First-line Treatment of Metastatic Cell Renal Cell Carcinoma

Subjects: Oncology

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Immune checkpoint inhibitors (ICI) are now the bedrock for the treatment of metastatic renal cell carcinoma (RCC). Clear cell RCC (ccRCC) represents the most common subtype of this malignancy. For ccRCC, pembrolizumab-axitinib, pembrolizumab-lenvatinib, and avelumab-axitinib or nivolumab-cabozantinib are now FDA-approved frontline options for all risk groups while nivolumab-ipilimumab is reserved for intermediate- and poor-risk groups. Monotherapy with pembrolizumab or nivolumab is a potential option for patients who are unable to take vascular endothelial growth factor inhibitors (VEGF)-tyrosine kinase inhibitors. While outcomes have improved with the adoption of ICI therapies, many patients develop therapy-resistant disease, creating an unmet need for further investigation. The efficacy of novel therapies as well as novel combinations in the post-ICI era is unclear.

clear-cell renal cell carcinoma immunotherapy immune checkpoint inhibitor

1. Introduction

Renal cell carcinoma (RCC) is among the top ten most common cancer diagnoses in the USA, with an estimated 76,000 new cases projected per year [1]. Approximately one third of these patients with RCC will present with metastases at diagnosis. Clear cell RCC (ccRCC) accounts for approximately 80% of all kidney cancers and historically has been associated with a poor prognosis in the metastatic setting [2][3]. Prior to 2005, there were few effective systemic treatment options for the management of RCC. The mainstays of treatment previously included cytokine-based therapies such as interferon-alpha (IFN-a) and high-dose interleukin-2 (IL-2). These therapies were associated with a poor overall response rate [4], as well as considerable toxicities [5].

Thankfully, the last two decades have witnessed remarkable progress in the management of RCC. An increased understanding of the oncogenesis of RCC has led to the development of several targeted treatment options, including tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) targeted agents, and mammalian target of rapamycin (mTOR) inhibitors. Furthermore, immune checkpoint inhibitors (ICIs) have emerged as an effective treatment option, both as a monotherapy and in combination with these other agents, leading to marked improvements in clinical outcomes.

The emergence of immune-checkpoint inhibitor (ICI)-based therapies has transformed the treatment landscape for patients with mRCC. Data from multiple clinical trials examining ICIs either as dual immunotherapy or in combination with anti-VEGF targeted agents demonstrate significantly improved overall survival (OS), progression

free survival (PFS), and overall response rate (ORR), compared to sunitinib. These clinical trials have led to the FDA approval of multiple ICI-based combination regimens as first-line treatment options for RCC. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria classify RCC subclassified into favorable, intermediate, and poor prognosis groups [6]. The criteria that incorporate clinical and laboratory risk factors were initially validated in patients undergoing VEGF therapies yet now continue to be used to guide systemic treatment selection in the era of ICI-based therapies. Current guidelines from the European Association of Urology recommend dual immunotherapy (ICI/ICI) as a first-line treatment for IMDC intermediate- and poor-risk groups and recommend combined ICI/VEGF therapies as first-line treatments across all IMDC risk groups. While the treatment options for RCC have shown significant advancements in recent years, the 5-year relative survival rate remains low, at only 13% in distant stage mRCC [7].

2. ICI/ICI Combination Therapy for Intermediate- and Poor-Risk Groups

RCC is one of the most immune-infiltrated tumor types, thus, ICIs have been identified as a promising therapeutic option [8]. ccRCC has significant intratumor heterogeneity with known cases of negative PD-L1 that are responsive to ICI therapy. PD-L1 immunohistochemistry is not used in the IMDC risk stratification of mRCC. In fact, PD-L1 expression in mRCC is not a predictive biomarker for treatment selection, unlike many other tumor types [9][10]. ICIs have been shown to have efficacy as monotherapies or in combination with other agents, including other ICIs and VEGF-targeted agents. The ICIs currently used in the treatment of mRCC include agents that target the programmed cell death 1 (PD-1) receptor (nivolumab, pembrolizumab), programmed death ligand 1 (PD-L1) (e.g.,atezolizumab, avelumab, and durvalumab), and cytotoxic T lymphocyte antigen 4 (CTLA-4) (ipilimumab).

To date, the only approved dual ICI combination regimen is nivolumab plus ipilimumab, which has emerged as one of the major first-line treatment options for patients with intermediate- or poor-risk- RCC based on data from the **CheckMate-214** trial [11]. The trial is a phase 3 study investigating the efficacy of nivolumab and ipilimumab (experimental arm) vs. sunitinib (control arm) in 1096 treatment-naïve patients with intermediate- or poor-prognostic risk advanced RCC. The co-primary endpoints for the trial were OS, ORR, and PFS.

The OS and ORR were significantly improved with nivolumab-ipilimumab compared to sunitinib in the intermediate-poor risk group. The median follow-up was 25.2 months. The 18-month OS was 75% in nivolumab-ipilimumab compared to 60% in sunitinib. The median OS was not reached in the nivolumab-ipilimumab group versus 26.0 months in sunitinib. The ORR was 42% in nivolumab-ipilimumab compared to 27% in sunitinib. A trend was observed in favor of nivolumab-ipilimumab vs. sunitinib for PFS (11.6 vs. 8.4 months, respectively), although there was no statistical significance. These findings led to the FDA approval of this dual immunotherapy regimen in April 2018.

Nivolumab-ipilimumab is one of the most effective ICI options with the caveat that treatment-related toxicities are common in the initial period of the treatment [12]. Although there were fewer grade 3–4 TRAEs in nivolumab-ipilimumab (48%) vs. sunitinib (64%), a high index of suspicion for immune-related adverse events is needed when

patients are receiving both drugs in the first four cycles (before switching to maintenance nivolumab alone). Establishing itself as the longest phase 3 follow-up for ICI combination therapy, an extended 5-year follow-up of CheckMate-214 continued to demonstrate the clinical benefits of nivolumab-ipilimumab over sunitinib. In an intention-to-treat (ITT) analysis, improved OS was sustained in nivolumab-ipilimumab compared to sunitinib in intermediate-poor risk groups [55.7 months vs. 38.4 months; HR 0.68 (95% CI: 0.58–0.81, $p < 0.0001$)] [13]. The conditional response in the ITT analysis was preserved beyond the 3-year point in 89% vs. 63% of patients on nivolumab-ipilimumab or sunitinib, respectively [14]. Thus, this dual immunotherapy regimen currently continues to serve as one of the main first-line treatment options for patients in IMDC intermediate- and poor-risk groups.

3. ICI/VEGF Combination Therapy Options for All Risk Groups

Nearly 90% of ccRCC tumors have a loss of heterozygosity at chromosome 3p, with a resulting loss of function of the pVHL tumor suppression protein (von Hippel-Lindau), leading to the activation of the hypoxia inducible factor-2-alpha (HIF-2α) transcription factor. HIF-2α is involved in angiogenesis, cell migration, and tumor proliferation. VEGF inhibitors and TKIs are efficacious in targeting the downstream effects of HIF-2α activation, leading to tumor response in RCC. Several ICI/VEGF combination therapy regimens have been approved as first-line therapy options for patients of all IMDC risk groups based on promising results from four major clinical trials: JAVELIN-101, Keynote 426, CheckMate 9ER, and CLEAR.

The **JAVELIN Renal 101** was the first trial to report on ICI/VEGF combination therapy for RCC [15]. JAVELIN-101 was a phase 3 trial that examined a combination of axitinib with avelumab compared to sunitinib in 886 treatment-naïve patients with advanced RCC across all IMDC risk groups. The primary endpoints included PFS and OS in patients with tumors positive for PD-L1 expression (PD-L1+). The overall response rate (ORR) was also assessed. PD-L1+ patients were found to make up 63.7% of the cohort and demonstrated a significantly greater PFS [(13.8 vs. 7.2 months; HR 0.61 (95% CI: 0.47–0.79, $p < 0.001$)] and ORR (55.2% vs. 25.5%) in axitinib-avelumab vs. sunitinib, respectively. In the cohort overall (irrespective of PD-L1 expressivity), PFS was also found to be higher in the axitinib-avelumab group compared to sunitinib [(13.8 vs. 8.4 months; HR 0.69 (95% CI: 0.56–0.84, $p < 0.001$)]. In terms of the safety profiles for these agents, TRAEs were similar between experimental and control groups (AEs occurred in 99.5% vs. 99.3%; AEs of grade 3 or higher occurred in 71.2% vs. 71.5%). The findings of the JAVELIN Renal 101 trial led to the FDA approval of the axitinib-avelumab combination regimen for all IMDC risk groups in May of 2019.

The follow-up data published in August 2020 from the JAVELIN-101 trial continued to show the therapeutic advantage of axitinib-avelumab over sunitinib with respect to PFS in both PD-L1+ patients and in the overall population [(**PD-L1+:** HR 0.62 (95% CI 0.490–0.777), $p < 0.0001$; median PFS: 13.8 months (95% CI 10.1–20.7) vs. 7.0 months (95% CI 5.7–9.6); **Overall population**: HR 0.69 (95% CI 0.574–0.825); $p < 0.0001$; median PFS: 13.3 months (95% CI 11.1–15.3) vs. 8.0 months (95% CI 6.7–9.8)]; however, the OS data were immature for all groups in the most recent analyses [16]. An updated analysis had enrolled 886 patients by 2021 and continued to show maintained efficacy consistent with prior studies [17]. The lack of demonstrated OS benefit continues to deter

many clinicians from using this regimen at this time. According to the current European Association of Urology Guideline, updated in October 2021, this combination therapy is not recommended until a significant survival signal can be demonstrated [18].

Keynote-426 was another phase 3 trial examining the efficacy of ICI/VEGF combination therapy [19]. This comprised 861 patients of all IMDC risk groups, who were randomly assigned either to a combination of pembrolizumab and axitinib or to the control arm of sunitinib. The primary endpoints were OS and PFS in the ITT population. The ORR was also assessed. At a median follow-up of 12.8 months, pembrolizumab-axitinib was associated with significantly improved clinical outcomes compared to the sunitinib arm, including greater PFS [(15.1 months vs. 11.1 months; HR 0.69 (95% CI: 0.57–0.84, $p < 0.001$)], improved 12-month OS rate [(90% vs. 78.3%; HR: 0.53 (95% CI: 0.38–0.74; $p < 0.0001$)], and higher ORRs (59.3% vs. 35.7%). These outcomes were found across all IMDC groups, irrespective of tumor PD-L1 expression. The frequency of TRAEs was similar between the experimental and control arms, with TRAEs of grade 3 or higher observed in 75.8% of patients in pembrolizumab-axitinib and 70.6% in sunitinib. The results from this trial led to the FDA approval of pembrolizumab-axitinib for all IMDC risk groups in April 2019. Follow-up data in October 2020 showed a sustained clinical benefit in the pembrolizumab-axitinib group compared to sunitinib with respect to OS [(NR vs. 35.7 months; HR 0.68 (95% CI 0.55–0.85), $p = 0.0003$] and PFS (median 15.4 months vs. 11.1 months HR 0.71, $p < 0.0001$) [20]. An extended follow-up published in May 2021 further demonstrated the advantage of pembrolizumab-axitinib vs. sunitinib with respect to the 42-month OS rate (57.5% vs. 48.5%) and PFS rate (25.1% vs. 10.6% with sunitinib), and the ORR (60.4% vs. 39.6%) [21]. Of note, the 42-month OS benefit compared to sunitinib is smaller than expected (less than 10%) as the OS curves for each appear to be very close to the extended follow-up.

Another pivotal trial investigating the efficacy of ICI/VEGF combination therapy was **CheckMate 9ER**, a phase 3 study that assessed the efficacy of combination therapy with nivolumab and cabozantinib compared to sunitinib in previously untreated patients with advanced ccRCC [22]. The study comprised 651 patients, with the primary endpoint being PFS. The secondary endpoints included OS and ORR, and an exploratory endpoint of the health-related quality of life was also assessed. The dose of cabozantinib in the trial was 40 mg daily, which is less than the 60 mg daily dose when cabozantinib is used alone. At a median follow-up of 18.1 months, the median PFS was significantly higher in nivolumab-cabozantinib compared to sunitinib (16.6 months vs. 8.3 months) in all risk groups, regardless of their PD-L1 status. Nivolumab-cabozantinib also showed improved clinical outcomes compared to sunitinib with respect to the 12-month OS rate (85.7% vs. 75.6%) and ORR (55.7% vs. 27.1%). The safety profiles were similar between nivolumab-cabozantinib and sunitinib, with rates of TRAEs of grade 3 or higher observed in 75.3% and 70.6%, respectively. In the nivolumab-cabozantinib group, 19.7% discontinued at least one of the drugs, and 5.6% discontinued both. Overall, patients reported better health-related quality of life with nivolumab-cabozantinib compared to sunitinib. Based on these findings, the combination nivolumab-cabozantinib therapy received FDA approval for all IMDC risk groups in January 2021.

Updated results from the CheckMate 9ER study were published in March 2021 [23]. At a median follow-up of 23.5 months, nivolumab-cabozantinib continued to show a significant improvement in PFS compared to sunitinib [(17.0 months vs. 9.3 months; HR 0.52 (95% CI: 0.43–0.64, $p < 0.0001$)]. Nivolumab-cabozantinib was also

advantageous to sunitinib with respect to OS [(NR vs. 29.5 months, HR: 0.66 (95% CI: 0.050–0.87, p = 0.0034)] and ORR (54.8% vs. 28.4%).

Most recently, the results from the phase 3 **CLEAR** study compared pembrolizumab-lenvatinib (pem-len), an ICI/VEGF combination therapy, to either lenvatinib-everolimus (len-eve) or sunitinib in a 1:1:1 ratio [24]. The CLEAR trial examined a cohort of 1069 treatment-naïve patients with advanced RCC across all IMDC groups. The primary endpoint was PFS, with OS and ORR also assessed. The results indicated a PFS benefit with pem-len compared to sunitinib (HR 0.39, median PFS: 23.9 months versus 9.2 months, p < 0.001). Pem-len also showed an advantage over sunitinib with respect to OS [HR 0.66 (95% CI: 0.49–0.88, p = 0.005)] and ORR (71% in pem-len vs. 36.1% in sunitinib). These improved clinical outcomes were observed across all IMDC risk groups, irrespective of PD-L1 expressivity. The dose reductions for treatment-related toxicity were common in the experimental arm (68.8% vs. 50.3%), with TRAEs of grade 3 or higher occurring in 82.4% and 71.8% in pem-len and sunitinib, respectively. Such a high incidence of grade 3 or higher TRAEs could be explained by the 20 mg/day lenvatinib dosing in the trial, which is higher than 18 mg/day when used in combination with everolimus. This also explains the frequent requirement for dose modification. Importantly, CLEAR had the highest ORR difference between the experimental arm and sunitinib, leading some investigators to propose that this could be a regimen of choice as it is most important to achieve a rapid disease response.

The CLEAR study also demonstrated a statistically significant improvement in PFS in the pem-len group relative to the len-eve and sunitinib groups [HR 0.65 (95% CI: 0.53–0.80, p < 0.001); median PFS: 23.9 vs. 14.7 vs. 9.2 months)]. The OS was longer with pembrolizumab plus lenvatinib than with sunitinib [(HR 0.66 (95% CI: 0.49–0.88; p = 0.005)]. These results led to the FDA approval of pem-len as a first line treatment for advanced ccRCC in August 2021. On the other hand, lenvatinib-everolimus is not currently recommended as a first-line treatment for mRCC; however, it is frequently used as a subsequent therapy [25].

For patients who cannot tolerate PD-1 inhibitors, sunitinib, pazopanib, and tivozanib can be offered as alternatives to immunotherapy for all IMDC risk patients. Cabozantinib is another option that serves as a PD-1 inhibitor alternative and is available for patients with IMDC intermediate- or poor-risk disease [26]. Recent studies have moved towards evaluating the efficacy of cabozantinib in the real-world setting, reporting it as a commonly utilized VEGF therapy and increasingly used as 2 L therapy after dual ICI therapy [27][28][29][30].

4. Treatment Section in the First Line Setting

A sizeable minority of patients with mccRCC are unable to receive ICI-doublet or ICI-VEGF due to comorbid conditions. For patients who have a contraindication to ICI, sunitinib, pazopanib, and tivozanib can be offered as alternatives for all IMDC risk patients. Cabozantinib is also available for patients with IMDC intermediate- or poor-risk disease [26]. Recent studies support the efficacy of cabozantinib in the real-world setting, reporting it as a commonly utilized VEGF therapy and that it is increasingly used as 2 L therapy after dual ICI therapy [27][28][29][30].

While ICI/VEGF are better than ICI/ICI for the treatment of mccRCC in patients with favorable risk groups, there is currently no consensus on whether ICI/ICI or ICI/VEGF shows the greatest therapeutic benefit for intermediate- or poor-risk disease groups, which make up approximately 75% of patients with advanced RCC. Further, clinicians also have a number of ICI/VEGF combinations to choose from with no head-to-head comparison [31].

The choice of therapy, ICI/ICI vs. ICI/VEGF, is determined by several factors, including the long-term survival, initial burden of disease, dosing, and metastatic involvement. Dual ICI is preferred in patients where the most desired outcome is long-term survival as previously noted in the discussion of the Checkmate-214 trial. However, more patients could achieve disease progression early on, especially those who might be highly symptomatic. ICI/VEGF has been increasingly evaluated in the real-world setting demonstrating both improvement in symptoms and a favorable efficacy. ICI/VEGF is preferred in patients with an initial high burden of disease in terms of symptoms and metastatic sites. For instance, an organ-specific metastatic involvement analysis of patients receiving a combination of nivolumab-cabozantinib showed ≥30% tumor size reduction in the kidney (89% of patients), lung (76%), lymph nodes (88%), and liver (73%) [32]. The downsides of the ICI/VEGF approach include the less mature OS data compared to Checkmate 214 along with the potential for overlapping toxicities (such as diarrhea) that would be difficult to differentiate as indicative of ICI-related vs. VEGF-related.

The specific involved disease sites are also important in the initial treatment selection approach. A recent pivotal multi-institutional study demonstrated significantly improved intracranial activity and a tolerable safety profile with cabozantinib therapy [33]. A total of 88 patients were divided into two cohorts, cohort A containing 33 patients without concomitant brain-directed local therapy at cabozantinib initiation, and cohort B with 55 patients receiving concomitant brain-directed local therapy. The extracranial response rate was 48% (95% CI: 31–66%) in cohort A vs. 38% (95% CI: 25–52%). The median OS was 15 months in cohort A (95% CI: 9.0–30.0 months) vs. 16 months (95% CI: 12.0–21.9 months) in cohort B. While those results require validation, they suggest that the use of cabozantinib can be started before brain-directed therapy.

Patient preferences may be influenced by several different variables, including treatment schedule, treatment-related toxicities, management options for these potential toxicities, and whether the approach would be covered by the patient's insurance provider [34][35]. For instance, pembrolizumab can be given every 6 weeks as opposed to every 4 weeks with nivolumab therapy—making pembrolizumab a preferred drug for patients who face a distance barrier to accessing an infusion center. Of the TKIs, lenvatinib is the only medication that can be crushed and mixed with water. A thorough discussion with patients can help guide the treatment selection among the array of possible drug regimens. Lastly, clinicians can also accumulate experience using a specific regimen (e.g., the ICI/VEGF regimen of choice that is supported by data) to improve patients' outcomes through their being well versed in the specifics of the used regimen. This is important as head-to-head comparisons of the frontline ICI/VEGF in the clinical trial setting are lacking, and such studies are unlikely to be conducted.

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