



# New Perspectives in the Treatment of Advanced Kidney Cancer

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## Abstract

Treatment scenario of advanced renal cell carcinoma (RCC) has been characterized in the last decade by the approval of a number of new drugs. Choice of first line treatment falls essentially on sunitinib or pazopanib, two tyrosine kinase inhibitors (TKI), both exerting anti-tumor activity through inhibition of neoangiogenesis. In the second line setting, nivolumab, an immune checkpoint inhibitor antibody, has been shown to prolong overall survival (OS) vs. the mTOR inhibitor everolimus by restoring the adaptive anti-cancer immune response. Cabozantinib, a multi target TKI, may also get use in second line based on OS advantage vs. everolimus although toxicity appears substantial. The TKI axitinib remains still a viable option. Finally, combination therapy seems a very promising area and is under frenetic investigation in those patients progressing or refractory to angiogenesis inhibition as well as in first line setting.

**Keywords:** Renal cell carcinoma; Nivolumab; Anti-PD-1 antibody; Cabozantinib; Tyrosine kinase inhibitor

## Introduction

Worldwide incidence of renal cell carcinoma (RCC) is 338,000 of new cases per year with 30% of patients presenting with metastatic disease at diagnosis [1,2]. After almost 25 years of silence since the first use of cytokines in early 1980's, treatment scenario of advanced RCC has been characterized in the last decade by the frenetic approval of a number of new drugs. Choice of first line treatment falls essentially on sunitinib or pazopanib. Both are tyrosine kinase inhibitors (TKI) of vascular endothelial growth factor receptor (VEGFR) pathway and exert anti-tumor activity through suppression of neoangiogenesis. Sunitinib is the standard whereas pazopanib seems to be not inferior in terms of efficacy and apparently less toxic as shown by the head-to-head COMPARZ trial [3]. However, several methodological aspects have raised doubts about the reliability of this study. The indication of anti-VEGF bevacizumab plus interferon alpha has been actually overcome by clinical practice [4]. Same thing happened to the mTOR inhibitor temsirolimus in poor prognosis patients whereas tumors with non clear cell histology are a separate category and require further investigations [5].

What happens to those patients progressing or refractory to VEGFR inhibition? At least half of them starts a second line treatment and even 15% a third line. Among TKIs, axitinib is better than sorafenib after first line sunitinib whereas the mTOR inhibitor everolimus exerts its activity after one as well as after two TKIs [6,7]. Toxicities to first line TKI and disease burden may drive the choice. Everolimus has a toxicity profile quite different from TKIs but you won't give it to your patient if you need significant tumor shrinkage to control symptoms. Finally, there is an unmet need for treatment of RCC patients who progress after treatment with VEGF targeted therapies and mTOR inhibitors.

In daily practice we learned how to sequence all available drugs pursuing the slogan "use them all but use them well" to optimize treatment and provide to our patients longer progression-free survival (PFS) intervals along with a better quality of life. However, none of the above mentioned agents taken individually has been shown to significantly increase the overall survival (OS) of RCC patients. This was the story, at least until late 2015 when data on nivolumab and cabozantinib started to be released.

## Programmed death-1 (PD-1) inhibition to restore the adaptive immune response against RCC

Immune-oncology is one of the most exciting areas in cancer research today. This is especially

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**Table 1:** New therapeutic options in metastatic renal cell carcinoma.

	AXITINIB	NIVOLUMAB	CABOZANTINIB
Disease setting	2 <sup>nd</sup> line	2 <sup>nd</sup> line (72% 1 prior TKI)	2 <sup>nd</sup> line (70% 1 prior TKI)
vs.	Sorafenib	Everolimus	Everolimus
OS, months	20.1	25	21.4
PFS, months	6.7	4.6	7.4
ORR	19%	25%	21%
Toxicity G3-G4 (patients with an event)	50% G3	18% G3	63% G3
	6% G4	1% G4	8% G4
Dose reduction	30%	not allowed	60%
Discontinuation due to AE	7%	8%	9%

OS: Overall Survival; PFS: Progression-Free Survival; ORR: Objective Response Rate; AE: Adverse Events

true in kidney cancer traditionally linked to immunotherapy studies, which led in 1992 to the approval of high dose IL2 due its ability to induce durable responses in a small percentage of patients [8]. The immune system is capable of recognize and eliminating tumor cells through a complementary network of self-defense. The innate immune response is the first line of defense; it identifies and attacks tumor cells without antigen specificity. Natural Killer cells are the main effector cells of innate immunity. However, a durable response that attacks tumor antigens is induced by the adaptive immune response. Once activated, it can be sustained through a memory response. Cytotoxic T cells are the main effectors cells of adaptive immunity. Tumor cells can use various mechanisms to escape detection and enable growth. Pathways that can be modulated to restore the adaptive immune response are currently under frenetic investigation in RCC.

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of the cellular adaptive immune response. It has been postulated that disruption of PD-1/PD-L1 signaling mediated by nivolumab leads to restored antitumor immunity [9]. Checkmate 025 is the nivolumab pivotal study in RCC [10]. This study is an open-label phase III trial in which 821 advanced or metastatic patients progressing to one or two regimens of antiangiogenic therapy were randomly assigned (1:1 ratio) to receive 3 mg of nivolumab per Kg of body weight intravenously every 2 weeks or a 10-mg everolimus tablet orally once daily. Seventy-two percent of patients received only 1 prior antiangiogenic drug before the study entry in both arms, mostly sunitinib. Primary endpoint was OS. Patients treated with nivolumab had a 27% reduction in the risk of death as compared to those treated with everolimus. Median OS was 25 months with nivolumab and 19.6 months with everolimus. Survival benefit with nivolumab was observed regardless of number of prior antiangiogenic treatments and PDL-1 expression but not in the subgroup of patients aged  $\geq 75$  years (about 10% of study population). Objective response rate (ORR) was higher with nivolumab than with everolimus, namely 25% vs. 5%. Median time to response was 3.5 months among patients responding to nivolumab vs. 3.7 months in the everolimus responding group of patients. Median PFS was almost the same, namely 4.6 months in the nivolumab group and 4.4 months in the everolimus group. However, the late separation of PFS curves suggests a potential delayed benefit in PFS with nivolumab, which probably contributes

to the OS benefit. Patients receiving subsequent treatments were lesser in the nivolumab group as compared to the everolimus group, namely 55% vs. 63%. Anti-PD-1 therapy was given as subsequent therapy to only 7 patients in the everolimus group thus reducing the potential confounding bias of crossover. Moreover, treatment with nivolumab beyond progression can be associated with late tumor shrinkage after first progression especially in those patients with good performance status and less bulky tumor burden [11]. This is not unexpected since immunotherapy response patterns differ from traditional therapies, and patients may benefit from treatment after initial RECIST progression. Finally, long-term OS results from phase I and II nivolumab studies have been recently reported with about one-third of patients treated with nivolumab alive at 5 years in the phase I study and 3 years in the phase II study [12].

Nivolumab has proven to be a very well tolerated treatment in RCC patients with specific adverse events mostly reflecting its immune stimulating activity. In the Checkmate 025 trial the most common treatment-related adverse events among patients treated with nivolumab were fatigue, nausea, and pruritus. Grade 3 or 4 treatment-related adverse events occurred in 19% of patients treated with nivolumab and in 37% of patients treated with everolimus. Treatment-related adverse events leading to treatment discontinuation occurred in 8% of patients treated with nivolumab and in 13% of patients treated with everolimus.

#### Targeting multiple tyrosine kinases involved in RCC pathogenesis to overcome resistance

Mechanisms of resistance to first line TKI are various. In particular, increased expression of the oncogenes MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers including RCC [13] and drugs targeting these multiple pathways are now under investigation. The most promising of these drugs is cabozantinib, an oral small-molecule inhibitor of tyrosine kinases, including MET, VEGFR and AXL.

METEOR is a randomized, open-label, phase III clinical trial comparing cabozantinib to everolimus in patients with advanced RCC that had progressed after VEGFR/TKI therapy [14]. A total of 658 patients were randomly assigned (1:1 ratio) to receive cabozantinib 60 mg orally once daily or everolimus 10 mg orally once daily. About 70% of patients received only 1 prior antiangiogenic drug before the study entry in both arms, mostly sunitinib. Primary endpoint was PFS. The rate of progression was 42% lower with cabozantinib than with everolimus with a median PFS of 7.4 and 3.8 months, respectively. The ORR was 21% with cabozantinib and 5% with everolimus. The secondary endpoint of improved OS for cabozantinib-treated patients was met as recently reported [15]. The median OS was 21.4 months for cabozantinib vs. 16.5 months for everolimus, with a 33% reduction in the rate of death. OS benefit with cabozantinib was observed regardless of number of prior antiangiogenic and anti-PD-1/PD-L1 treatments, as well as tumor MET expression level. In summary, cabozantinib is the only agent to demonstrate a significant benefit in OS, PFS, and ORR in a phase III trial in previously treated patient with advanced RCC.

Toxicity is an "issue" with cabozantinib and dose reductions occurred in 60% of patients treated with cabozantinib and 25% treated with everolimus enrolled in the METEOR trial. The most common adverse events (any grade) leading to dose reductions with cabozantinib were diarrhea, the palmar-plantar erythrodysesthesia

syndrome, and fatigue. Incidence of adverse events of grade 3 or 4 was 68% with cabozantinib and 58% with everolimus. However, rate of treatment discontinuation due to adverse events potentially drug-related was similar, namely 9% in the cabozantinib group and 10% in the everolimus group.

## Conclusion and Future Direction

Table 1 resumes the new options we have to treat metastatic RCC patient's refractory or progressing to first line VEGFR inhibition. Nivolumab is likely to be the second line standard of care based on OS advantage and tolerability. Cabozantinib may also get use in second line although toxicity appears substantial whereas axitinib remains still a viable option.

What's next? Combination therapy seems a very promising area and data on combination of everolimus with lenvatinib, a multiple TKI against VEGFR1, VEGFR2 and VEGFR3, have been recently reported in the second line setting [16]. OS and PFS were 25.5 and 12.8 months, respectively, with 35% ORR. However, efficacy results were not matched by a good tolerability profile and incidence of adverse events of grade 3 or 4 was 71%. Combinations of nivolumab with cabozantinib in patients with genitourinary cancers, including RCC, are currently being investigated (ClinicalTrials.gov number, NCT02496208).

Checkmate 016 is a phase I study designed to evaluate safety, effectiveness and best dose of nivolumab in combination with sunitinib, pazopanib or ipilimumab in RCC patients who did not receive any prior treatment for metastatic disease (ClinicalTrials.gov number, NCT01472081). Checkmate 214 is a phase III, randomized, study of nivolumab combined with ipilimumab vs. sunitinib in previously untreated advanced RCC (ClinicalTrials.gov number, NCT02231749). Both these studies will tell us if nivolumab may move to the first line setting. Other combination trials focusing on first line setting are currently enrolling. In particular, a phase I/II study aimed to evaluate the combination of pazopanib with pembrolizumab, another PD-1 immune checkpoint inhibitor antibody (ClinicalTrials.gov number, NCT02014636), and JAVELIN Renal 101 a phase III randomized study evaluating avelumab, an anti-PD-1L antibody, in combination with axitinib vs. sunitinib (ClinicalTrials.gov number, NCT02684006).

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