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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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 specified 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.
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.
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* (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 (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%     |
| IMDC distribution        | Favorable 18.8%* 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%* <1%: 60.3%      | ≥1%: 63.2%* <1%: 28.4% Unknown: 8.3% | ≥1%: 57.5%* <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%* <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                      | 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 2. SUCRA values of different treatments for all outcomes in patients with metastatic renal cell carcinoma.

| Study type | 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+ (NEJM 2021) |
|------------|-----------------------------|---------------------------------|--------------------------------|--------------------------------|----------------------------|---------------------|
| RR (CR)    | 43% (9%) versus 35% (4%) [PD-L1+] | 55.9% (5.6%) versus 27.2% (2.4%) [PD-L1+] | 60.2% (8.8%) versus 39.9% (3.0%) | 41.9% (10.4%) versus 26.8% (1.4%) [I-P risk] | 55.7% (8%) versus 27.1% (4.6%) | 71.0% (16.1%) versus 36.1% (4.2%) |
| Number of patients enrolled | 915 | 886 | 861 | 1096 | 651 | 712 |
| Previous nephrectomy | 74% versus 72% | 80% versus 80% | 83% versus 84% | 80% versus 76% [I-P risk] | 69% versus 71% | 74% versus 77% |
| IMDC distribution | Favorable 18.8% | Intermediate 64.1% | Poor 17.1% | Favorable 21.4% | Intermediate 61.7% | Poor 16.1% | 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% |
Table 2. (Continued)

| Study                | 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+ (NEJM 2021) |
|----------------------|----------------------------|-----------------------------------|---------------------------------|--------------------------------|--------------------------|-------------------|
| Tumor PD-L1 expression | ≥1%: 39.7%*<br> <1%: 60.3% | ≥1%: 63.2%<br> <1%: 28.4%<br> Unknown: 8.3% | ≥1%: 57.5%<br> <1%: 37.3%<br> Unknown: 5.2% | ≥1%: 25.3% [I-P risk]<br> 21.9% [ITT]<br> <1%: 66.3% [I-P risk]<br> 69.5% [ITT]<br> Unknown: 8.4% [I-P risk] – 8.6% [ITT] | ≥1%: 25.5%<br> <1%: 74.5%<br> Unknown: 38.1% | ≥1%: 31.7%<br> <1%: 30.2%<br> Unknown: 38.1% |
| No. of sites of lesions | Not reported | Not reported | 1: 24.4%<br> 2: 75.0%<br> Unknown: 0.6% | 1: 20.5% [I-P risk]<br> 21.9% [ITT]<br> 2: 79.5% [I-P risk] – 78.1% [ITT] | 1: 20.3%<br> 2: 79.1%<br> Unknown: 0.6% | 1: 28.8%<br> 2: 70.2% |
| Liver metastases | 17.4% [PD-L1 +]<br> 17.5% [ITT] | Not reported | 15.9% | 20.9% [I-P risk]<br> 18.8% [ITT] | 19.3% | 16.9% |
| Bone metastases | 20.2% [PD-L1 +]<br> 19.7% [ITT] | Not reported | 23.9% | 22.7% [I-P risk]<br> 21.1% [ITT] | 23.0% | 25.6% |
| Sarcomatoid features | 23.8% [PD-L1 +]<br> 15.5% [ITT] | Not reported [PD-L1 +]<br> 12.2% [ITT] | 12.2% | 16.4% [I-P risk]<br> 13.2% [ITT] | 11.5% | 6.9% |
| Median PFS (months) | 11.2 versus 7.7<br> [PD-L1 +]<br> 11.2 versus 8.4 [ITT] | 13.8 versus 7.0<br> [PD-L1 +]<br> 13.3 versus 8.0 [ITT] | 15.4 versus 11.1 | 11.2 versus 8.3 [I-P risk]<br> 12.2 versus 12.3 [ITT] | 16.6 versus 8.3 | 23.9 versus 9.2 |
| Median OS (months) | 34.0 versus 32.7<br> [PD-L1 +]<br> 33.6 versus 34.9 [ITT] | NR versus 28.6<br> [PD-L1 +]<br> NR versus NR [ITT] | NR versus 53.7 | 48.1 versus 26.6<br> [I-P risk]<br> NR versus 38.4 [ITT] | NR | NR versus NR |
| RR (ICR) | 43% [9%] versus 35% [4%]<br> [PD-L1 +]<br> 37% [5%] versus 33% [2%] [ITT] | 55.9% [5.6%]<br> versus 27.2% [2.4%]<br> [PD-L1 +]<br> 52.5% [3.8%]<br> versus 27.3% [2.0%] [ITT] | 60.2% [8.8%]<br> versus 39.9% [3.0%] | 41.9% [10.4%]<br> versus 26.8% [1.4%]<br> [I-P risk]<br> 39.1% [10.7%]<br> versus 32.4% [2.6%] [ITT] | 55.7% [8%]<br> versus 27.1% [4.6%] | 71.0% [16.1%]<br> 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.

* Lenvatinib + everolimus arm was not considered.
* Follow-up for overall survival.
* IMDC distribution available for PD-L1-positive patients.
* PD-L1 expression measured on tumor-infiltrating immune cells.
* 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
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/tolerance 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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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.

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