Research Review™
PRODUCT REVIEW

Nivolumab plus ipilimumab for the first-line treatment of intermediate- or poor-risk, advanced renal cell carcinoma

Making Education Easy 2019

Independent commentary by Dr Laurence Krieger
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Independent commentary by Dr Laurence Krieger, who graduated with honours from the University of Bristol (UK) in 2002 and moved to Australia in 2005. He completed Specialist training with a particular interest in thoracic, urogenital and neurological malignancy, under Associate Professor Nick Pavlakis and Dr Helen Wheeler at Royal North Shore Hospital. In 2010, he returned to London to pursue a Fellowship in renal, prostate and thoracic oncology with Dr Peter Harper and Dr Simon Chowdhury at Guys' and St Thomas' Hospital. During that time, he remained active in undergraduate and postgraduate teaching, phase 1 and 3 clinical trials, and establishing the Guys and St Thomas' Thymoma Database and Registry. On returning to Sydney in 2011, his interest in research continued as the Director of Clinical Trials for the Riverina Cancer Care Centre and clinical trials clinic at Royal North Shore Hospital. Laurence is now the lead clinician and Principal Investigator for numerous clinical trials in urogenital malignancies at the Northern Cancer Institute, Sydney. Laurence is a Consultant General Physician at Royal North Shore Hospital and Clinical Lecturer with the University of Sydney. Laurence serves on the renal cell subcommittee for the Australian and New Zealand Urogenital and Prostate (ANZUP) trials group

Abbreviations used in this issue:

CL = geometric mean clearance;
CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4;
HRQoL = health-related quality of life; **IgG4** = immunoglobulin G4;
IFN-α = interferon-α;
IMDC = International Metastatic Renal Cell Carcinoma Database Consortium;
KPS = Karnofsky Performance Status; **PBS** = Pharmaceutical Benefits Scheme;
PD-1(2) = programmed death-1(2); **PD-1(2)L** = programmed death-1(2) ligand;
RCC = renal cell carcinoma; **TKIs** = tyrosine kinase inhibitors;
ULN = upper limit of normal; **VEGF** = vascular endothelial growth factor.

Nivolumab (Opdivo®) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the programmed death-1 (PD-1) receptor. In Australia, nivolumab, in combination with the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab (Yervoy®), is indicated and subsidised under the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with intermediate- or poor-risk, previously untreated advanced renal cell carcinoma – PBS listing.

The aim of this review is to demonstrate that nivolumab plus ipilimumab should be the treatment of choice for patients with previously untreated intermediate- or poor-risk advanced renal cell carcinoma, as demonstrated in the phase 3 CheckMate 214 trial, and as recommended in recent international guidelines.

Renal cell carcinoma

Renal cell carcinoma (RCC) denotes cancer originating from the renal epithelium.[1] It is the most common cancer of the kidney, accounting for >90% of cases.[1] RCC is a heterogeneous cancer and is classified into three major histological types; clear-cell RCC (80-90% of cases), papillary RCC (10-15%) and chromophobe RCC (4-5%).[2] About 25-30% of patients with RCC have advanced disease.[3]

Various risk models have been developed to determine the prognosis of patients with advanced RCC.[4-6] The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) has developed a prognostic model that classifies advanced RCC based on six established risk factors: Karnofsky Performance Status (KPS) <80, <1 year from diagnosis to treatment, haemoglobin concentration <lower limit of normal, calcium concentration >upper limit of normal (ULN), neutrophil count >ULN and platelet count >ULN. Based on these risk factors, three groups have been identified: favourable risk (0 factors), intermediate risk (1-2 factors) or poor-risk (3-6 factors).[5,6]

Worldwide, kidney cancers represent approximately 2% of all cancers, with 403,262 new cases being diagnosed in 2018.[7] In Australia, kidney cancer is estimated to be the ninth most commonly diagnosed cancer in 2019, with an estimated 3,814 new cases being diagnosed in Australia (2,539 males and 1,275 females).[8] The estimated age-standardised incidence rate for 2019 is 12.9 per 100,000 person, which represents a 108% increase from 1982 when the age-standardised incidence rate was 6.2 per 100,000 persons.[8] RCC is approximately twice as common in men as in women. The five-year survival rate (2011–2015) for those diagnosed with kidney cancer is 77%.[8]

Treatments for previously untreated advanced RCC

RCC is an immunologically active cancer and until targeted therapies were introduced in 2006, the treatment of advanced clear cell RCC was generally based on immunotherapy such as interferon-a (IFN-α) and interleukin-2.[9] However, response rates are low and these agents are associated with considerable toxicity.

Significant advances were made with the identification of drug targets, which enabled the stabilisation of the disease and prolonged survival.[9-11] Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells (including tumour cells).[11]

Approved targeted therapies for previously untreated advanced RCC now include orally available, multi-targeted tyrosine kinase inhibitors (TKIs), such as sunitinib,[12] sorafenib,[13] pazopanib,[14] and cabozantinib,[15] and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus.[16] Bevacizumab in combination with INF-α is also indicated for the treatment of patients with advanced and/or metastatic RCC.[17] In addition, the TKI axitinib is available for the treatment of patients with advanced RCC after failure of one prior systemic therapy.[18] Similarly, the mTOR inhibitor everolimus is available for the treatment of advanced RCC after failure of treatment with sorafenib or sunitinib.[19]

Nivolumab and ipilimumab represent a new treatment option that emerged as a result of outcomes from the recent CheckMate 214 study.[20] The reported superiority of nivolumab and ipilimumab over sunitinib in intermediate- or poor-risk patients with previously untreated advanced RCC (see below) has resulted in the recent European[9] (**Figure 1**) and the National Comprehensive Cancer Network[10] guidelines recommending this combination as the first-line option for this group of patients.

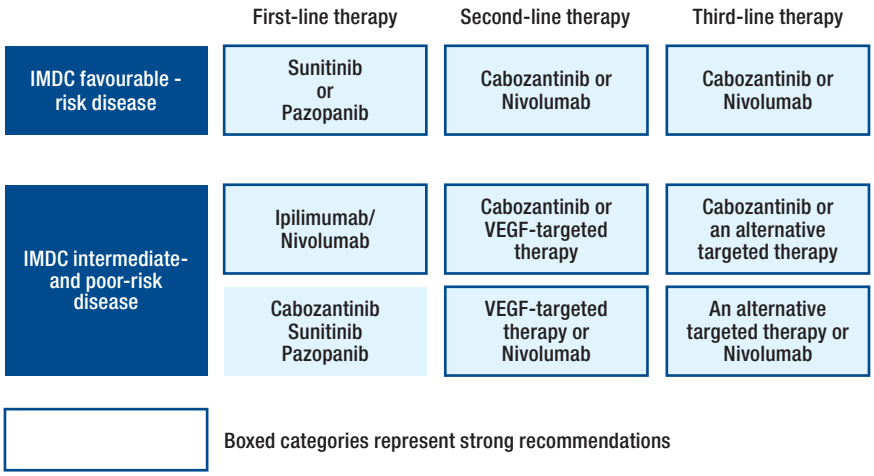

Figure 1. European Association of Urology guideline recommendations 2019, for the systemic treatment of advanced or metastatic clear-cell renal cell carcinoma[9]
IMDC = International Metastatic Renal Cancer Database Consortium; **VEGF** = vascular endothelial growth factor.

Expert commentary on previously untreated advanced RCC and its recommended treatment

Treatment options for patients with advanced RCC have changed significantly over the last year, let alone decade. Motzer et al. established the first significant survival benefit of sunitinib over interferon (11 vs 5 months) in 2007.[21] Incremental benefit was observed in all prognostic groups, but was statistically not significant for those in the poor-risk group given that they represented less than 10% of the trial population. Similar paucity of data exists with the equally efficacious first-line therapy pazopanib. No other TKI has unequivocally demonstrated superiority in the first-line setting.

None-the-less, there has been significant room for improving prognosis, with 20% of patients in the poor and 50-60% of patients in the intermediate risk groups. For many years, there has been concern about replacing a VEGF TKI with immunotherapy, for a predominantly VEGF-driven tumour. However, the potential for durable responses (albeit a significant minority) with interferon and interleukin prior to the advent of sunitinib reaffirm the potential role of immunotherapy. This principal was subsequently substantiated with nivolumab in the second-line setting (CheckMate 025).[22] Whilst the toxicity profile is far more appealing with a PD-1 monotherapy compared with older immune related treatments, only 20-30% of patients benefit, albeit far more durably.

Up to 30% of patients that progress following first-line therapy become too unwell or die before being able to contemplate second-line options and so the need to improve the overall response rates and duration have been a key driver in evaluating the role of doublet immunotherapy in treatment-naïve patients. However, dual therapy does come with increased toxicity, so defining patients in whom this added risk is negated by the benefits is also of great importance. Seemingly, the relatively simple IMDC criteria has proven to be very useful in delineating just this, but one has to remember that there are still patients in whom immunotherapy is not feasible due to co-morbidities, active auto-immune disease or poor performance status.

And so, in 2019, we are in a position whereby we must first classify patients by their IMDC prognostic category and offer sunitinib or pazopanib TKI monotherapy for those in the good-risk group. For the intermediate- and poor-risk patients, doublet immunotherapy is preferable, unless there are contraindications or poor performance status (ECOG 2 or less) whereby TKI monotherapy remains a default option (but only for those with intermediate risk). Phase 2 (CABOSUN) data[23] have demonstrated efficacy and improved disease control with cabozantinib in the poor-risk group, although this pluripotent TKI, as with sunitinib and pazopanib, is not currently funded in Australia for this indication.

Nivolumab

Nivolumab, in combination with ipilimumab, is indicated and subsidised under the Pharmaceutical Benefits Scheme (PBS) for use in patients with intermediate- or poor-risk, previously untreated advanced RCC.

The following is a summary of the pharmacological properties of nivolumab and relevant pharmacological properties of ipilimumab. For full details, the nivolumab[24] and ipilimumab[25] product information should be consulted.

Mechanism of action

Binding of the programmed death-1 (PD-1) ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production.[26, 27] The upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumours.

Nivolumab is a fully human, genetically engineered, immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 (**Figure 2**).[24, 26, 28] Through the blockade of PD-1 binding to PD-L1 and PD-L2, nivolumab thus potentiates T-cell responses, including anti-tumour responses.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks its interaction with its ligands.[24, 25, 26]

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CLTA-4) may thus result in enhanced T-cell function that is greater than the effects of either antibody alone, leading to improved anti-tumour responses (**Figure 2**).

Pharmacokinetics

The pharmacokinetics of nivolumab are linear, with exposure to nivolumab increasing dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.[24]

Based on a population PK analysis, using data from patients with melanoma, non-small cell lung cancer, or RCC at steady state with nivolumab 3 mg/kg every 2 weeks, the geometric mean clearance (CL) was 7.9 mL/h, the terminal half-life was 25 days, and average exposure at steady state was 86.6 µg/mL.[24]

Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold.[24]

In a population PK analysis of combined administration of nivolumab and ipilimumab, nivolumab 1 mg/kg had no effect on the CL of ipilimumab, and ipilimumab 3 mg/kg resulted in a 24% increase in the CL of nivolumab.[24] The CL of nivolumab increased by 42% in the presence of anti-nivolumab antibodies, but there was no effect of anti-ipilimumab antibodies on the CL of ipilimumab.

Age, weight, gender, race, mild or moderate renal impairment, and mild or moderate hepatic impairment did not affect the CL of nivolumab.[24]

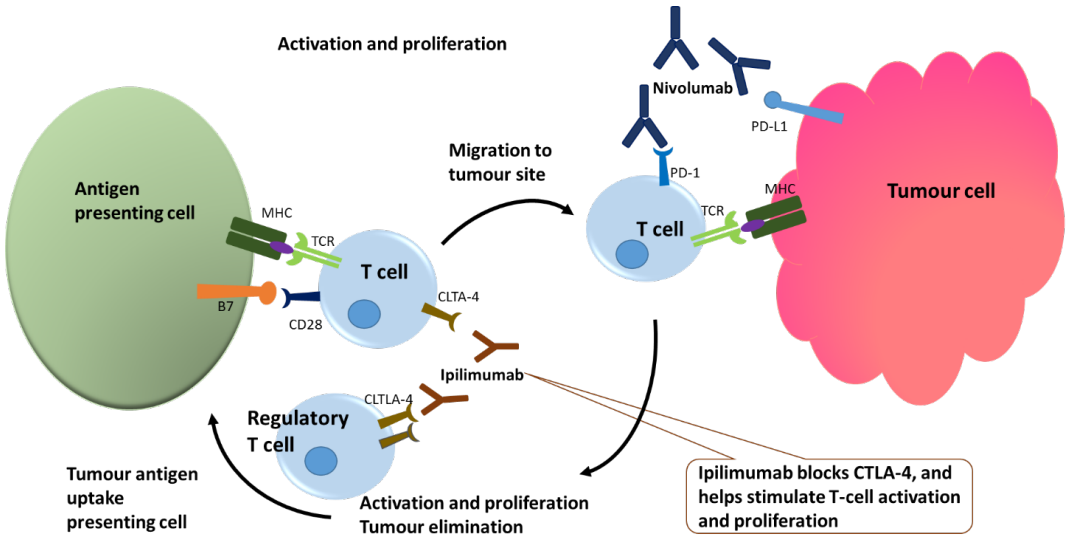

Figure 2. Mechanism of action of nivolumab and ipilimumab[24, 25, 26]

CTLA-4 = cytotoxic T-lymphocyte antigen-4; **MHC** = major histocompatibility complex; **PD-1** = programmed death-1; **PD-L1** = programmed death-1 ligand; **TCR** = T-cell receptor.

Drug interactions

Nivolumab is a human monoclonal antibody, and since it is not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not expected to affect the pharmacokinetics of nivolumab.[24]

Nivolumab is not expected to have an effect on CYP or other drug metabolising enzymes in terms of inhibition or induction.[24]

Dosage and administration

Nivolumab and ipilimumab must be administered and monitored by specialist physicians experienced in the use of immunotherapy.[24] An infusion of nivolumab must not be administered as an intravenous push or bolus injection.[24]

- Nivolumab 3 mg/kg should be administered intravenously over 30 minutes every 3 weeks for the first four doses in combination with 1 mg/kg ipilimumab on the same day, followed by nivolumab monotherapy (3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks).[24]
- After the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks (for 3 mg/kg or 240 mg) or after 6 weeks (for 480 mg).[24]
- Treatment with nivolumab in the single-agent phase should be continued as long as clinical benefit is observed or until the patient can no longer tolerate the treatment.[24]

When nivolumab is co-administered with ipilimumab, if either agent is withheld, the other agent should also be withheld.[24]

Contraindications

Nivolumab is contraindicated in patients who have known hypersensitivity to nivolumab or any of its excipients.[24]

Warnings and precautions

Nivolumab is associated with immune-related adverse events which occur at higher frequencies when nivolumab is co-administered with ipilimumab compared with nivolumab as a monotherapy.[24] These immune-related adverse reactions can affect a variety of organ systems.

- Patients should be monitored continuously as an immune-related adverse reaction with nivolumab monotherapy or in combination with ipilimumab may occur at any time during or after discontinuation of therapy.[24] The majority of these immune reactions were initially manifest during treatment; however, a minority can occur weeks to months after discontinuation.
- Based on the severity of the adverse reaction, nivolumab monotherapy or in combination with ipilimumab should be withheld and corticosteroids administered.[24]
- Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.[24]
- Nivolumab monotherapy or in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.[24]

Clinical efficacy and tolerability

The CheckMate 214 study demonstrated, that in patients with intermediate- or poor-risk advanced clear-cell RCC, first-line therapy with nivolumab plus ipilimumab, compared with sunitinib, was associated with significantly higher overall survival (OS) and objective response rates (ORR), and an improved health-related quality of life (HRQoL).[20, 29, 30]

The safety profile of nivolumab plus ipilimumab was consistent with that reported in previous studies with this combination in multiple tumour types, including advanced RCC.[31-33] Immune-related adverse reactions are seen more frequently, and are more severe, with nivolumab and ipilimumab combination therapy than with monotherapy with either agent (see Warnings and precautions).[24] As with other checkpoint inhibitors, the adverse effects are generally manageable with supportive measures and corticosteroids in some cases. However, rarely, they can be fatal.[24] Early diagnosis and appropriate management of any immune-related adverse events are essential to minimise life-threatening complications. It is recommended that patients be monitored at least prior to each dose and patients should be advised to immediately report possible symptoms.[24]

CheckMate 214

The study methodology and outcomes from the CheckMate 214 trial are described below.

Aim

To compare treatment with nivolumab plus ipilimumab versus sunitinib in patients with previously untreated clear-cell advanced RCC.[20, 29]

Methods

In the phase 3, randomised CheckMate 214 trial, patients aged 18 years and older with previously untreated, advanced or metastatic RCC with a clear-cell component were recruited from 175 hospitals and cancer centres in 28 countries (**Figure 3**).[20] Patients were categorised by risk status into favourable, intermediate-, and poor-risk subgroups (according to IMDC risk score) and randomly assigned (1:1) to open-label nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks, or sunitinib 50 mg/day for 4 weeks of each 6-week cycle (**Figure 3**). A total of 1096 patients were randomised to nivolumab plus ipilimumab (n=550) or sunitinib (n=546 patients); 425 and 422, respectively, had intermediate- or poor-risk RCC.[24]

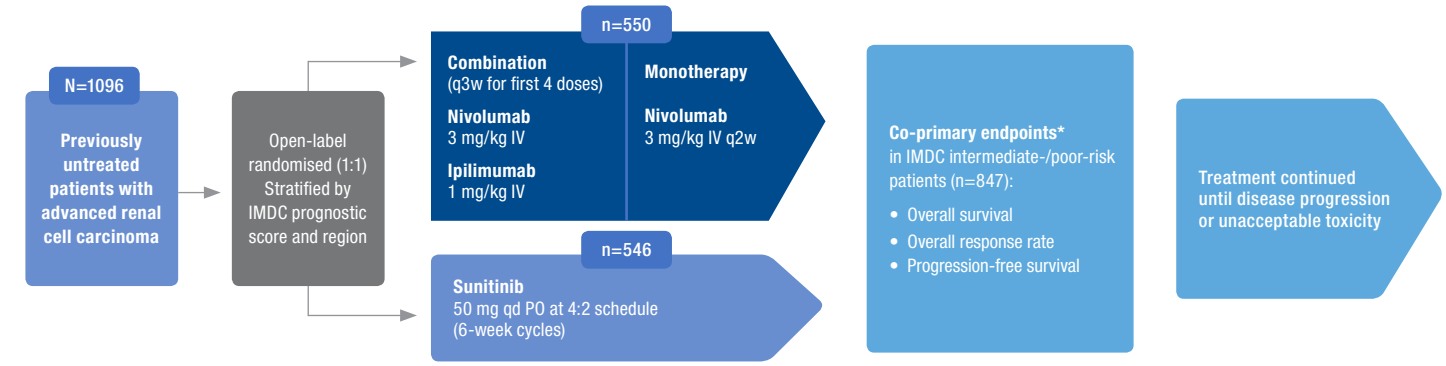

Figure 3. Study design of CheckMate 214 trial[20]

*The overall alpha level was 0.05, split among three coprimary end points. The overall response rate was at an alpha level of 0.001, progression-free survival was at an alpha level of 0.009 and overall survival was at an alpha level of 0.04.

The primary efficacy outcome measures were OS, ORR and progression-free survival (PFS) as determined by a Blinded Independent Central Review in intermediate- or poor-risk patients. In addition, HRQoL was assessed using various generic instruments designed for the general population (EuroQol five dimensional three level [EQ-5D-3L28]) and cancer-specific instruments (Functional Assessment of Cancer Therapy-General [FACT-G13; and the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index [FKSI-1917]).[30]

Results

Efficacy

The following efficacy outcomes were obtained in the group of intermediate- or poor-risk patients.

- At a median follow-up of 25.2 months, the median OS had not been reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (hazard ratio [HR], 0.63; p<0.001).[20] The 18-month OS survival was 75% (95% confidence interval [CI] 70, 78) with nivolumab plus ipilimumab and 60% (95% CI 55, 65) with sunitinib. With continued follow-up (32.4 months), OS still had not been reached with nivolumab plus ipilimumab, and it remained significantly higher versus sunitinib (**Figure 4**).[29]
- At a median follow-up of 25.2 months, the ORR was 42% versus 27% (p<0.001) with nivolumab plus ipilimumab versus sunitinib; this included complete response (CR) rates of 9% versus 1%, respectively (p<0.001).[20] The ORRs were maintained with continued follow-up at a median 32.4 months (42% vs 29%; p<0.0001), including investigator-assessed CR rates of 11% versus 1%, respectively.[29]
- PFS for nivolumab plus ipilimumab versus sunitinib at a median 25.2 months follow-up was 11.6 versus 8.4 months, respectively (HR=0.82; 99.1% CI 0.64, 1.05); p=0.03, not significant per the pre-specified 0.009 threshold).[20] Continued follow-up to a median 32.4 months indicated a PFS benefit emerged with nivolumab plus ipilimumab versus sunitinib, starting at 9–12 months, and with a plateauing of the nivolumab plus ipilimumab curves (**Figure 5**).[29]

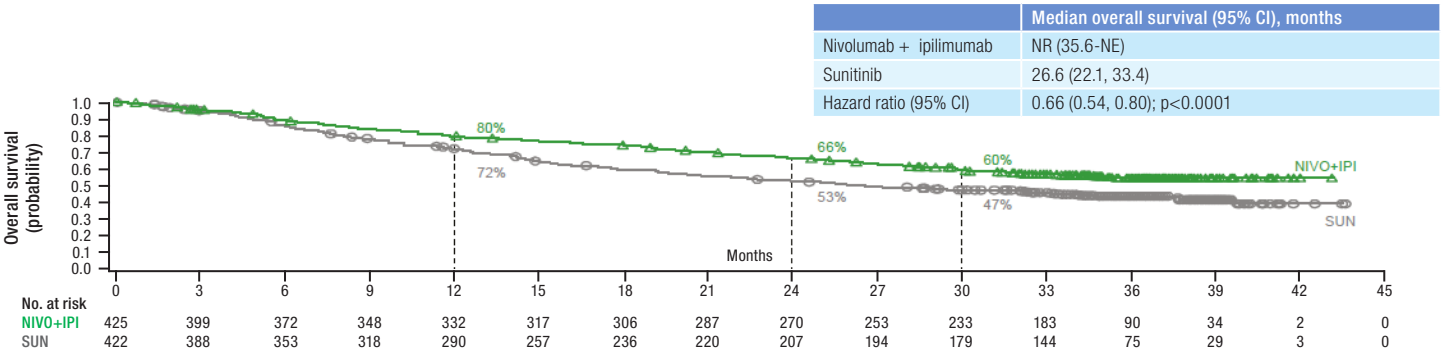

Figure 4. Overall survival in intermediate- or poor-risk patients with renal cell carcinoma in the CheckMate 214 study[29]

NR = not reached; **NE** = not estimable.

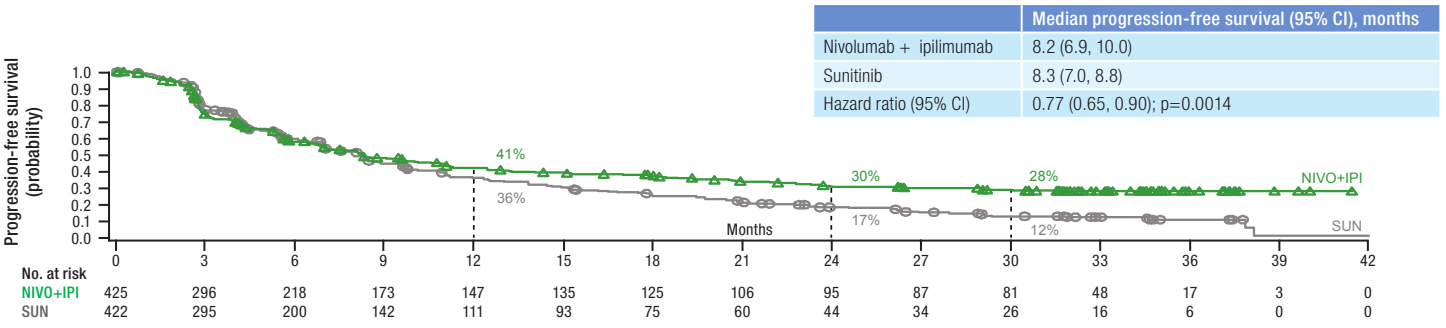

Figure 5. Investigator-assessed progression-free survival in intermediate- or poor-risk patients with renal cell carcinoma in the CheckMate 214 study[29]

- At a median follow-up of 25.2 months, the median duration of response had not been reached with nivolumab plus ipilimumab and was 18.2 months with sunitinib.[20] With continued follow-up to a median 32.4 months, the median duration of response had not been reached with the combination therapy and was 13 months with sunitinib.[29]
- At a median follow-up of 25.2 months, nivolumab plus ipilimumab lead to a better health-related quality of life than sunitinib, when assessed according to EQ-5D-3L28, FACT-G13, and FKSI-1917 scales.[30]

Safety

At a median follow-up of 25.2 months, treatment with nivolumab plus ipilimumab versus sunitinib was associated with treatment-related:[20]

- discontinuation rates due to adverse reactions in 22% versus 12% patients, respectively;
- adverse events of any grade in 93% versus 97% patients, respectively;
- grade 3 or 4 adverse events in 46% versus 63% patients, respectively;
- deaths in 1.5% and 0.7% of patients, respectively.

At a median follow-up of 25.2 months, with nivolumab plus ipilimumab, the most common adverse events (any grade) were fatigue (37%), pruritus (28%), diarrhoea (27%), rash (22%), nausea (20%), increased lipase levels (16%) and hypothyroidism (16%).[20] The most common treatment-related grade 3 or 4 adverse events ≥2% were increased lipase levels (10%), fatigue (4%) and diarrhoea (4%). Of the 436 patients who had a treatment-related select (immune-mediated) adverse event (including skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories), 35% received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent).[20]

With longer follow-up (median 32.4 months), no new safety signals emerged.[29]

Expert commentary on CheckMate 214 data

We have several goals and considerations when starting treatment with advanced disease. First, in the knowledge that patients that progress may not have the chance to benefit from second-line therapy, what agents give the best chance of response? Second, (and arguably now a realistic consideration), could this response be complete? Third, if patients do respond, will it be durable? Fourth, is the side-effect profile and toxicity acceptable?

Ipilimumab and nivolumab doublet therapy provide a significant improvement in overall survival for patients with intermediate- and poor-risk disease for those who are ECOG 0-1 and without contraindications to starting immunotherapy. The progression free survival is improved by 3 months compared to that of sunitinib because a small proportion of patients will not respond at all (and is therefore not necessarily as good a reflection of overall efficacy, unlike overall survival). Despite this, and in answer to the first question, overall response compared with sunitinib is still much higher and improved from 29% to 47%, with up to 11% being complete. In fact, when stratified according to PDL-1 positivity (>1%), the complete response rate rises to 16%. For those patients that do respond, the response appears to be durable, a phenomenon now well recognized with immunotherapy.

Doublet immunotherapy still makes the unfamiliar prescriber wary of side effects. However, the low dose of ipilimumab, as well as a much greater understanding, recognition and confidence of managing immune toxicities, makes this a tolerable regimen for many patients. Quality of life scores were better than sunitinib, and the nature, timing and severity of side effects congruent with what we see in many other cancer types. The discontinuation rate was higher (22% vs 12%), although in clinical practice one would argue many of these patients may have continued with nivolumab monotherapy. Often those patients with immune-related toxicities do derive benefit. Although a third of patients did require high-dose corticosteroids, one would argue that this is an acceptable and treatable risk in a patient population who fare poorly otherwise.

It is important to recognize that doublet immunotherapy was not superior to sunitinib in the good-risk patients for which this remains the current standard of care.

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Take home message

- In Australia, it is estimated that kidney cancer will be the ninth most commonly diagnosed cancer in 2019, with RCC being the most common type.
- Treatment options for this immunologically active cancer have changed over the past two decades.
- Recent international guidelines now recommend nivolumab plus ipilimumab for the first-line treatment of IMDC intermediate- or poor-risk advanced RCC.
- In the CheckMate 214 trial, nivolumab plus ipilimumab, compared with sunitinib, was associated with significantly longer OS, higher ORR, a greater chance of CR, a more durable responses and enhanced HRQoL than sunitinib.
- The safety profile of nivolumab plus ipilimumab was consistent with that reported in previous studies with this combination in multiple tumour types, including advanced RCC.
- Patients treated with nivolumab plus ipilimumab should be monitored for immune-related adverse reaction and managed promptly and appropriately should any of these events be reported.

Expert concluding comments

Nivolumab and ipilimumab set a new standard of care for the majority of patients diagnosed with advanced RCC. We must still tailor our treatment options according to many clinical variables such as contraindications to treatment, performance status, compliance, patient preference, psycho-social support and safety of managing toxicity when it occurs. There is still a role for first-line TKI therapy in those with good-risk and a subset of intermediate-risk disease patients for these reasons. However, we now have renewed hope in improving efficacy while maintaining quality of life with doublet immunotherapy associated with a manageable and predictable toxicity profile in patients who would otherwise do poorly. For a small, but significant proportion, there is even hope of complete radiological response.

References

1. Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009.
2. Moch H, Cubilla AL, Humphrey PA, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol. 2016;70:93-105.
3. Wallis CJD, Klaassen Z, Bhindi B, et al. First-line systemic therapy for metastatic renal cell carcinoma: a systematic review and network meta-analysis. Eur Urol. 2018;74:309-21.
4. Noe A, de Bruijn RE, Blank C, et al. Comparison of pre-treatment MSKCC and IMDC prognostic risk models in patients with synchronous metastatic renal cell carcinoma treated in the era of targeted therapy. World J Urol. 2016;34:1067-72.
5. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14:141-8.
6. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27:5794-9.
7. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
8. Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW; 2019.
9. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol. 2019;75:799-810.
10. National Comprehensive Cancer Network. NCCN Guidelines version 3.2019 - kidney cancer. 2019.

11. Ross K, Jones RJ. Immune checkpoint inhibitors in renal cell carcinoma. Clin Sci (Lond). 2017;131:2627-42.
12. Pfizer Australia Pty Ltd. Australian product information - Sutent® (sunitinib malate) 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02256-3. Accessed March 28, 2019.
13. Bayer Australia Ltd. Australian product information - Nexavar® (sorafenib tosylate). 2014. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-07403-3&d=201903281016933. Accessed March 28, 2019.
14. Novartis Pharmaceuticals Australia Pty Limited. Australian product information - Votrient® tablets (pazopanib hydrochloride). 2017. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-07077-3. Accessed March 28, 2018.
15. Ipsen Pty Ltd. Australian product information - Cabometyx® (cabozantinib as (S)-malate) 2018. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01133-1. Accessed March 28, 2019.
16. Pfizer Australia Pty Ltd. Australian product information - Torisel® (temsirolimus). 2016. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-01377-3. Accessed March 28, 2019.
17. Roche Products Pty Ltd. Australian product information - Avastin® (bevacizumab). 2017. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04263-3. Accessed March 28, 2019.
18. Pfizer Australia Pty Ltd. Australian product information Inlyta® (axitinib). 2017. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-02467-1&d=201904261016933. Accessed April 26, 2019.
19. Novartis Pharmaceuticals Australia Pty Limited. Australian product information: Afinitor® (everolimus) tablets and dispersible tablets. 2018. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03171-3. Accessed April 26, 2019.
20. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378:1277-90.
21. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356:115-24.
22. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803-13.
23. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018;94:115-25.
24. Bristol-Myers Squibb Australia Pty Ltd. Australian product information -Opdivo® (nivolumab). 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1&d=201903281016933. Accessed March 29, 2019
25. Bristol-Myers Squibb Australia Pty Ltd. Australian product information- Yervoy® (ipilimumab). 2019. https://0ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02907-3. Accessed March 29, 2019.
26. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39:98-106.
27. Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther. 2013;13:847-61.
28. Venur VA, Joshi M, Nepple KG, et al. Spotlight on nivolumab in the treatment of renal cell carcinoma: design, development, and place in therapy. Drug Des Devel Ther. 2017;11:1175-82.
29. Tannir N, Frontera O, Hammers H, et al. 30-month follow-up of the phase 3 CheckMate 214 trial of first-line nivolumab plus ipilimumab or sunitinib in patients with advanced renal cell carcinoma. 2019 Genitourinary Cancers Symposium; February 14-16, 2019; San Francisco, CA, USA. 2019.
30. Cella D, Grunwald V, Escudier B, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol. 2019;20:297-310.
31. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. J Clin Oncol. 2017;35:3851-8.
32. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369:122-33.
33. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17:1558-68.

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