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Update on the treatment of metastatic renal cell carcinoma

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Abstract

Metastatic renal cell cancer (mRCC) management has undergone a paradigm shift in recent decades. The first revolution came with the emergence of vascular endothelial growth factor inhibitors; there was a second wave with the unprecedented success of checkpoint inhibitors, and then the latest approach, which is becoming the new care standard in mRCC, of combining these two strategies in different ways. Updated results of Checkmate-214 after 42 mo of follow-up were consistent with previously published results showing the superiority of nivolumab/ipilimumab over sunitinib in progression free survival (PFS), overall survival (OS), and objective response rate (ORR) in intermediate and high-risk patients. However, several studies presented at the American Society of Clinical Oncology 2020 suggested that the best place, and so far, the only one for nivolumab/ipilimumab is the frontline setting. The update on Keynote-426 after 23 mo of follow-up showed no superiority of pembrolizumab/axitinib over sunitinib in favorable-risk mRCC, suggesting that it should no longer be the first line of choice in low-risk patients. Finally, the phase III Checkmate 9ER trial results revealed the superiority of nivolumab/cabozantinib *vs* sunitinib in PFS, OS, and ORR, providing a new first-line option among all International Metastatic RCC Database Consortium risk patients. Some phase II clinical trials also presented this year showed promising results with new combination therapies such as nivolumab/sitravatinib, cabozantinib/atezolizumab, and lenvatinib/pembrolizumab, providing promising grounds upon which to start phase III studies. In addition, other works are using novel therapeutic agents with different mechanisms of action, including telaglenastat (a glutaminase inhibitor), entinostat [an inhibitor of histone deacetylases (HDACs)],

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and olaparib and talazoparib, poly(ADP-ribose) polymerase inhibitors widely used in other tumors. However, some questions regarding mRCC management still need to be addressed, such as head-to-head comparisons between the current options, treatment sequencing, non-clear cell mRCC, and the role of biomarkers to ascertain the best treatment choice.

Key Words: Metastatic renal cell carcinoma; Systemic treatment; Immune checkpoint inhibitors; Antiangiogenic; Update; Biomarkers

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Core Tip: Kidney cancer therapeutics is a fast-changing field, and the outcome of metastatic renal cell carcinoma (mRCC) has thus improved considerably in recent years with the introduction of different combinations of immune checkpoint and vascular endothelial growth factors inhibitors. State-of-the-art systemic therapy regimens must be addressed to be in a position to offer patients the best options. The aim of this editorial is to provide an update and insight on future directions on mRCC management.

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INTRODUCTION

Historically, the therapeutic strategy for metastatic renal cell carcinoma (mRCC) relied on cytokines. These drugs had a moderate response rate and were associated with substantial side effects[1].

Since then, the treatment of mRCC has improved considerably with the introduction and regulatory approval of agents that block vascular endothelial growth factor (VEGF) or mechanistic target of rapamycin (mTOR) pathways and significantly improve objective response rates (ORR) and/or median progression free survival (PFS) compared to previous treatment approaches. Since 2005, the United States Food and Drug Administration and the European Medicines Agency have approved VEGF receptors; tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib; the anti-VEGF antibody bevacizumab (in combination with interferon); and mTOR inhibitors everolimus and temsirolimus to treat mRCC[2].

Despite the notable efficacy of these targeted therapies, which changed the treatment landscape, tumor resistance to TKI made it necessary to investigate different treatment mechanisms. In this context, stimulating the immune system through drugs targeting the so-called checkpoint pathways through the blockage of programmed cell death 1 (PD1), programmed cell death ligand 1 (PDL1), and the cytotoxic T-lymphocyte antigen 4 have been tested in RCC with successful results. As a result, nivolumab was the first immune checkpoint inhibitor (ICI) approved based on data from the phase III Checkmate 025 study of nivolumab *vs* everolimus in patients who had received prior antiangiogenic therapy for mRCC[3].

Combination therapies, based on the rationale that using drugs that work by different mechanisms may decrease the likelihood of cancer resistance, emerged in an effort to improve outcomes. The treatment landscape for first-line therapy has thus changed dramatically in recent years with the publication of a phase III clinical trial (CT) that showed three combinations' advantage over sunitinib: (1) Nivolumab/ipilimumab (Checkmate-214), which proved a higher overall survival (OS), PFS, and ORR in intermediate and high-risk patients[4,5]; (2) Avelumab/axitinib, which showed longer PFS (JAVELIN Renal 101)[6]; and (3) Pembrolizumab/axitinib, which proved higher in OS, PFS, and ORR among all International Metastatic RCC Database Consortium (IMDC) risk patients (KEYNOTE-426)[7]. This work has led to the current standard practice recommendations set in the European Association of Urology[8],

Table 1 Results from clinical trials

Checkmate 214	Nivolumab/ipilimumab (n = 425)	Sunitinib (n = 422)
Minimum follow-up	42 mo	42 mo
OS IP	52%; 47 (35.6-NE) mo	39% 26.6 (22.1-33.5) mo
ORR IP	42% (37-47)	26% (22-31)
CR IP	10%	1%
Checkmate 025	Nivolumab (n = 410)	Everolimus (n = 411)
Minimum follow-up	5 yr	5 yr
OS	26% (22.2-29.8)	18% (17.6-22.1)
ORR	23% (19-27)	4% (2-7)
mDOR	18.2 (12.9-25.8) mo	14 (8.3-19.2) mo
Keynote 426	Pembrolizumab/axitinib (n = 432)	Sunitinib (n = 429)
Minimum follow-up	23 mo	23 mo
OS	74%	66%
	HR: 0.68; 95%CI: 0.55-0.85; <i>P</i> < 0.001	
PFS favorable risk	20.8 (15.4-28.8) mo	18 (12.5-20.8) mo
Checkmate 9ER	Nivolumab/cabozantinib (n = 323)	Sunitinib (n = 328)
Minimum follow-up	10.6 mo	10.6 mo
PFS	16.6 (12.5-24.9)	8.3 (7-9.7)
OS	NR (NE)	NR (22.6-NE)
ORR	55.7% (50.1-61.1)	27% (22.4-32.3)
CR	8%	4.6%
Adverse events grades 3-5	60.6%	50.9%

PFS: Progression free survival; OS: Overall survival; ORR: Objective response rate; CR: Complete response; mDOR: Median duration of objective response; NR: No results; NE: Not ended; HR: Hazard ratio; CI: Confidence interval; IP: Poor risk.

ESMO[9], and National Comprehensive Cancer Network guidelines[10].

UPDATES IN AMERICAN SOCIETY OF CLINICAL ONCOLOGY GENITOURINARY, AMERICAN SOCIETY OF CLINICAL ONCOLOGY, AND ESMO CONGRESSES

American Society of Clinical Oncology genitourinary 2020

Updated results of Checkmate 214 after 42 mo of follow-up have been presented[11]. These results were consistent with the superior performance of nivolumab/ipilimumab *vs* sunitinib in intermediate and poor-risk patients. An OS of 52% with nivolumab/ipilimumab *vs* 39% with sunitinib [hazard ratio (HR): 0.66; 95% confidence interval (CI): 0.55-0.80]; ORR of 42% with nivolumab/ipilimumab *vs* 26% with sunitinib (*P* = 0.0001); and complete response (CR) of 10% with nivolumab/ipilimumab *vs* 1% with sunitinib have been observed (Table 1).

The final analysis of Checkmate 025 after 5 years of follow-up was also presented [12]. An OS of 26% with nivolumab *vs* 18% with everolimus; ORR of 23% with nivolumab *vs* 4% with everolimus; and median duration of objective response (mDOR) of 18.2 mo with nivolumab *vs* 14 mo with everolimus were presented (Table 1).

The first phase II in-human study of the hypoxia-inducible factor (HIF)-2 α inhibitor Midkine (MK)-6482 was also presented[13]. This is an oral agent with antiangiogenic activity. Preliminary results on 55 patients treated in the second, third, and fourth line settings revealed a disease control of 80%, ORR of 24%, and tumor reduction of 67%. The median PFS was 11 mo. After 1 year, 30% continued under treatment, which was

well tolerated. These results provided promising grounds upon which to start the phase III trial (MK-6482 005 against everolimus).

Finally, another interesting approach was the combination of nivolumab/sitratinib, a novel TKI that modulates the tumor microenvironment in order to render it more responsive to immunotherapy[14]. Administration in the first, second, and third line settings ($n = 40$) demonstrated a tumor reduction of 92%, disease control of 90%, ORR of 39%, and PFS of 10.5 mo. Again, this is promising data for the next phase III trial.

American Society of Clinical Oncology 2020

Updated data for Keynote-426 after a minimum follow-up of 23 mo were presented [15]. OS was 74% with pembrolizumab/axitinib *vs* 66% with sunitinib. Patients with favorable-risk disease no longer presented a significant difference in OS or PFS, with a median PFS of 20.8 mo with pembrolizumab/axitinib and 18 mo with sunitinib. However, patients with IMDC intermediate or poor-risk disease showed significant differences in OS and PFS with an HR of 0.63 for OS and 0.69 for PFS. The CR rate increased from 6% at 12 mo of follow-up[16] to 9% after 23 mo. A new *post hoc* analysis of the relationship between depth of response and OS showed that in patients receiving pembrolizumab/axitinib, deeper responses, as measured by percent shrinkage of target lesions, correlated to better OS (See Table 1).

Two studies, the OMNIVORE study[17] ($n = 83$) and the HCRN GU16-260 study[18] ($n = 123$), were presented to investigate whether treating mRCC patients with nivolumab initially and later adding ipilimumab in patients with either stable or progressive disease would be as effective as an upfront combination therapy. The results showed only 4% and 11% additional partial responses, respectively, suggesting that delaying treatment with ipilimumab decreased the overall efficacy of upfront combination treatment.

The results of the phase II FRACTION-RCC CT[19] to assess nivolumab/ipilimumab after progression to an ICI (PD-1) were also presented ($n = 46$). The ORR was 15.2%, which suggests that this combination should ideally be administered as first-line therapy.

However, one study showed the results of a phase II bevacizumab/erlotinib study in 83 patients, of which 50% had hereditary leiomyomatosis (HLRCC) and 50% had sporadic (PSRCC) advanced papillary RCC[20]. This combination proved to be very active in papillary RCC, especially in HLRCC, with an ORR of 64%, tumor shrinkage of 95%, and PFS of 21.1 mo.

Finally, a phase III study (SAVOIR) with savolitinib *vs* sunitinib for papillary RCC with abnormal *MET* gene was presented ($n = 60$)[21]. The results showed a PFS of 7.0 and 5.6 mo in the savolitinib and sunitinib groups, respectively, with better tolerability in the savolitinib group. Initial data look promising, despite the small cohort study.

ESMO 2020

The results of Checkmate 9ER[22], a phase III study of nivolumab/cabozantinib *vs* sunitinib in previously untreated mRCC with a clear cell component, were presented. Patients were stratified by IMDC, PD-L1, and region ($n = 651$). At a median follow-up of 18.1 mo, nivolumab/cabozantinib led to higher rates of PFS, OS, and ORR *vs* sunitinib (Table 1), with consistent improvements observed across all pre-specified subgroups according to IMDC risk and PD-L1 expression. The combination was generally well tolerated, and patients had significantly better quality of life than those treated with sunitinib. These results support nivolumab/cabozantinib as a potential first-line option for patients with advanced renal cell carcinoma in every IMDC risk (Table 1).

The results of COSMIC 021, a phase II study that tested an escalation dose of cabozantinib from 40 mg to 60 mg with atezolizumab in first-line treatment, was also reported[23]. Data of 70 mRCC patients were presented, showing encouraging clinical efficacy with reasonable safety profiles. The findings suggested that PD-L1+ tumors with high CD8+ T cell infiltrates were more likely to respond to therapy. There is a phase III study (CONTACT-03) currently underway to confirm this combination's efficacy.

A phase II trial of lenvatinib plus pembrolizumab in 104 mRCC patients that were not responding to treatment with immunotherapy was also presented[24]. The ORR was 51%, PFS 11.7 mo, and mDOR 12.2 mo. These results are currently being studied in the phase III CLEAR trial [(lenvatinib + pembrolizumab) *vs* (lenvatinib + everolimus) *vs* sunitinib].

FUTURE DIRECTIONS AND BIOMARKERS

Updates and new trials presented in conferences this year may establish new care standards for mRCC. The update of Keynote 426 presented during American Society of Clinical Oncology (ASCO) 2020[15] suggested that pembrolizumab/axitinib should no longer be offered as the first line of choice of treatment in favorable risk mRCC. Moreover, the results of Checkmate 9ER presented at ESMO[22] showed some advantages of nivolumab/cabozantinib over sunitinib in first-line treatment among all IMDC subgroups and proposed it as a potential first-line option for mRCC.

At this point, there are multiple combination options for first-line treatment and the medical community is divided over which choice is better - two immunotherapies or immunotherapy plus an antiangiogenic drug - considering that the different combinations appear to have similar rates of efficacy, and there are no clear recommendations as to which is the most appropriate for each patient. More data and longer follow-up are needed to clarify the issue and learn whether there are certain populations who would benefit more from one of these combinations, as well as head-to-head comparisons between the combination therapies approved for first-line treatment. Additionally, biomarker-based studies are advisable when several approaches are available and clinical criteria are insufficient to guide treatment strategies.

Until then, taking into account the usual caveats pertaining to this practice, some insight may be gleaned from comparing CTs. At ASCO 2020, for example, the current first-line treatments in intermediate and high-risk mRCC patients (Checkmate 214[11] and Keynote-426[15]) were compared and discussed. Regarding OS data, outcomes in KEYNOTE426 appear to be slightly better at 2 years, and the ORR appears to be slightly higher with pembrolizumab/axitinib in KEYNOTE-426 (55%) than with nivolumab/ipilimumab in Checkmate 214 (42%). However, the percentage of patients who experienced primary progression with tumor growth while on treatment is more striking: 27% for nivolumab/ipilimumab and approximately half that, 15%, for pembrolizumab/axitinib. In clinical practice, pembrolizumab/axitinib appears to be the better choice, compared with nivolumab/ipilimumab, for a patient who needs a response to a rapidly progressing disease or to ameliorate symptoms, based on this cross-study comparison. For other patients, the adverse event profile of each combination would likely help to choose the most appropriate treatment.

An additional consideration is that the choice of first-line treatment may impact selection of second-line therapy. Starting with a combination of immune therapy only forces an automatic choice to use an antiangiogenic drug in the second line. However, starting with a combination of immune therapy and an antiangiogenic makes the second-line choice less clear. For this reason, more data are needed on the most suitable order of therapy for the population at large and specific groups, such as high *vs* slow-growing disease. Indeed, some ongoing CTs are trying to find the best alternative in second and third lines: Atezolizumab/cabozantinib *vs* cabozantinib (CONTACT-03)[25]; MK-6482 *vs* everolimus[26].

Also noteworthy is the recent trend toward three-part strategies, with various ongoing CTs, which have so far provided only preliminary results, including nivolumab + ipilimumab +/- cabozantinib (COSMIC 313)[27]; and the PDIGREE study [28], which proposes the use of nivolumab and ipilimumab followed by nivolumab or nivolumab with cabozantinib.

Conversely, other trials, such as the Checkmate 209-8Y8[29] and the KEYNOTE-427, are looking at maintaining monotherapies. The former proposes the use of nivolumab alone after nivolumab/ipilimumab in intermediate to poor-risk mRCC, while the latter studies the use of pembrolizumab in the frontline setting, showing promising activity (ORR of 36.4%, and disease control of 57.3%)[30].

Another field of study pertains to neoadjuvants and adjuvants, where either nivolumab or pembrolizumab is being evaluated in treatment before surgery (NCT02595918 and NCT02212730, respectively). The PROSPER trial (NCT03055013) assesses nivolumab in neoadjuvant and adjuvant use in node-positive or stage T2-T4 patients compared to observation[31].

Generally speaking, ongoing trials are moving away from sunitinib as the control arm and focus their research on triple therapies or novel therapeutic agents. PIVOT-9, a phase III randomized study, compares NKTR-214 plus nivolumab *vs* sunitinib or cabozantinib in previously untreated mRCC (NCT03729245). A phase II CT (NCT03634540) is studying the combination of HIF-2 α inhibitor (PT2977) and cabozantinib.

Telaglenastat, a glutaminase inhibitor, is being studied in previously treated mRCC in combination with cabozantinib and everolimus in two phase II trials (CANTATA and ENTRATA, respectively), and entinostat, an orally available inhibitor of HDACs,

is being considered in several combination therapies[32].

Poly(ADP-ribose) polymerase inhibitors, widely used in other tumors, have been proposed for RCC: Olaparib for patients with DNA repair gene mutations and talazoparib with avelumab.

Finally, the great challenge in mRCC treatment remains to find predictive and prognosis biomarkers. Interesting data are emerging from mRCC patients enrolled in CTs. PD-L1 expression, for example, was associated with poor outcomes in a meta-analysis[33]; but as a predictive marker, the results have been varied[4,34]. Genes have also been studied, including BRCA1-associated protein, which correlates with a poor survival[35], and PBRM1 mutation, which was associated with a longer PFS in the sunitinib and atezolizumab/bevacizumab group in IMotion150[36]. Another attempt to find a gene expression signature tool was made in IMmotion 151[34], where tumors characterized by angiogenesis-high signatures had better PFS with sunitinib and tumors with T effector/interferon- γ -high or angiogenesis-low signatures exhibited better outcomes with atezolizumab/bevacizumab. However, to date, the only predictive biomarker likely to be validated in a phase III randomized controlled trial is the IMDC risk model.

CONCLUSION

In conclusion, we are hopeful that in the coming years, patients and oncologists will continue to move away from a “one-size-fits-all” approach to treatment sequencing and instead move toward a more personalized treatment paradigm in mRCC.

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