observed in our analysis [44]. As this study did not contain information on survival from ICB plus VEGF–TKI, our study updated the comparative information on therapeutic regimens for advanced RCC in the elderly by incorporating the current evidence of standard of care. Several phase 3 trials investigating the combination treatment with ICB and VEGF–TKI are ongoing and will provide additional insights into therapeutic choices (NCT03793166: nivolumab plus ipilimumab followed by randomization to nivolumab versus nivolumab plus cabozantinib, NCT04736706: pembrolizumab plus lenvatinib plus belzutifan vs or pembrolizumab plus lenvatinib plus quavonlimab vs pembrolizumab plus lenvatinib, NCT03937219: nivolumab plus ipilimumab plus cabozantinib or placebo).

Several limitations are noted in the present network meta-analysis. Because the safety information based on the age-stratified subgroup was not available, a comparison of toxicity was not made. One recent meta-analysis evaluating the safety of ICB-containing regimens for advanced RCC suggested that nivolumab plus ipilimumab appeared more feasible than other ICB-TKI regimens in the overall population, but no dedicated meta-analyses focusing on the safety of treatments for the elderly with advanced RCC have been performed [45]. Upon treatment decision, the unique toxicity profile of each treatment regimen is one of the biggest determinants when choosing therapy for elderly patients. Subgroup analysis of the JAVELIN Renal 101 trial demonstrated that avelumab plus axitinib had a higher rate of discontinuation in elderly patients (75 years and older) than younger groups (< 65, 65–75 years old), whereas no obvious difference of discontinuation rate was observed among each age group treated with sunitinib [46]. In contrast, in several studies, the rate of immune-related adverse events (irAEs) was similar between older and younger groups [46,

47]. Nevertheless, different toxicity profiles among each regimen for elderly patients must be investigated for clinical decision, and thus, further study is needed. Second, we used data curated from subgroup analysis in RCTs; therefore, the selected population in each RCT was not fully randomized. Given this nature, the number of patients according to the IMDC risk in the age subgroup in eligible studies was not available. This could result in under- or overestimation of efficacy in a certain treatment. However, no prospective studies only focusing on the elderly population have been conducted, and thus, our study provides useful information for clinical decision-making. Additionally, our analysis lacks data from major trials such as the IMmotion151 trial comparing atezolizumab plus bevacizumab with sunitinib, and the IMPRINT trial comparing IMA901 plus sunitinib versus sunitinib [48, 49]. Furthermore, every comparison has one RCT and no data on a direct comparison between ICB plus VEGF–TKI regimens was available, making it difficult to evaluate heterogeneity and inconsistency of therapeutic efficacy.

Despite these limitations, this is the largest and most updated, comprehensive network meta-analysis indirectly comparing first-line therapy for the elderly with advanced RCC. Our study found that several approved regimens were superior to others by improving OS and PFS, and therefore, offers meaningful insights into treatment decisions for older patients with advanced RCC. As the immuno-oncology field is expanding dramatically, immunotherapy-based regimens will continue to be mainstream for advanced RCC regardless of age. Multiple trials are ongoing to evaluate the new combination regimens such as the modulation of the gut microbiome, inhibition of other inhibitory immune checkpoints, and use of other molecular targeted agents with ICB. Analysis of host immune status, safety, and potential biomarkers not only in the overall population but also in elderly patients would be strongly encouraged to identify the appropriate treatment options and develop better therapeutic strategies for older patients with advanced RCC [4, 17, 42].

Conclusion

Pembrolizumab plus lenvatinib and pembrolizumab plus axitinib provided better OS benefits in elderly patients as a first-line treatment for advanced RCC. Pembrolizumab plus lenvatinib showed improved PFS compared with pembrolizumab plus axitinib, but no difference compared with nivolumab plus cabozantinib or cabozantinib alone. For generally "fit" elderly patients, the combination of ICB and VEGF–TKI should not be avoided, but further validation using real-world data or prospective trials is needed to confirm the efficacy and safety of first-line regimens for the geriatric population with advanced RCC.

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Authors' contribution YF helped in conceptualization, formal analysis, investigation, data curation, resources, statistical analysis, writing—original draft, and visualization. HM contributed to formal analysis, investigation, data curation, statistical analysis, writing—review & editing. BCL performed conceptualization, writing—review & editing, visualization, and supervision.

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Data availability Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Conflict of interest None of the authors have a conflict of interest to report for the submitted work.

Ethics approval and consent to participate Not required.

Consent for publication Not applicable.

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