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Immunotherapy: A new standard in the treatment of metastatic clear cell renal cell carcinoma

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Abstract

Renal cell cancer (RCC) represents 2%-3% of all adulthood cancers and is the most common malignant neoplasm of the kidney (90%). In the mid-nineties of the last century, the standard of treatment for patients with metastatic RCC was cytokines. Sunititib and pazopanib were registered in 2007 and 2009, respectively, and have since been the standard first-line treatment for metastatic clear cell RCC (mccRCC). Renal cell cancer is a highly immunogenic tumor with tumor infiltrating cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells (NK) and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy has emerged, and new clinical trials have been designed. In the last few years, several therapeutic options have been approved [immunotherapy and immunotherapy/tyrosine kinase inhibitors (TKI)] for the first-line treatment of mccRCC. Nivolumab/ipilimumab is approved for the treatment of patients with intermediate and poor prognoses. Several checkpoint inhibitors (pembrolizumab, nivolumab, avelumab) in combination with TKI (axitinib, lenvatinib, cabozantinib) are approved for the treatment of patients regardless of their International mRCC Database Consortium prognostic group and PD-L1 expression. There is no specific and ideal biomarker that could help in selecting the ideal patient for the appropriate first-line treatment.

Key Words: Renal cell carcinoma; Immunotherapy; Checkpoint inhibitors; Biomarkers; Tumor microenvironment; Programmed cell death 1 receptor

Core Tip: Renal cell cancer is a highly immunogenic tumor infiltrated by cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy has emerged, and new clinical trials have been designed. In the last few years, several therapeutic options have been approved (immunotherapy and immunotherapy/tyrosine kinase inhibitors) as first-line treatment for metastatic clear cell renal cell cancer.

INTRODUCTION

Renal cell cancer (RCC) represents 2%-3% of all adulthood cancers and is the most common malignant neoplasm of the kidney (90%)[1]. Clear cell cancer (75%) is the most prevalent histological subtype of RCC, followed by papillary (10%), chromofobe (5%), collecting ducts (0.4%-1.8%) and unclassified (4%-6%)[2]. RCC typically occurs in the fifth and sixth decade of life and is twice as frequent in men than in women[3]. At the time of diagnosis, one-third of all patients have metastatic disease, while a quarter of all patients, with initially localized disease, relapse after nephrectomy[4]. According to two prognostic models, Memorial Sloan Kettering Cancer Center (MSKCC) and International mRCC Database Consortium (IMDC), metastatic RCC (mRCC) patients can be divided into 3 prognostic categories: favorable, intermediate and poor risk[5,6] (Table 1).

In the mid-nineties of the last century, the standard of treatment for patients with metastatic RCC was cytokines, typically interferon-alpha and interleukin 2. Beside the high toxicity profile of cytokines, patients who were treated achieved an objective response rate (ORR) of 10-20%, while the median overall survival (OS) was 11-14 mo [7-9].

Renal clear cell carcinoma is commonly associated with Von Hippel-Lindau (VHL) gene mutations (70% of patients) located on chromosome 3p and mediates cell apoptosis in response to hypoxia[10,11]. If this mutation is present, apoptosis does not occur, hypoxia-induced factor (HIF) accumulates and activates vascular endothelial growth factor (VEGF), and platelet growth factor (PDGF) and others engage in the angiogenesis process, which is one of the key promoters of cell growth in RCC[12]. This knowledge leads to the development of new antiangiogenetic drugs. Other mutations, such as PBRM1 (40%), SETD28 (15%) and BAP1 (15%), have recently been discovered. Sunititib and pazopanib were registered in 2007 and 2009, respectively and have been the standard first-line treatment for mRCC ever since. The median survival of patients treated with these drugs is 24-29 mo, while the objective response rate (ORR) is 30%-33%[13,14].

RCC is a highly immunogenic tumor with infiltrating cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells (NK) and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy[15]. Checkpoint inhibitors are monoclonal antibodies targeting the link between programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2[16]. The PD-1 receptor is located on T cells, while PD-L1 and PD-L2 are present on other immune cells. The ligand can be found on both tumor cells and immune infiltrate cells, allowing them to bind to the PD-1 receptor of T-cells and escape the host immune response[17,18]. Checkpoint inhibitors block this interaction and permit the host's immune response to the tumor[16].

Nivolumab is humanized PD-1 monoclonal antibody. The first data on nivolumab in mRCC were the results of the phase I Checkmate 033 trial, where nivolumab was

Table 1 Poor prognostic factor

Poor prognostic factor	MSKCC	IMDC
Time from diagnosis to treatment	< 12 mo	< 12 mo
Hemoglobin	< lower limit of normal	< lower limit of normal
Corrected serum calcium	> 10 mg/dl (2.5 mmol/L)	> upper limit of normal
Karnofsky performance score	< 80%	< 80%
Neutrophil count	/	> upper limit of normal
Platelet count	/	> upper limit of normal
Lactate dehydrogenase	> 1.5 x upper limit of normal	/
Good risk	0 risk factor	0 risk factor
Intermediate risk	1 or 2 risk factors	1 or 2 risk factors
Poor risk	3, 4 or 5 risk factors	3, 4, 5 or 6 risk factors

MSKCC: Memorial Sloan Kettering Cancer Center; IMDC: International mRCC Database Consortium.

investigated in pretreated patients. The objective response rate was 24%; after a median follow-up of 63.9 mo, the ORR was 29%, the median duration of response (DOR) was 12.9 mo, and the median OS was 22.4 mo[19]. In the phase 2 trial, nivolumab was again investigated in pretreated mRCC patients. Patients received 0.3 mg/kg, 2 mg/kg or 10 mg/kg nivolumab. There was no difference in PFS in these subgroups. At 3 years, ORR was 21% while OS was 41%[20]. The phase 3 trial, CheckMate 025, investigated nivolumab in comparison to everolimus in pretreated patients. The primary endpoint was OS, while the secondary endpoints were response rates and safety profile. The median OS in patients treated with nivolumab was 25 mo, compared to 1.6 mo with everolimus (HR 0.73). Differences in OS were recorded across all subgroups of patients regardless of PD-L1 expression. The objective response rate was 25% in the nivolumab cohort and 5% in the everolimus cohort. There was no significant difference in PFS of 4.6 *vs* 4.4 mo for nivolumab and everolimus, respectively. Grade 3 and 4 adverse events were reported in 19% of patients in the nivolumab group and 37% of patients in the everolimus group[21]. The results of this trial led to FDA approval of nivolumab as a second-line treatment of mccRCC.

In April 2018, nivolumab and ipilimumab combination therapy was approved by the FDA for the first-line treatment of intermediate- and poor-risk mRCC patients. This approval was a result of the phase 3 trial, CheckMate 214, which compared nivolumab and ipilimumab *vs* sunitinib in treatment-naïve patients. The trial included 1096 patients, 847 of whom were intermediate- and poor-risk IMDC risk groups. Patients were randomized 1:1. The primary endpoints were OS, PFS and ORR in intermediate- and poor-risk patients, while the secondary endpoints were OS, PFS and ORR in the intended-to-treat (ITT) population. Intermediate- and poor-risk patients in the nivolumab/ipilimumab group had significantly longer PFS than those in the sunitinib group. The favorable-risk prognostic group had longer PFS when treated with sunitinib. Patients with PD-L1 expression > 1% had significantly longer PFS when treated with nivolumab/ipilimumab *vs* sunitinib, while the treatment groups did not differ in patients with PD-L1 < 1%. Nivolumab/ipilimumab significantly prolonged patient OS compared to sunitinib. There were 46% grade 3-4 adverse events in the nivolumab/ipilimumab group *vs* 63% in the sunitinib group[22]. After 48 mo of follow-up, patients in the intermediate- and poor-risk groups treated with nivolumab/ipilimumab achieved significantly longer overall survival[23].

Nivolumab also proved efficacious in patients with brain metastasis: the ORR was 12%, and the PFS was 2.7 mo[24]. When nivolumab was combined with ipilimumab, the ORR and PFS were 29% and 9 mo, respectively[25].

Angiogenesis is one of the key initiators of disease in RCC, which itself is an immunogenic tumor. In patients with VHL gene mutations, instead of apoptosis, HIF accumulates and activates VEGF and PDGF, which mediate the activation of the angiogenesis process[10-12]. It has been shown that accumulation of VEGF leads to suppression of the host's immune response. It also interferes with monocyte differentiation into mature dendritic cells that are essential for the activation of the host's immune system. VEGF increases the number of myeloid suppressing cells present in

the tumor infiltrates that disable the activity of tumor infiltrating lymphocytes, the expression of PD-L1 in dendritic cells, as well as PD-1 and CTLA-4 on immune cells. It inhibits the differentiation of progenitor cells into CD4+ and CD8+ cells. Proangiogenic factors also modify the expression of proteins on endothelial cells, blocking the infiltration of the tumor by immune cells[26,27]. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy emerged, and new clinical trials have been designed[28].

Atezolizumab is a humanized monoclonal PD-L1 antibody investigated in combination with bevacizumab *vs* sunitinib. After the phase I study reported a 40% ORR , a phase II study was conducted (atezolizumab or atezolizumab/bevacizumab or sunitinib), and ORRs of 32%, 25% and 29%, respectively, were observed. In the ITT population, the PFS difference was not significant, while in the PD-L1-positive patients, a significant difference was noticed in the cohort treated with atezolizumab/bevacizumab *vs* sunitinib. PFS was not significant when atezolizumab alone was compared with sunitinib in PD-L1-positive patients[29]. The phase 3 trial, IMmotion 151, followed these results and compared atezolizumab/bevacizumab *vs* sunitinib in treatment-naïve patients. Patients were randomized 1:1 according to the MSKCC score, PD-L1 expression (< 1% *vs* > 1%), and presence of liver metastases. Patients with sarcomatoid tumor features were also included. The co-primary endpoints were PFS in the PD-L1-positive population and OS in the ITT population. Secondary endpoints were PFS, ORR and duration of response in the ITT population. In the PD-L1-positive patients, PFS was 11.2 mo (atezolizumab/bevacizumab) in comparison to 7.7 mo (sunitinib), HR 0.74. In the ITT population, PFS was 11.2 mo (atezolizumab/bevacizumab) *vs* 8.4 mo (sunitinib), HR 0.83. The ORR in the PD-L1+ population was 43% (atezolizumab/bevacizumab) *vs* 35% (sunitinib), while the ORR in the ITT population was 37% *vs* 33% (atezolizumab/bevacizumab *vs* sunitinib)[30]. After 24 mo of follow-up, there were no differences in survival (HR 0.93) in the ITT population[31]. Considering the results of IMmotion 150 and 151, data subanalysis was performed according to the molecular profile of tumor tissue. IMmotion 150 patients were classified into angio-high, T effector-high and myeloid-high. The subanalysis showed that angio-high patients had a higher benefit from TKIs and were in the favorable prognostic group, while T effector-high patients had a greater benefit from immunotherapy and were in the intermediate and poor prognostic groups. It was also observed that patients with BAP1 mutations had a worse prognosis and shorter PFS when treated with sunitinib, while patients with PBRM1 mutations had a worse prognosis and shorter PFS when treated with immunotherapy. IMmotion 151 included patients with sarcomatoid features, who generally had a worse prognosis. The results of this subanalysis showed that half of these patients were T effector-high, had higher PD-L1 expression and achieved the highest benefit from immunotherapy[29,32].

Cosmic-021 was a phase 1b trial that investigated the efficacy of atezolizumab in combination with cabozantinib in different solid tumors. One of the cohorts consisted of mccRCC patients. Seventy patients were included in the study: 34 patients were treated with cabozantinib 40 mg, and 36 patients were treated with cabozantinib 60 mg and 1200 mg atezolizumab. Most of the patients were in the intermediate prognostic group. After a median follow-up of 11.5 mo (cabozantinib 60 mg) *vs* 22 mo for cabozantinib 40 mg, the ORR in the cabozantinib 60 mg group was 58% *vs* 47% in the cabozantinib 40 mg group. The median PFS was 19.5 mo (cabozantinib 40 mg) and 20.4 mo (cabozantinib 60 mg). Two years PFS was 67% (cabozantinib 40 mg) and 71% (cabozantinib 60 mg). Treatment-related grade 3-4 adverse events were reported in 71% (cabozantinib 40 mg) and 67% (cabozantinib 60 mg) of the patients. The most common adverse events were hypertension, hypophosphatemia, diarrhea and elevation of liver enzymes[33].

The Contact-03 trial investigating atezolizumab in combination with cabozantinib in patients with mRCC who have progressed on previous immunotherapy is underway [34].

Pembrolizumab is a humanized monoclonal PD-L1 antibody studied in combination with axitinib in a phase 1b trial. The response rate was 73%[35]. In the randomized phase 3 clinical trial (Keynote-426), pembrolizumab/axitinib was compared to sunitinib. Patients were randomized 1:1. The primary endpoints were OS and PFS in the ITT population, while the secondary endpoint was ORR. After 12.8 mo of follow-up, the one-year OS was 89.9% (pembrolizumab/axitinib) *vs* 78.3% (sunitinib), HR 0.53, *P* < 0.0001. PFS was 15.1 mo (pembrolizumab/axitinib) *vs* 11.1 mo (sunitinib), HR 0.69, *P* < 0.0001. The ORR was 59.3% and 37.5% in the pembrolizumab/axitinib *vs* sunitinib group, respectively. Treatment-related grade 3 adverse events accounted for 75.85% of the patients in the combination cohort. Benefit was observed across all

subgroups analyzed regardless of the IMDC risk score or PD-L1 expression[36]. At 27 mo, PFS and OS were significantly longer in all subgroups of patients[37]. Pembrolizumab was investigated in combination with levantinib in a phase 2 trial (Keynote 146) in patients with mccRCC who were previously treated with immunotherapy. The primary endpoint of the trial was an ORR of 51%, a median PFS of 11.7 mo, and a median DOR of 9.9 mo[38]. The phase 3 trial, CLEAR/Keynote 581, investigated pembrolizumab/Lenvatinib *vs* everolimus/Lenvatinib *vs* sunitinib in patients with mccRCC. The primary endpoint was PFS, while the secondary endpoints were ORR and OS in the ITT population. All three prognostic MSKCC and IMDC risk score groups were included in the trial. After 26.6 mo of follow-up, PFS in the group of patients treated with pembrolizumab/Lenvatinib *vs* those treated with sunitinib was 23.9 *vs* 9.2 mo (HR 0.39, *P* < 0.0001). In patients treated with everolimus/Lenvatinib *vs* sunitinib, PFS was 14.7 and 9.2 mo, respectively, HR 0.65, *P* < 0.0001. Median overall survival was not reached; however, OS was longer with pembrolizumab/Lenvatinib than with sunitinib, HR 0.66, *P* = 0.005. There was no significant OS difference in patients treated with everolimus/Lenvatinib and patients treated with sunitinib, HR 1.15, *P* = 0.30. The objective response rate in the pembrolizumab/Lenvatinib cohort *vs* the everolimus/Lenvatinib *vs* sunitinib cohort was 71%, 53.5%, and 36.1%, respectively. Median DOR in the pembrolizumab/Lenvatinib cohort *vs* everolimus/Lenvatinib *vs* sunitinib was 25.8, 16.6 and 14.6 mo, respectively. All subgroups of patients had a benefit in PFS when treated with pembrolizumab/Lenvatinib. Grade 3 or higher toxicity was observed in 82.4% *vs* 83.1% and 71.8% of the patients treated with pembrolizumab/Lenvatinib, everolimus/Lenvatinib and sunitinib, respectively. The most common grade 3 toxicities were diarrhea, hypertension, and elevated lipase and triglyceride levels[39].

Avelumab is a humanized PD-L1 monoclonal antibody. It was investigated in a phase 1b trial in combination with axitinib in treatment-naïve patients with mccRCC. The objective response rate was 58%[40]. The phase 3 trial, JAVELIN Renal 101, compared avelumab/axitinib with sunitinib in patients who were not previously treated. The co-primary endpoints were PFS and OS in PD-L1-positive patients, while the secondary endpoint was PFS in the ITT population. In PD-L1-positive patients, PFS was 13.8 mo for avelumab/axitinib in comparison to 7.2 mo for patients treated with sunitinib, HR 0.61, *P* < 0.0001. In the ITT population, PFS was 13.8 mo for avelumab/axitinib in comparison to 8.4 mo for patients treated with sunitinib, HR 0.69, *P* < 0.0001. In the PD-L1-positive population, the ORR was 55.2% in the avelimab/axitinib group and 25.5% in the sunitinib group. Adverse grade 3 or higher events were reported in 71.2% of patients treated with avelumab/axitinib and 71.5% of patients treated with sunitinib[41]. At 13 mo PFS was significantly longer for the patients treated with avelumab/axitinib *vs* sunitinib in both PD-L1 positive (HR 0.62, *P* < 0.0001, 13.8 *vs* 7 mo) and ITT populations (HR 0.69, *P* < 0.0001, 13.3 *vs* 8 mo). Data for OS are still pending[42]. In May 2019, this combination was approved for the first-line treatment of mccRCC patients, regardless of the IMDC score prognostic subgroup.

In January 2021, nivolumab in combination with cabozantinib was approved by the FDA for the first-line treatment of patients with mRCC based on the results of the CheckMate 9ER trial. The trial included treatment-naïve patients, regardless of the PD-L1 expression or IMDC prognostic score. Patients were randomized into two cohorts: nivolumab/cabozantinib and sunitinib. The primary endpoint was PFS, and the secondary endpoints were OS and ORR. At 18.1 mo, PFS and OS were both significantly longer in the nivolumab/cabozantinib *vs* the sunitinib cohort in all patient subgroups analyzed[43] in Table 2.

Most of the trials that examined the efficacy of immunotherapy or immunotherapy/TKI combinations did not include mnccRCC. Some of the retrospective trials with immunotherapy reported ORRs of 9-20%. The greatest benefit occurred in patients with the papillary histology subtype[44,45]. In the phase 2 trial, Keynote 427, pembrolizumab was investigated in previously untreated mnccRCC patients. Most of the patients had papillary subtype (72%). In the ITT population, the ORR was 24.8%, while the ORRs of papillary, chromofobe and nonclassified subtypes patients were 25.4%, 9.5% and 34.6%, respectively. The twelve-month PFS and OS were 22.8% and 72%. After 11 mo of follow-up, the median DOR was not reached in either subgroup of patients[46].

Nivolumab was investigated in the phase 3b/4 trial, Checkmate 374, which included treatment-naïve patients as well as patients previously treated with a maximum of 3 Lines of therapy. Most of the patients (66%) were treatment naïve. After 11 mo of follow-up, the median OS was 16.3 mo, with no difference in OS between patients regardless of PD-L1 expression. The median PFS was 2.2 mo. At one year, PFS was 14%. The median DOR was 10.2 mo, and ORR was 13.6%[47]. The Cosmic-021

Table 2 Results of phase 3 studies in first line treatment of patients with metastatic clear cell renal cell cancer

Drug/Study	No. of patients	Follow-up (mo)	PFS (mo)	OS (mo)	ORR, %	Ref.
Nivolumab/Ipilimumab *vs* Sunitinib (Checkmate 214)	1096	48	ITT 12.2 *vs* 12.3; HR 0.89; I/P risk 11.2 *vs* 8.3; HR 0.74	ITT NR *vs* 38.4; HR 0.69; I/P risk 48.1 *vs* 26.6; HR 0.65; F risk; HR 0.93	ITT 39.1 *vs* 32.4; I/P risk 41.9 *vs* 26.8; F risk 29.6 *vs* 51.6	[24]
Pembrolizumab/Axitinib *vs* Sunitinib (Keynote 426)	861	27	ITT 15.4 *vs* 11.1; HR 0.71; *P* < 0.0001	ITT NR *vs* 35.7; HR 0.68; *P* = 0.0003	ITT 60 *vs* 40	[39]
Avelumab/Axitinib *vs* Sunitinib (Javelin 101)	560	13	ITT 13.3 *vs* 8; HR 0.69; *P* < 0.0001; PD-L1 + 13.8 *vs* 7; HR 0.62; *P* < 0.0001	ITT NR; HR 0.80; *P* = 0.0392; PD-L1 + NR; HR 0.83; *P* = 0.1301	ITT 52.5 *vs* 27.3; PD-L1 + 55.9 *vs* 27.3	[44]
Nivolumab/Cabozantinib *vs* Sunitinib (Checkmate 9ER)	651	18.1	ITT 16.6 *vs* 8.3; HR 0.51; *P* < 0.0001	ITT NR *vs* NR; HR 0.60; *P* = 0.0010	ITT 55.7 *vs* 27.1	[45]
Pembrolizumab/Lenvatinib *vs* Everolimus/Lenvatinib *vs* Sunitinib (Clear/Keynote 581)	1069	26.6	ITT Pembro/lenva *vs* sunitinib 23.9 *vs* 9.2; HR 0.39; *P* < 0.000; Everolimus/lenva *vs* sunitinib; 14.7 *vs* 9.2; HR 0.65; *P* < 0.0001	ITT Pembro/lenva *vs* sunitinib NR *vs* NR; HR 0.66; *P* = 0.005; Evero/lenva *vs* sunitinib NR *vs* NR; HR 1.15; *P* = 0.30	ITT Pembro/lenva *vs* Evero/lenva *vs* sunitinib; 71% *vs* 53.5% *vs* 36.1%	[41]

phase 1b trial analyzed the efficacy of atezolizumab in various solid tumors. One of the cohorts was patients with mnccRCC. These patients were treated with cabozantinib 40 mg and 1200 mg of atezolizumab.

According to the IMCD, all three prognostic subgroups were included in the trial, and most of them were in the intermediate prognostic group. After a median follow-up of 9.2 mo, the ORR was 33%, with no difference between subgroups. The median DOR was 7.9 mo. Grade 3-44 adverse events were reported in 30% of the patients, and a low phosphorus level was the most common adverse event[48]. The Calypso trial, phase 1b/2, examined the combination of durvalumab and savolitinib in patients with papillary mnccRCC previously treated, as well as treatment naïve. The primary endpoint was ORR, while the secondary endpoints were PFS, OS and safety. The trial included all IMDC score prognostic groups. Most of the patients (63%) were in the intermediate prognostic group. Median follow up was 8.9 mo. In the ITT population, the ORR was 27%, while the median PFS was 3.3 mo. In the subgroup of patients who were treatment naïve, the ORR was 27%, and the median PFS was 12.2 mo. Fifteen out of 42 patients included had grade 3-4 toxicities[49] (Table 3).

Predictive biomarkers

Is there a biomarker that can predict the response to either immunotherapy or tyrosine kinase inhibitors (TKIs)? One of the essential promoters of cell growth in RCC is angiogenesis. Patients in the favorable prognostic group had abundant tumor infiltrates with blood vessels. However, RCC is also an immunogenic tumor with inflammatory tumor infiltrates and is a characteristic in patients with intermediate and poor prognoses. The Bionikk trial assessed the response to immunotherapy and TKI therapy relative to the molecular tumor profile (35 genes). Patients were classified into four subgroups: group 1 (immune-low), group 2 (angio-high), group 3 (normal-like), and group 4 (immune-high). They were randomized so that groups 1 and 4 were treated with either nivolumab or nivolumab/ipilimumab, while patients in groups 2 and 3 received either sunitinib or nivolumab/ipilimumab. Primary endpoint was ORR. In group 1, the ORR was 33.3% and 20.7% for patients treated with nivolumab/ipilimumab or nivolumab, respectively. There was no difference in ORR between patients in group 4 who were treated with nivolumab *vs* nivolumab/ipilimumab 42.9% *vs* 41.2%. In group 2, the ORR was 58.3% *vs* 34.5% in patients treated with sunitinib *vs* nivolumab/ipilimumab. A very small number of patients were included in group 3, and responses were only achieved in patients treated with the nivolumab/ipilimumab combination[50]. PD-L1 is the most commonly analyzed biomarker that predicts the response to immunotherapy. Several trials pointed out that high expression of PD-L1 in patients with RCC is a predictor of poor prognosis[21,23]. Checkmate 025 reported that nivolumab is superior to everolimus in previously treated patients. Higher expression of PD-L1 was related to worse prognosis regardless of whether patients were treated with nivolumab or everolimus. The median OS was longer in PD-L1-negative patients regardless of the treatment[21].

Table 3 Results of checkpoint inhibitors in treatment of patients with metastatic clear cell renal cell cancer

Drug/Study	Phase	Indication	Follow-up	Results	Ref.
Pembrolizumab (Keynote 427)	II	mnccRR	11	ITT ORR 24.8%; ORR Papillary *vs* phromophobe *vs* unclasified 25.4% *vs* 9.5% *vs* 34.6%; 12 mo PFS 22.8%; 12 mo OS 72%	[50]
Nivolumab (Checkmate 374)	IIIb/IV	mnccRR	11	ITT; OS 16,3 mo; PFS 2,2 mo; ORR 13,6%	[51]
Atezolizumab/Cabozantinib (Cosmic 021)	Ib	mnccRR	9,2	ITT ORR 33%	[52]
Durvalumab/Savolitinib (Calypso)	Ib/II	mnccRCC-papillaryuntreated or previously treated	8,9	ITT; ORR 27%; PFS 3,3 mo; Untreated ORR 29%; PFS 12,2	[53]

In the Checkmate 214 trial, intermediate- and poor-risk patients who were also PD-L1 positive had longer PFS when treated with nivolumab/ipilimumab *vs* sunitinib. There was no PFS difference in the PD-L1-negative population[22]. According to the JAVELIN Renal 101 and Keynote 426 trials, all subgroups of patients had significantly longer PFS regardless of the prognostic group or PD-L1 expression[37,42]. Different histology subtypes of RCC have different TMB values. The lowest TMB is found in chromofobic subtype, and the highest was found in the papillary and clear cell histology subtypes[51]. In other malignancies, such as lung cancer and melanoma, TMB is a predictor of a favorable response to treatment. Although they have relatively low TBM, patients with RCC have higher rates of response to immunotherapy[52,53]. The results of trials that analyzed the prognostic value of TBM in RCC are inconclusive [54,55]. A retrospective analysis showed that TMB values do not correlate with either survival or PD-L1 expression[56]. Subanalysis of the IMmotion 150 trial showed that TMB did not influence the response to nivolumab[31]. Tumor infiltrates in RCC consist of CD8+ T lymphocytes, dendritic cells, NK cells and macrophages[15]. Some trials have shown that if tumor infiltrates are abundant with CD8+ cells and M1 macrophages, patients have a better prognosis, while infiltrates rich in regulatory T cells and M2 macrophages predict poor prognosis[57-60]. Other trials indicated that if tumor infiltrate is abundant with CD8+, patients will have a better response to immunotherapy[61]. IMmotion 150 and IMmotion 151 confirmed these results[29,31].

To date, there are no biomarkers that can predict the response to immunotherapy. Some drugs approved for first-line treatment may benefit many patients regardless of prognostic group or PD-L1 expression[36,39,42]. Further investigations are warranted to improve the selection of patients for the best possible choice of first-line therapy.

CONCLUSION

We are witnessing the evolution of mccRCC treatment. Starting with interferon-alpha and interleukin 2 in the late twentieth century, the first TKI was administered in 2007. In the last few years, several therapeutic options have been approved (immunotherapy and immunotherapy/TKI) as first-line treatment options. Nivolumab/ipilimumab is approved for the treatment of patients with intermediate and poor prognoses. Several checkpoint inhibitors (pembrolizumab, nivolumab, avelumab) in combination with TKIs (axitinib, lenvatinib, cabozantinib) are approved for the treatment of patients regardless of their IMDC prognostic group and PD-L1 expression. There is no specific and ideal biomarker that could help select the ideal patient for the appropriate first-line treatment. If patients are symptomatic, have visceral metastasis and require prompt response, then checkpoint inhibitors/TKIs are deemed most beneficial. If the patient is asymptomatic, then other factors, such as toxicity profile, may influence the first-line treatment option.

REFERENCES

1 **Gupta K**, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev* 2008; **34**: 193-205 [PMID: 18313224 DOI: 10.1016/j.ctrv.2007.12.001]

2 **Cheville JC**, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic

features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol* 2003; **27**: 612-624 [PMID: 12717246 DOI: 10.1097/00000478-200305000-00005]

3 **Murai M**, Oya M. Renal cell carcinoma: etiology, incidence and epidemiology. *Curr Opin Urol* 2004; **14**: 229-233 [PMID: 15205579 DOI: 10.1097/01.mou.0000135078.04721.f5]

4 **Dabestani S**, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. *World J Urol* 2016; **34**: 1081-1086 [PMID: 26847337 DOI: 10.1007/s00345-016-1773-y]

5 **Motzer RJ**, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002; **20**: 289-296 [PMID: 11773181 DOI: 10.1200/JCO.2002.20.1.289]

6 **Heng DY**, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, Eigl BJ, Ruether JD, Cheng T, North S, Venner P, Knox JJ, Chi KN, Kollmannsberger C, McDermott DF, Oh WK, Atkins MB, Bukowski RM, Rini BI, Choueiri TK. 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**: 5794-5799 [PMID: 19826129 DOI: 10.1200/JCO.2008.21.4809]

7 **Minasian LM**, Motzer RJ, Gluck L, Mazumdar M, Vlamis V, Krown SE. Interferon alfa-2a in advanced renal cell carcinoma: treatment results and survival in 159 patients with long-term follow-up. *J Clin Oncol* 1993; **11**: 1368-1375 [PMID: 8315435 DOI: 10.1200/JCO.1993.11.7.1368]

8 **Klapper JA**, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, Sherry RM, Royal RE, Steinberg SM, Rosenberg S. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. *Cancer* 2008; **113**: 293-301 [PMID: 18457330 DOI: 10.1002/cncr.23552]

9 **Allard CB**, Gelpi-Hammerschmidt F, Harshman LC, Choueiri TK, Faiena I, Modi P, Chung BI, Tinay I, Singer EA, Chang SL. Contemporary trends in high-dose interleukin-2 use for metastatic renal cell carcinoma in the United States. *Urol Oncol* 2015; **33**: 496.e11-496.e16 [PMID: 26210683 DOI: 10.1016/j.urolonc.2015.06.014]

10 **Latif F**, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, Stackhouse T, Kuzmin I, Modi W, Geil L. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 1993; **260**: 1317-1320 [PMID: 8493574 DOI: 10.1126/science.8493574]

11 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 2013; **499**: 43-49 [PMID: 23792563 DOI: 10.1038/nature12222]

12 **Kaelin WG Jr**. The von Hippel-Lindau tumour suppressor protein: O2 sensing and cancer. *Nat Rev Cancer* 2008; **8**: 865-873 [PMID: 18923434 DOI: 10.1038/nrc2502]

13 **Motzer RJ**, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356**: 115-124 [PMID: 17215529 DOI: 10.1056/NEJMoa065044]

14 **Sternberg CN**, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; **28**: 1061-1068 [PMID: 20100962 DOI: 10.1200/JCO.2009.23.9764]

15 **Nakano O**, Sato M, Naito Y, Suzuki K, Orikasa S, Aizawa M, Suzuki Y, Shintaku I, Nagura H, Ohtani H. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. *Cancer Res* 2001; **61**: 5132-5136 [PMID: 11431351]

16 **Aoun F**, Rassy EE, Assi T, Kattan J. PDL-1/PD1 inhibitors: antibody or antinobody? *Future Oncol* 2017; **13**: 1669-1671 [PMID: 28831825 DOI: 10.2217/fon-2017-0215]

17 **Chen DS**, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; **39**: 1-10 [PMID: 23890059 DOI: 10.1016/j.immuni.2013.07.012]

18 **Postow MA**, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. *J Clin Oncol* 2015; **33**: 1974-1982 [PMID: 25605845 DOI: 10.1200/JCO.2014.59.4358]

19 **Topalian SL**, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Drilon A, Wolchok JD, Carvajal RD, McHenry MB, Hosein F, Harbison CT, Grosso JF, Sznol M. Five-Year Survival and Correlates Among Patients With Advanced Melanoma, Renal Cell Carcinoma, or Non-Small Cell Lung Cancer Treated With Nivolumab. *JAMA Oncol* 2019; **5**: 1411-1420 [PMID: 31343665 DOI: 10.1001/jamaoncol.2019.2187]

20 **McDermott DF**, Motzer RJ, Atkins MB, Plimack ER, Sznol M, George S, Drake CG, Rini BI, Choueiri TK, Kuzel T, Sosman JA, Smith DC, Vaishampayan UN, Powderly JD, Topalian SL, Zhao H, Waxman IM, Hammers HJ. Long-term overall survival (OS) with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and II studies. *J Clin Oncol* 2016; **34**: 4507 [DOI: 10.1200/JCO.2016.34.15]

21 **Motzer RJ**, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P; CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015; **373**: 1803-1813 [PMID: 26406148 DOI: 10.1056/NEJMoa1510665]

22   **Motzer RJ**, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2018; **378**: 1277-1290 [PMID: 29562145 DOI: 10.1056/NEJMoa1712126]

23   **Albiges L**, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthélémy P, Porta C, Powles T, Donskov F, George S, Kollmannsberger CK, Gurney H, Grimm MO, Tomita Y, Castellano D, Rini BI, Choueiri TK, Saggi SS, McHenry MB, Motzer RJ. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open* 2020; **5**: e001079 [PMID: 33246931 DOI: 10.1136/esmoopen-2020-001079]

24   **Flippot R**, Dalban C, Laguerre B, Borchiellini D, Gravis G, Négrier S, Chevreau C, Joly F, Geoffrois L, Ladoire S, Mahammedi H, Rolland F, Gross-Goupil M, Deluche E, Priou F, Laramas M, Barthélémy P, Narciso B, Houedé N, Culine S, Oudard S, Chenot M, Tantot F, Chabaud S, Escudier B, Albiges L. Safety and Efficacy of Nivolumab in Brain Metastases From Renal Cell Carcinoma: Results of the GETUG-AFU 26 NIVOREN Multicenter Phase II Study. *J Clin Oncol* 2019; **37**: 2008-2016 [PMID: 31194611 DOI: 10.1200/JCO.18.02218]

25   **Emamekhoo H**, Olsen M, Carthon BC, Drakaki A, Percent IJ, Molina AM, Cho DC, Bendell JC, Gordan LN, Kalebasty AR, George DJ, Hutson TE, Lee RJ, Young TC, Johansen J, Tykodi SS. Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: interim analysis of CheckMate 920. *J Clin Oncol* 2019; **37**: 4517 [DOI: 10.1200/JCO.2019.37.15]

26   **Rassy E**, Flippot R, Albiges L. Tyrosine kinase inhibitors and immunotherapy combinations in renal cell carcinoma. *Ther Adv Med Oncol* 2020; **12**: 1758835920907504 [PMID: 32215057 DOI: 10.1177/1758835920907504]

27   **Zhou X**, Hou W, Gao L, Shui L, Yi C, Zhu H. Synergies of Antiangiogenic Therapy and Immune Checkpoint Blockade in Renal Cell Carcinoma: From Theoretical Background to Clinical Reality. *Front Oncol* 2020; **10**: 1321 [PMID: 32850419 DOI: 10.3389/fonc.2020.01321]

28   **Motz GT**, Coukos G. The parallel lives of angiogenesis and immunosuppression: cancer and other tales. *Nat Rev Immunol* 2011; **11**: 702-711 [PMID: 21941296 DOI: 10.1038/nri3064]

29   **Wallin JJ**, Bendell JC, Funke R, Sznol M, Korski K, Jones S, Hernandez G, Mier J, He X, Hodi FS, Denker M, Leveque V, Cañamero M, Babitski G, Koeppen H, Ziai J, Sharma N, Gaire F, Chen DS, Waterkamp D, Hegde PS, McDermott DF. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016; **7**: 12624 [PMID: 27571927 DOI: 10.1038/ncomms12624]

30   **Motzer RJ**, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, Bracarda S, Stadler WM, Donskov F, Lee JL, Hawkins RE, Ravaud A, Alekseev BY, Staehler MD, Uemura M, Donaldson F, Li S, Huseni MA, Schiff C, Rini BI. IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab *vs* Sunitinib in Untreated Metastatic Renal Cell Carcinoma (mRCC). *J Clin Oncol* 2018; **36**: 578 [DOI: 10.1200/JCO.2018.36.6]

31   **Rini BI**, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, Bracarda S, Stadler WM, Donskov F, Lee JL, Hawkins R, Ravaud A, Alekseev B, Staehler M, Uemura M, De Giorgi U, Mellado B, Porta C, Melichar B, Gurney H, Bedke J, Choueiri TK, Parnis F, Khaznadar T, Thobhani A, Li S, Piault-Louis E, Frantz G, Huseni M, Schiff C, Green MC, Motzer RJ; IMmotion151 Study Group. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet* 2019; **393**: 2404-2415 [PMID: 31079938 DOI: 10.1016/S0140-6736(19)30723-8]

32   **Bersanelli M**, Cortellini A, Buti S. The way towards tailored treatment for metastatic renal cancer patients in the *omics* era: are we getting a "transcriptomic compass"? *Ann Transl Med* 2019; **7**: S190 [PMID: 31656769 DOI: 10.21037/atm.2019.07.37]

33   **Pal S**, Tsao C, Suarez C, Kelly W, Pagliaro L, Vaishampayan UN, Loriot Y, Srinivas S, McGregor BA, Panneerselvam A, Curran D, Choueiri TK, Agarwal N. Cabozantinib in combination with atezolizumab as frist line therapy for advanced clear cell renal cell carcinoma: result from the Comsic-021 study. *Annals of Oncology* 2020; **31**: S550 [DOI: 10.1016/annonc/annonc274]

34   **Clinicaltrial**.   gov (NCT04338269). A study of azetolizumab in combination with cabozantinib compared wth cabozantinib alone in participants wuth advanced renal cell carcinoma after immune checkpoint inhibitor treatment (CONTACT-03)

35   **Atkins MB**, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, Vaishampayan U, George S, Olencki TE, Tarazi JC, Rosbrook B, Fernandez KC, Lechuga M, Choueiri TK. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. *Lancet Oncol* 2018; **19**: 405-415 [PMID: 29439857 DOI: 10.1016/S1470-2045(18)30081-0]

36   **Rini BI**, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2019; **380**: 1116-1127 [PMID: 30779529 DOI:

10.1056/NEJMoa1816714]

37   **Plimack ER**, Rini BI, Stus V, Gafanov R, Waddell T, Nosov D. Pembrolizumab plus axitinib *vs* sunitinib as first line therapy for advanced renal cell carcinoma (RCC): Updated analysis of Keynote 426. *J Clin Oncol* 2020; **38**: 5001 [DOI: 10.1200/JCO.2020.38.15]

38   **Lee CH**, Shah AY, Hsieh JJ, Rao A, Pinto A, Bilen MA, Cohn AL, Simone CD, Shaffer DR, Sarrio RG, Ribe SG, Wu J, Schmidt EV, Perini RF, Kubiak P, Smith AD, Motzer RJ. Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). *J Clin Oncol* 2020; **38** [DOI: 10.1200/JCO.2020.38.15]

39   **Motzer R**, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med* 2021; **384**: 1289-1300 [PMID: 33616314 DOI: 10.1056/NEJMoa2035716]

40   **Choueiri TK**, Larkin J, Oya M, Thistlethwaite F, Martignoni M, Nathan P, Powles T, McDermott D, Robbins PB, Chism DD, Cho D, Atkins MB, Gordon MS, Gupta S, Uemura H, Tomita Y, Compagnoni A, Fowst C, di Pietro A, Rini BI. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. *Lancet Oncol* 2018; **19**: 451-460 [PMID: 29530667 DOI: 10.1016/S1470-2045(18)30107-4]

41   **Motzer RJ**, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, Venugopal B, Kollmannsberger C, Negrier S, Uemura M, Lee JL, Vasiliev A, Miller WH Jr, Gurney H, Schmidinger M, Larkin J, Atkins MB, Bedke J, Alekseev B, Wang J, Mariani M, Robbins PB, Chudnovsky A, Fowst C, Hariharan S, Huang B, di Pietro A, Choueiri TK. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2019; **380**: 1103-1115 [PMID: 30779531 DOI: 10.1056/NEJMoa1816047]

42   **Choueiri TK**, Motzer RJ, Rini BI, Haanen J, Campbell MT, Venugopal B, Kollmannsberger C, Gravis-Mescam G, Uemura M, Lee JL, Grimm MO, Gurney H, Schmidinger M, Larkin J, Atkins MB, Pal SK, Wang J, Mariani M, Krishnaswami S, Cislo P, Chudnovsky A, Fowst C, Huang B, di Pietro A, Albiges L. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol* 2020; **31**: 1030-1039 [PMID: 32339648 DOI: 10.1016/j.annonc.2020.04.010]

43   **Choueiri TK**, Powles T, Burotto M, Bourlon MT, Zurawski B, OyervidesJuárez VM. Nivolumab+cabozantinib *vs* sunitinib in first line treatment for advanced renal cell carcinoma: First results from the randomized phase III CheckMate 9ER trial. *Ann Oncol* 2020; 31: S1142-S1215 [DOI: 10.1016/annonc/annonc325]

44   **McKay RR**, Bossé D, Xie W, Wankowicz SAM, Flaifel A, Brandao R, Lalani AA, Martini DJ, Wei XX, Braun DA, Van Allen E, Castellano D, De Velasco G, Wells JC, Heng DY, Fay AP, Schutz FA, Hsu J, Pal SK, Lee JL, Hsieh JJ, Harshman LC, Signoretti S, Motzer RJ, Feldman D, Choueiri TK. The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma. *Cancer Immunol Res* 2018; **6**: 758-765 [PMID: 29748390 DOI: 10.1158/2326-6066.CIR-17-0475]

45   **Koshkin VS**, Barata PC, Zhang T, George DJ, Atkins MB, Kelly WJ, Vogelzang NJ, Pal SK, Hsu J, Appleman LJ, Ornstein MC, Gilligan T, Grivas P, Garcia JA, Rini BI. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. *J Immunother Cancer* 2018; **6**: 9 [PMID: 29378660 DOI: 10.1186/s40425-018-0319-9]

46   **Lee JL**, Ziobro M, Gafanov R, Matveev VB, Suarez C, Donskov F, Pouliot F, Alekseev BY, Wiechno PJ, Tomczak P, Climent MA, Shin SJ, Silverman RK, Perini RF, Schloss C, McDermott DF, Atkins MB. Keynote 427 cohort B: First-line pembrolizumab (pembro) monotherapy in advanced non clear cell renal cell carcinoma (nccRCC). *J Clin Oncol* 2019; **37**: 4569 [DOI: 10.1093/annonc/mdz249]

47   **Vogelzang NJ**, Olsen MR, McFarlane JJ, Arrowsmith E, Bauer TM, Jain RK, Somer B, Lam ET, Kochenderfer MD, Molina A, Doshi G, Lingerfelt B, Hauke RJ, Gunuganti V, Schnadig I, Van Veldhuizen P, Fleming M, Galamaga R, Gupta M, Hool H, Hutson T, Zhang J, McHenry MB, Johansen JL, Tykodi SS. Safety and Efficacy of Nivolumab in Patients With Advanced Non-Clear Cell Renal Cell Carcinoma: Results From the Phase IIIb/IV CheckMate 374 Study. *Clin Genitourin Cancer* 2020; **18**: 461-468.e3 [PMID: 32718906 DOI: 10.1016/j.clgc.2020.05.006]

48   **McGregor BA**, Agarwal M, Suarez C, Tsao C-K, Kelly W, Pagliaro L, Vaishampayan UN, Castellano D, Loriot Y, Werneke S, Currran D, Choueiri TK, Pal S. Cabozantinib in combination with atezolizumab as frist line therapy for advanced non-clear cell renal cell carcinoma: result from cohort 10 of the Comsic-021 study. *Ann Oncol* 2020; **31**: S558 [DOI: 10.1016/j.annonc.2020.08.78]

49   **Powles T**, Larkin JMG, Patel P, Pérez-Valderrama B, Rodriguez-Vida A, Glen H, Thistlethwaite F, Ralph C, Srinivasan G, Mendez-Vidal MJ, Liu WK, Prendergast A, Vosper L, Mousa K, Suárez C. A phase II study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO). *J Clin Oncol* 2019; **37**: 545 [DOI: 10.1200/JCO.2019.37.7]

50   **Vano Y**, Elaidi RT, Bennamoun M, Chevreau CM, Borchiellini D, Pannier Det, Maillet D, Gross-Goupil M, Tournigand C, Laguerre B, Barthelemy P, Joly F, Gravis G, Caruso S, Sun C, Verkarre V, Fridman W, Zucman-Rossi J, Sautez-Fridman C, Oudard S. Results from the phase II biomarker

driven trial with nivolumab (N) and ipilimumab or VEGFR tyrosine kinase inhibitor (TKI) in naïve metastatic kidney cancer (m-ccRCC) patients: The BIONIKK trial. *Ann of Oncol* 2020; **31**: S1142-S1215 [DOI: 10.1061/annonc/annonc325]

51   **Thompson RH**, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, Kwon ED. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res* 2007; **13**: 1757-1761 [PMID: 17363529 DOI: 10.1158/1078-0432.CCR-06-2599]

52   **de Velasco G**, Miao D, Voss MH, Hakimi AA, Hsieh JJ, Tannir NM, Tamboli P, Appleman LJ, Rathmell WK, Van Allen EM, Choueiri TK. Tumor Mutational Load and Immune Parameters across Metastatic Renal Cell Carcinoma Risk Groups. *Cancer Immunol Res* 2016; **4**: 820-822 [PMID: 27538576 DOI: 10.1158/2326-6066.CIR-16-0110]

53   **Alexandrov LB**, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. *Nature* 2013; **500**: 415-421 [PMID: 23945592 DOI: 10.1038/nature12477]

54   **Zhang C**, Li Z, Qi F, Hu X, Luo J. Exploration of the relationships between tumor mutation burden with immune infiltrates in clear cell renal cell carcinoma. *Ann Transl Med* 2019; **7**: 648 [PMID: 31930049 DOI: 10.21037/atm.2019.10.84]

55   **Samstein RM**, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 2019; **51**: 202-206 [PMID: 30643254 DOI: 10.1038/s41588-018-0312-8]

56   **Labriola MK**, Zhu J, Gupta RT, McCall S, Jackson J, Kong EF, White JR, Cerqueira G, Gerding K, Simmons JK, George D, Zhang T. Characterization of tumor mutation burden, PD-L1 and DNA repair genes to assess relationship to immune checkpoint inhibitors response in metastatic renal cell carcinoma. *J Immunother Cancer* 2020; **8** [PMID: 32221016 DOI: 10.1136/jitc-2019-000319]

57   **Kawashima A**, Uemura M, Nonomura N. Importance of Multiparametric Evaluation of Immune-Related T-Cell Markers in Renal-Cell Carcinoma. *Clin Genitourin Cancer* 2019; **17**: e1147-e1152 [PMID: 31473121 DOI: 10.1016/j.clgc.2019.07.021]

58   **Zhang S**, Zhang E, Long J, Hu Z, Peng J, Liu L, Tang F, Li L, Ouyang Y, Zeng Z. Immune infiltration in renal cell carcinoma. *Cancer Sci* 2019; **110**: 1564-1572 [PMID: 30861269 DOI: 10.1111/cas.13996]

59   **Şenbabaoğlu Y**, Gejman RS, Winer AG, Liu M, Van Allen EM, de Velasco G, Miao D, Ostrovnaya I, Drill E, Luna A, Weinhold N, Lee W, Manley BJ, Khalil DN, Kaffenberger SD, Chen Y, Danilova L, Voss MH, Coleman JA, Russo P, Reuter VE, Chan TA, Cheng EH, Scheinberg DA, Li MO, Choueiri TK, Hsieh JJ, Sander C, Hakimi AA. Tumor immune microenvironment characterization in clear cell renal cell carcinoma identifies prognostic and immunotherapeutically relevant messenger RNA signatures. *Genome Biol* 2016; **17**: 231 [PMID: 27855702 DOI: 10.1186/s13059-016-1092-z]

60   **Yao J**, Xi W, Zhu Y, Wang H, Hu X, Guo J. Checkpoint molecule PD-1-assisted CD8^{+} T lymphocyte count in tumor microenvironment predicts overall survival of patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. *Cancer Manag Res* 2018; **10**: 3419-3431 [PMID: 30237743 DOI: 10.2147/CMAR.S172039]

61   **Zhu Q**, Cai MY, Weng DS, Zhao JJ, Pan QZ, Wang QJ, Tang Y, He J, Li M, Xia JC. PD-L1 expression patterns in tumour cells and their association with CD8^{+} tumour infiltrating lymphocytes in clear cell renal cell carcinoma. *J Cancer* 2019; **10**: 1154-1161 [PMID: 30854124 DOI: 10.7150/jca.29052]