EUROPEAN UROLOGY 79 (2021) 783–792

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Kidney Cancer

Editorial by Laurence Albiges, Ronan Flippot and Bernard Escudier on pp. 793–795 of this issue

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

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Article info

Article history:
Accepted October 9, 2020

Associate Editor:
Giacomo Novara

Keywords:
Renal cell carcinoma
Meta-analysis
Immune-checkpoint inhibitor
Programmed death ligand 1

Abstract

Context: Immune-checkpoint inhibitors (ICIs) are a mainstay treatment of metastatic renal cell carcinoma (mRCC). As not all patients benefit from ICIs, a biomarker-driven clinical decision-making strategy is desirable.
Objective: To assess the predictive value of programmed death ligand 1 (PD-L1) in mRCC patients treated with ICIs.
Evidence acquisition: Multiple databases were searched for articles published up to April 2020 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. Studies comparing objective response rate (ORR), complete response rate (CRR), progressive disease rate (PDR), or progression-free survival (PFS) based on tumor PD-L1 status in mRCC patients were eligible.
Evidence synthesis: Six studies matched our eligibility criteria. Treatment with ICIs was associated with significantly higher ORRs and CRRs, and lower PDRs in patients with PD-L1–positive tumors than in those with PD-L1–negative status (odds ratio [OR] 1.84, 95% confidence interval [CI] 1.48–2.28; OR 3.11, 95% CI 2.04–4.75; and OR 0.43, 95% CI 0.31–0.60, respectively). ICI treatment was associated with significantly better PFS in PD-L1–positive patients than in sunitinib-treated patients (hazard ratio 0.65, 95% CI 0.57–0.74), whereas this was not found in patients with PD-L1–negative tumors. Compared with sunitinib, ICI combination therapy improved ORRs and PFS significantly in PD-L1–positive patients of all examined ICIs. Nivolumab plus ipilimumab had the highest likelihood of providing the highest ORR and longest PFS in PD-L1–positive patients.
Conclusions: PD-L1 positivity of the tumor is associated with improved ORRs and prolonged PFS in mRCC patients receiving ICI treatment and thus helps identify mRCC patients most likely to benefit from ICI treatment.

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https://doi.org/10.1016/j.eururo.2020.10.006

Patient summary: The use of an immune-checkpoint inhibitor for the treatment of metastatic renal cell carcinoma (mRCC) improved oncological outcomes, and the status of programmed death ligand 1 could contribute to guiding patients and clinicians when determining personalized treatment strategies for mRCC.

1. Introduction

Renal cell carcinoma (RCC) is among the 10 most frequently diagnosed cancers worldwide [1–3]. Approximately 25% of patients with RCC initially present with metastatic disease and typically require systemic therapy. Moreover, a significant proportion of patients with localized disease will develop metastatic RCC (mRCC) despite local therapy [1–3]. The advent of immune-checkpoint inhibitors (ICIs) has, nevertheless, transformed the treatment landscape of mRCC. ICIs exert their effect via suppression of the inhibitory effects of T-cell activation by a set of cell surface receptors, termed as immune checkpoints, which upregulate their receptors, such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), to protect the host from an excessive immune response [4]. Therefore, ICIs allow the adaptive immune system to mount an effective antitumor response.

Unlike many other solid tumors, RCC is an immunogenic and immune-responsive tumor, given the high expression of immunosuppressive ligands on tumor cells and the ability of tumors to upregulate immunosuppressive receptors on T lymphocytes and natural killer cells [5–7]. In recent clinical trials, ICI-based combination therapies, such as nivolumab plus ipilimumab, atezolizumab plus bevacizumab, pembrolizumab plus axitinib, and avelumab plus axitinib, have improved overall survival (OS) and/or progression-free survival (PFS) in patients with mRCC compared with the previous standard of care sunitinib [8–12].

Despite statistically significant benefits provided by ICI-based therapy in mRCC, patients exhibit highly variable responses to treatment, ranging from rapid disease progression to sustained complete remissions [13]. Currently, the proportion of patients experiencing clinical benefit from ICIs is still comparatively limited, with some patients showing a better response to treatment with tyrosine kinase inhibitors (TKIs) [7,14]. Thus, in the present era of personalized medicine, identification of prognostic and predictive biomarkers is crucial with respect to determining whether patients are more likely to benefit from ICIs than from other available and effective therapeutic options, and unnecessary adverse events in patients who are unlikely to respond could be avoided [15,16]. Although these new treatments bring a high economic burden to the healthcare system, better treatment selection based on biomarkers may help reduce treatment-related costs. To date, PD-L1 has been the most promising biomarker of response to ICIs, including in RCC [17]. PD-L1 exhibits a prognostic value for various malignancies; notably, research suggests that PD-L1 has not only a predictive, but also a prognostic value in ICI treatment for non–small-cell lung cancer (NSCLC), which has led to PD-L1 expression being included as an indication for pembrolizumab administration in case of NSCLC [18–20]. Furthermore, previous studies have also shown that, among all patients who received ICI treatment for melanoma, those with high PD-L1 expression tended to fare better [18,21,22], with the caveat that clinical trials of ICIs conducted to date have employed a wide range of cutoff points for PD-L1 expression in determining PD-L1 "positivity" versus "negativity", from as low as 1% in most phase 3 trials of RCC and 5% in most melanoma trials, to as high as 50% in the phase 3 trial of pembrolizumab in case of NSCLC [18,23].

RCC patients with high PD-L1 expression have been found to have lower survival after TKI treatment [24]. However, the predictive value of PD-L1 expression for response to ICI treatment in mRCC remains contentious. Therefore, we conducted a systematic review and meta-analysis of all clinical trials that included an assessment of the predictive value of PD-L1 in mRCC patients treated with ICIs. Our aim was to assess the predictive value of PD-L1, based on a biomarker assessment of prospective randomized clinical trials (RCTs) of ICIs. We thus hypothesized that PD-L1 status of the tumor might be associated with oncological outcomes in patients with mRCC treated with ICIs.

2. Evidence acquisition

2.1. Search strategy

The systematic review, meta-analysis, and network meta-analysis of RCTs for mRCC treated with ICIs were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement [25]. A completed PRISMA 2009 checklist was used to describe the methodology of our study (Supplementary Table 1). The PubMed, Web of Science, and Scopus databases were searched to identify reports published until April 2020, which investigated the PD-L1 expression and oncological outcomes of patients with mRCC treated with ICIs. 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). The primary outcome of interest was objective response rate (ORR), and the secondary outcomes were complete response rate (CRR), progression disease response (PDR), and PFS. Initial screening was performed independently by two investigators based on the titles and abstracts of the articles to identify ineligible reports, and the 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. Disagreements were resolved via consensus with the coinvestigators.

2.2. Inclusion and exclusion criteria

Studies were included if they investigated metastatic clear cell RCC patients with PD-L1–positive tumor (patients) who received ICIs (intervention), compared with those with PD-L1–negative tumor (comparator), to assess ORR, CRR, PDR, and PFS (outcome) in randomized design. We excluded observational studies, reviews, letters, editorials, meeting abstracts, replies from authors, case reports, and articles not published in English. In cases of multiple publications on the same cohort, either the higher-quality or the most recent publication was selected. References of all papers included were scanned for additional studies of interest.

2.3. Data extraction

Two investigators independently extracted the following information from the included articles: first author's name, publication year, period of patient recruitment, number of patients, treatment dosage, age, sex, study design, risk group, component of RCC, oncological outcomes (ORR, CRR, and PDR), survival outcomes, and PD-L1 status. Subsequently, hazard ratios (HRs) and 95% confidence intervals (CIs) associated with PFS were retrieved. All discrepancies regarding data extraction were resolved by consensus with the coinvestigators.

2.4. Risk of bias assessment

The "risk of bias" (RoB) evaluation of each study was assessed according to the Cochrane Collaboration's tool [26]. 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 consultation with coauthors.

2.5. Statistical analyses

2.5.1. Meta-analysis

First, forest plots were used as the summary variables for dichotomous outcomes and for describing the relationships between PD-L1 status and ORR, CRR, and PDR. Second, forest plots were used to assess the HRs and to describe the relationships between treatment and PFS based on PD-L1 status (ICI vs sunitinib). PFS was defined as the time from randomization to the first radiographic progression or death due to any cause. ORR was defined as the proportion of enrolled and randomly assigned patients, who achieved the best complete or partial response based on investigator assessment. Regarding PFS, subgroup analyses were performed among favorable- and intermediate/poor-risk patients with PD-L1–positive tumors (defined according to the Memorial Sloan Kettering Cancer Center [MSKCC] or International mRCC Database Consortium [IMDC] risk categorization) [27,28]. All study outcomes included in this meta-analysis were evaluated for heterogeneity by using Cochrane's Q test. Significant heterogeneity was indicated by $p < 0.05$ in Cochrane's Q tests. We used fixed-effect models for calculation of pooled HRs and odds ratios (ORs) [29–31].

2.5.2. Network meta-analysis

We conducted a network meta-analysis using random and fixed-effect models for direct and indirect treatment comparisons with sunitinib as the common comparator arm [32,33]. In the assessment for PFS, contrast-based analyses were applied, with estimated differences in the log HR and the standard error calculated from the published HR and CI values [34]. The relative treatment effects were presented as HRs and 95% credible intervals (CrIs) [32]. For the assessment of the ORR, arm-based analyses were performed to estimate ORs of ORR (and 95% CrI) from raw data presented in selected manuscripts [32]. With regard to PFS and ORR, analyses were conducted among PD-L1–positive and PD-L1–negative patients. We also estimated the relative ranking of different treatments for each outcome by using the p score, which can be considered a frequentist analog to the surface under the cumulative ranking curves [35,36]. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of PFS and ORR. All statistical analyses were performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and RevMan 5.3 (Cochrane Collaboration, London, UK); statistical significance was set at $p < 0.05$.

3. Evidence synthesis

3.1. Study selection and characteristics

Our initial search identified 4116 publications, and after eliminating duplicates, a total of 3667 publications were available. A further 3635 articles were excluded after screening the titles and abstracts, and full-text reviews were performed for the remaining 32 articles (Fig. 1). In accordance with the selection criteria, we identified six articles comprising 4866 patients for the systematic review, meta-analysis, and network meta-analysis [8–11,37,38]. Extraction of data from these six studies is outlined in Figure 2, Table 1, and Supplementary Table 2. Five studies, published from 2018 to 2019, involved assessment of first-line therapy and compared ICI-based combination therapy with sunitinib monotherapy [8–12,37]. The remaining study, published in 2015, investigated second- and third-line therapies by comparing the ICI nivolumab with the mTOR inhibitor everolimus [38]. In these six RCTs, a total of 2492 patients were treated with an ICI alone (n = 513, 21%) or ICI-based combinations (n = 1979, 79%). All six RCTs included patients diagnosed with mRCC with a predominant clear cell component. Clinical trials evaluating atezolizumab plus bevacizumab and the CheckMate 214 trial also included patients with at least a minor component of clear cell

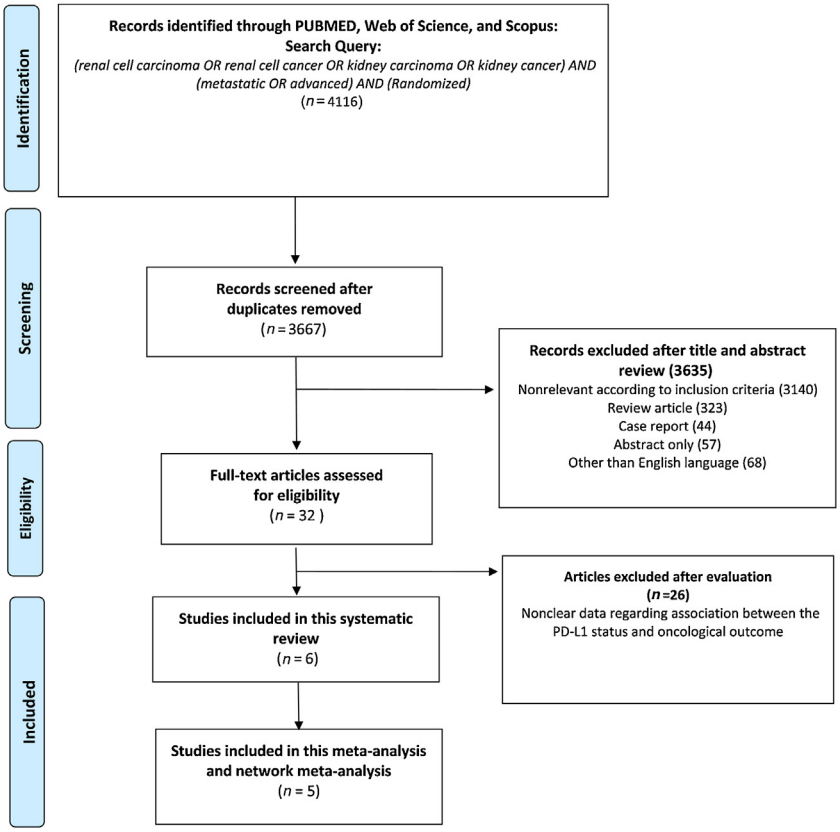

Fig. 1 – The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart, detailing the article selection process. Papers evaluating the programmed death ligand 1 (PD-L1) status in metastatic renal cell carcinoma treated with immune-checkpoint inhibitors were included.

histology and/or sarcomatoid histology [8,9,37]. PD-L1 expression on tumor cells, tumor-infiltrating immune cells, or both was examined immunohistochemically. Among the patients with quantifiable PD-L1 expression, 26–61% showed PD-L1 expression >1%.

3.2. *Meta-analysis*

3.2.1. *Association of PD-L1 status with ORR*

Four studies on first-line ICIs provided data regarding the association between PD-L1 status and ORR among patients

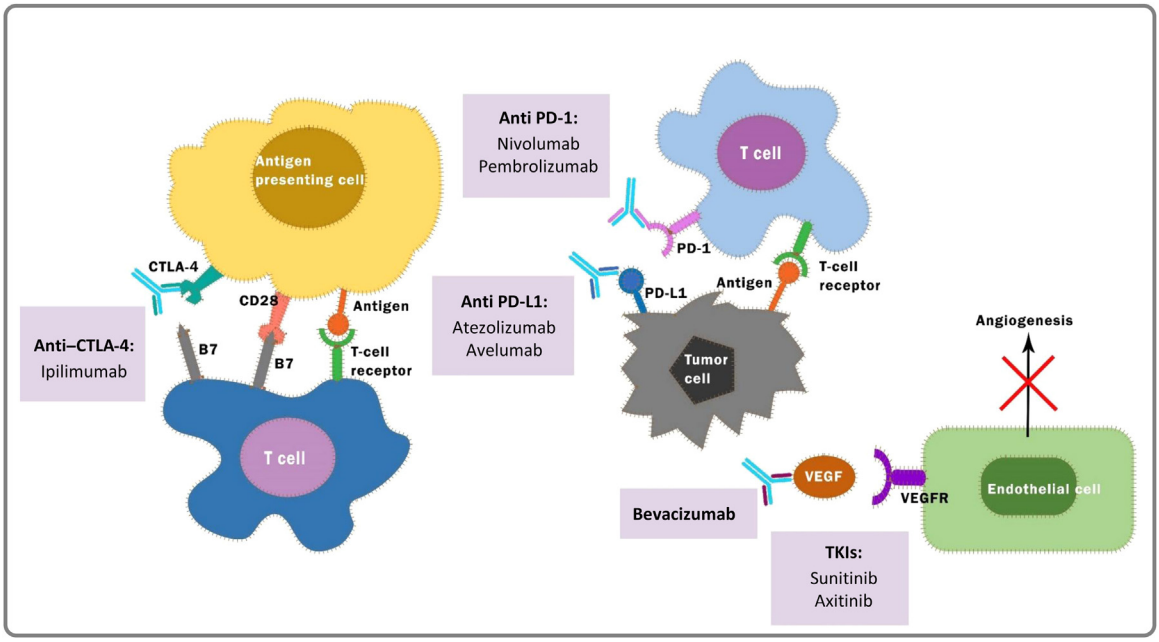

Fig. 2 – Immune-checkpoint inhibitor demographics. CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death 1 receptor; PD-L1 = programmed death ligand 1; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

Table 1 – Study demographics regarding the programmed death ligand 1 (PD-L1)

Study	CheckMate 214	IMmotion150		IMmotion151	JAVELIN Renal 101	KEYNOTE-426
Treatment (*n*)	Nivo + Ipi (550)	Atezo + Bev (101)	Atezo (103)	Atezo + Bev (454)	Ave + Axi (442)	Pembro + Axi (432)
Control (*n*)	Sunitinib (546)	Sunitinib (101)		Sunitinib (461)	Sunitinib (444)	Sunitinib (429)
Target	PD-1 + CTLA-4	PD-L1 + VEGF	PD-L1	PD-L1 + VEGF	PD-L1 + TKI	PD-1 + TKI
Antibodies	28-8 (rabbit)	SP142 (rabbit)		SP142 (rabbit)	SP263 (rabbit)	22C3 (mouse)
Platform	Dako	Ventana		Ventana	Ventana	Dako
Cell type	TC	IC		IC	IC	TC/IC
Cutoff	≥1%	≥1%		≥1%	≥1%	CPS ≥1
PD-L1 positivity (%) Treatment	26	50	52	39	61	59
PD-L1 positivity (%) Control	29	59		40	65	62
ORR (PD-L1+; %) Treatment	58	46	28	43	55	NR
ORR (PD-L1+; %) Control	22	27		35	26	NR
ORR (PD-L1−; %)T reatment	37	18	22	33	45	NR
ORR (PD-L1−; %) Control	28	32		32	26	NR
Median follow-up (mo)	32.4	20.7		15	9.9 (treatment) 8.4 (control)	12.8

Atezo = atezolizumab; Ave = avelumab; Axi = axitinib; Bev = bevacizumab; CPS = combined positive score; CTLA-4 = cytotoxic T-lymphocyte antigen-4; IC = immune cell; Ipi = ipilimumab; Nivo = nivolumab; NR = not reported; ORR = objective response rate; PD-1 = programmed death 1 receptor; Pembro = pembrolizumab; TC = tumor cell; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

with mRCC [8,9,11,37]. The forest plot in Figure 3A revealed a significantly improved ORR in patients with PD-L1–positive tumors than in patients with PD-L1–negative tumors (OR 1.84, 95% CI 1.48–2.28; $p < 0.001$). Cochrane's *Q* test ($p = 0.09$) revealed no significant heterogeneity.

3.2.2. Association of PD-L1 status with CRR

Four studies on first-line ICIs provided data on the association between PD-L1 status and CRR among patients with mRCC [8,9,11,37]. The forest plot in Figure 3B revealed that patients with PD-L1–positive tumors had significantly higher CRRs than patients with PD-L1–negative tumors (OR 3.11, 95% CI 2.04–4.75; $p < 0.001$). Cochrane's *Q* test ($p = 1$) revealed no significant heterogeneity.

3.2.3. Association of PD-L1 status with PDR

Two first-line ICI studies provided data on the association between PD-L1 status and PDR among patients with mRCC [9,11]. The forest plot in Figure 3 C revealed a significantly lower PDR in patients with PD-L1–positive tumors than in patients with PD-L1–negative tumors (OR 0.43, 95% CI 0.31–0.60; $p = 0.009$). Cochrane's *Q* test ($p = 0.05$) revealed no significant heterogeneity.

3.2.4. Association of PD-L1 status with PFS

Five studies on first-line ICIs provided data on the association between PD-L1 status and PFS in patients with mRCC [8–11,37]. The forest plot in Figure 4A revealed that ICI treatment was associated with significantly longer PFS among patients with PD-L1–positive tumors than among patients having sunitinib treatment (HR 0.65, 95% CI 0.57–0.74; $p < 0.001$). Cochrane's *Q* test ($p = 0.19$) revealed no significant heterogeneity. In contrast, ICI treatment was not associated with significantly better PFS in patients with PD-L1–negative tumors (HR 0.95, 95% CI 0.82–1.09; $p = 0.4$; Fig. 4B). Cochrane's *Q* test ($p = 0.8$) revealed no significant heterogeneity.

3.2.5. Association of risk group with PFS (in patients with PD-L1–positive tumors)

The forest plot in Supplementary Figure 2A revealed that ICI treatment was associated with significantly longer PFS in favorable-risk patients with PD-L1–positive tumors than in patients undergoing sunitinib treatment (HR 0.60, 95% CI 0.39–0.94; $p = 0.027$). Cochrane's *Q* test ($p = 0.4$) revealed no significant heterogeneity. The forest plot in Supplementary Figure 2B revealed that ICI treatment was associated with significantly longer PFS in the intermediate/poor-risk patients with PD-L1–positive tumors than in sunitinib-treated patients (HR 0.69, 95% CI 0.56–0.83; $p < 0.001$). Cochrane's *Q* test ($p = 0.6$) revealed no significant heterogeneity.

3.3. Network meta-analysis

Networks of eligible comparisons were graphically represented in network plots with respect to ORR (Supplementary Fig. 3A and 3B) and PFS (Supplementary Fig. 3C and 3D).

3.3.1. Objective response rate

A network meta-analysis of six treatments was performed to determine the primary outcome of ORR. Compared with sunitinib, combinations of avelumab plus axitinib, nivolumab plus ipilimumab, and atezolizumab plus bevacizumab resulted in significantly higher ORRs among patients with mRCC with PD-L1–positive tumors (OR 3.59, 95% CrI 2.22–5.82; OR 4.92, 95% CrI 2.50–9.68; and OR 1.61, 95% CrI 1.02–2.54, respectively; Supplementary Table 3). According to

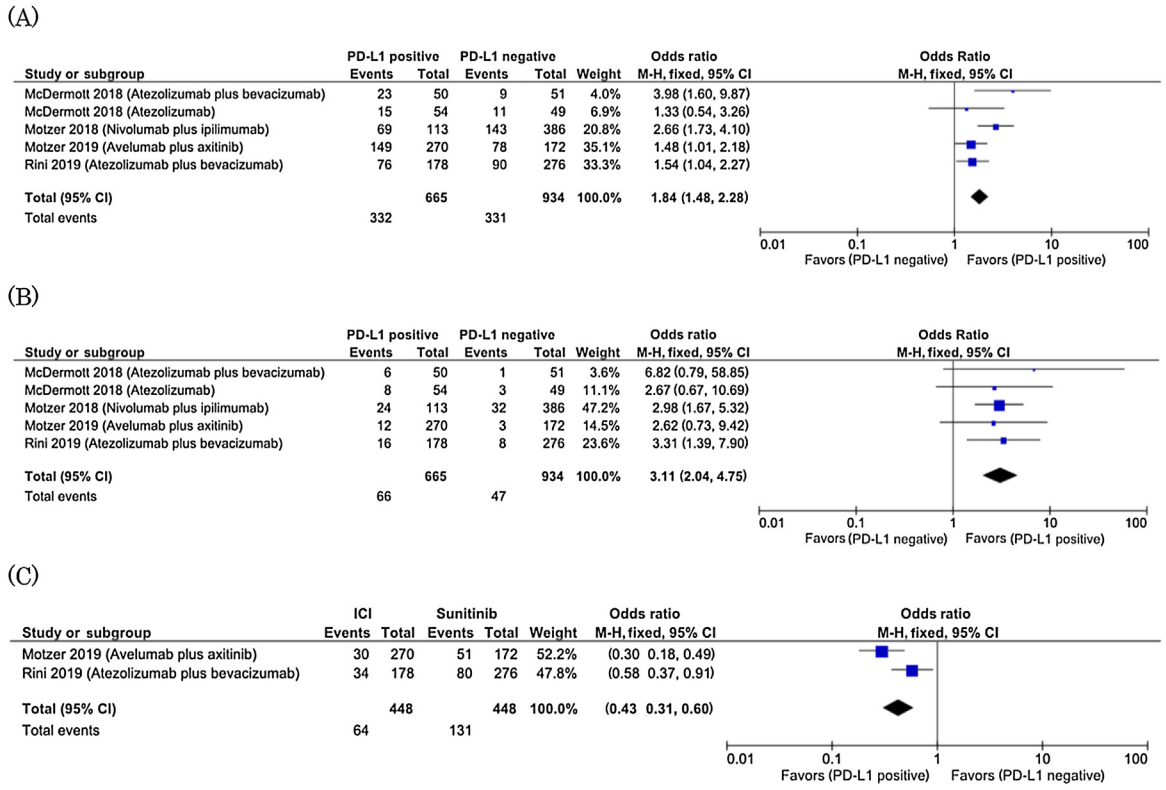

Fig. 3 – Forest plots showing the association of programmed death ligand 1 (PD-L1) status with tumor response in metastatic renal cell carcinoma treated with immune-checkpoint inhibitors: (A) Objective response rate, (B) complete response rate, and (C) progressive disease rate. CI = confidence interval; M-H = Mantel-Haenszel.

the analysis of treatment ranking, it appears that nivolumab plus ipilimumab yielded the highest ORR (*p* score: 0.95; Supplementary Table 4). In contrast, none of the four ICIs was associated with better ORRs among patients with mRCC with PD-L1–negative tumors (Supplementary Table 3).

3.3.2. *Progression-free survival*

A network meta-analysis of six different treatments was conducted for the secondary outcome of PFS. Compared with sunitinib, combinations of avelumab plus axitinib, nivolumab plus ipilimumab, and pembrolizumab plus axitinib improved PFS significantly among patients with

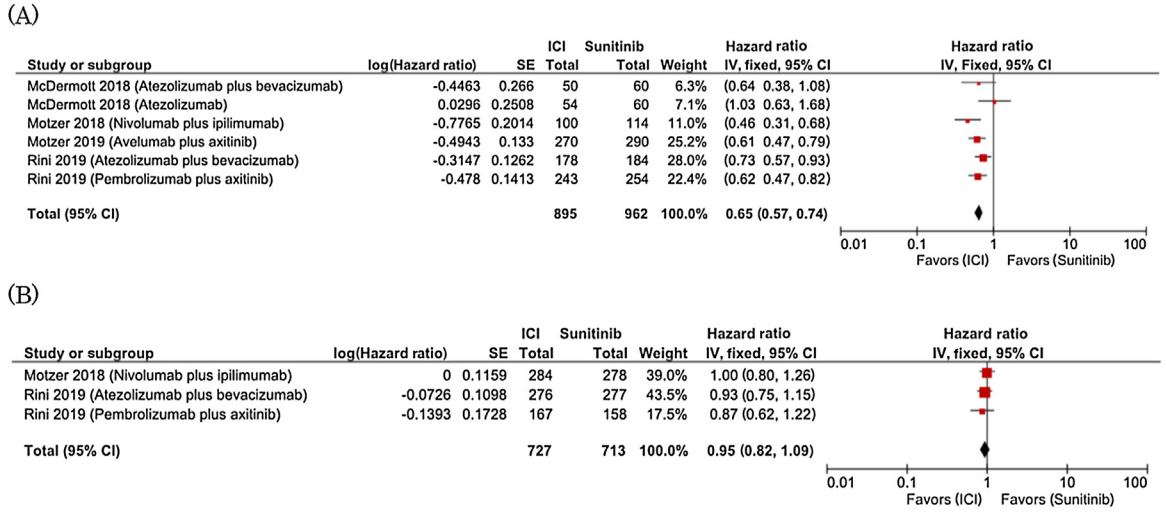

Fig. 4 – Forest plots showing the association of treatment with progression-free survival (PFS) based on programmed death ligand 1 (PD-L1) status in metastatic renal cell carcinoma (mRCC): (A) PFS in mRCC patients with PD-L1–positive tumors, (B) PFS in mRCC patients with PD-L1–negative tumors. CI = confidence interval; ICI = immune-checkpoint inhibitor; IV = inverse variance; SE = standard error.

mRCC with PD-L1–positive tumors (HR 0.81, 95% CrI 0.69–0.95; HR 0.71, 95% CrI 0.60–0.85; and HR 0.81, 95% CrI 0.69–0.96, respectively; Supplementary Table 5). According to the analysis of treatment rankings, nivolumab plus ipilimumab had the highest likelihood of providing the maximal PFS (*p* score: 0.90; Supplementary Table 6). In contrast, none of the three ICIs was associated with longer PFS among patients with PD-L1–negative tumors (Supplementary Table 5).

3.4. Discussion

We conducted a systematic review and meta-analysis of the predictive value of PD-L1 for response to ICIs in RCTs including patients with mRCC. We also performed a network meta-analysis and indirectly compared clinically relevant ICI treatment options. This approach generated several important findings.

First, in the first-line setting, mRCC patients with PD-L1–positive tumors showed significantly improved ORRs and CRRs, and lower PDRs compared with those with PD-L1–negative tumors. Second, treatment with ICIs, compared with treatment with sunitinib, was associated with significantly improved PFS in patients with PD-L1–positive tumors. In contrast, ICI treatment did not improve PFS in patients with PD-L1–negative tumors compared with sunitinib treatment. Third, compared with sunitinib, all ICI combination therapies resulted in significantly higher ORRs and improved PFS in patients with mRCC with PD-L1–positive tumors, based on a network meta-analysis. However, these differences were not seen for mRCC patients with PD-L1–negative tumors. Fourth, for patients with PD-L1–positive tumors, the combination of nivolumab plus ipilimumab represented an excellent treatment option among evaluated alternatives, in terms of ORR and PFS, even though we were unable to include ORR data of KEYNOTE-426 trial in this network meta-analysis. Selection of an appropriate first-line treatment is crucial, given that data obtained in the targeted therapy era indicate that only 50% of patients receive second-line treatment and only 20% of patients receive third-line treatment [39].

PD-1 is an immunoregulatory receptor expressed on CD4+ and CD8+ T cells, natural killer cells, B cells, and monocytes in response to immunological activation [40]. Its expression is induced by several cytokines including interleukin (IL)-2, IL-7, IL-15, and IL-21. To date, two PD-1 ligands have been described, namely, PD-L1 (also referred to as B7-H1) and PD-L2 (also referred to as B7-DC). Although PD-L1 is expressed on a number of cell types, including resting T cells, B cells, macrophages, dendritic cells, vascular endothelial cells, and pancreatic islet cells, PD-L2 is expressed only on macrophages and dendritic cells. Both PD-L1 and PD-L2 inhibit T-cell proliferation, adhesion, and cytokine production, and also modulate T-cell function in peripheral tissues. In addition, PD-L2 regulates immune T-cell activation in the lymphoid organs [41]. As a consequence, the expression of PD-L1 by tumor cells, including RCC cells, may allow them to escape immune surveillance. Indeed, multiple studies have shown that PD-L1 expression is associated with a poor prognosis in RCC [42,43]. In a previous meta-analysis of studies examining the association between PD-L1 expression and mortality in RCC prior to the widespread adoption of ICI therapy, the adjusted HR for cancer-specific death was found to be 1.81 (95% CI 1.31–2.49) among patients with tumoral PD-L1 expression compared with PD-L1–negative patients [44]. Our analyses have revealed that among patients receiving first-line treatment, ICIs are more effective for the treatment of patients with PD-L1–positive tumors than for the treatment of patients with PD-L1–negative tumors. These data thus indicate that PD-L1 could be used as a predictive biomarker for patients with mRCC treated with ICIs and may contribute to identifying those mRCC patients who are most likely to benefit from ICIs. The reason why nivolumab plus ipilimumab appeared to be an excellent treatment option with respect to ORR and PFS is not yet fully understood. However, the expression of PD-L1 is associated with a poor treatment response and shorter PFS in patients receiving TKI therapy compared with those with a PD-L1–negative status [24]. Thus, the combination of ICI and TKI therapy may be less effective in mRCC patients with PD-L1–positive status than nivolumab plus ipilimumab, the only approved dual-ICI combination for mRCC [8].

Although our findings support the predictive value of tumoral PD-L1 expression in mRCC treated with ICIs, several points regarding PD-L1 expression require consideration. Routinely, PD-L1 is investigated in primary nephrectomy specimens. However, approximately 20% of individual patients with mRCC show discordance in PD-L1 expression between primary tumor and metastatic sites [45]. Furthermore, PD-L1 expression within the same lesion is highly heterogeneous and can change over time [46,47]. Moreover, PD-L1 expression may vary between spatially separated metastases. However, performing multiple biopsies is deemed unacceptable in clinical practice. The ideal cutoff to define PD-L1 positivity is still unclear, and concurrent or prior cancer treatment such as TKIs or radiotherapy can alter PD-L1 expression [14]. Another caveat is the technical issues in clinical practice, with the availability of several anti–PD-L1 antibodies (eg, 22C3, 28-8, SP263, and SP142) and platforms (Ventana and Dako), analysis of different tumor specimens (current vs archival tissue), use of various scoring systems (immune cells vs tumor cells), and defined thresholds of positivity [14,17]. Furthermore, tumoral PD-L1 positivity is associated with a poor response to treatment and decreased PFS compared with patients with PD-L1–negative tumors when treated with vascular endothelial growth factor receptor (VEGFR) targeting TKIs. Therefore, whether its expression is more likely to be a positive or a negative predictive biomarker is debatable among patients treated with VEGFR TKI plus ICI combinations [42–44]. Although PD-L1 status can be used as a potential predictive marker, more complex predictive biomarkers, such as genomic signatures of angiogenesis or immunogenicity, are currently under investigation. The future of predicting clinical efficacy and survival lies in the use of different biological variables capturing the full biological

and clinical behavior of the tumors rather than a single-time sensitive biomarker snapshot.

Despite the comprehensive nature of the systematic review undertaken, some limitations of this study need to be considered. First, although indirect treatment comparison analyses have been used for the network meta-analysis and validated for comparing outcomes from RCTs, this approach falls short of a head-to-head treatment comparison. Thus, well-designed comparative trials are required to validate the findings of this study. Second, this meta-analysis was based on the quality of reporting of the reviewed trials. In consequence, several types of biases inherent to the original studies may limit the validity of the overall findings. Third, although the p value was nonsignificant, close to significant heterogeneity ($p = 0.09$ and 0.05, respectively) was detected in the analysis of ORR and PDR. This could be due to large differences shown in PD-L1 positivity rate and thus in treatment outcome between the studies included in the meta-analysis. In addition, as the number of studies included was small, the Cochrane's Q test had low power as a test for heterogeneity in this meta-analysis. Fourth, patient characteristics may have differed significantly between studies, which limit the comparability of the evaluated trials. Notably, caution should be exercised in assessing data on nivolumab plus ipilimumab from the CheckMate 214 trial. Whereas most of the RCTs enrolled patients from all risk strata, the CheckMate 214 trial enrolled patients with intermediate- and poor-risk disease in primary analysis, even though secondary analysis included all-risk patients, suggesting a biased estimate of the efficacy of nivolumab plus ipilimumab in comparison with the other systemic treatment. Moreover, the benefits of treatment regarding OS were not evaluated in some trials that assessed PFS as the primary endpoint, which accordingly did not permit a comprehensive evaluation of OS among all existing treatments. Given the limitations of the published data, it was not possible to perform a meta-analysis of adjusted-effect estimates. Finally, the recommendation of first-line mRCC therapy is based on IMDC risk classifications. In PD-L1–positive patients, analysis of the interactions between risk groups and PD-L1 status revealed significantly improved PFS for patients in all risk groups when treated with ICIs compared with sunitinib. It must be noted, however, that only two studies were included in the favorable-risk group analysis and that only insufficient data for PD-L1–negative patients and ORR were available to allow further analyses.

4. Conclusions

ICI or ICI combination therapies for mRCC have been approved independently of the tumor's PD-L1 status, while our analysis indicates a superior benefit for first-line ICI-based therapies in patients with PD-L1–positive tumors. Findings of our analysis suggest that the negative prognostic impact of PD-L1 expression for treatment with TKI can be overcome by ICI-based therapies for patients with mRCC. These findings could contribute to guiding patients and clinicians when determining biomarker-driven personalized treatment strategies for mRCC. Further research is needed to evaluate whether patients with PD-L1–negative tumors derive a similar or greater response with non-ICI–based therapies in the first-line settings.

Author contributions: Keiichiro Mori had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.*Study concept and design*: Mori, Shariat, Gust.
Acquisition of data: Mori, Abufaraj.
Analysis and interpretation of data: Mori, Mostafaei.
Drafting of the manuscript: Mori, Shariat, Gust.
Critical revision of the manuscript for important intellectual content: Abufaraj, Mostafaei, Quhal, Fajkovic, Remzi, Karakiewicz, Egawa, Schmidinger, Shariat, Gust.
Statistical analysis: Mori, Mostafaei.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Shariat.
Other: None.

***Financial disclosures*:** Keiichiro Mori certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Shahrokh Shariat owns or co-owns the following patents: Methods to determine prognosis after therapy for prostate cancer (granted September 6, 2002), Methods to determine prognosis after therapy for bladder cancer (granted June 19, 2003), Prognostic methods for patients with prostatic disease (granted August 5, 2004), and Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma (granted July 20, 2010); he has a consulting or advisory role for Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Jansen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi, Takeda, Urogen, and Wolff. Kilian M. Gust has received advisory board fees from Cepheid, Roche, MSD, and Ferring; speaker fees from Amgen, Astellas, AstraZeneca, BMS, Ipsen, Janssen, MSD, and Roche; and meeting/travel expenses from Allergan, Astellas, AstraZeneca, Bayer, BMS, Janssen, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. The other authors made no disclosures.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2020.10.006.

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