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Is there a preferred first-line therapy for metastatic renal cell carcinoma? A network meta-analysis

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Abstract

Background: In recent years, new therapeutic combinations based on immunotherapy provided significant benefits as a first-line treatment for patients with advanced renal cell carcinoma (mRCC).

Objective: This work aims to address the lack of head-to-head comparisons and the uncertainty of the benefit from immunotherapy-based combinations in all the International Metastatic RCC Database Consortium (IMDC) subgroups.

Design, setting, and participants: A systematic review and a network meta-analysis were performed. Overall survival (OS) in the intention-to-treat (ITT) population was the primary endpoint. OS according to IMDC subgroups (favorable, intermediate, poor), PD-L1 expression, and grade ⩾3 adverse events (AEs) were secondary endpoints. A SUCRA analysis was performed.

Results and limitations: Six randomized phase III trials with 5121 patients were included. There was a high likelihood (82%) that nivolumab-cabozantinib was the preferred treatment in OS. The benefit of ICI-based combinations over sunitinib was unclear in the favorable-risk subgroup. Nivolumab-ipilimumab had the best risk/benefit ratio among all the ICI-based combinations. The limitations were the lack of individual patient data; the heterogeneity of patients' characteristics, trial designs, and follow-up times; and a limited number of studies for indirect comparisons.

Conclusions: A customized approach for the first-line treatment of patients with mRCC should consider the risk/benefit profile of each treatment option, especially considering the likeliness of long-term survival finally reached in this setting.

Keywords: first-line, immune checkpoint inhibitors, meta-analysis, renal cell carcinoma, tyrosine kinase inhibitors

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Introduction

New therapeutic combinations based on anti-PD-1/PD-L1 immune checkpoint inhibitors (ICI) plus anti-CTLA-4 or anti-VEGF/VEGFR targeted therapies (TT) provided significant benefit compared with the anti-VEGFR tyrosine kinase inhibitor (TKI) sunitinib alone for the first-line treatment of patients with metastatic renal cell carcinoma (mRCC).[1–6] These combinations showed different toxicity profiles, class- and agent-specific, and different efficacy profiles. The lack of head-to-head comparisons raises the question of what the best combination strategy might be and whether there is still room for TKI monotherapy in naïve patients, taking into account the International Metastatic RCC Database Consortium (IMDC) subgroup.

We planned the present network meta-analysis to identify the likely preferred strategy for the first-line treatment of mRCC, considering the most clinically relevant parameters able to define

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the risk–benefit profile of a therapeutic choice, namely, the survival improvement and the tolerability.

Methods

We performed a systematic review of the literature and a network meta-analysis to indirectly compare the efficacy and safety of the available ICI-based combinations for the first-line treatment of mRCC. Also, we explored the outcome of patients to these combinations according to the IMDC and PD-L1 expression subgroups. Overall survival (OS) in the intention-to-treat (ITT) population was the primary endpoint. OS according to IMDC subgroups (favorable, intermediate, poor), PD-L1 subgroups (positive *versus* negative with 1% threshold), and grade ⩾3 adverse events (AEs) were secondary endpoints.

The literature search was performed on PubMed, Embase, and Cochrane Library using the following terms: (renal cell carcinoma OR renal cell cancer OR kidney carcinoma OR kidney cancer) AND (metastatic OR advanced) AND (Randomized) AND (phase III OR phase 3) from database inception to 8 March 2021. Conference abstract with no full-text publication was excluded. Inclusion criteria were (1) ICI-based experimental arm, (2) control arm with tyrosine kinase monotherapy (corresponding to the prior standard of care), and (3) availability of efficacy data. Exclusion criteria were (1) unavailable data about the outcomes of interest, (2) early phase studies (phase I/II), (3) non-randomized studies, (4) non-first-line therapy, and (5) exclusive non-clear cell histology. Data extraction was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Two authors performed study selection independently (M.B. and S.B.), and disagreements were resolved by consensus. One author (C.M.) performed the data abstraction with independent verification by two other authors (M.B. and C.C.).

The Jadad score was used for the quality assessment of the studies included (G.R.).

OS was defined as in the original studies included, and the most updated data were used for the meta-analysis. Toxicity was calculated as the odds ratio of grade ⩾3 AEs in experimental and control arms. We performed a network meta-analysis using fixed- or random-effects models, based on heterogeneity value assessed using I2, with a Bayesian approach for the direct and indirect treatment comparisons for each outcome. For time-to-event data, hazard ratio (HR) and 95% confidence interval (CI) were used to compare results. The relative treatment effects were presented as HR and 95% credible interval (CrI). If not available, data for the 'poor/intermediate' subgroup were obtained by pooling the HR and 95% CIs (or performing a meta-analysis) of the estimates from poor and intermediate subgroups. We estimated the relative ranking of the different treatments for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA).

All statistical analyses were performed using R v. 3.5.1 with package (gemtc).

Results

Six randomized phase III trials fulfilled the prespecified inclusion criteria for this network meta-analysis (Figure 1).[1–6] Four other papers reported updated results of these trials.[7–10] Trials' quality was assessed using the Jadad scale (Supplementary Table S1). The main characteristics of the trials included are summarized in Table 1. Overall, 5121 patients were included. According to our results, collected in Figure 2, nivolumab-cabozantinib (HR = 0.60, 95%CrI = 0.40–0.90), pembrolizumab-lenvatinib (HR = 0.66, 95%CrI = 0.49–0.88), pembrolizumab-axitinib (HR = 0.68, 95% CrI = 0.54–0.85), and nivolumab-ipilimumab (HR = 0.69, 95%CrI = 0.59–0.81) were all associated with significantly lower risk of death compared with sunitinib in the ITT population. Based on SUCRA analysis, there was a high likelihood (82%) that nivolumab-cabozantinib was the preferred treatment in terms of OS benefit, followed by pembrolizumab-lenvatinib (72%), pembrolizumab-axitinib (68%), and nivolumab-ipilimumab (56%) (Table 2). Pembrolizumab-axitinib (78%) and pembrolizumab-lenvatinib (74%) had the highest probability to be the preferred therapy for the intermediate and poor IMDC subgroups, respectively (Figure 2(d)–(f)). In contrast, the benefit of the ICI-based combinations over sunitinib was unclear in the favorable-risk subgroup (Figure 2(c)).

The forest plots according to PD-L1 expression were reported in Figure 3.

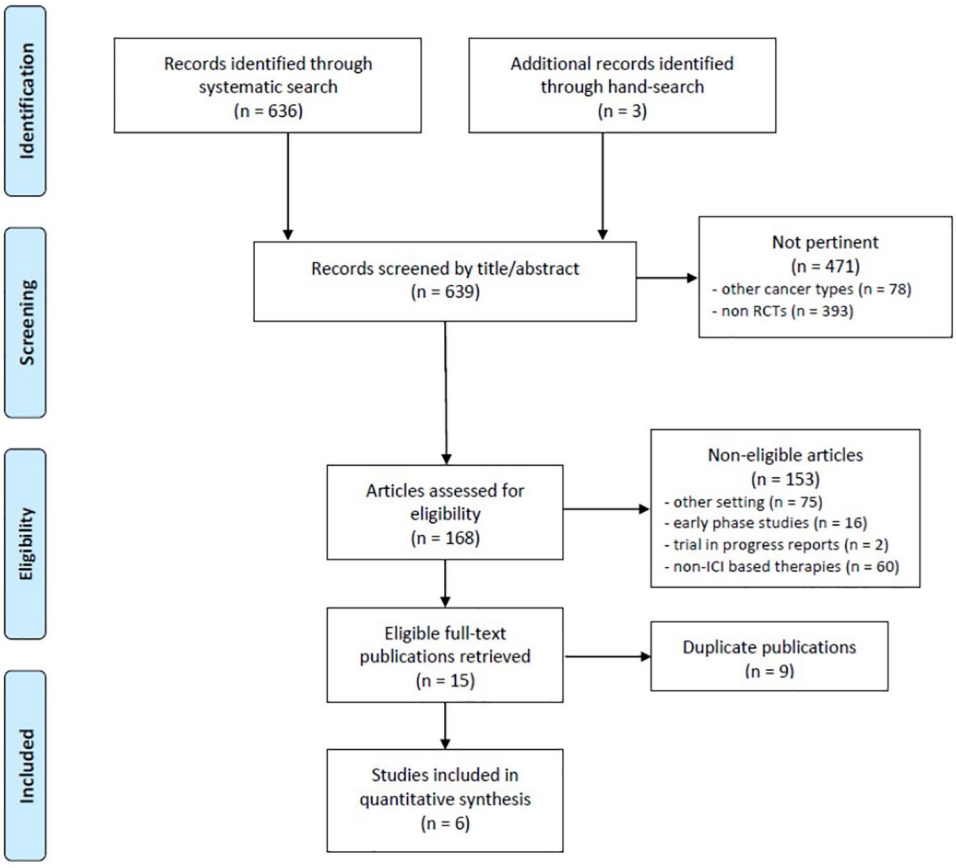

Figure 1. PRISMA flow chart of the studies' selection process.

Concerning toxicity, there was a high likelihood (96%) that nivolumab-ipilimumab was the preferred option in terms of tolerability, followed by atezolizumab-bevacizumab (87%), sunitinib (55%), and avelumab-axitinib (54%) (Table 2 and Figure 1(b)). The clustered analysis of efficacy and toxicity (Figure 1(g)) showed that nivolumab-ipilimumab had the best risk/benefit ratio among all the ICI-based combinations.

Discussion

Our network meta-analysis provides circumstantial evidence regarding the likely preferred first-line treatment option for patients with mRCC. An OS benefit in the ITT population was observed for all the combinations with anti-PD-1 ICI (pembrolizumab or nivolumab), whereas it was inconclusive in patients treated with anti-PD-L1 (atezolizumab or avelumab). This observation might be related to intrinsic differences among drugs, different trials' design, population, and follow-up duration (Table 1). Figure 2(f) shows that the survival improvement obtained by any ICI-based combination over sunitinib was marked in patients with poor-risk disease. This benefit remained significant for nivolumab-ipilimumab and pembrolizumab-axitinib combinations in patients with intermediate-risk disease (Figure 2(e)). These results are consistent with the expectedly highest benefit from immunotherapy in intermediate-poor risk disease.[3]

Conversely, data on the favorable-risk population showed unclear benefit in OS with ICI combinations compared with sunitinib (Figure 2(c)). This finding could support a sequential strategy (i.e. first-line TKI monotherapy followed by ICI in second line) as a preferable option in this subgroup. Of note, none of these trials was specifically powered to test the efficacy of the experimental combination in the favorable-risk patient subgroup, and caution should be used when interpreting unpowered subgroup analyses.[11] The lack of adequate follow-up for each study could also prevent observing a long-term survival improvement, mitigating conclusive reliability.

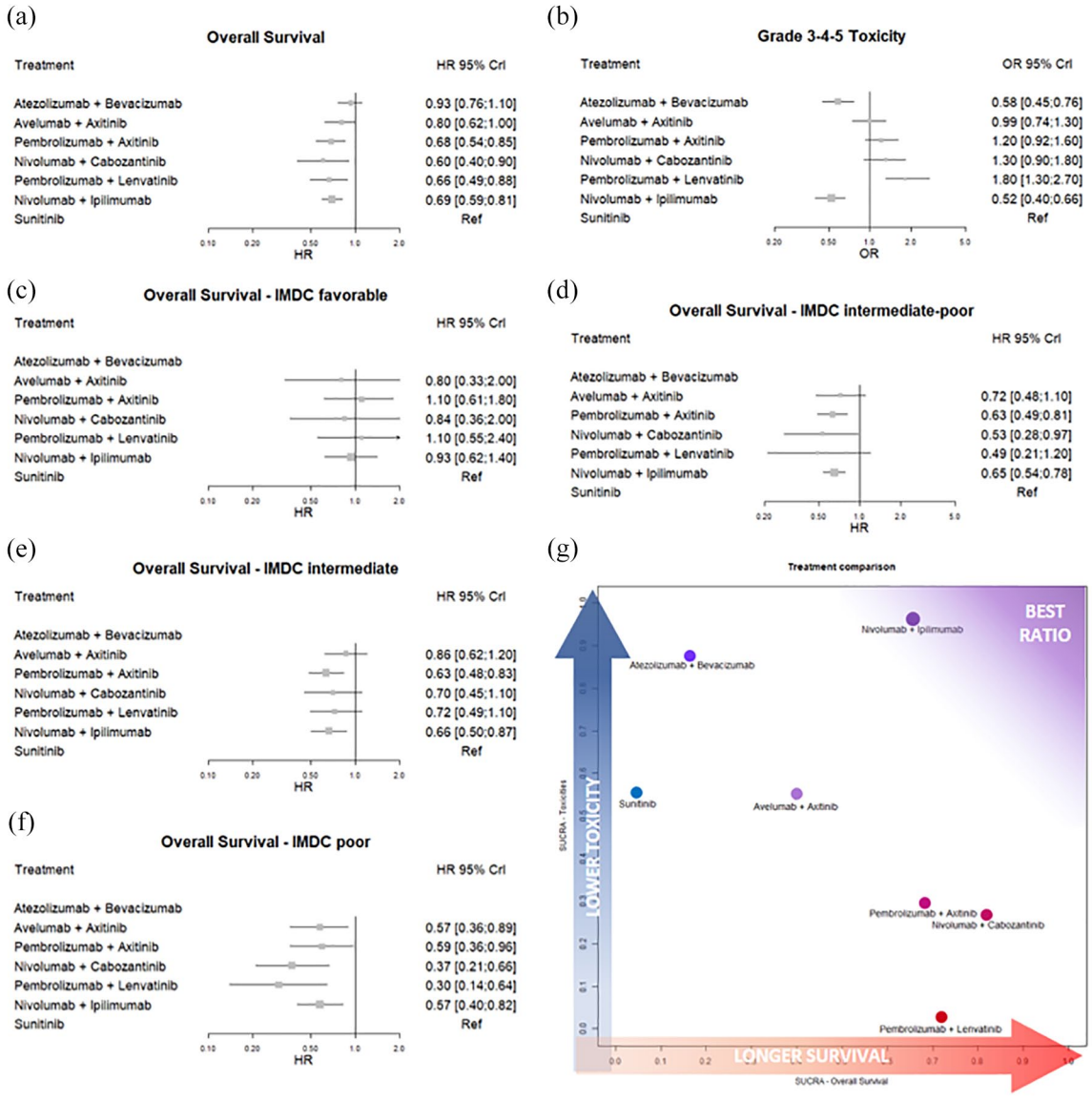

Figure 2. Forest plot of overall survival (OS) (a) and grade ⩾3 toxicity (b) in the intention-to-treat (ITT) population. Analysis of OS in the International Metastatic RCC Database Consortium (IMDC) favorable (c), intermediate-poor (d), intermediate (e), and poor (f) subgroups. Clustered analysis of efficacy and AEs (g) according to SUCRA values. Heterogeneity was negligible, with I2 lower than 20% for all networks performed, and a fixed effect model was applied.

On the contrary, the results demonstrated an OS benefit of all ICI combinations, irrespective of the PD-L1 expression (Figure 3(a) and (b)), suggesting that this biomarker alone should not be used as potentially predictive in this setting, maybe also due to the heterogeneity of assays employed for its assessment.

Regarding toxicity, the chance that nivolumab-ipilimumab was the preferred option was extremely high (96%), and this should be considered an essential element for the choice when comparing options with similar efficacy outcomes for intermediate- and poor-risk patients. The clustered analysis of efficacy and AEs (Figure 2(g)) clearly shows that nivolumab-ipilimumab represents the best option from a risk/benefit standpoint.

Despite the lowest chance to be the preferred option for OS in the ITT population and poor-intermediate risk subgroups, sunitinib showed a significantly lower odds ratio of grade 3 and 4

Table 1. Main characteristics of the trials included in the network meta-analysis.

	IMmotion 151 (*Lancet* 2019)	**Javelin Renal 101 (*Ann Oncol* 2020)**	**Keynote 426 (*Lancet Oncol* 2020)**	**CheckMate 214 (*ESMO Open* 2020)**	**Checkmate 9ER (*NEJM* 2021)**	**CLEAR[a] (NEJM 2021)**
Study type	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial
Experimental arm treatment	Atezolizumab + Bevacizumab	Avelumab + Axitinib	Pembrolizumab + Axitinib	Nivolumab + Ipilimumab	Nivolumab + Cabozantinib	Lenvatinib + Pembrolizumab
Control arm treatment	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Number of patients enrolled	915	886	861	1096	651	712
Primary end point(s)	PFS, OS	PFS, OS	OS, PFS	OS, PFS, ORR	PFS	PFS
Population for the primary end point	PD-L1 + population (PFS), ITT population (OS)	PD-L1 + population	ITT population	I-P risk (sec. IMDC) patient population	ITT population	ITT population
Median follow-up[b] (months)	24.0	19.3	30.6	55.0	18.1	26.6
Previous nephrectomy	74% *versus* 72%	80% *versus* 80%	83% *versus* 84%	80% *versus* 76% [I-P risk] 82% *versus* 80% [ITT]	69% *versus* 71%	74% *versus* 77%
IMDC distribution	Favorable 18.8%[c] Intermediate 64.1% Poor 17.1%	Favorable 21.4% Intermediate 61.7% Poor 16.1%	Favorable 31.2% Intermediate 56.2% Poor 12.5%	Favorable 0% [I-P risk] – 22.7% [ITT] Intermediate 78.7% [I-P risk] – 60.8% [ITT] Poor 21.3% [I-P risk] –16.4% [ITT]	Favorable 22.4% Intermediate 57.8% Poor 19.8%	Favorable 32.9% Intermediate 56.5% Poor 9.8%
Tumor PD-L1 expression	⩾1%: 39.7%[d] <1%: 60.3%	⩾1%: 63.2%[d] <1%: 28.4% Unknown: 8.3%	⩾1%: 57.5%[e] <1%: 37.3% Unknown: 5.2%	⩾1%: 25.3% [I-P risk] – 21.9% [ITT] < 1%: 66.3% [I-P risk] – 69.5% [ITT] Unknown: 8.4% [I-P risk] –8.6% [ITT]	⩾1%: 25.5% <1%: 74.5%	⩾1%: 31.7%[e] <1%: 30.2% Unknown: 38.1%
No. of sites of lesions	Not reported	Not reported	= 1: 24.4% ⩾2: 75.0% Unknown: 0.6%	= 1: 20.5% [I-P risk] – 21.9% [ITT] ⩾2: 79.5% [I-P risk] – 78.1% [ITT]	= 1: 20.3% ⩾2: 79.1% Unknown: 0.6%	= 1: 28.8% ⩾2: 70.2%
Liver metastases	17.4% [PD-L1 +] 17.5% [ITT]	Not reported	15.9%	20.9% [I-P risk] 18.8% [ITT]	19.3%	16.9%
Bone metastases	20.2% [PD-L1 +] 19.7% [ITT]	Not reported	23.9%	22.7% [I-P risk] 21.1% [ITT]	23.0%	25.6%
Sarcomatoid features	23.8% [PD-L1 +] 15.5% [ITT]	Not reported [PD-L1 +] 12.2% [ITT]	12.2%	16.4% [I-P risk] 13.2% [ITT]	11.5%	6.9%
Median PFS (months)	11.2 *versus* 7.7 [PD-L1 +] 11.2 *versus* 8.4 [ITT]	13.8 *versus* 7.0 [PD-L1 +] 13.3 *versus* 8.0 [ITT]	15.4 *versus* 11.1	11.2 *versus* 8.3 [I-P risk] 12.2 *versus* 12.3 [ITT]	16.6 *versus* 8.3	23.9 *versus* 9.2

(Continued)

Table 1. (Continued)

	IMmotion 151 (*Lancet* 2019)	Javelin Renal 101 (*Ann Oncol* 2020)	Keynote 426 (*Lancet Oncol* 2020)	CheckMate 214 (*ESMO Open* 2020)	Checkmate 9ER (*NEJM* 2021)	CLEAR[a] (NEJM 2021)
Median OS (months)	34.0 *versus* 32.7 [PD-L1 +] 33.6 *versus* 34.9 [ITT]	NR *versus* 28.6 [PD-L1 +] NR *versus* NR [ITT]	NR *versus* 53.7	48.1 *versus* 26.6 [I-P risk] NR *versus* 38.4 [ITT]	NR	NR *versus* NR
RR (CR)	43% (9%) *versus* 35% (4%) [PD-L1 +] 37% (5%) *versus* 33% (2%) [ITT]	55.9% (5.6%) *versus* 27.2% (2.4%) [PD-L1 +] 52.5% (3.8%) *versus* 27.3% (2.0%) [ITT]	60.2% (8.8%) *versus* 39.9% (3.0%)	41.9% (10.4%) *versus* 26.8% (1.4%) [I-P risk] 39.1% (10.7%) *versus* 32.4% (2.6%) [ITT]	55.7% (8%) *versus* 27.1% (4.6%)	71.0% (16.1%) *versus* 36.1% (4.2%)

CR, complete responses; IMDC, International Metastatic RCC Database Consortium; I-P risk, intermediate and poor risk; ITT, intention to treat; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]Lenvatinib + everolimus arm was not considered.
[b]Follow-up for overall survival.
[c]IMDC distribution available for PD-L1-positive patients.
[d]PD-L1 expression measured on tumor-infiltrating immune cells.
[e]PD-L1 expression measured as combined positive score (CPS) which was calculated as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

Table 2. SUCRA values of different treatments for all outcomes in patients with metastatic renal cell carcinoma.

	IMmotion 151 (*Lancet* 2019)	Javelin Renal 101 (*Ann Oncol* 2020)	Keynote 426 (*Lancet Oncol* 2020)	CheckMate 214 (*ESMO Open* 2020)	Checkmate 9ER (*NEJM* 2021)	CLEAR[a] (NEJM 2021)
Study type	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial	Randomized, phase III trial
Experimental arm treatment	Atezolizumab + Bevacizumab	Avelumab + Axitinib	Pembrolizumab + Axitinib	Nivolumab + Ipilimumab	Nivolumab + Cabozantinib	Lenvatinib + Pembrolizumab
Control arm treatment	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Number of patients enrolled	915	886	861	1096	651	712
Primary endpoint(s)	PFS, OS	PFS, OS	OS, PFS	OS, PFS, ORR	PFS	PFS
Population for the primary endpoint	PD-L1 + population (PFS), ITT population (OS)	PD-L1 + population	ITT population	I-P risk (sec. IMDC) patient population	ITT population	ITT population
Median follow-up[b] (months)	24.0	19.3	30.6	55.0	18.1	26.6
Previous nephrectomy	74% *versus* 72%	80% *versus* 80%	83% *versus* 84%	80% *versus* 76% [I-P risk] 82% *versus* 80% [ITT]	69% *versus* 71%	74% *versus* 77%
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(Continued)

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	IMmotion 151 (*Lancet* 2019)	Javelin Renal 101 (*Ann Oncol* 2020)	Keynote 426 (*Lancet Oncol* 2020)	CheckMate 214 (*ESMO Open* 2020)	Checkmate 9ER (*NEJM* 2021)	CLEAR[a] (NEJM 2021)
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No. of sites of lesions	Not reported	Not reported	= 1: 24.4% ⩾2: 75.0% Unknown: 0.6%	= 1: 20.5% [I-P risk] – 21.9% [ITT] ⩾2: 79.5% [I-P risk] – 78.1% [ITT]	= 1: 20.3% ⩾2: 79.1% Unknown: 0.6%	= 1: 28.8% ⩾2: 70.2%
Liver metastases	17.4% [PD-L1 +] 17.5% [ITT]	Not reported	15.9%	20.9% [I-P risk] 18.8% [ITT]	19.3%	16.9%
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Sarcomatoid features	23.8% [PD-L1 +] 15.5% [ITT]	Not reported [PD-L1 +] 12.2% [ITT]	12.2%	16.4% [I-P risk] 13.2% [ITT]	11.5%	6.9%
Median PFS (months)	11.2 *versus* 7.7 [PD-L1 +] 11.2 *versus* 8.4 [ITT]	13.8 *versus* 7.0 [PD-L1 +] 13.3 *versus* 8.0 [ITT]	15.4 *versus* 11.1	11.2 *versus* 8.3 [I-P risk] 12.2 *versus* 12.3 [ITT]	16.6 *versus* 8.3	23.9 *versus* 9.2
Median OS (months)	34.0 *versus* 32.7 [PD-L1 +] 33.6 *versus* 34.9 [ITT]	NR *versus* 28.6 [PD-L1 +] NR *versus* NR [ITT]	NR *versus* 53.7	48.1 *versus* 26.6 [I-P risk] NR *versus* 38.4 [ITT]	NR	NR *versus* NR
RR (CR)	43% (9%) *versus* 35% (4%) [PD-L1 +] 37% (5%) *versus* 33% (2%) [ITT]	55.9% (5.6%) *versus* 27.2% (2.4%) [PD-L1 +] 52.5% (3.8%) *versus* 27.3% (2.0%) [ITT]	60.2% (8.8%) *versus* 39.9% (3.0%)	41.9% (10.4%) *versus* 26.8% (1.4%) [I-P risk] 39.1% (10.7%) *versus* 32.4% (2.6%) [ITT]	55.7% (8%) *versus* 27.1% (4.6%)	71.0% (16.1%) *versus* 36.1% (4.2%)

IMDC, International Metastatic RCC Database Consortium; I-P risk, intermediate and poor risk; ITT, intention to treat; NR, not reported; ORR, objective response rate; OS, overall survival; PDL, progression-free survival; PFS, progression-free survival; SUCRA, surface under the cumulative ranking curves.
[a]Lenvatinib + everolimus arm was not considered.
[b]Follow-up for overall survival.
[c]IMDC distribution available for PD-L1-positive patients.
[d]PD-L1 expression measured on tumor-infiltrating immune cells.
[e]PD-L1 expression measured as combined positive score (CPS) which was calculated as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

AEs than most of the ICI-based combinations. Consequently, a combination strategy preference in the favorable subgroup should be reserved for selected patients with high tumor burden, hepatic involvement, or rapidly progressive disease, especially in young individuals.

A new scenario could open up with the awaited results of an ongoing phase III randomized trial investigating the combination of cabozantinib, nivolumab, and ipilimumab *versus* nivolumab-ipilimumab in intermediate-poor risk mRCC patients.[12]

Several limitations of the present network meta-analysis should be acknowledged; these include the lack of individual patient data, different patients' characteristics and population among

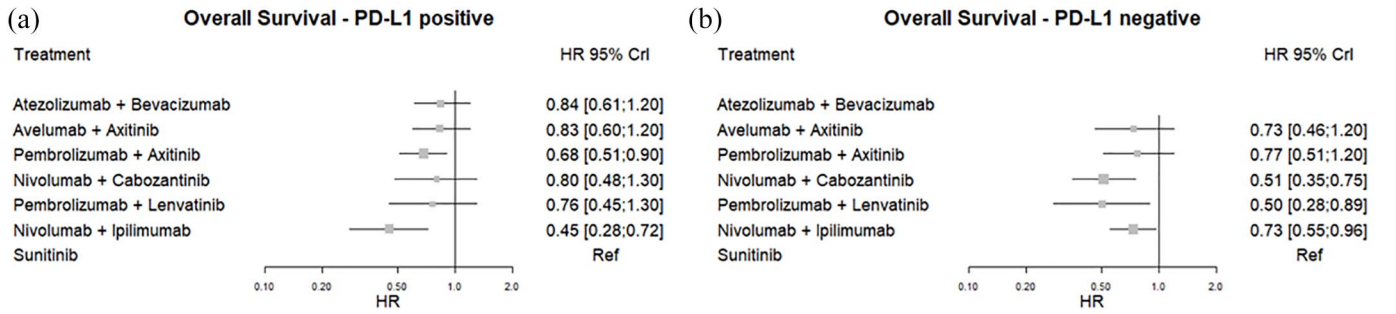

Figure 3. Forest plot of overall survival (OS) in the PD-L1-positive (a) and PD-L1-negative (b) subgroup (1% threshold).

trials, distinct clinical trial designs, a limited number of studies for indirect comparisons, and different lengths of follow-up (see Table 1). Major strengths are the quality of the trials included and the same agent used as the control for all studies.

A previous meta-analysis, with similar objectives, strengths and limitations, was recently published by other authors.[13] We believe that the true usefulness of such a type of work is considering the efficacy end point together with the safety/tolerability of the treatment, trying to provide a 'combined' recommendation, taking into account both elements jointly. For this reason, we combined the rankings for both OS and toxicity, reporting the global ranking in graphical form (see Figure 2(g)). The clinical utility of separately considering each end point, as done in the cited meta-analysis, in our opinion is quite limited, beyond the undoubtful scientific relevance. To guide the treatment choice in the real-life setting, we need to consider the risk/benefit ratio. Of note, we identified nivolumab-ipilimumab as the option with the best risk/benefit ratio profile, providing a new original result with respect to prior data available. In addition, we provided data and results about the intermediate-risk and poor-risk groups separately, offering the opportunity to verify the survival outcome with different ICI-based combinations according to the patient's subgroup and to identify differences between the two subgroups, if any. Finally, our data were updated with those from the most recent publications of the trials included.

In conclusion, several new ICI-based combinations demonstrated a significant survival advantage over sunitinib, becoming the new standard of care for the upfront treatment of mRCC. As a matter of facts, despite different rankings according to the end point considered, there is no relevant difference in patient outcomes within the nivolumab-cabozantinib, pembrolizumab-axitinib, pembrolizumab-lenvatinib, and nivolumab-ipilimumab combinations. With the current wide range of opportunities, a customized approach for the primary treatment of patients with mRCC, without questioning that the survival gain is likely the most crucial objective, should take into account the risk/benefit profile of each treatment option, especially considering the likeliness of long-term survival finally reached in this setting.

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Carlo Cattrini and Carlo Messina equally contributed.

Author contributions

All the authors substantially contributed to the concept or design of the work or acquisition, analysis, or interpretation of data; drafted the article or revised it critically for important intellectual content, and approved the version to be published. Each author participated sufficiently in this work to take public responsibility for appropriate portions of the content. The first two authors (Dr. Cattrini and Dr. Messina) equally contributed.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.C. received Travel/Accommodation/Expenses from Novartis, Pfizer, Janssen, and Ipsen; advisory board from Janssen. C.M. received honoraria as a speaker for scientific events from Astellas and Ipsen. S.B. received honoraria as a speaker at scientific events and advisory role from Bristol-Myers Squibb (BMS), Pfizer, MSD, Ipsen,

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Research ethics and patient consent

The present research was conducted according to the World Medical Association Declaration of Helsinki. Patient consent was not required, and approval by Ethics Committee or Institutional Review Board was waived (not applicable) due to the nature of the study (meta-analysis on published data). The present manuscript conforms to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

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Supplemental material

Supplemental material for this article is available online.

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