Immune Checkpoint Inhibitor Rechallenge in Renal Cell Carcinoma

Subjects: Oncology

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Immune checkpoint inhibitor-based therapies represent the current standard of care in the first-line treatment of advanced renal cell carcinoma.

renal cell carcinoma (RCC) immune checkpoint inhibitors (ICIs) rechallenge

1. Introduction

The advent of immune checkpoint inhibitors (ICIs) has radically changed the treatment of advanced renal cell carcinoma (RCC), resulting in a meaningful impact on survival in these patients, with a good tolerability profile.

Nivolumab monotherapy demonstrated clinically significant improvement in overall survival compared to Everolimus in patients who had advanced RCC with a clear cell component and had previously been treated with antiangiogenic therapy [1]. More recently, randomized clinical trials have shown superiority in terms of the efficacy of immunotherapy-based combination therapies over receptor tyrosine kinase inhibitor (TKI) monotherapy in previously untreated advanced RCC. In the last few years, combination therapies based on the use of checkpoint inhibitor (CPI) and TKI, including Pembrolizumab/Axitinib [2], Pembrolizumab/Lenvatinib [3], Nivolumab/Cabozantinib [4], and Avelumab/Axitinib [5], have demonstrated longer progression-free survival than Sunitinib in patients with untreated advanced RCC; these treatments are currently approved in Europe in the first-line treatment of advanced RCC, regardless of Heng score. A further therapeutic approach, based on dual immune checkpoint inhibition with Nivolumab/Ipilimumab, has demonstrated superior long term survival benefits than Sunitinib in patients with untreated advanced RCC with intermediate/poor risk [6] and is currently available in Europe. In accordance with these results, the main international guidelines recommend the use of an immunotherapy-based combination treatment in first-line therapy of advanced RCC [7][8].

Despite these clear advantages, most patients experience disease progression, requiring the choice of a new systemic treatment. Prospective data to determine the efficacy of further treatments after an ICI-based first-line therapy are lacking and are limited to small phase II trials focused on the use of TKI [9][10][11][12]. The role of ICI rechallenge (defined as the reintroduction of an ICI-based therapy after disease progression to previous ICI therapy) in this setting remains unclear; this strategy is not currently considered a standard of care in the treatment of advanced RCC, but it may be a reasonable option according to clinical activity data from other diseases, such as advanced melanoma [13] and non-small cell lung cancer (NSCLC) [14].

2. ICI Rechallenge in RCC: Current Evidence of Therapeutic Strategies for Overcoming Resistance

2.1. Combination of ICIs

The use of combination of drugs targeting different immune checkpoints represents a widely studied and currently used strategy in several diseases. This approach could improve the response to immunotherapy in previously untreated patients or allow a rechallenge of ICIs in patients who have experienced progression disease.

Adding a monoclonal antibody directed against CTLA4 to an anti-PD1 can bypass resistance to single agent immunotherapy; dual immune checkpoint blockade with Nivolumab/Ipilimumab has already been approved in previously untreated renal cell carcinoma and many other diseases, such as melanoma, NSCLC, and colorectal cancer. The clinical benefit of combining these two drugs derives from their complementary mechanisms: anti-CTLA4 plays a crucial role in T cell priming by enhancing their activation, whereas anti-PD1 is involved in the reversion of T cell exhaustion and subsequent reactivation of effector response [15].

2.1.1. Retrospective Data

A retrospective analysis evaluated antitumor activity and safety of 45 patients with metastatic RCC who had prior exposure to anti-PD1 or anti-PDL1 antibodies and were subsequently treated with salvage Ipilimumab and Nivolumab. More than half of the patients had received at least three prior lines of treatment. Of the 45 patients, 27 (60%) received monotherapy with prior anti-PD-1 or anti-PDL-1 antibodies, 8 (18%) received an ICI that targeted the PD-1 pathway in combination with a VEGF receptor inhibitor (Axitinib, Sunitinib, or Cabozantinib), 4 (9%) received an ICI in combination with Bevacizumab, and 6 (13%) received an ICI in combination with another drug. The objective response rate (ORR) to salvage Ipilimumab/Nivolumab was 20%, whereas the disease control rate (DCR) was 36% and the median PFS was 4 months. The immune-related adverse events (irAEs) of any grade were reported by 29 (64%) of 45 patients; grade 3 irAEs were recorded in 6 (13%) patients. The most common grade 3–4 irAEs were hepatotoxicity (7%) and pneumonitis, rash, diarrhea, thrombocytopenia, and colitis (2% each) [16]. Similar results were reported by another multicenter retrospective study of 69 patients with mRCC who received rechallenge immunotherapy (as single agent or in combination with another ICI or another drug, such as TKI). The ORR was 30% in patients receiving single ICI as rechallenge immunotherapy, 25% in those receiving dual checkpoint blockade, and 23% in those receiving ICI in combination with target therapy. ICI rechallenge showed a manageable safety profile, with 16% of patients developing grade 3–4 irAEs. The risk of experiencing an irAE with CPI rechallenge was higher in patients who had an irAE with a previous line of immunotherapy (41%) compared with those who did not (20%) [17].

2.1.2. Data from Prospective Trials

FRACTION-RCC (Fast Real-time Assessment of Combination Therapies in Immuno-Oncology Study in Patients with advanced RCC) is a signal-seeking randomized phase 2 trial with an adaptive-platform design; in track 2, the efficacy and safety outcomes of treatment with Nivolumab/Ipilimumab in patients with metastatic RCC whose

disease previously progressed during or after ICI were evaluated. All 46 patients included received previous anti-PD1 or anti-PDL1 therapy; half of the patients had received at least three lines of treatment previously. After a median follow up of 33.8 months, the ORR in the whole population was 17.4%, with eight partial responses and no complete responses. Stable disease was achieved as the best overall response (BOR) in 19 of 46 patients (41.3%), while 14 patients (30.4%) developed progressive disease as BOR. Antitumor activity was not evaluable or available in five patients. The median time to response was 2.9 months, with a median duration of response (DOR) of 16.4 months. Of the eight responders patients, five presented an ongoing response. Median PFS (95% CI) was 3.7 (2.0–7.3) months, while median OS (95% CI) was 23.8 (13.2 to not estimable) months. Grade 3–4 treatment-related adverse events (TRAEs) were reported in 13 patients (28.3%), TRAEs leading to discontinuation of treatment were reported in 4 patients (8.7%) [18].

In addition, several clinical trials have aimed to define a sequential use of immunotherapies, through an adaptive strategy of treatment intensification (or discontinuation) based on response.

In OMNIVORE, a multicenter, phase 2 adaptive trial, 83 patients with ICI-naïve advanced RCC were enrolled and received Nivolumab monotherapy (240 mg every 3 weeks) with subsequent arm allocation based on response within 6 months: patients who developed a complete or partial response discontinued Nivolumab and were observed (arm A), whereas patients with stable disease or progressive disease received two doses of Ipilimumab and continued Nivolumab (arm B; in combination treatment, patients received Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg every 3 weeks). The primary endpoint in arm B was the proportion of Nivolumab non-responders who were converted to responders after the addition of Ipilimumab; only 2 of 57 patients (4%) allocated to arm B experienced a conversion to a confirmed partial response, with no complete response observed [19].

An adaptive strategy was assessed in another phase 2 trial, the cohort A of HCRN GU16-260. Eligible patients with previously untreated advanced RCC received Nivolumab monotherapy as first-line treatment until progressive disease, toxicity, or completing 96 weeks (part A); subsequently, patients experiencing progressive disease before or stable disease at 48 weeks could receive salvage treatment with Nivolumab/Ipilimumab (part B). Of 123 enrolled patients, 35 received salvage treatment in part B; the ORR by RECIST to Nivolumab/Ipilimumab was 4 of 35 (11.4%) with 1 complete response, whereas by irRECIST was slightly greater (17.2%) [20].

TITAN-RCC (Tailored ImmunoTherapy Approach with Nivolumab in RCC), a multicenter, phase 2 trial, evaluated the activity and safety of a tailored immunotherapy approach in patients with intermediate/poor risk (by IMDC score) and CPI-naive advanced RCC with a clear cell component. Of 209 recruited patients, 109 were previously untreated, and 98 received a first-line treatment with TKI for RCC. All patients received Nivolumab monotherapy; early progressors (at week 8) or non-responders (at week 16) received 2–4 doses of Ipilimumab in combination with Nivolumab, while responders to Nivolumab monotherapy continued with maintenance and could receive Nivolumab/Ipilimumab in case of subsequent disease progression. Of all patients, 67% (139/207) received at least one boost cycle of Ipilimumab; the rescue strategy with dual checkpoint blockade led to ORR of 17% in both patients who previously received Nivolumab monotherapy as first-line and second-line treatment [21][22].

The activity, efficacy, and safety of salvage treatment with Nivolumab/Ipilimumab were also reported by a recent meta-analysis that included (three out of the seven trials had an adaptive design) 310 ICI-pretreated patients from a total of seven studies (three out of the seven trials had an adaptive design). The ORR to dual checkpoint blockade was 14% higher in the standard trials compared to adaptive ones (21% vs. 10%, respectively). There was no correlation between response to prior immunotherapy and response to salvage dual checkpoint inhibition. Median PFS ranged between 3.7 and 5.5 months, while the overall incidence of grade 3–4 AEs was 27% [23].

2.2. Combination of Antiangiogenics Drugs and ICIs

The role of drugs targeting the vascular endothelial growth factor receptor (VEGFR) and its pathway in improving the response to ICI is well known and based on a strong rationale. Antiangiogenic drugs determine the normalization of the tumor vascular structure, consequently increasing immune cell infiltration [24]. In addition, these drugs may restore an immune-sensitive TME by reducing the levels of cells with immunosuppressive functions, such as MDSCs and regulatory T cells and promoting the differentiation of monocytes into mature dendritic cells [25]. Hypoxia alleviation afforded by TKIs also limits the differentiation of macrophages toward the M2 phenotype, endowed with immunosuppressive activity [26].

Data from Prospective Trials

In IMmotion150, a multicenter, open-label, phase 2 trial, 305 patients with untreated metastatic RCC (with clear cell component and/or sarcomatoid component) were randomized to receive Atezolizumab/Bevacizumab, Atezolizumab, or Sunitinib. After disease progression on Atezolizumab or Sunitinib, cross-over to Atezolizumab/Bevacizumab was allowed. Overall, 44 patients in the first-line Atezolizumab arm received Atezolizumab/Bevacizumab after disease progression within the second-line part of the trial. The ORR to second-line treatment was 25%; 4 patients of 21 (19%) with progressive disease, as the best response to first-line Atezolizumab monotherapy, achieved a partial response on Atezolizumab/Bevacizumab; the median PFS was 11.1 months [27].

Data on the activity of combination of antiangiogenics and ICIs on a larger sample size are provided by KEYNOTE-146, an open-label, single-arm, phase 1b/2 study of Lenvatinib/Pembrolizumab in patients with selected advanced solid tumors. Overall, 145 patients with metastatic RCC (with predominant clear cell component) were enrolled in this trial; three groups were identified: treatment-naïve patients, patients previously treated without ICI, and patients previously treated with at least one prior CPI (anti-PD1 or anti-PDL1 therapy). The latter group represented the majority of the whole population (104 out of 145); almost all of the ICI-pretreated patients (92.3%) had an ICI as their most recent treatment. Nivolumab/Ipilimumab was the previous ICI-based therapy in 39 patients, while 18 patients received anti-VEGF therapy in combination with ICI and 47 patients received an ICI with or without other treatment. The ORR by investigator assessment in the whole ICI-pretreated population was 62.5%, with a median duration of response of 12.5 months; in the Nivolumab/Ipilimumab subgroup, the ORR was higher (61.5%) compared to anti-VEGF/ICI subgroup (38.9%) and was similar to those who received ICI with or without other therapy (57.4%). Median PFS was 12.2 months, while median OS was not reached (median follow up time of 16.6

months). All patients developed at least one TRAE, while grade 3–5 TRAEs were reported in 64% of patients. There were two treatment-related deaths (gastrointestinal hemorrhage and another not otherwise specified death); hypertension was the most common grade 3 TRAE (21% of patients) [28].

Currently available data (on 1 April 2023) from prospective trials concerning ICI rechallenge are reported in **Table 1**.

Table 1. Summary of selected prospective trials of ICI rechallenge in advanced RCC.

Clinical Trial Identifier	Histology	Line	Phase	Treatment Arm(s)	Accrual	Primary Endpoint(s)	Results
NCT02996110 FRACTION-RCC (track 2)	ccRCC	≥2	II	Nivolumab + Ipilimumab (in ICI-pretreated)	46	ORR, DOR, PFS rate at 24 weeks	ORR 17.4%, DCR 58.7% mDOR 16.4 months PFS rate at 24 weeks 43.2% mPFS 3.7 months mOS 23.8 months Grade 3–4 TRAEs 28.3%
NCT03203473 OMNIVORE (arm B)	ccRCC or nccRCC	≥2	II (adaptive design)	Nivolumab + Ipilimumab (two doses of Ipilimumab for non-responders to Nivolumab induction)	57	Proportion of non-responders to Nivolumab induction converted to response	ORR 4% DCR 50% mPFS 4.7 months OS rate at 18 months 79% Grade 3–4 TRAEs 25%
NCT03117309 HCRN GU16-260 (part B)	ccRCC or nccRCC	2	II (adaptive design)	Nivolumab + Ipilimumab (for non-responders	35	ORR	ORR 11.4% ORR by irRECIST

Clinical Trial Identifier	Histology	Line	Phase	Treatment Arm(s)	Accrual	Primary Endpoint(s)	Results
				to Nivolumab 1st line therapy)			17.1% Grade 3–4 TRAEs 42.9%
NCT02917772 TITAN-RCC (second-line subgroup)	ccRCC (only intermediate/poor risk by IMDC score)	≥2	II (adaptive design)	Nivolumab + Ipilimumab (2–4 doses of Ipilimumab for non-responders to Nivolumab induction)	139	ORR	ORR 17% DCR 38.9%
NCT01984242 IMmotion150 (second-line part)	ccRCC or sRCC	2	II	Atezolizumab + Bevacizumab (in previously treated with first-line Atezolizumab monotherapy)	44	ORR, PFS, DOR (secondary endpoints of the whole trial)	ORR 25% mPFS 11.1 months
NCT02501096 KEYNOTE-146 (RCC cohort)	ccRCC	≥2	II	Lenvatinib + Pembrolizumab (in ICI-pretreated)	104	ORR at week 24 by irRECIST	ORR at week 24 55.8% ORR 62.5% mDOR 12.5 months mPFS 12.2 months Grade 3–4 TRAEs 64%

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