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EXPERT OPINION

Approaches to Treating High Risk and Advanced Renal Cell Carcinoma (RCC): Key Trial Data That Impacts Treatment Decisions in the Clinic

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Abstract: The treatment paradigm for high risk localized and advanced kidney cancer has been characterized by ongoing changes, with the introduction of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) and later with immune checkpoint blockade. In this article, we review how current evidence informs our decision-making on post-checkpoint inhibitor systemic therapies, the role of adjuvant and/or neoadjuvant therapies, and the role of cytoreductive nephrectomy in the evolving systemic therapy landscape. While some studies support a post-checkpoint inhibitor benefit from the VEGFR TKIs cabozantinib or axitinib, the benefit of doublet therapies including a VEGF receptor inhibitor and a checkpoint inhibitor remains an area of active investigation, with the combination of lenvatinib plus pembrolizumab showing promise but with a Phase III trial of the combination of atezolizumab plus cabozantinib showing no benefit over cabozantinib alone. The role of adjuvant therapy in patients with high-risk disease who have undergone cytoreductive nephrectomy and potentially metastasectomy is also an area of continuing interest. While the S-TRAC study demonstrated a disease-free survival benefit for adjuvant sunitinib, no overall survival benefit was shown, and multiple other studies of adjuvant VEGFR TKI therapy have been negative. Subsequently, adjuvant pembrolizumab has shown a benefit in overall survival, whereas trials of neoadjuvant and adjuvant nivolumab, adjuvant atezolizumab, and adjuvant ipilimumab plus nivolumab have all been negative. Finally, the role for cytoreductive nephrectomy continues to be an area of active debate. The CARMENA study raised important questions about the role of cytoreductive nephrectomy given the advances in VEGFR TKI therapy but was characterized by accrual difficulties and a significant number of patients not receiving treatment according to the study protocol. Two ongoing studies (NORDIC-SUN and PROBE) seek to further address the role of cytoreductive nephrectomy in the doublet therapy era.

Keywords: kidney cancer, cytoreductive nephrectomy, immunotherapy, adjuvant therapy

Introduction

The treatment paradigm for advanced kidney cancer has continued to evolve over the past several years. The VEGFR TKI sunitinib demonstrated improved progression-free survival when compared to interferon alfa in the treatment of metastatic renal cell carcinoma in 2007, representing a significant paradigm shift in the treatment of this disease.[1] The PD-1 inhibitor nivolumab subsequently showed efficacy in 2015 when compared to everolimus in the second-line setting in a large phase III trial, demonstrating the efficacy of checkpoint inhibition in the treatment of clear cell kidney cancer.[2] The efficacy of the combination of the CTLA-4 inhibitor ipilimumab with nivolumab in the first-line setting was demonstrated in a 2018 study, initiating the era of doublet therapy for clear cell kidney cancer. Multiple VEGFR TKI and PD-1 combinations have since been proven to be effective, providing additional options for clinicians and for patients.[2–6] These advances in systemic therapy have added to the uncertainty around the way therapies should be sequenced in patients who have received prior checkpoint inhibitor therapy and the role and sequencing of cytoreductive nephrectomy in patients with metastatic disease. The role of systemic therapy in the adjuvant setting is also evolving,

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with conflicting data despite the success of the one positive pembrolizumab trial. In this article, we will review how the available evidence guides us in navigating these questions in the clinic and will discuss how upcoming trials may add clarity for the clinician, in general, as well for individualized clinical contexts.

Data on Treating Patients with Metastatic Disease in the Post-Checkpoint Inhibitor Setting

Checkpoint inhibition has become the main stay of first-line standard of care for patients with metastatic clear cell kidney cancer, whether as part of a doublet with a VEGFR TKI or via dual checkpoint blockade. The increasing utilization of immunotherapy in the adjuvant setting will further increase the number of patients who require a post-checkpoint inhibitor regimen as some of these patients will nonetheless develop recurrent disease. Table 1[7–12] details trials of systemic therapy in the post-checkpoint inhibitor setting.

Cabozantinib, axitinib, the combination of lenvatinib plus pembrolizumab, and the combination of cabozantinib plus atezolizumab have all been evaluated in the post-checkpoint inhibitor setting. The CaboPoint trial is evaluating the VEGFR TKI cabozantinib in patients with metastatic clear cell kidney cancer who had been previously treated with either ipilimumab + nivolumab (60 patients enrolled as of the published interim analysis) or with a checkpoint inhibitor and a VEGFR-TKI (28 patients). Notably, responses were seen in both groups, with 31.7% (95% confidence interval (CI) 20.3–45.0) of patients responding following dual checkpoint inhibition and 25.0% (95% CI 10.7–44.9) of patients responding following a VEGFR-TKI plus checkpoint inhibitor combination.[10] The VEGFR TKI axitinib has also been evaluated in the post-checkpoint inhibitor setting. In a phase II trial, 40 patients with metastatic clear cell kidney cancer who had received checkpoint inhibitor therapy as their most recent line of therapy received axitinib. Axitinib was provided at a starting dose of 5 mg twice daily and was titrated via an algorithm based on the presence or absence of adverse events to a maximum dose of 10 mg twice daily. The study was designed to test whether this customized dosing algorithm would lead to an improved length of progression-free survival as compared to two retrospective studies of axitinib. Notably, 28 of the 40 patients had also received a prior VEGFR TKI at some point in their disease course. Median progression-free survival was 8.8 months (95% CI 5.7–16.6), which was not statistically superior to the progression-free survival identified in the two retrospective studies of 6.5 months and 6.6 months, respectively. Notably, however, 45% of patients (18/40) achieved at least a partial response, demonstrating the efficacy of axitinib in the post-immunotherapy setting in a prospective trial.[7]

Doublet therapies with a checkpoint inhibitor and VEGFR TKI have also been evaluated in the post-immunotherapy setting. CONTACT-03 was a phase III trial which evaluated patients with metastatic clear cell or non-clear cell kidney cancer who had progressed on prior immune checkpoint inhibitor therapy. Patients were randomized to receive either atezolizumab (1200 mg given every three weeks) plus cabozantinib (60 mg once daily) or to cabozantinib alone; 522 patients were randomized, with 263 receiving atezolizumab plus cabozantinib and 259 receiving cabozantinib alone. Progression free and overall survival were the two primary endpoints. With a median follow-up of 15.2 months, median progression-free survival was 10.6 months for patients receiving the doublet and 10.8 months for patients receiving cabozantinib alone (Hazard Ratio (HR) for progression-free survival or death 1.03 (95% CI 0.83–1.28); $p = 0.78$). Patients with dominant clear cell histology, dominant non-clear cell histology, and with any sarcomatoid component all failed to benefit from the addition of atezolizumab. Median overall survival was 25.7 months in patients receiving the doublet and not evaluable in patients receiving cabozantinib (HR for death 0.94 (95% CI 0.70–1.27); $p = 0.69$). Serious adverse events were more common with the doublet and were seen in 48% of patients as compared to 33% receiving cabozantinib alone. In addition, there were three deaths related to adverse events in patients receiving doublet therapy, as compared to no patients in the cabozantinib monotherapy arm. As such, the addition of atezolizumab to cabozantinib in the later line setting did not appear to benefit patients.[13] One may observe that atezolizumab does not have an RCC-specific label and was also in the negative IMmotion-010 adjuvant study. The Phase III TiNivo 2 study is currently underway and will evaluate the combination of the VEGFR TKI tivozanib with the PD-1 inhibitor nivolumab in the post-immunotherapy setting.[14]

Table 1 Selected Trials of Systemic Therapy Given Subsequent to Immunotherapy

Study	Year of Publication	Key Eligibility	Number of Patients	Arm 1	Arm 2 (If Applicable)	Primary Outcome	Result
Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study	2019	Locally recurrent or metastatic kidney cancer with clear cell histology having received prior checkpoint inhibitor therapy	40 patients	Axitinib 5 mg BID	N/A	Progression free survival (PFS)	8.8 months (95% Confidence Interval (CI) 5.7–16.6)
Lenvatinib plus pembrolizumab in patients with either treatment-naive or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study	2021	Metastatic clear cell-predominant kidney cancer; data provided for the cohort having received prior PD-1 directed checkpoint inhibitor therapy	104 patients were previously treated with immune checkpoint inhibitor therapy	Lenvatinib 20 mg daily plus pembrolizumab 200 mg given every 3 weeks	N/A	Objective response rate (ORR) at week 24	55.8% (95% CI 45.7–65.5)
Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial	2023	Advanced or metastatic kidney cancer, having previously received immune checkpoint inhibitor therapy	522 patients randomized	Atezolizumab (1200 mg IV every three weeks) plus cabozantinib (60 mg once daily)	Cabozantinib (60 mg once daily)	PFS and overall survival (OS)	Median PFS was 10.6 months for atezolizumab plus cabozantinib and 10.8 months for cabozantinibHazard ratio 1.03 (95% CI 0.83–1.28); p=0.78.
							Median OS was 25.7 months for atezolizumab plus cabozantinib and not evaluable for cabozantinibHazard ratio 0.94 (95% CI 0.70–1.27); p=0.69

(*Continued*)

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Table 1 (Continued).

Study	Year of Publication	Key Eligibility	Number of Patients	Arm 1	Arm 2 (If Applicable)	Primary Outcome	Result
CaboPoint: A phase II study of cabozantinib as second-line treatment in patients with metastatic renal cell carcinoma	2023	Cohort A: Metastatic clear cell kidney cancer; Progression after ipilimumab plus nivolumab; No prior treatment with cabozantinib	57 patients enrolled as of the interim results	Cabozantinib (50 mg/day), given for up to 18 months	N/A	ORR	31.7% (95% CI 20.3–45.0)
		Cohort B: As above, but prior treatment with a checkpoint inhibitor plus VEGF-targeted therapy instead of with ipilimumab plus nivolumab	25 patients enrolled as of the interim results	Cabozantinib (50 mg/day), given for up to 18 months	N/A	ORR	25.0% (95% CI 10.7–44.9)
LBA88 Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): Randomized open-label phase III LITESPARK-005 study	2023	Advanced clear cell kidney cancer, having treated with 1–3 prior regimens including anti-PD1/L1 and VEGFR-TKI targeted therapies	746 patients randomized	Belzutifan 120 mg daily	Everolimus 10 mg daily	PFS and OS	PFS was significantly improved for belzutifan as compared to everolimus at the first interim analysis (HR 0.75 (0.63–0.90); p<0.01). At 18 months, 22.5% of patients treated with belzutifan were free from progression, as compared to 9.0% of patients treated with everolimus.

KEYNOTE-146 evaluated the combination of lenvatinib plus pembrolizumab in patients with clear cell kidney cancer and included a cohort of 104 patients who had previously received checkpoint inhibitor therapy. Notably, 55.8% of patients exhibited an objective response at week 24, demonstrating the efficacy of this combination in the post-checkpoint-inhibitor setting. Toxicity was characteristic of VEGFR-TKI plus immunotherapy regimens. Specifically, 57% of patients had grade 3 treatment-related adverse events, and 7% of patients had grade 4 treatment-related adverse events; three treatment-related deaths were noted.[8] A conjecture about the high response rate of the regimen is that there may have been VEGFR responsive patients who had had VEGFR therapy, then immune therapy treatment with a hiatus of VEGFR pathway medications, and that this, more so than the immune therapy-induced responses.

The combination of ipilimumab plus nivolumab has also been evaluated after prior checkpoint inhibitor therapy. In one retrospective study, 45 patients treated with prior immune checkpoint inhibitor therapy targeting the PD-1 pathway were treated with ipilimumab plus nivolumab. Twenty percent of patients responded to therapy, and the median progression-free survival was 4 months.[15] The OMNIVORE study also evaluated the role of the combination of ipilimumab plus nivolumab in the post-nivolumab setting. In this study, patients were treated with nivolumab as first-line therapy. Patients who had a partial or complete response within 6 months took a break from treatment until progression. Patients with stable disease or progression, however, had their treatment intensified to the combination of ipilimumab plus nivolumab. Notably, of 57 patients progressing on nivolumab monotherapy, only two patients (4%) had a partial response, and no patients had a complete response. In addition, both of the patients who responded ultimately discontinued treatment due to progressive disease. Further, grade 3–4 treatment related adverse events occurred in 25% of patients. As such, the study raises some question as to the utility of dual checkpoint blockade in patients following prior PD1/L1 inhibitor therapy.[16]

The HIF-2α inhibitor belzutifan has also been approved in the subsequent-line setting. LITESPARK-005 is a randomized Phase III study which evaluated patients with clear cell kidney cancer who had previously been treated with 1–3 prior systemic therapy regimens, including a VEGFR TKI and a PD1/L1 inhibitor, and randomized patients to either belzutifan or to everolimus. Progression-free survival at the first interim analysis was significantly superior for belzutifan as compared to everolimus (HR 0.75 (0.63–0.90); $p < 0.01$), and after 18 months, 9.0% of patients treated with everolimus were free from progression, as compared to 22.5% of patients treated with belzutifan. Anemia was the most common adverse event in patients treated with belzutifan and was seen in 82.8% of patients as compared to 56.7% of patients treated with everolimus. Hypoxia was seen in 14.5% of patients treated with belzutifan as compared to 1.1% of patients treated with everolimus.[11] The FDA approved belzutifan in the post-checkpoint inhibitor and post-VEGFR TKI setting on 12/14/2023 based on the LITESPARK-005 data.[17] Another study evaluating the efficacy of belzutifan with one of the two VEGFR TKIs (cabozantinib or lenvatinib) in the subsequent-line setting is also currently underway.[11,18]

Based on the above data, we primarily utilize VEGFR TKI-based therapy in patients who have progressed on prior immunotherapy, with belzutifan being a new therapeutic option based on its recent approval. That said, ongoing research on VEGFR TKI plus checkpoint inhibitor doublets in the second line and later line settings may influence our approach. Of note, absent further supporting data, we would also be reluctant to trial further immunotherapy in patients who have progressed on a triplet therapy, as has been evaluated in the COSMIC-313 study of ipilimumab, nivolumab, and cabozantinib.[19] While post-triplet therapy has not been specifically studied to our knowledge, the results of OMNIVORE in particular give us some doubt about the ability of immunotherapy alone to salvage progression following prior immunotherapy.

The Use of Novel Systemic Therapies in the Adjuvant and/or Neoadjuvant Settings for Patients with High Risk or Oligometastatic Disease

The changing systemic therapy landscape has started to shift the neoadjuvant and adjuvant therapy paradigms in patients with localized high risk or oligometastatic kidney cancer away from VEGFR TKIs towards immunotherapy and immunotherapy combinations. Table 2[9,20–27] details trials of neoadjuvant and/or adjuvant therapy for patients with high risk or oligometastatic kidney cancer. Figure 1[9,20–26] provides a timeline of the positive and negative trials, highlighting the preponderance of negative trials.

Table 2 Selected Trials of Neoadjuvant and/or Adjuvant Systemic Therapy for High-Risk Kidney Cancer

Study	Study Abbreviation	Date of Publication	Key Eligibility	Number of Patients Randomized	Arm 1	Arm 2	Arm 3	Primary Outcome	Results
Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial	ASSURE	2016	Medullary kidney cancer and collecting duct kidney cancer excluded; ≥T1b (G3-4) N0 or N+; no metastatic disease	1943	Sunitinib, (50 mg per day, 4-weeks-on, 2-weeks-off, for 1 year; later amended to 37.5 mg per day), for 54 weeks	Sorafenib (400 mg twice daily), for 54 weeks	Placebo	DFS (disease free survival)	Median DFS was 5.8 years for sunitinib, 6.1 years for sorafenib, and 6.6 years for placebo Hazard ratio (HR) of 1.02 for sunitinib (95% Confidence Interval (CI) 0.85–1.23); p=0.8038 HR of 0.97 for sorafenib (95% CI 0.80–1.17); p=0.7184
Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma)	PROTECT	2017	Clear-cell predominant histology. Any of T2a (G3-4), ≥T2b, N+; no metastatic disease	1538 (1135 received an initial dose of 600 mg of pazopanib)	Pazopanib (800 mg daily; initial dose later lowered to 600 mg due to toxicity), for 1 year	Placebo	N/A	DFS *in patients treated with an initial dose of 600 mg* (updated due to toxicity from the 800 mg dose)	DFS analysis was performed after 350 events. HR 0.86 (95% CI 0.70–1.06); p=0.165
Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial	ATLAS	2018	>50% clear-cell histology; ≥T2 or N+; no metastatic disease	724	Axitinib (5 mg twice-daily for at least 1-year unless recurrence, up to 3 years)	Placebo	N/A	DFS	Trial stopped due to futility at 203 DFS events HR 0.870 (95% CI 0.660– 1.147); p=0.3211
Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy	S-TRAC	2018	Clear cell histology; ≥T3 or N+; no metastatic disease	615	Sunitinib, (50 mg per day, 4-weeks-on, 2-weeks-off, for 1 year)	Placebo	N/A	DFS	Median DFS was 6.8 years for Sunitinib and 5.6 years for Placebo HR 0.76 (95% CI 0.59–0.98); p=0.03

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Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy	PROSPER RCC	2021	RCC (Any histology); ≥T2 or N+; radical or partial nephrectomy planned; oligometastatic disease permitted if patient could be rendered NED within 12 weeks of surgery	819	Nivolumab (480 mg IV q4 weeks) with 1 dose prior to surgery and then 9 adjuvant doses	Surveillance	N/A	Recurrence Free Survival	Trial stopped early due to futility
Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial	IMmotion010	2022	Clear cell or sarcomatoid histology; T2 (G4), T3a (G3-4), ≥T3b (any grade), N+, or M1 s/p definitive treatment (no evidence of disease)	778	Atezolizumab 1200 mg intravenously, every three weeks, for 16 cycles or 1 year (whichever occurred first)	Placebo	N/A	DFS	Median DFS was 57.2 months for atezolizumab, 49.5 months for placebo HR 0.93 (95% CI 0.75–1.15); p=0.50
Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma	KEYNOTE-564	2022	Clear cell component present; T2 (G4 or sarcomatoid), ≥T3, N+, or M1 s/p definitive treatment (no evidence of disease)	984	Pembrolizumab (200 mg) q3 weeks for up to 17 cycles	Placebo	N/A	DFS	DFS at 24 months was 77.3% for pembrolizumab vs 68.1% for placebo HR 0.68 (95% CI 0.53–0.87); p=0.002

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Table 2 (Continued).

Study	Study Abbreviation	Date of Publication	Key Eligibility	Number of Patients Randomized	Arm 1	Arm 2	Arm 3	Primary Outcome	Results
Adjuvant everolimus after surgery for renal cell carcinoma (EVEREST): a double-blind, placebo-controlled, randomised, phase 3 trial.	EVEREST	2023	RCC (Any histology but collecting duct or medullary); T1b (G3 or G4), ≥T2, or N+; no metastatic disease	1545	Everolimus 10 mg daily for 54 weeks	Placebo	N/A	Recurrence-free survival (RFS)	5-year RFS was 67% for everolimus vs 63% for placebo; Stratified HR 0.85 (95% CI 0.72–1.00; p=0.05); prespecified p value of 0.044 was not reached.
Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): A double-blind, randomised, phase 3 trial.	CHECKMATE 914	2023	Clear-cell predominant histology; T2a (G3-4), ≥T2b, or N+; no metastatic disease	816	Nivolumab (240 mg) every two weeks plus Ipilimumab (1 mg/kg) every 6 weeks) for up to 12 cycles of nivolumab	Placebo	N/A	DFS	Median DFS not yet reached in the ipilimumab + nivolumab group and 50.7 months in the placebo group HR 0.92 (95% CI 0.71–1.19); p=0.53

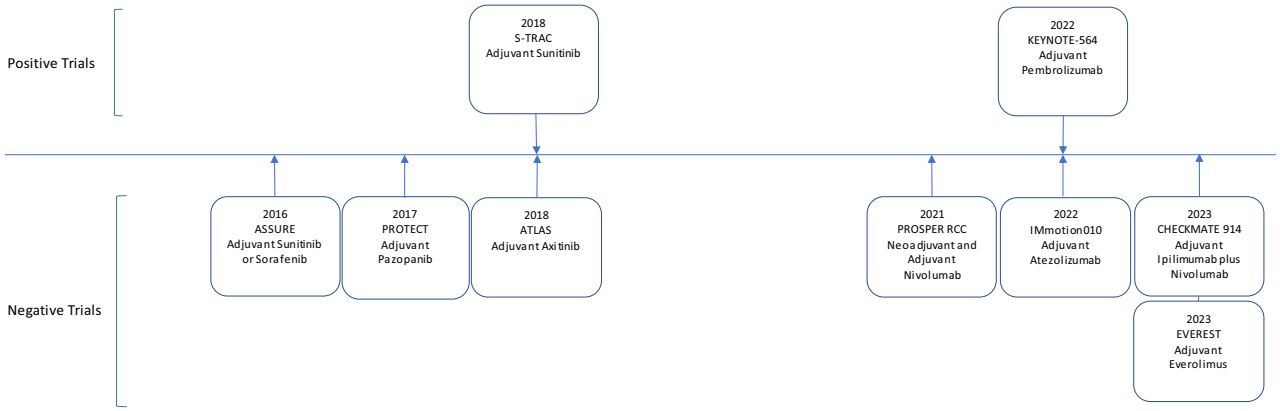

Figure 1 A timeline of positive and negative trials is detailed, highlighting the preponderance of negative trials.

After many negative large VEGFR adjuvant studies, that pattern changed with the S-TRAC study which evaluated the role of adjuvant sunitinib following nephrectomy in patients with kidney cancer with histology showing higher risk attributes. The study did show an improvement in median disease-free survival of 6.8 years for adjuvant sunitinib as compared to 5.6 years for placebo (HR 0.76 (95% CI 0.59–0.98) p = 0.03), but adverse events of grade 3 (48.4% vs 15.8%) or 4 (12.1% vs 3.6%) and treatment discontinuations (28.6% vs 5.6%) were more common compared to placebo,[23] and after 8 years of follow-up, no improvement in overall survival was observed.[28] These data nevertheless led to approval by the United States Food and Drug Administration for this indication although not elsewhere. This trial is seen in the context of multiple other clinical trials addressing adjuvant VEGF receptor inhibitor therapy (eg, ATLAS, ASSURE, and PROTECT) which failed to demonstrate a benefit in disease-free survival, raising the question as to why conflicting results were shown across these studies.[22,29,30] One reason for this discordant result may be that S-TRAC enrolled only patients with Stage III disease, as compared to 66% of patients in ASSURE, 86% of patients in PROTECT, 89% of patients in ATLAS. All of the adjuvant VEGFR TKI trials were plagued by high rates of treatment discontinuations and dose reductions due to toxicities. As such, our practice is to thoroughly discuss the benefits and risks of adjuvant sunitinib in the context of other unsuccessful trials of VEGF inhibitors with patients to enable informed decision-making.

The EVEREST study examined the role of adjuvant everolimus (an mTOR inhibitor) following surgery for RCC. Patients were eligible if they had at least T1b disease that was grade 3 or 4, at least T2 disease (any grade), or the presence of nodal involvement. No metastatic disease was permitted. The intervention arm received 54 weeks of everolimus given as 10 mg once daily. Grade 3 or higher adverse events were seen in 46% of patients receiving everolimus as compared to 11% of those receiving placebo, with the common grade 3 or higher adverse events including mucositis (14%), hypertriglyceridemia (11%), and hyperglycemia (5%). The estimated 5-year recurrence free survival was 67% for everolimus as compared to 63% for placebo; the stratified HR was 0.85 (95% CI 0.72–1.00; p = 0.05) but the prespecified p value of 0.044 was not reached.[27] As such, the study did not support the use of adjuvant everolimus in this setting.

Immunotherapy has more recently been extensively evaluated in the neoadjuvant and adjuvant settings for patients with localized high-risk or oligometastatic disease. Notably, the KEYNOTE-564 study was a double-blind randomized trial evaluating one year of adjuvant pembrolizumab in patients with high-risk kidney cancer who were status post nephrectomy with or without metastasectomy. Patients were defined as being at high risk for recurrence if they had T2 disease with nuclear grade 4 or sarcomatoid differentiation or if they had at least T3 disease or nodal disease. Patients were also defined as being at high risk for recurrence if they had metastatic disease which had been surgically resected at the time of nephrectomy or within one year and had no evidence of radiographically active disease at the time of enrollment into the study. The study had 994 subjects who were randomized to placebo or pembrolizumab for one year. Grade 3 or higher adverse events were seen in 32.4% of patients receiving pembrolizumab, and in 17.7% of those

receiving placebo. The initial positive outcome observed was disease-free survival at 24 months (77.3% for patients receiving pembrolizumab versus 68.1% in patients receiving placebo).[25] The updated 30-month report again showed that those receiving adjuvant pembrolizumab had significantly improved disease-free survival (HR 0.63 (95% CI 0.50–0.80)); a subgroup analysis found a notable benefit in those who were status-post metastasectomy (HR 0.28 (95% CI 0.12–0.66)). Results on overall survival were subsequently released, and with a median of 57.2 months of follow-up, a statistically significant improvement in overall survival was in fact observed with pembrolizumab as compared to placebo (HR 0.62, 95% CI 0.44–0.87; p = 0.0024). Additionally, the estimated OS rate at 48 months was 91.2% for pembrolizumab and 86.0% for placebo.[31]

Despite the positive results of KEYNOTE-564, other large format prospective trials of neoadjuvant and adjuvant immunotherapy have not shown a significant benefit. The PROSPER RCC trial aimed to see whether patients with at least T2, lymph node positive, or oligometastatic disease (if the patient had been resected to no evidence of disease within 12 weeks of nephrectomy) would benefit from one dose of neoadjuvant nivolumab followed by nephrectomy and then by 9 additional every-four-week doses of nivolumab. The neoadjuvant dose aimed to prime the immune system prior to nephrectomy.[32] The trial was stopped due to futility, as recurrence free survival was similar between the arms (HR 0.97, 95% CI: 0.74–1.28).[24] This trial enrolled and included a greater proportion of patients with non-clear cell RCC, who appear to be less responsive to immunotherapy; this is consistent with a conjecture that clinical heterogeneity may be limiting factor in the trials' power to discern benefit. Another conjecture, extending the observation of the success of a longer duration of neoadjuvant therapy in melanoma, would be that this paradigm could be revisited in clear cell RCC, with a longer adjuvant phase.

The CHECKMATE 914 trial subsequently evaluated a combination of ipilimumab and nivolumab in the adjuvant setting, based on the efficacy of a similar combination of the treatment of metastatic disease via CHECKMATE 214. In this adjuvant study, patients with high-risk localized clear cell kidney cancer were randomized to receive 240 mg of nivolumab every 2 weeks for 12 doses plus ipilimumab 1 mg/kg every 6 weeks for four doses versus placebo. Of note, the CHECKMATE 214 schedule was somewhat different and included nivolumab 3 mg/kg/dose and ipilimumab 1 mg/kg/dose for 4 doses at 3-week intervals and then nivolumab monotherapy 3 mg/kg/dose every 2 weeks.[3] Patients with oligometastatic disease were not eligible, contrasting with the pembrolizumab study. A total of 816 patients were randomized, and 405 received nivolumab plus ipilimumab. Grade 3 or higher adverse events were seen in 38% of patients receiving active treatment (with treatment discontinuation in 32%) as compared to 10% of patients receiving placebo (treatment discontinuation in 2%). Also, 4 deaths were attributed to treatment with nivolumab plus ipilimumab. Adjuvant ipilimumab plus nivolumab did not significantly improve disease-free survival (HR 0.95 (95% CI 0.71–1.19); p = 0.53); one may conjecture that the significant toxicities were a factor impeding an observable improvement.[26]

An additional large checkpoint adjuvant trial was IMmotion-010, which evaluated the use of adjuvant atezolizumab, a PD-L1 inhibitor, for 1 year. Of the 778 subjects (including those with metastasectomy to no evident disease) enrolled, 390 were randomized to atezolizumab. High grade adverse events in the treatment group were at 18% vs 12% in the placebo group; no treatment-related deaths occurred. Disease-free survival was, again, not demonstrated to be different (HR 0.93 (95% CI 0.71–1.15; p = 0.50)). Notably, fourteen percent of patients had metastatic disease which had been definitively treated.

The above results raise the question as to why adjuvant pembrolizumab, as compared to the other studied immunotherapy regimens, showed an improvement in disease-free and overall survival. The proportion of patients with metastatic disease (either definitively treated or, as in the case of PROSPER RCC, intended for definitive treatment) differs significantly between these studies, with fourteen percent of patients in IMmotion-010, six percent in KEYNOTE-564, three percent in PROSPER RCC, and none per the protocol in CHECKMATE 694. Thus, if the presence of metastatic disease was to explain the positive result in KEYNOTE-564, we might have also expected a positive result in IMmotion-010, although it should again be noted that atezolizumab does not have an FDA approved indication specifically for kidney cancer. While the nivolumab plus ipilimumab regimen was given on a somewhat modified schedule as compared to that used in the metastatic setting, and while only six months of therapy were provided in this study, the efficacy of dual checkpoint inhibition in

metastatic kidney cancer is well studied and the lack of a disease-free survival benefit in the adjuvant setting is notable.

In light of the negative results from PROSPER RCC, IMmotion-010, and CHECKMATE 694 and the positive data from KEYNOTE-564, our practice is to discuss the divergent results with patients while also noting the demonstrated overall survival benefit of adjuvant pembrolizumab. The RAMPART trial is comparing durvalumab alone or combined with tremelimumab as adjuvant therapy and may help to further clarify the role of adjuvant therapy.[33] Also of note, LITESPARK-022 is investigating a novel direction of the combination of pembrolizumab with or without the HIF-2α inhibitor belzutifan in the adjuvant setting.[34] The role of prognostic models incorporating molecular data, molecular residual disease and predictive biomarkers to select suitable high-risk patients for adjuvant therapy warrants aggressive investigation.[13,35]

The Role of Cytoreductive Nephrectomy in a Changing Systemic Therapy Landscape

The role of cytoreductive nephrectomy in patients with metastatic kidney cancer remains an area of some uncertainty both in the general sense and for individualized decision recommendations. For the individual, factors such as projected non-cancer life expectancy, surgical complexity, and projected post-operative renal reserve may outweigh generalizations from selected on-trial patient populations. While randomized controlled trials, now decades old, from the era of interferon-based therapy showed an overall survival benefit in patients receiving a cytoreductive nephrectomy, systemic therapy has changed dramatically since the cytokine era.[2–6,36,37] As such, studies addressing how much benefit should be allocated to initial surgery or deferred surgery can help determine for which contexts patients still benefit from cytoreductive nephrectomy given the availability of the newer systemic therapies with bigger and more general survival impacts. Table 3[38,39] details trials evaluating the role of cytoreductive nephrectomy.

The CARMENA trial was an open-label randomized phase 3 trial in which patients with intermediate or poor risk International Metastatic RCC Database Consortium (IMDC) metastatic clear cell kidney cancer who were assessed otherwise to be suitable candidates both for cytoreductive nephrectomy and for sunitinib were randomized to receive either nephrectomy followed by sunitinib or to sunitinib alone, with the trial designed to test the non-inferiority of sunitinib alone. Notably, the trial could not complete the targeted accrual and several confounding events occurred: in the group assigned to nephrectomy, 7.1% of patients did not have the operation, 17.7% of patients in the group did not receive sunitinib; In the group assigned to receive sunitinib alone, 4.9% of patients never received sunitinib, and 17.0% nonetheless underwent a cytoreductive nephrectomy despite not being assigned to receive one. Patients assigned to receive sunitinib alone had a numerically longer median overall survival (18.4 months (95% CI 14.7–23.0)) than those in the group assigned to nephrectomy-then-sunitinib (13.9 months (95% CI 11.8 to 18.3)). For the statistical analysis, thus, the study showed that sunitinib alone was non-inferior to nephrectomy followed by sunitinib.[40]

There are several conjectures and concerns about the generalizations from CARMENA. For example, one is that the CARMENA trial's slow recruitment (450 of a target of 576 patients were recruited over eight years) suggests that patients with a lower metastatic burden were being treated with nephrectomy and diverted outside of the trial.[41] Along these lines is an analysis suggesting that CARMENA recruited patients had a higher number of metastatic sites as compared to patients in the National Cancer Data Base and with a higher proportion of patients having metastases to the lymph nodes, bone, and lung.[42] The fact that 17.0% of patients who were assigned to sunitinib alone nonetheless received a nephrectomy (often after some sunitinib treatment) also raises questions about the generalizability of the data beyond the question of an immediate nephrectomy ("now vs never" as compared to "now vs maybe-later"). Subgroup analyses showed that patients in the sunitinib plus cytoreductive nephrectomy arm with one site of metastatic disease lived significantly longer than those with two or more metastatic sites (median 23.2 vs 14.4 months; $p = 0.03$), and that patients with only one IMDC risk factor lived significantly longer than those with two or more such factors (31.4 vs 17.6 months; $p = 0.03$).[38] As such, one conjecture is that cytoreductive nephrectomy still has a potential role in patients with a limited burden of metastatic disease.[43]

Table 3 Selected Trials Evaluating the Role of Cytoreductive Nephrectomy

Study	Date of Publication	Key Eligibility	Number of Patients Randomized	Arm 1	Arm 2	Primary Outcome	Result
Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma	2018	Histologically confirmed, previously untreated metastatic clear cell kidney cancer with a resectable primary tumor	450 (original target was 576 patients)	Immediate nephrectomy; sunitinib (50 mg/day for 4 weeks followed by 2 weeks of rest) started 4–6 weeks after surgery	Sunitinib (50 mg/day for 4 weeks followed by 2 weeks of rest) alone	Overall Survival	13.9 months for patients receiving immediate nephrectomy and 18.4 months for patients receiving sunitinib alone Hazard Ratio 0.89 (95% Confidence Interval 0.71–1.10)
Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial	2019	Histologically confirmed, previously untreated metastatic clear cell kidney cancer with a resectable primary tumor	99 (original target was 458 patients)	Immediate nephrectomy, then sunitinib (50 mg/day for 4 weeks followed by 2 weeks of rest) started 4 weeks after surgery	Deferred nephrectomy with presurgical sunitinib (50 mg/day for 4 weeks followed by 2 weeks of rest); sunitinib then restarted 4 weeks after surgery	Intention-to-treat 28-week progression free survival (revised based on poor accrual)	42% for the immediate cytoreductive nephrectomy arm and 43% in the deferred cytoreductive nephrectomy arm 1-sided Fisher test, p=0.61

SURTIME was another trial which attempted to evaluate the role of cytoreductive nephrectomy in the VEGFR TKI era, enrolling patients with previously untreated metastatic clear cell kidney cancer with a resectable primary tumor. The trial randomized patients to either immediate cytoreductive nephrectomy followed by sunitinib or to 3 cycles (lasting 18 weeks) of sunitinib followed by cytoreductive nephrectomy, then followed by additional sunitinib therapy. Recruitment did not meet the planned goal, however, with only 99 of planned 458 patients enrolled after 5.7 years. The study's revised primary outcome (based on the very slow accrual rate) was to determine whether there was a 20% increase in the 28-week progression-free rate in the group receiving a delayed cytoreductive nephrectomy. These rates were ultimately similar between the two groups, with 42% of patients being free from progression in the group receiving an immediate cytoreductive nephrectomy and 43% in the group receiving a deferred cytoreductive nephrectomy ($p = 0.61$). Of note, of the 49 patients in the deferred cytoreductive nephrectomy arm, 14 were not recommended to proceed with nephrectomy due to disease progression per the protocol, but 6 patients nonetheless underwent this surgery off protocol, again demonstrating the difficulty of studying this question. Due to the issues mentioned above, it is unclear to what extent the results of this study can be generalized.[39]

The development of checkpoint-inhibitor-based therapy and doublet therapies with VEFR inhibitor and a checkpoint inhibitor (or dual checkpoint blockade) for the first-line treatment of metastatic clear cell kidney cancer also adds to the uncertainty around the role of cytoreductive nephrectomy as CARMENA was conducted before the implementation of these regimens, and sunitinib was the inferior arm in the VEGFR-combination contexts.

Two ongoing phase III trials seek to address this important question. The NORDIC-SUN trial seeks to evaluate the role of deferred cytoreductive nephrectomy in patients treated with either ipilimumab plus nivolumab or with a VEGFR TKI plus checkpoint inhibitor combination. Patients will be evaluated by a local multidisciplinary tumor board after three months of systemic therapy, and patients found suitable for surgery and who have no more than three IMDC risk factors will be randomized to surgery followed by additional systemic therapy versus additional systemic therapy alone. Patients not deemed eligible for randomization at three months will be re-evaluated via the same algorithm at six months, with the primary endpoint being overall survival.[44] The PROBE study will also seek to evaluate the addition of delayed cytoreductive nephrectomy to modern systemic therapy. Patients are started on a recommended doublet therapy and those patients without progressive disease at 9–12 weeks who are surgical candidates are randomized to cytoreductive nephrectomy plus continued systemic therapy or to continued systemic therapy alone, with the primary outcome again being overall survival.[44] These trials may add valuable knowledge regarding the potential benefit of cytoreductive nephrectomy in the setting of modern doublet therapies, but the impact of selective enrollment as well as treatment with cytoreductive nephrectomy outside of study assignment will need to be carefully evaluated.

Pending the results of the NORDIC-SUN and PROBE trials, our practice reflects a balanced approach to cytoreductive nephrectomy. While the CARMENA data must be seriously considered, questions regarding the effect of selective enrollment of patients, the fact that a proportion of patients did not proceed as initially randomized, and findings that patients with a lower burden of metastatic disease did quite well after cytoreductive nephrectomy should also be considered. As such, we often discuss these procedures in a multi-disciplinary manner with input from medical oncology and from urology, and more often offer them to patients with limited burdens of metastatic disease or who have had their disease effectively stabilized on systemic therapy, with some flexibility on timing of nephrectomy.

Conclusion

The role of cytoreductive nephrectomy in patients with metastatic disease, immunotherapy in the neoadjuvant and/or adjuvant settings, and the sequencing of these novel therapies in the metastatic setting continue to evolve. The NORDIC SUN and PROBE trials should help to provide additional data regarding the role of cytoreductive nephrectomy in the era of doublet systemic therapies. Similarly, TiNivo2 should add valuable phase III data on the role of doublet therapies in the post-immunotherapy setting. In addition, LITESPARK-005 has demonstrated the promise of belzutifan in the later line setting, and LITESPARK-022 may further evaluate the role of belzutifan in combination with VEGFR TKI targeted therapy. With KEYNOTE-564 having now demonstrated an overall survival benefit for adjuvant pembrolizumab, further evaluation is needed to assess the role of further immunotherapy in patients who subsequently recur, and particularly

whether the timing of such a recurrence (eg, whether recurring while still on adjuvant therapy versus years later) impacts the utility of further checkpoint inhibition.

While it may be convenient to declare kidney cancer a disease with generalizable treatment parameters, the reality is that incident populations have significant heterogeneity compared to trial populations. Treatments for patients with limited renal reserve, with CNS-pattern of spread, with very-long latency recurrence, with treatment of localized progression with local treatment (despite not changing systemic treatment), and pre-existing auto-immune diseases, among many comorbidities challenge the clinician to understand these clinical trials. And so, as for any oncologic setting, we apply the principles with clinical judgment which should not be replaced by a simple tabulation of trial outcomes. Finally, ongoing advances in our understanding of tumor biology and systemic therapy continue to inform drug development. For example, patients with tumors high in T-effector and cell-cycle transcription appear to benefit more from checkpoint inhibitor therapy, whereas tumors with mutations associated with high angiogenesis (PBRM1 and KDM5C) appear to respond more effectively to VEGFR TKI-based therapy.[45] As our understanding of the interaction between tumor biology and systemic therapy develops, this may further assist us in personalizing and advancing therapy for our patients.

Disclosure

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