Review

Immune Checkpoint Inhibition, the Key to Success in Renal Cell Carcinoma?

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Abstract. Treatment of renal cell carcinoma (RCC) has evolved rapidly since the development of checkpoint inhibitors. Most of the studies have been conducted in patients with metastatic disease and led to a significant change in the treatment landscape. Currently, many studies are investigating immune checkpoint inhibition (ICI) in the neoadjuvant and adjuvant setting and the efficacy of combination therapies. It remains difficult to predict which patients will respond best. Consequently, there is a high need for predictive biomarkers. In this review, we discuss the different studies with ICI in RCC and the molecular correlates with clinical outcome.

Keywords: Renal cell carcinoma, immune checkpoint inhibition, cancer immunotherapy, molecular profiling, review

INTRODUCTION

In the Netherlands, renal cell carcinoma (RCC) is the ninth most common type of cancer in men and the tenth in women with an increasing incidence over the past years. In 2017, an estimated 2,600 new cases occurred with a stable mortality of around 900 cases per year. Currently, the 5-year survival is 66% (cijfersoverkanker.nl). The increasing incidence is partly due to incremental use of non-invasive imaging techniques, but can also be attributed to an increase in etiological factors like obesity [1]. Clear-cell carcinoma is the most common pathological subtype and accounts for 70% of all RCCs. Non-clear-cell carcinomas include mainly papillary and chromophobe RCCs. Approximately 2-3% of all RCCs are hereditary. Patients with genetic alterations in the Von Hippel-Lindau gene (*VHL*), a tumor suppressor gene, have a 35–45% risk of developing clear-cell RCC at

relatively young age. Several tumor suppressor genes involved in the development of RCC are *PBRM1*, *BAP1* (BRCA1-associated protein), and *SETD2*, all located on the same short arm of chromosome 3 where the *VHL* gene is located [2]. Germline mutations in *MET*, *fumarate hydratase*, or *folliculin* can cause different histological subtypes of RCC [3].

Patients with RCC can present with a range of symptoms and according to recent Dutch figures 18% of patients have metastatic disease at time of diagnosis. The classic triad of RCC, a strong predictor of metastatic disease, is present in 10% of patients and consists of flank pain, hematuria, and a palpable abdominal mass [4]. Around 30% of patients develop metastatic disease following prior nephrectomy.

Prognostic factors in RCC have previously been composed by The Memorial Sloane Kettering Cancer Center (MSKCC) and were the gold standard for the risk assessment during cytokine treatment in metastatic RCC (mRCC) [5]. Further refinement has been done by the International Metastatic RCC Database Consortium (IMDC) in the tyrosine kinase inhibitor (TKI) or Vascular Endothelial

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Growth Factor Receptor inhibitor (VEGFR) era, which extended the prognostic model to 6 factors [6]. This model has also been evaluated in second-line treatment and held its prognostic value [7]. Patients are divided in favorable, intermediate, or poor prognosis according to these prognostic factors. The choice of treatment is also based on the prognosis and is discussed in the recently published guidelines of the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO) [8, 9].

Therapeutic options in mRCC have increased extensively over the past 10–15 years. Until 2005, interferon-alpha (IFN-α) was one of the few available treatments. Without any effect on survival, this cytokine was not an attractive option considering the very modest overall response rate (ORR) of 12% in combination with substantial toxicity [10]. Interleukin-2 (IL-2), which was approved in the United States based on phase II trial results with a durable complete remission rate of 7-8%, was never widely adopted in Europe because of its serious toxicity with vascular leak syndrome, high fever, chills, low blood pressure, dyspnea, and sometimes renal insufficiency, nausea, diarrhea, and erythema [11]. Attempts to combine IFN-α and IL-2 never led to improvement of survival compared to single agent therapy [12, 13].

As of 2005, oral TKIs like sunitinib and sorafenib, targeting VEGFRs, as well as the combination of the VEGF-targeting antibody bevacizumab plus IFN-α, demonstrated improvement of progression-free survival (PFS) compared to IFN-α single agent, and became standard of care [14–17]. To date, for first-line treatment of clear-cell mRCC, sunitinib and pazopanib are the most widely used drugs, independent of risk groups, although most evidence is available for IMDC good and intermediate risk group patients [18]. At present, apart from sorafenib, sunitinib and pazopanib, also axitinib has been approved as multitargeted TKI. Similarly, cabozantinib, tivozanib, and lenvatinib have been approved and target VEGFR in addition to other kinases like MET, AXL, and FGFR. Besides angiogenesis, also constitutive activation of the mammalian target of rapamycin (mTOR) inhibitor signaling pathway plays a role in the pathogenesis of RCC, for which everolimus and temsirolimus have been investigated and approved [19–21].

RCC has been considered an immunogenic type of cancer for many decades. This was based on rare observations of spontaneous regressions of metastases, the beneficial effects on outcome of cytoreductive nephrectomy followed by IFN-α compared to IFN-α alone in primary metastatic disease [22], and the low but very consistent ORR of 15% to high dose IL-2 treatment with half of the patients (those obtaining complete responses) deriving long term benefit [11]. Therefore, it was not surprising that with the introduction of immune checkpoint inhibitors (ICI), anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed death (ligand) 1 (PD-1/PD-L1), clear-cell RCC appeared responsive. CTLA-4 inhibits T-cell proliferation and function whereas upon ligation of PD-1 on T-cells by PD-L1, which is expressed by tumor and stromal cells, T-cell receptor signaling is inhibited providing a rationale for the development of anti-CTLA-4 and anti-PD-1/PD-L1 [23, 24]. The role of ICI in the treatment of RCC will be discussed in this review.

SINGLE-AGENT CHECKPOINT INHIBITION AS NEW THERAPY FOR mRCC

In the past years, several studies have been published regarding treatment with ICI in mRCC. The first study investigating the potential benefit of immunotherapy with ICI in RCC has been published in 2007 and demonstrates the effect of single-agent ipilimumab, a CTLA-4 inhibitor, in a phase II trial [23]. This trial showed responses in both treatment-naive patients with clear-cell mRCC and patients that were previously treated with IL-2. The highest response rates (i.e. 30%) were seen in patients who experienced grade 3 and 4 immune-mediated toxicities.

Later, several phase I/II studies investigated the role of single-agent anti-PD-1. In 2012, a phase I study with nivolumab was conducted in 296 patients with different metastatic solid tumors [24]. The analysis including mRCC was published in 2015, followed by a phase II study published in the same year. In this phase I study, 34 previously treated patients with mRCC, received either 1 mg/kg or 10 mg/kg nivolumab every two weeks [25]. Twenty-nine percent of patients achieved an objective response with a median duration of 12.9 months (8.4–29.1). Median overall survival (OS) in these heavily pretreated patients was 22.4 months (12.5 – not estimable [NE]). All of the treatment-related grade 3/4 adverse events (AEs) that occurred in 18% of patients were reversible. In the phase II study, Motzer et al. inves-

tigated the dose-response relationship of 3-weekly nivolumab in 168 patients by randomly assigning patients to 0.3 mg/kg, 2 mg/kg or 10 mg/kg [26]. All patients had received prior systemic therapy. Overall, ORR was 20%, 22%, and 20% and median PFS 2.7 months (80% confidence interval [CI], 1.9–3.0), 4.0 months (80% CI, 2.8–4.2), and 4.2 months (80% CI, 2.8–5.5) for the 0.3 mg/kg, 2 mg/kg, and 10 mg/kg groups, respectively without a statistically significant difference between the groups. Median OS was 18.2 months (80% CI, 16.2–24.0) in the low dose group and close to 25 months in both the higher dose groups. Recently, the updated OS data of both the phase I and II study on nivolumab monotherapy have been presented and demonstrated that about one third of patients is still alive after 3 (phase II study; median follow-up of 38.0 months) to 5 years (phase I study; median follow-up of 50.5 months) [27].

The effect of nivolumab monotherapy has also been investigated in non-clear-cell RCC in the CheckMate-374 trial (NCT02596035). In this study, 44 patients with non-clear-cell RCC and mostly treatment-naive (66%) were treated with nivolumab [28]. ORR was 13.6% (95% CI, 5.2–27.4) with responses observed in several histological subtypes. Median OS was 16.3 months (95% CI, 9.2 - NE) and regardless of baseline PD-L1 expression. Apart from nivolumab, also pembrolizumab has been studied as a single-agent PD-1-inhibitor. The Keynote-427 trial, a phase II study, evaluated the efficacy of 3-weekly pembrolizumab (200 mg) as first-line therapy in two separated cohorts [29]. Cohort A included 110 patients with clear-cell RCC and demonstrated an ORR of 38% with durable responses of ≥6 months in 75% of these patients and mostly in patients with higher PD-L1 expression in tumor cells (combined positivity score of ≥1% in 42% of patients) and intermediate/poor IMDC risk (63% of patients). Cohort B consisted of 165 patients with non-clear-cell RCC of which the first data were presented at ASCO-GU 2019 by McDermott [30]. The ORR for the total population was 24.8% (95% CI, 18.5–32.2) with 4.8% complete responses and 20% partial responses. These high ORR were seen mostly in patients with papillary RCC and unclassified RCC. The ORR in chromophobe RCC was a dismal 10%. Both nivolumab and pembrolizumab had a comparable safety profile with grade 3/4 events of 15%.

The effect of the single-agent PD-L1 inhibitor atezolizumab has been studied in a phase I trial published in 2016 [31]. In this study, 70 patients with mRCC that received prior systemic therapy were treated with 3-weekly atezolizumab. It resulted in an overall ORR of 15% (95% CI, 7–26). There was a positive correlation between baseline PD-L1 tumor expression and ORR. Median PFS was 5.6 months (95% CI, 3.9–8.2) and median OS 28.9 months (95% CI, 20.0 – not reached [NR]). Importantly, atezolizumab had a manageable safety profile with 17% grade 3 AEs.

The promising results of these phase I and II trials have been confirmed in a phase III trial with single-agent anti-PD-1. In the CheckMate-025 study, two-weekly nivolumab 3 mg/kg was compared with everolimus 10 mg once daily as second- or third-line treatment after failure of TKI in 821 patients (Table 1) [32]. Twenty-eight percent of patients were treated with nivolumab as third-line therapy. Although PFS was not statistically significantly different between the two arms, the difference in OS was in favor of nivolumab (19.6 vs. 25.0 months; hazard ratio [HR] 0.73 [98.5% CI, 0.57–0.93]; $P = 0.002$). ORR was 25% with nivolumab and grade 3/4 AEs occurred in 19% of patients with fatigue as most commonly reported AE. With everolimus, ORR was 5% and grade 3/4 adverse events were reported in 37% of patients, mostly anemia. This trial resulted in the approval of nivolumab as second-line treatment. The lack of difference in PFS but major increment in OS is hypothesized to be due to a better response to the next line of treatment after ICI. The response to nivolumab was independent of PD-L1 expression, even when a cut-off of ≥5% was used. It has been shown that a subgroup of patients (13%) can also benefit from nivolumab beyond RECIST progression with a possible tumor reduction post-progression and an acceptable safety profile [33].

DUAL-AGENT THERAPIES

ICI-ICI combination

The differential effects of CTLA-4 and PD-1 blockade on immune cells have resulted in studies in which both agents are combined to investigate synergism between these agents. At first, the phase I CheckMate-016 study evaluated the efficacy and safety of nivolumab plus ipilimumab [34]. Patients received either 1 mg/kg nivolumab and 3 mg/kg ipilimumab, 3 mg/kg nivolumab and 1 mg/kg ipilimumab, or 3 mg/kg of both. The arm with 3 mg/kg of both agents was stopped early due to dose-limiting toxicity. ORR was 40% in both other arms and durable responses were seen in 40% of patients with

Table 1
Overview of phase III trials with ICI in RCC

Study	NCT number	Patients	Experimental arm (N)	Control arm (N)	Median OS (mo) (HR, 95% CI)	Median PFS (mo) (HR, 95% CI)
Metastatic disease						
CheckMate 025	NCT01668784	821	Nivolumab 3 mg/kg (2-weekly) (410)	Everolimus 10 mg once daily (411)	25.0 vs. 19.6 (0.73, 0.57–0.93)	4.6 vs. 4.4 (0.88, 0.75–1.03)
CheckMate 214	NCT02231749	1096	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (550)	Sunitinib 50 mg per protocol (546)	NR vs. 26.0 (0.63, 0.44–0.89)	11.6 vs. 8.4 (0.82, 0.64–1.05)
Keynote 426	NCT02853331	861	Pembrolizumab 200 mg (3-weekly) plus axitinib 5 mg BID (432)	Sunitinib 50 mg per protocol (429)	NR vs. NR (0.53, 0.38–0.74)	15.1 vs. 11.1 (0.69, 0.57–0.84)
JAVELIN Renal 101	NCT0264006	886	Avelumab 10 mg/kg (2-weekly) plus axitinib 5 mg BID (442)	Sunitinib 50 mg per protocol (444)	NR	13.8 vs. 8.4 (0.69, 0.56–0.84)
IMmotion 151	NCT02420821	915	Atezolizumab 1200 mg plus bevacizumab 15 mg/kg (3-weekly) (454)	Sunitinib 50 mg per protocol (461)	NR vs. NR (0.81, 0.63–1.03)	11.2 vs. 8.4 (0.83, 0.70–0.97)
Adjuvant						
IMmotion 010	NCT03024996	Recruiting	Atezolizumab 1200 mg (3-weekly)	Placebo		
Keynote-564	NCT03142334	Recruiting	Pembrolizumab 200 mg (3-weekly)	Placebo		
CheckMate 914	NCT03138512	Recruiting	Nivolumab plus ipilimumab	Placebo		
RAMPART	NCT03288532	Recruiting	Durvulamab 1500 mg (4-weekly) or durvalumab plus 2 cycles tremelimumab 75 mg	Active monitoring		
Neoadjuvant						
PROSPER	NCT03055013	Recruiting	Nivolumab (2 cycles neoadjuvant plus 12 cycles adjuvant)	Observation		

NR, not reached

a 2-year OS of 68%. The study resulted in the phase III CheckMate-214 study, in which the combination of 3-weekly nivolumab 3 mg/kg and ipilimumab 1 mg/kg was compared to sunitinib in predominantly IMDC intermediate and poor risk patients [35]. After 4 cycles of nivolumab/ipilimumab, patients continued nivolumab in a 2-weekly cycle until disease progression or unacceptable toxicity. Twenty-six percent of patients in the nivolumab/ipilimumab arm and 29% in the sunitinib arm had elevated PD-L1 expression defined as ≥1% of tumor cells. In the 847 patients with intermediate and poor risk, the PFS for nivolumab/ipilimumab was 11.6 months (95% CI, 8.7–15.5) compared to 8.4 months (95% CI, 7.0–10.8) for sunitinib, which was not statistically significant (HR 0.82; $P = 0.03$ with a prespecified 0.009 threshold). Median OS has not yet been reached for the combination arm compared to 26 months (95% CI, 22.1 – NE) for sunitinib treatment ($P < 0.0001$). ORR was 42% (95% CI, 37–47) and complete responses were seen in 9% of patients compared to an ORR of 27% (95% CI, 22–31) with sunitinib ($P < 0.0001$). A recent 30-month follow-up update presented at ASCO-GU 2019 demonstrated an 11% (investigator-assessed) complete response rate [36]. Grade 3/4 events occurred more frequently in the sunitinib group (63% vs. 46%, respectively) but did less often lead to discontinuation of treatment (12% vs. 22%). Of the patients with an immune-mediated AE, 35% received high-dose glucocorticoids. An explorative analysis showed that the favorable IMDC risk patients ($N = 249$) benefit more from sunitinib with a PFS of 25.1 months (95% CI, 20.9 – NE) and an OS that has not yet been reached compared to 15.3 months (95% CI, 9.7–20.3) in the nivolumab/ipilimumab arm ($P < 0.0001$) and 32.9 months (95% CI, NE), respectively. Based on these data the combination of nivolumab plus ipilimumab has been approved as first-line treatment of patients with metastatic clear-cell RCC belonging to the intermediate and poor risk subgroups by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA).

At ASCO-GU 2019 Gupta et al. demonstrated preliminary evidence of anti-tumor activity of nivolumab/ipilimumab in non-clear-cell RCC [37]. In this study, 18 patients with different non-clear-cell histology were included regardless of IMDC risk group. It was administrated as per CheckMate-214. Most patients (78%) received it as first-line treatment. Partial responses were seen in 28% and 14% experienced stable disease.

ICI and TKI

RCC is characterized by aberrant angiogenic signaling and an immunogenic tumor microenvironment providing a rationale for combining ICI with VEGF(R) targeting treatment. Several TKIs change the tumor microenvironment and make it more permissive for ICI, such as reduction of the number of intratumoral myeloid-derived suppressor cells (MDSCs), allowing better expansion of tumor infiltrating lymphocytes leading to reversal of immune suppression [38, 39]. The combination of ICI and TKI has also been investigated in the CheckMate-016 study. Patients received 3-weekly nivolumab, with dose escalation of 2 mg/kg to 5 mg/kg, combined either with sunitinib or pazopanib per protocol (i.e. 50 mg/day, 4 weeks on/2 weeks off for sunitinib or pazopanib 800 mg/day). The 33 patients that received both nivolumab and sunitinib, had an ORR of 54.5% (95% CI, 36.4–71.9) and the median OS was not reached (median follow-up of 50.0 months; 95% CI, 36.8 - NR) [40]. However, treatment-related AEs were 100%. The arm with pazopanib was closed due to toxicities, i.e. 70% grade 3/4 AEs, mostly hepatitis. The 20 enrolled patients had an ORR of 45% (95% CI, 23.1–68.5) and a median OS of 27.9 months (95% CI, 13.3–47.0). Although the initial combination of ICI and TKI seemed too toxic, several trials are or have been conducted with different agents. Recently, the phase III Keynote-426 trial has been published in which 861 patients were randomized between axitinib (5 mg bis in dies (BID)) in combination with 3-weekly pembrolizumab (200 mg) and sunitinib per protocol [41]. Since axitinib is a selective VEGFR1-3 inhibitor, it is thought to be better tolerated in combination with ICI than less-selective TKIs. Previously, this combination had proven to be safe and showed very promising antitumor activity in a phase Ib trial with an ORR of 73% (95% CI, 59–84.4) [42]. In the Keynote-426 trial, ORR was 59.3% (95% CI, 54.5–63.9) for pembrolizumab/axitinib versus 35.7% (95% CI, 31.1–40.4) for sunitinib showing benefit for the combination regardless of IMDC risk group, PD-L1 expression or other subgroups. PFS differed with 15.1 months (95% CI, 12.6–17.7) in the pembrolizumab/axitinib group and 11.1 months (95% CI, 8.7–12.5) for sunitinib (HR 0.69; 95% CI 0.57–0.84; $P < 0.001$). Median OS has not yet been reached in both treatment arms with a median follow-up of 12.8 months. Based on these results, the FDA recently approved pembrolizumab/axitinib for first-line treatment of mRCC.

The final decision of the EMA is to be expected. The preferred use of first-line pembrolizumab/axitinib versus nivolumab/ipilimumab needs to be further explored.

Axitinib also demonstrated favorable results in combination with avelumab, a PD-L1 inhibitor, compared to sunitinib in the JAVELIN Renal 101 study [43]. In this phase III trial, 886 patients were randomly assigned to receive 2-weekly 10 mg/kg avelumab plus axitinib (5 mg BID) or sunitinib per protocol as first-line treatment. The combination arm showed an ORR of 51.4% (95% CI, 46.6–56.1) with a median PFS of 13.8 months (95% CI, 11.1 – NE) irrespective of PD-L1 expression status compared to 25.7 (95% CI, 21.7–30.0) and 8.4 months (95% CI, 6.9–11.1) for sunitinib, respectively. Median OS data were not mature at the time of publication [43]. In non-clear-cell carcinoma the combination of a MET inhibitor (savolitinib) and durvalumab (anti-PD-L1) has been explored in the CALYPSO study (NCT02819596). This single arm phase I/II trial included patients with metastatic papillary renal cancer regardless of IMDC risk group [44]. ORR was 27% (11/41 patients) with a median PFS of 3.3 months (95% CI, 1.5 – NR).

ICI and bevacizumab

Treatment with bevacizumab leads to an enhanced dendritic cell maturation and increased T-cell and B-cell levels resulting in an increase of intratumoral immune infiltrates [45]. It is thought that bevacizumab enhances the T-cell mediated cancer cell-killing effect of atezolizumab by reversing VEGF-mediated immunosuppression. In a phase I study where 10 previously untreated mRCC patients were treated with atezolizumab and bevacizumab, partial responses were observed in 4 patients and 4 patients had stable disease [46]. Treatment was well tolerated. Collected tissue specimens during treatment showed an increase of intra-tumoral CD8+ T-cells suggesting that combination treatment improves antigen-specific T-cell migration. It resulted in the conduction of two trials in which first-line atezolizumab in combination with bevacizumab was compared to sunitinib [47, 48]. In IMmotion 150, a phase II study, patients were allocated to 3-weekly atezolizumab 1200 mg and bevacizumab 15 mg/kg, 3-weekly atezolizumab 1200 mg, or sunitinib per protocol. Cross-over was only allowed in the United States. The ORR in the combination

treatment arm was 32% in the intention-to-treat analysis and 46% in the PD-L1+ subgroup (defined by ≥1% expression of PD-L1 on tumor infiltrating immune cells) compared to an ORR of 29% (and 27% when PD-L1+) with sunitinib. PFS was 11.7 months (95% CI, 8.4–17.3) with atezolizumab/bevacizumab compared to 8.4 months (95% CI, 7.0–14.0) with sunitinib and 6.1 months (95% CI, 5.4–13.6) with atezolizumab monotherapy, however, not statistically significant (HR 1.19; [95% CI 0.82–1.71]; $P = 0.358$). In the patients with PD-L1 positive tumor infiltrating immune cells, PFS was doubled in the combination arm compared to atezolizumab monotherapy and sunitinib (14.7 vs. 5.5 vs. 7.8 months), respectively. The subset analysis after cross-over showed an ORR of 26% after crossing to the combination arm (28% for cross-overs post-sunitinib and 24% post-atezolizumab [49]. Thus, treatment with atezolizumab and bevacizumab might become an attractive option in patients with PD-L1 positivity when approved by FDA and EMA.

Next to IMmotion 150, the successor trial IMmotion 151 investigated the combination of atezolizumab and bevacizumab. In this two-arm phase III study atezolizumab/bevacizumab was compared with sunitinib in treatment-naive patients regardless of the prognostic group [48]. It demonstrated a significant difference in PFS in favor of the combination arm (11.2 vs. 8.4 months; $P = 0.0219$). In this study cross-over was not allowed. Patients were stratified for PD-L1 expression (≥1% or <1%) in tumor resident immune cells. For PD-L1+ patients in the IMmotion 151 study, the ORR was 43% (95% CI, 35–50) for atezolizumab/bevacizumab compared to 37% (95% CI, 32–41) in all patients. The difference between ORR in PD-L1+ vs. all patients was 35% (95% CI, 28–42) vs. 33% (95% CI, 29–38) when treated with sunitinib. OS data were immature at first interim analysis. Discontinuation of therapy due to treatment-related AEs took place in 12% for atezolizumab/bevacizumab vs. 8% for sunitinib. In a pooled analysis of the IMmotion 150 and IMmotion 151 in which the safety data were carefully examined, patients on sunitinib reported more grade 3/4 events (54% vs. 40%) and discontinued therapy more often (8% vs. 5%) [50]. When treated with the combination of atezolizumab/bevacizumab, corticosteroids were needed in 16% of patients because of immune toxicity.

In a systematic review that included CheckMate-214, IMmotion 150, and CheckMate-025 in the

meta-analysis, ICI has shown to decrease the risk of death over standard of care by 25% [51]. In the PD-L1+ subpopulation this increases to 36%. When including the IMmotion 151 study, in which the OS data are still immature, ICI demonstrated a decrease in progression by 11%. However, no significant improvement in PFS was found in treatment-naive or PD-L1+ patients compared to sunitinib. Considering ORR in treatment-naive patients, ICI increased the relative risk for response by 14% over sunitinib.

The combination of atezolizumab and bevacizumab has also been investigated in non-clear-cell RCC and clear-cell RCC with >20% sarcomatoid differentiation [52]. In a single-arm phase II trial 65 patients were enrolled of whom 52 underwent a response assessment and were included in the analysis. Of these 52 patients, 16 patients had sarcomatoid differentiated RCC. The ORR in the overall cohort was 31%. Data on PD-L1 expression status and survival are not yet mature.

Currently, several trials combining ICI with TKI are ongoing in RCC [53]. For example, an ongoing three-arm phase III trial (CLEAR; NCT02811861) will investigate the combination of lenvatinib plus everolimus or pembrolizumab compared to sunitinib in the first-line. Since the phase II CABOSUN trial, cabozantinib has shown to be an attractive and possibly more active alternative to sunitinib in intermediate and poor risk treatment-naive patients [54]. Median PFS was 8.6 months vs. 5.3 months for cabozantinib vs. sunitinib (HR 0.48 [95% CI, 0.31–0.74]; $P = 0.0008$) and with limited time of median follow-up, OS was in favor of cabozantinib. Based on these results cabozantinib has been approved as a first-line option in RCC. Currently, a phase III trial is investigating the combination of cabozantinib and nivolumab compared to sunitinib (CheckMate-9ER; NCT0314117). The study originally had an experimental arm of triplet therapy in which also ipilimumab was added. However, this arm has been discontinued for toxicity reasons. The COSMIC-313 trial (NCT03937219), however, adds ipilimumab and will investigate the combination of cabozantinib with nivolumab and ipilimumumab versus nivolumab and ipilimumab. Preliminary results of the phase Ib trial demonstrated an acceptable toxicity profile of this combination and moreover, promising antitumor activity in genitourinary malignancies [55]. We are eagerly awaiting the results from these trials.

MOLECULAR CORRELATES OF CLINICAL OUTCOME TO ICI

Multiple studies underscore the importance of mutational analysis in order to better predict response to treatment [56–58]. Primary RCCs however, despite being responsive to immunotherapy, do not harbor a high mutational burden [59]. Turajlic et al. showed that frameshift mutations occur more frequently in RCC tumors compared to other solid tumors [60]. They hypothesized that per mutation, frameshift mutations have a higher propensity to contribute to neoantigen formation compared to single nucleotide mutations, in other words, that despite low single nucleotide variant burden, neoantigens may still be important for recognition by T-cells in RCC. In addition, an association between expression of endogenous retroviral sequences and cytolytic T-cell activity was demonstrated [61], suggesting that endogenous retroviral gene segments may give rise to neoantigens that can be recognized by tumor infiltrating T-cells.

The majority of trials have been limited to patients with clear-cell histology. However, within the different histologic subtypes of RCC, it might be that each subtype has different markers and targets for therapy and different prognostic factors. An important predictive factor for the response to ICI is the expression of immune cell gene-specific signatures of which nearly universal upregulation has been shown in clear-cell RCC [62]. However, non-clear-cell RCC have also shown to be responsive to ICI [63]. In the past years, several markers have been explored in order to better predict response to treatment. It has been investigated whether tumor mutational load or expression of cytolytic genes like granzyme A (*GZMA*) and perforin (*PRF1*) as a marker of immunoreactive tumor microenvironment differ between the risk groups due to the observation that IMDC poor-risk patients have greatest OS benefit from treatment with nivolumab [64]. This study did not reveal any differences across the different risk groups and in addition, no differences in PD-1, PD-L1, PD-L2, and CTLA-4 expression was observed. PD-L1 has not yet been proven to be a good marker for response to ICI in mRCC. In the CheckMate-214 study, which resulted in the approval of nivolumab/ipilimumab as first-line therapy for intermediate and poor risk patients, ORR was 37% in PD-L1 negative patients and 58% in PD-L1 positive patients [35]. However, both PD-L1 positive and PD-L1 negative patients benefited from

ICI with an improved OS. In this study, the expression of PD-L1 was measured in tumor cells whereas other studies used tumor infiltrating immune cells to determine the PD-L1 status. Therefore, the role for PD-L1 testing remains unclear and negative PD-L1 status would not exclude patients from treatment with ICI.

Interestingly, in Microphthalmia Transcription Factor (MITF) family translocation RCC, a rare subtype of RCC, PD-L1 expression was reported in 90% and therefore this subtype of RCC patients may possibly be responsive to ICI. In a retrospective study of 24 patients, 7 patients had clinical benefit defined as partial response or stable disease [65]. They analyzed genomic alterations in eight patients of whom two had stable disease and two partial response and found mutations in bromodomain-containing genes (*PBRM1* and *BRD8*) that might be associated with clinical benefit.

In IMmotion 150, the investigators evaluated the expression of previously defined genes representing angiogenesis and immune biology in the pretreatment tumor specimens. The expression of the angiogenesis gene signature was higher in both *VHL* and *PBRM1* mutants compared to non-mutants. Previously, it had been shown that patients with *PBRM1* mutations have a favorable outcome compared to those with a *BAP1* mutation [66]. Besides, patients with loss-of-functions mutations in the *PBRM1* gene have more clinical benefit from ICI [67]. This was confirmed in the IMmotion 150 study in which patients with a *PBRM1* mutation had an improved PFS on atezolizumab/bevacizumab and sunitinib compared to non-mutants. However, *PBRM1* mutants had worse PFS when treated with atezolizumab monotherapy. These results might explain the finding that *PBRM1* mutations are found in patients with extreme responses to TKI [68].

In IMmotion 150, it was shown that high expression of the angiogenesis gene signature was associated with an improved ORR (46% vs. 9% when low expressed) when treated with sunitinib [47]. In the group with low expression of this angiogenesis gene signature, PFS was improved in the atezolizumab/bevacizumab group compared to sunitinib (11.3 vs. 3.7 months). This finding was confirmed when this gene signature was prospectively tested in the 823 patients in the IMmotion 151 study [69]. Moreover, similar results from biomarker analyses of 886 tumor samples of the JAVELIN Renal 101 study (avelumab/axitinib vs. sunitinib) were recently presented by Choueiri et al. [70]. It was demonstrated

that high expression of the angiogenesis gene signature was associated with a longer PFS when treated with sunitinib and a low expression improved PFS in the avelumab/axitinib arm. Tumor mutational burden did not distinguish patients considering PFS.

Next, the expression of a gene signature corresponding to the presence of a pre-existing immune response (T_{eff}) and the expression of a gene signature consistent with myeloid inflammation (Myeloid) was tested in IMmotion 150. Previously, the presence of MDSCs had been associated with suppression of the (antitumor) T-cell response [71]. Patients treated with atezolizumab monotherapy had worse activity when there was a high expression of the T_{eff} gene signature (T_{eff}^{high}) together with a high expression of the Myeloid signature ($Myeloid^{high}$). This subgroup (T_{eff}^{high} $Myeloid^{high}$) showed improved PFS when treated with atezolizumab plus bevacizumab. In contrast, there was no difference between treatment with atezolizumab/bevacizumab or atezolizumab monotherapy in the patient subgroup with a T_{eff}^{high} and $Myeloid^{low}$ signature suggesting that this subgroup could benefit from ICI alone instead of ICI + anti-VEGF.

To test the clinical value of molecular subgroups, the phase II biomarker driven BIONIKK trial (NCT02960906) will investigate the efficacy of a treatment choice (nivolumab and ipilimumab or TKI) based on molecular subgroups. In melanoma, an extensive study in responders and non-responders to ICI has been executed. By using single-cell sequencing both 'cold' (low number of tumor infiltrating T-cells) and 'hot' (high number of tumor infiltrating T-cells) tumors were characterized resulting in a malignant cell signature whose expression was strongly correlated (positively and negatively) with T-cell abundance [72]. The gene signature was able to predict PFS in patients treated with ICI and outperformed 47 alternative response predictors. Interestingly, it was shown that CDK4/6 inhibitors were capable of repressing the gene signature and sensitizing malignant cells to ICI. This provides a rationale for combining both ICI and CDK4/6 inhibitors in patients resistant to ICI. However, it is not exactly known if this gene signature can be used in patients with RCC. Yet, it has been demonstrated that, overall, clear-cell RCC has a high immune infiltration score and T-cell infiltration score which can possibly be used as a predictor of response to nivolumab [73]. Both T-cell infiltration and MHC class I antigen presenting machinery expression (APM) were elevated in patients responsive to nivolumab

whereas they were low in patients with progressive disease.

ICI AS (NEO)ADJUVANT TREATMENT

Several studies are currently investigating the role of ICI as adjuvant treatment. In IMmotion010 (NCT03024996) and Keynote-564 (NCT03142334) atezolizumab or pembrolizumab are used as adjuvant therapy in high-risk patients after nephrectomy, respectively. The combination of nivolumab and ipilimumab in patients with localized renal cell carcinoma is studied in CheckMate-914 (NCT03138512). RAMPART (NCT03288532) is a recent multi-arm trial platform that investigates durvalumab plus tremelimumab (anti-CTLA-4) versus durvalumab monotherapy versus active monitoring in patients with intermediate and high risk RCC according to the Leibovich risk score. A neoadjuvant combination of durvalumab plus tremelimumab is currently being investigated in the United States (NCT02762006) and may be factored in as another arm as the trial moves along. In The Netherlands, the NEOAVAX study (NCT03341845) adds neoadjuvant avelumab to axitinib in patients with localized RCC and a moderate to high risk of recurrence in a single arm phase II Simon-two stage design. Meanwhile, nivolumab is investigated as both neoadjuvant and adjuvant treatment in the United States-led PROSPER trial (NCT03055013), a phase III trial randomizing between perioperative nivolumab versus observation.

Recently, data on the use of neoadjuvant nivolumab with bevacizumab or ipilimumab have been presented (NCT02210117) [74]. Patients received six weeks of neoadjuvant therapy followed by cytoreductive nephrectomy or metastasectomy, and subsequent nivolumab maintenance. The study demonstrated a best overall response of 70% with neoadjuvant nivolumab, compared to 93% when bevacizumab was added, and 70% when ipilimumab was added.

UPCOMING TRIALS

There remains uncertainty about the optimal sequence following progression on ICI combinations. Not all patients benefit from ICI and besides, it can be associated with possible severe immune-related AEs. An attempt to decrease the amount of immune-related AEs is investigated in the Tailored Immunotherapy

Approach with Nivolumab in RCC (TITAN) study (NCT02917772). In this study, patients that have been previously untreated or pretreated with one prior TKI undergo nivolumab induction and ipilimumab is added in case of stable or progressive disease. A slightly different approach is done in the phase II OMNIVORE study (NCT03203473) where all patients start with nivolumab alone and response is evaluated at 6 months. In case of partial or complete response nivolumab is discontinued. In case of stable or progressive disease two cycles of ipilimumab are added [75].

Preclinical insights suggest that cytokines like IL-2 can synergize with ICI. NKTR-214, a conjugated IL-2, has shown to increase the ratio of CD8+/Treg cells in preclinical studies and mediates anti-tumor activity both as a single-agent and synergistic when combined with an anti-CTLA-4 antibody [76]. More recently, it has been shown to have a favorable safety profile in a phase I dose escalation trial (NCT02869295). Administration of NKTR-214 increased PD-1 expression on CD4+ and CD8+ T-cells in the tumor, providing a rationale for the currently recruiting clinical trial in which NKTR-214 is combined with PD-1/PD-L1 inhibitors. Preliminary results of the PIVOT-02 trial (NCT02983045) in which NKTR-214 is combined with 3-weekly nivolumab showed an ORR of 46% was demonstrated in treatment-naive mRCC patients [77].

In the PDGREE trial (NCT03793166), a phase III trial, the usual treatment with ipilimumab and nivolumab followed by nivolumab alone is compared to treatment with ipilimumab and nivolumab, followed by a combination of nivolumab and cabozantinib believing that the addition of cabozantinib makes ICI work better.

Another field of high interest in the treatment of RCC is targeting the metabolic pathway. Previous studies have demonstrated that the metabolism of tryptophan, arginine and glutamine is reprogrammed in many RCCs. These changes enable the RCC cells to survive in conditions of nutrient depletion and hypoxia which results in the production of immunosuppressive metabolites [78]. The glutaminase inhibitor CB-839 is able to suppress the upregulated glutamine pathway and is therefore of interest in the treatment of RCC. A Phase I study in which CB-839 was combined with cabozantinib 60 mg once daily showed promising results in the 12 evaluable and pretreated patients with an acceptable toxicity profile and an ORR of 42% with partial responses in 42% and stable disease in

58% of patients [79]. Another phase I is upcoming (NCT02071862).

Next, the Keynote-679/ECHO-302 study will investigate the addition of an indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor (epacadostat), an enzyme involved in the metabolism of tryptophan [80], to pembrolizumab. The efficacy and safety of the combination of pembrolizumab/epacadostat will be compared to sunitinib or pazopanib.

CONCLUSION

The recent studies in ICI have led to a rapid change in the treatment landscape of mRCC. However, despite all the practice-changing clinical trials in the field, sequencing of therapy remains challenging. Currently, treatment-naive patients with intermediate and poor risk disease are treated with ipilimumab and nivolumab as first-line therapy and with VEGF TKI after treatment failure. Patients with good risk disease that have been treated with VEGF TKI in the first-line can be treated with nivolumab monotherapy in the second-line or TKIs like cabozantinib, axitinib or lenvatinib plus everolimus [81]. The treatment paradigm is changing again now with approval of avelumab and axitinib, and pembrolizumab plus axitinib in first-line for all IMDC risk groups, pushing VEGFR-TKI from the standard of care position into alternatives for patients who cannot tolerate or receive ICI. It might be of interest to directly compare pembrolizumab/axitinib with nivolumab/ipilimumab in order to determine which strategy works best for the intermediate and poor prognosis patients. New combinations are tested with special interest in the involvement of targeting the metabolic pathway which may lead to new treatment strategies. The optimal choice and sequence of therapies needs to be determined and therefore there remains an unmet need for predictive biomarkers in order to further optimize and personalize the systemic treatment of mRCC.

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