short review

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First-line treatment of metastatic renal cell carcinoma: current standard of care

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Summary The introduction of immune checkpoint inhibitors has further improved response and survival rates in patients with metastatic renal cell carcinoma. In this context, the most promising trial results in the past 12 months include KEYNOTE 426 and the 30-month update of CheckMate 214. Both trials, similar to IMmotion 151 and JAVELIN Renal 101, reported improved survival and response data. CheckMate 214 reported an overall survival benefit in intermediate and poor risk patients, however, such benefit was observed irrespective of conventional risk groups in KEYNOTE 426. These results prompted the European Association of Urology (EAU) to update their guidelines on the treatment of metastatic renal cell carcinoma and to recommend the combinations pembrolizumab/axitinib and nivolumab/ipilimumab as standard of care in previously untreated intermediate and poor risk patients and the combination pembrolizumab/axitinib as standard of care in previously untreated favorable risk patients. Inflammatory and angiogenic markers profiles may have the potential to become a tool aiding to better individualize treatment regimens in the future. Exploratory analyses of the IMmotion 151 trial present first results supporting such approach. Sarcomatoid variant histology remains an unfavorable prognostic parameter. Subgroup analyses of CheckMate 214 revealed exceptional response in patients with sarcomatoid histology. Whereas conventional therapy was inferior in such patients, more than 50% of patients responded to combined checkpoint inhibitor therapy. Increasing evidence points towards a crucial role of the gut microbiome in the response of patients to modern immune therapies. Any antibiotic treatment prior to the inition of immune checkpoint therapy can have detrimental impact on the intestinal microbiome, thereby dramatically reducing response rate to checkpoint inhibitors.

Keywords Combination · Immune therapy · Metastatic · Keynote · Checkmate

Abbreviations

CI	Confidence interval
CPS	Combined positive score
CTLA-4	Cytotoxic T lymphocyte associated protein 4
HR	Hazard ratio
mRCC	Metastatic renal cell carcinoma
PD1	Programmed cell death protein 1
PDL1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
RCC	Renal cell carcinoma
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor

The first-line treatment of metastatic renal cell carcinoma has changed in recent years. Widespread standard treatment with tyrosine kinase inhibitors has been augmented by the introduction of new immunotherapies with checkpoint inhibitors [1]. The combination of these two approaches has further improved response and survival rates. Significant studies have been published in the last 12 months, with response rates of up to 70% irrespective of PD-L1 (programmed cell death 1 ligand 1) status, and especially in previously difficult-to-treat patient groups such as those with sarcomatoid differentiated tumors.

The most relevant recent studies reported on combination therapies. The included patient populations

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Table 1 First-line CPI Trials-combination

	Checkmate 214 ITT *n* = 550 vs. *n* = 546	Keynotes 426 ITT *n* = 432 vs. *n* = 429	Javelin Renal 101 ITT *n* = 442 vs. *n* = 444	Immotion 151 ITT *n* = 454 vs. *n* = 461
mOS, months	NR vs. 37.9	NR vs. NR	NR vs. NR	33.6 vs. 34.9
HR, (CI)	0.71 (0.59–0.86)	0.53 (0.38–0.74)	0.78 (0.554–1.084)	0.93 (0.76–1.14)
p-value	0.0003	<0.0001	0.0679	0.09
OS@12 months	83% vs. 78%	90% vs. 78%	86% vs. 83% (est.)	80% vs. 79% (est.)
mPFS, months	9.7 vs. 9.7	15.1 vs 11.1	13.8 vs. 8.4	11.2 vs. 8.4
HR, (CI)	0.85 (0.73–0.98)	0.69 (0.57–0.84)	0.69 (0.563–0.840)	0.83 (0.70–0.97)
p-value	0.0267	0.0001	0.0001	0.02
ORR, %	41 vs. 34	59 vs. 36	51 vs. 26	37 vs. 33
p-value	0.0154	<0.0001	NA	NA
CR, %	9 vs. 2	6 vs. 2	3 vs. 2	5 vs. 2
mDOF, months	32.4	12.8	12.0 vs. 11.5	15

Key studies demonstrating the efficacy of combined checkpoint inhibitor therapy
ITT intention to treat, *mOS* median overall survival, *NR* not reached, *HR* hazard ratio, *OS* overall survival, *ORR* objective reseponse rate, *NA* not available, *mDOF* median duration of follow up

were previously untreated. In this context, combination therapies of tyrosine kinase inhibitors with PD-1 or PD-L1 inhibitors are important, such as axitinib in combination with avelumab or pembrolizumab [2, 3], but also the combination of atezolizumab with bevacizumab [4] and the combination of PD-L1 and CTLA-4 inhibitors, such as ipilimumab and nivolumab ([5]; Table 1). The most promising studies on combination therapy for metastatic renal cell carcinoma in the past 12 months are certainly the KEYNOTE 426 trial [2] and the 30-month update of the CheckMate 214 trial, showing significant overall survival benefit data [6].

KEYNOTE 426 included 861 previously untreated patients with metastatic renal cell carcinoma who were randomized between treatment with pembrolizumab in combination with axitinib and a standard therapy with sunitinib in schedule 4/2 [2]. In addition to a histological clear cell component, the inclusion criteria requested a Karnofsky index of at least 70%. Coprimary endpoints of the study were overall survival and progression-free survival, key secondary endpoint was the objective response rate. The study was positive in all the above endpoints. Evaluation after 18 months showed a significant benefit of 41.1% vs. 32.9% in progression-free survival. The median PFS (progression-free survival) was 15.1 months in the combination arm compared to 11.1 months under sunitinib. The risk of disease progression was reduced by 31% (HR 0.69, 95% CI 0.57–0.84, $p = 0.0001$). As one of the key factors, overall survival at 18 months improved from 72.1% under sunitinib to 82.3% under the combination therapy (HR 0.53, 95% CI 0.38–0.74, $p < 0.0001$). The response to the combination therapy of pembrolizumab and axitinib was clearly superior to the comparator sunitinib (59.3% vs. 35.7%, $p < 0.001$). Subgroup analyses of common risk factors such as age, sex, IMDC (International Metastatic RCC Database Consortium) risk category, Karnofsky performance status, PD-L1 CPS (combined positive score) and the number of organs affected by metastasis did not reveal a reduction in response to combination therapy. Only in patients with favorable risk profile and low PD-L1 CPS <1 was a numerical benefit for combination therapy observed that did not reach statistical significance. The rate of treatment discontinuations was similar in both groups (10.7% vs. 13.9%). Grade 3–5 adverse events, especially with regard to liver function and diarrhea, were more common in the combination arm.

JAVELIN Renal 101 is as a prospective randomized trial of 886 previously untreated patients with metastatic renal cell carcinoma who were randomized between treatment with avelumab 10 mg/kg iv q2w in combination with axitinib 5 mg bid po and standard therapy with sunitinib 50 mg daily in schedule 4/2 [3]. Although overall survival data are not mature as of today, response rate and progression-free survival results prompted approval of this combination. Progression-free survival was 13.8 months in the combination arm vs. 8.4 months in the sunitinib arm ($p < 0.001$), and the risk of disease progression was reduced by 31% (HR 0.69, 95% CI 0.56–0.84, $p = 0.001$). The response rate in the combination arm with avelumab and axitinib was clearly superior to the comparator sunitinib (51.4% vs. 25.7%, $p < 0.001$). Analysis of progression-free survival 2, defined as the time from the date of randomization to discontinuation of second-line treatment after disease progression or death from any cause showed an ongoing survival advantage for patients treated with the combination of avelumab and axitinib in the first

line (PFS2: not reached vs. 18.4 months; HR: 0.56, CI 0.42–0.73). Most common grade 3–5 adverse events in the combination arm were hypertension (24.4%), palmar–plantar erythrodysesthesia syndrome (5.8%) and diarrhea (5.1%).

IMmotion 151 is a prospective randomized trial evaluating the combination of the PD-L1 inhibitor atezolizumab in combination with bevacizumab in the first-line treatment of 915 previously untreated patients with metastatic renal cell carcinoma [4]. Due to a lack of overall survival benefit, this combination is currently not approved for the treatment of metastatic renal cell carcinoma (Table 1).

CheckMate 214 has demonstrated efficacy in terms of combined treatment regimen; however, other mechanisms compared to KEYNOTE 426 compounds are driving response in this approach. The mechanism, how PD-1 and PD-L1 blocking molecules exert their effect in the treatment of mRCC (metastatic renal cell carcinoma), is to enable T-cells to detect and attack tumor cells. This reaction is aborted under normal circumstances by tumor cells inactivating T-cells via the PD-1 receptor. The application of PD-1 and PD-L1 inhibitors prevents this inactivation of T-cells and enables them to induce an immune response against the tumor cell. On a different level, the CTLA-4 receptor interferes with this immune reaction and prevents an excessive response of the immune system. By blocking the CTLA-4 receptor, the immune response against the tumor is subsequently boosted instead of being moderated.

The combination of these two mechanisms is the underlying principle of the combined checkpoint inhibitor therapy in CheckMate 214 [5]. This study included previously untreated patients with advanced or metastatic clear cell renal cell carcinoma. A total of 847 patients were randomized to either experimental treatment with nivolumab combined with ipilimumab for four doses, followed by nivolumab as ongoing immune backbone therapy, or standard treatment with sunitinib in 4/2 schedule. After 30 months of treatment, progression-free survival was 28% with the combination compared to 12% with sunitinib. Median overall survival was 26.6 months with sunitinib, while not reached in the combination arm (HR 0.66, 95% CI 0.54–0.80, $p<0.0001$; intermediate- and poor-risk population). Objective response to treatment was higher with ipilimumab and nivolumab than with sunitinib (42% vs. 29%, $p<0.0001$) in the intermediate- and poor-risk population [6]. In patients with favorable risk profile, no significant difference in response to either treatment was observed. However, there was a numerical advantage in response for treatment with sunitinib in this subset of patients (50% vs. 39%, $p=0.1436$). In the initial publication of CheckMate 214, this advantage for anti-VEGF treatment of favorable risk patients was significant, but with longer follow-up, more responses were seen in the combination arm.

The relation of inflammatory and angiogenic markers profiles and treatment response is nicely documented in the supplementary analyses of the IMmotion 151 trial comparing the experimental treatment of PD-1 checkpoint inhibitor atezolizumab in combination with bevacizumab versus sunitinib [4]. Two marker profiles, inflammatory and angiogenic, were defined, including a variety of experimental molecular markers [7]. Stratification of patients according to these marker subsets showed that patients with high angiogenic gene signature would respond better to anti-VEGF treatment than to immune checkpoint blockade (46% vs. 24%). Conversely, patients with a high inflammatory gene signature would respond better to immune checkpoint blockade than to anti-VEGF therapy (25% vs. 49%). Unfortunately, the majority of these markers is still experimental and not available for routine clinical use. Nevertheless, these are promising results in the ongoing search for how to better individualize and tailor different treatment regimens.

Sarcomatoid histology is an unfavorable prognostic parameter in patients with renal cell carcinoma, even more in the metastatic setting [8]. Response to conventional anti-VEGF therapy was inferior in such patients [9, 10]. Exploratory subgroup analyses of CheckMate 214 revealed an exceptional response in patients with sarcomatoid RCC [11]. A total of 112 patients with sarcomatoid features were identified within the intermediate- and poor-risk population, of whom 60 patients were treated in the experimental arm and 52 received standard treatment. An overwhelming difference in response was seen, with 56.7% of patients responding to ipilimumab and nivolumab compared to only 19.2% with sunitinib. Of note, an exceptional rate of complete responses was seen in the combination arm compared to the standard treatment arm (18.3% vs. 0%). Progression-free survival was almost doubled with the combination treatment compared to standard treatment (ipilimumab/nivolumab: 8.4 months sunitinib: 4.9 months, HR: 0.61, $p=0.0329$). Also overall survival was substantially increased from 13.6 months in the standard treatment arm to 31.2 months in the combination arm ($p=0.0155$). Due to the unfavorable course of this histologic variant of RCC and the impressive results documented in CheckMate 214, patients with metastatic sarcomatoid RCC should receive upfront combination treatment with ipilimumab and nivolumab.

Does this mean that there is no further role for tyrosine kinase monotherapy in first line treatment of mRCC? Not necessarily. Some studies have demonstrated promising marker sets in subgroup analyses that might point towards a possibility to better stratify patients into “immunotherapy” and “antiangiogenic therapy” in the future. IMmotion 151 was one of those studies, showing that patients with high expression of inflammatory marker profiles respond

better to checkpoint inhibitor therapy, while patients expressing high angiogenic marker profiles respond better to TKI (tyrosine kinase inhibitor) therapy [7]. Unfortunately, such markers are not ready for clinical routine use yet, and PD-1 status alone seems to be unreliable in this context. However, these promising results suggest that there still exists a population of patients, probably those with early, still differentiated and VEGF dependent tumors, that might well respond, even long-term, to tyrosine kinase inhibitor monotherapy. Also patients with already impaired hepatic function or chronic irritable bowel disease might be candidates for upfront TKI monotherapy with regard to conserving quality of life and reducing the risk of potentially life-threatening side effects.

The role of the intestinal microbiome is another important factor to be considered when establishing first line checkpoint inhibitor therapy, either as monotherapy or in combination with CTLA-4 blockade or TKIs. There is increasing evidence pointing towards a crucial role of the microbiome in the response of patients to modern immune therapies. A variety of microbes has been identified to be favorable (e.g. Akkermansia muciniphila) or unfavorable (e.g. Bacteriodes nordii) regarding response to checkpoint inhibitor therapy; however it is unclear how to establish a favorable microbiome in a nonresponding patient at the moment [12]. Fecal microbiome transplantation showed impressive results in the mouse model in this context [12, 13]. What emerges is that antibiotic treatment, unless there is a strong indication, should be carefully indicated within an 6 week period before the start of checkpoint inhibitor treatment [14]. During this time period, any antibiotic treatment can have detrimental impact on the intestinal microbiome, thereby dramatically reducing response rates to checkpoint inhibitor therapies [12]. This is not only important with regard to treatment outcomes [15], but also when considering the enormous cost that immune checkpoint inhibitors, especially in modern combination therapies confer upon the health care system.

Take home message

- The combination of PD-1/PD-L1 and anti-VEGF blockade (pembrolizumab/axitinib, avelumab/axitinib) might be regarded as a therapeutic standard for the first-line treatment of metastatic RCC with IMDC favorable-, intermediate- and poor-risk profile, whereas the combination of PD-1 and CTLA-4 blockade (nivolumab/ipilimumab) might be used for IMDC intermediate and poor-risk disease.
- Patients with metastatic RCC and a sarcomatoid histologic component should receive upfront combined treatment with ipilimumab and nivolumab.
- First line anti VEGF monotherapy might still play a role in patients with low PD-L1 positivity and low anti-inflammatory and high angiogenic marker profiles.
- Avoid antibiotic treatment 6 weeks before to 2 weeks after the initiation of immune checkpoint inhibitor treatment in order to preserve intestinal microbiota potentially favorable for treatment response.

Conflict of interest M. Marszalek serves as an advisor for Pfizer, Bristol Myer Squibb, Eusa Pharma, Eisai.

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