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Neoadjuvant Systemic Therapy in Localized and Locally Advanced Renal Cell Carcinoma

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While the majority of renal cell carcinoma (RCC) cases present at an early stage, a significant number of patients are diagnosed with either locally advanced or metastatic disease. While surgical resection remains the definitive curative management in the localized setting, many patients experience disease relapse and the 5-year recurrence rate following nephrectomy nears 60% for patients with high-risk localized disease. As systemic therapies including anti-angiogenesis, immune checkpoint blockade, and combinations thereof have evolved with dramatic improvements in survival outcomes for patients with metastatic RCC, there is a renewed interest in exploring the utility of these agents in the upfront neoadjuvant and adjuvant setting. Neoadjuvant therapy, administered prior to definitive surgery, aims to eradicate micro-metastatic disease early on and reduce surgical complexity with the overall goals of lowering perioperative morbidity and increasing post-operative recurrence-free and progression-free survival. In this chapter, we present an overview of previously completed and ongoing neoadjuvant systemic therapy clinical trials for patients with localized and locally advanced RCC and discuss potential considerations regarding the utility and future study of neoadjuvant therapy for the optimal management of localized RCC.

Keywords: neoadjuvant, targeted therapy, systemic therapy, renal cell carcinoma, clear cell

1 INTRODUCTION

While renal cell carcinoma (RCC) accounts only for 2-3% of all adult malignant neoplasms, it is considered highly lethal, with a 16.9% five-year mortality rate (1). One cause for this high mortality is the significant proportion of patients who present with localized stage III and/or advanced stage IV disease (13.9% and 18.7%, respectively) (2). Another cause for the persistent high mortality rate of RCC is the relatively high rate of disease recurrence and metastases following surgical resection for high-risk localized disease patients [such as T3 stage, Fuhrman grade ≥ 2, sarcomatoid differentiation, and nodal involvement (3, 4)], with 5-year recurrence rates near 60% (3, 5, 6), and corresponding 5-year survival rates of 63% and 53% for stage II and stage III RCC (7).

The management of advanced RCC has undergone many advancements in the past 2 decades, with the introduction of targeted therapy agents – particularly vascular endothelial growth factor inhibitor (VEGFi), and immune checkpoint inhibitor (IO) agents, and IO/IO or IO/VEGFi combination therapies. As these agents have become standard agents for disease control for

patients with advance disease (8, 9), their use in the adjuvant setting has been explored (8, 10–14). However, only two completed prospective studies have noted significant improvement in disease-free survival (DFS). S-TRAC, which studied adjuvant sunitinib for 1 year, showed an improvement in DFS [HR 0.76; 95% CI, 0.59 to 0.98, p = 0.03 (10)] but no significant improvement in overall survival (OS). Recently, KeyNote-564, a phase III study investigating adjuvant pembrolizumab for 1 year for high risk disease, noted a significant improvement in DFS [HR 0.54; 95% CI, 0.30 to 0.96 (15)] while benefit to OS, if any, has not yet been established pending maturation of data (15). This introduction of IO therapy in the adjuvant setting has expanded the options for patients with high-risk disease, and its impact on the natural history of disease will require further study.

As with most treatments in cancer therapy, the above targeted therapy agents were first investigated in treatment-refractory advanced RCC, then as first-line therapy for advanced RCC, followed by evaluation in the adjuvant and, finally, in the setting of neoadjuvant systemic therapy (NA-ST), as it offers several theoretical benefits over adjuvant therapy. These advantages are broadly classified into (1) perioperative benefits, including downsizing or downstaging of a surgically difficult or otherwise unresectable tumors, reducing surgical morbidity by reduction of tumor complexity, and allowing for an organ sparing approach in patients with limited baseline renal function; and (2) early and prompt oncologic control, reducing post-operative recurrence risk and eradication of micrometastatic disease (16–18).

Here, we provide an overview of current literature and ongoing trials of NA-ST in localized and locally advanced RCC. Of note, our review focuses on the implementation of NA-ST in RCC patients with no evidence of metastatic disease (M0) at the time of surgery, which we and others define as the target for true neoadjuvant ST (18, 19), in contrast to trials of presurgical systemic therapy followed by consolidative or cytoreductive surgery for patients with limited M1 disease (20–23), a topic that is outside the scope of this review. We will review published trials of NA-ST, studying their outcomes and adverse effects of their therapeutic agents, followed by a review of ongoing trials and future directions in this field, and discuss the current state and limitations of NA-ST for RCC as the current treatment landscape evolves.

2 MATERIALS AND METHODS

We queried PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov using the keywords ("neoadjuvant" and "renal cell") to identify candidate articles, including published and ongoing trials. Inclusion criteria for ST trials and retrospective series reviewed in this chapter were: use of neoadjuvant targeted ST (VEGFi and/or IO), treatment of localized or locally advanced M0 RCC, and having a publication or full-article translation in the English language. Articles with no corresponding English language publication, editorials, case reports, and studies of non-targeted therapy (such as IL-2, IFN-gamma) were excluded, as well as trials that included both M0 and M1 patients, as we believe such studies to be of presurgical systemic therapy followed by cytoreductive nephrectomy, a currently debated topic that is outside the scope of this chapter. Based on this distinction, we excluded 2 published and one ongoing prospective trial that enrolled both M0 and M1 cases (20, 21, 24), and a retrospective series of presurgical sunitinib for tumor downsizing prior to partial nephrectomy in a select group of M0 and M1 patients (25).

Adverse events (AEs) including toxicity profile of implemented systemic therapies and post-operative complications in included trials were also summarized using CTCAE (Common Terminology Criteria for Adverse Events) grading, focusing on grade 3-5 events (26).

3 RESULTS

3.1 Overview of Literature Search Results

We identified 4 published prospective trials, and 13 ongoing and/or recently completed trials in NA-ST of localized or locally advanced M0 RCC. We also identified two unpublished studies that were terminated early due to poor accrual (phase I pembrolizumab study (27), phase II sunitinib study (28)). In terms of ST agents, all published trials utilized VEGFi monotherapy agents, while most ongoing trials have shifted to IO-based therapy. Only 1/4 published trials evaluated preoperative objective response rate (ORR) as a primary outcome, while all (10/10) of the ongoing phase II trials list ORR or pathologic response rates as their primary outcomes of interest.

3.2 Summary of Published Clinical Trials

We identified 4 published and completed trials of NA-ST for localized RCC. All studies utilized neoadjuvant VEGFi tyrosine kinase inhibitor (TKI) monotherapy (pazopanib, axitinib, sorafenib), with objective response rate (ORR) as a primary or secondary outcome. The results of published prospective clinical trials are discussed below by the implemented ST agent, with a summary in **Table 1**. Incidence and nature of AEs for the agents utilized in these trials are summarized in **Table 2**.

3.2.1 Axitinib

Axitinib is a potent oral TKI used for treatment of advanced RCC as a monotherapy and, more recently, in combination with IO agents in the first-line setting (33, 34). Unlike multi-targeting earlier TKIs (e.g., sorafenib, sunitinib, pazopanib), axitinib is more selective for VEGFR, with a shorter plasma half-life and less need for dose titration (35). Axitinib was first evaluated as NA-ST in a single arm, single center, phase 2 trial by Karam et al. (2014; NCT01263769) (29). A course of pre-operative axitinib 5 mg twice daily for up to 12 weeks was investigated in 24 patients with surgically resectable cT2-T3b disease and biopsy-confirmed clear cell carcinoma (ccRCC), followed by partial or radical nephrectomy. The primary outcome was objective response rate (ORR) by RECIST v1.1 criteria (36). Most (22/24) patients

TABLE 1 | Published Trials in Neoadjuvant Therapy in Locally Advanced, Non-Metastatic Renal Cell Carcinoma.

Author, Year,	Agent	Trial Phase and design	N	Dose and Duration	Pathologic Inclusion Criteria	Primary Outcomes	Secondary outcomes	Objective response rate
Karam* (29)	Axitinib	Phase II, single arm	24	5 mg BID, 12 wk	cT2-T3,N0,M0; ccRCC on preoperative biopsy	Preop ORR**	Safety, tolerability, and QoL*	46% PR
Rini (30)	Pazopanib	Phase II, single arm	25	800 mg PO QD, 8-16 wk	cTany,Nany,M0; ccRCC on preoperative biopsy ***	Percentage of patients who could undergo PN following pazopanib therapy	Amount of parenchymal mass preserved by surgery following therapy****; tumor diameter reduction, and ORR, safety, morbidity	33% PR
Hatiboglu (31)	Sorafenib	Pilot, Study; double blinded RCT	12	400 mg PO BID in sorafenib arm, 4 weeks	cT1-3, N0, M0; any RCC	Reduction in tumor volume	Change in tumor R.E.N.A.L nephrometry score and histologic morphological heterogeneity	Not measured
Lebacle (32)	Axitinib	Phase II, single arm	18	5 mg PO BID for 2-6 months	cT2a, N0, M0 ccRCC	Patients receiving PN for tumors < 7 cm in size following NA-ST	ORR	22% PR

**ClinicalTrials.gov identifier: NCT01263769. The trial is listed as ongoing but not recruiting.*

***ORR, objective response rate; QoL, Quality of Life.*

****1 of the 25 enrolled patients was found to have chromophobe RCC despite enrollment criteria specifying ccRCC for inclusion in trial.*

*****The amount of preserved parenchyma was based on pre-operative CT scan-based volumetric measurement of renal parenchyma pre- and post-therapy.*

completed their 12-week axitinib regimen without requiring dose modification; one patient completed only 11 weeks due to transient grade 3 elevation of liver enzymes and thrombocytopenia, and another stopped treatment at 7 weeks due to development of AKI, with later recovery, then was taken to surgery earlier than scheduled. The authors noted a partial response (PR) in 11/24 (46%) patients, and no disease progression on pre-operative CT scans taken following

TABLE 2 | Systemic Treatment Toxicity Profiles Based on Published Trials.

Author, Year	Agent	Dose/ Duration	Description of Adverse Events	Notable Post-operative Complications	Overall Grade ≥ 3 Events (%)*
Karam (29)	Axitinib	5 mg BID 12 weeks	Grade 1-2: fatigue, hoarseness, oral mucositis, hypothyroidism, hand-foot syndrome, nausea, and diarrhea. Grade 3 complications: Hypertension (41.7%), elevated LFTs (8.3%), abdominal pain (8.3%), AKI (4.2%), Thrombocytopenia (4.2%), oral mucositis (4.2%), hand-foot syndrome (4.2%) No grade 4-5 complications	Chylous ascites (12.5%), PE (8.3%), superficial wound dehiscence (4.2%), bleeding (4.2%)	≥ 41.7%**
Rini (30)	Pazopanib	800 mg QD 8-16 weeks	Grade 1-2: Fatigue (76%), nausea/vomiting (48%), diarrhea (52%), mucositis (44%), hair depigmentation (44%), anorexia, hand-foot syndrome (36%) Grade 3: Hypertension (36%), elevated LFTs (20%), thrombocytopenia (4%), No grade 4-5 complications	Urine leak (25%), periop transfusion (25%), wound dehiscence (8%), long term need for dialysis (21%), chylous ascites (4%)	64%
Lebacle (32)	Axitinib	5 mg BID 2-6 months	Grade 1-2***: 66% Grade 3***: 27.7% Grade 4: 1 patient (suicide attempt) Grade 5: 1 patient (massive MI 1 month following surgery)	Severe bleeding requiring embolization and urine leak, (1 and 2 pts, respectively)	27.7%
Hatiboglu (31)	Sorafenib	400 mg BID 4 weeks	Grade 1-2: Not reported Grade 3: incompletely reported, but ≥ 7 patients (58.3%) developed AEs, including hand-foot syndrome (4 patients), and hypertension (1 patient) Grade 4-5: not reported	Not reported	58.3*%

**Includes complications during pre-operative NA-ST treatment as well as peri/post operative complications.*

***Overall rate of grade 3+ complication rate was not provided.*

****Exact AE frequencies not reported, but most common were hypertension, fatigue, dysphonia and hand-foot syndrome. Rate of grade 3 complications was 6.3% during NA-ST treatment.*

completion of axitinib regimen, with a corresponding reduction in median tumor size of 28.3%.

In a more recent trial by Lebacle et al. (2018) (32), axitinib was investigated for downstaging of cT2aN0-NxM0 ccRCC patients who were deemed not suitable for partial nephrectomy (PN). The primary outcome was the number of patients receiving PN for tumors < 7 cm in size following NA-ST, a decision determined by the surgeon based on the preceding pre-operative CT scan. Axitinib 5 mg twice daily was given for 2-6 months pre-operatively, depending on radiologic response – patients received radical nephrectomy (RN) if the tumor continued to enlarge and continued therapy stable per investigator review. Patients who tolerated axitinib with AEs > grade 2 during a 2-week period had their dose gradually up-titrated to a maximum of 10 mg twice daily per FDA label. The study enrolled 18 patients, with most (12) receiving 2 months of axitinib 5 mg BID; 3 and 3 patients received 4 and 6 months of axitinib pre-operatively, and only one patient required dose reduction to 3 mg for unclear reasons. At the end of the study, the primary outcome was considered reached in 12 of the 18 enrolled patients, with 16 undergoing PN. ORR was the secondary outcome, with partial response and stable disease in 3 and 14 patients, respectively. Median reduction in tumor diameter and R.E.N.A.L nephrometry score (37) were 12 mm and 1, respectively. The study reported the incidence of local recurrence and metastatic disease at 2-year follow-up (2 and 6 patients, respectively), which was attributed to the upstaging of 41% (7) tumors from cT2 to pT3a on final pathology, and the 11% rate of positive margins. The authors ultimately concluded that axitinib was a feasible neoadjuvant ST that produced a modest decrease in size and complexity of cT2 tumors, and may in turn make tumors more amenable to PN over RN.

3.2.2 Pazopanib

Pazopanib is an oral, multi-targeting TKI agent that inhibits tyrosine kinases associated with VEGFR, platelet-derived growth factor (PDGF) receptor and Kit receptor (38). In addition to being evaluated in the management of metastatic RCC (39), pazopanib was also evaluated in the adjuvant setting in the phase III PROTECT trial (1 year of pazopanib 800 mg daily, later dose reduced to 600 mg daily due to due high attrition rates attributed to drug toxicity), but did not demonstrate a recurrence-free survival (RFS) or OS benefit compared to placebo (40). Similar to the aforementioned axinitib trial by Lebacle et al, neoadjuvant pazopanib was evaluated for improving the number of patients eligible for PN in a phase II trial of localized ccRCC by Rini et al (30). Specifically, patients enrolled in the trial had to meet at least one preoperative criteria: (1) their PN or RN was likely to yield a glomerular filtration rate of less than 30 ml/minute/1.73 m^2, or (2) their planned PN was deemed high risk due to high complexity, defined as either R.E.N.A.L. nephrometry score of 10-12 and/or tumor location being adjacent to hilar vessels. The primary endpoint was the percentage of patients who could undergo PN after pazopanib therapy, while secondary endpoints included estimated preserved functional renal parenchyma, based on CT scan-based volumetric measurement of renal parenchyma pre- and post-ST, along with reduction in tumor volume, and ORR. The trial enrolled 25 patients who received pazopanib 800 mg PO daily for up to 16 weeks. Of these, 13 patients were deemed ineligible for PN based on surgeon assessment pre-therapy, with 6/13 (46%) patients developing a sufficient response to be deemed PN-eligible post-therapy, along with an estimated improvement of preserved functional parenchyma from 107 cc pre-therapy to 173 cc post-therapy ($p = 0.0015$) and median tumor diameter reduction from 7.3 cm to 5.5 cm following therapy ($p < 0.0001$). However, overall ORR was only 33% for ccRCC patients, with 16 (64%) of patients developing grade 3 AEs.

3.2.3 Sorafenib

Sorafenib an oral multi-targeting TKI including VEGFR2, FLT3, PDGF receptor, and fibroblast growth factor receptor-1 (FGFR1). In addition to its proximal signaling effects, this molecule also inhibits downstream Raf kinases which serve as important mediators of the Ras/Raf/MEK pathway (41). Adjuvant sorafenib was evaluated in a phase 3 trial by Eisen et al (12), noting no improvement in DFS or OS compared to placebo. It was also studied as potential NA-ST agent for localized RCC in a randomized, placebo-controlled trial by Hatiboglu et al (31) in patients with clinical stage I-III RCC and cN0/M0 disease. Patients were enrolled into either sorafenib or placebo arms (allocation ratio 3:1, respectively; sorafenib 400 mg PO BID for 4 weeks). The primary outcome was reduction in tumor volume, along with assessment of R.E.N.A.L scores. However, despite enrolling 20 patients, only 12 proceeded with therapy followed by surgery (9 sorafenib, 3 placebo), as 3 had to be excluded for not meeting inclusion criteria following further investigation, and 5 withdrew due to concerns regarding side effects of surgery and/or delaying surgery. Of the 12 patients who proceeded with the trial, only 3 of the 9 patients in the sorafenib arm completed the planned course of sorafenib, while 4 patients underwent dose modification to 200 mg BID due to grade 3 toxicity, and 1 patient discontinued it completely due to serious AEs on day 5 of treatment, with recurrence of these AEs on resuming treatment at 100 mg BID. At the conclusion of the study, median reduction of tumor in the sorafenib arm was 29% with tumor shrinkage in 8/9 patients (range -4% to 61.1%), versus no change in the placebo arm, but with no statistically significant change in R.E.N.A.L scores compared to pre-treatment in either arm.

3.2.4 Adverse Effects of NA-ST in Published Trials

Adverse effects of treatment and post-operative complications for published trials are summarized in **Table 3**. While no CTCAE grade 4-5 complications related to treatment were noted with NA-ST, 27.7-64% of patients experienced grade 3 complications overall, which were predominantly hypertension, elevated liver AST/ALT, abdominal pain, and gastrointestinal side effects (ileus, nausea, vomiting, poor appetite). TKI-specific side effects including oral mucositis and hand-foot syndrome were mostly grade 1-2, and rarely required dose adjustment (**Table 2**). However, only a minority of patients required early discontinuation of treatment (2 in axitinib trial by Karam et al,

TABLE 3 | Trials in Neoadjuvant Therapy in Locally Advanced Renal Cell Carcinoma.

ClinicalTrials.gov ID	Agent	Design	N	Dose and Duration	Pathologic Inclusion Criteria	Primary Outcome	Secondary Outcome	Status
NCT02762006 (42)	Durvalumab +/- Tremelimumab	Phase I	29	Cohort 1: Durvalumab x 1 dose (n=6) Cohort 2: Durvalumab + Tremelimumab x 1 dose (n=6) Cohort 2a: Durvalumab + Tremelimumab x 1 dose (n=12) Cohort 3: Durvalumab + Tremelimumab x 1 dose (n=9)	T2b-4 and/or N1, M0 disease Radiographic RCC, any histology	Dose limiting toxicity	ORR	Completed
NCT02575222 (43)	Nivolumab	Phase I	17	3 mg/kg, IV on day 1 of each 2-week cycle, for a total of 3 doses prior to nephrectomy	T2a-T4NanyM0 or TanyN1M0 Histologic clear cell RCC	Adverse events	ORR 5-yr MFS, OS	Completed
NCT01361113 (44)	Pazopanib	Single arm Phase II	21	Pazopanib 800 mg PO QD for 8 weeks	≥T2, M0 disease Histologic clear cell RCC	ORR	2 year RFS	Completed
NCT01263769 (45)	Axitinib	Single Arm Phase II	40	5 mg by PO BID for 12 weeks	cT2-T3b, N0, M0 Histologic predominantly clear cell RCC	ORR	N/A	Active, not recruiting (estimated completion 2021)
NCT03680521 (46)	Sitravatinib + Nivolumab	Single arm Phase II	25	Sitravatinib oral capsule administered daily for 6-8 weeks in segments 1 and 2. Nivolumab administered as 240 mg IV every 2 weeks for 4-6 weeks in segment 2.	Imaging results consistent with locally-advanced RCC Candidate for partial or complete nephrectomy as part of treatment plan	ORR	3-yr DFS	Active, not recruiting (estimated completion 2023)
NCT04028245 (47)	Spartalizumab + Canakinumab	Pilot Study	14	Spartalizumab at 400 mg IV weeks x 2 doses prior to radical nephrectomy Canakinumab 300 mg IV Q4 weeks x 2 doses prior to radical nephrectomy	Any histology Localized M0 RCC that is clinical stage T2 and above, or clinical N1 disease with any T stage; Histologic clear cell or predominantly clear cell RCC	Feasibility of spartalizumab and canakinumab will be met if > 85% of patients proceed to radical nephrectomy	ORR	Recruiting
NCT04022343 (48)	Cabozantinib	Single Arm Phase II	17	PO QD for 12 weeks in the absence of disease progression or uNA-STceptable toxicity. The assigned starting dose for cabozantinib is 60 mg/day. Two dose reduction levels of cabozantinib are permitted	≥ T3Nx, M0 or TanyN+, M0 or deemed unresectable by surgeon Histologic RCC with clear cell component	ORR	3-yr DFS, OS	Recruiting
NCT03341845 (49)	Axitinib + Avelumab	Single arm Phase II	40	Axitinib 5MG BID and avelumab 10mg/kg IV every 2 weeks	Histologically confirmed diagnosis of non-metastatic clear-cell renal cell carcinoma of intermediate to high risk with completely resectable primary tumors	ORR	10-yr PFS	Recruiting
NCT04393350 (50)	Lenvatinib + Pembrolizumab	Single arm Phase II	17	Lenvatinib PO QD on days 1-21 and pembrolizumab IV over 30 minutes on day 1. Treatments repeat every 21 days for up to 4 cycles in the absence of disease progression or uNA-STceptable toxicity.	≥ T3Nx or TanyN+ or deemed unresectable by surgeon, M0 Histologic RCC with clear cell component	ORR	4-yr DFS, OS	Recruiting

(Continued)

TABLE 3 | Continued

ClinicalTrials.gov ID	Agent	Design	N	Dose and Duration	Pathologic Inclusion Criteria	Primary Outcome	Secondary Outcome	Status
NCT05172440 (51)	Tislelizumab + Axitinib	Single arm Phase II	20	Axitinib 5 mg BID for 12 weeks, and tislelizumab 200 mg IV on the first day of the first week, 4th week, 7th week, and 10th week	T2-T3 N0M0 RCC, any histology	ORR	2-yr DFS	Recruiting
NCT04995016 (52)	Pembrolizumab + Axitinib	Single arm Phase II	18	Pembrolizumab 200mg IV, every 3 weeks. Axitinib given 5 mg PO BID.	M0; clinical stage ≥ T3Nx or TanyN+; Histologic RCC with clear cell component	Major Pathologic Response Rate	ORR 2 year DFS, OS	Not yet recruiting (estimated completion 2023)
NCT04118855 (53)	Toripalimab + Axitinib	Single arm Phase II	30	Axitinib 5 mg PO BID combined with Toripalimab 3mg/kg IV q3w for up to 12 wk	T2-T3N0M0 Histologic clear cell RCC	ORR	Change in tumor complexity, assessed by R.E.N.A.L. nephrometry score	Not yet recruiting (estimated completion 2026)
NCT05148546 (54)	Nivolumab Nivolumab + Ipilimumab Relatlimab + Nivolumab	Randomized three-arm phase II trial	42	2 cycles of nivolumab 360mg every 3 weeks (arm A), 2 cycles of ipilimumab 1 mg/kg + nivolumab 3 mg/kg every 3 weeks (arm B) or 2 cycles of relatlimab 360mg + nivolumab 360mg every 3 weeks (arm C), prior to surgery at week 7.	Primary, resectable, intermediate to high-risk, stage III, M0 Histologic clear cell renal cell carcinoma	Pathologic Response Rate	ORR 5 year RFS, EFS	Not yet recruiting (estimated completion 2029)

IV, Intravenous infusion.
ORR, objective response rate (complete + partial response by RECIST criteria).

1 in sorafenib trial by Hatiboglu et al), and there were no reported treatment-related deaths.

While 3 of the 4 published studies reported post-operative complications, noted for chylous ascites and superficial wound dehiscence (12.5% and 8.3% with axitinib by Karam et al (29); 4% and 8% with pazopanib by Rini et al (30), respectively), it is difficult to determine if these complications were related to NA-ST or not without a control arm, particularly given the small cohort sizes and the preference for partial over radical nephrectomy in two of the trials due to their outcome of interest being the facilitation of performing this procedure.

3.3 Summary of Ongoing and Recently Completed Trials

We identified 13 ongoing and/or recently completed trials in NA-ST of localized or locally advanced M0 RCC: 1 pilot study, 2 phase I studies, and 10 phase II studies, summarized in **Table 3**. While only 1 of the published studies reported recurrence-free survival outcomes, most (9/13) of the ongoing trials plan to report disease-free, recurrence-free, or progression free survival (DFS, RFS, PFS) as secondary outcomes, and only 1 has OS as a secondary endpoint.

As with published studies, most (11/13) of the ongoing studies are focused on patients with a clear cell component. Not surprisingly, most of these trials have shifted from VEGFi monotherapy to investigating the use of IO agents as monotherapy or in combination with other IO or VEGFi agents in the neoadjuvant setting; only 2 ongoing studies utilize VEGFi monotherapy: NCT01263769 (aforementioned trial of axitinib by Karam et al (29); no longer recruiting), and NCT04022343 (cabozantinib, actively recruiting), while the remaining 11 studies utilize IO monotherapy (2 studies) or IO-based combination therapy (9 studies). This momentum in prospective trials on investigating the role of peri-operative immunotherapy reflects a significant paradigm shift in clinical oncology in the acceptance of this modality as an additional pillar in the treatment of localized disease. While outside the scope of this review, the incorporation of immune checkpoint inhibitors as adjuvant therapy is being actively pursued in parallel with many of the studies in the neoadjuvant space (55, 56).

The rationale for utilizing immunotherapy earlier in the course of the disease centers on the ability of immunotherapy to augment anti-tumor immune surveillance which may ultimately confer effective treatment of micro-metastatic disease compared with targeted therapies. NCT02575222 (43) was a recently completed phase I trial that accrued 17 patients with non-metastatic high-risk clear cell RCC to investigate the role of nivolumab monotherapy, an anti-PD-1 monoclonal antibody that is also currently under investigation in the adjuvant setting (55). Results from this study are pending; the primary outcome is safety as assessed by the number of participants experiencing AEs, with ORR and survival data as secondary outcomes. NCT02595918 (57) was another pilot phase I trial investigating nivolumab monotherapy in the pre-operative setting. The original inclusion criteria included a goal of 29 patients with localized RCC or low-volume metastatic disease. This study was ultimately terminated in August 2020 due to low accrual. Study outcomes, which include safety and feasibility (primary objective) as well as overall ORR and RFS (secondary

objectives), are pending report. Notably, the PROSPER trial [NCT03055013 (58, 59)] is an active, multicenter randomized Phase III study with planned enrollment of 766 patients and seeks to investigate nivolumab in the neoadjuvant setting. While the inclusion criteria allow for M1 disease, the presumed M1 site must be rendered "no evidence of disease" by metastasectomy, thermal ablation or stereotactic radiation within 12 weeks of the initial procedure. This study has completed recruitment with estimated study completion in late 2023 and will report event-free survival as a primary outcome, with overall survival, RFS, and incidence of toxicity as secondary outcomes.

Another treatment paradigm under active investigation in the neoadjuvant setting is that of combination VEGFi plus IO therapy agents. Recent pre-clinical research on intratumoral immune components after pretreatment of RCC suggest a potential synergism for TKI with anti-PD-1/L1 therapy (60–62), and the significant improvement in metastatic disease control demonstrated by trials of VEGFi/IO combination therapies (33, 34, 63–65), have in turn raised interest in neoadjuvant TKI/IO combination therapies. Six ongoing trials, NCT04118855 (53), NCT04995016 (52), NCT03680521 (46), NCT03341845 (49), NCT04393350 (50), and NCT05172440 (51) are currently investigating this strategy in the neoadjuvant setting. Several of the studies will include additional correlative studies to monitor the true effect on the tumor microenvironment and seek to define molecular biomarkers to associated with treatment response as secondary goals.

4 DISCUSSION

4.1 Current Evidence for NA-ST in RCC

In this chapter, we reviewed the current state of literature on NA-ST in RCC, focusing on published prospective trials of localized or locally advanced RCC, which we considered as "true" NA-ST, compared to presurgical systemic therapy for known metastatic or otherwise unresectable disease. Despite the theoretical benefits and advantages for NA-ST, we found the evidence for benefit of NA-ST in RCC to be quite limited, and not sufficient to support it as a treatment approach outside of a clinical trial.

The application of systemic therapies in the perioperative setting leverages the successful use of these agents in metastatic disease. Subsequently, trials investigating adjuvant VEGF inhibition in advanced localized disease have demonstrated mixed results especially in light of the significant side effects associated with its use. Pooled analyses in recent systematic reviews have demonstrated no significant improvement in disease-specific or overall survival (66, 67).

In the neoadjuvant setting, published studies on VEGFi TKIs have demonstrated modest responses. However, all 4 published prospective NA-ST in RCC trials were small scale pilot or phase II trials of VEGFi monotherapy for mostly clear cell carcinoma patients, with significant heterogeneity in the primary cohort and outcome of interest, therapeutic agent, and design. The primary outcome of interest for most (3/4) published trials was reduction of tumor volume and/or surgical complexity, which in turn was to allow for PN (2/4 trials) in patients at risk for significant decline in renal function with RN who were deemed to be difficult candidates for PN by the recruiting surgeon. The duration of NA-ST varied significantly, from only 4 weeks [sorafenib, Hatiboglu et al. (31)] to 6 months [pazopanib, Rini et al. (30)]. Similarly, the wait period between completion of systemic therapy and surgical intervention varied by study, from only 36 hours pre-operatively [axitinib, Karam et al. (29)], to ≥ 7 days pre-operatively [pazopanib, Rini et al. (30)], or was left to the discretion of the medical oncologist and surgeon [sorafenib, Hatibglou et al. (31); axitinib, Lebacle et al. (32)]. ORR was assessed in 3/4 of the published prospective trials, with a limited overall partial response rate (22-46%). Overall, it is difficult to generalize the results of these studies for clinical practice given the small study size, the use of different agents and regimens in each study with no control arm (except for one study), and the inherent selection bias in the 2 studies where patient enrollment was predicated on being deemed poor candidates for PN based on the recruiting surgeon's assessment. Of the 4 studies, only one study [Lebacle et al. (32)] attempted to evaluate oncologic outcomes by providing 2-year follow-up results, while the remaining studies focused on tumor response rates and feasibility of preforming PN following NA-ST.

Interestingly, despite being the only FDA-approved VEGFi TKI agent for high risk localized disease (68), neoadjuvant sunitinib was evaluated in only two clinical trials: a phase II, 20-patient trial by Hellenthal et al. (2010) (20) (excluded from our main analysis due to inclusion of M1 patients), and a single phase II trial (NCT00480935) which was terminated due to poor accrual (28). In the Hellenthal et al. series, the primary objective was assessing the safety of sunitinib (37.5 mg daily for 3 months) as NA-ST and of surgery following this NA-ST regimen. ORR was a secondary outcome for this study, with only one patient achieving formal partial response and the remainder deemed to have stable disease per RECIST criteria. However, 17/20 (85%) patients exhibited decrease in tumor size on two-month follow-up, with a median change in tumor diameter of -11.8% (range -27 to 11%).

In addition to the absence of strong evidence to support reliable oncologic benefits or improved survival outcomes in the discussed trials, further concerns with NA-ST include its potential effects on post-operative recovery and post-operative complications, and downstream effects of delay of surgery, particularly for non-responders to these agents. While post-operative complications were reported in 3/4 published trials, they were felt to be within expected complication rates by their respective authors and whether NA-ST had an effect on the incidence of these complications was difficult to discern due to the absence of a control arm. Finally, the relevance of these published studies to current and future management of RCC is significantly limited by their reliance on VEGFi monotherapy, while combination IO/TKI or IO/IO agents have become the new frontline therapy for advanced RCC.

Fortunately, ongoing and future trials of NA-ST in RCC address several of the above limitations, starting with the utilization of IO-based therapies, which have proven to be

more effective and, in some studies, less likely to result in cumulative and significant AEs compared to VEGFi agents. In addition to the change of utilized ST agents, these trials have notably shifted their focus from perioperative outcomes, such as facilitation of partial nephrectomy, towards improving oncologic outcomes (DFS, RFS, PFS, and in one study, OS), as well as more immediate outcomes, such as radiologic or pathologic response. Inclusion criteria for these studies generally require patients with higher risk for disease recurrence (≥ cT2) and, as most of the evidence for newer ST agents comes from trials in ccRCC patients, most trials require tumors to be biopsy-proven, predominantly clear cell RCC. Treatment regimens for these trials mirror those used in metastatic RCC, but with fewer cycles, and overall treatment periods of 4-12 weeks.

4.2 Future Directions

The management of advanced RCC has undergone many advancements in the past 2 decades, with the introduction of targeted therapy agents – VEGFi, mammalian target of rapamycin (mTOR), IO agents; and IO/IO or IO/TKI combination therapies. As with most treatments in cancer therapy, these agents were first investigated in treatment-refractory advanced RCC, then as first-line therapy for advanced RCC, followed by evaluation in the adjuvant and, finally, the neoadjuvant setting. This natural evolution of systemic therapies is reflected in the gradual progression of NA-ST in RCC from TKI monotherapies to IO monotherapies, and more recently, IO/TKI and IO/IO combination therapies.

In addition to IO/TKI and IO/IO combination therapies, recent studies have shown promise with targeting of hypoxia-inducible factor 2-α (HIF-2α), a transcription factor that is constitutively activated upon mutation of *VHL* gene, leading to induction of several oncogenic pathways involved in the pathogenesis of several benign and malignant neoplasms, including ccRCC (69), particularly in patients with von Hippel-Lindau disease (70, 71). In this regard, Belzutifan (MK-6482) is a potent small molecule inhibitor of HIF-2α that has shown impressive activity in neoplasms associated with VHL disease, with a recent phase 2 trial of this agent in patients with renal cell carcinoma associated with VHL disease, noting an ORR of 49% in patients with RCC kidney tumors (95% CI: 36-62) (72). As new agents like this are investigated in the advanced ccRCC (73, 74) space, their utility in the adjuvant and neoadjuvant setting may soon be explored.

As with ST in the metastatic setting, the potential benefits of NA-ST in RCC patients may be improved by the identification of candidates who are more likely to respond to NA-ST through biomarkers predictive of therapeutic response, thereby reducing concerns for unnecessary toxicity and delayed treatment in non-responders to NA-ST. While no such biomarkers have been investigated for NA-ST in RCC, genomic markers including mutational, transcriptomic, and epigenetic markers have been investigated in advanced RCC. Examples of such markers include expression of IO-targets (PD1, PDL1, CTLA-4), as well as composite gene expression signatures predictive of response to TKI monotherapy (75, 76) and IO-based therapies (75–78) in recent trials of IO-based agents in advanced RCC. However, none of the current markers for IO-based therapy and VEGFi-therapy have been externally validated or approved for clinical use for advanced RCC, and their applicability to predicting response to NA-ST in localized or locally-advanced RCC is unclear.

While radiation therapy has long been considered an ineffective modality to treat localized RCC due to the associated adverse effects of radiation on healthy tissue, as well as the documented radioresistance of RCC cells, newer radiation techniques have demonstrated the ability to overcome these limitations. New advances in radiotherapy recognized that while conventionally fractionated therapy (eg, 1.8 – 3.0 Gy) likely fails to generate the associated endothelial apoptotic response necessary for tumor death, high-dose, hypo-fractionated stereotactic ablative radiotherapy (SAbR) is a strategy that has demonstrated success in patients with extracranial metastases in several trials (79, 80).

Given this early success, Margulis et al. reported a single arm phase 1/2 prospective trial investigating the use of 40 Gy in 5 fractions to patients with RCC associated with IVC tumor thrombus. A total of 6 patients were included in the final analysis, with 3 patients who had M1 disease (81). These authors reported minimal treatment-associated adverse events and no intraoperative complications or technical difficulties (81). While the small number of this cohort limits conclusions in terms of oncologic outcomes, it highlights that Neo-SAbR is feasible and safe for evaluation in phase II setting which remains ongoing [NCT02473536 (82)].

Finally, multimodal neoadjuvant therapy approaches utilizing both systemic and radiation therapies are being investigated; NCT05024318 (24) will seek to assess the efficacy of stereotactic radiotherapy prior to nephrectomy in combination with neoadjuvant pembrolizumab versus SABR alone plus nephrectomy. The study plans to enroll 26 patients with locally advanced disease, but allows for low-volume metastatic disease in patients who are candidates for cytoreductive nephrectomy (24).

4.3 Summary

Currently, there is limited evidence for the use of NA-ST to improve oncologic outcomes in RCC, such as recurrence-free survival, metastasis-free survival, or cancer-specific survival, as well as perioperative outcomes – to facilitate surgery of potentially unresectable tumors, or cases where nephron sparing surgery is preferred. This is partly due to the heterogeneity within published studies in terms of patient selection criteria, differences in types and intensity of treatment regimens, and trial design endpoints. As the field looks forward to novel prospective neoadjuvant trials, it will be critical to incorporate both surgical outcomes, including pre-surgical complexity and morbidity along, with clinical outcomes like pathologic downstaging and RFS to ensure robust evaluation of the impact of NA-ST. Further, neoadjuvant studies offer the unique advantage of potentially pre- and post-treatment correlative tissue analyses, and distinctively present a window of opportunity to uncover novel biomarkers associated with the evolving effects of systemic therapy. With the rapidly changing landscape of IO and IO/VEGFi combinations in the adjuvant and metastatic setting, the neoadjuvant space is readily poised to integrate and build upon these efforts for future study.

AUTHOR CONTRIBUTIONS

SK and SJ have contributed equally to this work (manuscript writing, data collection, critical analysis) and share first authorship. AH and RK have contributed equally to this work and share last authorship (manuscript writing, critical analysis, and supervision of first authors). All authors contributed to the article and approved the submitted version.

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