International Immunopharmacology 108 (2022) 108720

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

The effect of immune checkpoint inhibitor combination therapies in metastatic renal cell carcinoma patients with and without previous cytoreductive nephrectomy: A systematic review and *meta*-analysis

Keiichiro Mori [a,b,*], Fahad Quhal [a,c], Takafumi Yanagisawa [a,b], Satoshi Katayama [a,d], Benjamin Pradere [a], Ekaterina Laukhtina [a,e], Pawel Rajwa [a,f], Hadi Mostafaei [a,g], Reza Sari Motlagh [a,h], Takahiro Kimura [b], Shin Egawa [b], Karim Bensalah [i], Pierre I. Karakiewicz [j], Manuela Schmidinger [a], Shahrokh F. Shariat [a,f,k,l,m,n,o]

[a] *Department of Urology, Medical University of Vienna, Vienna, Austria*
[b] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan*
[c] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia*
[d] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[e] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia*
[f] *Department of Urology, Medical University of Silesia, Zabrze, Poland*
[g] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[h] *Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[i] *Department of Urology, University of Rennes, Rennes, France*
[j] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Canada*
[k] *Research Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan*
[l] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[m] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic*
[n] *Department of Urology, Weill Cornell Medical College, New York, New York, USA*
[o] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria*

A R T I C L E I N F O

Keywords:
Cytoreductive nephrectomy
Combination therapy
Immune-combination therapy

A B S T R A C T

Background: Recently, immune checkpoint inhibitor (ICI)-combination therapies have radically altered the treatment landscape in metastatic renal cell carcinoma (mRCC). No phase 3 trials have assessed the impact of cytoreductive nephrectomy (CN) for efficacy in mRCC patients treated with ICI-combination therapy. We aimed to assess the role of ICI-combination therapy based on CN status.

Methods: Multiple databases were searched for articles published until June 2021. Studies comparing overall and/or progression-free survival (OS/PFS) in mRCC patients treated with ICI combination-therapy were deemed eligible.

Results: Six studies met the eligibility criteria. ICI-combination therapy was associated with significantly better OS/PFS than sunitinib in patients who had undergone CN (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.59–0.77/HR, 0.57; 95% CI, 0.44–0.74, respectively; both $P < 0.001$), and in those who had not (HR, 0.69; 95% CI, 0.57–0.85/HR, 0.63; 95% CI, 0.52–0.77, respectively; both $P < 0.001$). Although the OS and PFS benefits of ICI-combination therapy were larger in those undergoing CN, the HR for OS and PFS indicated that ICI-combination therapy's treatment effect did not differ substantially with or without CN. In network *meta*-analyses, nivolumab plus cabozantinib was the most effective regimen in those undergoing CN, and pembrolizumab plus lenvatinib for those not undergoing CN.

Conclusion: The effect of ICI combination therapy did not differ between mRCC patients undergoing and not undergoing CN. As each ICI combination regimen varied widely in its effect in patients undergoing and not undergoing CN, CN may contribute to better treatment decision-making for ICI-combination therapy recipients.

* Corresponding author at: Währinger Gürtel 18-20, 1090, Vienna, Austria.
E-mail addresses: morikeiichiro29@gmail.com, keiichiro.mori@meduniwien.ac.at (K. Mori).

https://doi.org/10.1016/j.intimp.2022.108720
Received 19 December 2021; Received in revised form 5 March 2022; Accepted 17 March 2022
Available online 24 March 2022

1. Introduction

The role of cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC) is yet to be established. Historically, CN has played a key role in the management of patients with mRCC ever since randomized trials demonstrated significant improvement in survival of patients receiving CN and interferon (IF)-α compared to those receiving IFα alone [1,2]. With the advent of targeted therapy (TT) as primary therapy for mRCC, the value of CN was readdressed.

Two recent prospective randomized trials, CARMENA and SURTIME, changed the treatment paradigm for mRCC [3,4]. The CARMENA trial investigated whether TT alone is inferior to CN followed by TT in terms of overall survival (OS) in patients with intermediate and poor risk features [3]. The SURTIME trial studied the role of immediate versus deferred CN in patients receiving sunitinib [4]. The CARMENA trial met its primary endpoint, demonstrating that sunitinib alone did not result in inferior survival when compared to upfront CN followed by sunitinib in intermediate-poor risk patients [3]. The SURTIME trial did not meet its primary (modified) endpoint (progression free survival [PFS] rate at 28 weeks). **The investigators initially sought to accrue 458 patients with its primary endpoint defined as PFS, but the trial** failed **to achieve its objectives because of not only a poor accrual rate but a high 18% ineligibility rate, resulting in early trial termination after enrolling 99 patients. To salvage the study and make it somewhat interpretable, however, the primary endpoint was later revised as a 28-week PFS survival rate.** However, the OS analysis suggested that upfront CN, thereby postponing systemic therapy, may be detrimental for patients who need a rapid control of their disease [4]. The results of these two trials suggest that CN is not appropriate for all patients, but that some may benefit from either immediate or delayed surgery; careful patient selection is required to determine whether and when CN is appropriate in patients with mRCC.

Immunotherapy has revolutionized the treatment of mRCC [5–7]. Immune checkpoint inhibitor (ICI) combination therapies have become the standard of first-line treatment of mRCC [6–9]. Despite the results of the CARMENA tiral, patients undergoing CN continue to account for a large proportion of patients enrolled in ICI combination randomized trials. Unlike in the TT era, no Phase III trial has assessed the effect of CN in patients receiving ICIs. Therefore, the value of CN remains unclear in the era of ICI combination therapy. **We sought to assess the role of ICI combination therapy based on CN status through a systematic review, *meta*-analysis, and network *meta*-analysis of all available data to date. Additionally, we discussed the value of CN in an era of ICI combination therapy.**

2. Methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42021262348).

2.1. Search strategy

A systematic review, *meta*-analysis, and network *meta*-analysis of randomized controlled trials in mRCC patients treated with first-line ICI combination therapies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [10]. A completed PRISMA 2009 checklist was used to describe the methodology of our study (Supplementary Table 1). PubMed, Web of Science, and Scopus were searched to identify reports published up to May 2021 that investigated first-line systemic therapy for mRCC. The following keywords were used in our search strategy: (renal cell carcinoma OR renal cell cancer OR kidney carcinoma OR kidney cancer) AND (metastatic OR advanced) AND (Randomized). Furthermore, we also reviewed relevant abstracts presented in major conferences including the American Society of Clinical Oncology, the European Society for Medical Oncology, and International Kidney Cancer Symposium. The primary outcome of interest was OS and the secondary outcome was PFS. Initial screening based on the titles and abstracts of the article was performed independently by two investigators to identify ineligible reports. Reasons for exclusions were noted. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process.

2.2. Inclusion and exclusion criteria

Studies were included if they had investigated mRCC patients with/without CN (patients) who had undergone ICI combination therapy as a first-line treatment (intervention) compared with patients treated with

Table 1
Study demographics.

Study	IMmotion151	JAVELIN Renal 101	CheckMate 214	KEYNOTE 426	CheckMate 9ER	CLEAR
Year	2019	2019	2018	2019	2021	2021
Compound	Atezolizumab plus bevacizumab	Avelumab plus axitinib	Nivolumab plus ipilimumab	Pembrolizumab plus axitinib	Nivolumab plus cabozantinib	Pembrolizumab plus lenvatinib
Control	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Number (treatment/control)	178/184	442/444	425/422	432/429	323/355	355/357
Age (treatment/control)	62/59	62/61	62/61	62/61	62/61	64/61
Male (treatment/control)	67%/79%	72%/78%	74%/71%	71%/75%	77%/71%	72%/77%
Poor risk (treatment/control)	11%/11%19vs20	12%/10% 72vs71	21%/21% 91vs89	13%/12% 56vs52	19%/21% 61vs68	9%/10% 32vs32
Nephrectomy (treatment/control)	84%/83%	80%/80%	80%/76%	83%/83%	69%/71%	74%/77%
PD-L1 positivity	100%/100%	61%/65%	26%/29%	59%/62%	26%/25%	30%/33%
Median OS (treatment/control)	34.0/32.7	NRE/NRE	NRE/26.0	NRE/35.7	NRE/NRE	NRE/NRE
Median PFS (treatment/control)	11.2/7.7	13.3/8.4	11.6/8.4	15.4/11.1	16.6/8.3	23.9/9.2
Median ORR (treatment/control)	43%/35%	51%/26%	42%/27%	60%/40%	56%/27%	71%/36%
Subsequent treatment	44%/55%	21%/39%	39%/54%	54%/69%	19%/33%	33%/58%
Median follow up	15 months	10.8/8.6 months	25.2 months	30.6 months	18.1 months	26.6 months

Abbreviation: NR (not reported), NRE (not reached), ORR (objective response rate), OS (overall survival), PD-L1 (programmed death ligand 1), PFS (progression free survival)

sunitinib as a first-line treatment (comparison) to assess the differential effects on OS and PFS (outcome) in Phase III randomized studies only. We excluded observational studies, reviews, letters, editorials, replies from authors, case reports, and articles not published in English. Studies were excluded if they had included no analysis of OS and PFS in patients undergoing and not undergoing CN. All references included in the relevant papers were scanned for additional studies of interest.

2.3. Data extraction

Two investigators independently extracted the following information from the included articles: study name, publication year, number of patients, treatment compound, age, sex, risk group, component of RCC, programmed death ligand 1 (PD-L1) status, subsequent treatment, oncological outcomes, and follow up. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with PFS and OS were retrieved.

2.4. Risk of bias assessment

The risk-of-bias (RoB) evaluation of each study was assessed according to The Cochrane Collaboration's tool for assessing RoB [11]. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other sources of bias (Supplementary Fig. 1). The RoB of each study was assessed independently by two authors. Disagreements were resolved by consulting with the coauthors.

2.5. Statistical analyses

2.5.1. Meta-analysis

First, forest plots were used to assess the HRs and describe the relationships between treatment (ICI combination therapy versus sunitinib) and survival outcomes in patients with CN. Second, forest plots were used to assess the HRs and describe the relationships between treatment (ICI combination therapy versus sunitinib) and survival outcomes in patients without CN. Regarding PFS, subgroup analysis was conducted in PD-L1-positive patients. Heterogeneity among outcomes of included studies in this *meta*-analysis was evaluated using Cochrane's Q test and the I^2 statistic. Significant heterogeneity was indicated by a $P \leqq 0.05$ in Cochrane's Q test and a ratio$\geqq$50% in the I^2 statistic. We used fixed-effects models to calculate non-heterogeneous results [12–14]. Random-effects models were used in cases of heterogeneity.

2.5.2. Network meta-analysis

A network *meta*-analysis was conducted with random- and fixed-effects models using a frequentist approach to compare treatments, with sunitinib as the common comparator arm [15,16]. In the assessment for OS, contrast-based analyses were applied with estimated differences in the log HR and the standard error calculated from the published HRs and CIs [17]. Relative treatment effects were presented as HRs and 95% credible intervals (CrIs) [15]. Also, for each outcome, the different treatments were assessed for relative ranking using the P-score, which can be considered a frequentist analog to the surface under the cumulative ranking curve [18,19]. All statistical analyses were performed using R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria; package 'netmeta') and Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study selection and characteristics

Our initial search identified 5,171 publications, of which 4,456 remained following the elimination of duplicates. A further 4,389

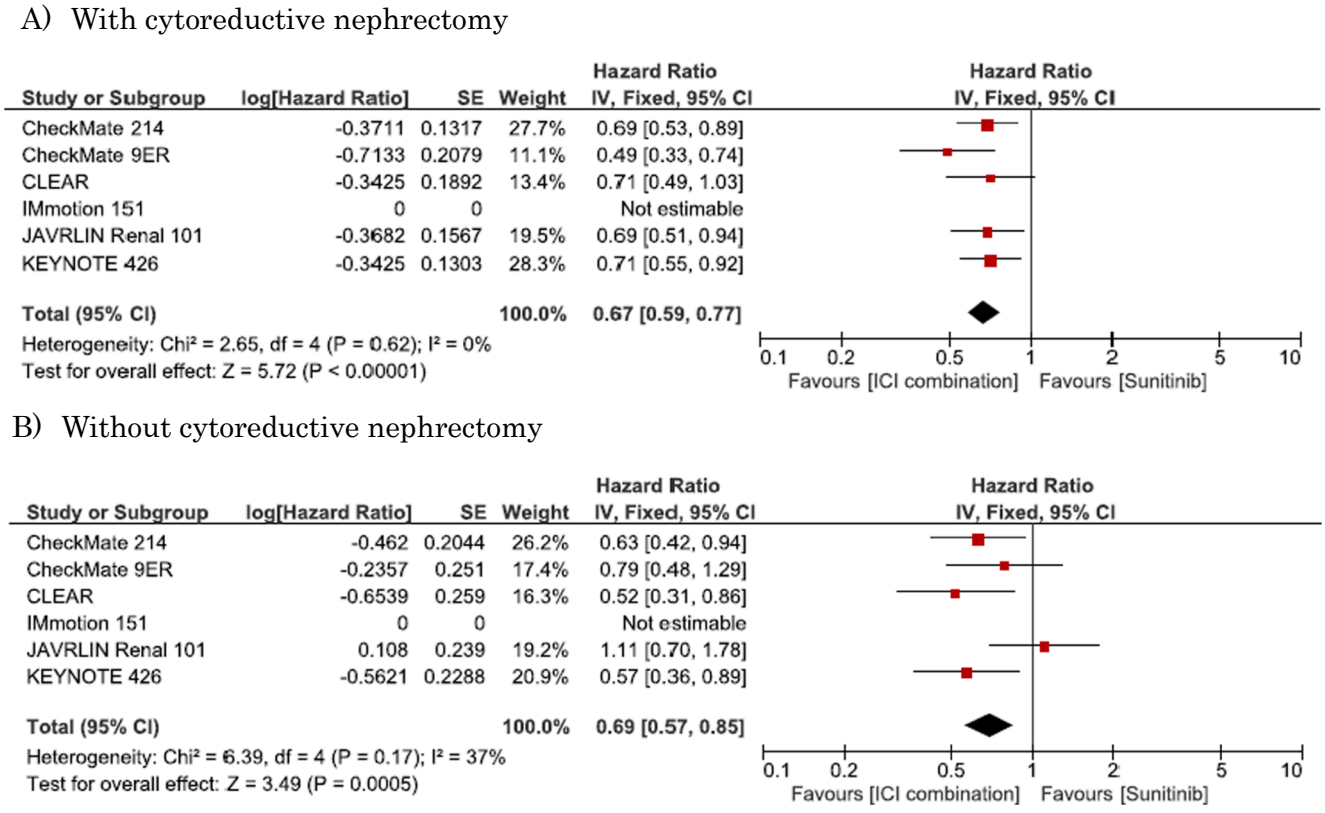

Fig. 1. Forest plots showing the association between treatment and overall survival in metastatic renal cell carcinoma (immune checkpoint inhibitor combination therapy versus sunitinib). With cytoreductive nephrectomy. (B) Without cytoreductive nephrectomy.

articles were excluded after screening the titles and abstracts, and full-text reviews were performed for the remaining 67 articles (Supplementary Fig. 2). Based on the selection criteria, six randomized controlled trials (RCTs) were identified for systematic review, *meta*-analysis, and network meta-analysis [20–27]. The data extracted from these six RCTs are listed in Table 1. In these RCTs, 4,346 patients were treated with ICI combination therapy (n = 2,155; 49.6%) or sunitinib (n = 2,191; 50.4%). All six RCTs included patients with mRCC with a predominant clear cell component, with 9–21% of the patients treated with ICI combination therapy being in the poor risk category. The proportion of patients undergoing CN ranged from 69 to 84% among those receiving ICI combination therapy. The median follow-up ranged between 10.8 and 30.6 months.

3.2. Meta-analysis

3.2.1. Os

ICI combination therapy was associated with significantly longer OS than sunitinib among patients who had undergone CN (pooled HR, 0.67; 95% CI, 0.59–0.77; $P < 0.001$) (Fig. 1A). Cochrane's Q test ($P = 0.62$) and the I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

ICI combination therapy was associated with significantly longer OS than sunitinib among patients who did not undergo CN (pooled HR, 0.69; 95% CI, 0.57–0.85; $P < 0.001$) (Fig. 1B). Cochrane's Q test ($P = 0.17$) and the I^2 test ($I^2 = 37\%$) revealed no significant heterogeneity.

3.2.2. Pfs

ICI combination therapy was associated with significantly longer PFS than sunitinib among patients who had undergone CN (pooled HR, 0.57; 95% CI, 0.44–0.74; $P < 0.001$) (Fig. 2A). Cochrane's Q test ($P < 0.001$) and the I^2 test ($I^2 = 84\%$) revealed significant heterogeneity.

ICI combination therapy was associated with significantly longer PFS than sunitinib among patients who did not undergo CN (pooled HR, 0.63; 95% CI, 0.52–0.77; $P < 0.001$) (Fig. 2B). Cochrane's Q test ($P = 0.45$) and the I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

3.2.3. mRCC patients with PD-L1 positive tumors (ICI-combination therapy versus sunitinib)

ICI combination therapy was associated with significantly longer PFS than sunitinib among patients with PD-L1-positive tumors who had undergone CN (pooled HR, 0.70; 95% CI, 0.59–0.83; $P < 0.001$) (Supplementary Figure 3A). Cochrane's Q test ($P = 0.91$) and the I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity. In contrast, ICI combination therapy was not associated with significantly longer PFS than sunitinib in patients with PD-L1-positive tumors who had not undergone CN (pooled HR, 0.72; 95% CI, 0.45–1.15; $P = 0.17$) (Supplementary Figure 3B). Cochrane's Q test ($P = 0.62$) and the I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

3.3. Network meta-analysis

3.3.1. mRCC patients with CN

A network *meta*-analysis of five treatments was performed for OS. Compared with sunitinib, all five ICI combination therapies resulted in significantly improved OS among patients having been treated with CN (Supplementary Table 2). Analysis of treatment ranking revealed that nivolumab plus cabozantinib had the highest likelihood of providing the maximal OS (P score: 0.99) (Supplementary Table 3).

3.3.2. mRCC patients not undergoing CN

Pembrolizumab plus lenvatinib, pembrolizumab plus axitinib, and nivolumab plus ipilimumab resulted in significantly improved OS

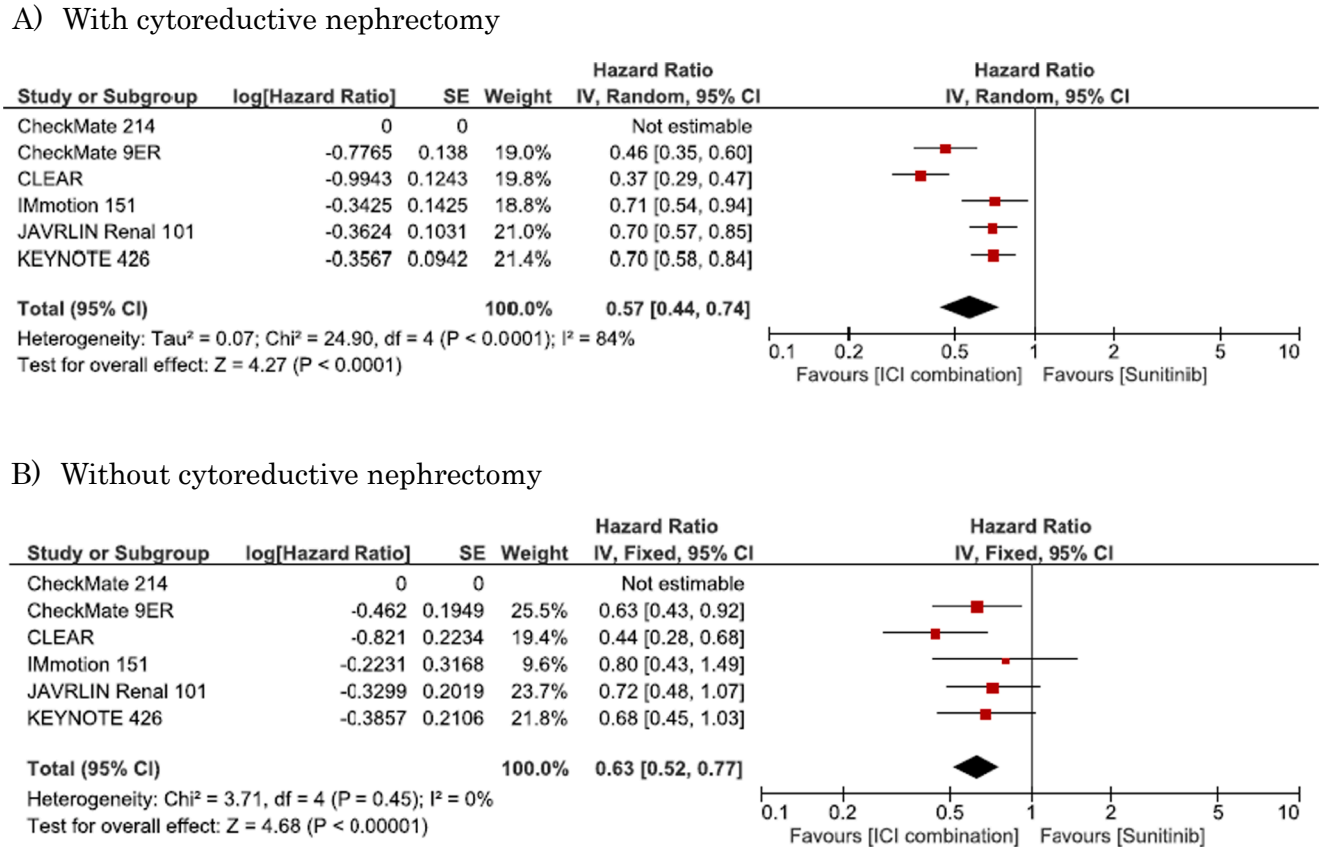

Fig. 2. Forest plots showing the association between treatment and progression free survival in metastatic renal cell carcinoma (immune checkpoint inhibitor combination therapy versus sunitinib). (A) With cytoreductive nephrectomy. (B) Without cytoreductive nephrectomy.

among patients having not been treated with CN (HR, 0.52; 95% CrI, 0.40–0.68/HR, 0.63; 95% CrI, 0.49–0.82) compared to sunitinib (Supplementary Table 2). Analysis of treatment ranking demonstrated that pembrolizumab plus lenvatinib had the highest likelihood of providing the maximal OS (P score: 0.89), closely followed by pembrolizumab plus axitinib and nivolumab plus ipilimumab (P score: 0.78 and 0.65, respectively) (Supplementary Table 3).

4. Discussion

Herein, a systematic review and *meta*-analysis was conducted to assess the role of ICI-combination therapy based on CN status in mRCC patients. We also conducted a network *meta*-analysis to indirectly compare available ICI treatment options in mRCC patients who have or have not undergone CN. This study yielded several findings of interest. First, ICI combination therapy was shown to be associated with significantly improved OS and PFS compared with sunitinib in mRCC patients, regardless of whether or not the patients had undergone CN. Second, while the OS and PFS benefits of ICI combination therapy were larger in those who underwent CN than in those who did not, the HR for OS (HR for those who underwent CN versus those who did not, 0.67 versus 0.69) and PFS (HR, 0.57 versus 0.63) indicated that the treatment effect did not differ much between mRCC patients who underwent CN and those who did not. Therefore, it can be deduced that CN offers limited survival benefits in mRCC patients receiving ICI combination therapy. Third, of the four ICI combinations compared, those who received nivolumab plus cabozantinib combination seemed to have benefitted from previous CN. Conversely, pembrolizumab plus lenvatinib seemed to give better OS benefits in patients who did not have CN.

CN was still being recommended despite a large shift in systemic therapeutic modalities and a lack of evidence that supports its use in mRCC patients receiving state-of-the-art therapies. Several hypotheses have been advanced to explain the potential benefit of CN. First, the resection of the primary tumor might help eliminate immunosuppressive cytokines and other bio-humoral events that may interfere with an otherwise effective anti-tumor immune response [28]. It is also known that RCC develops an immunosuppressive tumor microenvironment in which proinflammatory cytokines and chemokines serve to promote tumorigenesis. Several growth factors and distinct immune cell subsets have also been shown to contribute to the predominantly suppressive immune background in RCC [29]. It has been demonstrated that myeloid-derived suppressor cells are elevated in patients with RCC and that their levels increase with the metastatic tumor burden [30]. These suppressor cells lead to the downregulation of the immune responses coupled with the expression of specific molecules such as CTLA-4, B7-H1, B7-H3, B7-H4 and PD-1, on the surface of tumor cells and effector T cells [31,32]. Therefore, there appears to be a biological rationale for the use of CN in mRCC, specifically in the ICI era, given the close immunosuppressive interplay.

To address the lack of evidence, two recent trials (CARMENA and SURTIME) sought to assess the role and sequential use of CN in mRCC patients receiving TT [3,4]. However, caution should be exercised in interpreting these results. First, both the CARMENA and SURTIME trials experienced difficulties in patient recruitment; neither met the planned inclusion of their calculated sample size, while the CARMENA trial recruited substantially more patients than the SURTIME trial [33]. Second, the CARMENA trial included only those with intermediate- or poor-risk disease based on the MSKCC prognostic model, with 43% of patients being in the poor-risk category who typically do not benefit from CN [34,35]. Therefore, the use of CN in this poor-risk population may have led to the non-inferiority endpoint being met in this trial. Third, there was significant crossover in the two arms with 17% of patients randomized to sunitinib alone having undergone subsequent CN and 7% assigned to upfront CN not having undergone CN. In a non-inferiority trial, this tends to exhibit a bias towards non-inferiority. Finally, a study using the national cancer data base found that the CARMENA trial recruited those with a higher metastatic tumor burden than those in a real-world population [36,37]. Therefore, patients randomized in this trial may not truly reflect ideal candidates for CN in a real-world setting.

Despite the recent evidence from the CARMENA and SURTIME trials, the value of CN in patients with mRCC remains unclear, specifically in those receiving ICI combination therapy. In our analysis, there was no notable difference in the HR for OS and PFS between those receiving ICI combination therapy and those receiving sunitinib alone, when stratified by the presence of CN. In other words, the data suggests that CN may not have a role in mRCC patients receiving ICI combination therapy as was the case in those receiving TT. However, analysis of overall populations alone (to the exclusion of the CheckMate 214 trial which enrolled many poor-risk patients) depicted a slightly larger difference between those receiving CN and those not receiving CN in HR for OS and PFS when treated with ICI combination therapy versus sunitinib alone, suggesting the importance of patient selection for CN (data not shown). Interestingly, in our network *meta*-analysis, the efficacy of each ICI combination regimen varied greatly depending on whether or not the patients had undergone CN, with nivolumab plus cabozantinib probably best in those who had been treated with CN, and pembrolizumab plus lenvatinib probably best in those who did not receive CN. These findings may provide biologic and clinical clues in the understanding and selection of ICI combination regimens in mRCC patients.

PD-L1 status is one of the most promising biomarkers for predicting the response to ICI therapies [38,39]. In our subgroup analyses based on PD-L1 status, ICI combination therapy was associated with significantly longer PFS than sunitinib in PD-L1-positive mRCC patients who had undergone CN, but it was not associated with PFS compared to sunitinib in PD-L1-positive mRCC patients who did not undergo CN. **In patients without previous CN and PD-L1 positive tumors, ICI combinations did better than sunitinib (while non-significantly) with an HR of 0.72, which was almost similar to that for patients with previous CN and PD-L1 positive tumors. In other words, even though our sub-analysis suggests that PD-L1 status may help in the selection of patients who may benefit from ICI combinations, they had limited statistical power and validity, given no significant difference in HR regardless of the presence of CN and given the limited number of patients evaluated from as few as 2 studies included. As a consequence, any meaningful conclusions may be difficult to draw from these analyses alone. Furthermore, all study populations need to be adjusted for IMDC risk, which is a crucial factor in the clinical decision-making for patients with mRCC** [7]. **However, given the paucity of data, CN was not evaluable across the different IMDC risk categories. This was a major limitation of this study.**

Despite the comprehensive nature of the systematic review undertaken, this study has limitations. **First, the most significant limitation of our analysis was that its basis, described as the presence or absence of CN, was strictly the presence or absence of a priori nephrectomy, and that not all a priori nephrectomies were CN. This meant that all patients undergoing cytoreductive nephrectomy and a priori nephrectomy were lumped together in our analysis and therefore that the study findings need to be interpreted with caution.** Second, despite being similar in design, treatment lines, and target disease, attention should be paid to the differences in patient characteristics at study enrollment between the included trials. Further, the follow-up durations, proportions of poor-risk patients, PD-L1 status, and subsequent treatment differed greatly between the RCTs evaluated. These differences might have affected the survival outcomes. Notably, caution should be exercised in assessing nivolumab plus ipilimumab data from the CheckMate 214 trial. Whereas most RCTs enrolled patients from all risk strata, the CheckMate 214 trial enrolled patients with intermediate- and poor-risk disease in its primary analysis, while all-risk patients were included in its secondary analysis, suggesting a biased estimate of the efficacy of nivolumab plus ipilimumab compared with the other systemic treatment [21]. Moreover, only PD-L1-positive

patients were included for analyses in the IMmotion 151 trial [25]. Third, significant heterogeneity was detected in the PFS analyses, thereby limiting the value of findings pertaining to this endpoint. Despite the use of a random-effects model to address heterogeneity between the studies, our conclusions should be interpreted with caution. Fourth, although indirect comparative analyses have been used for network *meta*-analysis and validated for reliability in comparing outcomes from RCTs, this approach falls short of a head-to-head treatment comparison. Therefore, well-designed comparative trials are required to validate the findings of this study. Fifth, at the time of this review, the JAVELIN Renal 101 trial included only immature OS data, which may differ in the final analyses [24,40]. **In addition, this analysis included only fist publication of the most selected studies.** Sixth, due to a paucity of data, the current *meta*-analysis only inadequately evaluated the impact of heterogeneity in patient populations and selection criteria among the RCTs on the outcomes of the *meta*-analysis. In our analysis of OS, there was a trend toward a larger difference in the hazard ratio between those undergoing CN and those not undergoing CN before and after excluding the CheckMate 214 trial from analysis (intermediate- and poor-risk disease in the primary analysis), suggesting that IMDC risk is an important factor likely affecting the current *meta*-analysis (data not shown). On the other hand, our inclusion criteria (inclusion of Phase III randomized studies only, sunitinib as the only control, and first-line treatments only) may have contributed to the reduction of heterogeneity in the patient populations. Finally, in light of recently published post hoc analyses from the CARMENA trial, CN may need to make way for more effective systemic therapies in the evolving treatment paradigm for mRCC depending on the disease volume and the number of IMDC risk factors involved, and careful patient selection remains the key for upfront or deferred CN based on these criteria [41,42]. The current *meta*-analysis suffers from lack of data that made it rather difficult to assess the role of CN based on careful patient selection, particularly IMDC risk-based stratification. Therefore, it is eagerly hoped that CN will be assessed for its role in mRCC patients receiving ICI treatment, based on IMDC risk stratification and careful patient selection.

There are some clinical trials underway to help guide the use of CN and ICIs in mRCC. The PROBE trial will evaluate the sequential use of upfront CN followed by systemic therapy (ICI alone or tyrosine kinase inhibitor [TKI] + ICI) for mRCC as opposed to systemic therapy alone with ICI or TKI + ICI [43]. The NORDIC-SUN trial will evaluate the role of deferred CN in patients receiving an ICI combination regimen (nivolumab plus ipilimumab) [44]. The results of these trials directly evaluating the role of CN combined with ICI-based therapy are eagerly awaited.

5. Conclusions

Our analyses suggest that the effect of ICI combination therapy did not differ between mRCC patients who underwent CN and those who did not. CN may not improve survival in mRCC patients receiving ICI combination therapy as was the case in those receiving TT. This may provide a rationale for treating mRCC patients who require systemic therapy with drug therapy first, followed by deferred CN at a later stage if deemed beneficial. Careful patient selection is still paramount. Each ICI combination therapy differs greatly in efficacy depending on whether the included patients had undergone CN, suggesting that the use or non-use of CN may help with decision-making pertaining treatment in RCC patients. Due to a rapidly evolving treatment landscape, it appears difficult to re-assess the role of CN in this setting, suggesting the need for preplanned subgroup analyses in drug trials. Therefore, these data may help set up hypotheses and facilitate further discussion on the role of CN in the era of ICI combination therapy. **However, study limitations, i.e., the fact that the rate of patients in different prognostic groups varied between the RCTs evaluated and that patients undergoing cytoreductive nephrectomy and a priori nephrectomy were lumped together for analysis, need to be taken into account in interpreting the study results.**

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.

Acknowledgements

Dr. Laukhtina and Pradere are supported by the EUSP Scholarship of the European Association of Urology. Dr. Mori is supported by The Uehara Memorial Foundation.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author contributions

Conceptualization/ Investigation: K Mori, F Quhal, M Schmidinger, SF Shariat.

Data curation/ Methodology: K Mori, F Quhal.

Formal analysis/ Software: K Mori, H Mostafaei.

Supervision: SF Shariat Writing-original draft: K Mori Writing-review & editing: F Quhal, T Yanagisawa, S Katayama, B Pradere, E Laukhtina, P Rajwa, H Mostafaei, R Sari Motlagh, T Kimura, S Egawa, K Bensalah, M Schmidinger, SF Shariat.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.108720.

References

[1] R.C. Flanigan, S.E. Salmon, B.A. Blumenstein, S.I. Bearman, V. Roy, P.C. McGrath, J.R. Caton Jr., N. Munshi, E.D. Crawford, Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer, The New England journal of medicine 345 (23) (2001) 1655–1659.

[2] G.H. Mickisch, A. Garin, H. van Poppel, L. de Prijck, R. Sylvester, Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial, Lancet (London, England) 358 (9286) (2001) 966–970.

[3] A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.C. Bernhard, L. Albiges, M.O. Timsit, T. Lebret, B. Escudier, Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma, The New England journal of medicine 379 (5) (2018) 417–427.

[4] A. Bex, P. Mulders, M. Jewett, J. Wagstaff, J.V. van Thienen, C.U. Blank, R. van Velthoven, M. Del Pilar Laguna, L. Wood, H.H.E. van Melick, M.J. Aarts, J. B. Lattouf, T. Powles, D.I. de Jong Md, S. Ph, B. Rottey, S. Tombal, S. Marreaud, L. Collette, J.H. Collette, Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial, JAMA oncology 5 (2) (2019) 164–170.

[5] K. Mori, B. Pradere, F. Quhal, S. Katayama, H. Mostafaei, E. Laukhtina, V. M. Schuettfort, D. D'Andrea, S. Egawa, K. Bensalah, M. Schmidinger, T. Powles, S. F. Shariat, Differences in oncological and toxicity outcomes between programmed cell death-1 and programmed cell death ligand-1 inhibitors in metastatic renal cell carcinoma: A systematic review and meta-analysis, Cancer Treat. Rev. 99 (2021) 102242.

[6] J. Bedke, L. Albiges, U. Capitanio, R.H. Giles, M. Hora, T.B. Lam, B. Ljungberg, L. Marconi, T. Klatte, A. Volpe, Y. Abu-Ghanem, S. Dabestani, S. Fernández-Pello, F. Hofmann, T. Kuusk, R. Tahbaz, T. Powles, A. Bex, Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Nivolumab plus Cabozantinib Joins Immune Checkpoint Inhibition Combination Therapies for Treatment-naïve Metastatic Clear-Cell Renal Cell Carcinoma, Eur. Urol. 79 (3) (2021) 339–342.

[7] J. Bedke, L. Albiges, U. Capitanio, R.H. Giles, M. Hora, T.B. Lam, B. Ljungberg, L. Marconi, T. Klatte, A. Volpe, Y. Abu-Ghanem, S. Dabestani, S.F. Pello, F. Hofmann, T. Kuusk, R. Tahbaz, T. Powles, A. Bex, The 2021 Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint

Inhibitor-based Combination Therapies for Treatment-naive Metastatic Clear-cell Renal Cell Carcinoma Are Standard of Care, Eur. Urol. 80 (4) (2021) 393–397.
[8] K. Mori, H. Mostafaei, N. Miura, P.I. Karakiewicz, S. Luzzago, M. Schmidinger, A. Bruchbacher, B. Pradere, S. Egawa, S.F. Shariat, Systemic therapy for metastatic renal cell carcinoma in the first-line setting: a systematic review and network meta-analysis, Cancer immunology, immunotherapy : CII 70 (2) (2021) 265–273.
[9] F. Quhal, K. Mori, A. Bruchbacher, I. Resch, H. Mostafaei, B. Pradere, V. M. Schuettfort, E. Laukhtina, S. Egawa, H. Fajkovic, M. Remzi, S.F. Shariat, M. Schmidinger, First-line Immunotherapy-based Combinations for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis, European urology oncology 4 (5) (2021) 755–765.
[10] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (7) (2009), e1000100.
[11] J.P.T. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A.C. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ (Clinical research ed.) 343 (2011) d5928.
[12] R. DerSimonian, R. Kacker, Random-effects model for meta-analysis of clinical trials: an update, Contemporary clinical trials 28 (2) (2007) 105–114.
[13] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control. Clin. Trials 7 (3) (1986) 177–188.
[14] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ (Clinical research ed.) 327 (7414) (2003) 557–560.
[15] G. van Valkenhoef, G. Lu, B. de Brock, H. Hillege, A.E. Ades, N.J. Welton, Automating network meta-analysis, Res. synthesis methods 3 (4) (2012) 285–299.
[16] S. Dias, N.J. Welton, A.J. Sutton, A.E. Ades, NICE Decision Support Unit Technical Support Documents, NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, National Institute for Health and Care Excellence (NICE) Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved., London, 2014.
[17] B.S. Woods, N. Hawkins, D.A. Scott, Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial, BMC Med. Res. Method. 10 (2010) 54.
[18] G. Rücker, G. Schwarzer, Ranking treatments in frequentist network meta-analysis works without resampling methods, BMC Med. Res. Method. 15 (2015) 58.
[19] G. Salanti, A.E. Ades, J.P. Ioannidis, Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial, J. Clin. Epidemiol. 64 (2) (2011) 163–171.
[20] T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V. M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J. C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M. A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, R.J. Motzer, Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma, The New England journal of medicine 384 (9) (2021) 829–841.
[21] R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T. K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B. I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, B. Escudier, Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma, The New England journal of medicine 378 (14) (2018) 1277–1290.
[22] R.J. Motzer, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, B. Alekseev, S. Y. Rha, E. Kopyltsov, M.J.M. Vidal, S.-H. Hong, A. Kapoor, T.A. Gordoa, J.C. Goh, J.R. Merchan, A.D. Smith, K. Mody, R.F. Perini, D. Xing, T.K. Choueiri, Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study), J. Clin. Oncol. 39 (6_suppl) (2021) 269.
[23] R. Motzer, B. Alekseev, S.Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T. E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A. D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, T.K. Choueiri, Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma, The New England journal of medicine 384 (14) (2021) 1289–1300.
[24] R.J. Motzer, K. Penkov, J. Haanen, B. Rini, L. Albiges, M.T. Campbell, B. Venugopal, C. Kollmannsberger, S. Negrier, M. Uemura, J.L. Lee, A. Vasiliev, W. H. Miller Jr., H. Gurney, M. Schmidinger, J. Larkin, M.B. Atkins, J. Bedke, B. Alekseev, J. Wang, M. Mariani, P.B. Robbins, A. Chudnovsky, C. Fowst, S. Hariharan, B. Huang, A. di Pietro, T.K. Choueiri, Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma, The New England journal of medicine 380 (12) (2019) 1103–1115.
[25] B.I. Rini, T. Powles, M.B. Atkins, B. Escudier, D.F. McDermott, C. Suarez, S. Bracarda, W.M. Stadler, F. Donskov, J.L. Lee, R. Hawkins, A. Ravaud, B. Alekseev, M. Staehler, M. Uemura, U. De Giorgi, B. Mellado, C. Porta, B. Melichar, H. Gurney, J. Bedke, T.K. Choueiri, F. Parnis, T. Khaznadar, A. Thobhani, S. Li, E. Piault-Louis, G. Frantz, M. Huseni, C. Schiff, M.C. Green, R. J. Motzer, Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial, Lancet (London, England) 393 (10189) (2019) 2404–2415.
[26] B.R.D. Soulières, E.R. Plimack, J. Bedke, T. Waddell, V. Stus, R. Gafanov, D. Nosov, F. Pouliot, B. Melichar, I. Vynnychenko, S.J. Azevedo, D. Borchiellini, R. S. McDermott, S. Tamada, J. Lin, R. Perini, L.R. Molife, M.B. Atkins, T Powles., Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma: Subgroup Analysis From KEYNOTE-426 by Prior Nephrectomy, International Kidney Cancer Symposium (2020).
[27] B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R. S. McDermott, J. Bedke, S. Tartas, Y.H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, T. Powles, Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma, The New England journal of medicine 380 (12) (2019) 1116–1127.
[28] R.C. Flanigan, Debulking nephrectomy in metastatic renal cancer, Clinical cancer research : an official journal of the American Association for, Cancer Res. 10 (18 Pt 2) (2004) 6335s–6341s.
[29] A.W. Griffioen, F.A. Vyth-Dreese, Angiostasis as a way to improve immunotherapy, Thromb. Haemost. 101 (6) (2009) 1025–1031.
[30] A.H. Zea, P.C. Rodriguez, M.B. Atkins, C. Hernandez, S. Signoretti, J. Zabaleta, D. McDermott, D. Quiceno, A. Youmans, A. O'Neill, J. Mier, A.C. Ochoa, Arginase-producing myeloid suppressor cells in renal cell carcinoma patients: a mechanism of tumor evasion, Cancer Res. 65 (8) (2005) 3044–3048.
[31] X. Frigola, B.A. Inman, C.M. Lohse, C.J. Krco, J.C. Cheville, R.H. Thompson, B. Leibovich, M.L. Blute, H. Dong, E.D. Kwon, Identification of a soluble form of B7–H1 that retains immunosuppressive activity and is associated with aggressive renal cell carcinoma, Clinical cancer research : an official journal of the Am. Association for Cancer Res. 17 (7) (2011) 1915–1923.
[32] R.H. Thompson, M.D. Gillett, J.C. Cheville, C.M. Lohse, H. Dong, W.S. Webster, K. G. Krejci, J.R. Lobo, S. Sengupta, L. Chen, H. Zincke, M.L. Blute, S.E. Strome, B. C. Leibovich, E.D. Kwon, Costimulatory B7–H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target, PNAS 101 (49) (2004) 17174–17179.
[33] T. Kuusk, B. Szabados, W.K. Liu, T. Powles, A. Bex, Cytoreductive nephrectomy in the current treatment algorithm, Therapeutic advances in medical oncology 11 (2019) 1758835919879026.
[34] S.H. Culp, N.M. Tannir, E.J. Abel, V. Margulis, P. Tamboli, S.F. Matin, C.G. Wood, Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 116 (14) (2010) 3378–3388.
[35] D.Y. Heng, J.C. Wells, B.I. Rini, B. Beuselinck, J.L. Lee, J.J. Knox, G.A. Bjarnason, S. K. Pal, C.K. Kollmannsberger, T. Yuasa, S. Srinivas, F. Donskov, A. Bamias, L. A. Wood, D.S. Ernst, N. Agarwal, U.N. Vaishampayan, S.Y. Rha, J.J. Kim, T. K. Choueiri, Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium, Eur. Urol. 66 (4) (2014) 704–710.
[36] S. Arora, A. Sood, D. Dalela, H.J. Tang, A. Patel, J. Keeley, Q.D. Trinh, C.G. Rogers, M. Menon, F. Abdollah, Cytoreductive Nephrectomy: Assessing the Generalizability of the CARMENA Trial to Real-world National Cancer Data Base Cases, Eur. Urol. 75 (2) (2019) 352–353.
[37] B. Bhindi, E.B. Habermann, R.J. Mason, B.A. Costello, L.C. Pagliaro, R. H. Thompson, B.C. Leibovich, S.A. Boorjian, Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma, J. urology 200 (3) (2018) 528–534.
[38] K. Mori, M. Abufaraj, H. Mostafaei, F. Quhal, H. Fajkovic, M. Remzi, P. I. Karakiewicz, S. Egawa, M. Schmidinger, S.F. Shariat, K.M. Gust, The Predictive Value of Programmed Death Ligand 1 in Patients with Metastatic Renal Cell Carcinoma Treated with Immune-checkpoint Inhibitors: A Systematic Review and Meta-analysis, Eur. Urol. 79 (6) (2021) 783–792.
[39] K. Mori, B. Pradere, M. Moschini, H. Mostafaei, E. Laukhtina, V.M. Schuettfort, R. Sari Motlagh, F. Soria, J.Y.C. Teoh, S. Egawa, T. Powles, S.F. Shariat, First-line immune-checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: A systematic review and meta-analysis, European journal of cancer (Oxford, England 151 (2021) (1990) 35–48.
[40] T.K. Choueiri, R.J. Motzer, B.I. Rini, J. Haanen, M.T. Campbell, B. Venugopal, C. Kollmannsberger, G. Gravis-Mescam, M. Uemura, J.L. Lee, M.O. Grimm, H. Gurney, M. Schmidinger, J. Larkin, M.B. Atkins, S.K. Pal, J. Wang, M. Mariani, S. Krishnaswami, P. Cislo, A. Chudnovsky, C. Fowst, B. Huang, A. di Pietro, L. Albiges, Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma, Annals of oncology : official journal of the European Society for Medical Oncology 31 (8) (2020) 1030–1039.
[41] A. Méjean, A. Ravaud, S. Thezenas, C. Chevreau, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, S. Oudard, B. Laguerre, M. Gross-Goupil, J. C. Bernhard, S. Colas, L. Albiges, T. Lebret, J.M. Treluyer, M.O. Timsit, B. Escudier, Sunitinib Alone or After Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Is There Still a Role for Cytoreductive Nephrectomy? Eur. Urol. 80 (4) (2021) 417–424.
[42] E. Roussel, B. Beuselinck, M. Albersen, Three Years After CARMENA: What Have We Learned? Eur. Urol. 80 (4) (2021) 425–427.
[43] I.N. Group SO, Comparing the Outcome of Immunotherapy-Based Drug Combination Therapy with or without Surgery to Remove the Kidney in Metastatic Kidney Cancer, the PROBE Trial (PROBE).
[44] H.A. Donskov F, Aarhus UO, Deferred CytoreductiveNephrectomy in Synchronous Metastatic Renal Cell Carcinoma: The NORDIC-SUN-Trial (NORDIC-SUN).