

**Review Article****Systemic therapy in the management of localized and locally advanced renal cell carcinoma: Current state and future perspectives**

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**Abbreviations & Acronyms**

ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma  
CTLA4 = cytotoxic T-lymphocyte-associated protein 4  
DFS = disease-free survival  
eGFR = estimated glomerular filtration rate  
EVEREST = EVERolimus for Renal Cancer Ensuring Surgical Therapy  
IVC = inferior vena cava  
OS = overall survival  
PADRES = Prior Axitinib as a Determinant of Outcome of Renal Surgery  
PDL-1 = programmed death-ligand 1  
PN = partial nephrectomy  
PR = partial response  
RCC = renal cell carcinoma  
RECIST = Response Evaluation Criteria In Solid Tumors  
RENAL = Radius Exophytic Nearness Anterior Location  
RFS = recurrence-free survival  
SD = stable disease  
SSIGN = Stage, Size, Grade and Necrosis  
S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer  
TKI = tyrosine kinase inhibitor  
UISS = UCLA Integrated Staging System  
VEGF = vascular endothelial growth factor  
WHO = World Health Organization

**Abstract:** Systemic therapy strategies in the setting of localized and locally advanced renal cell carcinoma have continued to evolve in two directions: (i) as adjuvant therapy (to reduce the risk of recurrence or progression in high-risk localized groups); or (ii) as neoadjuvant therapy as a strategy to render primary renal tumors amenable to planned surgical resection in settings where radical resection or nephron-sparing surgery was not thought to be safe or feasible. In the realm of adjuvant therapy, the results of adjuvant therapy phase III randomized clinical trials have been mixed and contradictory; nevertheless, the findings of the landmark Sunitinib Treatment of Renal Adjuvant Cancer study have led to approval of sunitinib as an adjuvant agent in the USA. In the realm of neoadjuvant therapy, presurgical tumor reduction has been shown in a number of phase II studies utilizing targeted molecular agents and in a recently published small randomized double-blind placebo-controlled study, and an expanding body of literature suggests benefit in select patients. Thus, large randomized clinical trial data are not present to support this approach, and guidelines for use of presurgical therapy have not been promulgated. The advent of immunomodulation through checkpoint inhibition represents an exciting horizon for adjuvant and neoadjuvant strategies. The present article reviews the current status and future prospects of adjuvant and neoadjuvant therapy in localized and locally advanced renal cell carcinoma.

**Key words:** adjuvant, immune checkpoint inhibitor, neoadjuvant, renal cell carcinoma, tyrosine kinase inhibitor.

**Introduction**

RCC is the 17th most common cancer, globally contributing 2.2% of the total number of all cancers diagnosed in 2018. Worldwide, approximately 403 262 people were diagnosed with RCC in 2018, with 175 098 deaths and varying global incidence rates.<sup>1,2</sup> Because of the widespread use of cross-sectional imaging, the incidence of RCC has increased, with most cases presenting as localized disease.<sup>3</sup> Despite such stage migration, however, the risk of recurrence remains high.<sup>4–6</sup> Extirpative surgery, through radical or partial nephrectomy, remains the cornerstone of definitive management for most localized and locally advanced RCC. Nevertheless, the risk of recurrence and the poor prognosis of such patients with recurrence, and the risks associated with locally advanced resection or nephron-sparing surgery in the imperative setting for complex masses have served as an impetus to explore further approaches to improve outcomes.

Approval of TKI therapy for metastatic RCC in 2005 ushered in an era of improved response rates for and decreased risk of adverse events compared with early immunotherapeutic agents, and stimulated investigation into the utility of targeted agents as adjuvants in the setting of localized or locally advanced disease to reduce the risk of recurrence and improve survival. Furthermore, investigation of the efficacy of presurgical neoadjuvant systemic therapy to improve the feasibility and safety of complex or high-risk surgical resections has gained momentum.<sup>7</sup>

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Indeed, utilization of systemic therapy in the setting of localized and locally advanced disease is a field of active investigation and controversy. Recent US Federal Drug Administration approval of sunitinib as the first adjuvant agent for use to reduce the risk of recurrence in RCC and the subsequent impact on management guidelines have heralded a potential paradigm shift in the management of RCC,<sup>8</sup> and the advent of immune checkpoint inhibitor therapy as first-line agents for the management of metastatic RCC has been accompanied by further investigations into the utility of these agents in the adjuvant and neoadjuvant setting in localized RCC.<sup>9</sup>

We carried out a review of the current status of adjuvant and neoadjuvant therapeutic strategies in localized and locally advanced RCC, focusing on current literature and ongoing clinical trials in both areas.

## Methodology

### Literature search

PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, the American Society of Clinical Oncology and ClinicalTrials.gov were searched with keywords including “neoadjuvant,” “adjuvant,” “immunotherapy,” “targeted therapy,” “TKIs,” “VEGF antibodies,” “immune checkpoint (anti-PD-1) inhibitors” and “RCC.” Publications were included in the review if they included patients with localized RCC. Articles with language other than English, editorials and case reports were excluded; six reported and published adjuvant trials, and 15 neoadjuvant trials were included in the review. In addition, seven ongoing adjuvant, six ongoing neoadjuvant trials and one ongoing hybrid adjuvant/neoadjuvant trial were included.

### Assessment of response

In adjuvant therapeutic investigations, survival end-points included OS, DFS and RFS. Early investigations tended to focus on RFS as an end-point, with more recent studies focusing on OS and the primary end-point.<sup>10</sup> To assess tumor response in neoadjuvant investigations, a number of criteria have been utilized to evaluate therapeutic effect: change in tumor size measured in greatest diameter, two-dimensional product of tumor cross-section based on cross-sectional imaging (WHO criteria),<sup>11</sup> RECIST criteria (which defined PR as  $\geq 30\%$  reduction in the primary lesion size, progressive disease as an increase in tumor size  $\geq 20\%$  or the presence of new lesions or SD)<sup>12</sup> and changes in tumor morphometric score, such as the RENAL nephrometry score, a system used for defining tumor complexity.<sup>13</sup>

## Adjuvant therapy in the management of localized and locally advanced RCC

### Principles and patient selection

The aim of adjuvant therapy is to reduce the risk of recurrence and improve survival by eradicating microscopic loco-regional or metastatic foci of disease.<sup>14</sup> In addition to tumor–nodes–metastasis, histological and nuclear grading criteria, risk stratification and prognostic nomograms might quantify a patient’s

risk of recurrence post-resection. Nomograms reported and utilized for such purposes in RCC have included the UISS,<sup>15</sup> SSIGN score,<sup>16</sup> Karakiewicz nomogram,<sup>6</sup> Leibovich score<sup>17</sup> and Kattan nomogram.<sup>18</sup> More recently, gene assays have been utilized in recurrence risk prediction modeling.<sup>19</sup> The UISS and SSIGN models have been utilized to risk stratify and guide patient selection in adjuvant therapy trials, and future investigations might personalize patient selection to rely more heavily on molecular prognostication.<sup>20</sup>

Primary aims and major end-points have changed over time in adjuvant trials. Initially, aims were regarding safety and feasibility, with end-points of PFS; until more recently, large clinical trials assessed the efficacy of adjuvant therapy compared with placebo, with end-points of cancer-specific survival and OS. Toxicities have been reported using the National Cancer Institute terminology system.<sup>21</sup>

## Molecular targeted agents

VEGF pathway-based antiangiogenic agents exploiting the von Hippel–Lindau pathway have formed the bulk of early investigation into adjuvant therapeutic strategies.<sup>22</sup> Reported adjuvant clinical trials are shown in Table 1.

The ASSURE trial was the first North American clinical trial in the targeted therapy era. Designed as a double-blind placebo controlled randomized study, it eventually enrolled 1943 patients with non-metastatic high-risk RCC (Fuhrman grade 3–4 pT1bN0M0 to any grade pTpN + M0) with a study design to randomize according to a 1:1:1 ratio to receive sunitinib 50 mg, sorafenib 800 mg or a placebo for 1 year, with a primary end-point of DFS. At median follow-up period of 5.8 years no difference was observed in DFS between study groups (HR 1.02, 97.5% CI 0.85–1.23) and the clear cell histology subgroup, which was expected to benefit the most from adjuvant therapy, showed no difference from treatment. The study was hampered by the significant burden of treatment toxicity (indeed, despite dose reduction to mitigate toxicity-related discontinuation, both treatment arms experienced  $>55\%$  grade 3 or worse adverse events, and  $>40\%$  of patients in the treatment arms had toxicity-related discontinuation of study drugs) and a high proportion of patients whose ultimate benefit from a neoadjuvant agent would be limited (study design was powered for clear cell RCC, but enrolled non-clear cell histologies, which totaled 21% and 9% of study enrollees that had stage I tumors. Taken together, these potential drawbacks in the study might have contributed to a high proportion of lower-risk patients being enrolled, and/or patients on therapeutic arms having dose reduction and/or discontinuation, which might have affected the response.<sup>23</sup>

The S-TRAC trial enrolled only clear cell histology and American Joint Committee on Cancer stage III or greater disease (Fuhrman grade 2–4 pT3, or pT4 any grade, or nodal involvement). A total of 615 patients were randomized to receive sunitinib 50 mg or a placebo, and were followed for a median of 5.4 years, with a preplanned allowance for dose reduction. The median duration of DFS was improved in the sunitinib group over placebo (6.8 vs 5.6 years, HR 0.76, 95% CI 0.59–0.95,  $P = 0.03$ ), and the follow-up has yet to mature

to report OS. Grade 3–4 adverse event rates in the sunitinib group were higher relative to placebo (60.5% vs 19.4%), and early discontinuation for the sunitinib group occurred in 28.1% versus 5.6% for placebo.<sup>24</sup> A follow-up exploratory analysis found improved DFS over placebo in nearly all subgroups that received sunitinib.<sup>25</sup>

The PROTECT trial randomized 1538 patients with high-risk clear cell RCC (Fuhrman grade 3–4 pT2–T4N0M0 or pTxN1M0) to receive pazopanib (800 mg) or placebo, with a primary end-point of DFS. Notably, the protocol was amended to reduce the dose of pazopanib to 600 mg due to hepatotoxicity, and the majority of patients ( $n = 1135$ ) had the dose-reduced protocol. To address toxicity attrition, primary end-point analysis was changed to DFS for pazopanib 600 mg versus placebo, with secondary end-point analysis for DFS with pazopanib 800 mg. Primary analysis favored pazopanib 600 mg, but did not show significant improvement versus placebo (HR 0.86, 95% CI 0.70–1.06,  $P = 0.165$ ). However, secondary analysis of patients on the initial 800 mg dose yielded improved DFS (HR 0.69, 95% CI 0.51–0.94,  $P = 0.02$ ), with OS to be reported at a later date. Similar to ASSURE and S-TRAC, 60% of patients in the treatment arm experienced grade 3–4 adverse events.<sup>26</sup>

The ATLAS trial compared axitinib versus placebo in patients with  $\geq$ pT2 and/or N+, any Fuhrman grade RCC with primary end-point DFS with a subanalysis of DFS highest-risk subpopulation (pT3, Fuhrman grade  $\geq$ 3 or pT4 and/or N+, any T, any Fuhrman grade); 724 patients (363 axitinib vs 361 placebo) were randomized, and the trial was stopped due to futility. There was no significant difference in DFS (HR 0.87, 95% CI 0.660–1.147,  $P = 0.321$ ) overall, although in the highest-risk subpopulation, a 36% and 27% reduction in risk of a DFS event (HR, 95% CI) was observed per investigator ( $P = 0.005$ ).<sup>27</sup>

Two additional adjuvant clinical trials utilizing targeted molecular agents have closed, but the findings are not in the peer-reviewed literature. The SORCE trial randomized 1655 patients with intermediate- to high-risk localized RCC (clear and non-clear cell histology) to the TKI sorafenib or placebo.<sup>28</sup> The EVEREST trial randomized 1545 patients with intermediate- to high-risk RCC patients (clear cell or non-clear cell RCC) to receive everolimus, a mammalian target of rapamycin pathway inhibitor, an upstream regulator of the VEGF angiogenic pathway, as well as a promoter of cell division, versus placebo to a 12-month course of treatment.<sup>22</sup> That study has completed enrollment and the results are pending.<sup>29</sup>

Based on the results of the S-TRAC study showing a benefit in DFS, the USA Food and Drug Administration approved sunitinib as an adjuvant agent for high-risk localized RCC in November 2017, the first such agent in RCC.<sup>8</sup> Indeed, regulatory approval has heralded a paradigm shift, which has been reflected in the recently updated National Comprehensive Cancer Network guidelines that lists adjuvant therapy with sunitinib as an option for patients with stage III disease, clear cell histology and high risk for recurrence.<sup>30</sup> Nevertheless, due to concerns for toxicities and lack of published benefit with respect to OS, enrollment in a clinical trial is still considered a preferred option for most patients at higher risk for recurrence after complete resection for localized RCC. With data being anticipated from currently ongoing trials, future

approved therapies might be added to provide more options for patients at high risk for recurrence.

## Immune checkpoint inhibitors

The emergence of immune checkpoint inhibition as a front-line therapeutic strategy for metastatic RCC has also heralded investigation of these agents as potential adjuvant agents. The biological rationale is that Th1 immune-related response to tumors can be enhanced by blocking the immune cell-specific inhibitory pathways, namely the PD-1 receptor and PDL-1.<sup>31</sup> Currently, there are four clinical trials examining the potential of checkpoint inhibitors in localized RCC to reduce the risk of recurrence: atezolizumab (one trial, NCT03024996),<sup>32</sup> combination nivolumab and ipilimumab (one trial, NCT03138512),<sup>33</sup> pembrolizumab (one trial, NCT03142334),<sup>34</sup> and durvalumab monotherapy or in combination with tremelimumab (NCT03288532).<sup>35</sup>

The IMmotion010 trial randomizes resected high-risk clear cell or sarcomatoid RCC (pT3a+, high grade including M1 resected disease) to atezolizumab (PDL-1 inhibitor) or placebo. The primary end-point is RFS determined by a central radiological assessment.<sup>32</sup> Checkmate-914 is a trial enrolling patients to a combination PD-1 inhibitor + CTLA4 inhibitor (nivolumab with ipilimumab) or placebo for high-risk clear cell RCC.<sup>33</sup> Keynote-564 is enrolling patients for adjuvant pembrolizumab (PD-1 inhibitor) versus placebo for high-risk patients with clear cell histology including M1 resected disease.<sup>34</sup> The RAMPART study recently began enrolling clear and non-clear cell patients to one of three arms: (i) durvalumab with tremelimumab (PDL-1 inhibitor + CTLA inhibitor); (ii) durvalumab monotherapy; (iii) or placebo.<sup>35</sup> Current ongoing studies in the adjuvant setting are summarized in Table 2.

## Vaccines and targeted immunotherapy

Tumor vaccines and targeted immunotherapy have been investigated in the adjuvant setting for RCC (Table 1). This concept was first explored by Galligioni *et al.*, utilizing autologous tumor cells and bacillus Calmette–Guérin, with negative results.<sup>36</sup> Variations on the same theme have been attempted with the same result.<sup>37,38</sup> More recently, in the ARISER study, girentuximab, a chimeric antibody targeting carbonic anhydrase IX was evaluated as adjuvant in 864 patients with high-risk RCC. Girentuximab was well tolerated, with toxicity rates comparable with placebo. Overall, however, there was no significant difference between girentuximab and placebo for DFS (HR 0.97, 95% CI 0.79–1.18) or OS (HR 0.99, 95% CI 0.74–1.32).<sup>39</sup>

## Neoadjuvant therapy in clinically localized and locally advanced RCC

### Rationale for utilization of neoadjuvant therapy

Neoadjuvant therapy for RCC was initially implemented to accomplish a reduction in metastatic disease before surgical debulking and as a facilitator of more complex surgical

**Table 1** Summary of adjuvant trials: completed and reported

Trial	Design	Intervention	n	Inclusion criteria (stage/grade/histology)	Results	Adverse events
<b>Molecular targeted agents</b>						
ASSURE, Haas <i>et al.</i> <sup>23</sup>	Randomized, double-blinded, placebo-controlled	Sunitinib or sorafenib	1943	T1b N0 M0 (grade 3–4), pT2–pT4 N0 M0, pT (any) N1 M0; clear cell and non-clear cell	No difference in median DFS (HR 1.02, 97.5% CI 0.85–1.23)	Grade ≥3 toxicities of sunitinib, sorafenib: hypertension (17%, 16%), hand-foot syndrome (15%, 33%), rash (2%, 15%), fatigue (18%, 7%)
S-TRAC, Ravaud <i>et al.</i> <sup>24</sup>	Randomized, double-blinded, placebo-controlled	Sunitinib	615	pT3 N0 M0 (grades 2–4), pT4 N0 M0, pT (any) N1 M0; clear cell	Improved median DFS (6.8 vs 5.6 years; HR 0.76, 95% CI 0.59–0.98)	Increased grade 3 (48.4% vs 15.8%); grade 4 (12.1% vs 3.6%) in sunitinib; similar serious event rate
PROTECT, Motzer <i>et al.</i> <sup>26</sup>	Randomized, double-blinded, placebo-controlled	Pazopanib	1538	pT2 N0 M0 (grades 3–4), pT3–4 N0 M0, pT (any) N1 M0; clear cell	No differences in median DFS (HR 0.86, 95% CI 0.70–1.06)	Increased ALT/AST lead to treatment discontinuation in 600 mg (ALT 16%/AST 5%) and 800 mg (ALT 18%/AST 7%) mg
ATLAS, Gross-Goupil <i>et al.</i> <sup>27</sup>	Randomized, double-blinded, placebo-controlled	Axitinib	724	pT2–4 N0 M0, pT (any) N1 M0; clear cell	No difference in median DFS (HR 0.87, 95% CI 0.66–1.15, <i>P</i> = 0.321)	Similar and serious adverse events between groups; more grade 3/4 (61% vs 30%) for axitinib
<b>Immunotherapy</b>						
Jocham <i>et al.</i> <sup>37</sup>	Prospective, randomized	Autologous renal tumor cells	558	pT2–3b pN0–3 M0; clear and non-clear cell	Improved 5-year and 70-month PFS (HR 1.58, 95% CI 1.05–2.37; HR 1.59, 95% CI 1.07–2.36)	Local skin reactions
Wood <i>et al.</i> <sup>38</sup>	Prospective, randomized	Autologous tumor-derived protein	819	cT1b–4 N0 M0, cT (any) N1–2 M0; clear and non-clear cell	No difference in PFS at 1.9 years median follow up (HR 0.92, 95% CI 0.729–1.169)	Local skin reactions
ARISER, Chamie <i>et al.</i> <sup>39</sup>	Randomized, double-blinded, placebo-controlled	Girentuximab	864	pT1b–2 (Fuhrman ≥3), pT3–4 N0, pT (any) N+; clear cell	No difference in DFS (HR 0.97, 95% CI 0.79–1.18) or OS (HR 0.99, 95% CI 0.74–1.32)	Toxicity rate 21%, comparable to placebo

resections, as well as to select patients with appropriate disease response to systemic therapy who might benefit from surgical debulking.<sup>40</sup> In the setting of locally advanced disease, administration of neoadjuvant systemic therapy provided a potential avenue for increasing the likelihood of resection in high-risk surgical patients with tumor invading or extensively abutting adjacent organs or great vessels and necessitating potential organ resection or vascular reconstruction, and the concept of neoadjuvant therapy has also been extended into facilitation of nephron-sparing surgery for complex tumors.<sup>41</sup> There have been 15 studies reported in the literature for indications of downstaging tumor size for resection of locally advanced disease (nine studies), facilitating partial nephrectomy (five studies) and downstaging IVC thrombus level (four studies).

In assessing response to neoadjuvant therapy, researchers obtain radiological imaging before and after therapy to measure changes in disease objectively. Measurements include reduction in tumor size as, utilization of RECIST criteria and

tumor complexity, as reported by the RENAL nephrometry score.<sup>42,43</sup> Changes in objective tumor parameters inform subjective assessments of response to neoadjuvant therapy, including achieving planned resection, altering surgical planning and facilitating nephron-sparing surgery. Toxicity and complication rates are according to the CTCAE v3.0 NCI score and Clavien–Dindo scale, respectively.<sup>21,44</sup>

## Neoadjuvant therapy for resection of locally advanced disease

Table 3 summarizes neoadjuvant therapy studies reporting tumor size changes, adverse events of therapy and complications of surgery. The first study assessing the feasibility and efficacy of neoadjuvant therapy before resection of locally advanced disease was carried out by Thomas *et al.*, who examined 19 patients with locally extensive primary tumors considered otherwise unresectable and were administered sunitinib (initial dose 50 mg daily) for one 4-week cycle.

Analysis noted PR in 16% (3/19) of patients (by RECIST criteria) with a median size reduction of 24% and with 21% (4/19) eventually undergoing nephrectomy. Nevertheless, the authors also reported that 37% of patients experienced grade 3–4 toxicities. No unexpected surgical morbidity was found; however, the major complication rate was not reported.<sup>41</sup>

Hellenthal *et al.* carried out a prospective clinical trial with sunitinib (37.5 mg daily for 90 days) in patients with localized ( $n = 16$ ) or metastatic ( $n = 4$ ) RCC. Overall, 17 patients (85%) experienced a reduction in tumor size, with a mean tumor size reduction of 11.8%, and with one and two PR, according to RECIST and WHO criteria, respectively. All patients underwent laparoscopic radical or partial nephrectomy. Main toxicities related to sunitinib treatment included gastrointestinal ( $n = 13$ , 65%), hematologic ( $n = 11$ , 55%) and fatigue ( $n = 9$ , 45%).<sup>45</sup>

Cowey *et al.* carried out a non-randomized, prospective phase II trial and enrolled 30 patients (17 localized/13 metastatic diseases) to neoadjuvant sorafenib treatment (400 mg twice daily for median duration of 33 days). They reported a median diameter reduction of 9.6%, with two of 30 (9.6%) having PR and 26 of 30 (86.6%) having SD with no progressive disease while receiving therapy. The authors reported that all patients went on to nephrectomy, and no surgical complications related to sorafenib were observed.<sup>46</sup>

In a follow-up analysis of their phase II study, Rini *et al.* reported on their results with neoadjuvant sunitinib (50 mg, in two 6-week cycles) in 28 patients with unresectable primary tumors. They noted that after treatment with sunitinib, there was a 22% decrease in median tumor size (with 3/28 achieving PR by RECIST criteria), while 13 (45%) met the primary end-point of being able to undergo nephrectomy.<sup>47</sup>

Karam *et al.* reported on a phase II clinical trial of neoadjuvant axitinib in 24 patients with localized T3a biopsy-proven clear cell RCC. Axitinib has a significantly shorter half-life relative to other molecular targeted agents, and the authors treated patients with axitinib for 12 weeks, with the primary outcome being the response rate by the RECIST criteria. They noted a 28.3% reduction in the median tumor diameter, with 11 of 24 (46%) achieving PR (RECIST criteria). Toxicities included hypertension, fatigue, mucositis, hypothyroidism and hand-foot syndrome with 8% grade 3 and 54% grade 2. The authors also reported a 12.5% rate (3/24) of major (Clavien 3–5) complications (two chylous ascites that ultimately resolved with conservative measures and one significant hemorrhage requiring re-exploration).<sup>48</sup>

Hatiboglu *et al.* carried out a prospective randomized double blind placebo controlled trial to assess the downsizing effect of sorafenib before surgery in patients with localized and locally advanced RCC ( $n = 12$ ). Participants were randomized in a 3:1 ratio to either sorafenib 400 mg twice daily for 4 weeks or placebo. The treatment group experienced a 29% reduction in median tumor volume after 4 weeks of treatment compared with placebo ( $P < 0.05$ ). Furthermore, in the treatment group, four and five patients underwent partial and radical nephrectomy, respectively.<sup>49</sup>

## Facilitating nephron-sparing surgery

Another indication for investigation into the utility of neoadjuvant therapy has been to facilitate nephron-sparing surgery. The first study to focus on this particular aim was reported by Silberstein *et al.*, who carried out a prospective pilot study and a retrospective multicenter review analyzing outcomes of neoadjuvant sunitinib (50 mg daily for two 6-week cycles) in 12 patients (14 tumors) with clear cell RCC who had imperative indications for nephron-sparing surgery. The authors noted a mean tumor size reduction of 21.1% (7.1–5.6 cm) with four of 14 (28.6%) tumors having PR by the RECIST criteria. Ultimately, partial nephrectomy was achievable in all patients without positive margins or requirement for dialysis. Nevertheless, the authors reported that three of 14 (21.4%) renal units experienced urine leaks, all of which resolved with conservative measures.<sup>42</sup>

In their phase II study examining neoadjuvant axitinib before surgery in clinical T3a clear cell RCC, Karam *et al.* examined the impact of neoadjuvant axitinib on respectability as detailed above, and also looked at facilitation of partial nephrectomy. Of the 24 patients studied, five (22%) ultimately underwent nephron-sparing surgery, and the authors did not report any procedure-specific complications, such as urine leak or pseudoaneurysm.<sup>48</sup>

Rini *et al.* carried out a phase II trial assessing the effect of pazopanib as a neoadjuvant agent to facilitate PN in patients with limited renal function and complex renal masses ( $n = 25$ , median eGFR of 54 mL/min/1.73 m<sup>2</sup>, median RENAL score of 11); 56% (14/25) of patients had a solitary kidney. Patients received pazopanib 800 mg daily up to 16 weeks, with a dose reduction to 600 or 400 mg daily if intolerable toxicity was seen in the first cycle. No grade 4 or 5 toxicities were seen during and after pazopanib treatment. After treatment, the median tumor size and mean tumor volume reduced from 7.2 to 5.5 cm and 170 to 92 cc, respectively ( $P < 0.001$ ). According to the RECIST criteria, PR was seen in 10 (36%) tumors. However, five of the 20 patients (20%) who underwent PN had urine leaks, and the five patients who underwent RN required dialysis postoperatively.<sup>50</sup>

Lane *et al.* carried out a retrospective multi-institutional study evaluating the effects of neoadjuvant sunitinib treatment on downsizing tumors to enable PN in 72 patients (78 tumors, 43.5% cT1, 45% cT2 and 11.5%  $\geq$ cT3) with a median tumor size of 7.2 cm. Patients received 37.5 or 50 mg sunitinib daily for two 6-week cycles. The authors reported post-treatment reduction in tumor size to 5.3 cm (32% reduction in tumor bidirectional area) with 15 PRs (19%) and a reduction in the RENAL score in 59% of patients. Grade  $\geq$ 3 toxicity was seen in 14% of patients. Predictors of lesser tumor downsizing included lymph node metastases ( $P < 0.001$ ), non-clear cell histology ( $P = 0.002$ ) and higher nuclear grade ( $P = 0.023$ ). Surgery was carried out for 68 tumors (87%), and PN was carried out for 49 kidneys (63%). Grade  $\geq$ 3 surgical complications were noted in five (7%) patients, and included urine leak, arteriovenous fistula, incisional hernia and the requirement of permanent dialysis postoperatively. The authors concluded that neoadjuvant sunitinib leads to cytoreduction in most primary tumors, and most

**Table 2** Summary of adjuvant trials: currently ongoing or unreported

Trial	Design	Intervention	n	Inclusion criteria (stage/grade)	Inclusion criteria (histology)
Molecular targeted agents					
SORCE (NCT00492258) <sup>28</sup>	Prospective, double-blinded, placebo controlled	Sorafenib	1420	pT1a N0 M0 (grade 4), pT1b N0 M0 (grades 3–4), pT2–4 N0 M0, pT1b–4 N1 M0	Any
EVEREST, SWOG (NCT01120249) <sup>29</sup>	Prospective, double-blinded, placebo controlled	Everolimus	1545	pT1b N0 M0 (grades 3–4), pT2–4 N0 M0, pT (any) N1 M0	Any
Immune checkpoint inhibitors					
IMmotion010 (NCT03024996) <sup>32</sup>	Prospective, double-blinded, placebo controlled	Atezolizumab	664	Non-metastatic	Clear cell, sarcomatoid
Checkmate-914 (NCT03138512) <sup>33</sup>	Prospective, double-blinded, placebo controlled	Nivolumab + Ipilimumab	800	pT2a–4 N0 M0 (any), pT1–4 N1 M0 (any)	Clear cell
Keynote-564 (NCT03142334) <sup>34</sup>	Prospective, double-blinded, placebo controlled	Pembrolizumab	950	pT2 N0 M0 (grade 4 or sarcomatoid), pT3–4 N0 M0 (any), pT1–4 N1 M0, resectable M1	Clear cell
RAMPART (NCT03288532) <sup>35</sup>	Prospective, multicenter, double-blinded, placebo controlled	Durvalumab, Durvalumab + tremelimumab	1750	Leibovich score <sup>15</sup> 3–11	Any

patients can be subsequently treated with PN with acceptable morbidity.<sup>51</sup>

Lebacle *et al.* carried out a prospective multicenter phase II trial (AXIPAN) to evaluate the ability of neoadjuvant axitinib to reduce the size of T2 RCC and enable PN. Axitinib 5 mg, and up to 7–10 mg, was administered twice daily, for 2–6 months before surgery. The primary outcome was the number of patients receiving PN for tumor <7 cm after neoadjuvant axitinib. A total of 18 patients were enrolled (median tumor size 7.7 cm), and after axitinib treatment, tumor reduction was noted in 16 (89%) with a median size reduction of 17% (6.4 cm;  $P < 0.001$ ), while five (27.8%) patients experienced grade 3 adverse events. A total of 16 patients (89%) underwent PN, and the primary outcome was considered to be achieved in 12 (67%) patients who underwent PN for tumors <7 cm. Five (27.8%) patients experienced Clavien III–V post-surgery complications. Similar to Lane *et al.*, the authors concluded that neoadjuvant axitinib leads to a modest decrease in tumor size that permitted down-stage PN in most cases; however, procedures remained complex, requiring surgical expertise with morbidity.<sup>52</sup>

McDonald *et al.* carried out a multicenter retrospective study to compare the renal functional outcomes of patients with complex masses who underwent neoadjuvant sunitinib therapy for imperative indications when PN was thought not to be feasible ( $n = 47$ , median tumor size 7.2 cm, median RENAL 11) with a cohort of patients with complex masses who underwent PN without prior neoadjuvant therapy ( $n = 78$ , median tumor size 6 cm, median RENAL 10).<sup>41</sup> The neoadjuvant treatment group received 50 mg sunitinib daily for two 6-week cycles, and the authors noted that the median tumor size and RENAL score decreased to 5.8 ( $P = 0.012$ ) and 9 ( $P = 0.001$ ), respectively, with 16 (34%) patients achieving PR by RECIST criteria. High-grade (3 or 4) toxicities were seen in 14 (29.8%) patients. No significant

differences were found between the neoadjuvant and non-neoadjuvant groups in the incidence of complications ( $P = 0.728$ ), and median  $\Delta$ eGFR (mL/min/1.73 m<sup>2</sup>) was similar (neoadjuvant, 6.4 vs non-neoadjuvant, 6.1;  $P = 0.534$ ). The authors concluded that the use of neoadjuvant sunitinib might facilitate complex PN and result in renal functional outcomes similar to those of patients with a complex renal mass who had not required neoadjuvant sunitinib.<sup>43</sup>

Taken together, the available body of literature suggests that neoadjuvant therapy in non-metastatic RCC results in a modest but significant reduction in tumor size, and might facilitate locally advanced tumor resection and complex partial nephrectomy in select cases, with acceptable quality outcomes and morbidity. The lack of published large series of comparative analyses with non-neoadjuvant patients in similar circumstances whether by retrospective or randomized prospective analyses is a significant limitation and currently precludes widespread utilization of neoadjuvant strategies. Although current studies might provide further illuminating information on the utility and efficacy of upfront systemic therapy in non-metastatic disease, a widespread endorsement of adoption of such strategies is not supported by the current state of the literature.

## Downstaging IVC thrombus level

Investigation into neoadjuvant therapy before radical nephrectomy and IVC thrombectomy has yielded mixed results. Cost *et al.* reported 25 patients with IVC thrombi who received neoadjuvant sunitinib in 12 cases and alternative targeted therapies in 13; seven (28%) patients had a measurable increase in thrombus height, seven (28%) had no change and 11 (44%) had a decrease.<sup>49</sup> One (4%) patient had an increase in thrombus level, 21 (84%) had stable thrombi and in three (12%) the thrombus level decreased, all treated with first-line

**Table 3** Summary of neoadjuvant studies: completed and reported

Study	Design	Agent	n	Inclusion criteria	PN/RN	Outcomes	Adverse events/ complications
Thomas <i>et al.</i> <sup>41</sup>	Retrospective	Sunitinib	19	T1–4 NX-1 M0–1	0/4	24% tumor size reduction; 16% PR (RECIST)	37% Grade 3–4 toxicity
Hellenthal <i>et al.</i> <sup>45</sup>	Prospective	Sunitinib	20	T1–4 NX-1 M0–1	8/12	11.8% tumor diameter reduction; 40% patients underwent PN	30% Grade 3 toxicity, no unexpected perioperative complications
Cowey <i>et al.</i> <sup>46</sup>	Prospective	Sorafenib	30	T2–4 M0–1	0/30	9.6% tumor diameter reduction; 7% PR (RECIST)	20% Grade 3 toxicity, no unexpected complications
Silberstein <i>et al.</i> <sup>42</sup>	Prospective	Sunitinib	12	T1–3 N0–1 M0–1	14/0	21.1% tumor diameter reduction; 28% PR (RECIST)	Toxicities: fatigue (75%), diarrhea (33%); complications; urine leak (21%), wound hernia (8%)
Cost <i>et al.</i> <sup>53</sup>	Retrospective	Sunitinib (12), bevacizumab (9), sorafenib (1), temsirolimus (3)	25	T3b+M1 (21)	25/0	12% downstage thrombus level; 4% upstage level; 4% altered surgical strategy	Not reported
Rini <i>et al.</i> <sup>50</sup>	Prospective	Sunitinib	28	Localized (9), mRCC (19)	9/4	22% tumor size reduction; 37% PR (RECIST)	7% Grade 4 toxicity; no unexpected complications
Bigot <i>et al.</i> <sup>54</sup>	Retrospective	Sunitinib (11), sorafenib (3)	14	T3b+	14/0	8% downstaged IVC thrombus level; 8% upstaged thrombus level	21% Grade 3 toxicity
Karam <i>et al.</i> <sup>48</sup>	Prospective	Axitinib	24	T3a N0M0 clear cell	5/19	28.3% tumor diameter reduction; 46% PR	8% Grade 3 toxicity
Zhang <i>et al.</i> <sup>55</sup>	Retrospective	Sorafenib	18	T1–4 N0–1 M0–1 (7/18 M1 disease)	2/16	20.5% mean tumor diameter reduction; 22.2% PR (RECIST); 80% down-staged thrombus level (4/5)	Toxicities: skin reaction (89%) and hypertension (61%), no unexpected perioperative complications
Lane <i>et al.</i> <sup>51</sup>	Retrospective	Sunitinib	72	T1–4 N0–1 M0–1	49/13	18% tumor diameter reduction; 19% PR	14% Grade 3–4 toxicity, no unexpected complications
Rini <i>et al.</i> <sup>50</sup>	Prospective	Pazopanib	25	T1–4 N0–1 M0	18/7	26% tumor diameter reduction; 36% PR rate (RECIST)	64% Grade 3 toxicity, urine leak (20%); hemodialysis (8%)
Lebacle <i>et al.</i> <sup>52</sup>	Prospective	Axitinib	18	T2a NX-0 M0	2/16	17% tumor size; reduction; 12 (66%) achieved downstaging	27.8% (5/18) grade 3 adverse event and complication rate
Hatiboglu <i>et al.</i> <sup>49</sup>	Randomized, double-blind, placebo controlled	Sorafenib	12	T1–3 N0 M0	4/5 vs 1/2	29% vs 0% tumor size reduction	66% Grade 3 toxicity, no unexpected perioperative complications
McDonald <i>et al.</i> <sup>43</sup>	Retrospective case control	Sunitinib vs no sunitinib	125	T1–4 N0 M0	47/0 vs 78/0	19.4% tumor diameter reduction; 34% PR (RECIST)	29.8% Grade 3–4 toxicity, no significant difference in high grade complications
Field <i>et al.</i> <sup>56</sup>	Retrospective	Sunitinib	53	T3–4 N0–1 M0–1 (18/53 M1)		16.1% median tumor diameter reduction; 27.8% PR; 42.1% downstaged	73.7% any-grade toxicity, no difference in complication rate

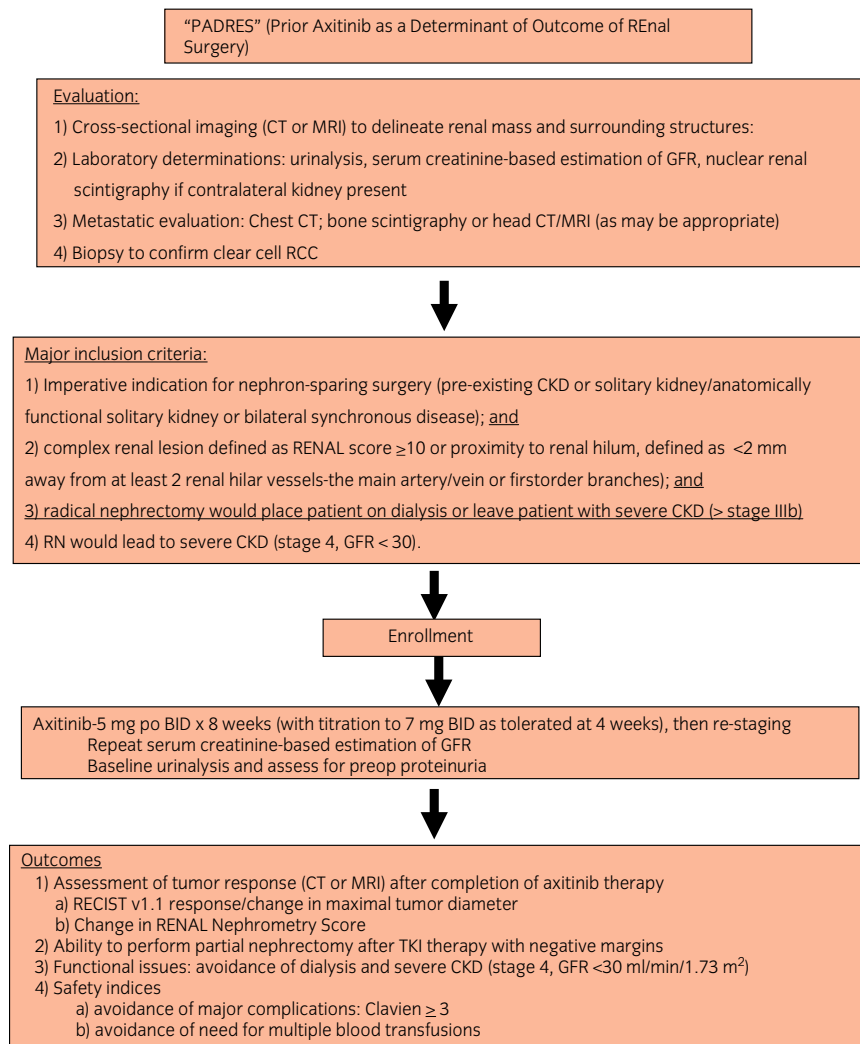
sunitinib. The authors concluded that neoadjuvant targeted therapy had a minimal clinical effect on RCC with IVC thrombi and that only patients treated with sunitinib had clinical thrombus regression; however, the clinical magnitude was not clear and required further investigation.<sup>53</sup> Similarly, in a retrospective study of patients who ultimately had surgery, Bigot *et al.* reported 14 patients with IVC thrombi who were administered sunitinib or sorafenib. Thrombus level was

downstaged in one (8%) patient and upstaged in one (8%) patient. Grade 3 toxicity was observed in 21% ( $n = 3$ ) of patients.<sup>54</sup>

In contrast, Zhang *et al.* reported a retrospective analysis of 18 patients with high-risk localized RCC who had received neoadjuvant sorafenib (400 mg twice daily), and reported a 20.5% mean tumor diameter reduction and PR in 22% of patients (4/18; RECIST criteria). Furthermore,

**Table 4** Summary of neoadjuvant studies: ongoing or unreported

Trial	Design	Agent	Planned accrual	Inclusion criteria (stage/grade)	Inclusion criteria (histology)
<b>Molecular targeted agents</b>					
PADRES (NCT03438708) <sup>63</sup>	Prospective, open label	Axitinib	50	cT1–4 NX-0 M0	Clear cell
<b>Immune checkpoint inhibitors</b>					
Merck Sharp Dohme Corp (NCT02212730) <sup>57</sup>	Prospective, open label, parallel assignment	Pembrolizumab	36	cT1b+ NX-0 M0	Any
Bristol-Myers Squibb (NCT02575222) <sup>58</sup>	Prospective, open label	Nivolumab	30	cT2a–T4 NX-1 M0, cT1–4 N1 M0	Clear cell
NCI (NCT02595918) <sup>59</sup>	Prospective, open label	Nivolumab	29	Stage I–III	Clear cell
Case Comprehensive Cancer Center (NCT02762006) <sup>61</sup>	Prospective, open label	Durvalumab, Tremelimumab	45	cT2b–4 NX-0 M0 cT1–4 N1, M0	Any
PROSPER (NCT03055013) <sup>60</sup>	Randomized, double-blind, placebo controlled	Nivolumab	766	cT2 NX M0, cT1–4 N1 M0	Any
<b>Vaccines</b>					
Roswell Park Cancer Institute (NCT02170389) <sup>62</sup>	Prospective, open label	RCC/CD40L RNA-transfected autologous vaccine	4	pT1, NX-0, M0	Any

**Fig. 1** Schema for the phase II “PADRES” clinical trial.



four of five patients with IVC thrombi had a clinical downstaging. Toxicities were grade  $\leq 3$ , and there were no findings of delayed wound healing.<sup>55</sup> Field *et al.* carried out a multicenter retrospective analysis of 53 patients with IVC thrombus (18 with metastatic disease), comparing 19 patients who received neoadjuvant sunitinib with 34 patients who did not. Recipients of neoadjuvant therapy had a 16.1% median primary tumor diameter decrease (8.1–6.8 cm) and median thrombus size decrease of 1.3 cm in 10 of 19 (52.6%) patients, with a decrease in thrombus level occurring in eight of 19 (42.1%) and PR in five of 19 (26.3%) by RECIST. Although those in the neoadjuvant group had improved median cancer-specific survival (72 vs 38 months,  $P = 0.023$ ), no difference between groups for OS (72 vs 37 months,  $P = 0.08$ ) was found between the neoadjuvant group and controls, and no difference in complication rate between groups was noted (50% vs 31.6%,  $P = 0.194$ ). The authors concluded that neoadjuvant sunitinib might be beneficial in select patients with IVC thrombus, and that further investigation was necessary to confirm their findings.<sup>56</sup>

## Neoadjuvant therapy in the management of localized RCC: Future directions

Further investigation in the neoadjuvant setting utilizing targeted agents, immune checkpoint inhibitors, combinations thereof or vaccine immunotherapy are currently under way. Currently, seven clinical trials investigating the neoadjuvant therapy in non-metastatic RCC are ongoing and are summarized in Table 4. Of these studies, four involve immune checkpoint inhibitors: the anti-PD-1 receptor antibodies pembrolizumab (one study; NCT02212730)<sup>57</sup> and nivolumab (three studies; NCT02575222, NCT02595918, NCT03055-013).<sup>58–60</sup> Another clinical trial involves an antibody directed against programmed cell death-1 ligand 1 (durvalumab/MEDI 4736)  $\pm$  tremelimumab, an antibody directed against human T-cell receptor protein, CTLA4.<sup>61</sup> An additional clinical trial that evaluated presurgical vaccine therapy was closed after enrolling four patients (NCT0217-0389).<sup>62</sup>

A recently opened phase II open label study by the senior author of the present article seeks to evaluate the ability of neoadjuvant axitinib to prevent renal replacement therapies in patients with imperative indication for nephron preservation with complex renal masses in whom a radical nephrectomy would otherwise render as dialysis dependent. Named “PADRES” (Prior Axitinib as a Determinant of Outcome of REal Surgery), the study seeks to evaluate tumor end-points (size and complexity reduction), as well as the impact on surgical outcomes (margins, complications) and function (Fig. 1). The selective TKI, axitinib (Pfizer, New York, NY, USA), was chosen due to its short half-life, which might lend itself ideally to a presurgical clinical setting and might minimize post-surgical morbidity associated with TKI after effects in agents with longer half lives. This multicenter study will aim to recruit 50 participants, and will be the largest North

American study solely examining the utility of pre-surgical therapy before PN.<sup>63,64</sup>

## Conclusion

The utility and efficacy of systemic therapy in the setting of localized and locally advanced RCC are areas of active investigation. The recent approval of sunitinib as an adjuvant agent has changed the paradigm of management of patients in the USA, although enrollment in a clinical trial is preferable if feasible in most patients due to conflicting clinical trial results. In contrast, neoadjuvant therapy has shown promising results in phase II studies and one small phase III clinical trial, although data to support utilization of neoadjuvant therapy on a larger scale is not available.

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## Conflict of interest

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## Editorial Comment

### Editorial Comment to Systemic therapy in the management of localized and locally advanced renal cell carcinoma: Current state and future perspectives

Although adjuvant therapy for renal cell carcinoma (RCC) has been much anticipated, previous studies were unable to show prolonged survival of patients. The ASSURE (sunitinib or sorafenib vs placebo),<sup>1</sup> PROTECT (pazopanib vs placebo)<sup>2</sup> and ATLAS (axitinib vs placebo)<sup>3</sup> studies failed to show prolongation of disease-free survival (DFS) in high-risk patients after nephrectomy. In the S-TRAC study (sunitinib vs placebo) in patients with locally advanced RCC (pT3 and pT4), although prolongation of DFS was reported, the efficacy for prolonging overall survival was not proved.<sup>4</sup> The benefit appeared to be restricted to patients with short DFS or short overall survival after surgery.

DFS typically represents the primary end-point in clinical studies of adjuvant therapy using tyrosine kinase inhibitors (TKIs). When an adjuvant therapy prolongs only DFS, but not overall survival, it is debatable whether there is any benefit in the treatment. Some patients not requiring the treatment are frequently enrolled in adjuvant therapy. Even if adjuvant therapy results prolong DFS after nephrectomy, the patient must continue taking the medication during this period. Furthermore, multiple patients experience adverse events with TKI therapy, leading to decreased quality of life. Because a subset of patients with metastatic RCC do show a complete response with TKI treatment, given that TKIs can cause tumor shrinkage through the inhibition of angiogenesis, adjuvant therapy using TKI seems to be limited in the adjuvant setting.

When administered as neoadjuvant therapy, TKI treatment is not indicated for all patients with advanced RCC scheduled to undergo nephrectomy, because evidence for an objective response rate is insufficient and no predictive marker of

treatment effectiveness has been reported to date. Neoadjuvant treatment should be used in patients likely to benefit from systemic therapy, such as surgical patients at high risk for inferior vena cava thrombus or imperative cases of partial nephrectomy. In patients with advanced RCC, the therapeutic effect might be of value in determining the surgical indication.

Berquist *et al.* also describe clinical trials that include ongoing or unreported studies on neoadjuvant and adjuvant therapy in high-risk patients with RCC, and discuss the adaptation of these studies.<sup>5</sup> However, the issue is not yet settled, because the results from clinical trials remain inconclusive. Several clinical trials investigating novel therapies, such as immune checkpoint inhibitors, are also ongoing, and future novel strategies for adjuvant and neoadjuvant therapy might provide real benefits for patients with RCC.

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### Conflict of interest

None declared.

### References

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