Curr. Treat. Options in Oncol. (2019) 20: 41
DOI 10.1007/s11864-019-0638-1

Genitourinary Cancers (S Gupta, Section Editor)

The Changing Landscape of Management of Metastatic Renal Cell Carcinoma: Current Treatment Options and Future Directions

Nicholas J. Salgia
Yash Dara
Paulo Bergerot, MD
Meghan Salgia, BSc
Sumanta K. Pal, MD[*]

Address
[*]Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA, 91010, USA
Email: spal@coh.org

Published online: 1 April 2019

This article is part of the Topical Collection on *Genitourinary Cancers*

Keywords Renal cell carcinoma · VEGF · Immunotherapy · PD-1 · PD-L1 · VEGF-TKI

Opinion statement

For the practicing clinician, the dilemma becomes how most appropriate to sequence the aforementioned regimens. It is challenging to be dogmatic, as there are no comparative studies juxtaposing novel front-line options directly—all of the available studies utilize a comparator arm of sunitinib. With this in mind, the selection of front-line therapy with a patient with mRCC should involve a thorough discussion of both efficacy and safety of available options. The oncologist must also weigh their ability to manage complex immune-related adverse events that can emerge from checkpoint inhibitors, particularly with dual regimens such as nivolumab/ipilimumab. For the patient with good-risk disease, VEGF-directed therapies should remain a component of treatment. The data from CheckMate-214 does not support the use of nivolumab/ipilimumab in this setting, and in fact suggests superiority with the approach of VEGF-TKIs. Until regulatory decisions have been made around bevacizumab/atezolizumab and axitinib/avelumab, sunitinib and pazopanib remain

options for patients with good-risk disease, although cabozantinib should be a consideration as well. Although the CABOSUN study did not include patients with good-risk disease, it is important to bear in mind that this was more of a pragmatic decision—inclusion of these patients in the original design could have potentially lengthened the extent of necessary follow-up. From a mechanistic standpoint, there is no reason to assume that cabozantinib would not also achieve superiority to sunitinib in patients with good-risk disease. For patients with intermediate- and poor-risk disease, cabozantinib and nivolumab/ipilimumab represent the only reasonable options thus far that have achieved regulatory approval. As previously noted, nivolumab/ipilimumab has proven benefit in this setting, but should be used only by the oncologist who has ready access to subspecialists who can aid in managing immune-related adverse events. Prompt recognition of colitis, hepatitis, and other sequelae from these therapies is critical, as these toxicities can be life-threatening. If such resources are not available, then cabozantinib should be considered. Cabozantinib should further be contemplated in the subset of patients with bony metastatic disease, where it appears to offer substantial control. Of course, it also represents an option for those individuals who have contraindications to immunotherapy, such as rheumatologic and autoimmune disorders.
When combinations of VEGF-directed and immunotherapies are approved, the clinician will have an even more complicated dilemma. Regimens such as a bevacizumab/atezolizumab offer an exceptional safety profile, which may weigh heavily in frail patients who cannot tolerate the side effect profile associated with VEGF-TKIs.

Introduction

In the 1990s, the prognosis for metastatic renal cell carcinoma (mRCC) was grim. At that point in time, the mainstay of treatment was cytokine-based therapies. With agents such as interferon-alfa (IFN-α), durable responses were rarely achieved, and median survival was roughly 1 year [1]. Agents such as interleukin 2 (IL-2) were also used at that time but produced modest response rates in a small subset of individuals. Durable responses were only seen in 5–7% of a carefully selected patient population [2, 3]. This had changed in the mid-2000s with the advent of targeted therapies for mRCC. The introduction of vascular endothelial growth factor (VEGF) receptor inhibitors, such as sorafenib and sunitinib, from 2005 onwards marked a substantial evolution in the management of mRCC [4]. These agents produced response rates approaching 40% in the front-line setting, with progression-free survival (PFS) estimates in the range of 9–12 months [5]. However, none of these agents were deemed curative, and further salvage approaches were developed beyond this. Initially, salvage therapy involved treatment with mammalian targeted rapamycin (mTOR) inhibitors such as everolimus [6]. These agents produced modest response rates at best. The salvage approach evolved, however, to include multi-targeted kinases such as cabozantinib and immunotherapeutic strategies such as programmed death-1 (PD-1) inhibitors [7, 8].

While these second-line therapies produced impressive results as salvage options, there was a temptation to move these therapies into the front-line setting. Agents such as cabozantinib demonstrated clinical benefit in a large proportion of patients, and agents such as nivolumab produced durable responses in a subset of individuals. Over the past 2–3 years, we have seen the evolution of clinical trials that test agents such as cabozantinib front-line. Furthermore, the strategy of combined immunotherapeutic approaches with cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibition has been tested. Most recently, there has been an opportunity to explore VEGF inhibitors and immunotherapeutic agents in combination. These emerging studies will be the subject of the current review.

Dual checkpoint inhibition

Dual checkpoint inhibition was first explored in the context of melanoma, producing impressive results [9]. In RCC, the Checkmate-214 trial explored the combination of nivolumab and ipilimumab [10••]. This study included 1082 patients, and randomized them to receive either sunitinib on a standard schedule or the combination of nivolumab with ipilimumab. Notably, the dose of nivolumab with ipilimumab was distinct from that explored in metastatic melanoma. Early phase 1 experiences suggested that a higher dose of nivolumab and lower doses of ipilimumab produced a more tolerable safety profile, and therefore the doses used in this phase 3 experience were nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg [11]. Patients in this study had previously untreated disease and were stratified by international mRCC database consortium (IMDC) criteria [12]. The primary endpoint of the study was set in patients with intermediate- and poor-risk disease. Amongst the 77% of patients characterized as having intermediate- or poor-risk disease, it was noted the response rates were higher with nivolumab and ipilimumab versus sunitinib (42% vs. 27%, $p < 0.0001$). The rates of complete response were also higher with nivolumab and ipilimumab, totaling 9% with this regimen. Overall survival was also improved with the combination of nivolumab with ipilimumab (not reached [NR] vs. 26 months, $p < 0.0001$). There were several differences noted in the toxicity profiles of nivolumab and ipilimumab that are worth noting. First, although immunotherapy is typically conceived as being quite tolerable, more patients discontinued nivolumab with ipilimumab versus sunitinib (24% vs. 12%). Multiple grade 3–4 immune-related adverse events were noted, including diarrhea, hepatitis, and hypophysitis. Approximately 60% of patients required corticosteroids for management of adverse events.

It is also important to note that patients receiving nivolumab and ipilimumab with good-risk disease did not fare as well. With this population, there was a substantial trend towards improvement in PFS with sunitinib versus nivolumab and ipilimumab, amounting to 25.1 months versus 15.3 months ($p < 0.0001$). Response rates were almost double with sunitinib versus nivolumab and ipilimumab amongst these patients, with 52% of patients receiving sunitinib receiving a partial or complete response versus 29% of those receiving nivolumab with ipilimumab. Survival data still has not been presented in this particular cohort.

Multikinase inhibitors

The CABOSUN clinical trial evaluated the multikinase agent cabozantinib [13•, 14]. Beyond VEGF receptors, cabozantinib inhibits targets including MET and AXL, both of which are associated with resistance to VEGF-directed therapy. In the CABOSUN clinical trial, cabozantinib at the standard dose of 60 mg was compared with sunitinib in a standard dosing schedule. Patients in this protocol, unlike Checkmate-214, specifically had intermediate and poor-risk disease—no patients with good-risk disease were included. As with the Checkmate-214 trial, risk stratification was based on IMDC criteria. The primary

endpoint of the study was PFS. The study met this primary endpoint with an improvement in PFS from 8.6 months with cabozantinib versus 5.3 months with sunitinib. The study initially reported a response rate of 46% with cabozantinib versus 18% with sunitinib. The study was initially criticized because it did not have independent review of radiographic findings, and therefore, an aggressive effort was made to collect scans in the context of this cooperative group trial. On independent review, it was determined that response rate with cabozantinib was 20% (95% confidence interval [CI] 12.0–30.8) versus 9% with sunitinib (95% CI 3.7–17.6). Overall survival was numerically higher with cabozantinib than sunitinib (26.6 months vs 21.2 months; hazard ratio [HR] 0.80; CI 0.53–1.21), but this difference was not statistically significant.

Adverse events encountered in the context of this study were not unexpected from previous experiences with cabozantinib. The most frequent toxicities included diarrhea, liver function test changes, fatigue, and decreased appetite. Although some data related to response was missing for the confirmatory analyses, it is worth noting that only 18% of patients on cabozantinib developed primary progressive disease. Subset analyses also demonstrated that cabozantinib had exceptional activity in the context of bony metastatic disease, with a hazard ratio for benefit that was similar in patients with bony metastatic disease versus not.

Combinations of VEGF monoclonal antibodies and checkpoint inhibition

Given the activity of VEGF-directed therapies and checkpoint inhibition separately in mRCC, there is logical interest in combining these classes of therapies for this disease. This has been tested in a prospective fashion in the Phase III IMmotion 151 clinical trial [15•]. This study took patients with previously untreated RCC with either clear cell or sarcomatoid histology. Mandatory tissue assessments for programmed death ligand 1 (PDL-1) staining were performed. Patients were stratified based on MSKCC risk score, the presence or absence of liver metastases, and PDL-1 expression using a 1% threshold. In total, 915 patients were randomized to receive either bevacizumab with atezolizumab every 3 weeks intravenously or sunitinib on a standard schedule. Although published results from this study are not available, initial data has been presented. The study had two primary endpoints. The first was rather unique, reflecting PFS in a PDL-1 positive population, again using a 1% threshold. Overall survival in the intention-to-treat population was the second primary endpoint, and this data has not yet been presented. Ultimately, the study met its primary endpoint with an improvement in PFS from 7.7 months with sunitinib to 11.2 months with the combination of bevacizumab with atezolizumab ($p = 0.02$). In the intention-to-treat population, there was also a compelling trend towards benefit with the PFS of 8.4 months with sunitinib versus 11.2 months with bevacizumab and atezolizumab. Objective response rate was slightly higher with bevacizumab and atezolizumab versus sunitinib (43% vs. 35%). It was also appreciated that the complete response rate with the combination was higher (9% vs.

4%) within the PDL-1 positive population. At first report, it does appear as though the responses associated with a combination of bevacizumab and atezolizumab are reasonably durable. The study did raise questions, however, when an independent radiographic review was performed. On independent review, it was noted that the benefit in terms of PFS with bevacizumab with atezolizumab was perhaps more marginal (8.9 months vs. 7.2 months), but the trend towards benefit was still appreciated in both the PDL-1 positive and intention-to-treat populations. Notably, complete response rates approached 15% on independent review in the PDL-1 positive population. Assessment of PDL-1-based subgroups revealed that higher PDL-1 expression appeared to be associated with greater clinical benefit from the combination of bevacizumab with atezolizumab. For instance, in the population of patients with greater than 10% expression of PDL-1 in tissue, the hazard ratio for benefit was 0.56, as compared with 0.93 in the population of patients with less than 1% PDL-1 expression. Although mature overall survival data has not been reported yet in the context of IMmotion 151, it appeared to be a compelling trend at the time of initial presentation with a hazard ratio of 0.68 (95% CI 0.46–1.00) in the PDL-1 positive population. In the intention-to-treat population, again where the data is not mature, a trend was also observed with a hazard ratio of 0.81 favoring bevacizumab with atezolizumab (95% CI 0.63–1.03; $p = 0.09$).

The safety profile of the combination of bevacizumab with atezolizumab was also presented in this preliminary analysis [15•]. With a median treatment duration of 12 months with bevacizumab and atezolizumab and 9.2 months with sunitinib, grade 3/4 adverse events appeared to be lower with the combination of therapies at 40% versus 54% with sunitinib. Furthermore, the rate of treatment related discontinuation on the basis of adverse events was lower with the combination of bevacizumab and atezolizumab versus sunitinib (5% vs. 8%). Grade 3/4 immune toxicities such as hypothyroidism, hyperthyroidism, adrenal insufficiency, colitis, pneumonitis, and liver dysfunction occurred in a very small proportion of patients in this experience. Furthermore, initial quality of life analyses suggested that bevacizumab with atezolizumab had a prolonged time-to-symptom interference versus sunitinib therapy. These results weigh heavily in favor of bevacizumab with atezolizumab versus sunitinib, but a regulatory decision on this combination is still pending.

Dovetailing on impressive phase I data, there has been substantial interest also in combinations of small molecules VEGF-inhibitors with PD-1 and PD-L1 inhibitors. The phase III JAVELIN-101 trial assessed axitinib and avelumab [16•]. Similar to atezolizumab, avelumab is a monoclonal antibody with affinity for PD-L1. Patients in this study had mRCC with a clear cell component and no prior therapy, and were randomized to receive a standard dose of axitinib at 5 mg oral twice daily with avelumab or a standard dose of sunitinib. As in the pivotal trials of axitinib alone, the dose of axitinib could be increased to a maximum of 5 mg oral twice daily. The co-primary endpoints of the study were PFS in the PD-L1 positive group based on central review, and OS in the same population. Secondary endpoints included PFS and OS in the overall study population.

At the time of most recent presentation, the study had achieved the primary endpoint of improved PFS with axitinib/avelumab in PD-L1 positive patients

(13.8 months vs 7.2 months; $p < 0.0001$). A similar improvement was seen in the overall population in PFS (13.8 months vs 8.4 months; $p = 0.0001$). Investigator assessments of PFS varied little from central assessments in the PD-L1 positive and overall study populations. At this early juncture, OS was immature. A slight trend towards improved survival was seen with axitinib/avelumab versus sunitinib (HR 0.78; $p = 0.0679$), but longer follow-up will be needed to identify whether this trend will ultimately bear statistical significance.

The toxicity profile of axitinib with avelumab was acceptable, with a cumulative rate of grade 3/4 adverse events that was similar to that of sunitinib alone (51% and 48%, respectively). The most common side effects with the combination were diarrhea, hypertension, fatigue, and hand-foot syndrome. Notably, hypertension was the only grade 3/4 adverse event occurring in more than 10% of patients receiving the combination. Rates of discontinuation of both study drugs were low (4%), and limited treatment-related deaths were observed.

Conclusions

A current review of mRCC therapies is a challenging endeavor due to continuous emergence of phase III data. Just as this review is being written, a press release has been issued for the KEYNOTE-426 study [17]. The study, similar in design to JAVELIN-101, randomized patients to the combination of axitinib with pembrolizumab or sunitinib. The press released data indicates that axitinib with pembrolizumab was superior to sunitinib across risk groups and independent of PD-L1 status. These data are sure to change our currently proposed algorithms (Table 1). Still on the horizon are phase III combination studies of lenvatinib with pembrolizumab and cabozantinib with nivolumab. In all likelihood, the regimen with the most potent VEGF-backbone will emerge as the most efficacious regimen.

The holy grail in mRCC therapy remains the development of biomarkers. Paradoxically, in a disease where all of the conceivable treatment strategies are targeted, there are no targeted approaches that are currently employed. As we have outlined, clinical considerations such as safety and efficacy steer much of current decision-making. Multiple biomarkers have been contemplated. PD-L1 status remains of prime interest. In CheckMate-214, patients deemed PD-L1

Table 1. Potential algorithm incorporating novel regimens for mRCC

Treatment	First-line	Second-line
Good risk	Bevacizumab/atezolizumab	Cabozantinib
	Axitinib/avelumab	
	Cabozantinib*	Nivolumab
Intermediate/poor-risk	Bevacizumab/atezolizumab	Cabozantinib
	Nivolumab/ipilimumab	
	Axitinib/avelumab	
	Cabozantinib*	Nivolumab

*For special populations (e.g., bony metastases)

positive (amounting to roughly one quarter of the study population) did appear to have a greater proportional benefit in both PFS and OS. Similarly, higher PD-L1 staining was associated with improved outcomes with bevacizumab/atezolizumab in the Immotion151 clinical trial. For the clinician who is undecided between current options (e.g., cabozantinib versus nivolumab/ipilimumab), it possible that PD-L1 status could be used as a deciding factor.

Biomarkers at earlier stages of development include inflammatory signatures (developed in the context of trials assessing bevacizumab/atezolizumab), but because these signatures have not been consistently applied in other studies, it is challenging to ascertain their optimal use [18]. Novel platforms such as the microbiome are emerging as a potential tool to identify patients with a higher likelihood of response to therapy, but from a clinical perspective, these biomarkers are in a relative infancy [19, 20]. At the moment, the decision around front-line therapy remains in the hands of the clinician.

Compliance with Ethical Standards

Conflict of Interest

Nicholas J. Salgia declares that he has no conflict of interest. Yash Dara declares that he has no conflict of interest. Paulo Bergerot declares that he has no conflict of interest. Meghan Salgia declares that she has no conflict of interest. Sumanta K. Pal has received compensation from Genentech, Aveo, Eisai, Roche, Pfizer, Novartis, Exelixis, Ipsen, Bristol-Myers Squibb, and Astellas for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999;17(8):2530–40.
2. Belldegrun A, Tso CL, Zisman A, Naitoh J, Said J, Pantuck AJ, et al. Interleukin 2 gene therapy for prostate cancer: phase I clinical trial and basic biology. Hum Gene Ther. 2001;12(8):883–92.
3. Atzpodien J, Kirchner H, Jonas U, Bergmann L, Schott H, Heynemann H, et al. Interleukin-2- and interferon alfa-2a-based immunochemotherapy in advanced renal cell carcinoma: a prospectively randomized trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). J Clin Oncol. 2004;22(7):1188–94.
4. Alsharedi M, Katz H. Check point inhibitors a new era in renal cell carcinoma treatment. Med Oncol. 2018;35(6):85.
5. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34.
6. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449–56.
7. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231–7.

8. Osanto S, van der Hulle T. Cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor targeted therapy: clinical trial evidence and experience. Ther Adv Urol. 2018;10(3):109–23.
9. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90.
10.•• •• Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90.
Large scale clinical trial exploring dual checkpoint inhibition in treatment of RCC.
11. Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, 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(34):3851–8.
12. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, 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(34):5794–9.
13.• • Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, 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.
Clinical trial evaluating use of multikinase inhibitor, cabozantinib, targeting VEGF receptors, MET, and AXL.
14. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. J Clin Oncol. 2017;35(6):591–7.
15.• Motzer RJ, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). J Clin Oncol. 2018;36(6_suppl):578.
Large clinical trial reporting efficacy of combined VEGF- and checkpoint inhibitor therapies.
16.• Motzer RJ, Penkov K, Haanen JBAG, Rini BI, Albiges L, Campbell MT, et al. LBA6_PRJAVELIN renal 101: a randomized, phase III study of avelumab + axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC). Ann Oncol. 2018;29(suppl_8):mdy424.036.
Large clinical trial reporting efficacy of combined VEGF- and checkpoint inhibitor therapies.
17. Press Release: Merck's KEYTRUDA® (pembrolizumab) in combination with Pfizer's Inlyta® (axitinib) significantly improved overall survival (OS) and progression-free survival (PFS) as first-line therapy for advanced or metastatic renal cell carcinoma (Available at: https://investors.merck.com/news/press-release-details/2018/Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Pfizers-Inlyta-axitinib-Significantly-Improved-Overall-Survival-OS-and-Progression-free-Survival-PFS-as-First-Line-Therapy-for-Advanced-or-Metastatic-Renal-Cell-Carcinoma/default.aspx; last accessed 21 Dec 2018.
18. McDermott DF, Huseni MA, Atkins MB, Motzer RJ, Rini BI, Escudier B, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med. 2018;24(6):749–57.
19. Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H, et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol. 2018;29(6):1437–44.
20. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91–7.

Publisher's note