Review Article

Perioperative systemic therapy in high-risk renal cell carcinoma following nephrectomy: a narrative review

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Background and Objective: For patients with resectable renal cell carcinoma (RCC), extirpative surgery with curative intent remains the standard of care. Despite surgical resection, most patients with high-risk features experience disease recurrence. The role of perioperative systemic therapy in the management of these patients' disease remains unclear. Several studies have evaluated the efficacy and safety of tyrosine kinase inhibitors (TKIs); however, most trials have yielded negative results. Adjuvant pembrolizumab demonstrated a disease-free survival benefit in the KEYNOTE-564 trial; however, multiple studies of other immune checkpoint inhibitors (ICIs) in a similar patient population did not yield consistent results. This review summarizes the current evidence for perioperative systemic therapy studies in RCC.

Methods: The PubMed, American Society of Clinical Oncology (ASCO), and clinicaltrials.gov databases were used to retrieve articles published from January 1, 2001 to December 31, 2023 using the following search terms: "adjuvant", "neoadjuvant", "perioperative", "VEGF inhibitors", "immune checkpoint inhibitors", and "renal cell carcinoma". The search was limited to articles published in English.

Key Content and Findings: We summarize the major perioperative systemic therapy studies in RCC patients and provide an analysis of study outcomes, comparing differences in trial design and patient selection. We also discuss ongoing trials and the emergence of novel biomarkers designed to improve patient selection.

Conclusions: The optimal use of perioperative systemic therapy in high-risk RCC is an area of active investigation. The use of adjuvant TKIs failed to demonstrate a survival benefit and was limited by high rates of toxicity. Several neoadjuvant and adjuvant ICI-based combination studies are being carried out to further improve clinical outcomes. Further studies will be needed to identify effective biomarkers to improve patient selection while avoiding overtreatment.

Keywords: Neoadjuvant; adjuvant; vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs); immune checkpoint inhibitors (ICIs); clear cell renal cell carcinoma (ccRCC)

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Introduction

In the United States (US), an estimated 81,800 new cases of kidney cancer, and nearly 15,000 deaths, will occur in 2023, the majority of which are renal cell carcinoma (RCC) (1). Clear cell RCC (ccRCC) is the most common tumor histologic subtype (2). Non-clear cell RCC (nccRCC) accounts for 20% of cases, and includes papillary, chromophobe, and medullary subtypes (3). The Von Hippel-Landau (VHL) gene is frequently mutated, and its complete loss of function is believed to be responsible for ccRCC pathogenesis. VHL loss leads to overexpression of hypoxia-inducible factors (HIFs), resulting in altered cellular metabolism, increased vascular endothelial growth factor (VEGF) production, angiogenesis, and enhanced cellular survival (4). These genetic alterations have formed the basis for targeted therapies, including VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs). More recently, immune checkpoint inhibitors (ICIs), which enhance the immune system's ability to recognize and eliminate cancer cells, have been incorporated into the RCC treatment landscape (5).

Most newly diagnosed cases are localized RCC. For patients with resectable disease, surgical treatment with curative intent via partial nephrectomy (PN) or radical nephrectomy (RN) remains the standard of care. Other treatment modalities include ablative techniques and active surveillance (6-9). Despite surgical resection, 40–80% of patients with high-risk RCC experience disease recurrence (10). High-risk RCC features include pT3 stage, Fuhrman grade ≥2, sarcomatoid differentiation, and nodal involvement (11,12). Patients with higher tumor node metastasis (TNM) stage disease are widely considered to have an increased likelihood of recurrence (13). Currently, the role of perioperative systemic therapy in the management of high-risk RCC following extirpative surgery is unclear due to conflicting study results and poorly defined criteria for high-risk disease. In this review, we summarize the current evidence for perioperative systemic therapy in ccRCC, as these patients were the most represented in clinical trials. This paper includes an analysis of study outcomes and compares differences in trial design and patient selection. We also discuss ongoing trials and the emergence of novel biomarkers designed to improve patient selection. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-16/rc).

Methods

A literature search identified relevant articles in PubMed, American Society of Clinical Oncology (ASCO), and clinicaltrials.gov databases. The search terms "adjuvant", "neoadjuvant", "perioperative", "VEGF inhibitors", "immune checkpoint inhibitors", and "renal cell carcinoma" were used. Eleven completed adjuvant and 14 completed neoadjuvant studies were included. Two ongoing adjuvant and 9 ongoing neoadjuvant studies were also included (see *Table 1*).

Table 1 Search strategy summary

Items	Specification
Date of search	September 15, 2023 (first search) to December 31, 2023 (last search)
Databases and other sources searched	PubMed, American Society of Clinical Oncology (ASCO), and clinicaltrials.gov
Search terms used	"adjuvant", "neoadjuvant", "perioperative", "VEGF inhibitors", "immune checkpoint inhibitors", "renal cell carcinoma"
Timeframe	January 1, 2001 to December 31, 2023
Inclusion and exclusion criteria	Inclusion: the search was limited to articles involving adult human subjects that were published in English. Original research and review articles were included
	Exclusion: case reports and articles not relevant to the topic were excluded
Selection process	A.K., T.G., S.D., and D.Z. conducted the article selection independently. E.A.S. and Y.Y. supervised the article selection

VEGF, vascular endothelial growth factor.

Prognostic factors and models for RCC recurrence risk assessment

RCC staging criteria include tumor size and extension outside the kidney (T), nodal involvement (N), and presence of metastasis (M). The clinical TNM stage is determined by computed tomography (CT) imaging findings, whereas the pathologic stage is established following examination of resected tissue (14). Several validated prognostic models serve as important tools in assessing a patient's recurrence risk following extirpative surgery. The Stage, Size, Grade, and Necrosis (SSIGN) score uses nuclear grade, necrosis, and tumor size to predict cancer-specific survival (CSS) in ccRCC patients (15). The University of California Los Angeles (UCLA) Integrated Staging System (UISS) categorizes ccRCC patients into low-, intermediate-, and high-risk groups based on TNM stage, grade, and Eastern Cooperative Oncology Group (ECOG) score, and is predictive of CSS and overall survival (OS) (16). Finally, the Leibovich scoring system categorizes patients into low-, intermediate-, and high-risk groups based on tumor stage, regional lymph node status, tumor size, nuclear grade, and tumor necrosis, and is associated with metastasis-free survival (MFS) (17).

American Urological Association (AUA) guidelines

Most patients with RCC have a low risk of recurrence following nephrectomy. Patients with low-risk RCC (pT1, grade 1/2) have a mass confined to the kidney without aggressive histologic features (18). Although most patients with low-risk RCC historically received PN or RN, alternatives like ablation or active surveillance have become more common. Patients with intermediate risk are defined as pT1, grade 3/4, or pT2 any grade (18). High-risk RCC patients are characterized by localized disease with aggressive histology, locoregional disease, or treated metastatic disease. Many patients with high-risk RCC may benefit from additional treatment following nephrectomy in the adjuvant or salvage setting to prolong CSS.

Contemporary clinical trial criteria

Several sets of criteria have been used to define high-risk RCC for clinical and research purposes. The most clinically useful are the inclusion criteria of KEYNOTE-564 because adjuvant pembrolizumab improved disease-free survival (DFS) and showed "a statistically significant improvement in OS" (from a press release; data is forthcoming) (19,20). KEYNOTE-564 included ccRCC patients with: (I) high-risk localized disease (pT2 with sarcomatoid features or high nuclear grade 4/4); (II) locoregional disease (pT3, pT4, or N1); and (III) known distant metastatic disease with no current evidence of disease [metastasis stage 1 no evidence of disease (M1 NED), e.g., a noncontiguous adrenal metastasis resected concurrently with nephrectomy].

Current clinical trials like LITESPARK-022 use analogous clinical criteria to KEYNOTE-564 (21). The authors of KEYNOTE-564 have indicated these criteria to define high-risk RCC are based upon prior studies (22-26). There are subtle variations in the criteria used in different studies to define high-risk RCC (27,28). For instance, patients with M1 NED were included in IMmotion010 but excluded from CheckMate-914. Additionally, IMmotion010 included patients with pT3a, grade 3/4 disease, whereas CheckMate-914 enrolled patients with pT3a, any grade (9). While not directly incorporated in KEYNOTE-564, additional criteria to indicate high-risk RCC include certain clinical features [symptomatic, poorer performance status (PS), increasing age] or pathologic factors (tumor size, tumor necrosis) (23).

Nomograms

Individualized risk prediction can be accomplished with a nomogram. A nomogram to predict recurrence risk based on the ASSURE study is freely available and easy to use in clinical practice (29). This nomogram is based on data from 1,735 patients with a median follow-up of 9.6 years. It incorporates age, tumor histology, tumor size, Fuhrman grade, coagulative necrosis, pathologic lymph node involvement, vascular invasion, and sarcomatoid features. Clinicians should exercise caution in directly applying this nomogram because the c-index of the model was 0.68 and survival outcomes have improved since the ASSURE study. Other nomograms such as the Mayo D-SSIGN, Leibovich RCC, and the UISS models have also been used for risk prediction (17,30,31). A comparative analysis of these and other RCC nomograms showed a considerable decrease in the predictive ability of all models when using prospective data validation measures (23). Therefore, a modified UISS is frequently used in ICI trials, in which a tumor is considered high-risk if it is ≥ pT3a, grade ≥2, has regional lymph node metastasis, or both (32).

Histology

ccRCC generally has a higher risk of recurrence than other

common RCC histologies like papillary or chromophobe RCC (29). Fumarate hydratase-deficient RCC and chromophobe RCC with sarcomatoid features are important exceptions. Clinicians should also be aware of some uncommon RCC variants with a high risk of recurrence such as collecting duct and medullary RCC (33-36).

In summary, the high-risk definition used in KEYNOTE-564 study is a reasonable criterion for selecting patients who are likely to benefit from adjuvant treatment.

Additional follow-up of studies like KEYNOTE-564, IMmotion010, and CheckMate-914 will undoubtedly yield updated risk prediction models (19,27,28). Promising options for improving risk assessment include radiomics and molecular markers (37,38).

Rationale for neoadjuvant approach in patients with high-risk RCC

Neoadjuvant systemic therapy in patients with high-risk RCC offers several potential benefits. From a surgical standpoint, it can promote tumor downsizing thus facilitating resection of surgically complex tumors and enabling preservation of adjacent organ structures. Additionally, it may enable organ-sparing surgery via PN for patients with compromised baseline renal function. Finally, it offers the potential to shrink inferior vena cava (IVC) tumor thrombus, thereby reducing surgical morbidity risk and minimizing the need for a major vascular procedure (39-41). In terms of oncologic benefits, it can facilitate early eradication of micrometastatic disease, thus reducing recurrence risk and improving survival outcomes. Additionally, it may facilitate a more effective anti-tumor immune response on a tumor *in situ*, given the intact immune cycle (42). Finally, the higher tumor antigen load may promote greater T-cell priming, augmenting the cancer-specific immune response (43).

However, there are also potential downsides to neoadjuvant treatment, including possible wound healing difficulties, surgical complications due to inflammatory changes and/or fibrosis, and the risk of disease progression with delay in surgical treatment (44-46). In a large retrospective study, increased time to nephrectomy (>10 weeks) in pT3 RCC was associated with worse 5-year OS (47). Additionally, preoperative TKI use was noted to increase the incidence of intraoperative adhesions, though this did not increase the rate of overall complications (48). Neoadjuvant treatment with ICIs poses additional challenges. There is a risk of developing immune-related adverse events (irAEs). Furthermore, the use of steroids or other immunosuppressants to treat irAEs can further delay surgery (49).

Neoadjuvant systemic therapy trials in patients with high-risk RCC

Targeted therapies (Table 2)

In 2006, sunitinib was approved for first-line use in metastatic RCC (mRCC) and served as the comparator arm for all modern US Food and Drug Administration (FDA)-approved first-line combination regimens in this setting (63-68). Sunitinib was investigated in the neoadjuvant setting for patients with high-risk RCC in three phase II trials. The first of these trials was published in 2010 and primarily evaluated the safety of 3 months of daily sunitinib in 20 patients with cT1b–T3, any N, or M RCC. The generalizability of these results to the neoadjuvant setting is challenging given the inclusion of M1 patients. However, perioperative sunitinib was deemed to be safe in this small study. Only one patient exhibited a partial response (PR) and the remainder had stable disease (SD) per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (50). The second trial involved 12 patients with locally advanced ccRCC who underwent two cycles of sunitinib before nephron-sparing surgery. Four patients experienced a PR and neoadjuvant use was deemed to be safe (52). The third trial investigated 28 patients with unresectable RCC who were treated with sunitinib continuously and underwent CT imaging 12 weeks later; 45% of patients underwent surgery following treatment (53).

Axitinib is approved for use in combination with either avelumab or pembrolizumab as first-line treatment for mRCC, or as second-line monotherapy (65,67,69). Axitinib was evaluated as a neoadjuvant agent in three phase II trials. The first trial included 24 patients with cT2–T3b biopsy-confirmed ccRCC who received up to 12 weeks of axitinib with the last dose 36 hours before extirpative surgery (54). The primary outcome, overall response rate (ORR), was determined using CT scans obtained upon study entry and at 12 weeks after axitinib initiation using RECIST criteria (70). Investigators noted a 45.8% PR rate with a 28.3% (range, 5.3–42.9%) median reduction of tumor diameter. There was no disease progression (PD) while on axitinib and no grade 4 or 5 treatment-related AEs (trAEs). Patients reported worse quality of life (QOL) during treatment but returned to baseline by 6–7 weeks postoperatively. This study is limited by its small sample size and lack of a control group. Additionally, a major shortcoming of the use of ORR as the primary outcome in this and other similar neoadjuvant trials

Table 2 Summary of prospective neoadjuvant trials in high-risk RCC

Author	N	Design	Agent	Subtype	Primary outcome	Results
Hellenthal (50)	20	Phase II	Sunitinib	ccRCC	Drug safety, and feasibility prior to surgery	• 40% grade 3 or higher AEs • No surgical complications attributable to drug
Cowey (51)	30	Phase II	Sorafenib	Mostly ccRCC	Drug safety and feasibility prior to surgery	• 30% grade 3 AEs • Superficial wound breakdown postop (1 pt)
Silberstein (52)	12	Phase II	Sunitinib	ccRCC	Tumor response, drug safety	• 16% with PR • Fatigue and diarrhea most common AEs
Rini (53)	28	Phase II, single arm	Sunitnib	Any	Proportion of pts with resectable tumors following tx	• 45% of pts with resectable tumors
Karam (54)	24	Phase II, single arm	Axitinib	ccRCC	ORR prior to surgery	• ORR 45.8%
Lebacle (55)	18	Phase II, single arm	Axitinib	ccRCC	No. of pts receiving PN for a tumor <7 cm in size after tx	• 12 pts achieved outcome
Rini (56)	25	Phase II, single arm	Pazopanib	ccRCC	% of patients who could undergo PN	• 46% able to undergo PN
Bilen (57)	16	Phase II, single arm	Cabozantinib	ccRCC	ORR	• ORR 31%
Hatiboglu (58)	12	Phase II, double blinded RCT	Sorafenib	Any	Response to tumor volume following tx	• Reduction of 29% in tumor volume in tx group
Gorin (59)	17	Phase II	Nivolumab	ccRCC	Safety and tolerability of tx	• All pts able to undergo surgery • 11.8% grade 3 AEs
Carlo (60)	18	Phase II	Nivolumab	ccRCC	Drug safety and feasibility prior to surgery	• All pts underwent surgery without delay • 2 pts experienced AEs, and 4 pts with surgical complications
Bex (61)	40	Phase II	Axitinib + avelumab	ccRCC	PR in primary tumor in ≥25% of pts	• PR achieved in 30% of pts
Stewart (62)	20	Phase II	Axitinib	ccRCC	% of evaluable pts with VTT improvement	• 35% of pts with VTT improvement

RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; AE, adverse event; PR, partial response; tx, treatment; pt, patient; PN, partial nephrectomy; ORR, overall response rate; RCT, randomized controlled trial; VTT, venous tumor thrombus.

is the inability to extrapolate a preoperative tumor response to cancer-specific outcomes such as recurrence and survival. The second trial investigated neoadjuvant axitinib for downstaging cT2a biopsy-proven ccRCC to promote organ-sparing surgery (55). Eighteen patients were on axitinib for 2–6 months depending on radiologic response before extirpative surgery. The median starting tumor size was 7.6 cm (range, 7.0–9.8 cm) and the median starting R.E.N.A.L. [Radius, Exophytic/endophytic properties of the tumor, Nearness of tumor deepest portion to the collecting system or sinus, Anterior (a)/posterior (p) descriptor and the Location relative to the polar line] nephrometry score was 11 (range, 7–11). After a median of 2 months on axitinib, 12 patients were downstaged to cT1b disease with a median tumor size of 6.4 cm (range, 5.8–7.5 cm) and a median nephrometry score of 10 (range, 7–11).

However, only 4 patients (22%) had a PR according to RECIST criteria; 13 had SD. Surgical management was at the discretion of an unblinded operating surgeon and 16 patients (88%) ultimately underwent PN. Axitinib caused downstaging of cT2a tumors, but the true clinical impact of this study is unclear. There was an absolute change in the median R.E.N.A.L. nephrometry score from 11 to 10, but a score of 10–12 correlates with a high-risk PN with a 21.9% complication rate (71). There was no control group, and inherent bias with an unblinded surgeon selecting the treatment option. Indeed, PN was chosen for most patients, including 4 who were not downstaged, despite high tumor complexity and overall modest response per RECIST criteria. The third trial involved 20 patients with ccRCC and venous tumor thrombus (VTT) who were treated with axitinib for up to 8 weeks before surgery. The primary outcome measured was the proportion of patients with VTT downstaging assessed by magnetic resonance imaging (MRI) imaging. Thirty-five percent of patients were found to have VTT improvement, resulting in less extensive surgery (62).

Pazopanib was approved for mRCC in 2009 as first-line treatment or after cytokine failure (72). Neoadjuvant pazopanib was investigated to promote eligibility for PN in a phase II trial (56). The study enrolled 25 patients with localized ccRCC and at least one of the following criteria: (I) extirpative surgery was likely to yield a glomerular filtration rate (GFR) less than 30, or (II) PN was deemed to be highly complex, defined as either a R.E.N.A.L. nephrometry score of 10–12 or tumor location adjacent to hilar vessels. The primary endpoint was the percentage of patients who underwent PN; secondary endpoints included ORR, reduction in tumor volume, and estimated preserved functional parenchyma. After a median of 8 weeks of treatment, 20 renal units (18 patients) ultimately underwent PN. Thirteen patients were deemed ineligible for PN at the start of the study and 6 (46%) had enough of a response to therapy to become PN eligible. Pazopanib reduced the median tumor diameter from 7.3 to 5.5 cm ($P<0.0001$), decreased R.E.N.A.L. nephrometry score from 11 to 9 (range, 5–12, $P<0.0001$), and increased the estimated amount of preservable parenchyma from 107 to 173 cc ($P=0.0015$). The median reduction in tumor diameter was 26%, and ORR by RECIST criteria was 36%. In patients who were PN eligible at the study's outset, pazopanib therapy increased the amount of parenchyma that could be saved by 15%. In patients who underwent PN, median GFR was decreased by 16.2% and no patients required renal replacement therapy (RRT). Of the 7 patients that required RN, 5 required long-term RRT. The rates of urine leak and perioperative transfusion were both 25%, and the rate of angioembolization was 5%. For comparison, the quoted rates in the literature have been estimated at <5% for urine leak and transfusion and <2% for embolization (73,74). The high incidence of perioperative complications could suggest treatment-related healing issues or simply reflect the high complexity of tumors enrolled in this study.

Sorafenib was approved for mRCC in 2005 as a second-line treatment after cytokine failure (75). Sorafenib was assessed as a neoadjuvant agent in a randomized, double-blind placebo-controlled pilot trial in patients with (presumed, no biopsy done) localized T1–3 RCC (58). The primary outcome was a reduction in tumor volume and a change in R.E.N.A.L. nephrometry score. Despite enrolling 20 patients, only 12 proceeded through the study (9 sorafenib, 3 placebo). Additionally, only 3 of 9 patients completed the planned 28-day course of sorafenib. The median tumor reduction in the sorafenib arm was 29% (range, –4% to 61.1%) versus no change in the placebo arm. There was no statistically significant change in nephrometry scores compared to pretreatment in either arm. There were no surgical safety concerns with sorafenib in this study. Another study evaluated the safety and feasibility of 30 patients treated with sorafenib preoperatively. Following treatment (median 33 days), a decrease in primary tumor size (median 9.6%) was observed, all patients were able to proceed with surgery, and there were no surgical complications related to sorafenib (51).

Cabozantinib is approved as second-line monotherapy or first-line therapy in combination with nivolumab in mRCC (68,76). The initial results of a phase II study (NCT04022343) on neoadjuvant cabozantinib in patients with ≥ cT3a or N1 or deemed unresectable with biopsy-proven ccRCC were presented at the 2022 GU ASCO meeting (57). The primary outcome was ORR per RECIST criteria in the final week of treatment (week 12). Secondary outcomes included safety, tolerability, DFS, OS, surgical outcome, and QOL. After 12 weeks of weekly cabozantinib, 16 patients underwent nephrectomy after a 4-week delay. Five patients (31.2%) experienced a PR and 11 had SD; there was no PD during treatment. The median reduction in primary tumor size was 24% (range, 6–45%). One patient who was deemed unresectable became resectable at the end of treatment, and 2 patients were converted from RN to PN. There were no intraoperative or postoperative complications related to cabozantinib. Additional data on long-term outcomes are expected.

In summary, there is currently no high-quality evidence to support the use of neoadjuvant TKI monotherapy in RCC. Many retrospective series and several phase II trials demonstrate that TKI monotherapy can reduce tumor volume, improve resectability, and enable nephron-sparing surgery. There were no major safety concerns resulting in delaying or canceling curative surgery, nor were there increased perioperative complications. However, the benefit of long-term survival is unclear.

ICIs (Table 2)

Compared to the available data on neoadjuvant TKIs in RCC, there is a dearth of trial results for ICI monotherapy and ICI/ICI or ICI/TKI combinations in this setting. Nivolumab is an anti-programmed cell death protein 1 (PD-1) monoclonal antibody approved as second-line monotherapy in advanced RCC or as first-line therapy in combination with ipilimumab or cabozantinib (64,68,77). Neoadjuvant nivolumab monotherapy was evaluated in two studies. A phase I primary safety/tolerability study examined 3 doses of nivolumab before nephrectomy in 17 patients with nonmetastatic high-risk ccRCC (59). Secondary endpoints included ORR, immune-related pathologic response rate, QOL, MFS, and OS. Ten patients (58.8%) experienced any grade AE attributable to nivolumab; no grade 4–5 AEs occurred. QOL remained stable during treatment. All patients had SD per RECIST criteria during treatment, and 1 patient demonstrated a favorable immunological response on pathologic specimens. MFS and OS were 85.1% and 85.7%, respectively, at 3 years. Though the radiographic response was not demonstrated, the presence of an immune response in one patient warrants further investigation of nivolumab in this setting. Additionally, a phase II trial evaluated up to 4 doses of nivolumab in 18 patients before surgery. All patients underwent surgery without delay; however, 2 patients experienced AEs, and 4 patients had surgical complications (60).

Regarding ICI/ICI combinations, initial results from a phase Ib safety/feasibility trial on neoadjuvant/adjuvant use of the anti-PD-L1 durvalumab +/– the anti-CTLA-4 tremelimumab in high-risk (T2b–4 and/or N1) localized RCC were presented at the 2020 GU ASCO meeting. Twenty-nine patients with adequate PS were divided into 4 perioperative regimens. There were no treatment-related delays to nephrectomy or surgical complications, but the trial was suspended because of a higher-than-anticipated rate of irAEs (78).

Regarding ICI/TKI combinations, neoadjuvant nivolumab was examined in combination with sitravatinib, a novel, multitarget TKI, in a phase II study of 17 patients with locally advanced ccRCC (79). In this trial, ORR was only 11.8% [95% confidence interval (CI): 1.5–36.4%; P=0.208], which was not significant based on the prespecified target of 30% and worse than other neoadjuvant TKI trials. There were no grade 4–5 trAEs. The 24-month recurrence-free survival (RFS) was 88% (95% CI: 61.0% to 97.0%).

Combination avelumab and axitinib is also currently under investigation for neoadjuvant use. A single-arm phase II trial examining 12 weeks of neoadjuvant avelumab + axitinib in patients with high-risk ccRCC (cT1b–4c or N1) reported initial results in 40 patients at the 2022 GU ASCO meeting (61). Twelve patients (30%) met the primary endpoint of PR ≥25% per RECIST criteria. No patients progressed on treatment. At a median follow-up of 23.5 months, recurrence occurred in 13 (32%) patients and 3 died of disease. Of the 12 patients who met the primary endpoint, 11 (92%) were disease-free at the time of initial trial reporting. Secondary outcomes of DFS and OS are not yet reached. Postoperative AEs occurred in 8 patients; 3 were grade 3a. This study is still actively recruiting.

Rationale and risk assessment for adjuvant approach in high-risk RCC

Despite undergoing surgery with curative intent, many patients with high-risk RCC experience disease recurrence, necessitating effective therapies to lower recurrence risk and improve outcomes (80). Compared to the neoadjuvant approach, surgical pathology may provide more accurate tumor staging resulting in improved risk stratification and patient selection (40,81). Adjuvant therapy may also eliminate micrometastatic residual disease following surgery (82). In patients treated with ICIs, there is potential for a durable treatment response following treatment discontinuation due to immune memory (83). However, one potential downside is subjecting patients to additional drug toxicities.

Adjuvant systemic therapy trials in high-risk RCC

In RCC adjuvant systemic therapy trials, DFS is often used as the primary endpoint as it was shown to moderately correlate with OS post-nephrectomy (84,85). The reason

Table 3 Summary of adjuvant targeted therapy trials in high-risk RCC

Trial	N	Agent	Duration of adjuvant tx	Primary outcome	Result	Tx discontinuation rate due to AEs
ASSURE (84)	1,943	Sunitinib, sorafenib	1 yr	DFS	Not significant	Sunitinib (20%), sorafenib (20%)
S-TRAC (86)	615	Sunitinib	1 yr	DFS	Significant	28%
PROTECT (87)	1,538	Pazopanib	1 yr	DFS	Not significant	800 mg dose (39%), 600 mg dose (35%)
ARISER (88)	864	Girentuximab	24 wks	DFS, OS	Not significant	2%
ATLAS (89)	724	Axitinib	1 yr minimum	DFS	Not significant	19%
SORCE (90)	1,711	Sorafenib	1 yr, 3 yr	DFS	Not significant	30% (1 yr), 34% (3 yrs)
EVEREST (91)	1,545	Everolimus	54 wks	DFS	Not significant	37%

RCC, renal cell carcinoma; tx, treatment; AE, adverse event; yr, year; DFS, disease-free survival; wks, weeks; OS, overall survival.

for this is that an OS benefit (the gold standard) requires a much larger sample size and longer follow-up for localized disease as compared with advanced RCC (fewer events) (82).

Targeted therapies (Table 3)

ASSURE was the first phase III trial assessing the efficacy of adjuvant TKIs in high-risk RCC. This study enrolled 1,943 patients with resected RCC (80% ccRCC histology) and ≥ pT1b high-grade (grade 3–4) disease or node-positive disease of any grade. Patients were randomized 1:1:1 to sunitinib (50 mg daily, 4 weeks on and 2 weeks off), sorafenib (400 mg twice daily), or placebo, and treated for up to 1 year. No significant difference in DFS (primary endpoint) or OS was demonstrated for either sunitinib or sorafenib relative to placebo. Additionally, treatment was associated with a high rate of toxicity even after dose reduction (84).

S-TRAC was a phase III trial that enrolled 615 patients with localized ccRCC at high risk for recurrence (≥ pT3 grade 2–4; pT4 or node-positive disease of any grade). Patients were randomized to receive either sunitinib 50 mg daily or placebo for 4 weeks on and 2 weeks off. In contrast to the ASSURE study, adjuvant sunitinib demonstrated a statistically significant difference in DFS [6.8 *vs.* 5.6 years; hazard ratio (HR) =0.76; 95% CI: 0.59–0.98; P=0.03]. This was the first study to demonstrate the benefit of systemic therapy in the RCC adjuvant setting (86). However, there was no OS benefit of sunitinib over placebo after extended follow-up (92). Like the ASSURE study, a high proportion of patients (48%) experienced grade 3–4 AEs. There are a few potential reasons for the discordant results between ASSURE and S-TRAC: (I) patients were more high risk in S-TRAC; (II) S-TRAC only included ccRCC patients; and (III) greater and more frequent dose reductions in ASSURE potentially affected efficacy (80).

PROTECT was a phase III trial of 1,538 patients with resected localized or locally advanced RCC at high risk for relapse who were randomized 1:1 to pazopanib 800 mg daily (later reduced to 600 mg daily due to toxicity) or placebo for 1 year. Like prior trials, there was no significant difference in DFS or OS between pazopanib and placebo in patients with high-risk locoregional RCC (87).

ATLAS was a phase III trial of 724 patients with at least pT2 or node-positive RCC. Patients were randomized 1:1 to axitinib 5 mg twice per day or placebo and treated for a minimum of 1 year. The trial was stopped early due to futility. In a subgroup investigator analysis of the highest-risk patients (pT3 with grade ≥3 or pT4 and/or N+, any T, any grade), there was a significant improvement in DFS (HR =0.641; 95% CI: 0.468–0.879; P=0.0051) (89).

SORCE was a phase III trial of 1,711 RCC patients with an intermediate to high risk of recurrence according to the Leibovich risk model. Patients were randomized 2:3:3 to 3 years of placebo, 1 year of sorafenib (400 mg once daily) followed by 2 years of placebo, or 3 years of sorafenib. No differences in DFS or OS were observed, even among high-risk patients (90).

Finally, EVEREST was a phase III trial involving 1,545 patients with resected RCC who were at intermediate-high, or very high risk of recurrence by modified UISS criteria. Patients were randomized 1:1 to the mammalian target of rapamycin inhibitor everolimus 10 mg daily or placebo. Improved DFS was observed in patients at very high risk (pT3a G2–4, ≥ pT3b any grade or N+) for recurrence (HR =0.79; 95% CI: 0.65–0.97; P=0.011); no

DFS difference was seen in those with intermediate-high risk of recurrence (91). Like previous studies, there was a high treatment discontinuation rate (37%).

In summary, targeted therapies may improve DFS in high-risk patients with localized RCC; however, the lack of OS benefit and significant toxicities discourage its use in the adjuvant setting. These results have prompted a shift toward immunotherapy-based approaches (93).

ICIs

KEYNOTE-564 is the only adjuvant immunotherapy trial that has found a DFS and possible OS benefit in intermediate- to high-risk RCC (19,94). Pembrolizumab remains the only ICI agent for RCC in the adjuvant setting approved by both the FDA and the European Commission (95,96).

KEYNOTE-564 is a phase III randomized, double-blind, multicenter trial that assessed the benefit of 1 year of adjuvant pembrolizumab in patients with intermediate- to high-risk RCC. Post-nephrectomy patients were randomized 1:1 to pembrolizumab or placebo. The primary endpoint was DFS. At the 30-month interim analysis, the threshold for DFS benefit was met with HR =0.63 (95% CI: 0.53–0.87; P=0.002). Median DFS was not reached in either group. Twelve percent of patients in the experimental arm had at least one grade 3–4 AE, compared with <1% of patients in the control arm. No deaths were attributed to treatment. Recently, Merck issued a press release reporting that KEYNOTE-564 met its key secondary endpoint of OS on interim analysis; additional data is forthcoming (20). Confirmation of OS benefit will further reinforce pembrolizumab as the standard adjuvant treatment for selected RCC patients following nephrectomy.

IMmotion010 is a phase III randomized, double-blind, multicenter trial examining the benefit of adjuvant atezolizumab. This trial included 778 patients with an increased risk of recurrence (T2 grade 4, T3a grade 3/4, T3b/c or T4 any grade, TxN+ any grade, or M1 NED). Post-nephrectomy patients were randomized 1:1 to atezolizumab 1,200 mg intravenously (IV) or placebo every 3 weeks for 1 year. The primary endpoint was DFS. Median DFS was 57.2 months with atezolizumab and 49.5 months with placebo, and HR =0.93 (95% CI: 0.75–1.15; P=0.5). OS data was immature at the time of analysis and median OS had not been reached in either arm. In the experimental arm, 27% of patients had at least 1 grade 3–4 AE compared with 21% of patients in the control arm. The study concluded that adjuvant atezolizumab did not improve DFS in patients with intermediate- to high-risk RCC (28).

CheckMate-914 is a phase III randomized, double-blind, multicenter trial assessing DFS with adjuvant nivolumab with and without ipilimumab. Results for part A with nivolumab plus ipilimumab have been reported. This study included 816 patients with ccRCC and an increased recurrence risk (pT2a grade 3/4, pT2b any grade, pT3 any grade, pT4 any grade, or any T any grade N1M0; M1 NED excluded). Post-nephrectomy patients were randomized 1:1 to nivolumab plus ipilimumab or placebo. Patients on the experimental arm received nivolumab 240 mg via IV every 2 weeks for 12 doses and ipilimumab 1 mg/kg via IV every 6 weeks for up to 6 months. The primary endpoint was DFS. Median DFS was not reached in the experimental arm and was 50.7 months in the control arm (HR =0.92; 95% CI: 0.71–1.19; P=0.53). In the experimental arm, 38% of patients had at least 1 grade 3–4 AE, compared with 10% in the control arm. There were 4 deaths in the experimental arm and none in the control arm (27). The study concluded that adjuvant nivolumab plus ipilimumab did not improve DFS in patients with high-risk RCC. Subgroup analysis suggested limited drug exposure (≤6 cycles) and early discontinuation due to increased AEs may have contributed to the lack of DFS benefit (27,97).

PROSPER RCC is a phase III randomized, open-label trial assessing RFS with peri-operative nivolumab. Patients were randomized to peri-operative nivolumab and nephrectomy or nephrectomy alone (98). Patients on the experimental arm received 1 dose of neoadjuvant nivolumab 480 mg via IV before nephrectomy, followed by 9 doses of nivolumab 480 mg via IV after nephrectomy. Both ccRCC and nccRCC histologies were allowed. The primary endpoint was RFS. This trial ended early due to futility. Median RFS was not reached, and numerical results were similar. OS data was immature at the time of analysis, and numerical results between each arm were again similar. About 20% of patients in the experimental arm had at least 1 grade 3–4 AE, compared with 6% of patients in the control arm (99).

It is unclear why KEYNOTE-564 yielded positive results while IMmotion010, CheckMate-914, and PROSPER were negative studies. Possible contributors may include differences in patient characteristics, eligibility criteria, treatment duration, length of follow-up, or subtle variations in therapy mechanisms (*Table 4*). Trial updates may facilitate a better understanding of which patients benefit most from immunotherapy. Adjuvant pembrolizumab for 1 year

Table 4 Adjuvant immunotherapy trials in high-risk RCC

Trial	KEYNOTE-564 (19,94)	IMmotion010 (28)	CheckMate-914 (27)	PROSPER (99)
Treatment	Pembrolizumab, placebo	Atezolizumab, placebo	Nivolumab + ipilimumab, placebo	Nivolumab, observation
Mechanism of action	Anti-PD-1	Anti-PD-L1	Anti-PD-1 and anti-CTLA4	Anti-PD-1
Primary endpoint met?	Yes, DFS	No, DFS	No, DFS	No, RFS
DFS/RFS (mo), HR (95% CI), P value	NR *vs.* NR, 0.68 (0.53–0.87), P=0.002	57.2 *vs.* 49.5, 0.93 (0.75–1.15), P=0.5	NR *vs.* 50.7, 0.92 (0.71–1.19), P=0.53	0.97 (0.74–1.28), P=0.43
Treatment duration (mo)	12	12	6	10 (including neoadjuvant and adjuvant)
Median follow-up (mo)	30	44.7	37	n/a
Histology included	Clear cell	Clear cell (93%) or non-clear cell with sarcomatoid features	Clear cell	Clear cell (83%) or non-clear cell
Risk stratification (% enrolled): stage, grade included	Intermediate-high risk (74%): pT2, G4; pT3, G any; high-risk (20%): pT4, G any, pTxN+, G any	Intermediate-high risk (65%): pT2, G4; pT3a, G3–4; high-risk (21%): pT3b–T4, G any, pTxN+, G any	Intermediate-high risk (56%): pT2a, G3–4; pT2b, G any; pT3, G1–2; high-risk (43%): pT3, G3–4; pT4, G any; pTxN+, G any	High-risk: cT2, G4; cT3–4, G any; cTxN+, G any
M1 NED allowed?	Yes	Yes	No	Yes
% M1 NED	5.8	14.4	n/a	4.0

RCC, renal cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; DFS, disease-free survival; RFS, recurrence-free survival; mo, months; HR, hazard ratio; CI, confidence interval; NR, not reached; n/a, not available; NED, no evidence of disease.

remains the standard of care for high-risk ccRCC patients. Future study design should carefully consider the risk to benefit ratio of experimental treatment. A regimen with increased toxicity may not be a good option in the adjuvant setting.

Future directions

Ongoing perioperative systemic therapy trials in high-risk RCC

There are several clinical trials examining ICI monotherapy or combination therapy for neoadjuvant use in RCC (*Table 5*). These include the SPARC-1 trial (NCT04028245), which is evaluating the safety and efficacy of neoadjuvant spartalizumab (PD-1 inhibitor) and canakinumab, a monoclonal antibody targeting interleukin-1 beta (IL-1β) (107). In preclinical studies, IL-1β blockade led to the inhibition of tumor growth via effects on the tumor microenvironment (108). The triple-arm NESCIO trial (NCT05148546) is investigating neoadjuvant nivolumab, nivolumab + ipilimumab, and nivolumab + relatlimab (lymphocyte-activation gene 3 inhibitor) (101). A phase II neoadjuvant trial investigating lenvatinib in combination with pembrolizumab (NCT05319015) is assessing tumor progression and postoperative complication rates among patients with IVC thrombosis (103). Additional neoadjuvant trials include pembrolizumab in combination with axitinib (NCT04995016), tislelzumab (PD-1 inhibitor) + axitinib (NCT05172440), and toripalimab (PD-1 inhibitor) + axitinib (NCT04118855) (100,105,109).

Adjuvant immunotherapy trials in intermediate- to high-risk RCC are also in progress (*Table 6*). LITESPARK-022 is a phase III randomized, double-blind, multicenter trial assessing DFS with the addition of belzutifan (a first-in-class HIF-2α inhibitor) to pembrolizumab in the adjuvant treatment of locally advanced RCC. Patients will be randomized 1:1 to pembrolizumab 400 mg via IV every 6 weeks plus belzutifan 120 mg by mouth daily or pembrolizumab 400 mg via IV every 6 weeks plus placebo. Pembrolizumab will be continued for up to 1 year, and belzutifan or placebo will be continued for up to 54 weeks.

Table 5 Ongoing neoadjuvant ST trials in high-risk RCC

NCT	Tx setting	Agent	Design	N	Primary outcome
05738694 (100)	Neoadjuvant	Axitinib + toripalimab	Phase II	256	• DFS
05148546 (101)	Neoadjuvant	Nivolumab, ipilimumab, relatlimab	Phase II	69	• Pathologic response rate
05733715 (102)	Neoadjuvant	Pembrolizumab + lenvatinib	Phase I	33	• Change in frequency of progenitor exhausted CD8 T cells (TEX prog) in peripheral blood
05319015 (103)	Neoadjuvant/ adjuvant	Neoadjuvant lenvatinib + pembrolizumab, adjuvant pembrolizumab	Phase II	30	• Disease control rate • Local and metastatic progression rate • 90-day post-op complications
05024318 (104)	Neoadjuvant	Pembrolizumab, stereotactic radiotherapy	Phase II	26	• mPR post-SABR with or without pembrolizumab • $CD8^+$ TRM in baseline biopsy and post-nephrectomy specimen • TCF-1 + TILs in baseline biopsy and post-nephrectomy specimen
05969496 (105)	Neoadjuvant	Axitinib + pembrolizumab	Phase II	17	• Change in IVC TT extent • Change in IVC TT size from baseline
06138496 (106)	Neoadjuvant	Cadonlimab + lenvatinib	Phase II	43	• ORR
03341845 (61)	Neoadjuvant	Axitinib + avelumab	Phase II	40	• Number of pts with partial remission
04028245 (107)	Neoadjuvant	Spartazilumab + canakinumab	Phase I	14	• Percentage of pts who proceed to RN

ST, systemic therapy; RCC, renal cell carcinoma; NCT, national clinical trial; tx, treatment; DFS, disease-free survival; TEX, exhausted T cells; mPR, major pathologic response; SABR, stereotactic ablative body radiotherapy; TRM, tissue resident memory T cells; TCF-1, T cell factor 1; TIL, tumor infiltrating lymphocyte; IVC, inferior vena cava; TT, tumor thrombus; ORR, overall response rate; RN, radical nephrectomy; pt, patient.

Table 6 Ongoing adjuvant immunotherapy trials in high-risk RCC

Trial	LITESPARK-022 (21)	RAMPART (110)
Treatment	Pembrolizumab + belzutifan	Durvalumab + tremelimumab
	Pembrolizumab + placebo	Placebo
Primary endpoint	DFS	DFS and OS
Treatment duration (mo)	12	12
Histology included	Clear cell sarcomatoid	Clear cell sarcomatoid
Stage, grade included	pT2, G4; pT3–4, G any; pTxN+, G any	pT2, G4; pT3a, G3–4; pT3b–T4, G any; pTxN+, G any
M1 NED allowed?	Yes	Yes

RCC, renal cell carcinoma; DFS, disease-free survival; OS, overall survival; mo, months; M1, metastasis stage 1; NED, no evidence of disease.

The primary endpoint is DFS (21).

RAMPART is a phase III randomized, multiarm, multistage trial evaluating the role of durvalumab, a PD-1 inhibitor, +/– tremelimumab, a CTLA-4 inhibitor, in the adjuvant treatment of locally advanced RCC. Patients will be randomized (3:2:2) to placebo, durvalumab 1,500 mg via

every 4 weeks, or durvalumab 1,500 mg every 4 weeks plus 2 doses of tremelimumab 75 mg via IV at day 1 of the first 2 cycles. All arms continue for up to 1 year. The co-primary endpoints are DFS and OS (110).

Another study (NCT05024318) is assessing stereotactic radiotherapy before nephrectomy in combination with neoadjuvant pembrolizumab versus stereotactic radiotherapy alone (104). Additionally, Neovax is a personalized tumor antigen vaccine that has shown benefit post-resection in patients with high-risk melanoma (111). A NeoVax-ipilimumab (NCT02950766) phase I trial for patients with RCC is currently recruiting (112). Finally, the STRIKE study is evaluating adjuvant tivozanib for 6 months plus pembrolizumab 400 mg every 6 weeks (8 doses total) versus pembrolizumab alone in high-risk ccRCC patients.

Biomarkers to improve patient selection in the adjuvant setting for high-risk RCC

Effective biomarkers are needed to improve patient selection for perioperative therapy in high-risk RCC. Seventy percent of patients in the placebo arm of KEYNOTE-564 did not experience recurrence or death within 24 months, suggestive of overtreatment for these patients. Circulating tumor DNA (ctDNA) is emerging as an important tool in the treatment of RCC. ctDNA is genetic material derived from apoptotic or necrotic cancer cells within the bloodstream (113). Liquid biopsy techniques using ctDNA offer several advantages including less invasive testing, which provides rapid results, as well as the opportunity to test numerous times during a patient's treatment course (114). ctDNA enables quantification of minimal residual disease (MRD) in high-risk RCC, thus identifying patients who would benefit the most from treatment. Additionally, ctDNA may enable earlier detection of disease recurrence following adjuvant treatment, resulting in changes to or escalation of treatment. However, the use of ctDNA in RCC is not without challenges, considering that it is present in lower amounts compared to other cancers (115). Furthermore, there are even lower levels of ctDNA in localized compared to advanced RCC (116). Assays with improved sensitivity and detection would be especially valuable (117). A study presented at the ESMO 2023 meeting assessed tissue-informed ctDNA MRD assay (Signatera^{TM}) in 82 patients with stage I–IV RCC post-nephrectomy +/– metastasectomy. The MRD detection window was 13 weeks post-surgery. The negative predictive value of MRD was 91.9% (57/62), and 7 patients with positive ctDNA had NED on imaging (118).

New techniques are emerging to address the diagnostic challenges associated with ctDNA. DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) is a highly sensitive assay capable of detecting early-stage tumors, based on cell-free methylated DNA (119). In a 2020 study using plasma samples, all 41 ccRCC patients were accurately classified with disease as they possessed higher methylation scores than healthy control patients (120). However, further research is needed to investigate this in the MRD setting.

Finally, genomic expression profiles (GEPs) are another tool that can help guide patient selection in the adjuvant setting. ClearCode34 is a validated prognostic tool that subdivides patients with nonmetastatic ccRCC into low-risk (ccA) and high-risk (ccB) groups based on the expression of 34 genes, and accurately predicts the risk of recurrence and death following nephrectomy (121,122). Additionally, a recurrence score based on a 16-gene GEP was developed and independently predicts the risk of disease recurrence following nephrectomy (123).

Conclusions

The optimal use of perioperative systemic therapy in high-risk RCC is an area of active investigation. The use of adjuvant targeted therapies failed to demonstrate a survival benefit and was limited by high rates of toxicity. The positive findings from KEYNOTE-564 further reinforce adjuvant pembrolizumab for 1 year as the standard of care in ccRCC at increased risk of recurrence. There remains a dearth of data on the treatment of high-risk RCC in the neoadjuvant setting. Several ICI-based combination studies in the neoadjuvant and adjuvant settings are being carried out to further improve clinical outcomes. Furthermore, the development of effective biomarkers will be necessary to improve patient selection, with the purpose of identifying those who might benefit from adjuvant treatments, or be especially prone to high grade toxicities, while avoiding overtreatment.

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