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Nivolumab in renal cell carcinoma: latest evidence and clinical potential

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***Abstract*:** Similar to melanoma, renal cell carcinoma (RCC) has been historically considered as an immunogenic tumor, with interleukin 2 (IL-2) and interferon alpha (IFN-α) being the first approved treatments in the 1990s. However, these therapies were effective in only 10–20% of cases and were not well tolerated. Recently, new insights on the interaction between the immune system and tumor have identified the programmed death-1/programmed death-ligand-1 (PD-1/PD-L1) pathway to be a key player in evading host immune responses. The strategy of immune checkpoint blockade is to reduce inhibitory signaling and restore the patient's natural tumor-specific T-cell-mediated immune responses. Nivolumab is the first PD-1 inhibitor to have gained approval for the treatment of patients with metastatic melanoma, squamous and nonsquamous non-small cell lung cancer (NSCLC), Hodgkin disease and recently RCC. In this review, we discuss results from studies of nivolumab in RCC, clinical experience with this agent, and its future development.

Keywords: immune checkpoint inhibitor, immunotherapy, nivolumab, programmed death-1, renal cell carcinoma

Background

Renal cell carcinoma (RCC) accounts for 2.4% of all adult malignancies, and its incidence has increased over recent years. Worldwide, it represents 338,000 new cases per year, and is responsible for 114,000 deaths [Ferlay *et al.* 2015]. Approximately 70% of all kidney cancers are clear cell renal cell carcinomas (ccRCC), so recommendations mainly relate to that histology. Median age at diagnosis is 64, and 30% present with synchroneous metastatic disease. Eventually, 40% of patients will die from metastases [Abe and Kamai, 2013].

RCC is classified as an 'immunogenic' tumor, based on several characteristics: incidence of spontaneous tumor regression, high level of tumor T-cell infiltration and responsiveness to immunotherapies such as interleukin 2 (IL-2) and interferon alpha (IFN-α) [Itsumi and Tatsugami, 2010]. However, these therapies have been disappointing because of low efficacy and high rate of adverse events, so that targeted agents such as vascular endothelial growth factor-targeting (VEGF) antiangiogenic agents and mammalian target of rapamycin inhibitors now form the backbone of most therapeutic strategies and have allowed an improved outcome in metastatic RCC (mRCC) [Escudier *et al.* 2014; Motzer *et al.* 2007]. Objective response rate (ORR) range from 30% to 47% in untreated patients and from 1.8% to 23% in the pretreated setting. Except for temsirolimus in poor-risk patients [Hudes *et al.* 2007] and sorafenib in second line setting [Hutson *et al.* 2014] these agents failed to demonstrate a statistically significant improvement in overall survival (OS) in pivotal studies [Sternberg *et al.* 2010; Escudier *et al.* 2007a; Motzer *et al.* 2007; Escudier *et al.* 2007b; Rini *et al.* 2010, 2011; Motzer *et al.* 2008].

In addition, tumors eventually develop resistance to targeted therapy and their toxicity is often responsible of treatment discontinuation.

Recently, immune checkpoint blockade has become a new avenue of immunotherapy; the strategy being to reduce inhibitory signaling and restore the patient's natural tumor-specific T-cell-mediated immune responses [Ascierto *et al.*

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2014]. Nivolumab (BMS-936558/ONO4538) is a programmed death-1 (PD-1) monoclonal antibody. It has been first approved for the treatment of patients with metastatic melanoma, squamous and nonsquamous non-small cell lung cancer (NSCLC), Hodgkin's disease, and recently in mRCC. In this review, we will discuss the development of nivolumab in metastatic clear cell RCC (mccRCC), our clinical experience and the potential of future directions.

Immune checkpoint inhibition and nivolumab: rationale for antiprogrammed-death 1 therapy in clear cell renal cell carcinomas

Tumor antigen presentation to T cells and T-cell activation lead to tumor cell killing. Immune response is initiated through antigen recognition by the T-cell receptor, and its amplitude and quality is regulated by interactions between costimulatory and inhibitory signals that are immune checkpoint. While this interaction does have a physiologic role to suppress autoimmunity, the expression of immune-checkpoint can be dysregulated by tumors and allow for tumor 'escape' from the immune system [Pardoll, 2012].

PD-1 (B7-H1) and its ligand, programmed death-ligand-1 (PD-L1) (B7-DC) were identified as novel therapeutic targets for immune checkpoint blockade. PD-1, a receptor expressed on CD4+ and CD8+ T cells (as well as B cells and natural killer cells), binds to PD-L1 and PD-L2, expressed in tumor cells, but also on inflammatory cells such as T lymphocytes and infiltrating mononuclear cells. This interaction between PD-1 and PD-L1 induces inhibition of a cytotoxic immune response [Dong *et al.* 1999].

Unlike PD-L1, the expression of PD-L2 is more limited, with expression mainly in macrophages and dendritic cells [Rozali *et al.* 2012], which suggests less efficacy in regulating T-cell response. In general, 20–25% of ccRCC tumor cells express PD-L1 and this expression is correlated with cancer-specific death [Thompson *et al.* 2006]. More than 50% of RCC's tumor-infiltrating lymphocytes express PD-L1, which is associated with distant metastatic relapse and poor survival [Thompson *et al.* 2006]. Inhibiting this axis has shown promising results in restoring tumor-specific T-cell-mediated immune responses.

Nivolumab is a fully humanized immunoglobulin G4 isotype monoclonal antibody that blocks PD-1 and can restore anticancer immune responses. It binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1, but no reactivity to the PD-L1 homologs CD28, CTLA-4 and inducible costimulators [Wong *et al.* 2007]. Nivolumab is approved for the treatment of patients with advanced melanoma, squamous and nonsquamous NSCLC, Hodgkin's disease and mRCC. It is associated with the most robust clinical development program to date on PD-1 pathway inhibition.

Early phase trials of nivolumab in renal cell carcinoma

The initial phase Ib 003 clinical trial of nivolumab in monotherapy was conducted in patients with melanoma, lung cancer, RCC and a few other malignancies. In this study, 34 patients with mccRCC received nivolumab at escalation doses of 1.0, 3.0 or 10.0 mg/kg every 2 weeks for up to 2 years. Of the 34 patients, almost 50% were heavily pre-treated, with 18% receiving 3 prior lines of therapy and 27% receiving 4 prior lines of therapy. At a minimum follow up of 50.5 months, objective responses were observed in 29% of patients and one patient had a complete response in the 10 mg/kg cohort. For all doses, the objective response rate (ORR) was 29.4%. Among the responders, 30% achieved objective response by 8 weeks (1st assessment) and 70% demonstrated response by 16 weeks (2nd assessment). Median duration of response was 12.9 months (8.4–29.1) and 40% of responses were ongoing at the time of data analysis [Topalian *et al.* 2012].

The phase I 009 clinical trial was the first prospective translational trial of nivolumab involving analysis of baseline and on-treatment biopsies for mccRCC. This study investigated the immunomodulatory activity of various dose levels of nivolumab in 91 patients with pre-treated (0.3, 2, or 10 mg/kg every 3 weeks) and untreated (10 mg/kg every 3 weeks) mccRCC. Baseline and on treatment biopsies were performed. Twenty six percentage of patients were treatment-naïve and 74% of patients were previously treated. Of 56 evaluable baseline biopsies, 32% had $\geq$ 5% PD-L1 expression and there was no change in tumor PD-L1 expression following nivolumab treatment relative to baseline. Response according to PD-L1 status using a $\geq$5% cutoff showed a

higher proportion of responder patients with PD-L1+ tumors (response rate 22%), but patients with PD-L1- tumors also demonstrated response (response rate 8%). Median overall survival (OS) was 23.4 months in patients with <5% PD-L1+ tumor expression; and was not reached in patients with ⩾5% PD-L1+ tumor expression. Across different dose levels, objective response rates ranged from 9% to 23%. In previously treated patients, median OS was 16.4 months, not reached, and 25.2 months in 0.3, 2, and 10 mg/kg nivolumab cohorts, respectively; in treatment-naïve patients (10 mg/kg), median OS was not reached. Baseline tumor T-cell infiltrates (CD3+, CD8+) correlated with a decrease in tumor burden. Median percent changes from baseline in tumor-associated lymphocytes were 69% (CD3+), 180% (CD4+), and 117% (CD8+). Significant increases in the expression of genes that are hallmarks of T-cell function were seen and the same increases were observed at the tumor site for genes involved in the trafficking behavior of T cells. The pharmacodynamics of nivolumab also included significant increase in the expression of genes linked to innate immunity. Additional analyses of these data are ongoing to better understand the relationship between the immunomodulatory activity of nivolumab and clinical outcomes, but this shows that treatment with nivolumab is associated with transcriptional changes in the tumor microenvironment and provide the rationale for developing combination therapies [Choueiri *et al.* 2016].

In the phase II 010 clinical trial, 168 pretreated patients received nivolumab in monotherapy at 0.3, 2 or 10 mg/kg every 3 weeks. After a minimum follow up of 38 months, ORRs ranged from 20% to 22% across doses. Median progression-free survival (PFS) was 2.7, 4.0, and 4.2 months and median OS was 18.5, 25.5, and 24.8 months in 0.3, 2, and 10 mg/kg nivolumab cohorts, respectively. The median duration of response was 22 months. There was no dose-dependent relationship for ORR, OS and PFS rates. Benefit from nivolumab was seen regardless of the number of prior antiangiogenic therapies. The association between OS benefit and PD-L1+ status was seen too. Duration of response exceeded 24 months in 14/35 responders [Motzer *et al.* 2015b]. Response rates are shown in the Table 1.

Recently, McDermott presented at the 2016 American Society of Clinical Oncology (ASCO) congress data of long-term OS with nivolumab from phase I and II studies. In the phase Ib 003 trial, the 3- and 5-year OS rates were 41% and 34% and in the phase II 010 trial the 3-year OS rate was 35%. This is the longest follow up reported to date with any anti-PD-1/PD-L1 agent in mccRCC [McDermott *et al.* 2016].

Currently, there is a lack of predictors of long-term survival with nivolumab in this previously treated population and they are being explored in ongoing trials.

New standard agent for second-line therapy

The Checkmate 025 trial is a phase III randomized open-label study investigating nivolumab 3 mg/kg every 2 weeks *versus* everolimus 10 mg daily in patients with mccRCC who had received one or two prior antiangiogenic therapies. In the trial, 50% of patients had an intermediate prognosis according to Memorial Sloan Kettering Cancer Center risk assessment, and 15% had a poor prognosis. Almost 30% of patients had received two prior antiangiogenic regimens. Median OS was prolonged by 5.4 months, from 19.6 months [95% confidence interval (CI), 17.6–23.1] with everolimus to 25 months (95% CI, 21.8−not estimable) with nivolumab. Interestingly, PFS was no different between the two groups (4.4 and 4.6 months in the nivolumab and everolimus groups, respectively). In a *post-hoc* analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab *versus* 11.7 months for everolimus.

ORR was 25% with nivolumab, with a median time to response of 3.5 months and a median duration of response of 12 months. Most of patients showed a response at first assessment. The primary reason for treatment discontinuation was disease progression, and 44% of patients had a subsequent therapy.

Nivolumab demonstrated an OS benefit across all risk groups, subgroups for number and sites of metastases, including bone and liver metastases. Interestingly, the poor-risk group showed a more significant benefit. OS benefit was conserved across all prior therapy subgroups, and no matter the duration of the first line therapy [Motzer *et al.* 2015a]. Survival benefit was observed in every subgroup, irrespective of PD-L1 expression. Recently at the 2016 ASCO congress, Motzer presented the outcomes by key baseline factors, prior therapy and subsequent therapy for the

Table 1. Response rate and survival of nivolumab trials in renal cell carcinoma.

Study	Phase	Population	Treatment	Primary endpoint	*n*	ORR	PFS	OS
CA209-003	Ib	Pretreated met RCC (⩾1 prior ttt)	Nivolumab (1 or 10 mg/kg) q2w	Safety and tolerability	34	29.4% across all doses	NA	NA
CA209-009	I	Untreated and pretreated met ccRCC (⩾1 prior antiangiogenic ttt, ⩽3 prior systemic ttts)	Nivolumab (0.3–2–10 mg/kg) q3w	Immunomodulatory activity	80	9–23% across all doses	NA	Untreated: NR pretreated: 16.4–NR–25.2 months for 0.3–2–10 mg/kg cohorts
CA209-010	II	Pretreated adv/met RCC (⩾ 1 prior antiangiogenic ttt, ⩽3 prior systemic ttts)	Nivolumab (0.3–2–10 mg/kg) q3w	PFS (dose relationship)	150	20–22% across all doses	2.7–4–4.2 months for 0.3–2–10 mg/kg cohorts	18.5–25.5–24.8 months for 0.3–2–10 mg/kg cohorts
CA209-016	I	Untreated and pretreated adv/met ccRCC	Arm I1, I3, IN3 : Ipilimumab + nivolumab Q3W then Nivolumab Q2W Arm S : Sunitinib + nivolumab q3w Arm P : Pazopanib + nivolumab q3w	Safety and tolerability	175	38.3% arm I1 40.4% arm I3	33 weeks arm I1 47.3 weeks arm I3	NR
CA209-025	III	Adv or met ccRCC	Nivolumab 3 mg/kg q2w	OS	822	25%	4.4 months	25 months

Met, metastatic; RCC, renal cell carcinoma; adv, advanced; ccRCC, clear cell renal cell carcinoma; ttt, treatment; Q2W, every 2 weeks; Q3W, every 3 weeks; I1, ipilimumab 1 mg/kg + nivolumab 3 mg/kg; I3, ipilimumab 3 mg/kg + nivolumab 1 mg/kg; IN3, ipilimumab 3 mg/kg + nivolumab 3 mg/kg; NA, not assessed; NR, not reached; PFS, progression-free survival; OS, overall survival, ORR, objective response rate.

Checkmate 025 study: 77% and 23% of patients received one or two prior antiangiogenic therapies, respectively, mainly sunitinib (63%) or pazopanib (32%). In patients who had prior sunitinib, median OS was 23.6 months for nivolumab *versus* 19.8 months for everolimus; in those who had prior pazopanib, median OS was not estimable for nivolumab *versus* 17.6 months for everolimus. Outcomes by subsequent anticancer therapy are planned [Motzer *et al.* 2016].

Safety and tolerability

In the phase Ib 003 study discussed previously, nivolumab was generally well tolerated, with 83% developing adverse events, but only 11% developing grade 3 or 4 toxicities [Topalian *et al.* 2012]. The phase II confirmed the favorable safety profile of nivolumab single agent with 67% of patients developing adverse events in the 2 mg/kg cohort, and 17% of grade 3 or 4 toxicity [Motzer *et al.* 2015b]. In the phase III with nivolumab at 3 mg/kg every 2 weeks, 79% of any grade adverse events were reported, with 18% grade 3 and only 1% grade 4 toxicities *versus* 33% and 4% in the everolimus cohort. The most common toxicity was fatigue, occurring in 33% of patients, gastrointestinal toxicities, with nausea (14%), diarrhea (12%), decreased appetite (12%), and skin toxicities, with pruritus (14%), and rash (10%). Treatment-related immune-mediated adverse events that may require specific intervention were rash, pruritus, diarrhea, increased transaminases, and hypothyroidism. Other toxicities included cough (9%), anemia (8%) and dyspnea (7%), with no grade 3 or 4 toxicities. No grade 4 pneumonitis was reported. There was no treatment-related death. In the phase III, scores of quality of life were assessed every 4 weeks during the treatment period and there were significantly better quality-of-life scores in the nivolumab group, compared with everolimus up to week 104, with the mean change between groups increasing over time [Motzer *et al.* 2015a].

Programmed-death-ligand 1 expression/biomarkers

In responding patients, although a clinically relevant 12 months median response duration is reported, only 1 of 4 patients will respond to therapy.

In a study that analyzed 306 samples of ccRCC, Thompson and colleagues showed that 24% of

samples expressed PD-L1 (with a threshold at 5% of tumor cells with membranous staining) and its expression was correlated with cancer-specific death [Thompson *et al.* 2006]. Furthermore, since nivolumab inhibits the interaction between PD-1 and its ligand, PD-L1, it was hypothesized that PD-L1 expression by the tumor or immune cells would be required for response to therapy. That is why PD-L1 expression was evaluated as a predictive biomarker for response to PD-1 inhibition therapy since the first steps of development.

In the phase I 009 trial, response rate was reported according to PD-L1 expression on immune cells using a 5% cut-off value and higher response rates were observed in PD-L1 positive (+) patients. However, some PD-L1 negative (–) patients had a response, too, occurring in 8% of them. Moreover, the survival benefit observed in the pivotal trial was irrespective of PD-L1 status: 24% of patients were PD-L1 (+) using a 1% cut-off value, OS was 21.8 months in PD-L1 (+) patients (*versus* 18.8 with everolimus) and 27.4 months in PD-L1 (–) patients (*versus* 21.2 with everolimus). These results suggest that although PD-L1 expression has demonstrated its prognostic importance because of its correlation with poor outcome, high TNM stage, and presence of tumor necrosis [Xu *et al.* 2015], it may not be discriminant enough for predicting response to PD-1-inhibition therapy.

However, many limitations have appeared with the use of PD-L1 expression as a potential biomarker for nivolumab activity, both across different tumor types and more specifically, in patients with RCC. These include the heterogeneity between primary and metastasis, as nephrectomy specimens are often used for staining, and PD-L1 heterogeneity within one tumor, as high-grade areas are more likely to express PD-L1. Furthermore, PD-L1 is a dynamic biomarker, and prior exposure to VEGF inhibitor agents [Powles *et al.* 2016] modulates its expression, therefore archival tissue may not be optimal for PD-L1 assessment. Finally, a growing body of evidence highlights the limitations due to the technical methods such as the choice of the optimal antibody, the selected cut offs to define positivity and the types of cells analyzed to score the staining (immune cells *versus* tumor cells). Taken altogether, many flaws are now well characterized around PD-L1 expression and suggest that more dynamic biomarkers should be scrutinized.

Other biomarkers are under investigation. Expression of PD-L2 is more limited, which could suggest less efficacy in predicting response to nivolumab, but some patients express PD-L2 and not PD-L1 and the expression of both ligands is predictive of poor outcome. Higher expression of PD-L2 was observed in responding patients.

T-cell infiltration is promising too. In the phase I 009 trial, baseline tumor T-cell infiltrates (CD3 and CD8) correlated with a decrease in tumor burden. Unlike majority of solid tumors, CD8 infiltration in ccRCC is associated with poorer survival. Its expression is correlated with LAG3 and PD-1 expression, which could explain this outcome. Interestingly, under nivolumab therapy, CD8 infiltration was correlated with better response.

Comparison of 311 gene expression profiles at baseline between responders and nonresponders identified genes associated with better response, including higher expression of immune system genes and lower expression of genes involved in cell proliferation and signaling.

Future directions

Rationale for combination therapies

Targeting the VEGF/ vascular endothelial growth factor receptor (VEGFR) pathway may attenuate RCC-induced immunosuppression, in studies with sunitinib showing increased percentage of IFN-γ–producing T cells, reduced number or function of T regs [Heine *et al.* 2011]. Moreover, increased PD-L1 expression has been associated with shorter survival in mccRCC patients treated with VEGF-targeted therapies pazopanib and sunitinib [Choueiri *et al.* 2015b]. The phase I study, checkmate 016, investigated nivolumab in association with VEGFR inhibition (sunitinib or pazopanib), as well as the combination of nivolumab with ipilimumab [two regimens were assessed: nivolumab 3 mg/kg + ipilimumab 1 mg/kg (nivo3+ipi1) and nivolumab 1 mg/kg + ipilimumab 3 mg/kg (nivo1+ipi3)], in 175 advanced or mccRCC patients. Objective response rates were 38.3% and 40.4% and median PFS was 33.3 weeks and 47.1 weeks in the (nivo3+ ipi1) and (nivo1+ipi3) cohorts, respectively. Responses were observed in patients with both PD-L1 (+) and PD-L1 (–) tumors. Median OS was not reached in either of the two arms. Toxicity was more important with this

association. The (nivo3+ipi1) regimen seemed better tolerated, with 34% grade 3–4 toxicities *versus* 63.8% in the (nivo1+ipi3) cohort. Systemic steroids were required in 28.6% of patients treated with the (nivo3+ipi1) regimen *versus* 69% of those treated with the (nivo1+ipi3) regimen. Types of toxicities were comparable with nivolumab monotherapy, with fatigue, skin and gastrointestinal toxicities. Colitis (12.8%) was described in the (nivo1+ ipi3) cohort. No high-grade pulmonary adverse events were observed. Initially, treatment in a third cohort of nivolumab 3 mg/kg + ipilimumab 3 mg/kg cohort was stopped, due to toxicity [ClinicalTrials.gov identifier: NCT01472081]. Considering these results, a phase III trial (CA209-214) is assessing PFS and OS in patients treated with nivolumab + ipilimumab for four cycles, followed by nivolumab single agent, compared with sunitinib as first-line therapy.

Other studies are ongoing, evaluating combinations with other anti-PD-1/ PD-L1 agents and VEGF-targeted therapies. The three major phase III trials ongoing in the first-line setting are assessing bevacizumab + atezolizumab (anti PD-L1), axitinib + avelumab (anti PD-L1) and axitinib + pembrolizumab (anti PD-1); all three compared with sunitinib, one of the standards of first-line therapy and the most widely prescribed agent in this setting.

Eventually, the most promising combination may be immunotherapy combinations, between immune checkpoints inhibitors, as described with ipilimumab, with encouraging results but higher toxicities, but also between immune checkpoint inhibitors and other immune pathway inhibition. Multiple phase I studies are ongoing, with nivolumab in association with new agents and are discussed below.

Therapy sequence

With targeted therapies such as anti-VEGF therapies, optimal sequence between drug classes following first-line treatment remains unknown [Al-Marrawi *et al.* 2013]. Two trials evaluated strategies of sequence with sunitinib and sorafenib and with pazopanib and sorafenib, and there were no significant differences in total PFS in both studies [Eichelberg *et al.* 2015; Rexer and AUO, 2014]. Nivolumab has shown its efficacy in prolonging survival for metastatic patients when used beyond first-line therapy. In the pivotal trial, the majority of patients who received anti-PD-1 therapy had one prior anti-VEGF therapy (72%), while 28% of them were in the third-line setting. Optimal timing to expose patients to anti-PD-1 therapy needs to be further discussed, especially when another new drug, cabozantinib, an oral inhibitor of VEGFRs MEK and AXL, has recently also improved survival in metastatic patients beyond first-line therapy [Choueiri *et al.* 2015a]. However, the good tolerability profile of nivolumab associated with an improved quality of life in the pivotal trial, may favor its use in second-line therapy in some patients. Moreover, the impressive duration of median response under nivolumab, could suggest that awaking the immune system early in the course of the disease could bring even more benefit to the patients.

The European Association of Urology guidelines strongly recommend (grade A recommendation) nivolumab after one or two lines of VEGF-targeted therapy for mccRCC [Powles *et al.* 2016]. In the National Comprehensive Cancer Network guidelines, any of axitinib, everolimus, cabozantinib and nivolumab are category 1 recommendations for treatment of patients who had at least one prior VEGF-targeted therapy [Motzer *et al.* 2009]. Despite the early integration of nivolumab in the international guidelines, there is a lack of data and recommendation regarding its optimal sequence and timing.

Challenge for optimal end point for response measurement

In the Checkmate 025 trial, OS was significantly better with nivolumab, when PFS was not different between the two groups, which suggests that PFS is not a good end point or surrogate marker for OS when evaluating anti PD-1 therapy. This also suggests a potential delayed benefit in PFS with nivolumab. This observation is important for designing new trials with nivolumab. Moreover, unusual tumor responses have been described under nivolumab: first increase of tumor burden at firsts assessments before objective response (pseudo progression), stability disease before ultimate shrinkage of the tumor, mixed response with decrease of some lesions but appearance of new lesions [de Velasco *et al.* 2016]. Response Evaluation Criteria In Solid Tumor (RECIST) criteria then appears to be insufficient to reflect this heterogeneity of

responses, and immune-related response criteria may be better for response assessment under nivolumab or other immune checkpoint inhibitors in renal carcinoma, but need to be validated.

Treatment beyond progression

A subgroup analysis of the phase II 010 trial evaluated the benefit from continued nivolumab beyond first RECIST-defined progression. Among 154 patients with progression, 36 were treated beyond first progression for more than 6 weeks, 26 were treated beyond first progression for ⩽6 weeks, and 92 discontinued treatment at first RECIST-defined progression. The RECIST-defined objective response rate was 14% and 16%, and median PFS was 4.2 and 2.6 months in patients treated and not treated beyond progression, respectively. Additionally, 69% of patients treated beyond progression experienced subsequent tumor reduction or stabilization [George *et al.* 2016]. Treatment with nivolumab beyond progression was also investigated among the phase III trial checkmate 025 and recently presented at ASCO 2016 congress. Among the 316 patients who progressed, 153 were treated beyond progression (⩾4 weeks), 18 were treated briefly beyond progression (⩽4 weeks) and 145 were not treated. Progression was defined according to RECIST 1.1. Median duration of treatment was 8.8 months (95% CI, 7.4–10.2) *versus* 2.3 months (95% CI, 1.7–3.3) in patients treated and not treated beyond progression, respectively. The Karnosfsky Performance Status (KPS) was ⩾90% in 73% patients treated beyond progression *versus* 48% of patients not treated. Quality-of life-score was better and there was less deterioration of KPS in patients treated beyond progression. Among the 142 patients treated beyond progression and who had tumor measurements pre- and postprogression, half had a reduction in tumor burden postprogression and 14% had ⩾30% reduction in tumor burden postprogression. Of those who were treated beyond progression, 31 had complete or partial response, 51 had stable disease and 70 had progressive disease [Escudier *et al.* 2016].

Regarding these encouraging results, there is a need to identify patients who will benefit from continuation of nivolumab beyond first RECIST progression, especially in a setting where other active agents may be available.

Nonclear cell renal cancer

Nonclear cell renal cancer (nccRCC) represents 25% of all renal cancers. They remain poorly characterized and new entities are continuing to emerge [Srigley and Delahunt, 2009]. Tyrosine kinase inhibitors targeting the VEGF pathway remain the standard treatment in the advanced setting. No data are available regarding the use of nivolumab in nccRCC. PD-L1 status was assessed in 101 nccRCC patients [Choueiri *et al.* 2014]. PD-L1 positivity was measured by immunochemistry in both tumor cells and tumor-infiltrating mononuclear cells (TIMC) with a 5% cut off. Also, 10.9% of patients were considered PD-L1 (+) in tumor cells and 56.4% in TIMC. PD-L1 positivity was associated with higher stage and grade, and shorter survival, especially when expressed on tumor cells. Only one case of a patient with metastatic collecting-duct carcinoma treated with nivolumab was reported: partial response (46% reduction) was observed after 3 months of therapy, with a good safety profile [Rimar *et al.* 2016].

Ongoing trials

Combination therapies

Considering excellent results with nivolumab in the advanced setting, multiple trials are ongoing and the majority of them are combination trials, as discussed above with nivolumab + ipilimumab association with or without VEGF-targeted therapy.

As discussed above, the phase I study, Checkmate 016, investigated nivolumab in association with VEGF inhibition therapy (sunitinib or pazopanib). The ORR was 52% in the sunitinib arm and 45% in the pazopanib arm. Grade 3−4 treatment-related adverse events were observed in 82% of patients receiving nivolumab and sunitinib and in 70% of patients receiving nivolumab and pazopanib. Overall, 36% of patients in the sunitinib arm and 25% of patients in the pazopanib arm discontinued treatment, given adverse events. Although PD-1 inhibition associated with VEGF inhibition approaches yielded promising response rate, such combination could be challenging due to increased toxicity and require further investigation to assess safety and feasibility [Amin *et al.* 2014].

Currently, there is a trial [ClinicalTrials.gov identifier: NCT02210117] assessing safety and tolerability of nivolumab + bevacizumab or nivolumab

Table 2. Ongoing trials with nivolumab in combination.

Study/ClinicalTrials.gov identifier status	Population	Phase/primary endpoint	Regimens
CA209-214/ NCT02231749: recruiting	Adv/met ccRCC with no prior systemic therapy (adjuvant allowed)	III/PFS, OS	Arm 1: nivo 3 mg/kg + ipi 1 mg/kg IV q3w × 4, then nivo 3 mg/kg IV q2w Arm 2: sunitinib 50 mg PO qd × 4 weeks (6-week cycles)
NCT02210117: recruiting	Untreated and pretreated met ccRCC, eligible for cytoreductive nephrectomy, metastasectomy or post ttt biopsy	II/safety, tolerability	ARM A: nivo 3 mg/kg IV q2w × 3 ARM B: nivo 3 mg/kg IV q2w × 3 + bevacizumab 10 mg/kg IV q2w × 3 ARM C: nivo 3 mg/kg IV q3w × 2 + ipi 1 mg/kg IV q3w × 2
NCT02293980: recruiting	Adv ccRCC	I/MTD	Dose escalation with PT2385 Tablets (HIF-2α Inhibitor) with or without nivo
NCT02335918: recruiting	Adv refractory solid tumors	II/ORR	Dose escalation of varlilumab (anti-CD27) with or without nivo
NCT02614456: recruiting	Adv solid tumors	I/safety and tolerability	Interferon gamma with or without nivo
NCT02718066: not yet recruiting	Melanoma, RCC and non-small cell lung cancer	Ib/II/safety and efficacy	HBI-8000 (histone deacetylase inhibitor) with nivo
NCT02496208: recruiting	Met genito-urinary tumors	I/Dose-limiting toxicity	Cabozantinib and nivo with or without ipilimumab
NCT02423954: recruiting	Adv cancers	Ib/II/safety and tolerability	Temsirolimus + nivo for the ccRCC cohort

Adv, advanced; met, metastatic; ccRCC, clear-cell renal cell carcinoma; nccRCC, nonclear-cell renal cell carcinoma; nivo, nivolumab; ipi, ipilimumab; PD, progression disease; ttt, treatment; MTD, maximum tolerated dose; HIF, hypoxia-inducible factor; ORR, objective response rate; IV, intravenous route: PO, oral route; q2w, every 2 weeks; q3w, every 3 weeks; qd, four times daily.

Table 3. Ongoing trials with nivolumab in monotherapy.

Study/ClinicalTrials.gov identifier status	Population	Phase/primary endpoint	Regimens
CA209-374/ NCT02596035: recruiting	Untreated and pretreated adv/met ccRCC and nccRCC	IIIB–IV/safety	ccRCC cohort: nivo 240 mg IV q2w nccRCC cohort: nivo 240 mg IV q2w Brain metastases cohort: nivo 240 mg IV q2w
NCT02575222: recruiting	Nonmet stage II–IV ccRCC eligible for nephrectomy	I/safety and tolerability	Three doses of nivo 3 mg/kg q2w prior to nephrectomy
ADAPTeR/ NCT02446860: recruiting	Met RCC eligible for nephrectomy	II/safety: biomarker analysis	Biopsy of primary tumor, followed by 8 weeks of nivo, followed by nephrectomy, then postoperatively until patient is no longer deriving clinical benefit
NCT02595918: not yet recruiting	High-risk nonmet kidney cancer	I/safety-biomarker analysis	Three doses of nivo and complete surgery

Adv, advanced; met, metastatic; RCC, renal cell carcinoma; ccRCC, clear-cell renal cell carcinoma; nccRCC, nonclear-cell renal cell carcinoma; nivo, nivolumab; q2w, every 2 weeks.

+ ipilimumab compared with nivolumab alone in patients with mRCC and who are eligible for nephrectomy, metastasectomy or post-treatment biopsies. Multiple phase I studies, not exclusively for RCC, are evaluating nivolumab associated with new agents such as varlilumab (anti-CD27), FPA008 (anticolony-stimulating factor-1 receptor, CSF1R), interferon gamma, AMM0010 (PEGylated recombinant human IL-10), HBI-8000 (histone deacetylase inhibitor) or CB-839 (glutaminase inhibior). Nivolumab is also evaluated in association with chemotherapy, or with cabozantinib with or without ipilimumab in a phase I trial. Interestingly, a phase II is evaluating the response rate when associated with stereotactic ablative radiation therapy in mRCC.

Monotherapy

The majority of trials with nivolumab in monotherapy are assessing its safety and feasibility in the neoadjuvant setting, for patients with high-risk RCC. These trials are of major interest because they will allow analysis of nephrectomy specimens, a better understanding of the effect of immunotherapy on the tumor, and potential identification of predictive biomarkers.

Eventually, a phase IIIb/IV trial is evaluating the safety of nivolumab in mRCC and is particularly interesting because of its expansion to non-ccRCC and patients with brain metastases, who were not included in the pivot trial.

Ongoing trials are listed in the Tables 2 and 3.

Conclusion

Nivolumab has shown a 25 months' median OS in mccRCC patients beyond first-line therapy compared with everolimus, with a benefit of 5.4 months for patients receiving nivolumab. It is now one of the treatment options for second or beyond-line therapies in mccRCC and its safety and tolerability profile is of great interest. Many questions have been raised, and further trials are needed to better understand the challenges of nivolumab in RCC. The identification of predictive markers is mandatory.

Future changes in our therapeutic strategy in mRCC will come from current ongoing trials evaluating combination therapy and nivolumab in earlier stages of the disease.

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