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REVIEW ARTICLE

Novel Therapeutic Approaches and Targets Currently Under Evaluation for Renal Cell Carcinoma: Waiting for the Revolution

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Abstract

Management of metastatic renal cell carcinoma has drastically changed in the last few years, witnessing the advent of more and more target therapies and, recently, of immune-checkpoint inhibitors. On the other hand, the adjuvant setting still lacks a clear beneficial treatment. Medical treatment still remains a compelling challenge. A large number of clinical trials is ongoing with the aim to identify new therapeutic approaches to expand the options in our repertoire. Several strategies are under investigation in renal cell carcinoma (RCC). These include new targeted agents and combinations of target therapy and immunotherapy. Programmed death receptor-1 (PD-1), programmed death receptor ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA4) are just part of the intricate network that regulates our immune response to cancer cells. Co-stimulators, such as glucocorticoid-induced TNFR-related protein (GITR) and tumor necrosis factor receptor superfamily, member 4 (OX40), and co-repressors, example.g. T cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3), also take part. As knowledge of the functioning of the immune system grows, so do these pathways to target with new drugs. This review is an overview of the current state of the clinical research, providing a report of ongoing Phase I, II and III clinical trials for localized and metastatic RCC, including novel target therapies, novel immunotherapy agents and new combinations strategies.

1 Introduction

Renal cell carcinoma (RCC) represents 5% of all cancers in men and 3% in women, with 65,340 estimated new cases and 14,970 estimated death in 2018 in the USA [1]. The biology of RCC, mainly depending on upregulation of angiogenic pathways, renders it very sensitive to anti-angiogenic therapies.

Key Points

We reported an overview of ongoing Phase I, II, III clinical trials for localized and metastatic RCC.

Novel target therapies, including MET inhibitors, glutaminase inhibitors, histone deacetylates inhibitors, are under evaluation.

New immunotherapeutic compounds are under investigation targeting co-modulatory pathways of the immune response, such as IDO, LAG-3, TIM-3, adenosine receptors.

Immunotherapies and target therapies are being combined in multiple ways in order to achieve better outcomes.

Tyrosine kinase inhibitors (TKI)-targeting angiogenic pathways such as vascular endothelial growth factor (VEGF) such as sunitinib, axitinib, sorafenib, pazopanib, cabozantinib, and mammalian target of rapamycin (mTOR) inhibitors, like everolimus, are the cornerstone of the treatment of metastatic

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RCC [2]. Even tivozanib, a target of VEGFR, has recently been approved despite the lack of clear survival benefit on the basis of a prospective Phase III trial comparing tivozanib to sorafenib in previously untreated patients with metastatic RCC [3]. In addition to these target therapies, the immune-checkpoint inhibitor nivolumab, an anti-programmed death receptor-1 (PD-1), in monotherapy [4] or in combination with ipilimumab [5], an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4), entered in the treatment scenario of the metastatic disease. In patients with metastatic disease, cytoreductive nephrectomy could be an option even if recent evidence seems to resize the effective role of this approach [6, 7]. For the adjuvant setting, there is not yet a consensus since no TKI has been beneficial in this scenario—the only exception being sunitinib, that, in a recently published trial investigating its role in patients with clear cell (cc) RCC at high risk of relapse, showed a benefit in terms of disease-free survival [8, 9]. However, for several reasons, including lack of improvement in overall survival, these agents may not be suggested as preferred options in adjuvant setting. Of note, further evidence seems to suggest that better patient selection may be a key issue in evaluating a new adjuvant treatment [10, 11].

Although these treatments have improved the outcomes of patients with RCC, relapse or progression to therapies eventually occurs and, in some cases, it could be an early event. Clinical research is continually evolving, always experimenting with novel drugs or combinations in order to improve clinical outcomes of our patients. As the knowledge of resistance mechanisms and biological characteristics of the tumor and its interaction with the immune system grows, so do the researchers' efforts to design more and more clinical trials to expand treatment options.

Here we present a review of the current state of ongoing active and recruiting Phase I, II and III clinical trials for patients with metastatic, locally advanced and resected RCC.

2 Combination of Immunotherapy and Target Therapy

Combining new immune-checkpoint inhibitors to 'standard' target therapy is a promising and emerging approach, which could potentially lead to a significant improvement of patient's clinical outcomes. As known, most target drugs currently adopted in the management of RCC have angiogenesis as a primary target, which is mainly represented by the VEGFR/VEGF pathway. When we look at pathways regulating immune response and angiogenesis, we need to imagine a very complex and strongly braided net in which external factors acting in one, are inexorably involved with the other. As a consequence, factors acting to inhibit angiogenesis seem to enhance immunity against a tumor and, conversely, factors acting on the immune system can promote or repress angiogenesis. This happens mainly because of an indirect action of angiogenesis on immune-suppressive cytokines and cells other than a direct activation of immune-checkpoint on the surface of cancer cells promoted by VEGF [12–16].

Not surprisingly, the adoption of combination treatment with new immune-checkpoint inhibitors and target therapy represents a very attractive approach that has already been investigated in some clinical trials.

The PD-1 inhibitor, pembrolizumab, has been tested in combination with axitinib or lenvatinib in Phase Ib and Ib/II trials, respectively, showing a good safety profile and a promising response rate (73% and 63% in overall population in combination with axitinib and lenvatinib, respectively) [17, 18]. Furthermore, when added to the selective inhibitor of indoleamine 2,3-dioxygenase-1, pembrolizumab showed an objective response rate (ORR) of 47% [19].

Nivolumab and cabozantinib, with or without ipilimumab, showed an ORR of 54% even if treatment was associated with a significant rate of grade 3–4 toxicities in both arms [20]. Similar response rate has also been observed with the combination of nivolumab and tivozanib (44%) and avelumab—an anti-programmed death-ligand-1 (PD-L1), and axitinib (58%), even if grade 3–4 toxicities were frequent in both these studies (32% and 52%, respectively) [21, 22].

Furthermore, the combination of atezolizumab, an anti PD-L1, and bevacizumab has been tested in Phase I and II trials and the positive results obtained have led to the design of a Phase III trial (IMmotion151) that is currently ongoing [23, 24]. Although promising preliminary results have been observed in this last Phase III trial, final results are still awaited.

Due to the promising results achieved, the combination of immune-checkpoint inhibitors and target therapy is one of the most promising approaches under investigation.

2.1 Phase III Trials Exploring the Combination of Immunotherapy and Target Therapy

Several Phase III trials are currently ongoing (Table 1). The randomized Phase III clinical trial NCT02811861 (CLEAR) is currently exploring if the combination of pembrolizumab and lenvatinib or the combination of lenvatinib and everolimus could result in a significant improvement of outcomes over sunitinib in patients with untreated metastatic RCC (mRCC). This study has a planned enrollment of 1050 patients with an estimated primary completion date in April 2020.

Results of two Phase III randomized clinical trials: JAVELIN RENAL 101 and KEYNOTE 426 have been recently reported [25, 26]. In JAVELIN RENAL 101 trial, the combination of axitinib and avelumab has been compared to

sunitinib in patients with metastatic RCC. Patients treated with the combination showed a longer progression free survival (PFS) [hazard ratio (HR) for PFS, 0.69; 95% CI 0.56–0.84] and higher objective response rate (55.2% vs 25.5%) [25]. In KEYNOTE 426, patients with metastatic RCC were randomized to receive sunitinib alone or the combination of pembrolizumab and axitinib. Again, patients in the combination group showed a significantly longer estimated 12-month overall survival (OS), HR 0.53, 95% CI 0.38–0.74), PFS (HR 0.69, 95% CI 0.57–0.84) and objective response rate (59.3% vs 35.7%) [26].

Nivolumab and cabozantinib with or without ipilimumab are under investigation versus sunitinib in previously untreated mRCC. With a planned recruitment of 630 patients, Checkmate 9ER (NCT03141177) is a randomized three-arm Phase III trial with PFS as primary endpoint in patients with intermediate/poor risk according to the International Metastatic RCC Database Consortium (IMDC) criteria.

The IMmotion 151 trial has investigated the combination of atezolizumab and bevacizumab over sunitinib in patients with metastatic RCC. Co-primary endpoints of the study were PFS in overall population and in patients expressing PD-L1. Despite that OS was immature at the first interim analysis, a PFS benefit was observed in all subgroups (HR 0.74 95% CI 0.57–0.96 in PD-L1-positive patients and HR 0.83 95% CI 0.7–0.97 in intention-to-treat population). ORR was 43% in the combination arm and 35% in the sunitinib arm. Despite these promising results, final survival analyses are still awaited [24].

2.2 Phase I and I/II Trials Exploring the Combination of Immunotherapy and Target Therapy

Other than combination with axitinib, bevacizumab and cabozantinib (NCT03341845, NCT02724878, NCT03141177, NCT03635892, NCT03172754, NCT03149822, NCT03595124, NCT03170960, NCT03200587, NCT03086174, NCT02496208), immune-checkpoint inhibitors are under investigation in combination with other target agents. As known, phosphorylation, acetylation, deacetylation, ADP ribosylation, sumoylation, citrullination, ubiquitination and deamination modulate histone functions and gene expression [27]. In particular, acetylation results in increased DNA accessibility as affinity between histones and DNA is reduced by addiction of acetyl groups. On the contrary, deacetylation results in lower DNA accessibility and gene silencing. Different agents targeting these functions are currently under investigation. Although a number of toxicities have been shown in some trials investigating molecules able to interact with histones physiology, the evaluation of deacetylase and acetylase histone inhibitors still remains an interesting approach mainly due to a strong biological rationale [28]. Thus, the class 1 histone deacetylases inhibitor entinostat is currently under investigation in combination with IL-2, bevacizumab and atezolizumab, and with the combination nivolumab and ipilimumab (NCT03501381, NCT03552380, NCT03024437). Panobinostat is another deacetylase inhibitor that is currently under investigation with the PD-1 inhibitor PDR001 and with LCL161 (a specific inhibitor of apoptosis protein IAP) (NCT02890069). Chidamide is a histone deacetylase inhibitor, which is able to inhibit several classes of histone deacetylases such as: HDAC1, HDAC2, HDAC3 and HDAC10. This drug is currently under investigation in combination with nivolumab (NCT02718066).

Sitravatinib (MGCD516) is a small multi-tyrosine kinase inhibitor, which is able to interact with several pathways including: TYRO3, AXL, MerTK, VEGFR, PDGFR, KIT, RET and MET, and has recently been demonstrated to enhance immune checkpoint blockade in refractory cancer models [29]. The combination of sitravatinib and nivolumab is currently under investigation in two Phase I/II clinical trials (NCT03015740, NCT03680521).

Savolitinib (AZD6094) is a selective MET tyrosine kinase inhibitor that has already been tested in a population of 109 patients with papillary RCC. In patients with recognized MET altered status, the administration of savolitinib resulted in an ORR of 18% with a PFS of 6.2 months [30]. A Phase I/II trial is currently testing the combination of savolitinib and durvalumab versus both the two treatments alone and versus the combination of durvalumab and tremelimumab (NCT02819596). Furthermore, the MET inhibitor bosutinib (CBT-101) in association with nivolumab is under investigation in previously treated metastatic hepatocellular carcinoma and RCC (NCT03655613). Bruton tyrosine kinase (BTK) is a key tyrosine kinase that drives lymphocyte B maturation and mast cell activation. As known, mutations in BTK gene lead to primary immunodeficiency (X-linked agammaglobulinemia). Ibrutinib (PCI-32765) is a selective BTK inhibitor, which has been shown to significantly improve clinical outcomes of patients with hematological malignancies [31, 32]. As BTK seems to be an interesting targetable pathway in solid tumors, this agent is currently being tested in solid malignancies [33]. In particular, the combination of nivolumab and ibrutinib is under investigation in a Phase I/II clinical trial (NCT02899078).

Other approaches under investigation involve the combination of the inhibitor of VEGF-A/B aflibercept and pembrolizumab while another Phase I trial is evaluating the combination using this latter PD-1 inhibitor and the angiopoietin 1–2 neutralizing peptibody (AMG386) (NCT02298959, NCT03239145).

A Phase II trial is investigating the combination of axitinib- and pembrolizumab-activated autologous D-CIK

Table 1 An overview of ongoing Phase III clinical trials in renal cell carcinoma. When available we reported preliminary results

NCT Name	Pts (no.)	Setting	Arm A	Arm B	Arm C	Primary endpoints	Estimated primary completion date	Preliminary results
NCT02811861 CLEAR	1050	First line	Sunitinib	Lenvatinib + pembrolizumab	Lenvatinib + everolimus	PFS	June 2020	Not available
NCT03141177 Checkmate 9ER	630	First line	Sunitinib	Nivolumab + Cabozantinib	Nivolumab + Ipilimumab + Cabozantinib	PFS	September 2019	Not available
NCT02420821 IMmotion 151	915	First line	Sunitinib	Atezolizumab + Bevacizumab	None	PFS/OS	October 2018	PFS benefit was observed in all subgroups with combination (HR 0.74 95% CI 0.57–0.96 in PD-L1 positive patients and HR 0.83 95% CI 0.7–0.97 in intention to treat population). ORR was 43% in combination arm and 35% in sunitinib arm
NCT03260894 KEYNOTE 679	129	First line	Sunitinib Or Pazopanib	Pembrolizumab + Epacadostat	None	PFS/OS	August 2018	Not available
NCT03592472 RENAVIV	413	First line	Pazopanib + placebo	Pazopanib + Abexinostat	None	PFS	January 2022	Not available
NCT03091192	53	First line	Sunitinib	Savolotinib	None	PFS	March 2020	Preliminar results: not available Note: patients with MET-driven papillary RCC.
NCT03138512 CheckMate 914	800	Adjuvant	Observation	Nivolumab + Ipilimumab	None	DFS	September 2022	Not available
NCT03142334 Keynote 564	950	Adjuvant	Observation	Pembrolizumab	None	DFS	November 2022	Not available
NCT03288532 RAMPART	1750	Adjuvant	Observation	Durvalumab	Durvalumab + Tremelimumab	DFS/OS	December 2023	Not available
NCT03024996 (IMmotion 010)	664	Adjuvant	Observation	Atezolizumab	None	DFS	May 2022	Not available
NCT03055013	766	Perioperative	Nephrectomy	Nephrectomy + Perioperative Nivolumab	None	DFS	November 2023	Not available

DFS disease-free survival, *OS* overall survival, *PFS* progression free survival

(cytokine-induced killer cells stimulated using mature dendritic cells). This approach consists of the acquisition of peripheral blood mononuclear cells by peripheral blood of patients, then these same cells are incubated with cytokines and pembrolizumab and finally re-infused in patients (NCT03736330).

As known, RCC, tumor cells often present an alteration of their metabolism, which mainly involves a switch, and thus increased production of pyruvate and lactate with a reduction of oxidative and mitochondrial activity. This switch is known as Warburg effect and several molecules that are able to interfere with these metabolic alterations have been tested in RCC [34]. In particular, metabolism of glutamine seems to be a key pathway for the production of lipids, amino acids, adenosine triphosphate (ATP) and nucleotides [35].

A Phase I/II clinical trial is currently evaluating if the combination of the glutaminase inhibitor CB-839 and nivolumab results in a safety profile and clinical activity in patients with melanoma, non-small cell lung cancer and clear cell RCC (ccRCC) (NCT02771626).

Curiously, another enzymatic inhibitor known as trigriluzole (BHV-4157) is under evaluation as combination treatment with nivolumab (NCT03170960). This agent has antidepressant and anxiolytic activity as it interferes with glutamate release and sodium channel activation and, due to its ability to interfere with glutamate transmission, it has also been evaluated in Alzheimer's disease [36]. However, maybe due to its ability to interact with some metabolic pathways still unknown, it also presented an interesting anti-neoplastic activity.

Liver X receptor is a member of a nuclear receptor family of transcription factors, which modulate important functions such as cholesterol, fatty acid, and glucose homeostasis. Very recently, its role appears to be of particular interest as it seems to be altered in cancer cells where it drives key functions leading to cancer progression and development [37, 38]. The liver X receptor inhibitor RGX-104 and the anti-PD-1 nivolumab are under investigation in a Phase I trial (NCT02922764) [37, 38].

Of interest, synthetic protein able to bind specific proteins on the surface of cancer cells and stimulate immune response against these same cells, is under development. RO6874281 is a fusion protein under investigation in a Phase I trial in combination with atezolizumab alone or with atezolizumab and bevacizumab. This protein consists of a human anti-fibroblast activation protein-alpha (FAP) antibody and an engineered interleukin-2 (NCT03063762). By targeting FAP-positive tumor cells, this compound could enhance local immune response and promote tumor regression.

3 Combination of Immunotherapies

Targeting different pathways of the immune response system, which is made up of an intricate web of stimulatory and inhibitory signals, is a strategy used to enhance response to therapies. Different combinations of immune checkpoint inhibitors are being studied in Phase I, II and III trials in the adjuvant and metastatic settings. The results of the combination of nivolumab plus ipilimumab investigated in the Phase III trial Checkmate 214 [5] have already been published and show an advantage in term of OS and ORR for the combination compared to sunitinib among intermediate- and poor-risk patients with previously untreated advanced ccRCC.

Currently, the combination of nivolumab plus ipilimumab is being investigated in seven Phase II trials in the metastatic setting in first or following lines in clear cell and/or non-clear cell (ncc) RCC (NCT03203473, NCT03075423, NCT03297593, NCT03117309, NCT02960906, NCT02917772, NCT03177239) and one Phase III randomized trial versus placebo in the adjuvant setting in patients with ccRCC at high risk of relapse after nephrectomy (NCT03138512) (Table 2).

Durvalumab, an anti-PLD-L1, in monotherapy or in combination with tremelimumab, an anti-CTLA4, is under investigation in a randomized Phase III trial (NCT03288532) in patients with RCC (Table 1), both cc and ncc, at high or intermediate risk of relapse compared with active monitoring. Durvalumab in monotherapy or plus tremelimumab is also being investigated in the neoadjuvant setting in a Phase Ib trial (NCT02762006) in patients with any histological subtype RCC T2b-4 and/or N1, M0 disease, followed by nephrectomy.

The combination of pembrolizumab with low-dose interleukin-2 is being evaluated in a Phase I/II trial in advanced RCC after failure of anti-PD-1/PD-L1 and TKI therapies (NCT03111901).

4 Novel Target Agents

Although the research of new combination strategies appears to be one of the most promising approaches under investigation in RCC, the identification of new targets still remains a key issue in management of RCC (Table 2). Other than new target inhibitors developed to inhibit specific altered pathways of the disease, several efforts directing on the inhibition or stimulation of immune receptors are under investigation.

As already described, mutations in tumor cells resulting in metabolic alterations are perhaps the more common event in all RCC subtypes. It is important to

Table 2 An overview of ongoing and active Phase II, I/II and I studies on RCC. We also reported a brief description of new molecules under evaluation

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT03297593	2	Metastatic	Nivolumab + ipilimumab			37	ORR
NCT03173560	2	Metastatic	Lenvatinib 18 mg plus everolimus 5 mg vs Lenvatinib 14 mg plus everolimus 5 mg			306	ORR, safety
NCT03200717	2	Metastatic	Pazopanib			100	PFS
NCT03013335	2	Metastatic	Nivolumab			450	Safety
NCT02330783	2	Metastatic	Bevacizumab + Sorafenib	Sorafenib		106	PFS
NCT03552380	2	Metastatic	Entinostat + Nivolumab + Ipilimumab		Inhibitor of Class 1 Histone Deacetylases (HDACs)	53	Safety
NCT02446860	2	Metastatic	Nivolumab			19	Safety
NCT03280667	2	Metastatic	Pembrolizumab + Denosumab			70	ORR
NCT03463681	2	Metastatic	Cabozantinib			49	PFS
NCT02019693	2	Metastatic	INC280 (capmatinib)		c-Met Inhibitor	22	ORR
NCT03117309	2	Metastatic	Nivolumab –> if PD Nivolumab + Ipilimumab			120	PFS
NCT03680521	2	Neoadjuvant	Sitravatinib + Nivolumab		Sitravatinib: RTKs including RET, TRK family, DDR2, MET, AXL and split RTKs (VEGFR, PDGFR and KIT).	25	ORR
NCT03354884	2	Metastatic	Cabozantinib			23	ORR
NCT02960906	2	Metastatic	Nivolumab vs Nivolumab + Ipilimumab vs Sunitinib or Pazopanib			150	ORR
NCT03635892	2	Metastatic	Cabozantinib + nivolumab			37	ORR
NCT03541902	2	Metastatic	Cabozantinib	Sunitinib		84	PFS
NCT02915783	2	Metastatic	Lenvatinib + everolimus			22	ORR
NCT02819596	2	Metastatic	Savolitinib vs Durvalumab (MEDI4736) vs Savolitinib + Durvalumab vs Tremelimumab + Durvalumab		Savolitinib: inhibitor c-MET	195	Safety
NCT02689167	2	Metastatic	Sunitinib 50 mg/day; regimen 2/3 (experimental arm) 2 weeks “on” alternating with 1 week “off”	Sunitinib 37.5 mg/day; regimen 4/6		248	MDT (median duration of treatment)
NCT02700568	2	Metastatic	Axitinib			21	PFS
NCT02917772	2	Metastatic	Nivolumab + Ipilimumab			200	ORR
NCT03092856	2	Metastatic	Axitinib + anti-OX40 antibody PF-04518600	Axitinib + placebo	An agonistic antibody that recognizes the co-stimulatory receptor OX40 (CD134;TNFRSF4), which induces proliferation of memory and effector T-lymphocytes	104	PFS
NCT02761057	2	Metastatic	Sunitinib vs cabozantinib vs crizotinib vs volitinib			180	PFS

Table 2 (continued)

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT03634540	2	Metastatic	PT2977 + cabozantinib		PT2977 inhibits hypoxia-inducible factor (HIF-2α)	118	ORR
NCT02996110	2	Metastatic	Nivolumab + Relatlimab vs Nivolumab + BMS-986205	Nivolumab + Ipilimumab	Relatlimab: anti-LAG-3. BMS-986205: IDO1 inhibitor	200	ORR, duration of response, PFSR
NCT03177239	2	Metastatic	Nivolumab + Ipilimumab			85	ORR
NCT03595124	2	Metastatic	Axitinib + nivolumab vs axitinib vs nivolumab			87	PFS
NCT03401788	2	Localized	PT2977		Inhibitor of HIF-2α	50	ORR
NCT03438708	2	Neoadjuvant	Axitinib			50	ORR
NCT03736330	2	Metastatic	Axitinib + pembrolizumab-activated autologous D-CIK cells		Autologous dendritic and cytokine-induced killer cells (D-CIK)	24	ORR
NCT03165721	2	Metastatic	Guadecitabine		Guadecitabine: antimetabolite	70	ORR
NCT03207347	2	Metastatic	Niraparib		Niraparib	47	ORR
NCT03207867	2	Metastatic	NIR178 + PDR001		NIR178: immune checkpoint inhibitor and antagonist of the adenosine A2A receptor (A2AR; ADORA2A). PDR001: anti PD1	260	ORR
NCT03229278	2	Metastatic	Trigriluzole + nivolumab or pembrolizumab		Trigriluzole: Enzyme Inhibitor Therapy	27	Safety
NCT02568267	2	Metastatic	Entrectinib		Entrectinib: TrkA/B/C, ROS1, and ALK inhibitor	300	ORR
NCT03341845	2	Neoadjuvant	Axitinib + Avelumab			40	ORR
NCT03203473	2	Metastatic	Nivolumab, Nivolumab + Ipilimumab			58	ORR
NCT03163667	2	Metastatic	CB-839 + Everolimus	Placebo + everolimus	CB-839 glutaminase inhibitor	63	PFS
NCT03501381	2	Metastatic	Entinostat + IL-2 high dose	IL-2 high dose	Inhibitor of Class 1 Histone Deacetylases (HDACs)	46	PFS
NCT03428217	2	Metastatic	CB-839 + Cabozantinib	Placebo + Cabozantinib	CB-839 glutaminase inhibitor	298	PFS
NCT01444807	2	Adjuvant after Metastasectomy	Sorafenib	BSC		132	RFS
NCT03075423	2	Metastatic	Nivolumab + Ipilimumab	Sunitinib		306	12 months OS
NCT01130519	2	Metastatic	Bevacizumab + Erlotinib			85	ORR

Table 2 (continued)

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT03097328	2	Metastatic	TAK-228 (sapanisertib)		TAK-228 works to inhibit or interfere with cellular functions involved in cell growth and survival. TAK-228 specifically targets a type of protein that can make chemicals that trigger cell growth, including cancer cell TORC1/2 Inhibitor	40	ORR
NCT02724878	2	Metastatic	Bevacizumab + Atezolizumab			60	ORR
NCT03126331	2	Metastatic	Nivolumab			40	Safety
NCT03066427	2	Metastatic	Sunitinib			23	ORR
NCT02721732	2	Metastatic	pembrolizumab			275	Non-progression rate,safety
NCT03655613	1/2	Metastatic	Bozitinib + Nivolumab		Bozitinib: CBT-101 c-Met inhibitor	119	Safety
NCT03393936	1/2	Metastatic	CCT301-59 vs CCT301-38		CAR T	66	Safety, ORR
NCT03015740	1/2	Metastatic	Sitravatinib (MGCD516) + Nivolumab		Sitravatinib: RTKs including RET, TRK family, DDR2, MET, AXL and split RTKs (VEGFR, PDGFR and KIT).	60	Safety
NCT03172754	1/2	Metastatic	Nivolumab + Axitinib			98	Safety
NCT02919371	1/2	Metastatic	Sunitinib + Bevacizumab			77	Safety
NCT02989714	1/2	Metastatic	High Dose Interleukin-2 + Nivolumab			23	Safety
NCT03149822	1/2	Metastatic	Pembrolizumab 200 mg + Cabozantinib 40 mg vs Pembrolizumab 200 mg + Cabozantinib 60 mg vs Pembrolizumab 200 mg + Cabozantinib at the recommended phase 2 dose			55	ORR
NCT01684397	1/2	Metastatic	Pazopanib + bevacizumab			35	PFS, safety
NCT02495103	1/2	Metastatic	Vandetanib + Metformin		Vandetanib: anti VEGFR, EGFR, RET	73	Safety
NCT03024437	1/2	Metastatic	Phase I and Phase II cohort A: Entinostat + Bevacizumab + Atezolizumab. Phase II cohort B: Atezolizumab, if PD + Entinostat		Entinostat: inhibitor of Class 1 Histone Deacetylases (HDACs)	62	Safety
NCT02771626	1/2	Metastatic	CB-839 + Nivolumab		CB-839: Glutaminase inhibitor	299	Safety, efficacy
NCT03111901	1/2	Metastatic	Pembrolizumab + LD-IL2			73	Safety/DFS
NCT02599324	1/2	Metastatic	Ibrutinib + everolimus		Ibrutinib	261	Safety
NCT03548467	1/2	Metastatic	VB10.NEO + checkpoint inhibitor		VB10.NEO: vaccine	65	Safety

Table 2 (continued)

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT02830724	1/2	Metastatic	Non-myeloablative lymphodepleting preparative regimen of cyclophosphamide and fludarabine + anti-hCD70 CAR transduced PBL + high-dose aldesleukin		Anti-hCD70 CAR transduced PBL (peripheral blood lymphocytes)	113	Safety
NCT02903914	1/2	Metastatic	INCB001158 (CB-1158)		Arginase Inhibitor	346	Safety
NCT02111850	1/2	Metastatic	Non-myeloablative lymphodepleting preparative regimen of cyclophosphamide and fludarabine + Anti-MAGE-A3-DP4 TCR PBL + high-dose aldeskin		Anti-MAGE-A3-DP4 TCR PBL	107	Safety
NCT02983045	1/2	Metastatic	NKTR-214 + Nivolumab vs NKTR-214 + Nivolumab + Ipilimumab		NKTR-214 is a CD122-biased agonist	480	Safety
NCT03633110	1/2	Metastatic	Part B (metastatic): GEN-009 + Nivolumab. Part C (have received at least 1 line of standard systemic therapy that included a PD-1 or PD-L1 inhibitor): GEN-009		GEN-009 Adjuvanted Vaccine	124	Safety
NCT02886897	1/2	Metastatic	D-CIK + anti-PD-1		Dendritic Cells and Cytokine-induced Killer Cell	50	PFS
NCT02089334	1/2	Metastatic	RX-0201 + everolimus		Akt-1 inhibitor	23	Safety
NCT02899078	1/2	Metastatic	Ibrutinib + Nivolumab		BTK Inhibitor	30	PFS
NCT02718066	1/2	Metastatic	HBI-8000 + nivolumab		Chidamide (histone deacetylase inhibitor): inhibits Class I HDAC1, HDAC2, HDAC3, as well as Class IIb HDAC10	78	Safety
NCT03308396	1/2	Metastatic	Phase I: Guadecitabine. Phase II: Guadecitabine + Durvalumab		Guadecitabine: antimetabolite	58	Safety/ORR
NCT03170960	1/2	Metastatic	Atezolizumab+cabozantinib	Cabozantinib		1000	Safety/ORR
NCT03576131	1/2	Metastatic	GEN1029		GEN1029 is a DR5 agonist	188	Safety
NCT03638206	1/2	Metastatic	CAR-T/TCR-T			73	Safety/ORR
NCT03435640	1/2	Metastatic	NKTR-262+NKTR214	NKTR-262+NKTR-214+Nivolumab	NKTR-262 is a TLRs 7/8receptor agonist, NKT3 214 is a CD122 agonist	393	Safety/ORR
NCT00722228	1/2	Metastatic	Autologus and allogenic cell cancer vaccine			50	Safety
NCT03602079	1/2	Metastatic	A166		AI66 is a Her2 inhibitor	82	Safety/ORR
NCT02697591	1/2	Metastatic	INCAGN01876		INCAGN01876 is a GITR agonist	146	Safety
NCT02608268	1/2	Metastatic	MBG453, PDR001		MBG453 is a TIM-3 inhibitor, PDR001 is a PD-1 inhibitor	250	Safety/ORR
NCT03126110	1/2	Metastatic	INCAGN01876+Nivolumab+Ipilimumab		INCAGN01876 is a GITR agonist	285	Safety/ORR
NCT02460224	1/2	Metastatic	LAG525,PDR001		LAG525 is a LAG-3 inhibitor	515	Safety/ORR

Table 2 (continued)

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT03294083	1	Metastatic	REGN2810+ONCOLYTIC VIRUS		Pexa-Vec is a vaccinia virus designed to stimulate the immune system; REGN2810 is a monoclonal antibody to Programmed Death-1 (PD-1)	89	Safety
NCT03063762	1	Metastatic	RO6874281		RO6874281 is a fusion protein consists of a human anti-fibroblast activation protein-alpha (FAP) antibody and an engineered interleukin-2, which may stimulate local immune response against FAP-positive tumor cells (NCI Drug Dictionary)	279	Safety/ORR
NCT03354390	1	Metastatic	HERV-E TCR		HERV-E TCR transduced CD8+/CD34+ T cells in HLAA* 11:01 positive patients with metastatic ccRCC.	24	Safety
NCT02762006	1	Locally advanced	Durvalumab/tremelimumab			45	Safety
NCT03200587	1	Metastatic	Avelumab/Cabozantinib			20	Safety
NCT03086174	1	Metastatic	JS001+axitinib		Anti PD-1	24	Safety
NCT02577458	1	Metastatic	CM082+everolimus		CM082(Vorolanib) a VEGFR/PDGFR inhibitor	18	Safety
NCT03260504	1	Metastatic	IL-2 + Pembrolizumab			27	Safety
NCT02595918	1	Locally advanced	Nivolumab			29	Safety/feasibility
NCT03502330	1	Metastatic	Nivolumab, Cabiralizumab, APX005 M	APX005 M, Cabiralizumab	APX005 M monoclonal activity against CD40, Cabiralizumab against CSF1R	120	Safety
NCT03483883	1	Metastatic	Avelumab/Gemcitabine			24	Safety
NCT02890069	1	Metastatic	PDR001+LCL161+Panobinostat		PDR001 is a PD-1 inhibitor, LCL161 is a Inhibitor of IAP (inhibitor of Apoptosis Protein), Panobinostat is a histone deacetylase inhibitor	350	Safety
NCT02767921	1	Locally advanced	sEphB4-HSA		A recombinant fusion protein composed of the full-length extracellular domain (soluble) of human receptor tyrosine kinase ephrin type-B receptor 4 (sEphB4) and fused, at its C-terminus, to full-length human serum albumin (HSA), with potential antineoplastic and anti-angiogenic activities.	30	Safety
NCT02974738	1	Metastatic	PT2977		HIF2alpha inhibitor	125	Safety
NCT03464032	1	Metastatic	BCD-135		PD-L1 inhibitor	30	Safety
NCT03652077	1	Metastatic	INCAGN02390		TIM-1 inhibitor	76	Safety

Table 2 (continued)

NCT	Phase	Setting	Experimental arm	Comparator arm	Compounds description	*n*	Primary outcome
NCT03549000	1	Metastatic	NZV930, PDR001, NIR178	NZV930 +/− PDR001 +/− NIR178	NZV930 is a CD73 inhibitor, PDR001 is a PD-L1 inhibitor, NIR178 is a A2A receptor antagonist	334	Safety
NCT03454451	1	Metastatic	CPI-006	CPI-006 +/− Pembrolizumab or CPI-444	CPI-006 is an anti CD73, CPI-444 is a A2A receptor antagonist	378	Safety/ORR
NCT02655822	1	Metastatic	CP-444+Atezolizumab	CPI-444	A A2A receptor inhibitor	323	Safety
NCT03175224	1	Metastatic	CBT-101		c-MET inhibitor	68	Safety
NCT03329950	1	Metastatic	CDX-1140	CDX-1140 + CDX-301	CDX-1140 is a CD40 inhibitor, CDX-301 is a dendritic cell growth factor	180	Safety
NCT02496208	1	Metastic	Cabozantinib + Nivolumab + Ipilimumab	Cabozantinib + Nivolumab + ipilimumab		152	Safety
NCT03538028	1	Metastatic	INCAGN02385		LAG-3 inhibitor	55	Safety
NCT02111850	1	Metastatic	MAGE-A3 T Cell Receptor Immunotherapy Targeting MAGE-A3			107	Safety
NCT02298959	1	Metasatic	ziv-aflibercept + Pembrolizumab			36	Safety
NCT03517488	1	Metastatic	XmAb20717		A PD-1/CTLA-4	87	Safety
NCT02947165	1	Metastatic	NIS793	NIS793-Nivolumab	NIS793: TGF Beta antibody; PDR001: PD-1 inhibitor	220	Safety
NCT03311334	1	Metastatic	DSP-7888 + Nivolumab	DSP-7888 + Atezolizumab	DSP-7888 Dosing Emulsion is a synthetic cancer peptide vaccine	84	Safety
NCT03628677	1	Metasatic	ABI154	ABI 154-ABI122	ABI154 is a TIGIT inhibitor, ABI122 is a PD-1 inhibitor	42	Safety
NCT03289962	1	Metastatic	RO7198457	RO7198457 + Atezolizumab	Personalized cancer vaccine	567	Safety
NCT03053466	1	Metastatic	cbt-501		PD-1 inhibitor	114	Safety
NCT03629756	1	Metastatic	AB928 AB122		AB928 is a A2aR and A2bR antagonist, AB122 is a PD-1 inhibitor	18	Safety
NCT03212404	1	Metastatic	CK-301		A PD-L1 inhibitor	80	Safety
NCT02628535	1	Metasatic	MGD009		CD3 and B7-H3 inhibitor	114	Safety
NCT02315066	1	Metasatic	PF-04518600	PF-04518600+PF-05082566	PF-04518600 a OX40 agonist; PF-05082566 a OX40 agnonist and 4-1BB agonist	210	Safety
NCT02922764	1	Metastatic	RGX-104	RGX-104 + Nivolumab	Liver X receptor agonist	150	Safety
NCT03239145	1	Metastatic	AMG386 + pembrolizumab		An angiopoietin (Ang) 1 and 2 neutralizing peptibody	60	Safety
NCT02219711	1	Metastatic	MGCD516		A multitarget inhibitor (MET)	260	Safety

DFS disease-free survival, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival

observe that several different mutations inevitably lead to metabolic shift, which often, but not always, results in a 'Warburg effect' [34]. The anaerobic degradation of glucose- more than mitochondrial-mediated oxidative phosphorylation is the main consequence of this shift, which also leads to augmented dependence on pentose phosphate shunt, higher fatty acid production, higher intracellular level of lactate, and reduction of Krebs cycle activity.

Several altered genes could explain the metabolic alteration observed in RCC. VHL is certainly the more frequently altered gene in ccRCC. Other genes of particular interest, which are frequently mutated in RCC, are MET and mTOR. Alterations occurring in these genes lead to important and metabolic alterations which can be targeted by specific drugs. [39–47]. Alteration of these genes results in one of the most important alterations observed in RCC, that of neo-angiogenesis. Thus, agents able to inhibit pathways related to metabolic alteration and angiogenesis promotion represent a successful strategy for the management of RCC. Thus, the investigation of new agents able to interfere with these two hallmarks of RCC are of particular interest.

The VEGFR and PDGFR inhibitor vorolanib was designed to maintain the same clinical efficacy and pharmacodynamic proprieties of sunitinib with a better safety and toxicity profile. This agent was recently evaluated in a Phase I trial in patients with solid tumors, and confirmed a safety profile with a standard dose of 400 mg/daily [48]. It is currently under evaluation as monotherapy or in combination with the mTOR inhibitor everolimus in a Phase I and II/III trial (NCT02577458, NCT03095040). Other inhibitors have been developed to specifically target the hypoxia-inducible factor 1 and 2. As known, VHL is the most frequently altered gene in ccRCC. This gene is one of the major regulators of the ubiquitin-dependent degradation of the hypoxia-inducible factor 1 and 2 alpha (HIF1-2α). Accumulation of HIF1-2α occurring during hypoxia (physiological condition) or VHL loss (pathological condition) leads to up-regulation of hypoxia-response elements such as VEGF, PDGF, EGF and GLUT1 (the glucose transporter). Moreover HIF1α enhances glycolytic enzyme expression and reduces mitochondrial pyruvate consumption [39–42]. PT2977 is a HIF-2α inhibitor currently under investigation in a Phase I trial (NCT02974738) and in a Phase II trial in combination with cabozantinib (NCT03634540).

One attractive target in RCC is the MET tyrosine kinase receptor. This is mainly due to its key role in regulation of several functions of tumor cells such as: angiogenesis, resistance and progression to other TKIs targeting VEGFR, acquisition of aggressive behaviors by tumor, including metastatic proprieties and bone invasion [49]. The importance of this pathway could be further highlighted by the results obtained with MET inhibitors in papillary RCC [30], and by the results obtained by the multi-target inhibitor cabozantinib in RCC [50, 51]. Thus, other inhibitors targeting MET are under investigation. A randomized Phase III clinical trial is evaluating if administration of savolitinib could result in a PFS benefit over sunitinib in patients with metastatic or locally advanced MET-driven papillary RCC (NCT03091192). Capmatinib is a selective c-MET inhibitor currently under evaluation in a Phase II trial in patients with RCC (NCT02019693), while a Phase I study is currently evaluating the MET and multi-tyrosine kinase inhibitor sitravatinib in patients with advanced cancers (NCT02219711). Furthermore, volitinib is a MET inhibitor currently under investigation in a Phase I/II trial comparing sunitinib, cabozantinib and crizotinib in metastatic papillary RCC (NCT02761057).

As already described, agents able to interfere with altered metabolism of RCC are under investigation. Among these, agents able to inhibit function and synthesis of glutamine appear to be of particular interest, as this molecule seems to play a key role in driving disease progression and development [36]. Thus, CB-839, a glutaminase inhibitor, is under investigation in combination with nivolumab in a Phase I/II clinical trial (NCT02771626), as already mentioned, and in combination with the mTOR inhibitor everolimus and the multi-target inhibitor cabozantinib in two different Phase II trials (NCT03163667, NCT03428217, respectively).

Modulation of DNA transcription by regulation of chromatin conformation as driven by histone status seems to be an attractive approach. Indeed, histone conformation makes DNA more or less accessible for transcription modifying tumor-cell transcription and protein synthesis. Agents able to interfere with acetylation status of histones are under investigation and, as already described, several deacetylase inhibitors are under evaluation with immune-checkpoint inhibitors. However, a Phase 3 trial is investigating if the addition of abexinostat (a deacetylase inhibitor) to standard first-line therapy with pazopanib could lead to a clinical benefit over pazopanib and placebo. The RENAVIV trial (NCT03592472) is currently ongoing and recruiting patients – the primary completion date is estimated in January 2022.

Of interest, a study carried out on murine model of RCC cell lines showed that RCC expresses arginase II regulating L-arginine metabolism, resulting in a stimulation of cell growth and immune inhibition (in particular T-cell inhibition) [52]. Arginase inhibitors are also under investigation in RCC. Indeed, the arginase inhibitor CB-1158 is currently under investigation in a Phase I/II trial (NCT02903914).

5 Novel Immunotherapy Approaches

The immune response to cancer cells is modulated by many checkpoints, any one of which could be a potential target for the development of new drugs. As PD-1/PD-L1 and CTLA-4 inhibitors continue to be a cornerstone of immunotherapy changing the natural history of many cancer patients, other immunomodulatory pathways, such as co-inhibitory receptors such as TIM-3 and LAG-3 or co-stimulatory receptors such as GITR and OX40, need to be considered in order to enhance the response to other biological or immunological compounds.

Chimeric antigen receptor (CAR) T cells are a novel immunotherapy approach that is entering in the treatment of hematological diseases and is being tested in solid tumors including RCC in Phase I/II trials (NCT03393936, NCT03638206, NCT02830724). Second-generation CARs are engineered receptors consisting of an extracellular domain that binds to tumor antigen, a transmembrane domain, and an intracellular domain that is made of costimulatory domains (CD28 and 4-1BB and the CD3ζ chain) that direct the expansion of functional T cells. CAR genes are then transferred into the patient's T cells and reinfused into the patients. CAR T cells can function independently from peptide-MHC presentation and possess the same cytotoxic effector function as endogenous CD8+ T cells [53, 54].

Lymphocyte activation gene-3 (LAG-3, CD223) is an immune checkpoint protein, and its upregulation prevents the onset of autoimmunity, but in the tumor setting can also lead to immunosuppression. The tumor microenvironment with its persistent antigen exposure leads to LAG3 overexpression. This can result in a state of immune exhaustion characterized by the negative regulation of T-cell function. LAG3 is also expressed on activated regulatory T cells (Tregs) at higher levels than on effector T cells (Teffs) [55, 56]. Relatlimab (BMS-986016) is an anti-LAG-3 antibody being tested in association with nivolumab in a Phase II trial on advanced RCC (NCT02996110). Other anti-LAG3 antibodies (LAG525, INCAGN02385) are being tested in Phase I and I/II trials alone (NCT02460224, NCT03538028) or in combination with an anti-PD1 (NCT02460224) in advanced malignancies including RCC.

Another interesting pathway that could mediate an important link between immune response and metabolic alterations in tumors is represented by adenosine interaction with adenosine receptors. Purinergic signaling is an important pathway that regulates the immune response and can lead to cancer immune evasion. Inflammation or cancer lead to cellular damage and a state of hypoxia that increases ATP levels, which is then dephosphorylated by ectonucleotidases (CD39, that dephosphorylates ATP to AMP, and CD73, that transforms AMP to adenosine) leading to accumulation of adenosine. Extracellular adenosine has a marked immunosuppressive effect, acting on effector cells by dampening their action and immunosuppressive regulatory cells by stabilizing them. Studies on these pathways are ongoing targeting both adenosine receptors and ectonucleotidases, which are overexpressed in the tumor microenvironment [57].

Adenosine activates cellular signaling pathways through G-protein-coupled adenosine receptors: in particular, adenosine receptors A2a (A2aR) and A2b (A2bR) are upregulated in response to immune cell activation. A2aR is expressed in T cells, natural killer, monocytes, macrophages, dendritic cells, while A2bR is expressed by macrophages and dendritic cells. The upregulation of these receptors leads to an immunosuppressive state in various ways: (1) suppressing the secretion of neutrophil chemoattractants, (2) impeding the maturation of dendritic cells, (3) altering dendritic cells to render them more suppressive by secreting IL-10, TGFβ, arginase and IDO (indoleamine 2,3-dioxygenase 1), (4) reducing IL-2 secretion by CD4 T cells thus reducing the expression of costimulatory receptor CD28, (5) inhibiting cell proliferation and cytotoxicity of CD8 T cells, (6) stabilizing Tregs, (7) increasing expression of checkpoint pathways such as PD-1, CTLA-4, and LAG-3 [57]. Therefore, adenosine signaling is an important checkpoint pathway that leads to suppression of immune response. Inhibitors of adenosine receptors are potential new drugs under development alone or in combination with anti-PD1/PDL1 or anti-CD73. Phase I and II trials on advanced malignancies are ongoing, testing NIR178 (NCT03207867, NCT03549000), CPI-444 (NCT03454451, NCT02655822) and AB928 (NCT03629756), which are immune checkpoint inhibitors that target the first two molecules A2aR and the third A2aR and A2bR. By inhibiting the interaction of adenosine with its receptors, these molecules reinstate the proliferation and activation of T lymphocytes and stimulate T-cell response against tumor cells. NIR178 is being tested in a Phase II trial in combination with PDR001, a new anti-PD1 (NCT03207867), and in a Phase I trial in combination with NZV930, a CD73 inhibitor (NCT03549000). Anti-CD73 inhibits the ectonucleotidase CD73 crucial for the production and accumulation of extracellular adenosine, thus reducing its formation and increasing activity of immune cells. CPI-444 is being tested alone or in association with atezolizumab in a Phase I/Ib trial (NCT02655822) or in combination with an anti-CD73 (CPI-006) in a Phase I trial (NCT03454451). AB928 is being evaluated in combination with a novel anti-PD1, AB122, in a Phase I study aimed to assess safety and toxicity profile (NCT03629756).

Glucocorticoid induced TNF receptor (GITR) is a costimulatory receptor of the TNF super family and is constitutively expressed at high levels on Tregs and at low levels on naïve and memory T cells. Its expression of Tregs and Teffs

is increased after activation of T cells. Its ligand, GITRL, is expressed by activated antigen-presenting cells, including dendritic cells, macrophage and activated B cells. GITR expands CD8 T effector memory cell population and promotes the loss or inhibition of Tregs. GITR agonist antibodies could bind the activating Fcγ receptor in the Teff cells, thus shifting the balance of CD8 Teff/Treg in favor of effector cells. Therefore, the reduced immunosuppression derived by Treg depletion and the enhanced costimulatory function of CD8 T cells increase the antitumor immunity [58]. INCAGN01876 is an agonistic anti-GITR antibody that binds and activates GITRs on T cells, thus promoting the proliferation of Teff cells and suppressing the function of Tregs, leading to an improved immune response. This compound is being studied in Phase I/II trials alone (NCT02697591) and in combination with nivolumab and ipilimumab (NCT03126110) in metastatic malignancies.

T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) is a type I transmembrane protein that acts as a checkpoint inhibitor of immune response against cancer. When overexpressed, it has been implicated in the suppression of T-cell responses and T-cell dysfunction, a state referred to as T-cell exhaustion [59]. Tim-3 has been found expressed in tumor cells, Teffs, Tregs, endothelial cells, dendritic cells. Tim-3 expressed on effector CD8 T cells in the tumor microenvironment bind to galectin-9 produced by myeloid-derived suppressor cells leading to apoptosis of effector T cells [59]. Tim-3 expression on CD8 TILs has been associated with PD-1 expression resulting in a subpopulation of T cells more exhausted than the Tim-3 negative PD-1+ CD8 T cells [60]. Tumor cells express PD-L1 and galectin-9 that bind PD-1 and Tim-3, respectively, resulting in downregulation of T-cell function that dampens anti-tumor immunity. In this immunosuppressive mechanism lies the rationale of combining PD-1 and Tim-3 blockade to restore Teff function. Tim-3 is also expressed on FoxP3+ Tregs within the tumor, resulting in higher expression of Treg effector molecules like IL-10 and inhibition of Teffs [59]. Furthermore, Tim-3 is expressed on tumor-infiltrating dendritic cells and its role is to bind high-mobility group box 1 (HMGB1) and block the transport of nucleic acids into endosomes, thus suppressing pattern-recognition receptor-mediated innate immune responses to tumor-derived nucleic acids [59]. High levels of Tim-3 expression have been associated with poor prognosis of patients with prostate cancer [61], ccRCC [62], colon cancer [63], bladder urothelial carcinoma [64], cervical cancer [65], and gastric cancer [66]. Currently, the TIM-3 inhibitors MBG453 and INCAGN02390 are being tested in a Phase I/II and I trial alone (MBG453 NCT02608268, INCAGN02390 NCT03652077) or in combination with PDR001 (MBG453 NCT02608268).

Indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase 2 (TDO2) are the enzymes that catalyze the first and rate-limiting step of the catabolic conversion of tryptophan into kynurenine, that is further converted in nicotinamide adenine dinucleotide (NAD) and ATP that fuel cellular metabolic functions.

IDO1 overexpression can impair the immune response in two ways. On one hand, tryptophan's depletion has been associated with apoptosis and dysfunction of Teff cells. On the other hand, kynurenine accumulates and binds to the ligand-activated transcription factor aryl hydrocarbon receptor (AhR) leading to the generation of immune-tolerant dendritic cells and Tregs that create a tumor microenvironment defective in recognizing and eradicating cancer cells [67, 68]. Thus, IDO1 seems to be an important immune checkpoint and target for novel immunotherapy agents. A Phase II trial analyzing the combination of nivolumab and BMS-986205, an IDO1 inhibitor, in patients with advanced RCC (NCT02996110) is recruiting at present.

OX40 (CD134) is a member of the tumor necrosis factor receptor superfamily with co-stimulatory functions expressed by activated T cells. Its co-stimulation of T cells activates T-cell signaling, which includes NF-kB and nuclear factor of activated T cells that enhance the expression of cytokines, survivin and Bcl-2 anti-apoptotic molecules. Thus, the main role of OX40 is to enhance proliferation and survival of CD4 and CD8 T cells [69]. PF-04518600 is an agonistic antibody of OX40 under evaluation in a Phase II trial in combination with axitinib (NCT03092856) and in a Phase I alone, or in association with PF-05082566 (NCT02315066), an agonist of the receptor 4-1BB (CD-137) expressed on CD4 and CD8 T cells and natural killer cells.

Vaccines against tumor-specific antigens, called neoantigens, are being developed in the treatment of many solid tumors, including RCC. Phase I and I/II trials are ongoing, exploring vaccine therapy alone or in combination with anti-checkpoint inhibitors in the metastatic setting (NCT03548467, NCT03633110, NCT00722228, NCT03294083, NCT03311334, NCT03289962). Furthermore, an oncolytic virus comprising a thymidine kinase-deactivated vaccinia poxvirus plus granulocyte-macrophage colony-stimulating factor (JX-594) is being studied in combination with a novel anti-PD1 (REGN2810) in a Phase I trial in patients with metastatic RCC (NCT03294083).

Oncolytic viruses find their rationale in the compelling task of cancer therapy of targeting selected cancer cells and are designed to stimulate the immune system by infecting and replicating in tumor cells. Oncolytic viruses have been engineered in order to infect, replicate and induce transgene expression in cancer cells, thus causing lysis of tumoral cells and contributing to enhance antitumoral immunity [70].

6 Conclusion

In a few short years, the therapeutic scenario of RCC has been revolutionized by the advent of effective TKI, which have drastically changed the prognosis and clinical outcomes of patients. A second wave of progress has been represented by immune-checkpoint inhibitors, which have further increased the benefit and survival of patients with metastatic and advanced RCC. The next challenges will be directed towards investigating better approaches and treatment strategies in RCC. In particular, a combination of immune-checkpoint inhibitors as well as a combination of immune-checkpoint inhibitors and tyrosine kinases inhibitors seem to be reliable and effective strategies, and their role will be clearer in the near future. On the other hand, new targets are under investigation and so it is probable that other immune-checkpoint inhibitors or agonists and other targeted treatments will show promising activity in a few years. As the availability of active treatments is increasing, selection of patients who present specific clinical and genetic features are of particular interest in order to better select patients who are more likely to benefit from a specific treatment or treatment strategy.

Compliance with ethical standards

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Conflict of interest Mollica V, Di Nunno V, Gatto L, Santoni M, Cimadamore A, Cheng L, Lopez-Beltran A, Montironi R, Pisconti S, Battelli N and Massari F declare no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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