Immunotherapy in renal cell carcinoma: latest evidence and clinical implications

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Abstract
Advances in understanding the mechanisms of tumour-induced immunosuppression have led to the development of immune-checkpoint inhibitors in cancer patients, including those with renal cell carcinoma (RCC). The optimal combination between immunotherapy and targeted agents (as well as the possible favourable sequential therapy of these two classes of drugs) remains an open question at this moment. Several trials are currently underway to assess the combination of anti-programmed-death 1 (PD-1) or anti-PD-ligand(L)1 agents with other immunotherapies or with anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs). In this editorial, we described the results of the most recent clinical trials on the use of immunotherapies in RCC and the emerging data on the research for reliable biomarkers of tumour response in this setting. In addition, we have focused on the role of the gut microbiome and tumour microenvironment in the development of future therapeutic strategies for RCC patients.

Keywords: immunoccheckpoint inhibitors, immunotherapy, PD-1, renal cell carcinoma, tyrosine kinase inhibitors.

Citation
Santoni M, Massari F, Di Nunno V, Conti A, Cimadamore A, Scarpelli M, Montironi R, Cheng L, Battelli N, Lopez-Beltran A. Immunotherapy in renal cell carcinoma: latest evidence and clinical implications. Drugs in Context 2018; 7: 212528. DOI: 10.7573/dic.212528

Introduction
Less than ten years ago, there were only a few drugs with demonstrated clinical efficacy in the management of metastatic renal cell carcinoma (mRCC) but without significant impact on clinical outcomes. However, in recent years, the approval of several agents has revolutionized treatment. Indeed, every new drug approved has provided a further step in the improvement of patient survival. Consequently, it is important to have a better understanding of tumour biological features as well as genetic assessment. Thus, we have discovered that renal cell carcinoma (RCC) involves a very large spectrum of tumours. Each of them is composed of a different spectrum of mutations and with different clinical behaviour. Clear cell RCC (ccRCC) accounts for approximately 75% of kidney cancer. In contrast, the other 25% of kidney cancer is classified as nonclear cell RCC (nccRCC). Of this last subgroup of tumours, the World Health Organization recognized a broad spectrum of over a dozen histopathological entities in 2016. Papillary renal cell carcinoma (pRCC) and chromophobe RCC (chRCC) are the most frequent subtypes of nccRCC; whereas, medullary, translocation and collecting duct RCC represent an infrequent diagnosis [1]. Each tumour subtype presents a specific and complex spectrum of gene and molecularly altered pathways resulting in a heterogeneous mixture of malignancies associated with different morphology, immunohistochemical features, clinical behaviour and prognosis.

Our growing understanding of the molecularly altered pathways related to cancer has led to the development of new classes of drugs that have rapidly replaced the first immunotherapies such as interleukin (IL)-2 and interferon-alfa (IFN-alfa) as the standard of care for RCC patients. Angiogenesis, the hallmark of RCC, is the first final target of several tyrosine kinase inhibitors (TKIs) (sunitinib, axitinib, sorafenib and pazopanib). After angiogenesis, the finding that deregulation of the PI3K–Akt–mTOR pathway, activated at different levels of the signalling cascade, drives RCC progression has led to the development of two mTOR inhibitors: everolimus and temsirolimus. Recently, the mesenchymal-epithelial transition...
(MET) and multityrosine kinases inhibitor cabozantinib has been included in clinical practice.

These drugs have led to an improvement in overall survival (OS) (sunitinib, pazopanib and cabozantinib) and in progression-free survival (PFS) (sunitinib, axitinib, cabozantanib, sorafenib, pazopanib, everolimus and temsirolimus), which was the endpoint of interest for FDA approval, until recently. All of these drugs showed a good safety profile combined with remarkable clinical activity in a disease that has always been difficult to treat [2–10].

**Immune-checkpoint inhibitors**

Although these drugs have significantly changed the course of this disease, the latest class of agents, the immune-checkpoint inhibitors, are predicted to provide further benefit. Programmed death receptor 1/programmed death receptor ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors target specific pathways related to the immune response, which are often hyperactivated by tumour cell interaction. By inhibiting these pathways, immune-checkpoint inhibitors could reactivate a specific immune response against tumour cells. The observation that RCC is related to a high mutation load and so maybe to high antigen expression has led to these drugs being tested at different stages of the disease. CheckMate 025 was the first large phase III clinical trial comparing the PD-1 inhibitor, nivolumab, to everolimus in patients with locally advanced or metastatic RCC who had progressed to at least one VEGF/VEGFR inhibitor. This study met its primary endpoint showing an OS benefit in patients receiving nivolumab. Furthermore, patients treated with immunotherapy showed a higher overall response rate (ORR) compared to everolimus with a considerable percentage of these achieving long-lasting response [11]. It is not surprising that the important results achieved in this trial led researchers to explore immunotherapy in other settings such as adjuvant/neoadjuvant stage and as first-line therapy [12–14]. Of note, Motzer and colleagues recently reported results of CheckMate 214, a phase III trial that tested the combination of ipilimumab and nivolumab over sunitinib in previously untreated patients with intermediate/poor-risk (according to IMDC) metastatic or locally advanced ccRCC. The combination resulted in a significant OS benefit (median overall survival not reached versus 26.0 months with sunitinib, hazard ratio [HR] 0.63) in this population of patients. In addition, ORR was significantly better in the combination arm (42% with 9% of CR) compared to sunitinib (27% with 1% of CR).

Regarding this last point, two different strategies have been adopted.

**Combination of an immune-checkpoint inhibitor and a VEGF inhibitor**

The combination of an immune-checkpoint inhibitor and a VEGF inhibitor has been evaluated in phase II trials. In the IMmotion150 study, 305 patients with locally advanced/mRCC and untreated RCC were randomized to receive atezolizumab (an anti-PD-L1 inhibitor) plus bevacizumab, atezolizumab alone or sunitinib. The combination arm resulted in a longer PFS compared to atezolizumab (6.1 months) and sunitinib arms with a higher percentage ORR in the combination arm. Of note, patients with PD-L1 positive expression (≥1%) showed a longer PFS (14.7 months) and higher ORR (46%) in the atezolizumab monotherapy arm [15].

The combination of two immune-checkpoint inhibitors has been recently tested in a large phase III trial: CheckMate 214. In this study, patients were randomized to receive nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) or sunitinib as first-line therapy. At the 2017 ESMO Conference, Escudier presented primary results after 17.5 months of follow-up showing that the ipilimumab plus nivolumab combination resulted in higher ORR and CR in intermediate/poor-risk patients. Of note, patients with intermediate/poor-risk disease and PD-L1 expression ≥1% showed higher ORR and PFS compared to sunitinib; whereas, patients with favourable category of risk (which showed lower PD-L1 expression) showed a longer PFS and a higher ORR with sunitinib [16].

These encouraging results may only be the ‘tip of the iceberg’ and could suggest that we are entering a new era for the management of mRCC. Nonetheless, even if immunotherapy represents a new hope for patients with mRCC, the relatively older targeted therapy is far from being abandoned. In other words, although CheckMate 025 showed that nivolumab is better than everolimus, there are other agents that are extremely effective after VEGF/VEGFR inhibitors progression; thus, the decision for second-line treatment should be weighted on the basis of the clinical outcome pursued as well as patient preference and drug toxicity profile. Immunotherapy has shown very interesting result in first-line therapy. Looking to CheckMate 214 results, it is probable that this positive effect could be restricted in patients with specific clinical features such as intermediate/poor-risk disease; whereas, patients with a favourable profile could benefit more from a standard treatment [14]. This would suggest that the worst clinical profile of the disease could be related to a high mutation load of tumour cells resulting in a higher antigen expression. In addition, preliminary data seem to indicate that these patients present a higher percentage of tumours with positive PD-L1 expression. However, to date, no mature data about the role of immunotherapy in favourable risk patients have been released. Furthermore, in an exploratory analysis of CheckMate 214, immunotherapy also showed a not-to-be-ignored clinical activity in patients with favourable risk (CR 11 versus 6%) even if the same combination was associated with a worse ORR (29 versus 52%) compared to sunitinib. Future studies will help us to better understand the role of PD-L1 as a prognostic and predictive response factor because, to date, we have strongly diverging information. Indeed, a meta-analysis of six published studies revealed that a higher level of PD-L1 expression increased the risk of death by representing, therefore, a negative prognostic factor [17]. Different to what was expected,
At present, we do have full knowledge of the underlying mechanisms of immune-checkpoint inhibitors-induced tumour response. To address this issue, Wei and colleagues investigated the effects of anti-PD-1 and anti-CTLA-4 inhibitors in human melanoma and murine tumour models [30]. They first revealed that these agents are able to target distinct tumour-infiltrating T-cell subpopulations. In particular, PD-1 blockade promotes the expansion of specific exhausted-like CD8 T-cell populations; whereas, CTLA-4 blockade induces both an ICOS+ Th1-like CD4 effector subset and exhausted-like CD8 T cells [30].

The complex interplay of inflammatory mediators and signalling pathways is absolutely crucial for RCC development and response to therapy [18–22] (Figure 1). Neutrophils, lymphocytes and macrophages have been implicated in promoting tumour angiogenesis and metastatic spread, as well as in the formation of pre-metastatic niches and in primary and acquired drug resistance [18–22]. In this scenario, the checkpoint molecules have gained wide interest since the introduction of anti-CTLA-4 and anti-PD-1/PD-L1 agents into daily clinical practice [23]. Beyond PD-1 and CTLA-4, a variety of molecules are emerging as potential therapeutic immunotargets in RCC [24]. This list includes the V-domain immunoglobulin containing suppressor of T-cell activation (VISTA), which has been recently shown to exert its inhibitory activity by acting as a ligand on antigen presenting cells (APCs) and as a receptor on T cells [25–27], chemokine receptors [28], the soluble lymphocyte-activation gene-3 (LAG-3), 4-1BB, B and T lymphocyte attenuator (BTLA) and OX40 (CD134) [29].

Future challenges

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This evidence strongly supports the results of different trials exploring this combination therapy in different diseases and favours the combined use of current and future checkpoint inhibitors in cancer patients, which seems to be characterized by a good tolerable safety profile [14,31–33].

The results obtained in recent years have raised enormous enthusiasm in cancer researchers, aimed at identifying, isolating and validating biomarkers associated with the dynamics of the tumour environment and the therapeutic response [17,34,35]. Indeed, tumour responsiveness varies according to the mutation load and the expression of immunotargets in the tumour environment, which is variable in the different phases of RCC development and progression [36]. Based on this evidence, assessing the expression of PD-1/PD-L1 or other emerging immunotargets only at the diagnosis of metastatic disease may not reflect tumour dynamicity. To improve the feasibility and reduce the clinical impact of re-biopsy, assessing biomarkers on circulating tumour cells (CTCs) or exosomes [37] may represent a noninvasive strategy that can be performed several times during cancer therapy to reflect changes that occurred in the tumour environment. The early identification of validated biomarkers will be crucial to definitively carry immunotherapy into the era of precision medicine and to optimize the cost-effectiveness of these agents in cancer patients [38,39].

More recently, Routy and colleagues revealed that primary resistance to immune-checkpoint inhibitors can be correlated with abnormal gut microbiome composition [40]. In this study, the effectiveness of PD-1 blockade was enhanced by transplanting faecal microbiota from responder cancer patients into germ-free or antibiotic-treated mice [40], thus representing another step on the way to personalized and precision immunotherapy in cancer patients.

Another factor that is fundamental to improve the efficacy of immunotherapy in RCC patients is a better understanding of the immunological effects of TKIs and mTOR inhibitors [18,41]. Indeed, these agents can indirectly exert their anti-tumour activity by targeting immune cells in the RCC microenvironment [18], and this should be considered to combine or sequence them with currently available and future immunotherapies. In this regard, sunitinib has been shown to inhibit the colony forming units (CFUs) driven by GM-CSF and FLT3 ligand (FLT3L) [42] as well as dendritic cell antigen presentation [40] (by decreasing the secretion of cytokines and the expression of MHC and CD1a molecules), to suppress the myeloid-derived suppressor cells (MDSCs, involved in RCC progression and drug resistance), to enhance tumour cell sensitivity to natural killer (NK) cell killing [43] and to reduce the total count of CD3 and CD4 T cells and regulatory T cells [44,45]. On the other hand, pazopanib showed lower inhibitory potency and affinity against FLT3 and c-kit compared to sunitinib [46]. Interestingly, we previously showed that axitinib can increase the surface NKG2D ligand expression, thus promoting NK cell recognition and degranulation in A-498 RCC cells in a ROS-dependent manner [47]. At present, little evidence is available on the immunomodulatory effects of cabozantinib and lenvatinib, both of which were recently introduced into RCC clinical practice. With regard to the association between immunotherapy and TKIs, the association between atezolizumab and both bevacizumab [48] and cabozantinib [49] as well as pembrolizumab and axitinib [50] has shown promising results in terms of clinical activity and safety profile – thus justifying the planning of several different

| Trial            | Treatment arms                                      | n   | Setting | Estimated primary completion date |
|------------------|----------------------------------------------------|-----|---------|-----------------------------------|
| NCT02811861      | Sunitinib versus lenvatinib + everolimus versus lenvatinib + pembrolizumab | 735 | First line | October 2019                      |
| NCT02684006      | Avelumab + axitinib versus sunitinib               | 830 | First line | December 2018                     |
| NCT03141177      | Nivolumab + cabozantinib versus sunitinib         | 630 | First line | September 2019                    |
| NCT02420821      | Atezolizumab + bevacizumab versus sunitinib       | 915 | First line | July 2020                         |
| NCT02853331      | Pembrolizumab + axitinib versus sunitinib         | 840 | First line | January 2020                      |
large trials exploring these associations in metastatic/locally advanced RCC (Table 2).

**Conclusions**

Optimizing the combination of immunotherapy and target agents, as well as the possible favourable sequence of treatment between these two classes of drugs, remains as open questions at this moment. We have only few data provided from IMmotion150, which demonstrated that association between a PD-L1 inhibitor and bevacizumab is feasible with a satisfactory safety profile. However, we do not know if this association results in an effective clinical benefit from our patients. Finally, it is important to observe that all the cited studies explored immunotherapy in patients with ccRCC and the role of immunotherapy still remains unknown in nccRCC.

There are several questions that need to be answered. It is undeniable that immunotherapy represents a revolution for the management of RCC resulting in a dynamic and evolving scenario. Future studies will increase our knowledge about the role of immunotherapy in this no-more orphan disease.

**Contributions:** MS and FM conceived and designed the study and contributed equally to the preparation of the manuscript. VdN, AcO and AcI conducted the structured literature review. MSc, RM, LC, NB and ALB drafted the manuscript. All authors analysed and interpreted the data, critically revised successive drafts of the manuscript and have approved the final version.

**Disclosure and potential conflicts of interest:** The authors declare no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/06/dic.212528-COI.pdf

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**Article URL:** http://www.drugsincontext.com/immunotherapy-in-renal-cell-carcinoma-latest-evidence-and-clinical-implications

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**Provenance:** invited; externally peer reviewed.

Submitted: 9 March 2018; Peer review comments to author: 27 March 2018; Revised manuscript received: 11 April 2018; Accepted: 16 April 2018; Publication date: 5 June 2018.

**Drugs in Context** is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 3PT. BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

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