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Systematic or Meta-analysis Studies

# Treatment options in first-line metastatic renal carcinoma: A *meta*-analysis of 2556 patients treated with immune checkpoint inhibitors-based combinations in randomised controlled trials

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ABSTRACT

*Background & Aims:* The average five-year survival of metastatic renal cell carcinoma (mRCC) is 71%. However, there is significant variability in patient prognosis. Immune checkpoint inhibitors (ICIs) have been introduced into the treatment landscape of mRCC. This *meta*-analysis aimed to estimate progression-free and overall survival probabilities and identify possible outcome predictors of mRCC patients treated with ICI combination as first-line treatment.

*Methods:* Studies comparing the combination of ICI combinations versus standard of therapy for first-line treatment of advanced renal-cell carcinoma were searched in MEDLINE, CANCERLIT, the Cochrane Controlled Trials Register, and the Cochrane Library from inception through September 2023. Data on patient populations and outcomes were extracted from each study by three independent observers and combined using the DerSimonian and Laird methods.

*Results:* Six studies met the inclusion criteria. Globally, 5121 patients were included in this *meta*-analysis: 2556 patients treated with immune checkpoint inhibitors and 2565 with sunitinib as control. The ICI combination was associated with improved PFS (hazard ratio (HR) 0.68; 95 % confidence interval (CI), 0.56–0.81, $p < 0.0001$). Furthermore, ICI combination was also associated with OS improvement (HR 0.85; 95 % CI, 0.78–0.92, $p = 0.001$). There is no statistical increase in adverse events.

*Conclusions:* Our findings show that PFS and OS are statistically increased in mRCC with ICI combination treatment by 32% and 15%, respectively.

## Introduction

Kidney cancer is diagnosed in more than 430.000 people worldwide every year, and it causes approximately 180.000 deaths [1,2]. The average five-year survival rate is 71 %, but there is a significant age gradient and variability based on the disease stage [3].

At the time of diagnosis, about 30 % of patients already present with advanced disease; in addition, 20 % to 40 % of patients undergoing radical nephrectomy for localised disease later develop metastases [4].

Understanding the role of angiogenesis in the growth and development of renal cell carcinoma (RCC) has introduced new therapeutic options. Since 2005, the United States Food and Drug Administration (FDA) and the European Medicines Agency have approved the anti-VEGF antibody bevacizumab (in combination with interferon); mTOR inhibitors everolimus and temsirolimus and tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib to treat metastatic renal cell carcinoma (mRCC). Despite the impact on progression-free survival (PFS) brought about by the use of

*Abbreviations:* IT, immunotherapy; RCT, randomised controlled trial; PFS, progression-free survival; OS, overall survival.

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TKIs, the need for novel treatment methods has arisen due to drug resistance [5].

Immune checkpoint inhibitors (ICIs) have been introduced in the mRCC treatment landscape in this scenario. Programmed death 1 (PD-1), programmed death ligand 1 (PD-L1) and T lymphocyte-associated antigen 4 (CTLA-4) are respectively involved in peripheral T-cell tolerance mechanism (PD1-PDL1 interaction) and immune evasion process during the priming phase (CTLA4-CD80/86 interaction), resulting in early and improper inactivation of immune cells and desensitisation to the immunological stimuli. ICIs, acting as PD1, PDL1 and CTLA4 inhibitors, stimulate the immune system to carry out its intrinsic antitumor action [6,7]. The treatment for mRCC has entered the immuno-oncology (IO) era with the FDA approval in November 2015 of nivolumab (anti-PD1) monotherapy as a second-line treatment based on the CheckMate 025 study. In this trial, nivolumab was compared with everolimus in patients who had received prior antiangiogenic therapy for mRCC, showing superior efficacy in terms of overall survival (OS) and objective response rate (ORR) [8].

Currently, IO-based combinations are the first-line standard-of-care for treating mRCC, and they consist of an anti-PD1 antibody plus either an anti-CTLA-4 antibody (IO/IO combination) or an anti-VEGF (IO/TKI combination) [9].

Validated prognostic factors that allow for the stratification of patients into different risk groups have helped clinicians in therapeutic choices. According to the Memorial Sloan–Kettering Cancer Center (MSKCC) model, a Karnofsky performance status lower than 80 %, high serum lactate dehydrogenase (LDH) and calcium level, low haemoglobin, and short interval from diagnosis of primary tumour to appearance of metastatic disease are all indicators of high-risk illness [10]. The International Metastatic RCC Database Consortium (IMDC) risk score model, which added platelets and neutrophil counts to the previous MSKCC criteria, has been used in most of the recent RCTs and represents the preferred model used in clinical practice. If none of the above variables are present, the disease is classified as having a favourable prognosis, an intermediate prognosis if one to two are present, and a poor prognosis if more than three [11].

Over the past few years, four phase III trials have examined the effectiveness of immunotherapy-based combinations as first-line therapy in mRCC and have demonstrated OS benefits compared to TKI monotherapy in the first-line setting: nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and pembrolizumab plus lenvatinib. In the CheckMate 214 trial, the combination of nivolumab + ipilimumab significantly improved OS and ORR compared with sunitinib in patients with intermediate/high-risk disease. KEYNOTE-426 (pembrolizumab + axitinib), KEYNOTE 581 (pembrolizumab + lenvatinib), and finally, CheckMate 9ER study (nivolumab + cabozantinib) further supported the superiority of the new drug combinations [12,13,14,15].

There are no direct comparisons between these ICI combinations. This *meta*-analysis aimed to estimate the PFS and OS probabilities of mRCC patients treated with first-line ICI-based combinations, identify possible predictors of outcomes, and discuss the clinical criteria that could guide physicians in choosing first-line treatment.

## Methods

### *Study selection and data extraction*

MEDLINE/PUBMED and EMBASE searches were performed to identify eligible studies, restricted to phase III, randomised, controlled trials comparing ICI-combination to a standard of care monotherapy for first-line treatment of advanced renal-cell carcinoma. The proceedings of the European Society of Medical Oncology, American Society of Clinical Oncology, European Uro-Oncology Group and American Urological Association annual meetings were examined for presented abstracts. Based on these criteria, the CheckMate 214, CheckMate 9ER, Clear, IMmotion151, Javelin and Keynote 426 studies were selected for our *meta*-analysis.

### *Data extraction*

Data extraction was conducted independently by three investigators (FT, ER, MM) following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For each study, the following information was extracted: publication or presentation date, first author's last name, sample size, primary endpoints, regimens used, follow-up period, number of outcome events, information about study design, PFS, OS, subgroup evaluation and toxicities. Discrepancies between reviewers were infrequent (overall interobserver variations $<$ 10 %) and were resolved by discussion.

### *Statistical methods*

The impact of first-line ICI-combination treatment on PFS and OS in mRCC patients was measured based on the hazard ratio (HR). For each study, the HR was either extracted directly from the reports or was estimated. Individual HR estimates were then combined into overall HR using random effects models. Heterogeneity was quantified by the $I^2$ coefficient, which measures the percentage of total variation across studies due to heterogeneity rather than chance [16]. By convention, an HR $<$ 1.00 implied a benefit of using an IO-drug combination regimen. This impact was considered statistically significant if the 95 % confidence interval (CI) for overall HR did not overlap 1.00. Immune checkpoint inhibitors toxicities and response rate were calculated using the same statistical methods described above.

In clinical trials with a time-dependent outcome (death or disease recurrence), survival curves were used to describe the risk of the event over time. The most informative finding was a summary survival curve in *meta*-analyses of studies reporting a survival curve. We used the nonparametric approach reported by Combescure et al. [17] to assess pooled survival probabilities from several single-arm studies. This approach is a version of aggregated data of the product-limit estimator of survival and uses random effects to model between-study heterogeneity. The between-study covariance matrix was estimated using the multivariate extension of DerSimonian and Laird's method [18,19]. This approach has several advantages compared to *meta*-analyses of survival probabilities at a single time point [20]. First, estimating the pooled survival probability at time $t$ also involves all studies ending before $t$ because these studies contribute to the estimated conditional survival probabilities for time intervals before $t$. Second, this approach does not require assumptions about the shape of survival curves. Finally, the pooled survival probabilities are guaranteed not to increase over time. For all analyses, a $p\text{-}value < 0.05$ was considered statistically significant. All analyses and graphics were completed with the R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria).

Furthermore, the risk difference (RD) is computed for ORR, CR, adverse events and discontinuation due to AEs between combination and standard treatment. We used this measure to compare the effectiveness of different combinations.

## Results

Six RCTs published between 2018 and 2022 fulfilled the inclusion criteria and were selected for review. All studies compared treatment with ICI versus sunitinib. In two studies, the ICI was pembrolizumab administered respectively in combination with the VEGF receptor TKI axitinib [13,21,22,23,24] and with the multiple receptor TKI lenvatinib [14,25,26]. In two studies, the ICI was nivolumab administered respectively with cabozantinib (a multi-target TKI) [15,27,28] and with another checkpoint inhibitor, ipilimumab[29,30,12]. Finally, an RCT used atezolizumab and bevacizumab (a monoclonal antibody against

VEGF) [31,32] and another one, avelumab with axitinib [21,22]. The population characteristics of the six trials are summarised in Table 1. Baseline demographics were balanced within and between the studies. A comparable rate of 2-year OS was reported for all control group arms treated with sunitinib, with a mean rate of 64 % ranging from 59-72 %.

Globally, 5121 patients were included in this *meta*-analysis: 2556 patients treated with ICIs and 2565 with sunitinib as control. The size of the single arm in each study ranged from 323 [15,27,28] to 550 [29,30,12]. The mean patient age was 62 for the experimental group and 61 for the control group. According to IMDC prognostic risk, 1267 patients had favourable, 3105 intermediate, and 737 poor-risk diseases. All studies but one [21,22] reported the metastatic involvement. Globally, 949 patients had bone metastases, 750 liver, 3014 lung and 1929 lymph node metastases.

*Progression-Free survival*

Fig. 1A shows the HR for PFS in each trial and the overall analysis. The HRs for PFS of ICI combination were compared to the control arm in all trials. The effect of treatment on PFS significantly favoured ICI therapy in all studies; a statistically significant difference was observed in all studies but one [29,30,12]. Our *meta*-analysis shows a statistically significant benefit obtained with ICI-based therapy for advanced renal cancer patients: the pooled estimate of the treatment effect was significant HR 0.68 (95 % CI, 0.56 to 0.81) $p < 0.00001$, corresponding to a 32 % reduction of the hazard of disease progression for immunotherapy-based therapy. A high heterogeneity was present between the studies ($X^2 = 32.64$), $I^2 = 85$ %. Using robust analysis, the pooled estimate of the treatment effect was significant.

PFS curves for ICI combination therapy were extracted from the studies, and the summary survival curves are shown in Fig. 1B. The median PFS time was 15.7 months (14.5–16.9).

*Progression-Free survival according to subgroups*

PFS was assessed according to IMDC prognostic risk (Fig. 2A). The ICI combination therapy showed no statistically significant benefit in favourable patients, HR 0.79 (95 % CI 0.51–1.21) $p = 0.27$. Instead, a statistically significant benefit was observed in intermediate and poor-risk patients, HR 0.64 (95 % CI 0.51–0.80) $p < 0.0001$ and HR 0.50 (95 % CI 0.36–0.69) $p < 0.0001$, respectively.

The ICI combination therapy shows a 36 % reduction of the hazard of progression in patients PD-L1 $\geq$ 1 treated with ICI combination compared to sunitinib corresponding to HR 0.64 (95 % CI 0.49–0.86) $p = 0.002$. Instead, a 29 % reduction was registered in PD-L1 < 1 patients, HR 0.71 (95 % CI 0.57–0.89) $p = 0.003$ (Fig. 2B). A moderate heterogeneity was identified in both groups, with $I^2$ of 66 and 56 %, respectively.

All studies analyse the PFS of ICI-combination in the RCC subtype with sarcomatoid dedifferentiation. Globally, 302 patients with sarcomatoid dedifferentiation were treated with combined therapy and 316 with sunitinib alone. In all studies, there is a benefit with ICI-combination reaching statistical significance in all but two [13,21,22,23,24]. The pooled result confirms a statistically significant benefit for ICI combinations compared to sunitinib in the subgroup of mRCC patients with sarcomatoid dedifferentiation, HR 0.49 (95 % CI 0.37–0.65) $p < 0.00001$ (figure S1). Many efforts were made to identify a correlation between ICI combination efficacy and the site of metastasis. Only two studies [15,27,28,31,32] reported outcomes according to the presence of liver metastasis. No difference was found in patients with or without liver metastasis, HR 0.54 (95 % CI 0.39–0.75) $p = 0.0003$ and HR 0.64 (95 % CI 0.48–0.854) $p = 0.002$. (figure S2).

*Overall survival*

Fig. 3A shows the HR for OS in each trial and the overall analysis. Individually, three studies [13,23,24,14,25,26,29,30,12] showed a significant OS benefit of IT combination; the other three showed no statistically significant benefit [21,22,15,27,28,31,32]. The pooled estimate of the treatment effect showed a significant survival improvement, HR 0.85 (95 % CI, 0.78 to 0.92) $p = 0.00001$, corresponding to a 15 % reduction in the hazard of death with ICI combination. No significant heterogeneity was observed between the studies ($X^2 = 4.70$), $I^2 = 0$. Using robust analysis, the pooled estimate of the treatment effect was significant.

OS curves for ICI combination therapy were extracted from the studies; the summary survival curves are shown in Fig. 3B. The median OS was 48.9 months (42.1–56.1).

*Overall survival according to subgroups*

OS was assessed according to IMDC prognostic risk (Fig. 4A). ICI combination therapy showed no statistically significant benefit in the favourable risk subgroup, HR 0.99 (95 % CI 0.79–1.25) $p = 0.96$, with no heterogeneity between the studies ($X^2 = 1.37$), $I^2 = 0$. Instead, a statistically significant benefit was observed in intermediate and poor-risk patients, HR 0.68 (95 % CI 0.56–0.83) $p = 0.00002$ and HR 0.49 (95 % CI 0.37–0.64), respectively, with no heterogeneity between studies. The ICI combination therapy shows a 36 % reduction of the hazard of death in patients PD-L1 $\geq$ 1 treated with ICI combination to sunitinib corresponding to HR 0.64 (95 % CI 0.52–0.78) $p < 0.0001$ and a moderate heterogeneity ($X^2 = 10.87$), $I^2 = 54$ %. A 34 % reduction of the hazard of death in patients PD-L1 < 1 was observed with HR 0.66 (95 % CI 0.55–0.79) $p < 0.00001$ and no heterogeneity ($X2 = 1.61$), $I2 = 0$ (Fig. 4B).

All studies but one [21,22] analyse the impact of the ICI combinations on the OS according to sarcomatoid features. Globally, 255 patients with sarcomatoid dedifferentiation were treated with combined therapy, the same number with sunitinib alone. In all studies, there is a benefit with combination reaching statistical significance in all but one [13,23,24]. The pooled result shows a significant OS benefit with ICI combinations compared to sunitinib in the subgroup of patients with sarcomatoid dedifferentiation, HR 0.57 (95 % CI 0.47–0.70) $p < 0.00001$ (figure S3), then a reduction of death risk of 43 %.

Many efforts were made to identify a correlation between ICI combination efficacy and the site of metastasis; however, no data was presented concerning overall survival.

**Table 1**
Patient characteristics of the studies in the Meta-Analysis.

| | | Treatment with Immuno-check point | Sunitinib |
|---|---|---|---|
| **n patients** | | 2556 | 2565 |
| **Age, years** | | 62 | 61 |
| **Sex** | | | |
| | Male | 1858 | 1918 |
| | Female | 698 | 647 |
| **IMDC prognostic risk** | | | |
| | Favourable (0) | 630 | 637 |
| | Intermediate (1 or 2) | 1552 | 1553 |
| | Poor (≥3) | 367 | 370 |
| **Most common metastatic sites** | | | |
| | Bone | 468 | 481 |
| | Liver | 376 | 374 |
| | Lung | 1519 | 1495 |
| | Lymph node | 956 | 973 |
| **Previous radiotherapy** | | 150 | 155 |
| **Previous nephrectomy** | | 1646 | 1658 |
| **Disease PD-L1 expression on tumour-infiltrating immune cells** | | | |
| | ≥1% | 994 | 1057 |
| | <1% | 1353 | 1313 |

†

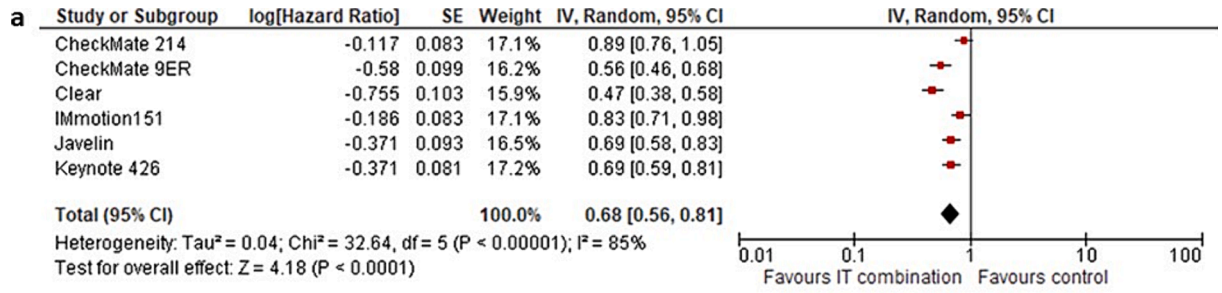


**Fig. 1A.** Forest plot of progression-free survival.

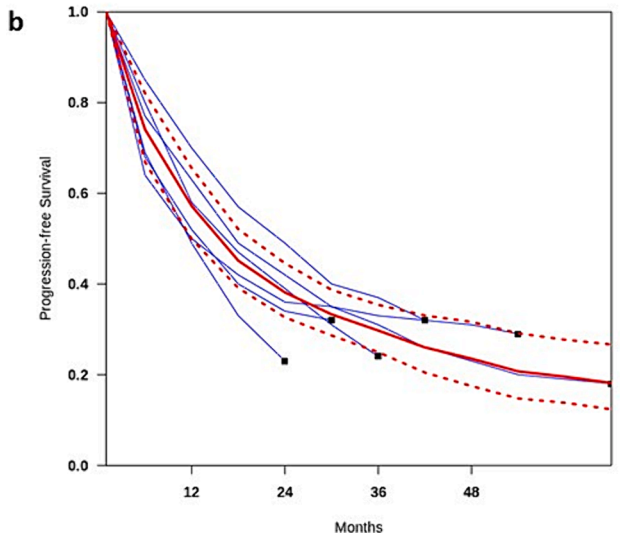


**Fig. 1B.** curve of progression-free survival. Black squares indicate the end of the follow-up. Thick lines represent the summarised recurrence curves with the 95% confidence bands (dashed lines) obtained using the approach of Combescure et al. with random effects.

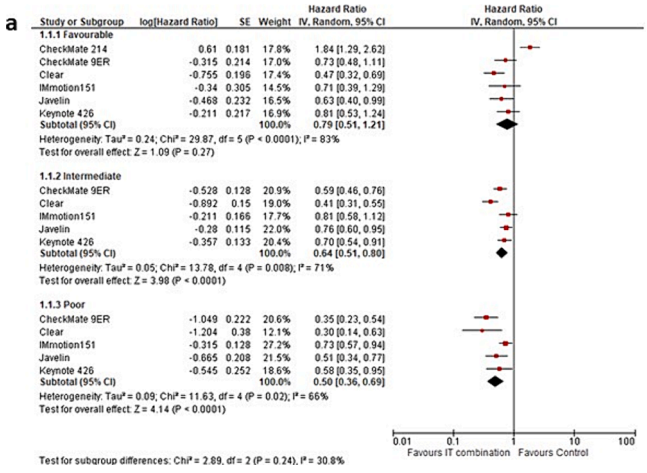


**Fig. 2A.** Forest plot of progression-free survival according to IMDC prognostic risk favourable, intermediate and poor.

*Objective response rate (ORR) and complete response (CR)*

Fig. 5A shows the HR for ORR in each trial and the overall analysis. Individually, all studies but one [31,32] showed a significant ORR benefit of the ICI combination. The pooled estimate of the treatment effect was significant HR 0.46 (95 % CI, 0.29 to 0.72) p = 0.0007,

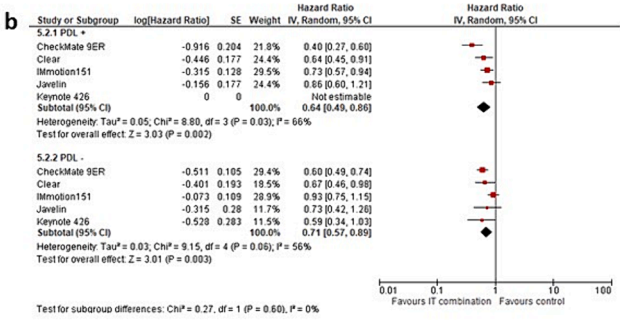


**Fig. 2B.** forest plot of progression of disease in function of PDL1 status.

corresponding to a 54 % increase in the hazard of ORR with ICI combinations. A high heterogeneity was observed between the studies ($X^2 = 76.98$), $I^2 = 94$ %. Using robust analysis, the pooled estimate of the treatment effect was significant.

The various combined treatments are different in increasing ORR rates (figure S4a); the most effective is a combination of TKI (cabozantinib and lenvatinib) with immune checkpoint inhibitors, reducing the ORR failure by 32 % (−38 % –– −26 %) p < 0,00001 than sunitinib. Afterwards, the combination of axitinib with IT −17 % (–33 % –– −2%) p = 0,03 and the combination of two immune checkpoint inhibitors −7% (−12 % —— −1%) p = 0,02. Then, the combination of bevacizumab and ICI had a non-statistically significant difference of −3% (−9% –– 3 %) p = 0,29. Figure S4b shows the HR for CR in each trial and the overall analysis. Individually, all studies but two [21,22,15,27,28] showed a significant CR benefit of ICI combination. The pooled estimate was significant, HR 0.33 (95 % CI, 0.24 to 0.47) p < 0.00001, corresponding to a 67 % increase in the hazard of CR with ICI combination. A low heterogeneity was observed ($X^2 = 7.69$), $I^2 = 35$ %. The various combined treatments are different in increasing CR rates (figure S4b); the most effective is the combination of two immune checkpoint inhibitors reducing the CR failure of −8% (−11 % —— −5%) p < 0,00001.

Afterwards, the combination of TKI (cabozantinib and lenvatinib) with immune checkpoint inhibitors −6% (−10 % –– −1%) p = 0,01, axitinib with ICI −5% (−11 % –– -2%) p = 0,15, and the combination of bevacizumab and ICI −3% (−6% –– −1%) p = 0,01.

*Safety profile of IT combination*

Globally, there is no statistical increase of adverse events HR 0.74 (95 % CI 0.54–1.02). The probability of major adverse events (≥G3) was higher by 11 % in the sunitinib group. Globally, there was 63.4 % of AE ≥ G3 in combined treatment and 65.9 % in the sunitinib group, with a non-statistical significant reduction of −1% (−10 % –– 8 %) p = 0,79. The various ICI-based combinations are different in producing AE ≥ G3: TKI and ICI combination gives an increased risk about 5 % than sunitinib (75,7% vs 70,7%). The combination of TKI (cabozantinib and lenvatinib) with immune checkpoint inhibitors increases about 8 % (4 % –– 13

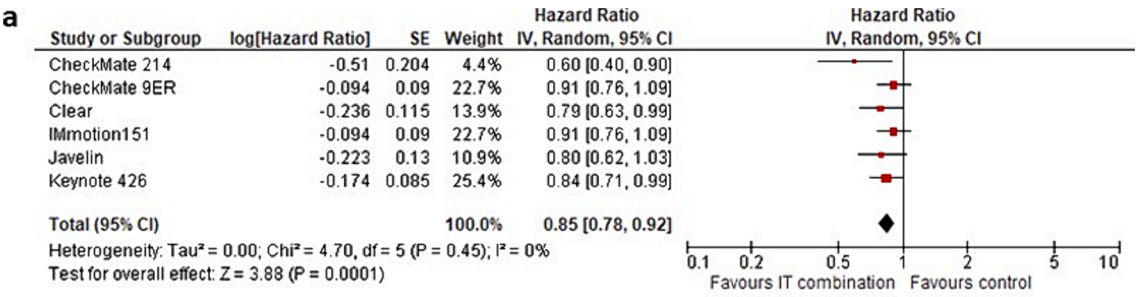


**Fig. 3A.** Forest plot of overall survival.

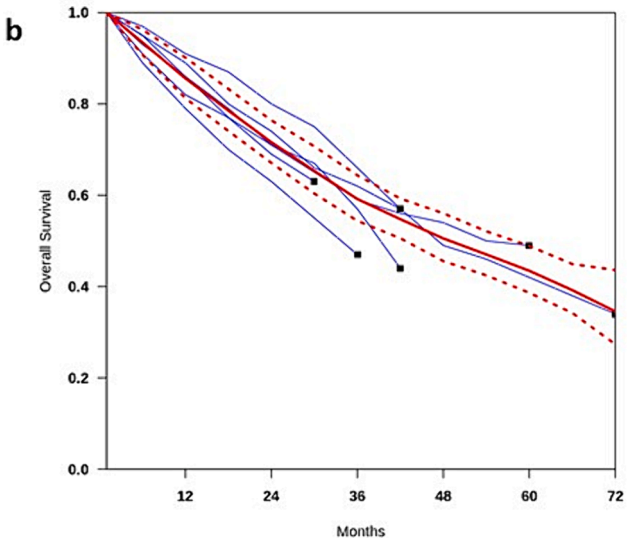


**Fig. 3B.** curve of overall survival. Black squares indicate the end of the follow-up. Thick lines represent the summarised recurrence curves with the 95% confidence bands (dashed lines) obtained using the approach of Combescure et al. with random effects.

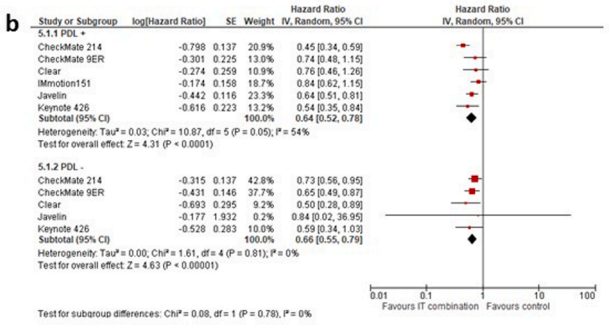


**Fig. 4B.** forest plot of overall survival in function PDL1 status.

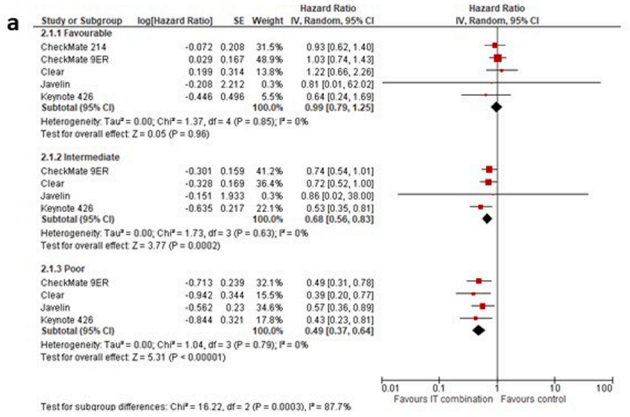


**Fig. 4A.** Forest plot of overall survival according to IMDC prognostic risk favourable, intermediate and poor.

%) p = 0,0006 the rate of AE ≥ G3 and axitinib with ICI 2 % (−3% −−8%) p = 0,38 (figure S5).

Contrarily, the combination of two immune checkpoint inhibitors reduces the AE ≥ G3 rate of 16 % (–22 % −— −10 %) p < 0,00001 and the combination of bevacizumab and ICI of 12 % (−18 % −– −6%) p = 0,0003.

Diarrhea (≥G3) was significantly increased in ICI-based treatment with an HR of 1.60 (95 % CI 1.23–2.08). No other toxicity rates were statistically significantly different (Fig. 6) between the two groups.

There was a higher probability of treatment discontinuation for AEs in the ICI combination group HR 1.67 (95 % CI 1.43–1.95). Globally, there were 20 % treatment discontinuations for AEs in combined treatment and 13,2% in the sunitinib group, with a non-statistically significant increase of 7 % (−2% −– 16 %) p = 0,13.

The combined treatments are different in producing treatment discontinuation for AEs: The combination of TKI and ICI gives an increased risk of about 9 % than sunitinib (23,3% vs 14,5%). The combination of TKI (cabozantinib and lenvatinib) with ICI 13 % (−7% −– 32 %) p = 0,19 and axitinib with ICI 5 % (−18 % −– 28 %) p = 0,65.

A discontinuation rate of 10 % (5 % −— 14 %) p < 0,0001 was obtained with the combination of two ICIs (figure S6). Contrarily, the combination of bevacizumab and ICI reduce the discontinuation rate of 3 % (−7 −– 0 %) p = 0,05.

## Discussion

Recently, the first-line treatment landscape of mRCC has been enriched by several new options with proven efficacy in outcomes and quality of life. Unfortunately, we do not have data from head-to-head studies, and we lack predictive biomarkers for ICI-based combinations. Consequently, choosing the best treatment for each patient is critical, and clinicians face daily therapy optimisation and personalisation.

Some clinical and disease features included in validated prognostic models should be considered in treatment choice. The CheckMate 214 study compared nivolumab plus Ipilimumab with sunitinib as first-line therapy in mRCC. All coprimary end points (ORR, PFS, and OS) in intermediate- or poor-risk patients were significantly higher with ICI combination [12]. Instead, exploratory analysis of favourable-risk patients showed an ORR of 29 % with the immunotherapy combination and of 52 % with TKI (P < 0.001), and a median PFS of 15.3 with the immunotherapy combination and 25.1 months with sunitinib (P < 0.001) [29]. Based on these results, the combination of nivolumab and ipilimumab represents one of the possible first-line treatment choices

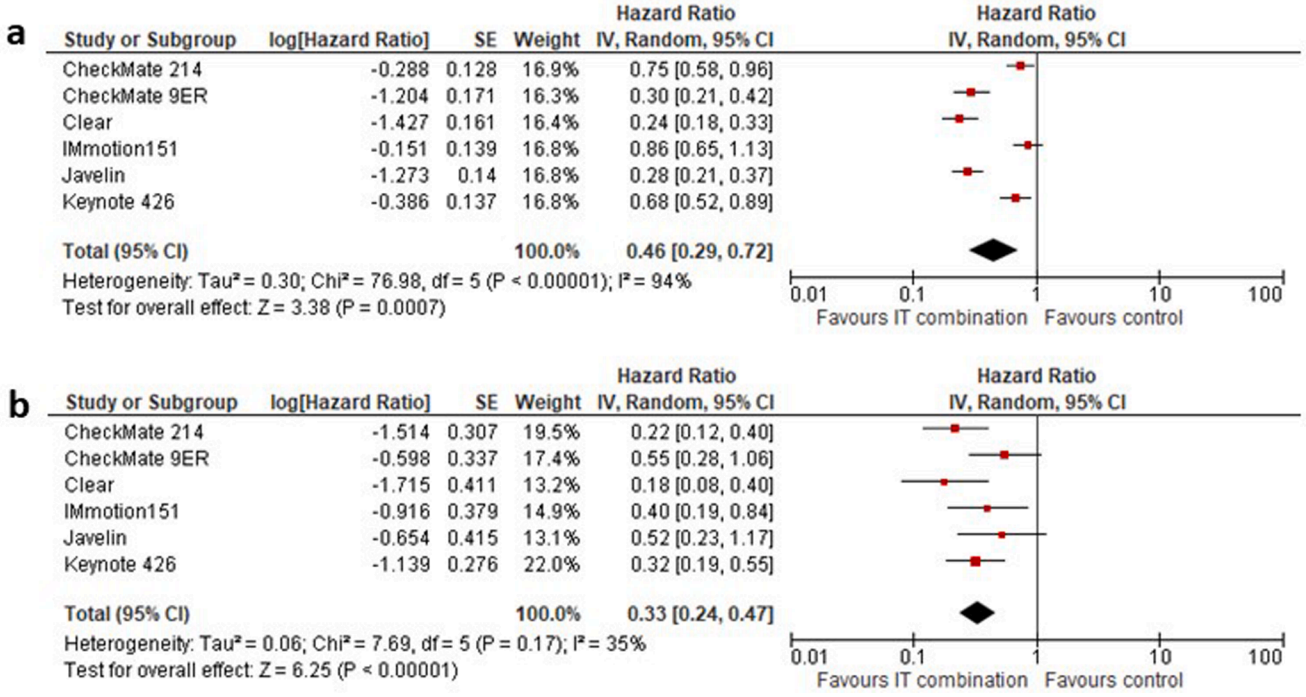


**Fig. 5A.** Forest plot of objective response rate (ORR) and B). forest plot of complete response (CR).

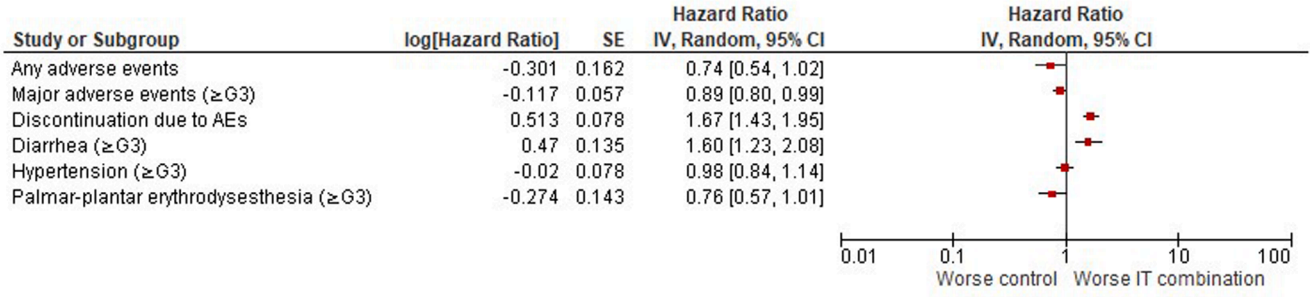


**Fig. 6.** Forest plot of adverse events.

only in the case of IMDC intermediate and poor-risk patients.

In addition, the efficacy of the outcome of ICI combinations is uncertain in IMDC favourable-risk patients when we consider the ICI and TKI association [33,34].

Our *meta*-analysis shows that the ICI combination was associated globally with improved PFS and OS. However, a statistically significant benefit was shown only in intermediate and poor-risk subgroups of patients.

Our data are in line with the results of other two recent *meta*-analyses. In the work of Ciccarese et al., the association of ICI and TKIs improved only PFS (HR 0.63; $p < 0.00001$) and not OS (HR 0.99; $p = 0.95$) in comparison with sunitinib in favourable risk sub-group [33]. Equally, an FDA pooled analysis based on individual data of 3447 patients from four pivotal randomised clinical trials demonstrated that ICI combination does not induce a statistically significant OS improvement in patients with favourable risk (HR 0.953, 95 % CI: 0.72–1.27) while increases OS in intermediate and poor risk patients (HR 0.696, 95 % CI: 0.62–0.78) [34].

Consequently, although ICI-based treatments are the mainstay of treatment according to international guidelines independently of IMDC classification, some well-selected favourable-risk patients could benefit from TKI monotherapy. mRCC favourable risk patients are often characterised by a heterogeneous disease, resulting in some cases in aggressive disease situations and others in indolent and asymptomatic clinical progressions. In patients with low-volume disease or lung, pancreatic, and thyroid metastases only characterised by indolent disease situations, TKI monotherapy could be a possible treatment [35]. In addition, in elderly patients or those with multiple comorbidities, deferred treatment could be a valid treatment choice [36]. In this regard, Rini et al. demonstrated in a phase II study that by enrolling 48 patients with metastatic, asymptomatic disease, surveillance before starting first-line therapy could be a viable option regarding risk/benefit [37].

In this complex treatment landscape, researching predictive biomarkers of response is mandatory. PD-L1 status is one of the most studied biomarkers as a prognostic and predictive factor in the ICI era. Our data demonstrate that ICI combination is associated with a significant increase in PFS and OS independently of PD-L1 status; these results are in line with past data showing the indefinite role of PD-L1 as a criterion to personalise therapy in mRCC [38,39].

Considerable efforts are being made to study and identify possible molecular biomarkers predictive of therapy efficacy to personalise treatment. In this regard, a recent work by Choueiri et al. analysed blood and tumour features of patients enrolled in the JAVELIN Renal 101, comparing avelumab + axitinib versus sunitinib as first-line therapy. This study provided new insights into the immunoregulation process involved in treatment response, confirming the prognostic utility of

some common blood biomarkers such as neutrophils, platelets levels and markers of inflammation. In addition, PFS was associated with increased lymphocyte number in the TKI arm and an abundance of innate immune subsets in the immunotherapy combination arm. Immunotherapy combination led to amplified T-cell modulation and fewer variations in T-cell compared with TKI [40].

In the absence of validated treatment efficacy predictive biomarkers, the goal of our therapy in each specific patient and disease could guide treatment choice. The percentage of treatment primary refractory patients is nearly twice with the dual ICI combination than with TKI and ICI associations [12,13,14,15]. In addition, although our *meta*-analysis demonstrates a significant advantage for all ICI combinations compared to sunitinib monotherapy in terms of ORR corresponding to a 54 % increase in the hazard ratio, the most effective ICI combinations are cabozantinib plus nivolumab and lenvatinib plus pembrolizumab able to reduce the ORR failure of 32 %. These data suggest the use of TKI and ICI combinations, in particular the association of cabozantinib or lenvatinib with ICIs, in symptomatic or high-burden disease and patients with bone or liver metastases, usually characterised by a poor prognosis, in which we must obtain a rapid and efficacious tumour shrinkage. In this respect, in our analysis, no difference in terms of PFS was found in patients with or without liver metastases. It should be noted, however, that only two studies [32,31,15,27,28] analysed this sub-group of patients.

Histological characteristics could guide clinicians in personalising treatment. It is well known that the presence of a sarcomatoid component in RCC is associated with a poor outcome. Available pre-clinical data show that RCC with sarcomatoid dedifferentiation is characterised by an immune-inflamed phenotype with immune system hyperactivation, increased cytotoxic immune infiltration, and upregulation of PD-L1 expression. Consequently, these tumours are deeply responsive to ICIs [41].

Tannir et al. [42] showed a significant advantage in terms of OS (48.6 months vs 14.2 months, HR 0.46, 95 % CI 0.29–0.71; $p = 0.0004$) and ORR (60.8 % vs 23.1 %; $p < 0.0001$; CR 23.0 %) for the use of dual immunotherapy combination compared to sunitinib monotherapy in RCC patients with sarcomatoid dedifferentiation.

In the *meta*-analysis of Buti et al., which enrolled 569 patients with mRCC subtype with sarcomatoid dedifferentiation from five pivotal RCTs, the association of cabozantinib plus nivolumab was the most efficacious combination therapy in terms of OS (p-score = 88 %) and PFS (p-score = 81 %) [43]. Our work confirms a significant advantage in terms of PFS and OS using ICI combinations compared to sunitinib in mRCC patients with sarcomatoid dedifferentiation.

Dual immunotherapy combination and TKI plus ICI associations are characterised by specific and different toxicity profiles that must be considered in the choice of therapy for each patient.

Our data did not show a statistically significant increase of all and > G3 adverse events with ICI-based combinations. The various combined treatments, however, were different in inducing AE ≥ G3. The association of cabozantinib or lenvatinib with ICI had the highest probability of AE ≥ G3 while combining two immune checkpoint inhibitors reduced the AE ≥ G3 by 16 %.

There was a higher probability of treatment discontinuation for AEs in patients treated with ICI combinations. The association of cabozantinib or lenvatinib with ICI and dual immunotherapy combination are those with the greatest chance of treatment discontinuation. In this respect, it should be noted that in the CheckMate-214 study, dual immunotherapy combination toxicity occurred mainly during the first four months of induction therapy, while in patients treated with TKI-ICI combinations, toxicity may persist for a longer time [44]. Our data are in line with the network *meta*-analysis of Quhal et al. [45], showing that lenvatinib + pembrolizumab had the highest rate of treatment-related AEs ≥ G3 (OR 1.84, 95 % CI 1.28–2.64) and treatment discontinuation (OR 3.55, 95 % CI 2.46–5.12). In contrast, Ipilimumab + nivolumab had the lowest probability of ≥ G3 AEs. These data should be considered in the treatment choice, together with the evaluation of clinical characteristics and comorbidities of the patients [46].

Our work is not the first to investigate this clinical issue. The strengths of our analysis encompass the inclusion of only phase III RCTs using the most recent reported follow-up data. This *meta*-analysis of aggregate survival data enables us to assess outcomes as time-dependent events. Furthermore, this study is the largest (>2556 patients) and updated attempt to produce a reconstructed individual patient data (IPD) analysis in this clinical scenario. The actuarial curve of OS and PFS obtained can be considered a useful reference for determining the sample size of future first-line systemic RCTs and for obtaining indirect comparisons among different trials estimating drug efficacy.

## Conclusion

Our study confirms the long-term advantage of using ICI combinations in the first-line therapy of patients with mRCC. We do not have head-to-head comparisons between the approved associations. Future research is needed to identify predictive biomarkers to individualise therapeutic choice [45].

In this respect, Motzer et al. categorised some molecular subtypes by transcriptomic analysis. Regardless of the therapy, better OS was shown in angiogenic/stromal and angiogenic clusters. Inferior OS was documented in the proliferative and stromal/proliferative clusters. Atezolizumab plus bevacizumab association increased OS in the T-effector/proliferative, proliferative and small nucleolar RNA subsets, while Sunitinib enhanced OS in the angiogenic cluster [31,46].

The study of molecular pathways responsible for the development and progression of RCC could be the keystone for therapy personalisation.

## CRediT authorship contribution statement

**Marcello Tucci:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Marta Mandarà:** Formal analysis, Writing – review & editing. **Jacopo Giuliani:** Investigation, Writing – review & editing. **Emilia Durante:** Resources, Investigation, Data curation. **Consuelo Buttigliero:** Resources, Writing – original draft, Writing – review & editing. **Fabio Turco:** Formal analysis, Writing – original draft. **Erica Palesandro:** Formal analysis, Investigation, Data curation. **Ilaria Campisi:** Resources, Data curation. **Navdeep Singh:** Software, Data curation. **Marco Muraro:** Investigation, Writing – review & editing. **Fernando Munoz:** Resources, Writing – original draft. **Francesco Fiorica:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2024.102745.

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