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Ipilimumab in combination with nivolumab for the treatment of renal cell carcinoma

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Abstract

Introduction: Renal cell carcinoma (RCC) is a highly immunogenic neoplasm, and cytokine-based immunotherapies have been used for decades with limited success. In recent years, antibody-based immunotherapies targeting immune checkpoint receptors PD-1 and CTLA-4 have demonstrated clinical efficacy in metastatic RCC (mRCC) patients, leading to regulatory approval of the combination of nivolumab and ipilimumab in treatment-naïve patients with intermediate- or poor-risk disease in April 2018.

Areas covered: The pharmacodynamics and pharmacokinetics of nivolumab and ipilimumab are reviewed. Clinical safety and efficacy results from pivotal phase I and III trials of the combination of nivolumab plus ipilimumab in mRCC are summarized, and the combination is reviewed in the context of other available systemic therapies for RCC. Ongoing clinical studies involving the combination of nivolumab plus ipilimumab in RCC are discussed.

Expert opinion: The combination of nivolumab and ipilimumab has demonstrated superior efficacy for treatment-naïve patients with intermediate- and poor-risk mRCC with clear cell histology and is likely to replace anti-angiogenic therapies as the treatment-of-choice in this patient population in the United States. Development of additional combination strategies, novel trial designs, and predictive biomarkers of response will be important to further optimize therapeutic selection and clinical outcomes.

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Declaration of Interests

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Keywords

CTLA-4; immune checkpoint therapy; ipilimumab; kidney cancer; nivolumab; PD-1; renal cell carcinoma

1. Introduction

Renal cell carcinoma (RCC) is a cancer of the kidney epithelium and has steadily increased in incidence globally in recent years.[1,2] Research has predominantly focused on clear cell histology RCC, which constitutes approximately 70% of all RCC cases.[3] Prognosis for metastatic RCC (mRCC) is especially poor, with a five-year survival rate of 12% in the United States.[4] Historically, few systemic treatment options existed for RCC, a tumor type characterized by a high degree of resistance to conventional chemotherapies.[5] Nevertheless, RCC has long been recognized as a strongly immunogenic neoplasm based on case reports of spontaneous tumor regression following nephrectomy.[6,7] Cytokine-based immunotherapies such as interleukin-2 and interferon alpha were the most commonly used systemic therapies for mRCC for several decades until the introduction of molecularly targeted agents in the mid-2000s.[8-11]

Efforts to develop novel effective therapies for patients with mRCC have led to multiple successful new drug approvals by the United States Food and Drug Administration (FDA). As of April 2018, thirteen systemic therapies targeting at least four distinct molecular pathways are available for patients with mRCC.[12,13] Drugs targeting cytokine signaling (interleukin-2), vascular endothelial growth factor (VEGF) (bevacizumab), VEGF receptor (VEGFR) and other receptor tyrosine kinases (sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and sorafenib), the mechanistic target of rapamycin (mTOR) pathway (everolimus and temsirolimus), and the immune checkpoint programmed cell death protein 1 (PD-1) (nivolumab) have all demonstrated clinical efficacy in patients with mRCC and gained regulatory approval. Immune checkpoint inhibitors are the newest class of medications to show efficacy in mRCC, first with single-agent PD-1 blockade with nivolumab in patients who had received previous treatment[14] and most recently with the combination of nivolumab plus the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody ipilimumab in treatment-naïve patients in the randomized phase III trial CheckMate 214.[15]

This article reviews the pharmacology of nivolumab and ipilimumab and summarizes the clinical efficacy and safety of the combination of nivolumab plus ipilimumab in the treatment of mRCC. We also discuss the role of nivolumab plus ipilimumab in the management of RCC in the context of a rapidly evolving treatment landscape and provide our opinions regarding ongoing and potential future studies involving the combination.

2. Overview of the market

Therapeutic options for advanced or mRCC have expanded significantly since the approval of the first VEGFR-targeted therapy sorafenib in 2005 and continue to grow. First-line treatment options for metastatic or surgically unresectable locally advanced disease include

VEGFR-targeted tyrosine kinase inhibitors sunitinib or pazopanib [16-19], cabozantinib targeting VEGFR as well as the receptor tyrosine kinases MET and AXL[20], cytokine-based immunotherapy in the form of high-dose interleukin-2[9,10], combination bevacizumab plus interferon alpha[21,22], the mTOR inhibitor temsirolimus[23], and most recently the combination of nivolumab and ipilimumab.[15] In addition, patients with disease refractory to first-line agents may receive single-agent nivolumab[24], axitinib[25], lenvatinib plus everolimus (phase II evidence)[26], everolimus monotherapy[27], or most of the aforementioned first-line treatment options.

Clinical risk-stratification criteria, including International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score and Memorial Sloan-Kettering Cancer Center (MSKCC) score, are useful tools for therapeutic selection in the first-line setting.[28,29] For example, temsirolimus has been a recommended first-line therapy for patients with poor-prognosis disease based on the randomized phase III ARCC study in previously untreated mRCC patients with clinical predictors of short survival with criteria similar to the MSKCC score.[23] More recently, CheckMate 214 demonstrated the clinical superiority of nivolumab plus ipilimumab over sunitinib in patients with IMDC intermediate- or poor-risk disease, leading to FDA approval of the combination in this subset of patients.[15] Similarly, first-line cabozantinib showed clinical benefit over sunitinib exclusively in patients with IMDC intermediate- or poor-risk mRCC in the phase II CABOSUN trial,[20] leading to frontline approval by the European Medicines Agency (EMA) for intermediate- and poor-risk patients and approval by the FDA for all mRCC patients regardless of IMDC risk status.[30,31]

The treatment landscape for mRCC is presently in flux due to multiple new drug approvals in the treatment-naïve setting. VEGFR-targeted therapies such as sunitinib and pazopanib have been the most commonly used first-line therapies in the United States over the past decade.[32] Sunitinib was shown in phase III study to confer improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) as compared to interferon alfa in treatment-naïve patients with clear cell mRCC.[16] Later, the randomized phase III COMPARZ trial demonstrated pazopanib to be non-inferior to sunitinib in OS and PFS,[18,19] and both COMPARZ and a separate randomized phase IIb study (PISCES trial) suggested pazopanib to be better tolerated than sunitinib.[33] Cabozantinib quickly advanced to the first-line treatment setting in December 2017 based on the randomized phase II CABOSUN study that showed PFS and ORR benefits over sunitinib in patients with IMDC intermediate- or poor-risk mRCC,[20] albeit some investigators have expressed concerns regarding the limitations of the trial.[34] Finally, the combination of nivolumab plus ipilimumab was approved in April 2018 based on results from CheckMate 214, which is summarized later in this review. Notably, while frontline cabozantinib is approved by the FDA for any patient with advanced RCC regardless of disease risk status and by the EMA for IMDC intermediate- and poor-risk patients, the nivolumab plus ipilimumab combination is FDA-approved for frontline treatment of IMDC intermediate- and poor-risk patients and received a negative opinion from the EMA's Committee on Human Medicinal Products (CHMP) in July 2018. In addition, the combination of the anti-PD-L1 antibody atezolizumab plus bevacizumab has also demonstrated clinical benefit compared to sunitinib in previously untreated advanced or mRCC patients with positive PD-L1 expression in the phase III IMmotion151 study, and application for regulatory approval is expected within the

upcoming year.[35] With multiple new drug approvals based on studies involving distinct subsets of patients, it remains to be seen how the market for mRCC therapies will realign in the upcoming years, particularly with additional ongoing clinical studies evaluating new combination therapies (e.g., VEGF-targeted therapy plus immune checkpoint blockade) and novel molecular targets (e.g., hypoxia-inducible factor [HIF], glutaminase).

The randomized phase III studies in RCC have largely focused on patients with clear cell histology disease and excluded non-clear cell RCC. Because non-clear cell RCC typically carries a poorer prognosis compared to clear cell RCC, clinical trial enrollment is recommended.[36] For non-clear cell mRCC patients who are not enrolled in a clinical study, the treatment approach is generally similar to those with clear cell histology.[12]

3. Introduction to the compounds

Nivolumab and ipilimumab are monoclonal antibodies that bind to the immune checkpoint proteins PD-1 and CTLA-4, respectively. Preclinical studies have revealed the distinct roles of PD-1 and CTLA-4 during differing stages of the immune response as negative regulators of T cell activation.[37-39] While CTLA-4 acts as an immune checkpoint during the early stages of T cell activation predominantly in subsets of Th1-like CD4+ effector T cells, PD-1 attenuates T-cell receptor signaling during later stages and primarily suppresses subsets of CD8+ T cells.[40] Monoclonal antibodies targeting PD-1/PD-L1 and CTLA-4 have rapidly advanced through clinical studies and have been successfully applied as either monotherapy or combination therapy for multiple cancer types, including RCC, melanoma, lung cancer, urothelial carcinoma, head and neck cancer, Hodgkin lymphoma, Merkel cell carcinoma, hepatocellular carcinoma, and microsatellite instability-high solid tumors.[41] Nivolumab and ipilimumab form the only FDA-approved combination therapy targeting PD-1/PD-L1 and CTLA-4. For mRCC, the dosing schedule of nivolumab plus ipilimumab in the randomized phase III CheckMate 214 trial was nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV every 2 weeks.[15]

3.1. Chemistry

Nivolumab is a human monoclonal IgG4 antibody against PD-1 and consists of four polypeptide chains - two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids.[42] The polypeptide chains are linked by interchain disulfide bonds to form the nivolumab immunoglobulin, which has a molecular mass of approximately 146 kDa.[43] Nivolumab is produced in large-scale Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.[42] CHO cells are transfected with an expression vector containing the coding sequences for the heavy and kappa light chains of nivolumab, with the variable region genes isolated from mouse hybridoma cells created via fusion of mouse myeloma cells with spleen cells from a PD-1 receptor immunized Human Ig transgenic mouse. Transfected CHO cells are expanded and transferred to a bioreactor for further large-scale cell culture. Nivolumab is purified using standard chromatography, viral inactivation, and filtration and ultrafiltration/diafiltration methods.

Ipilimumab is a human monoclonal IgG1 antibody against CTLA-4 with a molecular mass of approximately 148 kDa and is composed of four polypeptide chains - two identical heavy

chains of 447 amino acids and two identical kappa light chains of 215 amino acids.[44,45] Interchain disulfide chains link the heavy and light chains. Ipilimumab is produced in a similar fashion as nivolumab via recombinant DNA technology. CHO cells are transfected with an expression vector containing the coding sequences of the heavy and light chains of ipilimumab, subsequently expanded and cultured in large-scale format, and ultimately subjected to standard chromatography, viral inactivation, and filtration steps.

3.2. Pharmacodynamics

Nivolumab binds to PD-1 with high affinity ($K_d = 3.06$ nM)[42] at an N-terminal loop outside the immunoglobulin variable domain of PD-1.[46] PD-1 was first identified in 1992 as an inducer of cell death of an activated T-cell hybridoma and later shown to be an inhibitory regulator of T cell activity through binding of ligands PD-L1 and, to a lesser extent, PD-L2.[47-49] PD-L1 is broadly expressed on numerous immune cells (T cells, B cells, dendritic cells, NK cells, macrophages, and monocytes), some normal tissues, and certain cancer cells, while PD-L2 expression is more restricted to dendritic cells, macrophages, bone marrow-derived mast cells, and some peritoneal B cells.[50] The PD-1/PD-L1 interaction delivers an inhibitory signal that counters the positive signaling initiated by binding of the T-cell receptor and the co-stimulatory receptor CD28, resulting in decreased activation of multiple transcription factors involved in T cell activation.[51] Therefore, inhibition of the PD-1/PD-L1 interaction is the major driver of therapeutic efficacy by monoclonal antibodies like nivolumab and results in enhanced anti-tumor response by cytotoxic T cells within the tumor microenvironment.[38]

Ipilimumab binds to CTLA-4 with high affinity ($K_d = 5.25 \pm 3.62$ nM) and blocks the interactions of CTLA-4 with its ligands CD80 and CD86.[44] CTLA-4 was first described in 1987 as a member of the immunoglobulin superfamily and is constitutively expressed on regulatory T cells and on activated effector T cells.[52,53] CTLA-4 is highly homologous to the T cell co-stimulatory protein CD28 and competes with it for B7 ligands (CD80 and CD86) on antigen presenting cells.[54,55] The CTLA-4 interaction with B7 ligands counters the co-stimulatory function of the CD28:B7 binding and transmits inhibitory signals during the early stages of T cell activation and proliferation.[55] By inhibiting the interaction between CTLA-4 and B7 ligands, ipilimumab is thought to elicit a more non-specific immune activation than PD-1 blockade (Figure 1).

3.3 Pharmacokinetics and metabolism

Population pharmacokinetics (PK) analysis of nivolumab was performed using data from 909 patients who received single or multiple doses of nivolumab ranging from 0.1 to 20 mg/kg administered every 2 or 3 weeks.[43] Nivolumab has a mean clearance rate of 9.5 mL/h, mean volume of distribution of 8.0 L, mean elimination half-life of 26.7 days, and attains steady state by 12 weeks when administered every 2 weeks. Population PK analysis of ipilimumab was performed using data from 785 melanoma patients who received doses of 0.3, 3, or 10 mg/kg administered every 3 weeks for 4 doses.[45] Ipilimumab has a mean clearance rate of 16.8 mL/h, mean volume of distribution of 7.21 L, mean elimination half-life of 15.4 days, and attains steady state by the third dose when administered every 3 weeks.. Elimination of nivolumab, ipilimumab, and other monoclonal antibodies occur

primarily through intracellular uptake by pinocytosis or endocytosis followed by lysosomal degradation.[56]

4. Clinical efficacy

4.1. Phase I

CheckMate 016 was a multi-center, open-label, dose-escalation phase I study evaluating combinations involving nivolumab in patients with advanced or mRCC with clear cell component on histology.[57] The study included 5 treatment cohorts treated with three distinct dosing combinations of nivolumab plus ipilimumab as well as two cohorts who received the combination of nivolumab plus sunitinib or pazopanib. Patients in the combination nivolumab plus ipilimumab arms were randomized to one of three dosing regimens: 1) nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), 2) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or 3) nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3) given intravenously every 3 weeks for up to four doses during the induction phase, followed by nivolumab 3 mg/kg monotherapy every 2 weeks until disease progression or unacceptable toxicity during the maintenance phase. During the induction phase, nivolumab was given first, followed by ipilimumab 30 minutes later. Patients were allowed to proceed to maintenance nivolumab without completing all four doses of the nivolumab plus ipilimumab combination if ipilimumab-associated toxicity is encountered.

CheckMate 016 initially enrolled a small number of patients to evaluate the safety of combination therapy, and an expansion cohort was later added. Notable exclusion criteria included active central nervous system metastasis and current or recent history of autoimmune disorder requiring systemic corticosteroids equivalent to or greater than prednisone 10 mg/kg. Furthermore, while patients in the initial N3I1 and N1I3 cohorts may have been treatment-naïve or received prior systemic therapy, expansion cohort patients randomized to the N3I1 and N1I3 arms and all patients in the N3I3 arm were required to be naïve to systemic therapy for mRCC, with exceptions of cytokine therapy for mRCC or adjuvant or neoadjuvant therapy for localized or locally advanced RCC. The primary objective was to assess safety and tolerability of the combination (see Section 5. Safety and Tolerability), and secondary endpoints included ORR, best overall response, duration of response, time to response, PFS, and 24-week PFS.

A total of 100 patients were enrolled in the nivolumab plus ipilimumab combination arms: 47 patients assigned to N3I1, 47 patients to N1I3, and 6 patients to N3I3. Among patients in the N3I1 and N1I3 arms, the vast majority had MSKCC favorable- (45%) or intermediate-risk (49%) disease, and approximately half had received prior systemic therapy. Efficacy data for the N3I3 arm was not available as all 6 patients were censored at the time of analysis. At median follow-up of 22.3 months, major efficacy endpoints were similar between the N3I1 and N1I3 arms, including confirmed ORRs of 40.4% in both arms and median PFS of 7.7 months in the N3I1 arm vs 9.4 months in the N1I3 arm. Best overall response included complete response (CR) in 10.6% and partial response (PR) in 29.8% of patients in the N3I1 arm, while all responders in the N1I3 arm experienced PR. An exploratory endpoint of 2-year OS was 67% in the N3I1 arm and 70% in the N1I3 arm. Due to the promising anti-tumor activity and comparatively superior safety results observed in

the N3I1 arm (see Section 5. Safety and Tolerability), the dosing regimen of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg was selected to move forward in phase III evaluation.

4.2. Phase II

Efficacy data from phase II evaluation of nivolumab plus ipilimumab in RCC has not been reported. In light of the encouraging results with the combination of nivolumab plus ipilimumab from the phase I CheckMate 016 study[57] as well as with nivolumab monotherapy (phase II and III)[14,24] and ipilimumab monotherapy (phase II)[58] in mRCC, the regimen of nivolumab plus ipilimumab was evaluated directly in randomized phase III testing for patients with advanced or mRCC with clear cell histology in CheckMate 214. Several ongoing phase II studies of nivolumab plus ipilimumab in RCC are evaluating alternative dosing regimens, including response-modulated addition of ipilimumab based on initial response to nivolumab monotherapy, or non-clear cell histology (NCT03203473; NCT03029780; NCT03297593; NCT03117309; NCT03075423).

4.3. Phase III

The international randomized, open-label phase III CheckMate 214 trial compared nivolumab plus ipilimumab vs sunitinib in patients with previously untreated advanced or mRCC with a clear cell component histology.[15] A total of 1096 patients were randomized in a 1:1 ratio to receive nivolumab 3 mg/kg plus ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks or sunitinib 50 mg by mouth daily for 4 weeks of each 6-week cycle. Key exclusion criteria included central nervous system metastasis and auto-immune disease with glucocorticoid or immunosuppressant use. Patients were stratified according to IMDC risk (favorable vs intermediate vs poor) and geographic region (United States vs Canada and Europe vs rest of the world). The co-primary endpoints were ORR, PFS, and OS among intermediate- and poor-risk patients, which accounted for 61% and 16% of the enrolled patients, respectively. A summary of key efficacy and safety results from CheckMate 214 and the phase II CABOSUN study is shown in Table 1.

Efficacy results were presented at a median follow-up of 25.2 months in the intermediate- and poor-risk patients and demonstrated improved OS and ORR for nivolumab plus ipilimumab over sunitinib, and a trend toward improved PFS for nivolumab plus ipilimumab that did not meet statistical significance threshold. The 18-month OS rate was 75% with nivolumab plus ipilimumab compared to 60% with sunitinib (HR for death 0.63; 99.8% CI 0.44-0.89; $p < 0.001$). Median OS was not reached with nivolumab plus ipilimumab vs 26.0 months with sunitinib. In intermediate- and poor-risk patients, OS was improved with nivolumab plus ipilimumab over sunitinib across all subgroups examined, including age, gender, region, IMDC risk, prior nephrectomy status, baseline PD-L1 expression, and presence or absence of bone, liver, lung, or lymph node metastases. Intermediate- and poor-risk patients who received nivolumab plus ipilimumab had improved ORR of 42% compared to 27% for those who received sunitinib ($p < 0.001$). Complete response rates were 9% for nivolumab plus ipilimumab vs 1% for sunitinib. Median PFS in intermediate- and poor-risk patients was prolonged for the nivolumab plus ipilimumab arm compared to the sunitinib arm (11.6 vs 8.4 months; HR 0.82; $p = 0.03$), but did not reach the pre-specified significance

threshold of $p = 0.009$. Median time to response to nivolumab plus ipilimumab was 2.8 months and similar to the 3.0 months seen in the sunitinib-treated patients. Median duration of response was not reached for responders to nivolumab plus ipilimumab compared to 18.2 months for responders to sunitinib. At the time of analysis, 72% of the 177 responding intermediate- and poor-risk patients had ongoing response.

Secondary endpoints of CheckMate 214 included ORR, PFS, and OS in the intention-to-treat population. Nivolumab plus ipilimumab was superior to sunitinib with regards to OS (HR for death 0.68; 99.8% CI 0.49-0.95; $p < 0.001$), but not ORR or PFS in the intention-to-treat population. The 18-month OS rate was 78% (95% CI 74-81%) for nivolumab plus ipilimumab vs 68% (95% CI 63-72%) for sunitinib. Median OS was not reached for nivolumab plus ipilimumab vs 32.9 months for sunitinib. ORR in the intention-to-treat population was 39% for nivolumab plus ipilimumab vs 32% for sunitinib ($p = 0.02$), but did not reach the pre-specified significance threshold of $p = 0.001$. Median PFS in the intention-to-treat population was similar between the two treatment arms at 12.4 months with nivolumab plus ipilimumab and 12.3 months with sunitinib.

Exploratory endpoints included ORR, PFS, and OS in favorable-risk patients, which accounted for 23% of enrolled patients, as well as outcomes according to tumor PD-L1 expression and health-related quality of life assessments in intermediate- and poor-risk patients. In favorable-risk patients, ORR and PFS were both improved in the sunitinib arm compared to nivolumab plus ipilimumab. ORR was 52% vs 29% ($p < 0.001$) and median PFS was 25.1 vs 15.3 months ($p < 0.001$), both favoring the sunitinib arm. Complete responses were seen in 11% of favorable-risk patients treated with nivolumab plus ipilimumab compared to 6% with sunitinib. The 18-month OS rate in favorable-risk patients was high in both treatment arms - 88% with nivolumab plus ipilimumab vs 93% with sunitinib ($p = 0.27$). Notably, baseline tumor PD-L1 expression was lower in the favorable-risk patients (11.5% with PD-L1 $\geq 1\%$) compared to intermediate- and poor-risk patients (27.6% with PD-L1 $\geq 1\%$).

Tumor PD-L1 expression ($\geq 1\%$ vs $< 1\%$) was determined at a central laboratory using the Dako PD-L1 IHC 28-8 pharmDx test. In intermediate- and poor-risk patients, PFS was improved with nivolumab plus ipilimumab over sunitinib in patients with PD-L1 $\geq 1\%$, but not in those with PD-L1 $< 1\%$. In patients with PD-L1 $\geq 1\%$, median PFS was 22.8 months with nivolumab plus ipilimumab compared to 5.9 months with sunitinib (HR 0.46; 95% CI 0.31-0.67). In contrast, in patients with PD-L1 $< 1\%$, median PFS was similar between the nivolumab plus ipilimumab vs sunitinib arms at 11.0 and 10.4 months, respectively. In intermediate- and poor-risk patients, OS and ORR were improved for nivolumab plus ipilimumab regardless of tumor PD-L1 expression level, but the extent of OS and ORR improvements were greater for those with PD-L1 $\geq 1\%$ compared to those with PD-L1 $< 1\%$. In patients with PD-L1 $\geq 1\%$, the 12-month OS for nivolumab plus ipilimumab vs sunitinib was 86% vs 66%, respectively, while the 18-month OS rates were 81% vs 53%, respectively. Median OS for intermediate- and poor-risk patients with PD-L1 $\geq 1\%$ was not reached with nivolumab plus ipilimumab vs 19.6 months with sunitinib (HR 0.45; 95% CI 0.29-0.71). For patients with PD-L1 $< 1\%$, the 12-month OS for nivolumab plus ipilimumab vs sunitinib was 80% vs 75%, respectively, while the 18-month OS rates were 74% vs 64%,

respectively. In patients with PD-L1 $\geq 1\%$, ORR was 58% for nivolumab plus ipilimumab vs 22% for sunitinib ($p < 0.001$), while ORRs for those with PD-L1 $< 1\%$ were 37% vs 28% ($p = 0.03$), respectively.

Health-related quality-of-life assessments were also conducted via the National Comprehensive Cancer Network Functional Assessment of Cancer-Therapy - Kidney Symptom Index. While the mean baseline quality-of-life scores were similar between intermediate- and poor-risk patients treated with nivolumab plus ipilimumab vs sunitinib, the mean change from baseline was greater and in the direction of fewer symptoms for those in the nivolumab plus ipilimumab arm compared to the sunitinib arm at all assessments during the first 6-month period of the study.

4.4. Post-marketing surveillance

There is no post-marketing information available on the combination of nivolumab plus ipilimumab. All data on the combination exists within the context of clinical trials. Post-marketing surveillance will be important in providing additional data on immune-related toxicities and management strategies. Efficacy and safety results of potential off-label use of the combination in the second-line setting for mRCC patients would also be of interest.

5. Safety and tolerability

Treatment-related toxicities, particularly immune-related adverse events (AEs), are a major concern for the combination of nivolumab plus ipilimumab in RCC and other cancer types. In the phase I CheckMate 016 study comparing three different dosing regimens of nivolumab plus ipilimumab, grade 3 or 4 treatment-related AEs occurred in 38% of patients in the N3I3 arm, 62% in N1I3, and 83% in N3I1.[57] Common grade 3-4 treatment-related AEs occurring in $>10\%$ of patients in any arm included elevated lipase, elevated AST/ALT, colitis, and diarrhea. Notably, grade 3 or 4 colitis occurred in 15% of patients in the N1I3 arm compared to none of the patients in the N3I1 arm. Treatment-related AEs of any grade that resulted in treatment discontinuation occurred in 10.6% and 27.7% of patients in the N3I1 and N1I3 arms, respectively. No grade 5 treatment-related AEs occurred. Immune-modulating medications were used to treat AEs in 62% of patients in the N3I1 arm and 83% of patients in the N1I3 arm. In the N3I1 arm, systemic corticosteroids were used in 53% of patients, topical corticosteroids in 19%, and infliximab in 2.1%. In the N1I3 arm, systemic corticosteroids were used in 77% of patients, topical corticosteroids in 28%, and infliximab or mycophenolic acid in 26%. These safety results supported the N3I1 dose for the phase III study in mRCC. Interestingly, the N1I3 dose was the regimen approved for advanced melanoma and was associated with grade 3 or 4 treatment-related AEs in 69% of patients in the melanoma phase III study.[59]

In the phase III CheckMate 214 trial, grade 3 or 4 treatment-related AEs occurred in 46% of patients treated with nivolumab plus ipilimumab vs 63% of those treated with sunitinib.[15] The most common grade 3 or 4 treatment-related AEs included increased lipase (10%), fatigue (4%), and diarrhea (4%). Treatment-related deaths occurred in 8 patients in the nivolumab plus ipilimumab group and included pneumonitis, immune-mediated bronchitis, pneumonia and aplastic anemia, lung infection, hemophagocytic syndrome, liver toxic

effects, lower gastrointestinal hemorrhage, and sudden death. Treatment-related AEs resulting in discontinuation of therapy occurred in 22% of patients treated with nivolumab plus ipilimumab, and 79% of patients received all four doses of ipilimumab with nivolumab during the induction phase. Among patients in the nivolumab plus ipilimumab group who had treatment-related, immune-mediated AEs, 35% received high-dose systemic glucocorticoids equivalent to prednisone 40 mg daily or greater.

6. Regulatory affairs

Nivolumab monotherapy gained approval from the United States FDA in November 2015 for treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. The EMA approved nivolumab monotherapy for treatment of patients with adult RCC who have received prior therapy in February 2016. Ipilimumab monotherapy for the treatment of RCC is not approved by any major regulatory agency. The combination of nivolumab plus ipilimumab was approved by the FDA in April 2018 as first-line treatment of patients with advanced or mRCC with IMDC intermediate- and poor-risk disease.

7. Conclusion

CheckMate 214 has established the combination of nivolumab plus ipilimumab to be superior to sunitinib in patients with treatment-naïve advanced or mRCC on multiple measures of clinical efficacy, including OS and ORR in patients with IMDC intermediate- or poor-risk disease. Health-related quality-of-life indices were also consistently superior in patients treated with the combination of nivolumab plus ipilimumab compared to those receiving sunitinib. Yet, most of patients did not achieve a major response to treatment, and exploratory analyses of favorable-risk patients suggest an improved ORR and prolonged PFS with sunitinib compared to nivolumab plus ipilimumab. While grade 3 or 4 treatment-related AEs were less frequent in the nivolumab plus ipilimumab group compared to the sunitinib group, high-dose glucocorticoids were administered to more than one-third of patients treated with nivolumab plus ipilimumab who had treatment-related, immune-mediated AEs. Nevertheless, the approval of nivolumab plus ipilimumab as frontline treatment for mRCC patients with IMDC intermediate- or poor-risk disease represents a major advance in the field.

8. Expert opinion

The combination of nivolumab plus ipilimumab has demonstrated efficacy in treatment-naïve mRCC patients with IMDC intermediate- or poor-risk disease and will become the new treatment standard in this group of patients in the United States. Given the negative review of the combination by the EMA CHMP at the time of this review article, it remains unclear whether nivolumab plus ipilimumab may be adopted into the standard treatment algorithm in Europe. In the United States, the primary alternative will be VEGFR-targeted therapies such as cabozantinib, which has also shown efficacy as frontline therapy for IMDC intermediate- and poor-risk mRCC patients in the smaller phase II CABOSUN study. Although a direct comparison of the two treatment regimens is not available, a recent network meta-analysis of first-line systemic therapy for mRCC suggested that while

cabozantinib is more likely to confer a PFS advantage, the combination of nivolumab plus ipilimumab is more likely to confer an OS advantage (a more important endpoint) and be better tolerated with respect to AEs.[60]

Multiple factors may be considered in comparing nivolumab plus ipilimumab to cabozantinib and other VEGFR-targeted therapies, including the rate of complete response, baseline tumor characteristics, treatment-related AEs, patient comorbidities, and physician comfort. First, one of the exciting promises of immunotherapies is the potential for complete or long-lasting response in a subset of patients, which has not been shown with VEGFR-targeted therapies in mRCC. Indeed, the complete response rate with nivolumab plus ipilimumab in this patient population was 9% in CheckMate 214 compared to 1% with cabozantinib in CABOSUN. Long-term follow-up of patients treated with nivolumab plus ipilimumab will provide additional data regarding the durability of response and the potential for durable remission of metastatic disease. Second, IMDC risk criteria may be important in considering nivolumab plus ipilimumab or VEGFR-targeted therapies. Exploratory analyses in CheckMate 214 found sunitinib conferred superior ORR and PFS compared to nivolumab plus ipilimumab in IMDC favorable-risk patients.[15] Nevertheless, nivolumab plus ipilimumab resulted in a far superior complete response rate of 11% in favorable-risk patients. With the relatively low number of deaths at the time of data analysis, longer term follow-up is needed in order to determine the value of the immune checkpoint combination in favorable-risk patients. Third, while grade 3 or 4 treatment-related AEs were less frequent with nivolumab plus ipilimumab than with sunitinib, a significant portion (28%) of all patients receiving the immune checkpoint combination required high-dose glucocorticoids for treatment-related AEs.[15] Patient comorbidities (e.g., hypertension, gastrointestinal disorders, autoimmune disease) may also factor into treatment decision as hypertension, palmar-plantar erythrodysesthesia, diarrhea, nausea, and anorexia are commonly associated with VEGFR-targeted therapies, while immune-related toxicities are of key concern with nivolumab plus ipilimumab. Finally, while physician comfort with administering the immune checkpoint combination and managing the potential immune-related toxicities has improved, many oncologists may feel more equipped to offer cabozantinib and other oral VEGFR-targeted therapies that have been commonly used to treat mRCC patients for more than a decade. We propose a systemic treatment algorithm based on the above considerations (Figure 2).

Results from several forthcoming large randomized phase III studies evaluating combinations of VEGFR-targeted therapy plus immune checkpoint blockade will also impact the use of the combination of nivolumab plus ipilimumab in mRCC. Early phase studies have shown manageable toxicity profiles and encouraging anti-tumor activity with ORRs ranging from 54% to 73% with the combinations of axitinib plus the PD-1 inhibitor pembrolizumab[61], axitinib plus the PD-L1 inhibitor avelumab[62], lenvatinib plus pembrolizumab [63], and cabozantinib plus nivolumab with or without ipilimumab in mRCC[64]. All of these combinations of VEGFR-targeted therapy plus immune checkpoint inhibition are currently in phase III evaluation as frontline treatment (NCT02853331, NCT02684006, NCT02811861, and NCT03141177). The toxicity profile of any combination therapy, particularly potential three-drug combinations involving nivolumab plus ipilimumab, will need to be offset by clinically significant improvements in efficacy

outcomes. Moreover, it will be important to determine whether frontline combination therapies involving agents already approved as separate therapies are truly synergistic or merely additive in their clinical efficacy.

RCC joins melanoma as the second tumor type for which the combination of nivolumab plus ipilimumab is approved. In advanced melanoma, it appears that nivolumab may be the major driver of clinical benefit from the combination.[65] Further studies will be necessary to delineate the additional benefit of ipilimumab to nivolumab in mRCC, particularly given the recent negative review of the combination in mRCC by the EMA CHMP. In the second-line setting, CheckMate 025 showed an ORR of 25% with nivolumab monotherapy in mRCC patients who were previously treated with anti-angiogenic therapy, with grade 3 or 4 treatment-related AEs occurring in only 19% of patients.[24] Preliminary results from the single-arm phase II study of pembrolizumab as monotherapy for treatment-naïve advanced or mRCC (KEYNOTE-427; NCT02853344) showed an encouraging ORR of 34% (37% for IMDC intermediate- and poor-risk patients) and grade 3 or higher AE rate of 18%, although only one patient experienced a complete response at the time of data cutoff (median follow-up 7.2 months).[66] Additional studies using novel adaptive trial designs are investigating a response-modulated approach toward combination immunotherapy. HCRN: GU 16-260 (NCT03117309) and OMNIVORE (NCT03203473) are phase II trials evaluating nivolumab monotherapy followed by the addition of ipilimumab depending on the initial treatment response. Furthermore, because immunotherapies produce unique patterns of tumor response that are incompletely characterized by traditional outcome measures, future clinical studies involving nivolumab plus ipilimumab should include novel response endpoints optimized for evaluating immune-oncology agents. Outcome measures such as complete response rate, immune-related PFS, longer interval landmark PFS, and treatment-free survival may improve the ability to fully capture the benefits and ill effects of immunotherapies in RCC and other immune-responsive cancers.[67-70]

With multiple treatment options available for mRCC patients and several additional combination therapies under clinical investigation, development of predictive biomarkers of response will be important for the field. PD-L1 expression in tumor and/or immune cells has been studied with mixed results in multiple trials involving immune checkpoint inhibitors. In the CheckMate 214 exploratory analyses, IMDC intermediate- and poor-risk patients experienced OS and ORR benefit with nivolumab plus ipilimumab as compared to sunitinib regardless of tumor PD-L1 expression. Other candidate biomarkers for immune checkpoint therapy include tumor mutational burden, tumor-infiltrating lymphocytes, diversity of T cell repertoire, and immune-related gene expression and warrant further evaluation in RCC and cancer types.[71] Advances in next-generation sequencing technologies present exciting opportunities to develop more precise tissue-based biomarkers based on gene expression within the tumor microenvironment. For example, exploratory analyses based on RNA sequencing of pre-treatment tumor specimens from the phase II IMmotion150 study identified distinct angiogenesis- and immune-associated gene signatures to be correlated with response to sunitinib vs atezolizumab vs atezolizumab plus bevacizumab.[72] In mRCC, given the efficacy of therapies targeting multiple distinct molecular pathways in potentially different subsets of patients, developing robust biomarkers predictive of response

to immune checkpoint inhibitors vs VEGFR-targeted therapy vs combination therapies would be a major advance in optimizing treatment selection.

In summary, nivolumab plus ipilimumab is likely to become the treatment-of-choice for mRCC patients with intermediate- or poor-risk disease. Further studies evaluating additional combination strategies, novel trial design and response endpoints, and predictive biomarkers of response will help to refine the optimal use of the combination and guide treatment decision-making for patients with advanced or mRCC.

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Drug Summary Box

Info	Summary
Drug name	Combination Nivolumab + Ipilimumab
Phase	Evaluated in phase I, II, and III trials
Indication	Under priority review by the FDA for first-line treatment for intermediate- and poor-risk patients with advanced renal cell carcinoma
Mechanism of action	Nivolumab: Fully human monoclonal IgG4 antibody against PD-1 Ipilimumab: Fully human monoclonal IgG1 antibody against CTLA-4
Route of administration	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV every 3 weeks for four doses, followed by Nivolumab 3 mg/kg IV every 2 weeks
Pivotal trials	<p>Phase I - CheckMate 016: Nivolumab in Combination with Sunitinib, Pazopanib, or Ipilimumab in Subjects with Metastatic Renal Cell Carcinoma (NCT01472081).[57] The open-label, parallel-cohort, dose-escalation study evaluated the safety and efficacy of nivolumab plus ipilimumab, and nivolumab plus a tyrosine kinase inhibitor in mRCC. Three dosing regimens of nivolumab plus ipilimumab were evaluated: 1) nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), 2) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or 3) nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3) every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks until disease progression or toxicity. Patients treated with the N3I1 and N1I3 regimens had similar efficacy results, while the N3I1 dosing regimen was significantly better tolerated. The N3I1 regimen was advanced to phase III evaluation.</p> <p>Phase III - CheckMate 214: Nivolumab Combined with Ipilimumab versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (NCT02231749).[15] Patients were randomized to either nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV every 2 weeks or sunitinib 50 mg daily for 4 weeks out of each 6-week cycle. Primary endpoints included ORR, PFS, and OS in IMDC intermediate- and poor-risk patients. Nivolumab plus ipilimumab showed significantly improved OS and ORR as well as a trend toward improved PFS compared to sunitinib.</p>

Figure 1. Mechanisms of action of nivolumab and ipilimumab.

Ipilimumab and nivolumab are monoclonal antibodies targeting the immune checkpoint proteins CTLA-4 and PD-1, respectively. CTLA-4 acts as a negative regulator of T cell activation by binding to B7 ligands CD80 and CD86 expressed on antigen-presenting cells, thereby preventing the co-stimulatory interaction between CD28 and the B7 ligands. Ipilimumab binds to CTLA-4 and blocks the inhibitory signaling of the CTLA-4:B7 interaction. PD-1 acts as a negative regulator of T cell activity predominantly by binding to PD-L1 on either tumor cells or antigen-presenting cells, leading to downstream signaling that inhibits anti-tumor T cell responses. Nivolumab binds to PD-1 and blocks the inhibitory signaling of the PD-1:PD-L1 interaction.

Figure 2. Suggested systemic treatment algorithm for patients with advanced or metastatic RCC.

*Active surveillance may be considered for select, asymptomatic, good-risk patients.[74]

Summary of efficacy and safety results from randomized studies of first-line nivolumab plus ipilimumab, cabozantinib, and sunitinib in patients with mRCC.

Table 1.

Intermediate- and Poor-risk *			
	Nivolumab + Ipilimumab (CheckMate 214)[15]	Sunitinib (CheckMate 214)[15]	Cabozantinib (CABOSUN)[73]
Overall Survival	75% at 18 months Median OS not reached (median follow-up 25.2 months)	60% at 18 months Median 26.0 months	Median 26.6 months Median 21.2 months
Progression-free Survival	Median 11.6 months	Median 8.4 months	Median 8.6 months
Objective Response Rate	42% (complete response 9%)	27% (complete response 1%)	20% (complete response 0%)
Intention-to-treat			
Same as intermediate- and poor-risk			
Overall Survival	78% at 18 months Median OS not reached	68% at 18 months Median OS 32.9 months	--
Progression-free Survival	Median 12.4 months	Median 12.3 months	--
Objective Response Rate	39%	32%	--
Grade 3-4 Adverse Events	46%	63%	68%
Increased lipase level	10%	7%	--
Increased ALT	--	--	5%
Increased AST	--	--	2%
Fatigue	4%	9%	6%
Diarrhea	4%	5%	10%
Rash	1%	0%	--
Nausea	1%	1%	3%
Asthenia	1%	2%	--
Decreased appetite	1%	<1%	--
Decreased weight	--	--	4%
Vomiting	<1%	2%	1%
Anemia	<1%	4%	1%
Hypertension	<1%	16%	28%
			20%

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	Nivolumab + Ipilimumab (CheckMate 214)[15]	Sunitinib (CheckMate 214)[15]	Cabozantinib (CABOSUN)[73]	Sunitinib (CABOSUN)[73]
Palmar-plantar erythrodysesthesia	0%	9%	8%	4%
Thrombocytopenia	0%	5%	1%	11%
Decreased neutrophils	--	--	0%	4%
Blood creatinine increased	--	--	3%	3%
Hyperglycemia	--	--	0%	6%
Stomatitis	0%	3%	5%	6%
Mucosal inflammation	0%	3%	--	--

* OS, PFS, and ORR among intermediate- and poor-risk patients were co-primary endpoints in CheckMate 214, while CABOSUN only included intermediate- and poor-risk patients.