Meta-analysis of perioperative immunotherapy in renal cell carcinoma: Available but the jury is still out.

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Introduction

Surgical management of renal cell carcinoma (RCC) often provides a curative treatment in most patients. The prognosis of these patients varies greatly between stages and several additional risk factors have been identified(1). In oligometastatic patients, a surgical approach to the primary tumor and the metastasis may also provide long-term control of the disease and even cure in a selected group of patients (2). However, patients with locally advanced RCC, patients with risk factors such as high nuclear grade or sarcomatoid features, and resected metastatic patients have a high risk of relapse following surgery. These patients may benefit from adjuvant treatment to improve their survival. Historical immunotherapy approaches such as interleukin 2 (IL-2), interferon α (IFN-α), and tumor vaccines did not show clinical benefit in the adjuvant setting (3). In the metastatic setting, modern immunotherapy agents (anti PD-1/PD-L1 alone or in combination with anti CTLA4) have shown greater response rates with a greater duration of response, and significant improvements in overall survival with a better safety profile, compared to tyrosine kinase inhibitors (TKI) alone (4–6). These benefits of immunotherapy, with a greater tolerability, may provide some advantages in the adjuvant context compared to TKIs. However, recent adjuvant trials with immune checkpoint inhibitors (ICI) have shown discordant results as happened previously with tyrosine kinase inhibitors (TKI). Treatment with pembrolizumab has shown a significant increase in disease-free survival (DFS) while atezolizumab, nivolumab, and ipilimumab-nivolumab have not shown differences in survival outcomes. These trials have substantial differences in design and included population, which may explain these results (7–10). There is a need to define the benefit/risk ratio of immune checkpoint inhibitors (ICI) in this setting to optimize their use.

Methods

Study was registered in PROSPERO database. The databases that were searched to identify relevant trials were MEDLINE and EMBASE. These databases were reviewed in September 2022 to identify phase 3 randomized controlled trials. Relevant abstracts presented in the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) were reviewed and included if all inclusion criteria and no exclusion criteria were met. Records other than the English language and other that randomized phase 3 clinical trials were excluded.

The systematic literature search was performed independently by the members of the review team and, after removing duplicates, the members of the review team screened

titles and abstracts to select eligible articles for full text review. Disagreements were resolved by discussion between the review members. Following data from each study were extracted: first author's name, study name, national clinical trial number (NCT), number of participants, inclusion criteria, treatment arms, oncologic outcomes, AE outcomes, and duration of follow-up.

Primary oncologic outcomes of interest were:

- Overall survival (OS): The length of time from the date of the start of treatment that patients are still alive.
- Relapse-free survival (RFS) or DFS: the length of time after primary treatment without any signs or symptoms of cancer.

The hazard ratio (HR) and 95% confidence interval (CI) associated with DFS and OS will be used as measures of effect.

Other secondary outcomes of interest that were recorded were the toxicities derived from treatment. As defined in CTCAE guidelines, an adverse event is any unfavorable or unintended sign (including abnormal laboratory values), symptom, or disease temporally associated with the use of a medical treatment or procedure. Different versions of the CTCAE are used to classify and grade adverse events (AEs) in trials:

- Any-grade AEs: Proportion of events independently of severity
- High-grade AEs: Includes only grade 3 (severe AE), grade 4 (life-threatening or disabling AE), and grade 5 (death related to AE)

Statistical analysis

All statistical analyses were performed using Stata® (version 16, StataCorp, College Station, Texas). The statistical heterogeneity assumption was assessed using Cochran's Q test based on χ^2 (considered significant at p-value < .05) and quantified with the I^2 statistic (with values <25%, 25%-75%, and >75% interpreted as representing low, moderate, and high levels of heterogeneity, respectively), and with τ^2 (between-study variance)obtained using the DerSimonian and Laird method.

HRs with CIs were the parameters considered assessing the impact on OS and DFS of treatment as compared to standard of care in the meta-analysis. On the other side, odds ratios (ORs) with CIs were used to compare the adverse events and severity of treatment as compared to the standard of care. I^2 statistics will be used to assess the study heterogeneity among the included trials. Random and fixed-effects models were used to pool study depending on the heterogeneity of the studies included. The results of the meta-analysis were displayed in foresplots.

Subgroup analyses were performed according to baseline characteristics:

- Non-metastatic vs. metastatic patients
- Sarcomatoid features
- Sex
- Age
- Type of nephrectomy

Risk of bias assessment

The risk-of-bias (RoB) evaluation of each study was assessed with The Cochrane Collaboration's tool for assessing RoB, the RoB2 tool (11). The bias of interest were randomization process bias, deviations from intended interventions bias, missing outcome data bias, measurement of the outcome bias, and reporting bias. The RoB of each study will be assessed independently by two authors. Bias studies will be illustrated using Risk-of-bias VISualization (robvis) webapp (12).

Results

Published results of 4 phase III trials of perioperative treatment with ICIs in RCC are included in this meta-analysis. Figure 1 represents the flow-chart selection of the trials included in the meta-analysis.

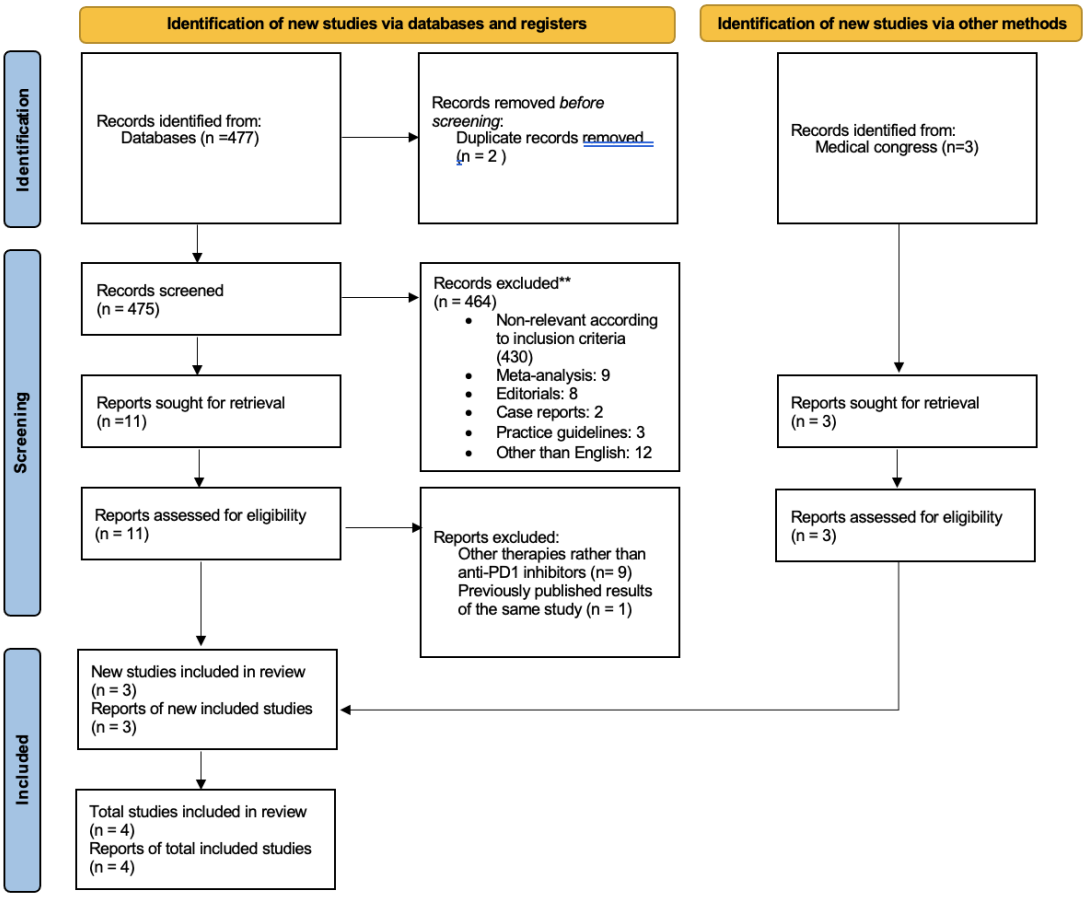

Figure 1: Flow-chart of the selection of trials included in the meta-analysis.

Table 1 summarizes the relevant characteristics of each study.

Study	NCT number	Main Author	Year	Population	N	Treatment arms (n)	Blinding
KEYNOTE-564	NCT03142334	Powles, T, Choueiri TK.	2022, 2021.	- IH: pT2G4 or S N0M0; pT3N0M0. - H: pT4N0M0; N+. - M1 NED†.	994	Pembrolizumab (496) vs. placebo (498)	Double
IMmotion-010	NCT03024996	Kumar Pal, S.	2022	- pT2G4, pT3a G3-4. - pT3b-c, pT4 any grade, N+. - M1 NED‡.	778	Atezolizumab (390) vs. placebo (388)	Double
PROSPER	NCT03055013	Allaf, M.	2022	- CC or non-CC. - ≥cT2, N any, M0. - M1 NED*.	805	Nivolumab (404) vs. observation (415)	None

CheckMate-914	NCT03138512	Motzer, R.	2022	- pT2aG3-4. - pT2b-pT4. - N1.	816	Nivolumab + Ipilimumab (405) vs placebo (411)	Double

Abbreviations: CC: Clear cell; G: Führman grade; H: High risk; IH: Intermediate-high risk; M1: Metastatic; N: number; N+: Node positive; NED: No evidence of disease; NCT: National Clinical Trials register; S: Sarcomatoid.
†: M1 NED definition: Metastatic disease was present in addition to the primary tumor at diagnosis, and metastases had to be completely resected at the time of nephrectomy or within 1 year after nephrectomy.
‡: M1 NED definition: Patients with synchronous metastatic disease to the adrenal gland or lung, or metachronous metastatic disease to the lung, lymph node, or soft tissue, with recurrence occurring more than 12 months following initial nephrectomy.
*: M1 NED definition: Metastatic disease planned to be resected or definitively treated with non-surgical techniques at the same time or up to 12 weeks after the date of the initial procedure.

In total, 3393 patients were included: 1695 patients received ICI (anti-PD1: 900 patients; anti-PD-L1 390 patients, antiPD1/anti-CTLA4 405 patients) whereas 1712 received no active treatment (1297 placebo, 415 observation). Figures 2 and 3 summarize the main results of the meta-analysis regarding DFS and OS.

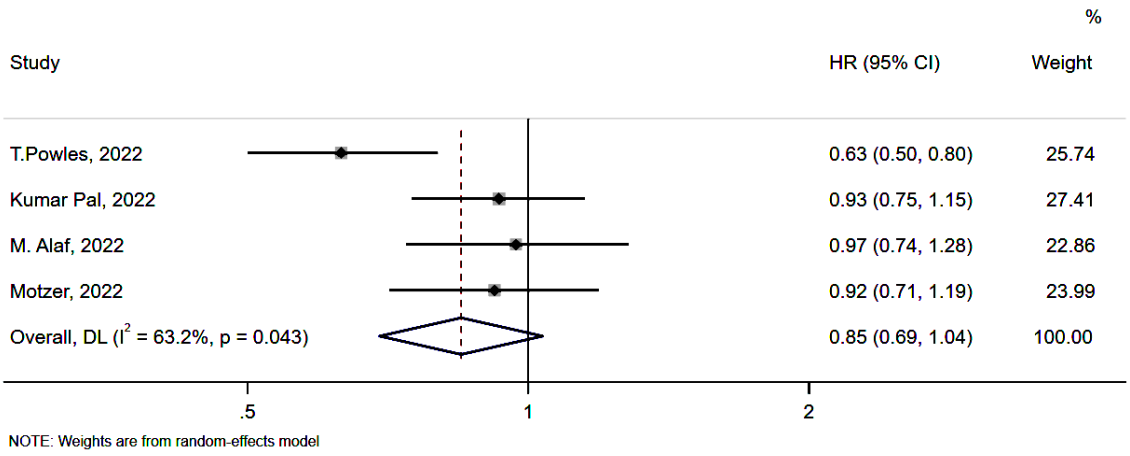

Figure 2. Meta-analysis results for DFS

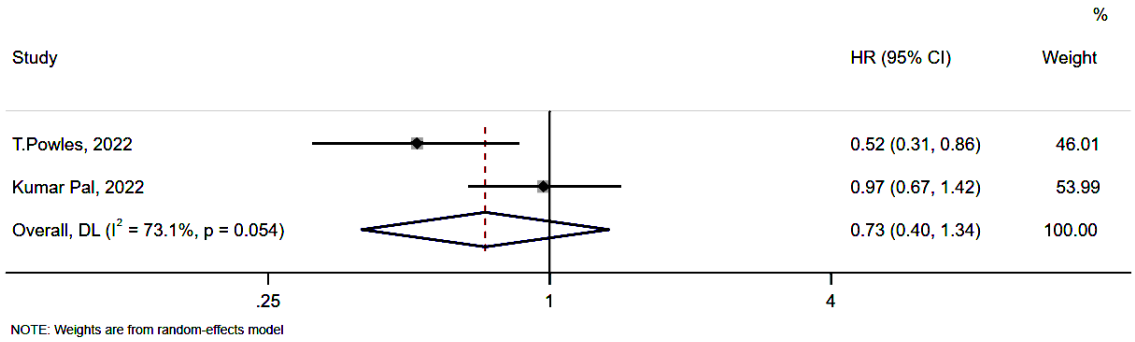

Figure 3: Meta-analysis results for OS.

No significant differences in DFS between treatment arms were noted [HR 0.847; 95%, confidence interval (CI) 0.693-1.036; p: 0.106]. No significant differences between treatment arms regarding OS were noted, although only two studies have provided OS data (HR 0.728; 95% CI 0.396-1.339; p: 0.307).

According to subgroup analysis, we noted significant differences in DFS favoring the experimental arm in females (HR: 0.72; 95 CI 0.557-0.931; p: 0.012), sarcomatoid features present in the tumor (HR: 0.597 95% CI 0.403-0.883; p: 0.010), and PD-L1 positive tumors (HR: 0.744; 95% CI 0.612-0.904; p: 0.003), which are reflected in figures 4, 5 and 6, respectively.

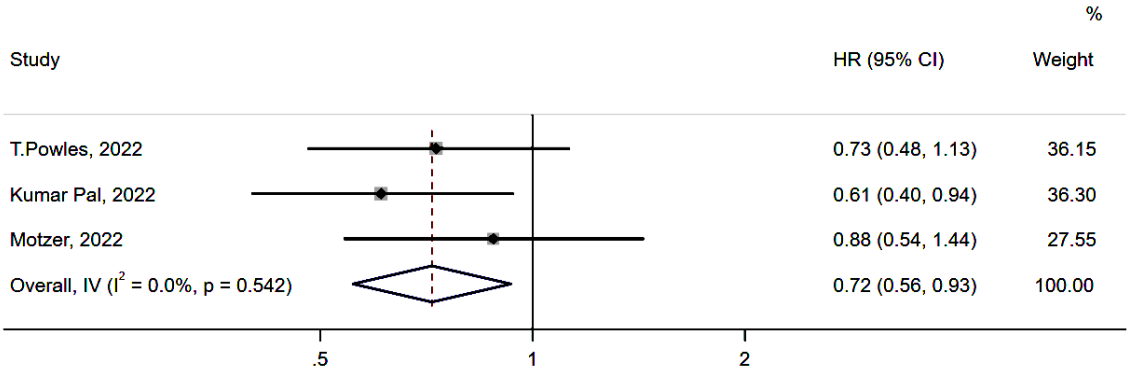

Figure 4: Subgroup analysis for females.

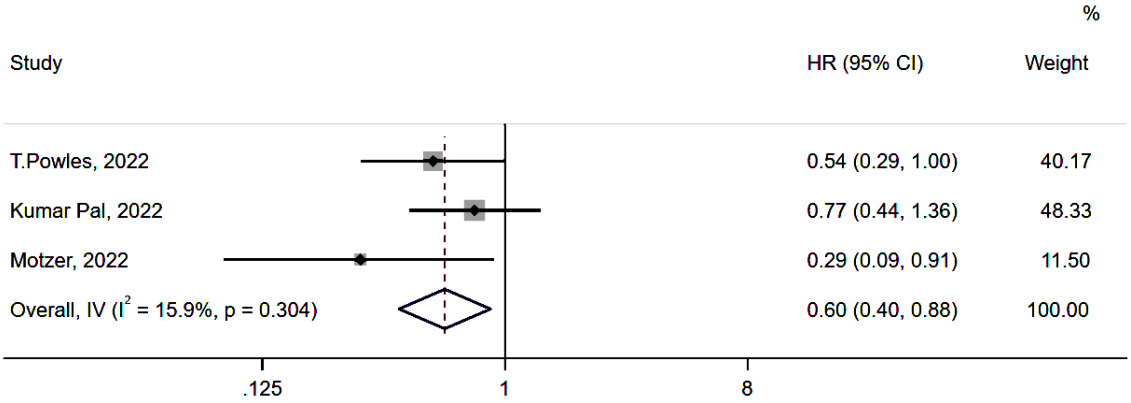

Figure 5: Subgroup analysis for sarcomatoid differentiation.

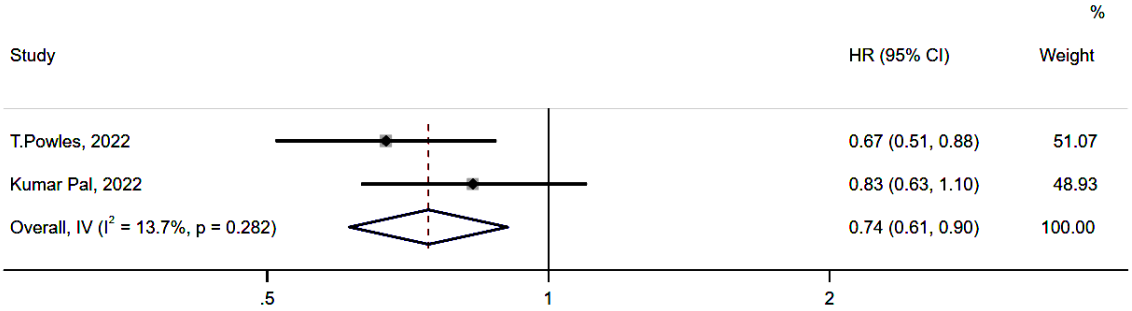

Figure 6: Subgroup analysis for PD-L1 positive tumors.

No significant differences were noted according to age [(<65 years; HR: 0.746, 95% CI 0.514-1.085; p: 0.125) (>65 years; HR: 0.865; 95% CI 0.688-1.087; p: 0.213)], metastatic status at baseline (M1 NED; HR: 0.644; 95% CI 0.306-1.353; p: 0.245) or type of nephrectomy (partial nephrectomy; HR: 0.545; 95% CI 0.147-2.014; p: 0.363). No analysis was done according to the tumor or nodal stage due to the heterogeneity of this group in the different trials included.

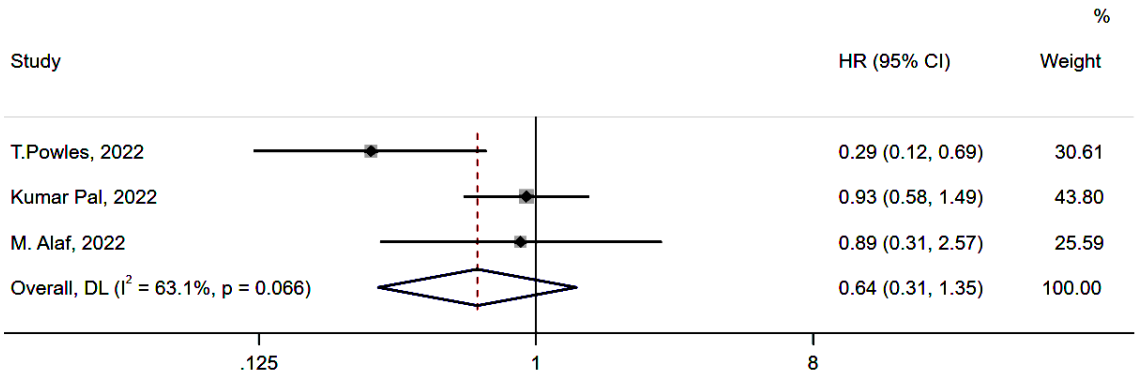

Figure 7: Subgroup analysis for M1 NED patients.

Regarding adverse events, figure 8 and 9 summarizes the main findings. Grade ≥ 3 AEs were two times more frequent [Odds ratio (OR): 2.694 95% CI 1.549 - 4.685; p: <0.001] and treatment-related grade ≥ 3 AEs were 8 times more frequent (OR: 8.603; 95% CI: 3.230- 22.916; p: <0.001) in the intervention arm.

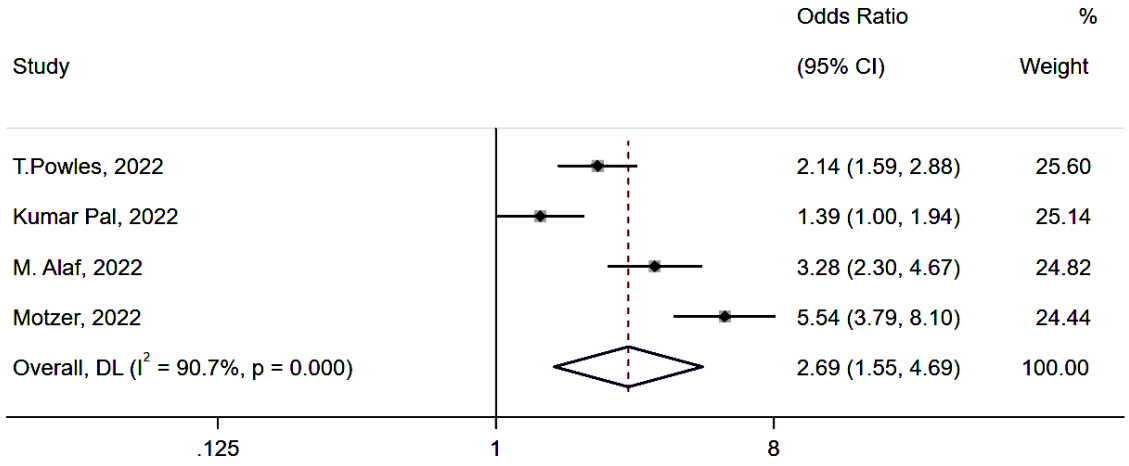

Figure 8: Meta-analysis results for grade ≥ 3 AEs of all-cause.

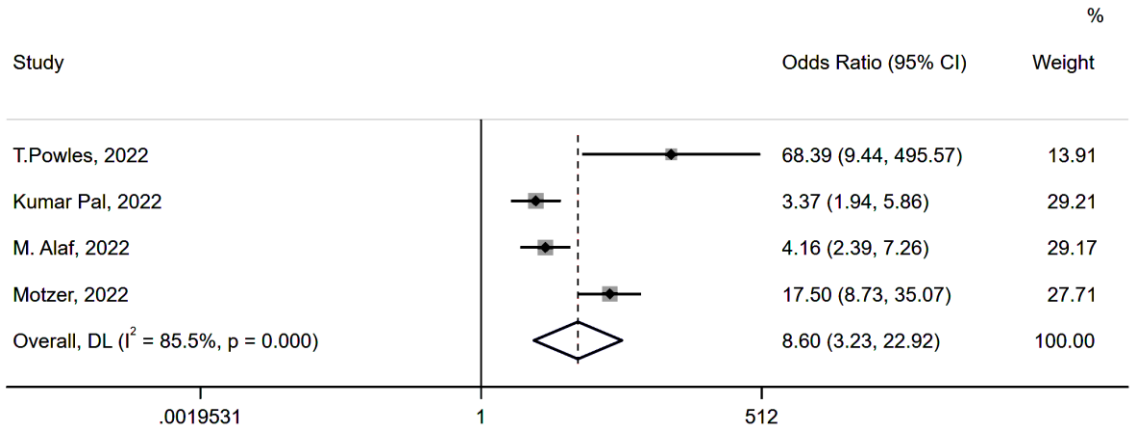

Figure 9: Meta-analysis results for treatment-related grade ≥ 3 AEs of all-cause.

Risk of bias assessment results are shown in figure 10. Some concerns of bias were noted in the PROSPER trial due to the open-label nature of the study.

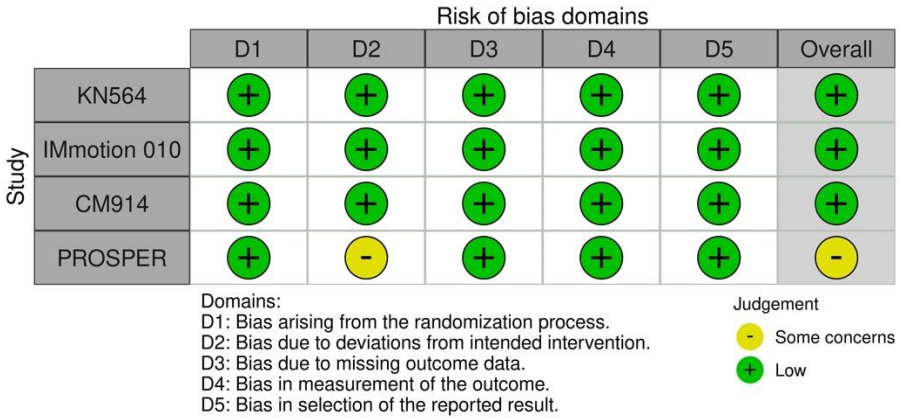

Figure 10. RoB assessment.

Discussion

Pembrolizumab, is the first immune checkpoint inhibitor that has demonstrated a DFS benefit in the post-operative scenario in RCC. Previously, only sunitinib had shown a DFS benefit in a high-risk population (tumor stage 3 or higher, regional lymph-node metastasis, or both), with no significant improvement in OS (13). Although approved by FDA, its use has not been widely adopted due to concerns of significant toxicity and because all other trials with tyrosine kinase inhibitors failed to show any benefit (13–17). This meta-analysis suggests an absence of a DFS benefit from the combined published results of ICI.

Nevertheless, there are relevant differences in the design of these trials that potentially may explain these findings. One of the main distinctions among trials is the target population of each study. PROSPER and IMmotion trials included clear-cell and no clear-cell histologies (15% of the population in the nivolumab arm and 7% in the atezolizumab arm) which are less responsive to single-agent ICI therapy (18). The definition of M1 NED varies widely between studies. In the KEYNOTE (6% of the study population) and PROSPER trial (3% of the study population), the presentation of the metastatic disease had to be synchronous with the diagnosis of RCC, in contrast to IMmotion (13.8% of the study population) which included synchronous metastases in lung and adrenal gland but metachronous (1 year after the initial resection) in the lung, nodes, and soft tissues. The IMmotion trial criteria may have selected a population with a better prognosis that may not benefit from adjuvant treatment after the resection of the metastatic disease (19). A previous phase II study with sorafenib after resection of metastases showed no differences in survival. The groups were not balanced as 72% were metachronous patients in the sorafenib arm in contrast to 58% of patients in the observation arm (20). A phase III trial with pazopanib in the same setting showed similar results (21).

Regarding the tumor stage, there are other remarkable differences. In the KEYNOTE trial, 90% of the patients were pT3, in contrast to 65% pT2-T3a in the IMmotion, 32% pT1-pT2 in the PROSPER trial, and 15% in the CheckMate-914. This may have selected an overall worse prognosis population in the KEYNOTE trial that may benefit from adjuvant therapy in contrast with the more favorable prognosis population in the rest of the studies.

Other factors that can be possibly related to the different outcomes in the trials are related to statistical considerations and study treatments. In the PROSPER trial, patients who did not get surgery or were not disease-free post-surgery were considered as an event on day 1. Approximately 10% of the patients in this trial had to be considered as an event on day 1 which may have diluted the trial results (in addition to other considerations). It

is also concerning that nearly half of the patients (43%) discontinued treatment in the nivolumab + ipilimumab trial, with 33% discontinuing due to toxicity.

OS is a critical endpoint in adjuvant trials but requires prolonged periods to events and substantial patient resources. Currently, there is lack of benefit even in the KEYNOTE-564 but this data is immature due to the short follow-up of these studies. Of note, evaluation of DFS has failed to be a good intermediate metric of overall survival in patients with localized renal cell carcinoma (22). However, this analysis has based only on adjuvant TKI data and newer results from adjuvant immunotherapy trials, with longer duration of response and longer survival as seen in metastatic setting, may challenge this notion.

Although exploratory, there are subgroups that may achieve higher benefit with adjuvant ICI. As seen in metastatic setting, sarcomatoid differentiation carries a poor prognosis but it is seems to be predictive of response to ICI agents (23). Approximately 10% of the patients of each trial (except for the 5% in the CheckMate-914) had sarcomatoid characteristics and a statistically significant DFS benefit has been reached in this analysis. This data is compelling and may help physicians to individualize treatments.

Other controversial results from subgroups include the benefit shown in female patients and PD-L1 positive tumors. Differences in ICI outcomes and immune features between sexes have been described but prospective data in RCC is limited (24). Additionally, PD-L1 expression measurement, intra-tumoral heterogeneity, variability of cut-offs and heterogeneous expression between the primary and the metastases has been extremely difficult to interpret in RCC which makes this information merely descriptive. Prognostic and predictive value of this PD-L1 has yet to be established in RCC (25).

An important concern in the adjuvant scenario is the additive toxicity for a patient that has a high chance of cure only with surgery. Our meta-analysis shows that serious AEs were two times more frequent in the intervention arm. It is important to note that, when attributed to study treatment, the OR of a grade ≥ 3 AEs rose to 8.6 times higher. It should be a priority to identify the patients at a higher risk of relapse in which the benefit in survival exceeds the probability of having a severe AE. This AE may resolve with appropriate treatment, but in a minority of cases, may lead to a chronic condition and quality of life deterioration and, in the worst scenario, to death.

Our study has some limitations. Data from the nivolumab monotherapy arm in the CheckMate-914 has not been published yet and will add more data. Besides, the lack of robust data on OS due to the short follow-up of most studies is a limitation of our study. Also, subgroup analyses regarding the local stage have not been done. Stratification groups in the trials are very heterogeneous and it is difficult to extract the weight each characteristic (i.e pT2G4, pT4, pN+) contributes to the final result. Individual participant data meta-analysis, with a longer follow-up of the trials, would shed light on the importance of every risk factor in the effect of the treatment and the prognosis of these patients.

Conclusions

Our meta-analysis shows no survival benefit from the treatment with ICIs in the peri-operative setting in RCC. Longer follow-up, pending and individual participant data, and future randomized clinical trials will help to identify the patients at a higher risk of relapse in which the use of ICI therapy outweighs the possible toxicity related to the treatment.

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