Kidney Cancer
An Overview of Current Therapeutic Approaches

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KEYWORDS

• Kidney cancer • Clear cell carcinoma • First-line immunotherapy • Tyrosine kinase inhibitors
• Atezolizumab • Pembrolizumab • Bevacizumab

KEY POINTS

- Recent approvals of immune checkpoint blockade have changed the standard of care for advanced renal carcinomas, ushering a new era of combination therapy.
- Improved first-line and second-line treatments are being investigated to reduce the risk of recurrence among patients with advanced disease.
- Upcoming treatment strategies involve new tyrosine kinase inhibitors, novel combinations, and alternative agents to improve targeted therapy.

INTRODUCTION

Worldwide, approximately 400,000 individuals were diagnosed with renal cell carcinoma (RCC) in 2018; that is, it is fairly common. In the United States, RCC is among the top 10 most common cancers, with a notable increase in incidence over the past several years.[1] For localized (organ-confined) disease, surgical resection potentially is curative. Unfortunately, 25% to 30% of patients present with distant metastatic disease at the time of diagnosis[2]; and approximately 40% of surgically resected patients eventually develop recurrence.[3]

The 2 pillars of therapy for metastatic RCC (mRCC), vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) that attenuate progression by inhibiting angiogenesis,[4] and immunotherapy, predominantly in the form of agents that block the immune checkpoint mediated by the interaction between Programmed cell death protein 1 (PD-1) on tumor-specific T cells and programmed death ligand 1 (PD-L1) expressed on either tumor cells or myeloid cells in the tumor microenvironment (TME) (**Fig. 1**). TKIs are broadly effective, with several agents, including sorafenib,[5] sunitinib,[6] pazopanib,[7] and cabozantinib,[8] approved in the first-line setting. More recent studies established combination regimes as the preferred front-line treatment, that is, the combination of anti–PD-1 (nivolumab) plus Cytotoxic T-lymphocyte associated protein

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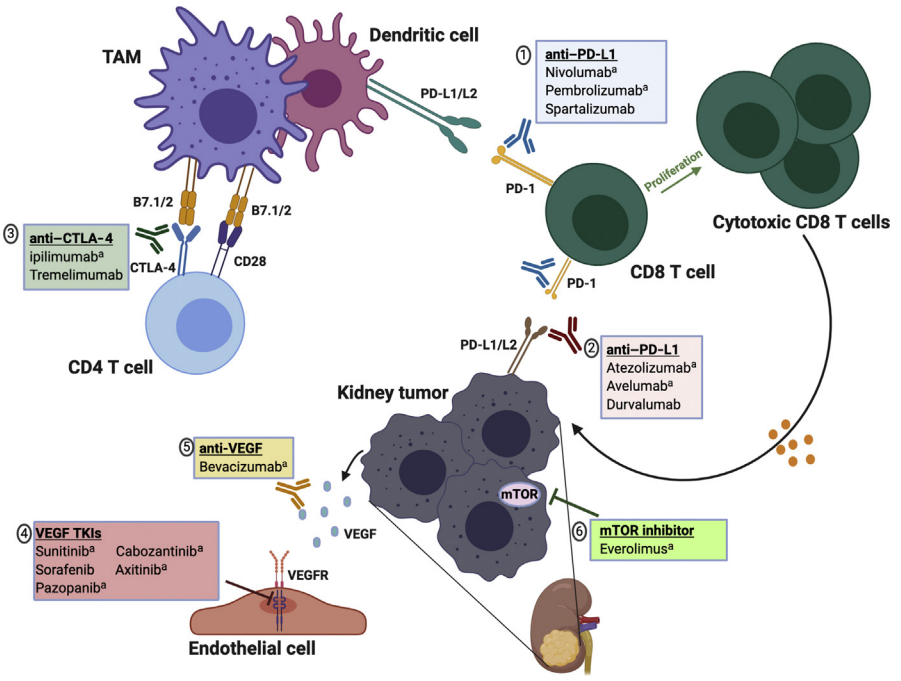

Fig. 1. Current molecular and immunotherapy targets in mRCC. ICIs of PD-1 (1) disrupt its interaction with PD-L1, leading to enhanced T-cell proliferation and activation. Antibodies targeting PD-L1 (2) prevent its interaction with PD1 on CD8 T cells, allowing their activation. Anti–CTLA-4 (3) antibodies allow CD28 to bind to its receptor, B7.1/2, and activate naïve CD4 T cells. Antiangiogenesis targets include TKIs (4) on VEGFR and the anti-VEGF monoclonal antibody, bevacizumab (5). Lastly, mTOR inhibitors (6) prevent tumor growth. TAM, tumor-associated macrophage. [a] FDA approved.

4 (CTLA)-4 (ipilimumab) for intermediate-risk and high-risk patients,[9] and the combination of anti–PD-1 (pembrolizumab) or anti–PD-L1 (avelumab) plus axitinib for patients regardless of performance status.[10,11] When anti–PD-1 or anti-PD-L1 is used in the first-line setting, second-line monotherapy[12] with anti–PD-1 is illogical, so current second-line regimens include monotherapy with agents that were not used in the first line (cabozantanib or axitinib) or the combination of the TKI lenvatinib with the mammalian target of rapamycin (mTOR) inhibitor everolimus.[13–15]

Given the relatively high rate of recurrence after surgery for primary, organ-confined disease, post-surgical (adjuvant) TKI therapy was tested in several phase III trials; these generally have been less than overwhelmingly successful.[16] More recent trials are testing the role of anti–PD-1 or anti–PD-L1 in the adjuvant setting; but those are long-term studies for which data are not yet available. Based on strong preclinical data[17] and some clinical data[18] showing an enhanced clinical benefit for immunotherapy prior to surgery (neoadjuvant immunotherapy), there are several ongoing neoadjuvant immunotherapy trials in RCC, including smaller trials aimed at understanding the biological effects of a given treatment or combination as well as a pivotal trial[19] (NCT03055013), testing whether the combination of neoadjuvant plus adjuvant immunotherapy improves progression-free survival (PFS) in surgically resected patients. Taken together, these data highlight the rapidly evolving clinical status of RC, as well as the interesting biological questions currently being addressed.

FIRST-LINE COMBINATION THERAPIES FOR METASTATIC RENAL CELL CARCINOMA

Combined Immune Checkpoint Blockade

As discussed previously, immune checkpoint blockade (ICB) involves blocking the interaction between immune checkpoint molecules on T cells and their ligands, which are expressed on either tumor cells or myeloid cells in the TME.[20] ICB thus reverses the exhausted phenotype of cytotoxic T cells, enhancing their ability to mount a tumor-specific immune response. Nivolumab and pembrolizumab are anti–PD-1 antibodies preventing its interaction with PD-L1/2, whereas the monoclonal antibodies atezolizumab, avelumab, and durvalumab block PD-L1. The other major immune

checkpoint involved in immunosuppression in the RCC TME is CTLA-4, which when expressed binds avidly to B7-1 and B7-2, thus inhibiting signal 2 and preventing full T-cell activation.[21] Based on the activity of PD-1 blockade in the second-line setting[12] as well as on preclinical data[22] and melanoma,[23] a phase III study (Checkmate 214)[9] was completed in treatment-naïve mRCC. This study compared combination immunotherapy with ipilimumab and nivolumab to standard-of-care treatment with the TKI sunitinib. The trial enrolled patients with all risk categories, but, based on previous data suggesting improved activity in patients with intermediate-risk and poor-risk disease, the primary endpoints were focused on intermediate-risk and poor-risk patients. The study met its primary endpoint, showing that intermediate-risk/poor-risk patients had an improved median PFS of 11.6 months versus 8.4 months (hazard ratio [HR] 0.82; $P = .03$), respectively, and an objective response rate (ORR) of 42% versus 27%, respectively, compared with sunitinib alone, regardless of PD-L1 expression. Patients with PD-L1 expression greater than 1% showed better PFS (HR 0.46; 95% CI, 0.31-0.67) and complete response (CR), 16% vs 7%, respectively, than patients with less than 1% PD-L1 expression. Perhaps most significantly, 9% of the patients treated with combination immunotherapy experienced a CR as opposed to 1% in the sunitinib arm. After 25.2 months of follow-up, the median OS was not yet reached for the combination and was 18.2 months in patients treated with sunitinib alone. Discontinuation of the study due to toxicity was higher (22% vs 8%, respectively) for combination immunotherapy than for sunitinib alone,[12] but patients on combination immunotherapy surprisingly reported a better quality of life compared with sunitinib. For patients with favorable-risk disease, sunitinib showed an improved PFS (HR 2.18; 99.1% CI, 1.29-3.68; $P<.001$) and ORR (52% vs 29%, respectively) compared with the combination therapy. As a result, the combination therapy was approved as a first-line treatment of intermediate-risk/poor-risk advanced RCC, supporting the rationale for combination immunotherapy in mRCC. Although these data (especially the rate of CRs) are impressive, the activity of this combination regimen needs to be balanced with its significant rate of immune-related adverse events (AEs) (approximately 60%).

Combining Immune Checkpoint Blockade with Tyrosine Kinase Inhibitors

RCC is a highly vascular disease with hallmark overexpression of hypoxia- inducible factor (HIF) 1a (as a result of von Hippel-Lindau tumor suppressor gene inactivation) and its downstream targets, predominantly VEGF. Several small molecule inhibitors of VEGF are currently Food and Drug Administration (FDA)-approved for RCC; these include sorafenib,[5] sunitinib,[6] pazopanib,[7] and axitinib,[24] among others.[25] These agents inhibit tumor angiogenesis, thus resulting in objective tumor responses in some cases and in disease stabilization in others. As a class, VEGF blocking agents generally are associated with several adverse events, including fatigue, hand-foot syndrome, bleeding, and rash.[25] A majority of recent trials in the first-line setting use sunitinib as a comparator arm; this is reasonable because its pivotal trial showed improved overall survival (OS) (26.4 months vs 21.8 months, respectively; HR 0.821; 95% CI, 0.673–1.001) and ORR of 47% compared with 12% for IFNγ, alone.[6]

Sunitinib and sorafenib are perhaps dirty TKIs, in that they inhibit multiple TKs beyond VEGF. More recently, axitinib, a more selective inhibitor of VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, was tested for its antiangiogenesis activity in a phase III trial for treatment-naïve mRCC patients. Initial data suggested no significant increase in median PFS compared with sorafenib.[26] Subsequent follow-up, however, revealed a similar safety profile and OS (21.7 months vs 23.3 months, respectively) as sorafenib,[27] on the whole, with a better OS (41.2 months vs 31.9 months, respectively) in patients with a good Eastern Cooperative Oncology Group (ECOG) performance status.

Because of their clear activity in RCC, combining VEGF TKI with anti–PD-1 seemed to be a logical next step in combination therapy. Initial efforts in this regard were not particularly successful; one arm of a trial combining anti–PD-1 (nivolumab) with the TKI pazopanib was halted due to excessive liver toxicity.[28] A similar result was observed when pazopanib was combined with pembrolizumab, even when the agents were administered sequentially.[29] The combination of sunitinib plus nivolumab was slightly better tolerated, but further development of that combination was not pursued, perhaps in favor of the anti–CTLA-4 plus anti–PD-1 combination, discussed previously.

The TKI axitinib appears to be a far better tolerated combination partner for immunotherapy, possibly because of its greater selectivity for VEGFR downstream signaling. A single-armed phase Ib trial combining axitinib with pembrolizumab[10] showed the combination to be generally well tolerated, with an ORR of 73% (95% CI, 59.0–84.4). The rate of grade III/IV AEs was significant, at approximately 60%, although a majority of these involved hypertension, an expected AE

for axitinib.[24] Based on these results, a phase III trial (Keynote-426[10]) was initiated in treatment-naïve mRCC patients. Here, the combination showed a longer median PFS (15.1 months vs 11.1 months, respectively; HR 0.69; 95% CI, 0.57–0.84; *P*<.001), ORR (59.3% vs 35.7%, respectively); and 12-month OS rate of 83.4% versus 79.5%, respectively, compared with sunitinib alone. This was consistent in patients from favorable-risk, intermediate-risk, and poor-risk groups and irrespective of PD-L1 expression. These data led to the approval of the combination of pembrolizumab/axitinib as a first-line treatment in previously untreated mRCC patients.

Axitinib also has been tested in combination with the anti–PD-L1 antibody avelumab in PD-L1 positive, treatment-naïve patients, leading to the recent approval of the first anti–PD-L1 therapy against mRCC in a combination setting.[11] The phase III trial (JAVELIN Renal 101) showed a median PFS of 13.8 months versus 7.2 months, respectively (HR 0.61; 95% CI, 0.47–0.79; *P*<.001), compared with sunitinib alone, in patients with PD-L1–positive tumors (63.2%). The combination ORR was significantly higher, at 55.2% versus 25.5%, respectively, with a median OS of 11.6 months versus 10.7 months, respectively, for sunitinib. The rate of adverse events was comparable in both arms of the study, with grade 3 or higher in 71.2% and 71.5% of the patients, respectively.

Taken together, these 3 trials established combination immunotherapy as a default treatment strategy for first-line RCC. The ipilimumab/nivolumab combination is appropriate for patients with intermediate-risk and high-risk disease, whereas the axitinib plus avelumab is appropriate for patients with PD-L1–positive tumors. The axitinib plus pembrolizumab combination is broadly approved and can be used regardless of risk group or PD-L1 status. Although combination immunotherapy produces impressive response rates and provides a clear improvement in PFS (and likely OS) compared with TKI monotherapy, all 3 of these combination regimens are associated with a significant rate of grade III/IV AE, and none has a rate of CRs greater than 20%, highlighting a need for further improvement.

Combination Therapy with Anti–Vascular Endothelial Growth Factor Antibodies

Bevacizumab is a monoclonal antibody that targets VEGF-A; it has shown a significant effect on survival and response in solid tumors, including RCC.[30] A phase III trial (IMmotion151) compared combination treatment with atezolizumab plus bevacizumab versus sunitinib alone in patients with PD-L1 expression.[31] The median PFS was 11.2 months versus 7.7 months, respectively (HR 0.74; 95% CI, 0.57-0.96; *P*<.0217), in combination compared with sunitinib alone. The improved PFS was maintained in all subtypes of PD-L1 expressing tumors, including liver metastases and favorable-risk groups. The median OS had an HR of 0.93 in the intention-to-treat population, with a favorable safety profile (8% vs 5%, respectively; discontinued treatment due to adverse events). Longer follow-up currently is under way for more definitive OS data, but bevacizumab + atezolizumab currently is not FDA approved for RCC. Thus, as with moving toward improving the outcomes and survival data for patients with metastatic disease (**Table 1**), these new immunotherapy combinations most likely are the standard-of-care treatment of most metastatic RCC patients.

SECOND-LINE TREATMENT STRATEGIES FOR METASTATIC RENAL CELL CARCINOMA

Because few mRCC patients obtain a CR to first-line treatment, even with the potent immunotherapy combinations, discussed previously, a majority of patients with mRCC progress and are treated with second-line therapy. Although anti–PD-1 (nivolumab) previously was favored in the second line, the evolving treatment landscape, in which an anti–PD-1 or anti-PD-L1 agent is used in the first-line means that second-line treatment with immunotherapy monotherapy no longer is clinically advisable, that is, based on mechanism of action, it is highly unlikely that patient who progresses on axitinib + pembrolizumab, axitinib + avelumab, or ipilimumab + nivolumab will respond to nivolumab monotherapy. Thus, currently favored second-line regimens include cabozantanib and axitinib monotherapy. Some first-line RCC patients with slowly progressing RCC still are treated initially with TKI monotherapy; for such patients, nivolumab monotherapy remains an appropriate second-line regimen (**Table 2**).

Cabozantanib

Cabozantinib, a TKI targeting multiple tyrosine kinases, including VEGFR, MET, and AXL, has been tested in treatment-naïve mRCC patients as well as in a second-line treatment setting. The up-regulation of MET and AXL as a result of VHL inactivation has been linked with poor outcome.[34] Cabozantinib initially was approved for use in mRCC patients who had progressed on prior treatment with another TKI. A phase III trial (METEOR)

Table 1
Study data and survival outcomes from key studies for first-line treatment of renal cell carcinoma

		Combination Therapies				Monotherapy		
		Nivolumab + Ipilimumab	**Pembrolizumab + Axitinib**	**Avelumab + Axitinib**	**Atezolizumab + Bevacizumab**	**Sunitinib**		**Cabozantinib**
Trial		CheckMate 214[9]	Keynote-426[10]	Javelin 101[11]	IMmotion151[31]	SUTENT[6]		CABOSUN[8]
N		861	886	1096	915	750		157
Median follow-up (mo)		25.2	12.8	12	24	11		34.5
ORR		39.0%[a]	59.3%[a]	51.4%[a]	37.0%[a]	47%		33%
CR		10.2%[a]	5.8%[a]	3.4%[a]	5.0%[a]	3%		NA
PFS (mo)	Combination arm	12.4	15.1	13.8	11.2	Treatment arm	11	8.6
	Sunitinib arm	12.3	11.1	8.4	8.4	IFN-α or sunitinib arm	5	5.3
	HR (CI)	**0.85** (95% CI, 0.73–0.98)	**0.69** (95% CI, 0.57–0.84)	**0.69** (95% CI, 0.56–0.84)	**0.83** (9% CI, 0.70–0.97)	HR (CI)	**0.539** (95% CI, 0.45–0.64)	**0.48** (95% CI, 0.31–0.74)
OS (mo)	Combination arm	NR	NR	NR	33.6	Treatment arm	26.4	26.6
	Sunitinib arm	37.9	NR	NR	34.9	IFN-α or sunitinib arm	21.8	21.2
	HR (CI)	**0.71** (95% CI, 0.59–0.86)	**0.53** (95% CI, 0.38–0.74)	0.78 (95% CI, 0.55–1.08)	0.93 (95% CI, 0.76–1.14)	HR (CI)	**0.821** (95% CI, 0.67–1.01)	**0.8** (95% CI, 0.53–1.21)

HR with statistically significant CIs are in bold.
Abbreviation: NR, not reached.
[a] ORR and CR rate in combination immunotherapy arm.

Table 2
Study data and survival outcomes from currently approved second-line treatments for metastatic renal cell carcinoma

		Nivolumab	Cabozantinib	Axitinib
Trial		CheckMate 025[12]	METEOR[32]	AXIS[33]
N		821	658	698
Median follow-up (mo)		25.2	18.7	26.5
ORR		25%	17%	52% (in favorable-risk)
CR		1%	NA	—
PFS (mo)	Treatment arm Other arm HR (CI)	4.6 Everolimus, 4.4 0.88 (95% CI, 0.75–1.03)	13.8 Everolimus, 8.4 **0.51** (95% CI, 0.41–0.62)	8.3 Sorafenib, 5.7 **0.656** (95% CI, 0.55–0.78)
OS (m)	Treatment arm Other arm HR (CI)	25 Everolimus, 19.6 **0.73** (98.5% CI, 0.57–0.93)	21.4 16.5 **0.66** (95% CI, 0,53–0,83)	20.1 19.2 0.969 (95% CI, 0,8–1,17)

HR with statistically significant CIs are in bold.
Data from Refs.[12,32,33]

compared cabozantinib to everolimus in TKI-refractory mRCC tumors. Improved median PFS (HR 0.51; 95% CI, 0.41–0.62), OS (HR 0.66; 95% CI, 0.53–0.83), and ORR (17% vs 3%, respectively) were seen in patients treated with cabozantinib compared with everolimus.[32] Importantly, patients with bone metastases showed significant responses to cabozantinib. Based on these data, a phase II trial (CABOSUN) was initiated, comparing it to sunitinib in the first-line setting for mRCC patients with intermediate-risk/poor-risk disease. Cabozantanib significantly improved PFS (HR 0.66; 95% CI, 0.46–0.95; $P<.012$) along with an ORR of 20% versus 9%, respectively, compared with sunitib.[8] The PFS benefit was seen in all patients, regardless of presence of bone metastases. Tumors with MET expression responded better to cabozantinib compared with MET tumors, indicating a potential additive effect of targeting both VEGFR and MET simultaneously. In the second-line setting (after first-line combination treatment), a phase II trial BREAKPOINT (NCT03463681) of cabozantinib after prior treatment with ICB currently is ongoing, with a preliminary reported increase in PFS from 3.8 months to 7.4 months.[14] Based on these results, cabozantanib likely will continue to be used in second-line.

Cabozantanib also is being tested, however, in the first-line setting as a combination partner with nivolumab. Results from a phase I study (NCT02496208) of using cabozantinib in combination with nivolumab with or without ipilimumab were presented at American Society of Clinical Oncology:Genitourinary Cancer Symposium 2018.[35] These data showed ORR of 54% in the RCC patients within a cohort of genitourinary tumors. Long-term response and benefit remain to be seen. A phase III study (CheckMate 9ER) tested the combination of cabozantinib/nivolumab in patients with treatment-naïve mRCC versus sunitinib alone.[36] The study recently completed has enrollment although details have not yet been published. If the cabozantanib/nivolumab regimen is used in the first line, then second-line treatment likely would involve axitinib or the lenvantinib/everolimus combination.

Axitinib

As discussed previously, the VEGF-specific TKI axitinib was evaluated in a phase III trial (AXIS) comparing second-line axitinib versus the TKI sorafenib. This trial enrolled mRCC patients with favorable risk/intermediate risk and no bone or liver metastases.[33] The AXIS trial was the first phase III study to compare 2 VEGF-based therapies in mRCC. The PFS was improved in patients treated with axitinib for both favorable-risk and intermediate-risk patients. The median PFS was 13.9 months versus 4.7 months, respectively (HR 0.476; 95% CI, 0.263–0.863; $P = .0126$), and less than 5 months versus less than 2 months, respectively (HR 0.378; 95% CI, 0.195–0.734; $P = .0032$), in favorable-risk versus poor-risk mRCC patients. No benefit in OS was seen in either treatment arm (20.1 months vs 19.2 months, respectively). Based on the longer PFS and safety profile, axitinib was approved as a second-line

treatment in mRCC. Axitinib performed better in patients with favorable risk and, thus, is a suitable treatment option for them. For patients who are treated with avelumab/axitinib or pembrolizumab/axitinib in the first line, axitinib is not a sensible second-line treatment option. Axitinib remains a viable treatment option, however, for patients treated with either ipilimumab/nivolumab, or with a monotherapy with a different TKI. More recent data from a phase II trial (NCT02579811) of 40 patients treated with individualized axitinib after prior treatment with ICB, revealed a median PFS as 8.8 months with an ORR of 45%,[13] supporting its activity in the second-line setting.

Immune Checkpoint Blockade: Nivolumab Monotherapy

ICB has shown better outcomes and survival data compared with other therapies in solid tumors, such as melanoma.[23] An open-label, phase III trial (CheckMate 025) in bevacizumab refractory mRCC patients compared nivolumab to everolimus (mTOR inhibitor, considered standard first-line treatment in patients, where targeting VEGF failed and with good survival data). There was an improvement in the median OS of 25 months versus 19.6 months, respectively (HR –0.72, $P<.02$) and ORR of 21.5% versus 3.9%, respectively, in patients treated with nivolumab. This was the first trial showing better survival data in a second-line setting for mRCC.[12] Not only did more patients respond to nivolumab, but also the duration of response was higher (23 months vs 13.7 months, respectively) than in those treated with everolimus. With 19% of the patients showing grade 3/4 adverse events (Compared with 37% in patients treated with everolimus), nivolumab was considered to have a modest safety profile and was approved by the FDA as a second-line treatment of mRCC patients. As discussed previously, at the current time, most mRCC patients likely receive an anti–PD-1 or anti–PD-L1 agent in the first-line setting; for such patients, second-line treatment with nivolumab monotherapy is not appropriate.

ADJUVANT TREATMENT IN RENAL CELL CARCINOMA

For RCC patients with localized tumors, frontline treatment involves the removal of the tumor via surgical resection and subsequent active surveillance. As discussed previously, 20% to 40% of patients recur after surgery.[3] The relatively high rate of recurrence suggests that many localized RCC patients have micrometastatic disease at the time of surgery and that treating these micrometastases with an appropriate agent might lead to an improved PFS and perhaps OS. One challenge with adjuvant studies in RCC is that there currently are no reliable prognostic biomarkers for recurrence in RCC. Some factors, such as VHL mutation status, PD-L1 expression, and presence of bone metastases, may affect the treatment strategy and use of TKIs, anti–PD-L1 immune checkpoint inhibitors (ICIs), and cabozantinib, respectively. These data, however, are based on single-armed studies and have not been broadly validated. Based on the relatively high rate of recurrence after primary therapies, several of the TKIs were tested in the adjuvant setting; several of these trials have been completed and published.[16,25]

Adjuvant Therapy with Tyrosine Kinase Inhibitors

Treatment with the TKIs, sorafenib, pazopanib, and sunitinib, in the adjuvant setting has been studied in SORCE, PROTECT, and S-TRAC, respectively. SORCE was a randomized placebo-controlled study testing sorafenib in patients with high-risk to intermediate-risk RCC after resection. After 3 years of treatment, no difference in PFS or OS was seen.[37] Additionally, no differences in 5-year and 10-year disease-free survival (DFS) rates were noted (67% vs 65%, respectively, and 54% vs 53%, respectively) and it was concluded that sorafenib is not appropriate as an adjuvant therapy for RCC. A similar result was observed in PROTECT, a phase III trial of adjuvant pazopanib in patients with localized RCC having a high risk of recurrence. After 12 months, DFS was slightly favorable for pazopanib (HR 0.86; 95% CI, 0.70–1.06) but pazopanib treatment did not show any significant improvement.[38] S-TRAC was a multi-institutional, placebo-controlled phase III study testing sunitinib for a year after surgery in patients with high risk of recurrence. Unlike SORCE and PROTECT, median DFS for S-TRAC was 6.8 years versus 5.6 years, respectively (HR – 0.76; 95% CI, 0.59–0.98; 2-sided $P = .03$).[39] Grade 3/4 AES were more common in the sunitinib arm compared with the placebo group (48.4% for grade 3 and 12.% for grade 4 vs 15.8% and 3.6%, respectively). Even though the toxicity was higher in the sunitinib arm, no deaths were recorded. These data led to the approval of sunitinib as an adjuvant treatment in RCC, although current practice patterns suggest that the agent rarely is used in this setting.

Immune Checkpoint Blockade in the Adjuvant Setting

RCC is an immunogenic tumor, and enhanced understanding of T-cell function and associated

inhibitory molecules has led to the use of monoclonal antibodies, including anti–CTLA-4 (ipilimumab[9]), anti-PD1 (pembrolizumab[10] and nivolumab[9,12,40]), and anti-PD-L1 (atezolizumab[31] and avelumab[11]). Disease progression usually occurs to distant sites via circulating tumor cells and micrometastases from residual disease. As such, efficient adjuvant therapy is based on the notion that initiating an immune response targeting micrometastases may be optimized when the tumor burden is lowest, that is, after surgery. One unique benefit of adjuvant trials is that collection of primary tumors offers the opportunity to potentially determine biomarkers associated with recurrence (in the placebo arms) as well as predictive biomarkers for response (in the treatment arms).

The phase III trial, IMmotion010 (NCT03024996), evaluates the efficacy of atezolizumab (anti–PD-L1) in the adjuvant treatment of RCC based on its success as first-line therapy in bladder cancer[41] as well as in RCC (phase III IMmotion151[31] study, discussed previously) with an ORR of 43%. IMmotion010 enrolls PD-L1–positive patients with intermediate-risk to high-risk disease postnephrectomy. The study is limited to clear cell RCC with or without sarcomatoid dedifferentiation. The primary endpoint of this trial is DFS; as is the case for most adjuvant trials, it likely will be some time before results are reported.[42] Additional adjuvant trials evaluating other ICIs include pembrolizumab (anti-PD1, KEYNOTE-564 [NCT03142334][43]); and the combination of ipilimumab (anti-CTLA4) with nivolumab (anti-PD1) the adjuvant setting (CheckMate 914 [NCT03138512][44]). Both these trials currently are ongoing with a primary endpoint of DFS.

Lastly, the PROSPER study is an ECOG randomized, multi-institutional phase III study (NCT03055013) testing neoadjuvant and adjuvant therapy with nivolumab in patients with either node-positive tumors or stage T2–T4 compared with observation.[19] With recurrence-free survival as the primary readout, this study is based on the notion that nivolumab will more efficiently prime the immune system with the primary tumor in place, consistent with key data in preclinical models showing vastly enhanced activity for neoadjuvant immunotherapy compared with adjuvant immunotherapy.[17] This study also will provide an opportunity to determine the presence of PD-L1 expression is a predictive biomarker in clear cell as well as non–clear cell RCC. Adjuvant nivolumab will ensure continued exposure to ICI compared with surgery alone. This study currently is ongoing and plans to enroll approximately 800 participants to determine the effect of neoadjuvant nivolumab on clinical outcome and OS. The reason for the innovative design is 2-fold. First, the mechanism ICI suggests that a more robust antitumor immune response is elicited in the presence of the primary tumor. Thus, administration of presurgical nivolumab theoretically should amplify its efficacy in the adjuvant setting. Second, it enables the collection of tumor tissue before and after administration of nivolumab in this treatment-naïve cohort. This will further facilitate molecular characterization of RCC that may differentiate between patients who do and do not respond to therapy. Tertiary objectives of the PROSPER trial will be to correlate PD-L1 on both the primary tumor, and tumor tissue at recurrence, with clinical outcomes.

NEOADJUVANT THERAPY IN RENAL CELL CARCINOMA

Neoadjuvant therapy differs from adjuvant therapy in 1 ways: (1) timing, that is, prior to surgical resection (preoperative therapy); and (2) target—because surgery removes primary tumor, there is no indication on whether the residual cells or micrometastases include immune subsets, such as T cells, that can be modulated by ICB or, alternatively, express immune checkpoints. Moreover, advanced RCC patients with no feasible primary surgical approach may be amenable to a neoadjuvant approach. Previously, neoadjuvant strategies, including chemotherapy, targeted therapy, and ICB, have been successful in melanoma,[45] providing the basis to adapt a similar strategy against RCC. A recent study on 2 preclinical models of metastatic breast cancer elucidated the improved efficacy of neoadjuvant anti-PD1 by eradicating metastases and increasing tumor-specific CD8 T-cell response in peripheral blood.[17] These data provide a strong rationale to extensively test the neoadjuvant approach in RCC. There currently are 3 phase I clinical trials from different groups, which are evaluating the effect of nivolumab and pembrolizumab in a neoadjuvant setting: NCT02595918 (nivolumab, mRCC, and non-mRCC patients), NCT02575222 (nivolumab, tumor stages T2–T4), and NCT02212730 (pembrolizumab, RCC). In addition, the authors' group currently is working on 2 neoadjuvant studies in patients with treatment-naïve localized or locally advanced RCC (**Table 3**).

SPARC-1

In addition to their potential therapeutic benefit, neoadjuvant studies provide an ideal platform to interrogate the precise biological effects a given treatment exerts in the RCC TME. As an example, preclinical studies showed that proinflammatory cytokines, such as interleukin (IL)-1ß, may induce

Table 3
Currently ongoing clinical trials for neoadjuvant and adjuvant therapies in treatment of metastatic renal cell carcinoma

Treatment	Phase	National Clinical Trial Identification identifier	Estimated Completion Date
Perioperative nivolumab with adjuvant nivolumab (PROSPER)	III	NCT03055013	November 2023
Nivolumab as a neoadjuvant before surgery	I	NCT02595918	April 2021
Nivolumab as a neoadjuvant before surgery in high-risk patients	I	NCT02575222	June 2020 (no results yet)
Pembrolizumab as a neoadjuvant before surgery	I	NCT02212730	July 2019 (no results yet)
Spartalizumab in combination with anti–IL-1ß (canakinumab) prior to surgery in patients with localized RCC (SPARC-1)	I	NCT04028245	December 2021
Nivolumab/cabozantinib combination before undergoing cytoreductive surgery in mRCC (Cyto-KIK)	I	NCT04322955	February 2027

myeloid-derived suppressor cells (MDSCs), leading to immune suppression in the TME.[46] The authors' group has used a mouse tumor model for RCC to determine the effects of targeting IL-1ß (David H. Aggen, MD, PhD, unpublished data, 2020). Treatment with canakinumab (anti–IL-1ß) depleted the perimorphonuclear MDSCs within the tumor myeloid compartment (0.76% ± −0.21 vs vehicular control: 1.89% ± −0.37; $P = .014$), without affecting the T-cell frequency.[47] Moreover, combining canakinumab with anti–PD-1 led to reduction in tumor burden. With the success of anti–PD-1 ICIs and combination therapy in patients with advanced RCC, the authors initiated an early phase I study to incorporate spartalizumab in combination with anti–IL-1ß (canakinumab) prior to surgery in patients with localized RCC (NCT04028245) (Fig. 2). Spartalizumab targets PD-1 and prevents its interaction with PD-L1/L2, leading to activation of tumor-specific T-cell–mediated response. Spartalizumab currently is being tested in a phase I trial for colorectal cancer

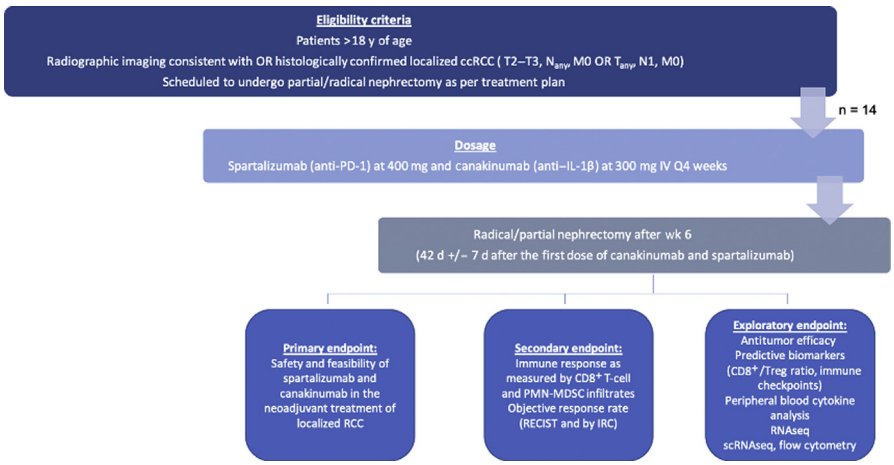

Fig. 2. Study design for SPARC-1 trial. ccRCC, clear cell renal carcinoma; IRC, immune-related response criteria; IV, intravenously; RECIST, response evaluation criteria in solid tumors; RNAseq, RNA sequencing; TNM Staging, tumor stage, node involvement, metastasis; Treg, regulatory T cells; PMN-MDSC, polymorphonuclear myeloid derived suppressor cells; scRNAseq, single-cell RNA sequencing.

(NCT04294160) and a phase III trial for melanoma (NCT02967692). Thus, the authors hypothesize that combination of PD-1 blockade with canakinumab can decrease the immunosuppressive MDSCs, inducing antitumor immune response in patients with localized RCC.

Combining Immunotherapy with Cytoreductive Nephrectomy—the CytoKIK Study

Although cytoreductive surgery alone has successfully improved survival[48] whereas TKI + surgery has not provided significantly better results,[49] the preliminary findings of the nivolumab/cabozantinib combination therapy suggest that priming the immune system might enhance the response further. As such, the authors' group hypothesized that use of this combination in a neoadjuvant setting would increase the number of patients with visible kidney cancer lesions during treatment. To test this hypothesis, the authors recently initiated a phase II trial, Cyto-KIK (NCT04322955) in treatment-naïve mRCC patients, where they will be treated with nivolumab/cabozantinib combination before undergoing cytoreductive surgery. The authors also intend to profile the immune microenvironment at the time of surgical resection to predict biomarkers of resistance to immunotherapy.

FUTURE DIRECTIONS

Combination therapies have proved feasible and are imminent to being approved as frontline as well as second-line treatment in mRCC. Additionally, determining the sequence of given treatment is of utmost importance and is dependent on various factors, including tumor stage, risk stratification, patient age, metastatic site, and Fuhrman grade, among others.

Sequential Order of Treatment

Although ICB-based combinations are standard of care for most patients with mRCC, currently, there is no optimal sequence of treatment of mRCC patients. As such, several groups are studying the effects of changing the order of the treatment on patient survival. A phase III study (COSMIC-313) of cabozantinib in combination with nivolumab and ipilimumab (triplet) followed by nivolumab/ipilimumab or matched placebo is ongoing. This trial includes previously untreated mRCC patients with intermediate-risk/poor-risk disease. The objective is to test the triplet combination and evaluate the PFS, with OS and ORR as secondary endpoints (NCT03937219). Another phase III study (PDIGREE [NCT03793166]) compares the combination of nivolumab/ipilimumab followed by either nivolumab alone or a combination of nivolumab/cabozantinib in intermediate-risk/poor-risk patients with advanced RCC. Evaluating OS as the primary endpoint of the trial, it is believed that the combination of cabozantinib/nivolumab will improve the OS compared with nivolumab alone. Median PFS and ORR will be measured as secondary endpoints.

Emerging Immunotherapy Targets in Metastatic Renal Cell Carcinoma

Several evolving immunotherapy agents currently are in phase I and phase II trials; these recently have been reviewed.[50] Agents of interest include the following.

NKTR-214 (Pegylated Interleukin-2)

A recent study demonstrated that high-dose IL-2 results in a complete response in 1%, an objective response in 25%, and a partial response in 22% of patients with RCC.[51] Effector T cells generally express the IL-2 β/γ receptor[37], which, when targeted, may enhance the proliferative effect of IL-2 on T cells. NKTR-214, a polyethene glycol complexed prodrug binds to CD122, a subunit of IL-2R, stimulating an increased immune response. In an ongoing phase I/II trial of NTRK-214 plus nivolumab, responses were noted in 46% (6 of 13) of patients, with a disease control rate of 85% (11 of 13 patients).[52] These results from a small number of patients highlights the clinical potential of NKTR-214 in RCC therapy.

Adenosine A2A Receptor Drugs

Binding of adenosine, a purine nucleotide to its receptor, adenosine A2A receptor (A2AR), can have variable immunosuppressive effects by increasing regulatory T cells, inducing differentiation of M2 macrophages, and inhibiting natural killer cell function.[53] A small molecule ciforadenant (CPI-444, Corvus Pharmaceuticals, Burlingame, CA), targeting A2AR on T lymphocytes, currently is under study in a phase I trial [NCT02655822] evaluating the safety and tolerability of ciforadenant alone as well as in combination with atezolizumab in solid tumors, including RCC.

Glutaminase Inhibitor

Metabolic changes, especially in glucose and glutamine levels, lead to tumor development and survival in many cancers, including RCC. As such, a glutaminase inhibitor, telaglenastat, which

inhibits proliferation in preclinical models of RCC, is being tested in combination with everolimus (phase II ENTRATA [NCT03163667]), cabozantinib (phase II, CANTATA [NCT03428217]), and nivolumab (phase I/II [NCT02771626]). With a tolerable safety profile, OS has not been reached for any of the trials but preliminary data for ENTRATA show an improved median PFS of 3.8 months versus 1.9 months, respectively, in telaglenastat/everolimus compared with matched placebo with everolimus.[54]

HIF2a Inhibitors

As a highly vascular disease, RCC usually develops with the overexpression of the oncogenic driver, HIF2a and its downstream targets, including VEGF. Targeting of HIF2a thus provides a promising therapeutic strategy to prevent the development of RCC. PT2977, an HIF2a inhibitor, is being tested alone (NCT03401788) as well as in combination with cabozantinib (NCT03634540) in patients with advanced RCC.[55] Of the 55 patients involved, 13 (24%) showed partial response whereas 31 (56%) had stable disease. The median PFS was 11 months (95% CI, 6–17), and the 12-month PFS rate was 49%.[56] The safety profile of PT2977 currently is unknown and is being investigated in these phase II trials.

SUMMARY

With the approval of multiple combination therapies for patients with mRCC, the standard-of-care practices, including first-line and second-line treatments, have transformed recently. There is, of course, a need for prognostic markers of recurrence and/or progression for better understanding of the TME. Absence of a consensus on order of treatment further complicates the standardization of the most optimal treatment strategy for each patient. With the results from some of the ongoing clinical trials involving more combination therapies, it is expected to shed some light on to the most effective and tolerable immunotherapy-based treatment.

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