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Article

Comparative efficacy of first-line immune-based combination therapies in metastatic renal cell carcinoma. A systematic review and network meta-analysis.

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Abstracts: Background: Three drug-combinations, ipilimumab-nivolumab (Ipi-Nivo), pembrolizumab-axitinib (Pembro-Axi) and avelumab-axitinib (Ave-Axi), have received regulatory approvals in USA and Europe for the treatment of metastatic renal cell carcinoma with clear cell component (mRCC). However, no head-to-head comparison data are available to identify the best option. Therefore, we aimed to compare these new treatments in the first-line setting. **Methods**: We conducted a systematic search in Pubmed, the Cochrane library and clinicaltrial.gov website from January 2015 to October 2019, for any randomized controlled trials of treatment-naïve patients with mRCC. The process was performed according to PRISMA guidelines. We performed a Bayesian network meta-analysis with two different approaches. The outcomes for analysis were overall survival, progression-free survival, and objective response rate. **Results**: Our search identified 3 published phase 3 randomized clinical trials (2835 patients). In the contrast-based model, Ave-Axi (SUCRA: 83%) and Pembro-Axi (SUCRA: 80%) exhibited the best ranking probabilities for PFS. For OS, Pembro-Axi (SUCRA: 96%) was the most preferable option against Ave-Axi and Ipi-Nivo. Objective response rate analysis showed Ave-Axi as the best (SUCRA= 94%) and Pembro-Axi as second best option. In the parametric models, risk of progression was comparable for Ave-Axi and Ipi-Nivo, whereas Pembro-Axi exhibited a lower risk during the first 6 months of treatment and a higher risk afterward. Furthermore, Pembro-Axi exhibited a net advantage in terms of OS over the two other regimens, while Ave-Axi was the least preferable option. **Conclusions**: Overall evidences suggested pembrolizumab plus axitinib may be the best option.

Keywords: metastatic renal cell carcinoma; immune-based combination therapies; network meta-analysis

1. Background

In the past few years, the treatment for metastatic renal cell carcinoma with clear cell component (mRCC) has drastically changed with the introduction of targeted therapy, immunotherapy and a better understanding of RCC biology.[1-4] So far, the first-line and second-line systematic thera-

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py for mRCC have been mainly composed of agents targeting the vascular endothelial growth factor receptor (VEGFR) and inhibiting the mammalian target of rapamycin (mTOR), with the last in class being axitinib and cabozantinib.[5-6] Currently, drug development in mRCC focuses on immune checkpoint inhibitors (ICI), targeting programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1) pathway or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[7] Four combinations have demonstrated either PFS or OS improvement over the VEGFR tyrosine kinase inhibitor (TKI) standard of care (SOC) sunitinib in the first-line setting for advanced or metastatic RCC with clear cell component: nivolumab (anti PD-1) plus ipilumumab (anti CTLA-4),[8] pembrolizumab (anti PD-1) plus axitinib (VEGFR-TKI),[9] avelumab (anti PD-L1) plus axitinib,[10] and atezolizumab (anti PD-L 1) plus bevacizumab (anti-VEGF).[11]

The shift in systemic therapy of mRCC has just begun and phase 3 results with these new available combinations raise many questions that need to be addressed in order to better use them in clinical practice are available,. In addition, we still lack the predictive biomarkers and prognostic characteristics in patients or the disease to guide treatment allocation. Results of these phase 3 trials should be interpreted in the context of this International Metastatic RCC Database Consortium (IMDC) risk classification, which has proven its utility since the targeted therapy era, .[12,13]

Comparison between these therapeutic options is one of the main concerns for clinicians and patients.[14] However, since no clinical trial has provided any head-to-head comparison data of these combinations, we conducted a network meta-analysis (NMA) to indirectly compare their efficacies in terms of progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) in the first-line setting for patients with mRCC.

2. Methods

2.1. Search strategy and selection criteria

We specifically focused on randomized controlled trials (RCT) including naïve-treatment patients with mRCC with clear cell component who received one of the combinations involving ICIs in the first-line setting and no patient restrictions on PD-L1, nor IMDC subgroup. The study was conducted based on PRISMA extended guidelines for network meta-analysis,[15]. We performed a systematic literature search for any article or abstract, in Pubmed, the Cochrane library, clinicaltrial.gov website and ESMO or ASCO congress from January 2015 to August 2019 (full search strategy detailed in supll. Page 6). References of relevant articles were checked to ensure no combination with ICI was missed. If several data reports were available from the same trial, we retained the latest updated source. The outcomes were PFS, OS and ORR in the intention-to-treat population, then per IMDC subgroups. Hazard ratios (HR), their 95% IC intervals and Kaplan-Meier curves (when available) were extracted for PFS and OS. Response rate in each study arms were extracted for ORR.

The whole process of trial selection, full text screening, and data extraction were performed by two investigators (R-E, L-P) independently and if disagreement occurred, it was resolved by discussion with other investigators. For all selected studies, risk of bias was assessed with the Cochrane handbook tool.[16]

2.2. Statistical analysis

We used two different approaches, a contrast-based method comparing the relative treatment effect in the intention-to-treat population and in IMDC subgroups, and an arm-based method using Kaplan-Meier curves to estimate the parametric survival model, in the ITT population only. We performed both fixed effect and random effect model for the contrast-based approach. To assess which treatment is likely to be the best option, we used rank probabilities and the surface under the cumulative ranking curve (SUCRA)[17] in the contrast-based NMA model and assessed time-dependent HRs derived from the arm-based NMA approach. Additionally, an exploratory analysis of the PFS of sarcomatoid carcinoma patients was performed to investigate the recently observed benefit of these combinations in this subpopulation.

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2.2.1. Contrast-based approach

This approach focused on relative effects using HR on a log scale to run an NMA model as described in Dias 2013.[19]

2.2.2. Arm-based approach

To circumvent the apparent violation of the proportional hazard assumption of Cox model in the published PFS Kaplan-Meier curves of the Checkmate 214 study [8], we also considered a method relying on time dependent HRs. We used fractional polynomial to estimate parametric functions from Kaplan-Meier curves in a Bayesian hierarchical model.[21, 22]

Statistical analyses were all performed within a Bayesian framework. Credible intervals were all reported at the 95% level. The contrast-based analysis was performed using R (version 3·6·0) and JAGS (version 4·3·0) with the package "getmtc" (version 0·8-2),[18] and Openbugs (version 3·2·3). Kaplan-Meier curves were reconstructed using GetData Graph Digitizer (version 2·26).

2.3. Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

Our search identified 72 results, of these, three published phase 3 randomized clinical trials matched our selection criteria (2843 patients, flowchart Figure 1) : the Checkmate 209-214[8], the Keynote 426[9] and the Javelin renal 101[10], evaluating three different combinations, nivolumab plus ipilimumab (Ipi-Nivo), pembrolizumab plus axitinib (Pembro-Axi) and avelumab plus axitinib (Ave-Axi) respectively (detailed search in Appendix page 6). The Immotion 151 trial (atezolizumab plus bevacizumab) was excluded due to non-superiority of OS compared to sunitinib in the intention-to-treat population. Therefore, it is unlikely that this combination will be a recommended treatment in a near future. In the three retained trials, the combination was compared to sunitinib (star-shaped network), which was the common comparator (trials characteristics are provided in Table 1). Risk of bias for each trial was considered acceptable in view of the Cochrane assessment grid (Table S1). Data sources for all the analysis are provided in table S2.

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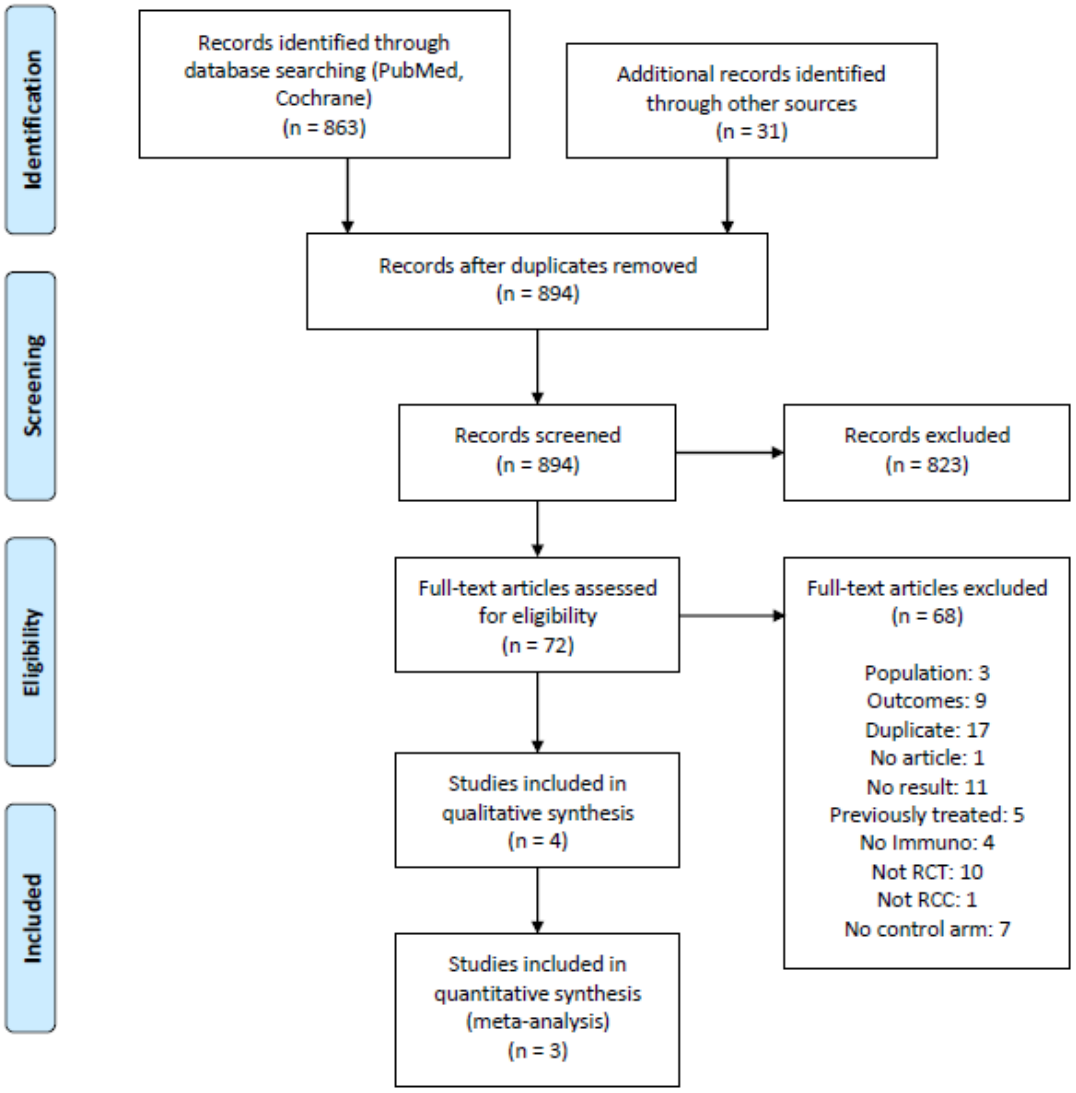

Figure 1. Flowchart of the systematic search. PRISMA Flow diagram.

Table 1. Outcomes reported in each trial of the network. NR = Not reached.

Study	Traitement	Number of patient	ORR (95% CI)	Median OS (Months)	Median PFS (Months)	HR OS (95% CI)	HR PFS (95% CI)
Checkmate 214	Sunitinib	546	32% [28-36]	37.9	12,3	-	-
	Nivo + Ipi	550	39% [35-43]	NR	12,4	0.71 [0.59 – 0.86]	0.85 [0.73 – 0.98]
Keynote 426	Sunitinib	429	35.7% [31-40]	NR	11,1	-	-
	Pembro + Axi	432	59% [54-64]	NR	15,1	0.53 [0.38 – 0.74]	0.69 [0.57 – 0.84]
Javelin Renal 101	Sunitinib	444	25% [22-30]	NR	8,4	-	-
	Ave + Axi	442	51% [47-56]	NR	13,8	0.78 [0.55 – 1.08]	0.69 [0.56 – 0.84]

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3.1. Contrast-based approach in intention-to-treat population

Both Pembro-Axi and Ave-Axi showed similar efficacy for PFS (HR: 1·00 [0·68–1·50]). However, the Ipi-Nivo combination was less efficient (HR: 0·81 [0·57–1·20]) compared to Ave- Axi or Pembro-Axi (HR: 0·82 [0·58–1·20]). Ranking suggested Ave-Axi as the best option (SUCRA = 83%) and Pembro-Axi as the second one (SUCRA = 80%), but the difference was not clinically relevant (Table S3). For OS, NMA suggested Pembro-Axi (SUCRA = 96%) had better efficacy than Ave-Axi or Ipi-Nivo (HR: 0·68 [0·35–1·30], HR: 0·75 [0·44–1·30] respectively). Similarly, for ORR, NMA suggested that Ave-Axi (SUCRA= 94%) was the most preferable option compared to Pembro-Axi or Ipi-Nivo (odds ratio (OR) 0·81 [0·46–1·40], OR: 0·44 [0·27-0·72] respectively). These results are summarized in the form of forest-plots for indirect comparisons (Figure 2A) and direct comparisons (Figure S1) for ITT population and per IMDC.

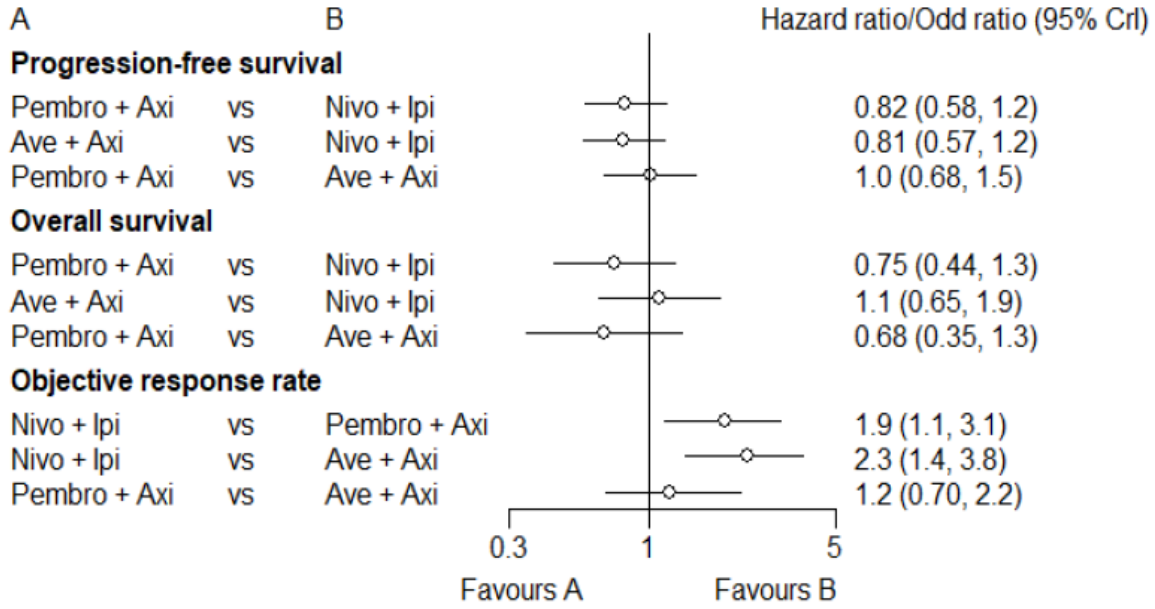

Figure 2. Indirect comparison upon contrast-based NMA (fixed effect) in the ITT population. Forest plot of the indirect comparison between each combination for the 3 outcomes in the ITT population. For the objective response rate, the odd ratio favoring treatment B means that treatment A has a lower response rate than treatment B.

Fixed effect and random effect models yielded similar results, with larger credibility interval for the random effect model (Figure S2 and Table S3). Sensitivity analysis, either adding the fourth combination atezolizumab plus bevacizumab or using slightly informative priors, provided very close results with an unchanged rank order for the three combinations of the main analysis (Figure S3).

3.2. Contrast-based approach by IMDC subgroup

The IMDC subgroup analysis was performed only for PFS and ORR, since OS data were immature with many censored patients from Javelin renal 101 trial. We pooled the intermediate and poor IMDC risk subgroups to match Checkmate 214 results with the other trials. Patient proportion in each subgroup is reported in Table 2. In the IMDC favorable risk group, Ave-Axi turned out to be superior to Pembro-Axi (HR for PFS: 0·67 [0·26–1·70], ORR: 1·8 [0·69–4·60]) and to Ipi-Nivo (HR for PFS: 0·44 [0·19–1·00], ORR: 5·6 [2·40–13·00]). In the intermediate and poor risk groups, Pembro-Axi and Ave-Axi were the two best options and compared favorably to Ipi-Nivo (Pembro-Axi: HR for PFS: 0·87 [0·58–1·30], OR: 1·1 [0·76–1·70], Ave-Axi: HR for PFS: 0·91 [0·58–1·40], OR: 1·7 [1·10–2·70]). The three combinations exhibited striking differences in the favorable risk group compared to the

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ITT analysis, in terms of treatment effect despite enlarged credibility intervals (Figure 3, A and B). Fixed effect and random effect models yielded similar results (Figure S2 and Table S3).

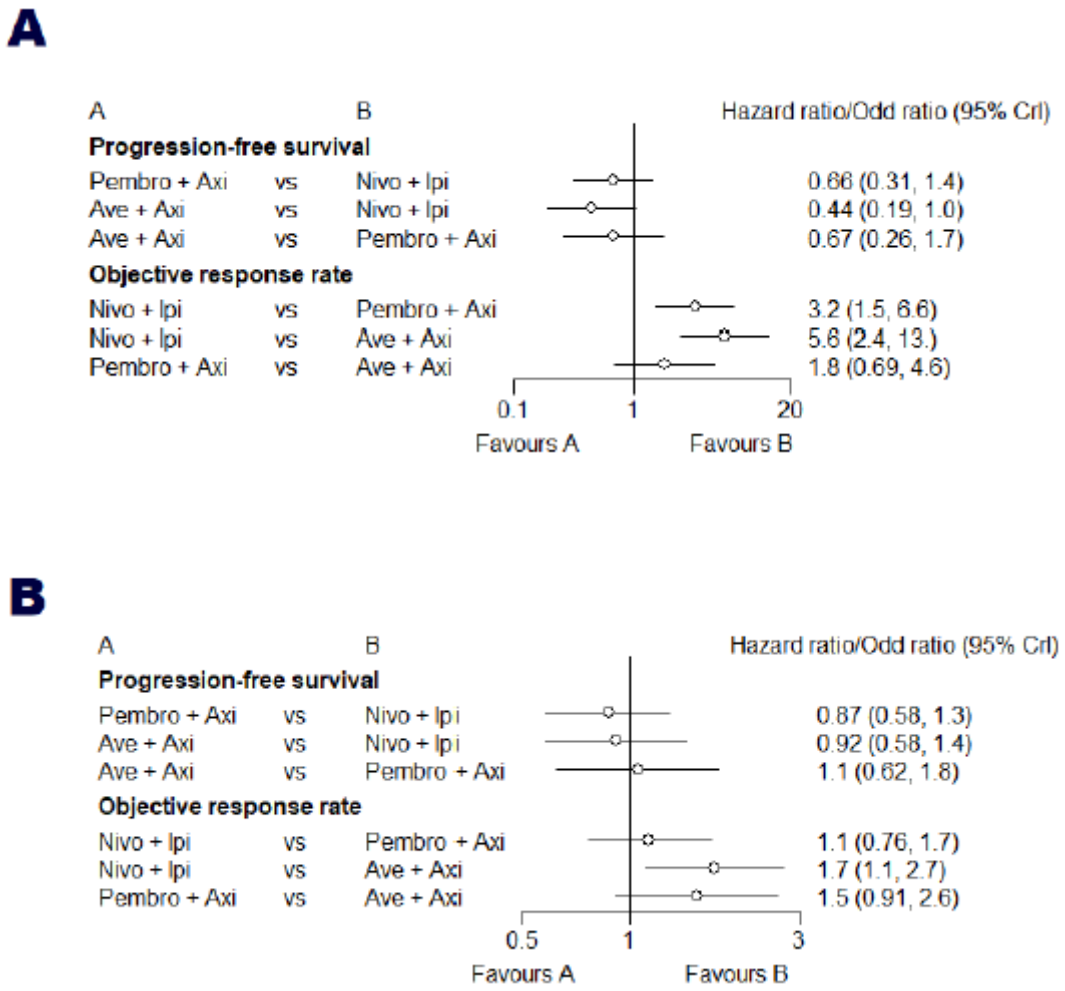

Figure 3. Indirect comparison upon contrast-based NMA (fixed effect) per IMDC subgroup. Forest plot of the indirect comparison between each combination for the 3 outcomes in IMDC subgroups. For the objective response rate, the odd ratio favoring treatment B means that treatment A has a lower response rate than treatment B.

Table 2. – Summary data in each IMDC subgroup.

Trial	Treatment	Favorable prognosis			Intermediate and poor prognosis		
		N (%)	HR IC 95%	ORR IC 95%	N (%)	HR IC 95%	ORR IC 95%
Checkmate 214	Sunitinib	124 (23)		50%	424 (77)		29%
	Nivo + Ipi	125 (23)	1.23 [0.90 - 1.69]	39%	423 (77)	0.77 [0.65 - 0.90]	42%
Keynote 426	Sunitinib	131 (31)		49.6%	298 (69)		29.5%
	Pembro + Axi	138 (32)	0.81 [0.53 - 1.24]	66.7%	294 (68)	0.67 [0.53 - 0.85]	55.8%
Javelin Renal 101	Sunitinib	96 (22)		37%	347 (78)		22.5%
	Ave + Axi	94 (22)	0.54 [0.32 - 0.91]	68.1%	343 (78)	0.70 [0.53 - 0.94]	46.9%

Note: the sum of patients in the (reported) subgroup analysis was different from the overall number of patients reported in articles.

3.3. Arm-based approach

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Among the different models tested, a Weibull model offered the best compromise between fit and complexity.

3.4. Progression-free survival in intention-to-treat population

The time-dependent HR of the drug combinations vs sunitinib clearly suggest a violation of the main assumption of proportional hazards in the three trials mainly for OS and especially in the Checkmate 214 trial for both OS and PFS (Figure 4A). Risk of progression was higher with Ipi-Nivo compared to other combinations during the first 15 months, and then this difference vanished past this time point. Pembro-Axi and Ave-Axi exhibited close HR over the follow-up period; we considered that the seemingly different curves of time-dependent HR (increasing Pembro-Axi vs decreasing Ave-Axi) were more a consequence of the models parameters than a real difference in combinations effects (See parameter estimations Table S4).

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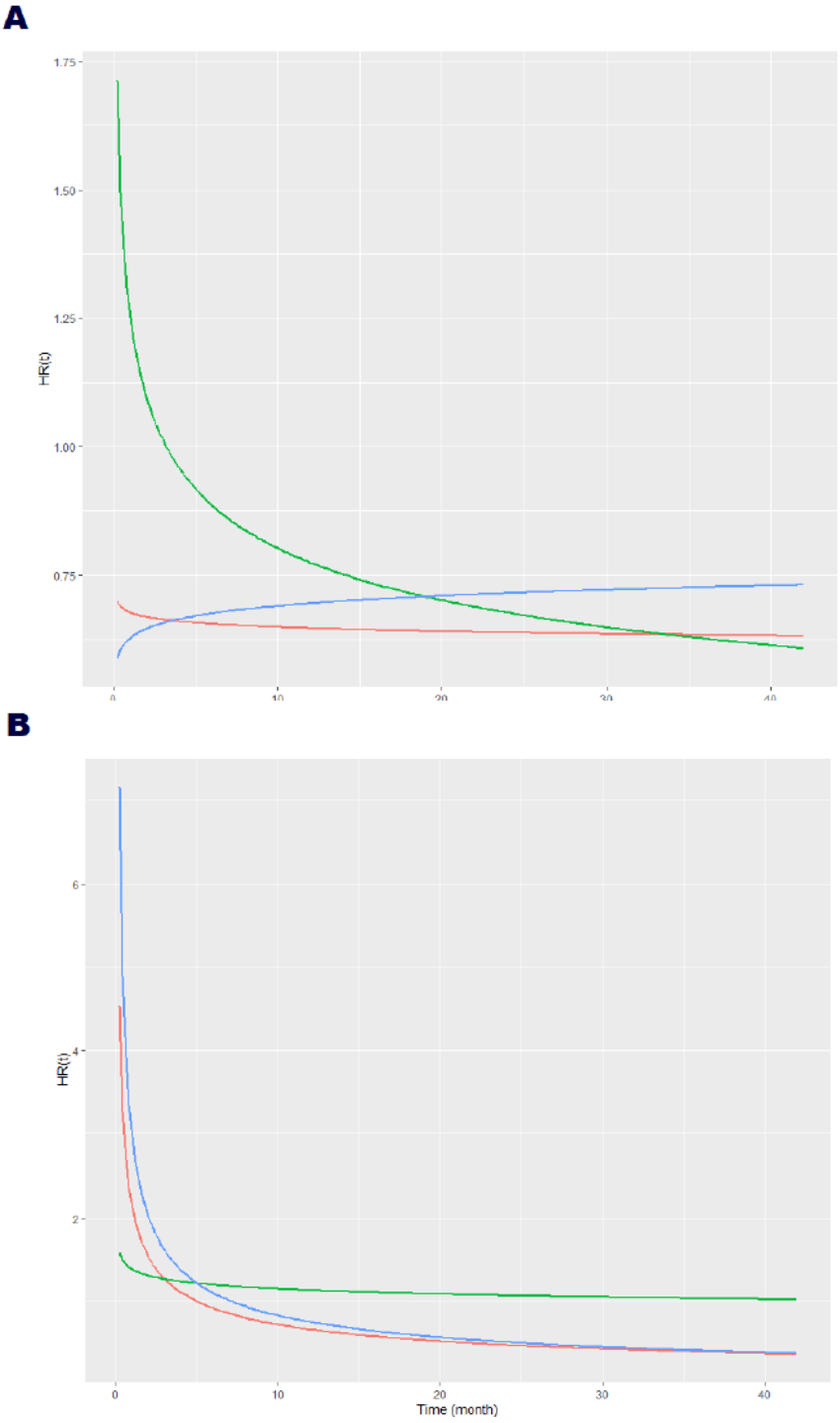

Figure 4. Time-dependent HRs for progression-free survival. A: time-dependent hazard ratio vs sunitinib**.** B: time-dependent hazard ratio between combinations.

The aim of this study was to provide an indirect comparison of the three combinations. We allowed sunitinib effect to be different across studies instead of arbitrarily taking a mean effect, accounting for variability of sunitinib effect observed in the different control arms. Benefit was in favor of Pembro-Axi over Ave-Axi and Ipi-Nivo during the first 5-7 months of treatment, which reversed afterward. Ipi-Nivo and Ave-Axi displayed a comparable benefit with, as in Figure 4B, a higher risk of progression for Ipi-Nivo at the beginning of the treatment period.

3.5. Overall survival in intention-to-treat population

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The time-dependent HR curves for OS suggested that all three drug combinations have comparable time effects on OS (Figure 5A). We also showed that for each trial, the computed mean HR across the follow up period exhibited fairly same estimates as in the contrast-based approach, and close to published HRs, which established the coherence between the two methods and conferred robustness to our results.

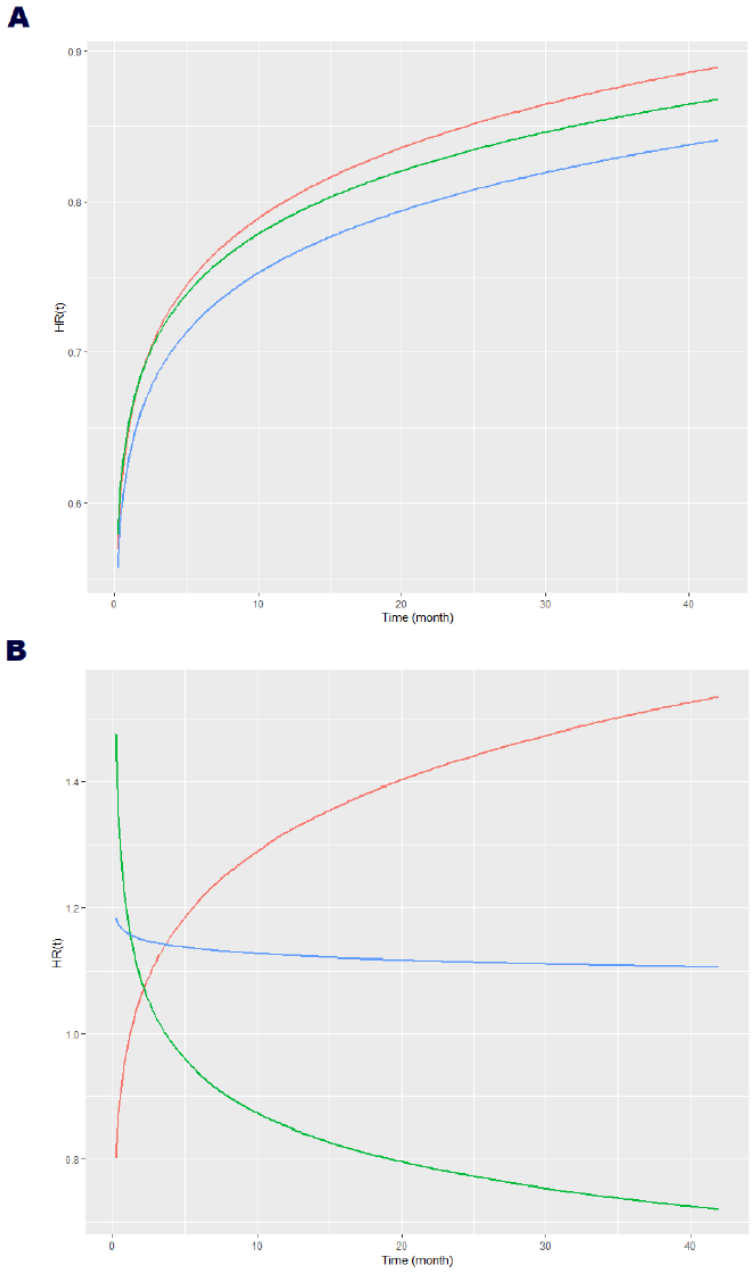

Figure 5. Time-dependent HRs for overall survival. A: time-dependent hazard ratio vs sunitinib. Red: Ave-Axi vs sunitinib, green: Ipi-Nivo vs sunitinib, Blue: Pembro-Axi vs sunitinib. B: time-dependent hazard ratio between combinations. Red: Ave-Axi vs Pembro, green: Ipi-Nivo vs Ave-Axi, blue: Ipi-Nivo vs Pembro.

The main observations resulting from the indirect pairwise comparison of the three combinations suggested a higher risk of death with Ipi-Nivo compared to Pembro-Axi throughout the study period (Figure 5B). The higher risk of death of Ipi-Nivo compared to Ave-Axi was only observed during the first 3 months, which decreased afterward. Pembro-Axi appeared as a better option compared to Ave-Axi, during the whole follow-up period (See parameter estimations Table S4).

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3.6. Exploratory analysis of PFS in sarcomatoid patients.

Upon indirect comparison, there was no significant difference between the trials suggesting that these patients may respond well to all combinations (Figure 6) with all HRs close to 1.

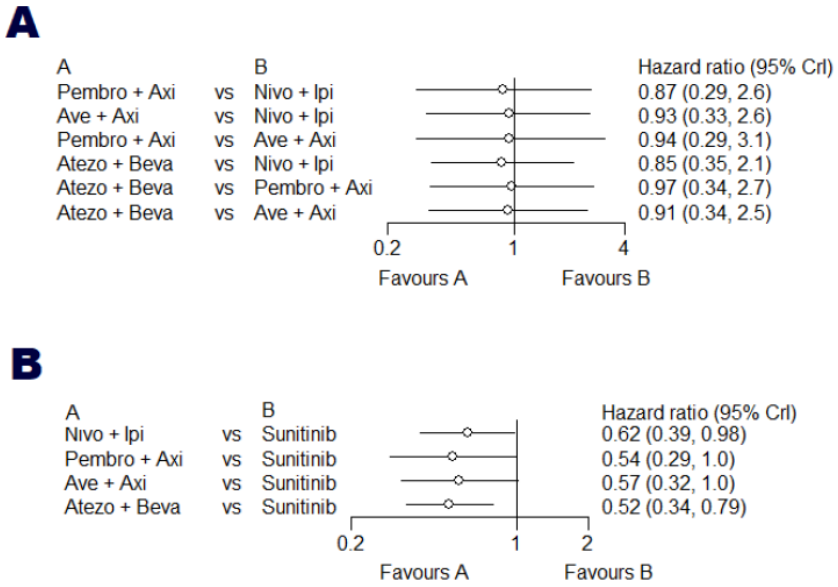

Figure 6. Forest plot of PFS in the sarcomatoid carcinoma population. A: direct comparisons. B: indirect comparisons.

4. Discussion

The three combinations considered in this study may soon become new standards of care in the first-line setting for mRCC, without any clear rationale to prefer one over the other. We aimed to fill this knowledge gap by conducting indirect comparisons and thus, hopefully provide clinicians critical aid in decision-making.

Network meta-analysis is a powerful and flexible method to compare multiple different therapeutic strategies. To our knowledge, few NMAs have been published in mRCC first-line setting. Andrew W. Hahn et al. concluded that cabozantinib, Pembro-Axi and Ave-Axi were preferable for PFS and Pembro-Axi appeared superior for OS in first-line mRCC.[23] But their network included twelve different treatments and highly heterogeneous populations. A recent study by Wang et al. included all available first-line options representing no less than twenty-five heterogeneous studies to conclude that Pembro-Axi was a preferred option with regards to OS whereas cabozantinib was better with regards to PFS.[24] However, in the last study included, HRs were compared assuming sunitinib had a same effect across the different trials, which did not reflect actual/observed data/results.

However, our approach significantly differs from these studies: we specifically focused our comparison on the efficacies of the three combinations with immune checkpoint inhibitors that have demonstrated a benefit in phase 3 trials, i.e. the drug combinations more likely to obtain a high-grade recommendation from academic societies and an approval from Health Authorities. We used most recent data (up to August 2019) and employed both fixed and random effect models. Moreover, we used two different approaches to assess these different therapeutic options: a contrast-based and an arm-based approach. In our arm-based approach, we relaxed the assumption of a common effect of sunitinib to best model the actual trial differences. We also looked for models that may take into account various confounding factors such as the between-study unbalanced prognostic risk groups, and be sufficiently flexible to model the complexities of these new combinations, for example adding a covariance term to model the presence of axitinib in both CPI-TKI combinations, and/or combine PFS and OS in a same model.

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In our study, we compared three large multicenter phase 3 randomized controlled trials which included 2843 patients in total. In the contrast-based approach, for the OS rate in the ITT population, Pembro-Axi was found to be the best option, whereas Pembro-Axi and Ave-Axi showed comparable efficacy for PFS, and Ave-Axi showed the best ORR efficacy. On the other hand, in the IMDC favorable risk group, Ave-Axi showed most favorable results for PFS. Contrast-based approach for both PFS and OS led to results close to what was reported in each independent updated study, due to the fact that only one study was available for each comparison and that we decided upon non-informative priors for treatment effects, i.e. no influencing data. In the arm-based approach, in the ITT population, Pembro-Axi seemed to be a preferable option only for the OS. We also observed that during the first 5 months of therapy, IO-TKI combinations exhibited a lower risk of progression compared with IO-IO combination; however, Ipi-Nivo exhibited longer PFS in patients who did not progress during the first 5 months. This may be partially related to pseudo progression induced by the double IO combination while having a high rate of complete response for the remaining patients in the checkmate 214 trial.

Our study has both strengths and limitations. First, we focused on the new promising regimens, with results from published phase III randomized clinical trials, in order not to inflate population and design heterogeneity. Second, we used two different but complementary approaches for more consistent results: the contrast-based approach, which uses HRs as a relative treatment effects, maintains the randomization structure within each study but requires strong assumptions. Arm-based approach is likely to relax these assumptions but the disadvantage is that it does not preserve the randomization structure. Moreover, in the contrast-based approach, HRs derived from Cox model rely on the assumption of proportional hazards which is commonly violated in many trials leading to biased estimates. Arm-based methods do not rely on HR but need parametric fit of KM curves. Third, combinations may have more complex mechanisms of action than monotherapies, and to this end arm-based methods provide time-dependent HR, interpretations of which may help to decipher such mechanisms better than constant HR and decide which combination may be the best and when. One main limitation is the overall lack of data, which may reflect in potential uncontrolled bias; more studies comparing these regimens and/or individual patient data would be needed in order to improve precision and heterogeneity estimations. These additional data would also allow us to test for inconsistency (confirm concordance between direct and indirect comparisons), which was not possible in our current star-shaped network. IMDC subgroups and geographic regions may be other confounding factors across comparison; more studies are needed to adjust the NMA model and confirm our findings. We tried more complex multivariate NMA to account for HRs per IMDC subgroup in one single model, but lack of data for OS in each risk group prevented us from refining the final model. It could also have been relevant to consider PD-L1 expression which may have differently influenced the PFS of the combinations, but given the different assays and thresholds used in each study, we could not proceed. Regarding toxicity, NMA using only counts of grade $\geq$3 events was too broad to efficiently compare toxicity between trials. Lastly, OS and possibly ORR data in Javelin renal 101 trial were still immature at time of analysis, thus Ave-Axi combination ranking may change with longer follow-up. Despite a comparable median follow-up, Pembro-Axi exhibited superiority in terms of OS, whereas Ave-Axi surprisingly did not; our indirect comparison was indeed in favor of Pembro-Axi, but more updates and trials would be needed to further investigate this difference. Therefore, results of our study should be interpreted cautiously given underlying hypothesis and potential bias of estimated effects.

Clinicians have concerns about sequencing and identifying predictive biomarkers. More follow-up and reported data from patients in second-line after IO-TKI and IO-IO combinations may be of great help to guide decisions about the line of treatment. Our NMA model can grow with each new trial to help decision-making. Other trials results are awaited, comparing Pembrolizumab plus lenvatinib vs Everolimus plus lenvatinib vs sunitinib (CLEAR, NCT02811861), triplet cabozantinib plus nivolumab plus ipilimumab vs nivolumab plus ipilimumab (COSMIC-313, NCT03937219), and nivolumab plus cabozantinib vs cabozantinib plus nivolumab plus ipilimumab vs sunitinib

(checkmate 9ER, NCT03141177). Personalized therapy driven trials based on molecular profiling such as the BIONIKK trial (NCT02960906) may also provide new insights for clinical decision.

5. Conclusions

Our results support the importance of IMDC risk score for the comparative efficacy assessment of new combinations in the first-line setting of metastatic clear-cell renal cell carcinoma. This is of importance given the lack of predictive validated biomarker. Our results suggest a PFS, ORR and OS superiority of IO-TKI- compared with IO-IO combinations regardless of the IMDC risk group. In favorable risk-group patients, PFS and OS were superior with IO-TKI, but these differences vanished in the intermediate/poor risk group. Overall, based on our evidence, pembrolizumab-axitinib may be the best option in this setting.

Competing interests: RE: no competing interests; **LP**: no competing interests; **DB**: consulting fees, travel support from BMS, PFIZER, IPSEN, IPSEN, ROCHE; **PB**: consulting fees, travel support from BMS, MSD, PFIZER, IPSEN, ROCHE, EUSAPHARMA; **AR**: BMS, MSD, PFIZER, MERCK, IPSEN, ROCHE; **SO**: consulting fees, travel support and honorarium from SANOFI, ASTELLAS, JANSSEN, MERCK; **YV**: travel support and honorarium from BMS, MSD, PFIZER, NOVARTIS, IPSEN, JANSSEN, ROCHE, SANOFI.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Forest plot for direct comparisons in the ITT population (A) and per IMDC subgroup (B). (Online only), Figure S2: Forest plot from the random effect model in the ITT population (Online only), Figure S3: Forest plot with added Atezo + Beva combination in the ITT population (Online only), Table S1: Bias assessment risk for the 3 selected studies of the network (Online only), Table S2: Sources of all data extracted (Online only), Table S3: Ranking from PFS, OS and ORR in the ITT population – contrast-based approach (Online only) and Ranking from PFS and ORR - contrast-based approach (Online only), Table S4: Parameter estimation of the arm-based Weibull model for progression-free survival and overall survival (Online only).

Authors' contributions: RE and **YV**: initiated the research; **RE**: designed the research; **RE** and **LP**: performed the statistical analysis; **RE, LP, DB, PB, AR, SO** and **YV**: writing, interpretation and critical revisions of the article. All authors gave final approval to the version submitted.

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Conflicts of Interest: The authors declare no conflict of interest

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