2022 WUOF/SIU International Consultation on Urological Diseases: Neoadjuvant and Adjuvant Therapy for Renal Cell Carcinoma

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Abstract

Patients undergoing definitive surgery or ablative techniques for nonmetastatic kidney cancer have varying degrees of risk of recurrent disease post procedure. The ultimate goal of "adjuvant therapy" is to reduce the incidence of recurrent disease, and to cure more patients. We summarize the current state of perioperative therapy for kidney cancer and explore future directions to develop optimal adjuvant strategies. We define risk and risk of recurrence post-definitive therapy, describe the controversies surrounding the trial landscape of adjuvant vascular endothelial growth factor receptor tyrosine kinase inhibitors and immune checkpoint inhibitors. We review data on neoadjuvant therapy before advanced kidney cancer resection. Radiologic, ethnic, economic, and geographic considerations with respect to adjuvant therapy are highlighted, as well as adjuvant therapy issues especially pertinent to patients, future directions in adjuvant trial design specifically targeted to biomarkers and patient selection, and sequencing of treatment after adjuvant therapy in those patients with recurrence.

Introduction

Patients undergoing definitive surgery or ablative techniques for nonmetastatic kidney cancer have varying degrees of risk for recurrent disease post-procedure. The ultimate goal of "adjuvant therapy" is to reduce the incidence of recurrent disease, and to cure more patients.

This review summarizes the current state of perioperative therapy for kidney cancer and explores future directions to develop optimal adjuvant strategies. We define risk and risk for recurrence post-definitive therapy and describe the adjuvant trials landscape of adjuvant vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) trials and immune checkpoint inhibitor (IO) trials. We review data on neoadjuvant therapy before advanced kidney cancer resection. Radiologic, ethnic, economic, and geographic considerations with regard to adjuvant therapy are highlighted. Also covered are adjuvant therapy issues especially pertinent to patients, future directions in adjuvant trial design specifically targeted to biomarkers and patient selection, and sequencing of treatment after adjuvant therapy in those patients with recurrence.

Key Words

Adjuvant therapy, neoadjuvant therapy, vascular endothelial growth factor receptor tyrosine kinase inhibitor, immune checkpoint inhibitor, renal cell carcinoma

Competing Interests

See "Acknowledgments" for details.

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Abbreviations

DFS disease-free survival
FDA United States Food and Drug Administration
GRANT Grade, Age, Node, and Tumor
IO immune checkpoint inhibitor
irAEs immune-related adverse events
OS overall survival
RCC renal cell carcinoma
RFS recurrence-free survival
SSIGN Stage, Size, Grade, Necrosis
UISS University of California LA Integrated Staging System
VEGF vascular endothelial growth factor
VEGFR-TKI vascular endothelial growth factor receptor tyrosine kinase inhibitor

Defining Risk

Risk for disease recurrence post-nephrectomy for renal cell cancer depends largely on the characteristics of the primary tumor. This risk can mainly be stratified based on stage and grade of the cancer. Patients with larger tumors and higher grade are at increased risk for recurrence after nephrectomy. Risk for recurrence for high-risk patients is greatest early (0–3 years) post-nephrectomy and plateaus after 4 to 5 years[1].

Some predictive models that have been used for survival outcomes post-nephrectomy for renal cell carcinoma (RCC) including the UISS (University of California LA Integrated Staging System)[2], SSIGN (Stage, Size, Grade, Necrosis)[3], Karakiewicz nomogram[4], GRANT (Grade, Age, Node, and Tumor)[5,6], and Leibovich[7,8]. The criteria used to determine risk in these staging systems can be found in **Table 1**.

Based on these predictive models, in general, patients with resected stage T3 or higher, and high-grade tumors, are at the highest risk for recurrent disease, and are most likely to benefit from an adjuvant agent that would decrease their risk for recurrence and improve overall survival (OS). Patients at lower risk (T1 and T2A disease) receiving adjuvant therapy for the most part may be overtreated, as the risk for recurrence is less than 20%. The patient population that would likely benefit the most from adjuvant therapy are those with resected metastases, as demonstrated in KEYNOTE-564[9].

Unanswered questions in adjuvant therapy include its role in non-clear cell histology. Non-clear cell histologies can have higher risk for recurrence, but are often excluded in adjuvant trials, including the recent landmark KEYNOTE-564 adjuvant pembrolizumab trial, which required a clear cell component[9].

TABLE 1.
Predictive models for renal cell carcinoma recurrence and survival

Risk stratification	Criteria used	5-year cancer-specific survival					
		Low risk		Intermediate risk	High risk		
UISS[2]	T-stage, Fuhrman grade, ECOG	91.1%		80.4%	54.7%		
SSIGN[3]	TNM stage, tumor size, Fuhrman grade, tumor necrosis	0–2 points 97.1%	3–4 points 89.8%	5–6 points 74.1%	7–9 points 38.6%	10+ points 19.2%	
GRANT[a][5,6]	Age, pT-stage, pN-stage, Fuhrman grade	0 or 1 risk factors		2 risk factors	3 or 4 risk factors		
		86%–94%		76%	16%–46%		
Karakiewicz[4]	TNM stage, Fuhrman grade, tumor size	N/A					
Leibovich[7,8]	T-stage, N-stage, tumor size, Fuhrman grade, tumor necrosis	N/A					

[a] 5-year survival outcome for GRANT score is overall survival.
ECOG: Eastern Cooperative Oncology Group; GRANT: Grade, Age, Node, and Tumor; SSIGN: Stage, Size, Grade, Necrosis; M: metastatic stage; N: node; T: tumor; UISS: UCLA integrated staging system.

Adjuvant Therapy Trials in Renal Cell Carcinoma

Cytokine Era: Several adjuvant trials with cytokines or other biologics have been previously completed, and summarized elsewhere, and are outside the scope of this review[10].

Adjuvant Trials with Targeted Agents

The rationale for testing agents targeting the angiogenic pathway in the adjuvant setting is based on multiple observations showing that vascular endothelial growth factor (VEGF) is involved in the pathogenesis of metastasis[11]. Five placebo-controlled, adjuvant, phase 3 studies investigated the benefit of targeted therapy with VEGFR-TKIs versus placebo (**Table 2**)[12–16]. The primary endpoint in all trials was disease-free survival (DFS); however, patient populations and study designs varied between the trials, with differing agents and duration of therapy.

Of these, only S-TRAC[14], which enrolled the highest risk group (pT3 and higher) demonstrated an improvement in DFS with sunitinib compared with placebo. Patients assigned to sunitinib had a significantly improved DFS (6.8 years; 95% CI, 5.8–not reached) when compared to patients in the placebo arm (5.6 years; 95% CI, 3.8–6.6), though in an updated analysis, there was no difference in OS[17]. Notably, the ASSURE[13] trial did not identify a significant difference between adjuvant sunitinib versus placebo with respect to DFS. The differences in patient population may have accounted for the differences in results between S-TRAC and ASSURE. Only patients with clear cell histology were eligible for

TABLE 2.
Adjuvant trials with targeted agents in RCC

Trial	N	Histology	Patient characteristics	Treatment arms (vs. placebo)	Duration	Endpoint	Results
S-TRAC[14]	615	Clear cell	High-risk RCC patients according to UISS	Sunitinib	1 year	DFS	HR, 0.76 95% CI, 0.59–0.98 (*P* = 0.03)
ASSURE[13]	1943	Clear cell Non-clear cell	Nonmetastatic RCC; disease stage II–IV selected by UISS	Sunitinib/ Sorafenib	1 year	DFS	HR, 1.02 (sunitinib) 97.5% CI, 0.85–1.23 (*P*=0.80) HR, 0.97 (sorafenib) 97.5% CI, 0.80–1.17 (*P* = 0.72)
SORCE[12]	1656	Clear cell Non-clear cell	Patients with Leibovich high- and intermediate-risk resected RCC	Sorafenib Sorafenib	1 year 3 years	DFS	HR, 0.94 (1 year sorafenib) 95% CI, 0.77–1.14 (*P* = 0.51) HR, 1.01 (3 years sorafenib) 95% CI, 0.83–1.23 (*P* = 0.95)
EVEREST[20]	1537	Clear cell Non-clear cell	Pathological stage intermediate or very high-risk RCC patients with full or partial nephrectomy	Everolimus	9 cycles	RFS	HR, 0.85 95% CI, 0.72–1.00 (*P* = 0.0246)a
PROTECT[16]	1540	Clear cell	Patients with moderately high or high risk after nephrectomy of localized or locally advanced RCC by AJCC TNM v.2010	Pazopanib	1 year	DFS	HR, 0.86 95% CI, 0.70–1.06 (*P* = 0.17)
ATLAS[15]	700	Clear cell	High-risk, nonmetastatic RCC with nephrectomy by AJCC TNM v.2010	Axitinib	3 years	DFS	HR, 0.87 95% CI, 0.66–1.15 (*P* = 0.32)

aOne-sided P value, not statistically significant (threshold for significance set at 0.022).
AJCC TNM: American Joint Commission on Cancer Tumor, Node, Metastasis staging system; CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; RCC: renal cell carcinoma; RFS: recurrence-free survival; UISS: UCLA integrated staging system.

TABLE 3.

Ongoing or completed adjuvant trials with immune checkpoint inhibitors in RCC

Trial	N	Histology	Patient characteristics	Treatment arms	Duration (months)	Endpoint	Result
KEYNOTE-546 NCT03142334[9,58]	994	Clear cell	pT2, G4/sarcomatoid, N0 or pT3, G3-4, N0 or pT4, any G, N0 or pTany, any G, N1 or M1 resected	Pembrolizumab	12	DFS	HR, 0.63 95% CI, 0.50–0.80
RAMPART NCT03288532[59]	1750	Clear cell Non-clear cell	Leibovich 3–11	Durvalumab + Tremelimumab	12	DFS OS	Pending
CheckMate-914 NCT03138512[24]	1628	Clear cell +/- sarcomatoid differentiation	pT2a,G3/4, N0 or pT2b, any G, N0 or pT3, any G, N0 or pT4, any G, N0 or pTany, any G, N1	Nivolumab + Ipilimumab	24	DFS	Pending[a]
IMmotion010[23]	778	Clear cell Non-clear cell with sarcomatoid differentiation	pT2, G4, or pT3a, G3-4 or pT3b, any G or pTany, any G, N1 or M1 resected	Atezolizumab	12	DFS	Pending[a]
PROSPER[37] adjuvant/ neoadjuvant	804	Clear cell Non-clear cell	>cT2aN0M0 or cTanyN1M0	Nivolumab	1 neoadjuvant 9 adjuvant	RFS	Pending
LITESPARK-022	1600	Clear cell	pT2, G4/sarcomatoid, N0 or pT3, any G, N0 or pT4, any G, N0 or pTany, any G, N1 or M1 resected	Pembrolizumab ± belzutifan	12	DFS	Pending

[a]*Presentations of CheckMate-914 (Arm A), IMmotion-010, and PROSPER (EA8143) at European Society of Medical Oncology meeting 2022 reported negative results.*
CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; G: tumor grade; N: nodal stage; M: metastatic stage; OS: overall survival; pT: pathologic T-stage; RFS: recurrence-free survival.

S-TRAC, while clear cell histology accounted for only 80% of patients in ASSURE. Additionally, the higher risk (tumor stage 3 or higher) of patients in S-TRAC may have also led to differences in study outcomes. It should be noted, however, that in a post-hoc analysis of a subpopulation subject to the S-TRAC inclusion criteria, DFS was similar between all 3 arms[18]. While this analysis was underpowered to statistically detect a difference between sunitinib and placebo, there was no obvious trend in favor of active treatment. It is also possible that differences in trial conduct between S-TRAC and ASSURE, such as disease imaging intervals (earlier and more frequent in S-TRAC), may have contributed to the observed differences in DFS, but they would not have impact on OS.

While there were differences in outcome of the individual VEGFR-TKI studies, a meta-analysis of adjuvant VEGFR-TKI trials for patients with RCC did identify a DFS benefit (HR, 0.84; 95% CI, 0.76–0.93)[19]. However,

the meta-analysis did not identify an OS benefit (nor have any of the individual trials), and due to the lack of a proven OS benefit, coupled with the high rates of unacceptable toxicity and dropout from the treatment arms of the VEGFR-TKI trials, adjuvant therapy with sunitinib has not achieved widespread adoption, even in countries where sunitinib is approved for adjuvant therapy in RCC.

EVEREST is a randomized, placebo-controlled, phase 3 trial of everolimus versus placebo for 54 weeks in patients with clear and non-clear cell RCC after nephrectomy or partial nephrectomy[20]. A total of 1545 patients with pathological stage intermediate- or high-risk status were enrolled. The primary endpoint of the trial was recurrence-free survival (RFS), and with median follow-up of 76 months, there was improvement in the everolimus arm that did not reach statistical significance (HR, 0.85; 95% CI, 0.72–1.00).

Adjuvant Trials with Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (IOs) targeting the programmed cell death protein 1 (PD-1) pathway, or the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) pathway have revolutionized the treatment of metastatic RCC. Their role in the adjuvant setting is currently under investigation in multiple clinical trials (**Table 3**), with one phase 3 trial—KEYNOTE-564—having published results so far.

KEYNOTE-564[9] is a randomized, double-blind, placebo-controlled, phase 3 trial testing the role of the PD-1 inhibitor pembrolizumab in patients with intermediate-high-risk, high-risk, or M1–no evidence of disease (NED) status including intermediate-risk (pT2, grade 4, N0M0 or pT3, any grade, N0, M0), high-risk (pT4, any grade, any N, M0 or any pT, any grade, N+, M0), and also patients who had undergone complete resection of metastasis (M1), within a year of primary surgery. Patients (n=994) were randomized to receive either pembrolizumab or placebo every 3 weeks for 1 year. The primary endpoint was investigator-assessed DFS, with OS as a secondary endpoint. After a median follow-up of 30.1 months, the DFS rate at 30 months was 75.2% and 65.5% for pembrolizumab and placebo, respectively (HR, 0.63; 95% CI, 0.50–0.80)[21]. OS data is not mature. The authors reported grades 3+4 treatment-related adverse events (AEs) for pembrolizumab and placebo in 18.9% and 1.2%, respectively, with no treatment-related deaths. In the pembrolizumab group, 22% of patients discontinued treatment due to AEs. Based on these findings, pembrolizumab has received United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval as an adjuvant treatment in patients with RCC and high risk for relapse.

While data has not yet been presented, recent press releases indicate that adjuvant atezolizumab (IMmotion010) and ipilimumab and nivolumab combination therapy (CheckMate-914) have not demonstrated benefit in the adjuvant setting[22–25]. Once full results are published, comparisons in trial design and patient selection will need to be carefully examined to determine why the results are inconsistent with KEYNOTE-564. Additional trials evaluating the utility of adjuvant IOs are ongoing (**Table 3**).

Neoadjuvant Therapy in RCC

The standard-of-care management of nonmetastatic disease remains surgical resection. Just as combination TKI and immunotherapy combinations have come to dominate the frontline metastatic space, so too are investigators attempting to capitalize on the synergy of these agents in the neoadjuvant setting[26–33]. A summary of ongoing trials investigating immunotherapy in the preoperative setting is found in **Table 4**.

Neoadjuvant therapy may have several potential advantages over adjuvant therapy: First, it may decrease tumor burden and improve surgical outcomes, allowing for nephron-sparing surgery in select cases, converting unresectable tumors to resectable, and decreasing venous involvement, thereby facilitating ease of surgery. Second, response of the primary tumor to therapy can predict long-term outcomes to a particular therapy, potentially allowing for adaptive adjuvant therapy trials. Also, neoadjuvant studies allow for collection of molecular correlative data from peripheral blood as well as paired biopsy and resection specimens to aid in response evaluation. Lastly, the in situ tumor may provide increased priming of the immune system compared with micrometastatic disease, leading to a more robust immune response[34,35].

The application of immunotherapy in the neoadjuvant setting is early. Two small phase 2 studies have demonstrated that neoadjuvant nivolumab prior to nephrectomy was safe and feasible, without delay to nephrectomy after receiving at least one dose of nivolumab[36,37]. The phase 3 study of neoadjuvant nivolumab, PROSPER RCC (NCT03055013), is the only phase 3 trial investigating preoperative immunotherapy versus observation, with results pending at the European Society Medical Oncology (ESMO)[38]. Perioperative durvalumab (anti–PD-L1) with or without tremelimumab (anti–CTLA-4) was investigated in a multicohort phase 1b trial evaluating combined IO[39]. There were no treatment-related delays or complications of surgery although the addition of tremelimumab was associated with excess immune-related AEs (irAEs) and the study was suspended.

TABLE 4.

Ongoing clinical trials investigating neoadjuvant therapy (± adjuvant component) in locally advanced or metastatic (with planned cytoreductive nephrectomy) RCC

Immunotherapy or immunotherapy combinations					
NCT Trial #	**Phase**	**Arm**	**Drug**	**Dose**	
NCT04393350	2	Single	Lenvatinib and pembrolizumab	Len:18 mg daily Pembro: 200 mg q3w	
NCT03680521	2	Single	Sitravatinib and nivolumab	Sitravatinib: oral capsule daily Nivolumab: 24 mg IV q2w	
NCT04385654	2	Single	Toripalimab and axitinib	Toripalimab: 240 mg IV q3w Axitinib: 5 mg PO BID	
NCT04118855	2	Single	Toripalimab and axitinib	Toripalimab: 240 mg IV q3w Axitinib: 5 mg PO BID	
NCT04995016 PANDORA	2	Single	Pembrolizumab and axitinib	Pembrolizumab: 200 mg q3w Axitinib: 5 mg PO BID	
NCT05024318 NAPSTER	2	Randomized	SABR (arm 1) vs. pembrolizumab and SABR (arm 2)	Arm 1: SABR: 42 Gy in 3 fractions Arm 2: Pembrolizumab 200 mg q3w x 3 cycles with SABR administered after cycle 1	
NCT03341845 NeoAvAx	2	Single	Axitinib and avelumab	Axitinib: 5mg BID Avelumab: 10mg/kg q2w	
NCT04028245 SPARC-1	2	Single	Spartalizumab and canakinumab	Spartalizumab: 400 mg q4w Canakinumab: 300 mg q4w	
NCT03055013 PROSPER RCC	3	Randomized	Perioperative nivolumab vs. observation	Nivolumab: 480 mg every 14 days x 1 neoadjuvant cycle and up to 9 cycles adjuvantly	
NCT04322955 Cyto-KIK	2	Single	Preoperative nivolumab and cabozantinib	Nivolumab: 480 mg every 4 weeks Cabozantinib: 40 mg daily	

[a]Or deemed unresectable by surgeon. [b]Clear cell must be predominant histology (> 50%). [c]Begins 2 weeks prior to nivolumab. [d]Clear cell component. [e]Including rhabdoid and sarcomatoid differentiation. [f]Feasibility if > 85% proceed. [g]First 3 to 6 subjects will hold cabozantinib for 3 weeks prior to surgery; if safe, all others will hold for only 2 weeks prior.

Rare instances of irAEs delaying surgery, include at least one grade 4 AE, which underscores the need for biologic markers of patient susceptibility to irAEs [36,39–42]. Notably, there was no signal regarding surgical complications across the above studies of neoadjuvant immunotherapy. These data, combined with retrospective data, suggest that IO is safe to continue through surgery without interruption[43]. Additionally, while patients are less likely to have an AE with immunotherapy in the adjuvant setting, these AEs can be debilitating and permanent, requiring long-term immunosuppression, whereas the AEs seen with VEGFR inhibition typically resolve with drug cessation.

Regulatory Issues

Uptake of new therapies into routine clinical practice is based on published peer-reviewed evidence, influenced by international guidelines and recommendations, and tailored to the needs of each specific patient based on their circumstances and comorbidities. The "real-world"

	Duration	Goal N	Stage	Histology	Primary endpoint	Status
	12 weeks	17	≥cT3Nx or T any N+a	cc[b]	ORR	Recruiting
	Sitravatinib: 6–8 weeks[c] Nivolumab: 4–6 weeks	25	Locally advanced RCC	cc	ORR and point in treatment course of ORR	Active, not recruiting
	6 weeks	40	cT ≥ 2 or cN+	non-cc	MPR, pCR, pNR	Not yet recruiting
	Up to 12 weeks	30	T2-3, N0, M0	cc	ORR	Not yet recruiting
	12 weeks	18	≥T3Nx or T any N+f	cc[d]	MPR	Not yet recruiting
	9 weeks	26	T1b-3, N0-1, M0 or low volume M1 planned for nephrectomy	cc[e]	MPR	Not yet recruiting
	12 weeks	40	"nonmetastatic, completely resectable primary tumor of intermediate to high risk"	cc	Rate of partial response	Results: 30% partial response rate
	8 weeks	14	≥ cT2Nx or cTanyN1	cc[b]	% of patients who proceed to radical nephrectomyf	Not yet recruiting
	7-28 days preoperative, up to 9 months post-operatively	766	≥ cT2Nx or cTanyN1	any	EFS	Completed
	Up to 12 weeks[g]	45	Metastatic	cc[b]	CR rate	Recruiting

cc: clear cell; EFS: event-free survival; Gy: Gray; Len: lenvatinib; M: metastatic stage; MPR: major pathologic response; N: nodal stage; ORR: objective response rate; pCR: pathologic complete response; Pembro: pembrolizumab; pNR: pathologic nodal response; RCC: renal cell carcinoma; SABR: stereotactic ablative radiotherapy; T: tumor stage.

access to and uptake of new therapies is influenced primarily by what is approved and, more importantly, reimbursed in each region or available to those with financial resources. The impact of heterogeneous regulatory approval processes was clearly illustrated with sunitinib. While sunitinib was granted approval as adjuvant therapy for patients with risk for RCC recurrence by the United States FDA, counterparts in the European Union and United Kingdom did not grant approval for an adjuvant indication. Additionally, the Kidney Cancer Research Network of Canada issued a consensus statement that did not support the use of VEGFR-TKI in the adjuvant setting following a systematic review and meta-analysis of trials in this space[44].

In November 2021, the FDA approved adjuvant pembrolizumab for patients who are at intermediate-high or high risk for recurrence after surgery based on the KEYNOTE-564 study results using investigator-assessed DFS as the major efficacy outcome[9]. The review of the pembrolizumab submission was

also conducted under Project Orbis, which facilitates concurrent review of oncology products among international partners, allowing for simultaneous decisions in all countries. The Australian Therapeutic Goods Administration, Health Canada, and Swissmedic participated in this review. The approval of pembrolizumab redemonstrated the FDA's acceptance of DFS as a regulatory endpoint for adjuvant RCC trials. In the UK, the appraisal of pembrolizumab in the adjuvant setting has started, the EMA has approved, and publication of the results from the National Institute for Health and Care Excellence (NICE) are pending[45].

Issues Important to Patients

Adjuvant and Neoadjuvant Therapy

Adjuvant therapy given after curative intent therapy can be likened to life insurance: "a bet you do not want to win." A life insurance policy is essentially saying to a company, "I bet I die," and the company saying, "We bet you don't." A decision to undertake adjuvant therapy employs similar thinking. Patients with no apparent residual disease will be offered adjuvant therapy to reduce their theoretical risk for recurrence and death from cancer. Most patients who receive adjuvant therapy cannot benefit from it, and are therefore only exposed to possible harms, which is evident in the high discontinuation rate seen in the above adjuvant studies. However, it may be possible to increase the proportion of patients who may benefit through careful patient selection.

Conversely, neoadjuvant therapy is "a bet you want to win"—an investment in treatment now, while cancer is still detectable, to try to improve outcomes from definitive treatment such as surgery. Currently for patients with renal cell cancer, this approach is nearly always in the context of a clinical trial, as its benefit is unproven.

Patient Preferences

Clinicians and patients often have different goals for treatment and expectations of outcomes. A patient preference substudy in the SORCE clinical trial[12] used a validated questionnaire aiming to understand what degree of improvement in survival would be judged by participants and investigators as sufficient to justify their participation and potential side effects from treatment with sorafenib[46]. Investigators judged that larger survival benefits were required than their patients to make adjuvant treatment worthwhile[46,47]. Patients and clinicians also perceive and report adverse events differently. Clinician assessment through the NCI Common Terminology Criteria for Adverse Events (CTCAE) is not always concordant with patient-reported outcomes (PRO)[48]. Owing to the differences between patient and clinician perspectives, it is imperative to work with community partners in the design of adjuvant clinical trials in RCC to ensure the outcomes align with community expectations and needs[49].

Unmet Needs

The most obvious unmet need in the context of clinical trials for RCC is for effective therapies. None of the trials so far have demonstrated a survival advantage, including the data with pembrolizumab in KEYNOTE-564[9]. It is therefore reasonable to advise patients that the standard of care remains observation, with access to life-prolonging therapies in the event of relapse. Patients want better treatments and outcomes with quicker results[50–53], and they want trials that examine and report the patient experience. These are all considerations for future trial designs but also apply to everyday treatment decision-making.

Future Directions

Several issues need to be considered when designing clinical trials of adjuvant therapy in RCC.

Statistical Designs for the Trials

There is equipoise in arguments for randomized control trials (RCTs) versus multi-arm multistage (MAMS) designs for adjuvant trials. RCTs are preferred in industry and ask well-defined controlled questions. This approach gives confidence that the trial will be delivered in the projected timescale and the simple design is easy for patients and physicians to understand. MAMS trials are ideal for academic consortia and can ask multiple questions simultaneously and in sequence and adapt to new data. Rapid advancements in prostate cancer have been made using this approach via STAMPEDE and in kidney cancer via RAMPART. This model allows adaptions that include adding arms, dropping arms, and changing control arms in light of new data. Although initially less attractive for commercial support, this approach, which demonstrated speed and quality of data at low cost, could be compelling.

Trial Endpoints

The aim of adjuvant treatment is to improve the cure rate or at least to prolong healthy life. OS remains the gold standard but in event-driven trials, this will either take a long time (generally 3 to 4 years to accrue and 3 to 7 years for maturity) or will require very large numbers of patients. This massively increases costs and slows potential progress. Moreover, there is expenditure of patients who may not need therapy and perhaps undertreatment of very high-risk patients. Thus, DFS has become a de facto approach and was an accepted endpoint for S-TRAC and KEYNOTE-564. However, in a recent meta-analysis encompassing 13 studies and more than 6400 patients treated with adjuvant therapies for RCC, correlation between 5-year DFS and OS rates was modest, suggesting DFS is not a good surrogate

marker of OS[54]. These results underline the difficulty of choosing the good primary objective in designing an adjuvant clinical trial in RCC.

Essential requirements for future trials include cost-effectiveness: need for innovation in therapies to reduce health care costs, including the medium (such as oral checkpoint inhibitors instead of intravenous), the duration of therapy, and access to care. Finally, quality of life remains underappreciated: the diarrhea and dysgeusia and fatigue experienced from VEGFR-TKIs continue to have poor remedy, and the autoimmune side effects from immunotherapy can be permanent. The risk/benefit ratio for adjuvant therapy must outweigh that of reserving treatment only for metastatic disease.

Biomarkers Needed

Contemporary metastatic clear cell cancer trial designs have failed to address whether both IO and antiangiogenic therapy are necessary for individual patients. Both pure antiangiogenic trials and pure IO monotherapy trials have been applied to the adjuvant setting with continued uncertainty as to whom would benefit from adjuvant therapy or neoadjuvant therapy and for how long. With the availability of molecular signatures, which could improve prognostication, there is opportunity to design smarter trials. Transcriptomics, which appear to indicate sensitivity or resistance of some metastatic renal cancers to IO or antiangiogenic therapy[55], need validation and could be used to select treatments when indicated, or could be used in the development of adaptive, biomarker-driven basket trials similar to I-SPY2 in breast cancer (NCT01042379). The PROSPER trial is undergoing such analysis retrospectively. Specimens from the ASSURE trial are undergoing whole-exome RNA sequencing, which likely will provide further insight into which patients are more likely to relapse and have worse prognosis. Furthermore, analysis of kidney injury molecule-1 (KIM-1) from blood correlates with detection of recurrence[56] and plasma DNA methylation immunoprecipitation analysis are being retrospectively validated to predict recurrence in this population[57]. If validated, these tools could be applied to future trials to guide patient populations to be offered or spared adjuvant therapy.

Sequencing of Treatments Postadjuvant Therapy

The new approval and future use of IO adjuvant therapy in some patients affects the design of first-line metastatic renal cancer trials. The timing of relapse may be important, as it is untested whether patients who relapse while receiving adjuvant therapy might still benefit from VEGFR-TKI monotherapy or VEGFR-TKI /IO or IO/IO. Furthermore, should patients who relapse 6 months after IO therapy be considered differently than those who relapse later post-therapy? For now, these are unanswered questions. The application of molecular typing becomes essential in this era, and tools such as KIM-1, DNA methylation, or circulating tumor DNA (ctDNA) if sensitive enough, could be used for cancer screening, as is in process in GRAIL[58], to identify earlier cancers and thereby obviate the use of adjuvant therapy in many patients.

Conclusions

While IO shows promise for the adjuvant treatment of high-risk clear cell RCC, there is still much to learn from ongoing clinical trials and longer follow-up data in this space, and the lessons learned from adjuvant targeted therapy trials must now be applied to this era. We must await and properly weigh OS data from trials of adjuvant IO, and we should strive to identify readily scalable biomarkers that can be used to hone patient selection criteria in future prospective therapeutic trials.

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T. Eisen: Employment: AstraZeneca (to March 2020); Employment as VP Oncology Early Clinical Dev Roche (from March 2020); Employment as VP GU Oncology Late Clin Dev AstraZeneca Research support. Stock options AstraZeneca and Roche. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Macmillan Cancer Support Trustee for 10 years to 2021; Cambridge University Health Partners non-executive director

Travel Support to Genitourinary Symposiums ASCO 2020 Roche.

M. Gross-Goupil: Participation on a data safety monitoring board or advisory board: MSD, BMS, Pfizer, Ipsen. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Member of the GETUG. Support for attending meetings and/or travel: MSD, Ipsen, BMS, Pfizer.

A. Kapoor: Participation on a data safety monitoring board or advisory board: Ipsen, Eisai, Merck, BMS, Janssen, Bayer, Abbvie (Advisory Boards). Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Chair, Kidney Cancer Research Network of Canada (KCRNC). Stock options: Verity Pharma.

V. Master: Participation on a data safety monitoring board or advisory board: Merck, Pfizer, BMS, Exilexis.

Support for attending meetings and/or travel: American College of Surgeons.

C. Ryan: Grants or contracts from any entity: Ayala, Bristol Meyer Squibb, Daiichi-Sankyo, Deciphera, Exelixis, Genentech, Novartis, Karyopharm, Merck, Nektar, Pfizer, Xynomic, Shasqi, Monopar, Boehringer Ingelheim, PTC Therapeutics, Trillium Therapeutic (to my institution for all). Consulting Fees: Exelixis (all payments to me) Aveo, Daiichi, Sankyo, Synox, Bristol Meyer Squibb, Astra Zeneca, Janssen.

M. Schmidinger: Consulting fees and honoraria: BMS, MSD, Ipsen, Exelixis, EISAI. Support for attending meetings and/or travel: MSD Ipsen BMS. Participation on a data safety monitoring board or advisory board: BMS MSD, Ipsen, EISAI.

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