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Mini Review

# Which Way Should be Chosen for Treatment of Metastatic Renal Cell Carcinoma?

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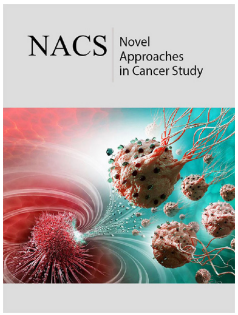


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## Introduction

There are two major pathways targeted for the treatment of metastatic renal cell cancer. One is VEGF inhibition that induces tumor shrinkage and increases progression-free survival and the other is Immune checkpoint inhibition that has been shown to increase overall survival. There are two clinically possible ways to block the antiangiogenic (VEGF) pathway. We can use Tyrosine kinase inhibitors (Sunitinib, Pazopanib, Cabozantinib, Axitinib, Sorafenib) that block the intracellular domain of the VEGFR or a monoclonal antibody (Bevacizumab) that binds to circulating VEGF and prevents it from activating VEGFR [1]. Checkpoint inhibition targeting the T lymphocyte-associated antigen 4 (CTLA-4) and/or programmed cell death receptor 1 (PD-1) pathway has led to significant improvements in the treatment of many malignancies, including renal cell carcinoma.

In a study conducted by Motzer et al. [2] in which Avelumab and Axitinib combination were compared with Sunitinib ; Avelumab plus Axitinib was given to 442 patients and Sunitinib was given to 444 patients in a total of 886 treatment naive metastatic patients. For PD-L1 positive 560 patients; mean progression-free survival was 13,8 months in the combination group and 7,2 months in the Sunitinib group ($p<0,001$). The objective response to treatment was 55.2% in the combination group and 25.5% in the Sunitinib group. In this trial; progression-free survival was significantly longer in Avelumab plus Axitinib group than in Sunitinib group. In another study by Rini et al. [3] Pembrolizumab plus Axitinib combination therapy were compared with Sunitinib in a total of 861 treatment naive metastatic renal cell carcinoma patients. The 12-month overall survival was 89.9% in the combination group and 78.3% in the group receiving Sunitinib. The mean progression-free survival was 15,1 month in the Pembrolizumab plus Axitinib group and 11,1 month in the Sunitinib group. The percentage of objective response to treatment was 59.3% in the combination group and 35.7% in the Sunitinib group. In conclusion, Pembrolizumab plus Axitinib combination therapy is associated with a longer overall and progression-free survival and a higher objective response to treatment than Sunitinib monotherapy.

Finally, in a study conducted by Motzer et al. [4] Nivolumab plus Ipilimumab was given to 550 patients and Sunitinib was given to 546. The 18-month overall survival was 75% in the combination group and 60% in the second group receiving Sunitinib. The percentage of objective response to treatment was 42% in the combination group and 29% in the Sunitinib group. The mean progression-free survival was 11,6 months in the Nivolumab plus Ipilimumab group and 8,4 months in the Sunitinib group. For patients with intermediate or poor risk disease; the overall survival and objective response to treatment were significantly higher in the Nivolumab-Ipilimumab group than in the Sunitinib group.

So which combination will be used in the future? In all of the above mentioned studies, the control group was Sunitinib. Pembrolizumab and Avelumab studies have similar mean follow-up periods (12,8 months and 11,6 months, respectively), but overall survival was significantly higher in the Pembrolizumab study. This may contribute to the theory that PD-1 inhibition has longer effects than PD-L1 inhibition. It is a matter of curiosity about the overall survival in case of longer follow-up with Avelumab. Contrary of these two studies, the Nivolumab-Ipilimumab study showed no significant increase in progression-free survival, but there is

a significant increase in overall survival. More importantly, the percentage of complete response to treatment was the highest in this study (10.2%). Despite the high success rates, the side effects observed with Ipilimumab should be kept in mind before starting this treatment.

Another question is what is the role of Axitinib in these combinations? In a study of 213 patients with metastatic renal cell carcinoma, patients were divided into two groups: Axitinib dose titrated group (5mg/day, 7mg/day, 10mg/day) and placebo titration group [5]. Progression-free survival was 14,5 months in the Axitinib titrated group and the percentage of objective response to treatment was 48%. This shows that Axitinib is a potent VEGF inhibitor with an excellent antitumor activity. However, Axitinib alone is not used as a standard first-line treatment in metastatic renal cell cancer. Therefore, in order to better understand the role of Axitinib in combination regimens, studies using Axitinib as monotherapy are needed. Some recent studies have shown that angiogenesis, T lymphocyte effector response, IF-gamma response and myeloid inflammatory gene expression may be important to understand the response to VEGF, PD-1 and PD-L1 inhibitors. A recent study showed that PD-L1 positivity increased the effect of immune checkpoint inhibitors [6]. As the subgroup studies gain momentum, it will be clear which patients will be given which treatment regimens.

Prognostic risk factors are important when choosing treatment in advanced disease. International Metastatic Renal Cell Carcinoma Database Consortium criteria [7]:

A. Karnofsky performance score <80%.

B. Time from original diagnosis to initiation of targeted therapy <1 year.

C. Hemoglobin less than the lower limit of normal.

D. Serum calcium greater than the upper limit of normal.

E. Neutrophil count greater than the upper limit of normal.

F. Platelet count greater than the upper limit of normal.

Patients with none of these risk factors are classified as favorable risk, those with one or two are classified as intermediate risk, and those with three or more risk factors are classified as poor risk. According to guidelines preferred regimens in first-line treatment are Axitinib plus Pembrolizumab, Pazopanib or Sunitinib for favorable risk patients. Recommended regimens for intermediate or poor risk disease are Ipilimumab plus Nivolumab, Axitinib plus Pembrolizumab or Cabozantinib [8]. The results of the future studies that will aim to obtain predictive markers for choosing appropriate patient group and most effective regimen for each patient will guide the treatment in metastatic renal cell carcinoma patients.

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