Review

Double Immune Checkpoint Blockade in Renal Cell Carcinoma

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Abstract. Long considered an immunogenic tumour, immunotherapy has been the cornerstone of systemic treatment in renal cell carcinoma (RCC) for decades, since the introduction of interleukin 2 and interferon-alfa in the 1980s to the more recently approved immune checkpoint inhibitors. Moreover, on the basis that anti-CTLA-4 and anti-PD-1/PD-L1 intrinsic mechanisms are different, double checkpoint inhibition was proposed to further improve anti-tumor immune response. The first trial to assess double checkpoint inhibition was Checkmate 016 (nivolumab and ipilimumab). It showed acceptable safety and promising antitumor activity that led to the first phase III trial with combination immunotherapy in RCC, Checkmate 214. This trial showed superior overall survival and response rate of the combination immunotherapy (nivolumab and ipilimumab) versus sunitinib in intermediate- and poor-risk advanced RCC, leading to its approval in this setting. Despite these advances, there is still room for improvement. In this context, cytokines and T-cell costimulatory molecules are currently under investigation. This review summarizes the principles of immunotherapy and its role in RCC, provides an update on double checkpoint blockade and discusses the major challenges with double checkpoint blockade.

Keywords: Immune checkpoint inhibitors, double immune checkpoint blockade, renal cell carcinoma, immunotherapy, clinical trials

RATIONALE FOR IMMUNOTHERAPY

Three steps need to be achieved in order to yield antitumor immunity: 1) immunization, which implies antigen presentation and dendritic cell maturation; 2) T-cell response, which requires interaction between stimulatory and inhibitory molecules and surface proteins; and 3) immunosuppression, which implicates tumor microenvironment strategies that alter T cell effects through suppressive ligands (such as PD-L1,PD-L2) or molecules (indoleamine 2,3-dyoxygenase-IDO) among others [1, 2].

T-cell response regulation has revolutionized cancer therapeutics. By removing known inhibitory pathways, T-cell response is allowed to act freely. One of the effectors of this carefully delineated balance are the cytotoxic T-cells surface proteins that allow for restraint of immune response, known as checkpoint proteins [3]. In nature, checkpoint proteins display a wide variety, but two have been well described in literature. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and Programmed cell death protein (PD-1) are surface proteins that undergo upregulation after T-cells are activated [4, 5]. These inhibitory checkpoint proteins exemplify different mechanisms and pathways but ultimately have the same objective: to improve antitumor immune response [6, 7].

T-cell activation requires interaction between CD28 on the T-cell surface and B7 on the antigen-presenting cell surface. CTLA-4 displaces CD28 from B7, which ensures T-cell suppression and at the same time enhances T regulatory cells activation and

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suppresses helper T-cells [4, 8]. *Mellman et al.* suggest that tumor-protective T-cells would then become activated after CTLA-4 blockade [1]. In contrast, PD-1 and its ligands (PD-L1 and PD-L2), members of the B7 gene family, operate through a different inhibitory pathway [9]. These transmembrane proteins, found in T- and B-cells, are responsible for activation of T regulatory cells through de novo conversion of CD4+ T-cells and inhibition of interferon-γ, tumor necrosis factor-α and IL-2 production, allowing for immunosuppressive function. Furthermore, if PD-1 is expressed persistently on T-cells an exhaustive phenotype emerges depicting diminished immune function [10]. PD-1 ligands (PD-L1 and PD-L2) are not only expressed by antigen presenting cells but many non-immune cells and even tumor cells [5, 11]. Thus, they present a diversity of ligands that differ in nature, function and implications for therapy.

The well-balanced immune structure can also be hijacked by the tumor microenvironment so cancer can develop, progress and prevail in the organism. This understanding introduced the concepts of immunoevasion and tumor-promoting inflammation among cancer hallmarks [12, 13]. Immune checkpoint blockade with an anti-CTLA-4 and anti-PD-1/PD-L1 represent part of these advances in several immunogenic cancer types such as melanoma, non-small-cell lung cancer (NSCLC) and renal cell carcinoma (RCC), among others [14].

Immunotherapy has been used in kidney cancer for decades [15, 16]. RCC has been considered as an immunogenic tumor because of the increased infiltration of immune cells including T-cells, dendritic cells, natural killer T-cells, macrophages and memory cells, and also increased cytokine secretion. In the 1980s and 1990s, RCC immunotherapy was based on high-dose interleukin-2 (IL-2) and interferon-alfa (IFNa), which elicited a high burden of toxicities and yielded low efficacy. More recently, Nivolumab, an anti-PD-1 monoclonal antibody, was the first immune checkpoint inhibitor approved by the FDA in 2015 based on results of the CheckMate 025 study [16–18]. This was later followed by subsequent other approvals.

In addition, based on the core concept that anti-CTLA-4 and anti-PD-1/PD-L1 intrinsic mechanisms are different, double checkpoint inhibition was proposed to further improve anti-tumor immune response. Anti-CTLA-4 acts in lymphoid organs in the early steps of immune response. In contrast, anti-

PD-1/PD-L1 acts in the tumor microenvironment later in the response. In this review we will summarize the current evidence of double immune checkpoint blockade in RCC.

Double immune checkpoint blockade

Simultaneous pathway blockade and sequential blockade are the backbone of combination therapy in RCC. The association of both immune checkpoint inhibitors in a preclinical setting is more effective disrupting the tumor microenvironment [19]. In RCC, the concept has been proven to be clinically effective within the Checkmate-016 and Checkmate-214 trials.

IPILIMUMAB-NIVOLUMAB COMBINATION IN ADVANCED RENAL CELL CARCINOMA

Checkmate-016

The first study to assess the combination of immune checkpoint inhibitors (ICI) in mRCC was the Checkmate-016 study (NCT01472081) [20]. This phase I trial was based on previous results on patients with melanoma and lung cancer where double immune checkpoint blockade was more effective than monotherapy and also on efficacy evidence of anti-CTLA-4 antibodies in mRCC [14, 21]. Its primary endpoint was the overall safety and tolerability of nivolumab plus ipilimumab. Eligible patients were divided in 3 groups that received nivolumab 3mg/kg plus ipilimumab 1mg/kg (N3I1), nivolumab 1mg/kg plus ipilimumab 3mg/kg (N1I3) or nivolumab 3mg/kg plus ipilimumab 3mg/kg (N3I3) every 3 weeks for four cycles and then only nivolumab 3mg/kg every 2 weeks until progression or toxicity. Accrual on N3I3 group was discontinued due to the observed high-grade 3 or 4 adverse effects (AEs) (83.3%). On the other hand, high-grade AEs in N3I1 and N1I3 treatment groups were 38.3% and 61.7%, respectively. N3I1 treatment group had also lower treatment-related AEs, lower treatment discontinuation rates and less patients requiring immune modulating medications (61.7% vs 83.0%). After a median follow-up of 22.3 months, the objective response rate (ORR) for both treatment-naive arms was 40% and the progressive disease (PD) rate as best response was 17%. Complete response (CR) and partial response (PR) rates in N3I1 treated patients were

10.6% and 29.8%, respectively. In comparison, there were no CR in N1I3 treated patients and the PR rate was 40.4%. Safety profile favoured N3I1 treatment group, therefore it was selected for further development in a phase III trial.

Checkmate-214

Ipilimumab plus nivolumab combination has not been compared with either nivolumab or ipilimumab alone in mRCC. However, results from Checkmate-016 led to the conduct of a phase III trial with the combination. In the Checkmate 214, 1096 patients with previously untreated mRCC were randomized 1:1 to receive nivolumab 3mg/kg plus ipilimumab 1mg/kg every 3 weeks for four doses, then only nivolumab 3 mg/kg every 2 weeks or sunitinib 50 mg, orally, daily, for 4 weeks on followed by 2 weeks off. Primary endpoints were overall survival (OS), ORR and progression-free survival (PFS) in the intermediate and poor IMDC risk-groups. After a median of 25.2 months, there was a significant improvement in 18-month OS (75% with the combination versus 60% with sunitinib) and ORR (42% vs 27%, respectively, $P < 0.001$), favouring nivolumab plus ipilimumab combination [22]. The median OS was not reached (NR) and 26 months for immunotherapy combination and sunitinib, respectively. Of note, the CR rate was 9% and 1%, respectively, and the median PFS was 11.6 and 8.4 months, respectively (HR 0.82, $p = 0.03$). Similar benefit was seen when evaluating the whole cohort including all IMDC risk-groups (favorable, intermediate and poor) (secondary endpoint). The safety profile showed any-grade and high-grade AEs of 93% and 46%, respectively, in the immunotherapy combination arm, and 97% and 63%, respectively, in the sunitinib arm. Interestingly, although the AE-related treatment discontinuation rate was superior in the ICI combination arm (22%) versus the sunitinib arm (12%), patients who discontinued in the experimental arm due to drug-related AEs experienced long-term benefit, with durable responses after the last dose of treatment. Moreover, the recently

reported PROs (patient reported outcomes) as an exploratory endpoint, showed an improvement of health-related quality of life (HRQOL) across all instruments (Assessment of Cancer Therapy Kidney Sympton Index-19, Functional Assessment of Cancer Therapy-General, and EuroQol five dimensional three level) for the immunotherapy combination arm in patients with intermediate or poor risk mRCC [23]. Efficacy in the favorable IMDC risk-group only was evaluated as an exploratory outcome. In this favorable-risk group, sunitinib treated patients had higher 18-month OS, ORR and PF. However, it should be mentioned that the CR rate in favorable-risk patients treated was higher with the immunotherapy combination (11% versus 5%). Also as an exploratory analysis, among intermediate and high risk patients who had quantifiable PD-L1 expression ($<$or $\geq 1\%$) the combination immunotherapy arm showed superiority in both OS and ORR irrespective of PD-L1 expression versus the control arm. However, mPFS among patients with $< 1\%$ PD-L1 expression was similar in both arms of treatment (HR 1.00; 95% CI, 0.80 to 1.26), whereas among patients with $\geq 1\%$ PD-L1 expression mPFS was superior with the immunotherapy combination (HR 0.46; 95% CI, 0.31–0.67) [22]. On April 16, 2018, the FDA approved the double immune checkpoint blockade, nivolumab plus ipilimumab, for the treatment of intermediate or poor risk, previously untreated advanced RCC patients.

OTHER COMBINATIONS

Despite the remarkable progress that has been achieved with ipilimumab and nivolumab combination, there is still room for improvement in efficacy and safety profile. It remains unclear whether the enhanced efficacy of combined anti PD-1 and anti-CTLA4 therapy is mediated by additive engagement or through independent mechanisms from each drug [24]. T-cell costimulatory molecules represent a vast number of proteins under investigation such as LAG3, TIM3 or TIGIT, VISTA from the immunoglobulin

Table 1
Efficacy outcomes in the Checkmate-016 and the Checkmate-214

Efficacy	Checkmate 016 (N3I1)	Checkmate 214
ORR	40% (95% CI 26.4 to 55.7)	42% (95% CI, 37 to 47)
Overall Survival	not reached (95% CI, 26.7 months to not reached)	not reached (95% CI, 28.2 months to not estimable)
12 -month OS	81%	80% (95CI, 76 to 84)
PFS	7 months (95% CI, 3.7 to 14.3 months)	11.6 months (95% CI, 8.7 to 15.5)

Table 2
Safety outcomes in the Checkmate-016 and the Checkmate-214 studies

Treatment related adverse effects.	Checkmate 016	Checkmate 214
N	47	547
Median Age (range)	54(26–68)	62(26–85)
MSKCC/ IMDC intermediate-poor risk	55.30%	77.70%
Treatment Arm	Nivo 3mg/kg+Ipi 1mg/kg	Nivo 3mg/kg+Ipi 1mg/kg
Any grade	92%	93%
Grade 3-4 toxicity	38.30%	46%
Discontinuation rate for toxicity	10.60%	22%

superfamily (IgSF) or OX40, GITR, 4-1BB, CD40 from the tumor necrosis factor receptor superfamily (TNFRSF) and others. Better understanding of each specific protein and its stimulatory role are required for an enhanced development of novel immune checkpoint blockade combinations [25]. Table 3 shows selected combinations in early clinical development phase.

Cytokines were the main treatment for mRCC during preceding decades; however the rate of response was low. A novel C122-biased cytokine (NTRK-214) is currently under development in combination with nivolumab and ipilimumab in the phase I/II PIVOT-02 trial. It is expected that NKTR-214 may unleash T cell proliferation and disrupt the tumor microenvironment. The combination of NKTR-214 and nivolumab assures a potentially non-overlapping effective synergistic mechanism. This study was conceived as a 4 part study (NCT02983045). Study part 1 determined doses and scheduling according to safety and efficacy profile of the combination. The selected dose and schedule was NKTR-214 0.006 mg/kg and nivolumab 360 mg every 3 weeks per intravenous infusion. In study Part 2, the combination was given to patients with metastatic melanoma, RCC, urothelial carcinoma, non-small cell lung cancer or triple negative breast cancer. The RCC cohort enrolled 48 patients of which PD-L1 status was unknown for 4 patients, negative for 30 patients, and positive for 14 patients. Preliminary results showed in previously untreated RCC patients an overall ORR of 46%. The median time on study was 5.6 months. The PD-L1 negative patients ORR was 53% (9/17), while it was 29% (2/7) for PD-L1 positive patients [26]. In part 3 of the study, a triple combination will be attempted in order to assess safety, tolerability and efficacy (ORR): NKTR-214 0.006 mg/kg plus nivolumab 360 mg every 3 weeks, and ipilimumab 1mg/kg every 6 weeks. Study part 4 will plan to enrol more patients to further evaluate the triplet combination.

KEY POINTS AND CHALLENGES WITH DOUBLE IMMUNE CHECKPOINT BLOCKADE

Why double and not single-agent?

Double immune checkpoint blockade has been shown to be more powerful than single-agent immunotherapy across different tumour types, but also more toxic [27]. However, the superiority of immunotherapy doublets versus single agents has not yet been demonstrated for mRCC. It is known that nivolumab alone benefits previously treated metastatic renal cell carcinoma patients [22, 28], but the magnitude of the benefit with the addition of ipilimumab was just recently clarified. Recent data with pembrolizumab monotherapy in untreated mRCC patients has shown encouraging activity [29], with a confirmed ORR of 38.2% ($n = 42$; 95%CI 29.1–47.9) with 3 complete responses (2.7%) and 39 (35.5%) partial responses. The durable clinical response rate was 59.1% with a favourable safety profile. It seems clear that the addition of ipilimumab is more toxic and some patients may not need the combinations [14]. Further research to better understand which patients do really benefit the combination is required to avoid toxicities (financial and non-financial). Clinical trials with adaptive design such as TITAN (NCT02917772) or OMNIVORE (NCT03203473) will help to understand this issue.

What is the optimal duration of treatment?

There is evidence showing that patients who respond to immunotherapy and combination immunotherapy achieve durable responses and long-term survival [30]. Although immune checkpoint blockade is already a standard of care across different tumour types, there is no clear evidence about the duration of treatment on responders. In recent data from the Keynote-006 4-year survival

Table 3
Summary of Selected Studies of Double Immune checkpoint blockade

Phase	Trial	Year	Treatment ongoing	Title
Phase IIIb/IV	NCT02982954 Checkmate 920	January 2023	Nivolumab plus Ipilimumab	Safety Trial of Nivolumab Combined With Ipilimumab in Subjects With Previously Untreated, Advanced or Metastatic RCC
Phase III	NCT03138512 Checkmate 914	July 2023	Nivolumab plus Ipilimumab	A Phase 3 Randomized Study Comparing Nivolumab and Ipilimumab Combination vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse
	NCT03288532 RAMPART	December 2037	Active Monitoring or Durvalumab or Durvalumab plus Tremelimumab	An International Investigator-led Phase III Multi Arm Multi Stage Multi-centre Randomised Controlled Platform Trial of Adjuvant Therapy in Patients With Resected Primary Renal Cell Carcinoma (RCC) at High or Intermediate Risk of Relapse
Phase II	NCT03203473 OMNIVORE Study	November 2014	Nivolumab or Nivolumab plus Ipilimumab	Phase II Study of Optimized Management of Nivolumab Based on REsponse in Patients With Advanced Renal Cell Carcinoma
Phase I/II	NCT02335918	January 2020	Nivolumab plus Varlilumab	A Phase l/ll Dose Escalation and Cohort Expansion Study of the Safety, Tolerability and Efficacy of Anti-CD27 Antibody (Varlilumab) Administered in Combination With Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors
	NCT02089685 KEYNOTE-029	June 2020	Pembrolizumab plus Pegylated Interferon alfa-2b or Pembrolizumab plus Ipilimumab	Pembrolizumab Plus Pegylated Interferon alfa- 2b or Ipilimumab for Advanced Melanoma or Renal Cell Carcinoma: Dose-Finding Results from the Phase Ib Study
	NCT02983045 PIVOT-02	June 2021	Phase I: NKTR-214 + nivolumab Phase II: NKTR-214 + nivolumab+ipilimumab	A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) or in Combination With Nivolumab and Anti-CTLA4 Antibody (Ipilimumab) in Patients With Select Advanced or Metastatic Solid Tumors
Phase I	NCT02496208	September 2019	Cabozantinib plus Nivolumab or Cabozantinib plus Nivolumab plus Ipilimumab	A Phase 1 Study of Cabozantinib Plus Nivolumab (CaboNivo) Alone or in Combination With Ipilimumab (CaboNivoIpi) in Patients With Advanced/Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

(*Continued*)

Table 3
(*Continued*)

Phase	Trial	Year	Treatment	Title
	NCT01975831	December 2019	Durvalumab plus Tremelimumab	Phase 1 study to evaluate the safety and tolerability of MEDI4736 (durvalumab, DUR)+tremelimumab (TRE) in patients with advanced solid tumors.
	NCT02210117	November 2020	Arm A: Nivolumab or Arm B: Nivolumab plus Bevacizumab or Arm C: Nivolumab plus Ipilimumab	A Pilot Randomized Tissue-Based Study Evaluating Anti-PD1 Antibody or Anti-PD1 + Bevacizumab or Anti-PD1 + Anti-CTLA-4 in Patients With Metastatic Renal Cell Carcinoma Who Are Eligible for Cytoreductive Nephrectomy, Metastasectomy or Post-Treatment Biopsy
	NCT02614456	December 2021	Nivolumab plus Interferon-gamma	Combination Immunotherapy With Interferon- gamma and Nivolumab for Patients With Advanced Solid Tumors: A Phase 1 Study

and outcomes after cessation of pembrolizumab showed that 86% of the patients who completed pembrolizumab 2 years remained progression-free 20 months after the last dose of treatment [31]. Also, it has been shown that nearly 70% of the melanoma patients who obtained a complete or partial response and discontinued single-agent nivolumab due to toxicity maintained their responses despite the discontinuation of treatment [30, 32]. Moreover, this may be even more complex when it comes to patients who achieve a complete response. The clinical trial Keynote-001 showed that a high proportion of patients who achieved a complete response are able to maintain the response for a long time after the end of treatment, with an estimated 24 month disease-free survival of 89% [31]. Altogether, these results suggest stopping immune checkpoint blockade after a certain period of time on treatment could be a reasonable approach. However, further research on this topic is warranted.

How should we assess atypical responses?

Although there is lack of evidence, we are now familiar with the so known "pseudoprogression" which usually appears as a radiological progression with target lesion increase but without clinical deterioration. There are data suggesting that treatment beyond progression may be an option for some patients [33, 34]. However, there is also evidence sup-

porting that some patients may have hyperprogressive disease, but little is known about the mechanisms involved [35]. It has been speculated to be a result of immunotherapy but it has also been suggested to be the consequence of aggressive natural tumour behaviour. Nonetheless, knowledge on this field is scarce and further studies are needed to better understand and define which patients are more likely to rapidly progress and which ones will instead experience pseudoprogression and therefore benefit of treatment beyond radiological progression [36].

CONCLUSIONS

Several trials will be conducted in the next years to elucidate the impact of novel combinations on RCC therapy. In the near future, the patient's tumor biology should be matched with the best corresponding first line option among a handful of options: either monotherapy or combinations. Double immune checkpoint blockade has shown favourable results, but adverse effects should be taken into consideration. The most definitive evidence of double checkpoint inhibitor therapy on intermediate-poor risk patients with previously untreated advanced RCC are the results from Checkmate trial 214 with a remarkable 9% complete response rate.

Although we are now familiar with immune checkpoint blockade therapies, there are still some open questions. Optimal duration of treatment or unex-

pected radiological responses, including primary refractory disease, require further study.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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