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Review

Role of perioperative immunotherapy in localized renal cell carcinoma

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***Abstract*:** Immunotherapy has proven effective in metastatic renal cell carcinoma (RCC). The current standard of treatment in localized RCC is partial or complete nephrectomy. However, after surgery, there is a high recurrence rate and survival rates ranging from 53% to 85% depending on the stage of disease at presentation. Given clinical response to immunotherapies in metastatic RCC, these therapies are being tested as monotherapy and in combination with vascular endothelial growth factor receptor tyrosine kinase inhibitors in the (neo)adjuvant setting. Here we describe the current landscape of these treatments in localized RCC.

Keywords: adjuvant, immunotherapy, kidney cancer, neoadjuvant, renal cell carcinoma

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Background

Renal cell carcinoma (RCC) is among the 10 most common cancers in the United States. About 81,800 new cases will be diagnosed in 2023 and 14890 of patients are likely to die from it.[1] Approximately 70% of cases of kidney cancer are diagnosed at a localized or locally advanced stage, and nephrectomy or partial nephrectomy is the standard of care treatment for these patients with a goal of cure. However, of these, about 25–30% recur after nephrectomy, with 5-year overall survival (OS) rates of 81%, 74%, and 53% in patients with stage I, II, and III diseases, respectively.[2,3]

To reduce the risk of recurrence, six clinical trials using adjuvant vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin pathway (mTOR) inhibitors have been published – ASSURE (adjuvant sunitinib, sorafenib), S-TRAC (sunitinib), PROTECT (pazopanib), ATLAS (axitinib), SORCE (sorafenib), and EVEREST (everolimus).[4–8] With the exception of the S-TRAC trial, which met its primary end point of improved median disease-free survival (DFS), all other adjuvant trials using targeted therapy have been negative. Updated analysis of the S-TRAC trial, however, did not show OS benefit and due to high toxicity and treatment discontinuation rates, the use of adjuvant sunitinib has not entered clinical practice.[9]

Given the recent success of immune checkpoint inhibitors (ICIs) in metastatic RCC, these treatments are now being studied in the (neo)adjuvant setting for the treatment of localized RCC. The rationale to use neoadjuvant ICIs stems from the hypothesis that the intact renal primary could provide antigen source for an enduring cancer-specific immune response.[10] Here we discuss the potential role of ICI and highlight the current known data and future perspectives for neoadjuvant and adjuvant treatments in localized RCC.

Neoadjuvant trials using single-agent ICI in localized RCC

Nivolumab. *Nivolumab* is an IgG4 immunoglobulin that inhibits the programmed cell death-1 (PD-1) receptor.[11] Two small single-arm phase II trials assessed the safety and feasibility of neoadjuvant nivolumab in high-risk clear cell RCC (ccRCC).[12,13] The first study by Carlo *et al.* included 18 patients with high-risk ccRCC defined by a 12-year probability of metastasis ⩾20% based on a preoperative nomogram.[14] Patients received nivolumab every 2 weeks for four doses, with surgery 7–14 days after the last

dose. Although the study closed early due to slow accrual, 17/18 patients received at least three nivolumab doses and all patients completed surgery without delay, suggesting safety and feasibility of the treatment approach. Two patients discontinued nivolumab for immune-related adverse events (irAEs), and four had surgical complications as per the Clavien–Dindo classification. However, significant responses in the primary tumor were not seen, with the best response of stable disease in all patients; the median change in the largest diameter was +0.85% (–6.2% to +7.9%). The median 1-year recurrence-free survival was 82% (95% CI: 65–100%)[12] (Table 1).

In a second study by Gorin *et al.*,[17] high-risk RCC patients, defined as cT2a-T4 Nany M0 or TanyN1M0, received three doses of neoadjuvant nivolumab.[13] The study met its primary end point of safety and tolerability. All patients completed three doses of nivolumab without delay in surgery, and grade 3 toxicity was seen in one patient. The most common AEs were grade 1 fatigue, pruritis, and rash. Only two patients developed grade 3 AEs that include kidney infection and lymphopenia. None of the patient developed grade 4 or 5 AE.

Similar to Carlo *et al.*'s study above, stable disease was the best response with a change in the sum of the project of the two largest perpendicular diameters of –1.5% (–8.1% to +4.5%). Interestingly, in one patient, an immune-related pathologic response was seen in the nephrectomy specimen. This was characterized by a regression bed with histologic features of wound healing and immune infiltration with some remaining residual viable tumor, suggesting treatment response.[13]

Based on the results of these two neoadjuvant trials, one can conclude that most patients do not have significant radiographic tumor shrinkage with 3–4 cycles of neoadjuvant nivolumab, and this should not be utilized to facilitate a nephrectomy. However, some patients may have an immunogenic response that may protect against future recurrence, and this was in part attempted to be studied in PROSPER (below). This is unlike neoadjuvant VEGFR TKI trials such as that using neoadjuvant cabozantinib and neoadjuvant axitinib in which an overall response rate of 31.2% and 30% in the primary tumor was reported, respectively, and as such may help facilitate a nephrectomy but would unlikely protect against future recurrences.[15,16]

Perioperative nivolumab. The PROSPER trial was a randomized phase III trial comparing perioperative nivolumab with observation in RCC patients undergoing radical or partial nephrectomy.[17] In the investigational arm, one dose of nivolumab 480 mg was administered prior to surgery with nine adjuvant doses. The study included 819 high-risk patients defined as ⩾T2 or TanyN+ RCC of any histology planned for radical or partial nephrectomy. The majority of cases were cT2 (53%), followed by cT3-4 (47%), cN1 (17%), and cM1 (4%). Most patients had clear cell histology (78%), 8% patients had papillary, and 7% had chromophobe histologies. Select oligometastatic diseases were permitted if the patient was rendered no evidence of disease (NED) within 12 weeks of nephrectomy (⩽3 metastases; no brain, bone, or liver). The primary end point of the study was recurrence-free survival. Interim analysis for futility at a median follow-up of 16 months, unfortunately, showed that the addition of perioperative nivolumab did not improve recurrence-free survival (HR 0.97 [95% CI: 0.74–1.28], $p = 0.43$) compared to standard of care surgery. The trial was stopped early for inefficacy.[10] Grade 3–4 AEs were seen in 20% of patients in the nivolumab arm, while in the control arm, only 6% of AE were observed. Treatment-related grade 3–4 AEs were kidney injury (1% *versus* 2%), rash (2% *versus* 0%), and elevated lipase (4% *versus* 1%). In addition, there were 15 (4%) deaths from RCC in the nivolumab arm and 18 (4%) from RCC in the surgery-alone arm (Table 1).

The results of this trial need to be interpreted in light of several factors. First, the study included patients based on clinical and not pathologic staging, which very likely led to inclusion of lower stage patients. In addition, the study also included non-ccRCC patients. Also, some patients did not receive planned nephrectomy for unspecified reasons. Out of 404 patients allocated to the nivolumab arm, 359 received surgery and of 415 patients in the surgery arm, only 387 received nephrectomy. Based on this result, single-agent neoadjuvant immunotherapy has no role in ccRCC at this point.

Neoadjuvant trials using ICI combinations in localized RCC

Nivolumab/sitravatinib. Sitravatinib is an oral spectrum-selective TKI that targets the TAM (TYRO3/AXL/MERTK) and split (VEGFR2/KIT) family

Table 1. Clinical trials in perioperative RCC.

Identifier, year	Phase	Adjuvant/ neoadjuvant	*N*	Intervention arm	Control arm	Primary outcome	Efficacy/dose modifications	Treatment discontinuation rate
Neoadjuvant/adjuvant trials using single-agent ICI in RCC								
Gorin *et al.*[13] NCT02575222	I, Single arm	Neoadjuvant	17	Neoadjuvant nivolumab prior to nephrectomy	Single-arm study	Study met primary outcome of safety and tolerability	MFS: 85.1%; OS: 100% at 2 years	0%
Carlo *et al.*[12]	II, Single arm	Neoadjuvant	18	Neoadjuvant nivolumab prior to nephrectomy	Single-arm study	Met primary outcome of safety and feasibility	—	2 (11%)
Allaf *et al.*[10,17] NCT03055013, 2017	III, RCT	Neoadjuvant and adjuvant	766	Neoadjuvant and adjuvant nivolumab with nephrectomy	Surgery alone	Did not meet primary outcome of improvement in EFS	No dose modifications to date	48 (11%) patients in Nivo arm and 50 (12%) patients in surgery alone arm
Pal *et al.*[23] NCT03024996	III, RCT	Adjuvant	778	Adjuvant atezolizumab	Adjuvant placebo	Did not meet primary outcome of improvement in DFS	No improved clinical outcomes *versus* placebo	135(34%) patients in Atezo group and 109 (28%) patients in placebo group
Powels *et al.*[27] NCT03142334	III, RCT	Adjuvant	994	Adjuvant pembrolizumab	Adjuvant Placebo	Met primary end point of improvement in DFS	Disease recurrence significantly (32%) lower compared to placebo	190 (38%) patients in pembro group and 130 (26%) in placebo group
Neoadjuvant/adjuvant trials using ICI combinations in localized RCC								
Karam[18] NCT03680521	II, Single arm	Neoadjuvant	25	Neoadjuvant sitravatinib and nivolumab	Single-arm study	Met primary end point of point in time objective response	Dose decreased from 120 mg QD to 80 mg QD due to toxicities	6 (30%)
Bex *et al.*[19] NCT03341845	II, Single arm	Neoadjuvant	40	Neoadjuvant axitinib and avelumab	Single-arm study	Met primary outcome of in number of patients with partial remission	Median DFS and OS are not reached	0%
Ornstein *et al.*[33] NCT02762006	Ib, Single-arm study	Perioperative	29	Perioperative durvalumab + or – tremelimumab	Single-arm study	Met primary outcome of safety and feasibility	No dose modifications and it is a feasible combination	1 (17%) in cohort 1, 0% in cohort 2, 3 (38%) in cohort 2a, and 5 (56%) in cohort 3
Bex *et al.*[35] NCT03138512	III, RCT	Adjuvant	1641	Adjuvant nivolumab, plus ipilimumab	Nivolumab plus placebo	Did not meet primary end point of improvement in DFS	Disease-free survival was not met at 37 months of median follow-up	173 (43%) patients in IPI + Nivo group and 46 (11%) patients in Nivo + placebo group

DFS, disease-free survival; EFS, event-free survival; ICI, immune check point inhibitor; MFS, metastasis-free survival; *N*, number of patients; OS, overall survival; RCC, renal cell carcinoma; RCT, randomized control trial.

receptor tyrosine kinases, as well as MET. The combination of neoadjuvant sitravatinib and nivolumab was investigated in a phase II clinical trial in patients with high-risk RCC with clear cell histology defined as cT2-T3bN0M0 (NCT03680521).[18] The study included 20 patients who received single-agent sitravatinib daily for 2 weeks followed by nivolumab/sitravitinib combination for 4–6 weeks. The primary end point was objective response rate (ORR) per RECIST 1.1. At a median follow-up of 9.4 months after initiation of systemic therapy, in the 17 patients evaluable for efficacy, the ORR was 11.8% in the ITT population, although in a subset of patients who received a higher dose of sitravatinib, an ORR of 33% was reported. The safety profile of the combination was manageable, with hypertension being the most common grade 3 toxicity seen in six patients and grade 3 deep vein thrombosis and pulmonary embolism were observed in one additional patient.[18] There were no grade 4 or 5 treatment-related AEs (TRAEs). Dose-limiting toxicities led to a dose de-escalation of sitravatinib in 13 patients.

Avelumab/axitinib. Avelumab is an anti-PDL-1 inhibitor and axitinib is an inhibitor of VEGFR 1–3, c-KIT, and PDGFR. This trial was a phase II single-arm trial that investigated 12 weeks of neoadjuvant avelumab and axitinib in non-metastatic high-risk ccRCC (NCT03341845).[19] The study included 40 patients with high-risk non-metastatic ccRCC defined as cT1b-T2a grade 4,cT2b-T3a, grade 3–4, cT3b-T4, and N1. The study met its primary end point of partial tumor response seen in 30% of patients. This is consistent with a partial response of 34.5% seen in the primary kidney tumor in Javelin 101 study of avelumab/axitinib in metastatic ccRCC.[20] Median primary tumor downsizing was 20% (0–43.5%) and median post-treatment vital tumor presence was 50% (1–100%). At a median follow-up of 23.5 months, disease recurrence occurred in 13 (32.5%) patients. One patient had surgery at week 6 for suspected primary tumor progression (biopsy related hematoma), one patient developed liver metastases during neoadjuvant treatment, and one patient had a delay of surgery due to grade 2 hypothyroidism. There were 13 (32.5%) serious AEs of which four were related to surgical complications, one related to avelumab and the rest not related to study treatment[19] (Table 1).

Based on these data, it appears that neoadjuvant ICI/TKI combinations may allow at least some tumor shrinkage potentially making surgery feasible in high-risk patients with locally advanced disease and those with borderline kidney function trying to undergo a partial nephrectomy. One could therefore consider neoadjuvant IO/TKI in those with a functionally solitary kidney to allow for a partial nephrectomy, those with locally advanced (e.g. T4 disease) to facilitate resection, and those with N+ disease or those with an inferior vena cava (IVC) or higher tumor thrombus. The number of cycles of neoadjuvant therapy to administer and the need for adjuvant therapy remain to be answered. Additional larger trials with longer follow-up are needed to assess the safety and efficacy of neoadjuvant IO/TKI in localized RCC. Ongoing trials using various other neoadjuvant ICI/TKI combinations in localized kidney cancer are shown in Table 1.

Adjuvant trials using single-agent ICI in localized RCC

Atezolizumab. Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-1 ligand (PD-L1).[21] IMmotion010 was a randomized, double-blind phase III clinical trial that enrolled patients with RCC with a clear cell or sarcomatoid component and who had a high risk of metastasis after nephrectomy. Patients with intermediate- to high-risk RCC were randomized to receive adjuvant atezolizumab or placebo for 1 year. The study included patients with high risk of recurrence (T2 grade 4, T3a grade 3–4, T3b/c any grade, T4 any grade, or TxN+ any grade) or have had complete resection of synchronous/metachronous metastasis (importantly, the latter group only included patients who had metastases *more* than 12 months post-nephrectomy, a group of patients with generally more indolent biology). The primary end point of study was DFS.[22]

In the atezolizumab group, 255 (65%) of the patients completed the full 16 cycles or 1 year of trial treatment; 135 (35%) patients discontinued treatment due to disease relapse (13%), AE (12%), withdrawal by patient (5%), other reasons (4%), physician decision (1%), or death (<1%). In the placebo group, 274 (72%) of the patients completed the full 16 cycles or 1 year of trial treatment; 109 (29%) patients discontinued treatment, due to disease relapse (16%), other reasons (7%), withdrawal by patient (3%), AE (3%), physician decision (<1%), or death (<1%). Grade 3–4 AEs occurred in 27% of patients in the atezolizumab group and 21% in the placebo group. The grade 5 AE occurred in < 1% in both groups, unrelated to

the treatment. The most common grade 3–4 AEs were hypertension observed in 2% *versus* 15% of patients, hyperglycemia (3% *versus* 2%), and diarrhea (1% *versus* 2%) in the atezolizumb group *versus* placebo, respectively.[23] In addition, 18% of patients who received atezolizumab and 12% who received a placebo had a severe AE. There were no treatment-related deaths.

Unfortunately, the study did not meet its primary end point of investigator-assessed DFS in the intention-to-treat population with a median DFS of 57.2 months in the atezolizumab arm *versus* 49.5 months in the placebo arm [HR 0.93 (0.75, 1.15); $p = 0.495$].[24] OS analysis is not mature.

Pembrolizumab. Pembrolizumab is a humanized monoclonal IgG4 antibody, and like nivolumab, it is also a PD-1 inhibitor[25] Unlike nivolumab and atezolizumab, adjuvant pembrolizumab has shown a DFS benefit based on KEYNOTE-564. This was a randomized phase III double-blind clinical trial in which 994 post-nephrectomy patients with clear cell or sarcomatoid differentiation RCC histology were randomized to adjuvant pembrolizumab *versus* placebo for 1 year.[26] These patients had intermediate to high (pT2 grade 4 or pT3 any grade), high-risk (pT4 or N+), and metastatic NED disease.

The most common grade 3 AEs in pembrolizumab group were fatigue (1%), diarrhea (1.6%), and skin rash (0.8%), and no grade 4 or 5 AE was observed in both placebo and pembrolizumab group. The median number of cycles received in both groups was 17. In the pembrolizumab group, 61.1% of the patients completed the full 17 cycles of trial treatment and in the placebo group, 73.6% of the patients completed the full 17 cycles.

At a median follow-up of 24 months, the DFS was 77.1% *versus* 68.1% (HR = 0.68, 95% CI: 0.53–0.87; $p = 0.0010$) which was maintained at 30-month follow-up as well (HR 0.63, 95% CI: 0.50–0.80; $p < 0.0001$).[26] Secondary end points such as distant metastasis-free survival, time to first subsequent anticancer therapy, and time of second progression were also improved in the pembrolizumab arm in a recent update.[27] Based on these data, on 17 November 2021, the Food and Drug Administration approved adjuvant pembrolizumab for patients with high-risk RCC.

The discrepancy in clinical benefit with adjuvant pembrolizumab *versus* other agents may be related to differences in recruited patients in each study. For example, there were non-clear RCC patients in IMmotion010 (7%) and PROSPER (22%) but none in KN-564. Patients with non-ccRCC, in general, have a poorer prognosis than ccRCC patients. In addition, 14% of patients in IMmotion010 were M1 NED *versus* 6% in KN-564 and 3% in PROSPER. M1 NED patients clearly have a less favorable prognosis than M0 patients. The definition of M1 NED was different between KN-564 and IMmotion010. In KN-564, M1 NED was defined as complete resection of oligometastases synchronous or *within 1 year* of nephrectomy. In IMmotion010, M1 NED was defined as NED with synchronous disease or metachronous metastatic disease with recurrence occurring *more than* 12 months after initial nephrectomy. This could indicate that the M1 NED patients in IMmotion010 may have more indolent disease compared to KN-564.

Another possible factor could be that in the control group of KN-564, only 59 (36%) of 166 patients received immunotherapy at the time of recurrence. However, this was also seen in IMmotion010 in which only about 12% patients in the placebo arm received subsequent immunotherapy. Another possible factor is censoring imbalance.[28] In KN-564, a higher rate of patients in the pembrolizumab arm were censored compared to the placebo group. Such imbalances were not found in IMmotion010 and CheckMate-914. Upon performing a modified time-to-treatment failure sensitivity analysis in KN-564, in which individuals censored in excess were modeled as events, the DFS between the two arms lost statistical significance.[28] Pembrolizumab may also be a superior PD-1/PD-L1 axis agent compared to atezolizumab or nivolumab.

In addition, the toxicity of pembrolizumab in KN-564 should also be considered. Immune-mediated AE occurred in 174 (36%) of patients in the pembrolizumab arm in KN-564 and grade 3+ immune-mediated AE occurred in 8.6% of the patients who received pembrolizumab and in 0.6% of those who received placebo. A total of 37 (8%) patients in the pembrolizumab arm experienced irAEs compared to three (1%) patients in the placebo arm. About 21% patients discontinued treatment due to toxicity.[27]

Recently, a meta-analysis of the randomized phase III trials of perioperative treatment with anti-PD-1/PD-L1 agents or anti-PD-1/anti-CTL4 in

combination was conducted. High-grade AEs were 2.6 times more frequent in the immunotherapy arm (OR: 2.64, 95% CI: 1.54–4.68; $p=0.001$) while high-grade TRAEs were eight times more frequent in the experimental arm (OR: 8.60, 95% CI: 3.23–22.91; $p=0.001$).[29] Similarly, in a living network meta-analysis which included 8480 patients from eight randomized clinical trials, pembrolizumab (pembro; rank 1) was associated with improved DFS when compared to atezolizumab (atezo; rank 6; hazard ratio: 0.68; 0.49–0.93), and nivolumab–ipilimumab (nivo/ipi; rank 5; 0.68; 0.48–0.97). However, no statistically significant difference was observed between pembrolizumab and atezolizumab for OS (0.53; 0.28–1.01).[30] These meta-analyses are based on published abstracts, and peer-reviewed publications are pending. Given the conflicting data supporting the use of adjuvant immunotherapy, clinicians eagerly await the OS data of KN-564 before fully adopting adjuvant pembrolizumab in clinical practice.

Adjuvant trials using ICI combinations in localized RCC

Durvalumab/tremelimumab. Durvalumab is a monoclonal antibody that inhibits PD-L1, whereas tremelimumab is a cytotoxic T-lymphocyte antigen 4 blocker that results in immune activation.[31,32] Durvalumab, in combination with tremelimumab, is being studied in the perioperative setting in RCC to evaluate the clinical benefit.

In a phase Ib trial, patients with radiographic evidence of high-risk localized RCC (clinical stage T2b-4 and/or N1, M0 disease) received perioperative durvalumab or durvalumab + tremelimumab administered at various schedules (NCT02762006).[33] At interim analysis with 29 enrolled patients, there were no treatment-related delays or surgical complications. However, there was a >40% discontinuation rate and given higher than expected irAEs, the study was suspended.

Durvalumab/tremelimumab is also being studied in an ongoing multi-arm multistage platform trial (RAMPART), in which high-risk RCC patients were randomized to observation *versus* durvalumab for 1 year or durvalumab + tremelimumab for two doses followed by durvalumab therapy for a total of 1-year therapy. The co-primary outcomes are DFS and OS[34] (Table 2).

Ipilimumab/nivolumab. CheckMate 914 was a phase III randomized placebo-controlled trial studying the role of adjuvant nivolumab and nivolumab + ipilimumab in patients with localized RCC with predominant clear cell histology at high risk of relapse after nephrectomy.[35] Patients with predominantly clear cell histology, pT2a (grade 3 or 4), any grade T2b-T4N0M0, or N1 disease were eligible. In part A of the study, 816 patients were randomized 1:1 to 6 months of adjuvant nivolumab + ipilimumab *versus* placebo. Nivolumab 240 mg was administered every 2 weeks for 12 doses with ipilimumab 1 mg/kg every 6 weeks for 4 doses. In part B, patients were randomized 1:1:2 to receive nivolumab + ipilimumab, placebo, or nivolumab + placebo.

Results of part A were recently reported.[36] At a median follow-up of 37 months, unfortunately, the primary end point of DFS was not met with HR 0.92 (95% CI: 0.71–1.91; $p=0.53$).[37] Median DFS was not reached with the combination and 50.7 months with placebo. Due to a hierarchical study design, no OS analysis will be conducted.

Of note, the treatment was associated with significant toxicity with 43% patients not completing the combination treatment and 33% discontinuing it due to toxicity.[37] In the nivolumab plus ipilimumab group, 230 (57%) of 404 patients completed all cycles of nivolumab and 266 (66%) of 403 patients completed all cycles of ipilimumab. Grade 3 or 4 toxicity occurred in 115 (28%) patients treated with nivolumab plus ipilimumab and 8 (2%) patients treated with placebo. Four deaths (1% of treated patients in the nivolumab plus ipilimumab group) were attributed to treatment with nivolumab plus ipilimumab and were due to cardiac arrest, immunotherapy-induced diarrhea or colitis, aortic dissection, ischemic cerebral infarction, or pulmonary embolism, and drug-induced myocarditis (in one patient each). There were no deaths attributed to treatment with placebo.

Based on the above data, it appears that the risk–benefit ratio of ICI/ICI combination therapy seems to favor the former and it is unlikely to enter clinical practice.

Discussion

VEGFR TKIs and ICI form the cornerstones of treatment in patient with metastatic RCC. These agents have now been tested in the (neo)adjuvant

Table 2. Ongoing clinical trials in ccRCC with perioperative immunotherapy.

Identifier, year	Adjuvant/ neoadjuvant	Phase	*N*	Intervention	Primary outcome	Recruitment status
Trials with ICI/TKI combinations						
NCT05319015, 2022	Neoadjuvant	II	30	Pembrolizumab + lenvatinib	Disease control rate	Not yet recruiting
NCT05485896, 2022	Neoadjuvant	II	20	Pembrolizumab + lenvatinib	Overall response rate	Recruiting
NCT04393350, 2020	Neoadjuvant	II	17	Pembrolizumab + lenvatinib	Overall response rate	Recruiting
NCT04995016, 2021 (PANDORA)	Neoadjuvant	II	18	Pembrolizumab + axitinib	Major Pathologic Response	Not yet recruiting
NCT05148546, 2021 (NESCIO)	Neoadjuvant	II	69	Nivolumab *versus* nivolumab + ipilimumab *versus* nivolumab + relatlimab	Pathological response rate	Recruiting
NCT04385654, 2020	Neoadjuvant	II	30	Toripalimab + axitinib	Major Pathologic Response	Unknown
NCT03341845, 2017	Neoadjuvant	II	40	Avelumab + axitinib	Rate of partial remission	Recruiting
NCT05172440, 2021	Neoadjuvant	II	20	Tislelizumab + axitinib	Overall response rate	Not recruiting
Trials with ICI/ICI combinations						
NCT03288532, 2020 (RAMPART)	Adjuvant	III	1750	Durvalumab ± tremelimumab	DFS and OS	Recruiting
NCT04028245, 2019 (SPARC-1)	Neoadjuvant	I	14	Spartalizumab + canakinumab	Feasibility	Recruiting
Trials with other ICI combinations						
NCT05239728, 2022 (LITESPARK-022)	Adjuvant	III	1600	Pembrolizumab + belzutifan/ placebo	DFS	Recruiting
NCT05024318, 2021 (NAPSTER)	Neoadjuvant	I	26	SABR ± pembrolizumab	Major pathologic response	Recruiting

ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; ICI, immune checkpoint inhibitors; OS, overall survival; TKI, tyrosine kinase inhibitor.

setting for high-risk localized RCC with the goal of attaining primary tumor response, reducing recurrence, and improving long-term oncologic outcomes. In addition to shrinking the primary tumor and enabling nephron-sparing surgeries, administering neoadjuvant ICIs may also theoretically offer an enduring immune response given the presence of antigens from the intact primary.

The results of the single-agent CPI studies discussed above suggest that while single-agent anti-PD-1 therapy is safe and feasible to administer in the neoadjuvant setting, it is not associated with significant tumor shrinkage, limiting its use in patients with bulky disease and borderline kidney function where the goal is to reduce the tumor size. In this setting, the use of neoadjuvant ICI/TKI combinations attains this goal more often, based on a primary tumor response rate of about 30–35%, similar to the metastatic setting. Whether the use of neoadjuvant ICI/TKI correlates with long-term DFS or OS benefit is not yet known.

In the adjuvant setting, while DFS is a meaningful end point supported by the Federal Drug Administration and European Medical Association, the treatment and associated toxicities are more acceptable to patients and physicians if associated with an OS benefit and are consistent between similar agents. This was evident in the S-TRAC trial using adjuvant sunitinib

which showed a DFS but no OS benefit, and although FDA approved for adjuvant use, is rarely utilized. Trials using adjuvant nivolumab and atezolizumab have not shown a DFS benefit, similar to ICI/ICI combinations used in the perioperative setting which have also been associated with significant toxicities and treatment discontinuation. While the DFS benefit of pembrolizumab was maintained at longer follow-up, in the background of several other negative adjuvant clinical trials, clinicians await OS data to enthusiastically recommend adjuvant pembrolizumab to patients. In addition, results of part B of the CM-914 trial comparing adjuvant nivolumab to placebo are also awaited. In the meantime, adjuvant pembrolizumab is a reasonable option for patients with high-risk RCC, after a shared decision-making discussion.

Several questions remain to be answered in this field. Do patients responding to neoadjuvant ICI/TKI therapy need additional treatment after surgery? What is the recommended duration of adjuvant therapy assessing the outcomes of patients who discontinued pembrolizumab early due to toxicity in the KEYNOTE-564 study would be informative? Do patients respond to these therapies when rechallenged the metastatic setting? What is the role of newer therapies such as HIF-2 alpha-based therapies in the adjuvant setting? Few patients with non-ccRCC were included in these perioperative clinical trials and further work is needed for these patients. In addition, there is a need to develop biomarkers to predict the need for adjuvant therapies.

When discussing adjuvant treatment options with a patient with high-risk RCC, clinicians should discuss the available data that support the use of adjuvant ICI as well as outline the unanswered questions which will be answered over time. Until we have answers to these important questions, the decision to administer adjuvant immunotherapy may be an individualized decision.

Conclusion

In conclusion, the use of neoadjuvant and adjuvant therapy in high-risk localized RCC is being actively investigated, with the aim of achieving a primary tumor response, reducing recurrence, and improving long-term oncologic outcomes. Neoadjuvant ICIs may offer an enduring immune response and enable nephron-sparing surgeries, but single-agent anti-PD-1 therapy is not associated with significant tumor shrinkage, limiting its use in patients with bulky disease and borderline kidney function. Neoadjuvant ICI/TKI combinations may be a more effective option in this setting, but their impact on long-term DFS and OS is yet to be determined. In the adjuvant setting, while DFS is a meaningful end point, clinicians await OS data to enthusiastically recommend adjuvant pembrolizumab to patients. Clinicians should discuss the available data with patients and outline the unanswered questions to make an informed decision on the individualized use of adjuvant immunotherapy. Further research and the development of biomarkers are needed to address these questions and improve outcomes for patients with RCC.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

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Author contribution(s)

Jasmeet Kaur: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

Goutham Patil: Data curation; Writing – review & editing.

Daniel M. Geynisman: Conceptualization; Writing – review & editing.

Pooja Ghatalia: Conceptualization; Data curation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

This is review article that involves the discussion of already published data.

ORCID iD

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