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REVIEW

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# The emerging landscape of neo/adjuvant immunotherapy in renal cell carcinoma

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**ABSTRACT**

Adjuvant and neoadjuvant therapies that reduce the risk of renal cell carcinoma (RCC) recurrence remain an area of unmet need. Advances have been made in metastatic RCC recently by leveraging PD-1/PD-L1 immune checkpoint inhibitors (ICIs). These agents are currently being investigated in the adjuvant and neoadjuvant settings to determine if intervention early in the disease trajectory offers a clinically meaningful benefit. While a disease-free survival benefit has been demonstrated with pembrolizumab, results from other ICI studies have not been positive to date. More mature data from these studies are needed to determine whether there is a survival benefit to ICIs in the curative-intent setting. The success of ICIs has also ushered a new wave of studies combining ICIs with other agents such as targeted therapies and vaccines, which are in early stages of investigation. We review the current state of adjuvant/neoadjuvant therapy in RCC and highlight opportunities for ongoing study.

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## Introduction

Renal cell carcinoma (RCC) is the 14th most common cancer globally, with over 400,000 new diagnoses each year.[1] For patients who are fit for surgery, the standard of care for localized RCC is radical nephrectomy (RN) or partial nephrectomy (PN). Other options include active surveillance or ablative techniques for selected patients.[2] Despite the definitive surgical treatment, the recurrence rate of RCC at 5-years is significant, varying from 2.2% to 58.1% depending on risk factors such as tumor size, histology, and other clinical features.[3] Therefore, adjuvant and/or neoadjuvant treatment to reduce the risk of recurrence and improve survival remains an area of unmet clinical need.

RCCs have long been recognized as tumors that are sensitive to immune-based therapies. In part, this may be owing to significant infiltration of CD8+ T-lymphocytes and the high cytolytic activity.[4] Historically, immune-based therapies such as interleukin-2[5] and interferon-α[6] were the standard of care in metastatic RCC. However, these therapies had low response rates of only 10–20%, were poorly tolerated, and demonstrated limited benefit in the adjuvant setting.[7–10] In recent years, immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have made significant advances in the management of metastatic RCC.[11–15] Currently, the standard of care in metastatic RCC involves a combination of two ICIs,[12] or one ICI combined with a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).[11,13,14] The success of ICIs in the metastatic setting has generated immense interest in their perioperative application to reduce disease recurrence.

In this paper we aim to summarize the various prognostic models for recurrence in patients who have undergone nephrectomy, which may guide decision-making in patient selection for adjuvant and/or neoadjuvant therapy. We will review a brief historical background on prior adjuvant and neoadjuvant therapies, and then examine the current literature around ICIs and other immune-based therapies. Finally, challenges in the application of immunotherapy including patient selection, intensity of treatment, and incorporating adjuvant ICIs in our current treatment algorithm will be discussed.

## Prognostic models

The ability to accurately predict the individualized risk of cancer recurrence after definitive therapy is a key aspect of patient care. In resected RCC, prognostic models highlighting recurrence risk scores are essential tools to guide surveillance approaches for localized disease and to help patients make informed decisions about ongoing care. As the treatment landscape of RCC evolves toward using systemic therapies in the curative setting, prognostic models will become crucial in selecting patients who would benefit from perioperative treatments.

The TNM system has been a longstanding staging tool, however its ability to predict mortality from RCC after RN is limited.[16] Consequently, several validated prognostic models have been developed for localized RCC. The Stage, Size, Grade and Necrosis (SSIGN) Score was reported in 2002. A total of 1801 patients with unilateral clear cell RCC treated with RN between 1970 and 1998 were identified. In addition to the 1997 TNM stage, other pathologic factors (nuclear grade, necrosis and tumor size) were found to be significantly associated with cancer-specific survival.[16] The SSIGN score has been validated as a predictive tool for death among patients treated with contemporary RN and PN.[17]

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The UCLA Integrated Staging System (UISS) was developed in 2001, among a cohort of 661 patients undergoing PN or RN for RCC between 1989 and 1999. All histologic subtypes were included. The TNM stage, nuclear grade and Eastern Cooperative Oncology Group (ECOG) performance status were found to be predictive factors for survival and are used to stratify patients into five prognostic groups, ranging from favorable disease (UISS I) to unfavorable disease (UISS V).[18]

The Memorial Sloan Kettering Cancer Centre (MSKCC) developed a prognostic nomogram in 2001, that estimates the probability of disease recurrence at 5 years. The nomogram was validated among 601 patients who underwent RN or PN for unilateral, localized RCC of any histologic subtype. Patient symptoms, histology, tumor size and pathological stage were found to have a predictive value for disease recurrence.[19]

The Leibovich score was subsequently developed in 2003, with the main goal of predicting progression to metastatic disease after radical nephrectomy. The purpose was to create a tool for patient stratification for potential participation in adjuvant clinical trials. The model was validated against 1671 patients with clinically localized, unilateral clear cell RCC, who underwent RN between 1970 and 2000. Multivariate analysis showed that tumor stage, regional lymph node status, tumor size, nuclear grade and necrosis were associated with progression to metastatic disease.[20] The Leibovich scoring system was updated in 2018 to incorporate updates from the AJCC system and to provide specific scoring systems for different RCC histologic subtypes, predicting both progression-free and cancer-specific survival.[21]

Several predictive clinical variables have been integrated into the Karakiewicz postoperative nomogram, which was developed in 2007 among a cohort of 2530 patients who underwent RN or PN for renal cancer. A second cohort of 1377 patients was used for external validation. The nomogram combines TNM stage, tumor size, nuclear grade and symptoms at presentation to provide an estimation of RCC-specific survival at 10 years.[22] The same group developed a preoperative nomogram that also predicts cancer-specific survival among patients with both localized and metastatic disease, based on a number of clinicopathologic features, including age, gender, symptoms, tumor size, T-stage and presence of metastasis.[23]

Despite the availability of several prognostic models (Table 1), there is a lack of consensus on the optimal stratification approach for localized RCC. Current practice guidelines provide different recommendations on the clinical implementation of prognostic models. The European Association of Urology states that prognostic models are more accurate than TNM stage or grade alone for predicting oncological outcomes (level of evidence 3). The guideline panel provides a strong recommendation for the use of models, both in localized and metastatic disease, but does not provide directions on which specific model should be used.[24] A recent prospective validation study evaluating eight different RCC recurrence models showed a considerable decrease in the predictive ability of all models compared to previous retrospective validations.[25] Based on these results, the American Urological Association guideline panel created a system that stratifies patients into low, intermediate, high and very high-risk disease based on T and N staging, grading and pathologic features. The presence of a surgical positive margin, which is associated with an increased risk of local recurrence,[26] is also incorporated into this system, unlike other prognostic models.[27] Similarly, the Canadian Urological Association uses pathological staging to stratify patients into four groups, from low- to very high-risk disease, and provides a surveillance strategy for each group. Although other recognized prognostic factors, such as nuclear grade, ECOG performance status and presence

**Table 1.** Comparison of six prognostic models for localized RCC.

| Prognostic model | Year | *N* | Prognostic variables | Main eligibility criteria | Endpoint |
|---|---|---|---|---|---|
| UISS[18] | 2001 | 661 | • TNM<br>• Nuclear grade<br>• ECOG | Any histologic subtype, RN or PN | Overall survival |
| MSKCC nomogram[19] | 2001 | 601 | • Symptoms<br>• Histology<br>• Tumor size<br>• Pathological stage | Any histologic subtype, unilateral, localized disease, RN or PN. | Disease-free survival |
| SSIGN[17] | 2002 | 1801 | • TNM<br>• Tumor size<br>• Nuclear grade<br>• Necrosis | Unilateral clear cell RCC, RN | Cancer-specific survival |
| Leibovich[20] | 2003 | 1671 | • Tumor stage<br>• Regional lymph node status<br>• Tumor size<br>• Nuclear grade<br>• Necrosis | Clear cell RCC, unilateral, localized, RN | Metastases-free survival |
| Karakiewicz nomogram (preoperative)[23] | 2007 | 2530 | • TNM stage<br>• Tumor size<br>• Nuclear grade<br>• Symptoms | RCC, RN or PN | RCC-specific survival |
| Karakiewicz nomogram (postoperative)[22] | 2008 | 2474 | • Age<br>• Gender<br>• Symptoms<br>• Tumor size<br>• T stage<br>• Presence of metastasis | RCC, RN or PN | RCC-specific survival |

UISS = UCLA Integrated Staging System; MSKCC = Memorial Sloan Kettering Cancer Center; SSIGN = Stage, Size, Grade and Necrosis; RN = radical nephrectomy; PR = partial nephrectomy; RCC = renal cell carcinoma; TNM = tumor, node, metastasis.

of symptoms are not included in their stratification strategy, the Canadian panel states that some patients may benefit from more intensive surveillance based on the presence of these risk factors.[28]

The substantial variability among the performance of these prognostic models was recently shown in a head-to-head comparison of five prognostic models (UISS, Leibovich score 2003, Leibovich score 2018, VENUSS score and GRANT score). Additionally, the accuracy of all models differed according to histologic subgroup, highlighting histology as a key prognostic factor in RCC.[29]

Whether historical prognostic models can be applicable to contemporary patients remains an ongoing question. A recent prospective observational evaluation of the performance of the Leibovich score among a contemporary patient cohort in the UK found an improved rate of metastases-free survival (MFS) in the contemporary cohort among intermediate- and high-risk patients (5-year MFS 85% and 50% respectively) compared to the original cohort (74% and 31%), generating hypotheses regarding evolution of clinical practice and tumor biology.[30]

As data regarding the benefit of perioperative targeted and immune-based systemic therapies emerges, accurate and applicable prognostic models will become crucial tools in selecting patients who would benefit from neoadjuvant and adjuvant strategies. Several molecular and genomic factors have been identified as having prognostic value in localized RCC[31] and might be incorporated to clinicopathologic factors in novel prognostic models.

## Adjuvant therapies – a historical perspective

Most recurrences of RCC tend to occur within the first 2 years post-nephrectomy,[32] although late recurrences beyond 10 years can occur in about 6% of patients.[33] The aim of adjuvant therapy is to target residual microscopic disease after curative surgery and reduce recurrence risk. In contrast to advanced disease, a clinically meaningful benefit is more challenging to demonstrate in an adjuvant trial, as clinical events are fewer (i.e., a proportion of patients may be cured with surgery alone and never develop a recurrence), which would require trials with larger sample sizes and/or longer follow-up. As such, the gold standard outcome of overall survival (OS) can be difficult to demonstrate in adjuvant trials, and instead disease-free survival (DFS) is often used as a primary endpoint. In RCC, DFS has been demonstrated to moderately correlate with OS post-nephrectomy,[34,35] and has been used as the primary endpoint in past adjuvant trials. Whether this correlation holds in the domain of immunotherapy is part of ongoing study.

Cytokines such as interferon-α and interleukin-2 were some of the first successful systemic treatments in RCC. However, they have not been demonstrated to have a significant benefit in the adjuvant setting.[7,8,10] Combinations of interferon-α, interleukin-2, and 5-fluorouracil have also been studied with no DFS benefit.[36,37] Vaccines are another approach to immunotherapy, which have the potential to induce a tumor-specific, durable immune response.[38] Historically, irradiated autologous tumor cells and tumor-derived antigens have been studied in the adjuvant setting.[39,40] One phase III study using autologous renal tumor cell vaccine did demonstrate a statistically significant progression-free survival and OS benefit in the experimental group;[39] however, the two arms of this study were not balanced with respect to stage and prognostic scoring, and the positive results were not replicated in subsequent vaccine studies. To date, there is no effective adjuvant vaccine therapy in RCC.

Regarding VEGF-TKIs, the only agent to have demonstrated benefit in the adjuvant setting was sunitinib, which is approved by the US Food & Drug Administration in this setting.[41] The S-TRAC trial enrolled high-risk clear cell RCC patients based on the modified UISS criteria, and randomized patients to sunitinib or placebo post-nephrectomy for one year. The study demonstrated a median DFS of 6.8 years in the sunitinib group, and 5.6 years in the control group (HR = 0.76; 95% CI, 0.59 to 0.98), although no OS benefit was demonstrated in a subsequent updated analysis.[42,43] The success of sunitinib has not been replicated in subsequent studies of other VEGF TKIs in the adjuvant setting.[44–46] Given the absence of survival benefit and side effect profile of TKIs, their use in the adjuvant setting has not been widely adopted.

## Emerging data for adjuvant ICIs

Pembrolizumab (anti-PD-1 antibody) is the first ICI to have demonstrated a clinically meaningful DFS benefit in the adjuvant setting in KEYNOTE-564.[47,48] This study randomized 994 patients with histologically confirmed clear cell RCC post-nephrectomy to either 1 year of pembrolizumab every 3 weeks started within 12 weeks of surgery, or placebo. Patients included in this study were of intermediate-to-high risk, high-risk, or had resected synchronous or metachronous metastases within 12 months of the initial nephrectomy with no evidence of disease (M1 NED, Table 2). In the most recent 30-month update, the risk of recurrence or death was 37% lower in the pembrolizumab arm (HR 0.63, 95% CI 0.50–0.80). The estimated 24-month DFS rates were 78.3% vs 67.3% in the pembrolizumab and placebo arms, respectively.[49] In subgroup analyses, the DFS benefit was the greatest in the M1 NED patients (HR 0.28, 95% CI 0.12–0.66). OS data remains immature, but favors pembrolizumab with an estimated 24-month OS of 96.2% vs. 93.8%. The hazard ratio for death was 0.52 (23 vs 43 deaths in the pembrolizumab and placebo arms, respectively), although statistical significance has not yet been reached for OS and longer follow-up is required. With regards to adverse events (AEs), grade 3 or higher events were observed in 18.9% in the pembrolizumab arm, compared to 1.2% in placebo. The most common events were fatigue, diarrhea, rash/pruritus, and thyroid dysfunction. Treatment-related AEs led to therapy discontinuation in 18.2% of patients receiving pembrolizumab vs. 0.8% in the placebo arm. Based on the demonstrated DFS benefit, pembrolizumab was approved for use in the adjuvant setting by the US Food and Drug Administration in Nov 2021,[48] and the Canadian Agency for Drugs and Technologies in Health in Sept 2022.[53]

IMmotion 010 is a phase III study of adjuvant atezolizumab (anti-PD-L1 antibody) that included resected RCC with either clear cell and/or sarcomatoid component at increased risk of recurrence (Table 2).[50] Notably in this study, the definition of

**Table 2.** Summary of adjuvant and neoadjuvant immune checkpoint inhibitors in renal cell carcinoma.

| Trial and Intervention | Inclusion Criteria | Trial design/sample size | Primary Outcome |
|---|---|---|---|
| KEYNOTE 564<br><br>Pembrolizumab<br>200mg IV Q3W x 17 cycles | Resected RCC with negative margins, clear cell component on histology, and:<br>• Intermediate-to-high risk:<br>○ pT2 (grade 4 or sarcomatoid histology), N0, M0<br>○ pT3 (any grade), N0, M0<br>• High-risk:<br>○ pT4 (any grade), N0, M0<br>○ pTany, N+, M0<br>• M1 NED:<br>○ Solid, isolated, soft tissue metastases present at screening<br>○ M1 disease present in addition to primary tumor at diagnosis and metastases were completely resected at the time of nephrectomy or within 1 year after nephrectomy<br>○ Bone and brain metastases excluded | Two-arm, placebo-controlled RCT<br>Pembrolizumab: $n$ = 496<br>Placebo: $n$ = 498 | Median disease-free survival – not reached in either group at median follow up of 30 months<br>HR: 0.63; 95% CI 0.50–0.80[47,49] |
| IMmotion 010<br><br>Atezolizumab<br>1200mg IV Q3W x 16 cycles | Resected RCC with *either* clear cell or sarcomatoid histology and:<br>• Intermediate-to-high risk:<br>○ T2 (grade 4), N0, M0<br>○ T3a (grade 3/4), N0, M0<br>• High risk:<br>○ T3b/c or T4 (any grade), N0, M0<br>○ Tany N+ M0<br>• M1 NED:<br>○ Adrenal, lung, lymph node, or soft tissue metastases<br>○ Synchronous metastasectomy or metachronous metastasectomy ≥12 months after primary surgery<br>○ Absence of brain metastases | Two-arm, placebo-controlled RCT<br>Atezolizumab: $n$ = 390<br>Placebo: $n$ = 388 | Median invasive disease survival:<br>Atezolizumab: 47.2 mo<br>Placebo: 49.5 mo<br>(HR: 0.93; 95% CI: 0.76–1.15)[50] |
| Checkmate 914<br><br>Nivolumab<br>240 mg IV Q2W x 12 cycles<br>Ipilimumab<br>1mg/kg Q6W x 4 doses | Resected RCC with negative margins, predominantly clear cell histology and:<br>• pT2a (grade 3 or 4), N0, M0<br>• pT2b and above (any grade), N0, M0<br>• pTany N+ M0<br>• Excluded: any metastatic disease | 3-arm, placebo-controlled RCT<br>• Nivolumab + ipilimumab: $n$ = 405<br>• Placebo + placebo: $n$ = 411<br>• Nivolumab + placebo (ongoing arm) | Median disease-free survival (at median follow up time of 37.0 mo):<br>Nivolumab + ipilumab: NR<br>Placebo + placebo: 50.7 mo<br>(HR: 0.95; 95% CI: 0.71–1.19)[51]<br>Nivolumab + placebo: data pending |
| RAMPART<br><br>Durvalumab<br>1500mg IV q4wks x 13 cycles<br>Tremelimumab<br>75 mg IV x q 4 weeks x 2 cycles | Resected RCC of any histology except oncocytoma, collecting duct, medullary and transitional cell cancer, and:<br>• Leibovich score 3 to 11 (Variables: tumor stage, size > 10 cm, lymph node status, histologic grade, presence/absence of necrosis; see Table 2)<br>• Only resected ipsilateral adrenal metastasis included; all other metastatic disease excluded<br>• Patients with microscopic positive resection margins included if no evidence of macroscopic/metastatic disease | Randomized multi-arm multi-stage trial (3:2:2 allocation).<br>(A) Active monitoring<br>(B) Durvalumab<br>(C) Durva/tremelimumab<br>(D) Possible addition of a 4$^{th}$ arm (if standard of care changes)<br>Target accrual = 1750 | Estimated Primary completion July 1, 2024<br>Primary: DFS and OS |
| PROSPER<br><br>Nivolumab<br>480 mg IV q4wks, one neoadjuvant dose prior to surgery followed by 9 doses adjuvant | RCC of any histology, and high-risk criteria based on radiographic imaging of:<br>• T2 and greater, N0, M0<br>• Tany, N+, M0<br>• M1 NED: oligometastatic disease (≤3 metastases) resected within 12 weeks of nephrectomy (lung, brain, and bone metastases were excluded) | Unblinded randomized trial<br>Nivolumab (perioperative): $n$ = 404<br>Surgery alone: $n$ = 415 | Median recurrence free survival not reached in either group<br>HR: 0.97; 95% CI 0.74–1.28[52] |

NED = no evidence of disease; RCT = randomized control trial; HR = hazard ratio; CI = confidence interval.

M1 NED allowed resection of metachronous metastases beyond 12 months after the initial nephrectomy. Patients were randomized to either atezolizumab ($n$ = 390) or placebo ($n$ = 388) for 1 year. With a median follow up of 44.7 months, the study found no significant difference in the DFS rate between the atezolizumab and control arms (median DFS 57.2 vs. 49.5 months, HR 0.93, 95% CI 0.75–1.15). DFS at two years was 67.3% in the experimental arm and 65.0% control arm. The subgroup of M1 NED patients in this study did not demonstrate improved outcomes. The rate of AEs leading to treatment discontinuation was 11.5% vs. 2.6%.

The role of adjuvant dual ICIs with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) was evaluated by Part A of the CheckMate 914 trial.[51] This phase III trial randomized patients with completely resected RCC with predominantly clear cell histology and at increased risk of recurrence based on TNM stage and histologic grade (Table 2) to 6 months of combined ipilimumab/nivolumab versus placebo. Importantly, this study excluded patients with any metastatic disease. In the primary analysis with a median follow-up of 37 months, no statistical difference was observed in median DFS (not reached vs. 50.7 months, HR 0.92, 95% CI 0.71–1.19). The estimated 24-month

DFS rates were 76.4% in the experimental and 74% in the control arms. Subgroup analysis from this study demonstrated that those with sarcomatoid features had a significant benefit from ipilimumab/nivolumab, although this observation is limited by small subgroup size. The rate of AEs leading to treatment discontinuation was 29% in the experimental arm vs 1% in the control arm. Of note, 23% of patients in the experimental arm required treatment with corticosteroids to manage immune-related AEs. Checkmate-914 also has an ongoing Part B, which will examine the role of nivolumab monotherapy as adjuvant treatment. This will add to the body of evidence around single PD-1 inhibition in the adjuvant setting (NCT03138512).

RAMPART (NCT03288532) is an ongoing multi-arm study that randomizes patients at high risk of recurrence post-nephrectomy to durvalumab (anti-PD-L1) monotherapy, combined durvalumab and tremelimumab (anti-CTLA-4), or active monitoring.[54] The Leibovich Score (scores 3–11) was used to select for patients with elevated risk of recurrence, which could include patients with small tumors and aggressive features (e.g. T1 with higher histologic grade or presence of necrosis). The study also allowed for patients with resected ipsilateral adrenal metastases, but other metastatic disease was excluded. Primary completion of the study is expected in 2024, and it will contribute to our understanding of combined PD-L1/CTLA-4 inhibition in the adjuvant setting.

It is postulated that neoadjuvant use of ICIs can prime the immune system prior to surgery,[55] and has been demonstrated in phase II studies of several tumor sites to have significant partial or complete pathological response rates, including urothelial carcinoma,[56,57] non-small cell lung cancer,[58] melanoma,[59] and colon cancer.[60] In RCC, at present there is no established role for neoadjuvant immunotherapy.[27] PROSPER is a phase III trial of nivolumab in high-risk RCC that randomized patients to perioperative nivolumab (one neoadjuvant cycle and nine adjuvant cycles) or surgery alone followed by active surveillance.[52] High-risk patients were selected based on clinical T stage, lymph node involvement, and/or M1 NED status (Table 2). Radiological staging was used to enroll participants, possibly resulting in a lower risk population compared to adjuvant studies that incorporated histologic information in their risk stratification. An interim analysis for futility revealed no difference in recurrence-free survival and the trial was stopped early for inefficacy (HR 0.97, 95% CI 0.74–1.28). Importantly, approximately 80% of patients had clear cell RCC, while the remaining 20% represented other RCC histologies that may be less sensitive to immune-checkpoint blockade. With only 16 months of median follow-up, significant censoring was observed. As the initial analysis of this study is still ongoing, several questions remain regarding surgery and (neo)adjuvant therapy completion rates, treatment delays, and AEs.

## Combination approaches

Since the benefit of pembrolizumab was demonstrated in KEYNOTE-564, several agents are being studied in combination with pembrolizumab in the adjuvant/neoadjuvant settings.

Lenvatinib is a tyrosine kinase inhibitor that targets the VEGF pathway, which has been demonstrated in the CLEAR trial to have an OS and PFS benefit when used in combination with pembrolizumab in metastatic RCC.[13] In the non-metastatic setting, the rapid onset of action of TKIs (compared to ICIs) presents a case for neoadjuvant therapy to downstage tumors and to improve the resectability of locally advanced RCC. Currently, a phase II trial (NCT04393350) is underway to examine the combination of lenvatinib and pembrolizumab in the neoadjuvant setting in locally advanced, non-metastatic disease that is at high-risk of recurrence (T3+, any N+, or unresectable disease).[61] Another instance where neoadjuvant treatment has a theoretical benefit is in locally advanced RCC with inferior vena cava (IVC) thrombosis. These tumors can be surgically challenging to resect and present a risk of tumor emboli to the pulmonary circulation. A phase II trial (NCT05319015) will examine neoadjuvant lenvatinib and pembrolizumab in patients with IVC thrombosis, with primary outcomes of tumor progression and post-operative complication rates.[62]

Belzutifan is a novel oral agent that inhibits the hypoxia-inducible factor (HIF) 2α transcription factor. HIF-2α acts upstream to the expression of several genes implicated in oncogenesis, including VEGF, erythropoietin, cyclin D1, and glucose transporter 1.[63] Inhibition of this pathway with belzutifan has been demonstrated in a phase II trial to have activity against von Hippel-Lindau associated RCC.[64] Litespark-022 (NCT05239728) is a phase III trial that aims to examine the role of adjuvant belzultifan and pembrolizumab in patients with RCC at intermediate-high or high-risk of recurrence according to the KEYNOTE-564 criteria.[65] This study also allows patients with M1 NED, defined as synchronous or metachronous metastases resected within 2 years from nephrectomy. The experimental arm will receive belzutifan and pembrolizumab, while the placebo arm will receive pembrolizumab and an oral placebo for up to 54 weeks. The primary end point is DFS, with OS as secondary endpoint. Primary results are expected in 2027.

## Vaccines

While ICIs have demonstrated clinical efficacy in the adjuvant setting, they represent only one therapeutic approach in the cancer-immunity cycle through the enhancement of antigen recognition and cytotoxic effect of T-cells.[66] Vaccines are another approach to immune therapy that introduces tumor antigens that can activate the immune system. While vaccines derived from autologous tumor cells have been studied in the past, none have demonstrated clinical benefit in a phase III setting.[39,40] However, there is now immense interest in combining ICIs with vaccines to achieve a multi-pronged approach to immunotherapy. NeoVax is a personalized vaccine that uses synthetic neoantigens based on tumor DNA sequencing, combined with a toll-like receptor agonist (poly-ICLC) to stimulate the immune system.[67] It has been demonstrated in a Phase I study of high-risk melanoma patients to have a durable response post-resection.[68] NeoVax is currently being investigated in RCC combined with ipilimumab in a phase I trial (NCT02950766).[69]

## Discussion

Efficacious therapies that significantly decrease the risk of RCC recurrence after nephrectomy and improve survival remains an area of unmet need. The DFS benefit observed in KEYNOTE-564 establishes the use of ICIs in the adjuvant setting and has garnered it regulatory approvals. While future studies appear to build upon the pembrolizumab backbone, at present other similar ICI trials have not shown similar efficacious top line data. Therefore, this peri-operative space in RCC remains an area worthy of ongoing study.

Examination of the differences in trial design, patient selection, and backbone of treatment may provide explanations for differences in outcomes across currently available trials, and possibly help optimize future immunotherapy trial designs. The intensity (i.e., single vs dual) and duration of treatment with ICIs are important variables among the studies. In the adjuvant setting for RCC, the results from Checkmate 914 showed that a 6-month treatment with combined PD-1/CTLA-4 inhibition is associated with 29% treatment discontinuation in the experimental arm due to treatment-related AEs without any DFS benefit. On the other hand, a 12-month treatment with single PD-1/PD-L1 inhibition was associated with lower rates of grade 3 or higher AEs in KEYNOTE-564 and IMmotion 010 (18.9% and 11.5%, respectively). The results from the ongoing RAMPART study will help to understand whether the higher toxicity associated with addition of CTLA-4 inhibitors could have a significant clinical benefit to justify higher intensity of treatment.

The mechanism of action of ICIs may also play a role in the efficacy of adjuvant ICIs in RCC. One possible explanation for the difference in the primary outcome of DFS between KEYNOTE-564 and IMmotion 010 may be the molecular targets of pembrolizumab and atezolizumab (PD-1 vs PD-L1) , which could elicit distinct immune responses and interrupt different cancer-to-immune cell interfaces (i.e., PD-1/PD-L2 interaction). Although atezolizumab has shown some activity in metastatic RCC,[50] its efficacy appears less remarkable than its ICI counterparts and has not been proven to improve OS in the metastatic setting.

Patient selection is another area that requires further investigation. Despite several prognostic tools becoming available over the years (Table 1), concerns remain regarding their applicability in the contemporary immunotherapy era. The adjuvant ICI studies outlined here have been selected for high recurrence using tools that are primarily based on TNM staging, tumor grade and histology. However, as the control arms of these trials demonstrate, 65–75% of patients are disease free at the 24-month timepoint without adjuvant treatment.[49–51] The evidence from KEYNOTE-564 suggests M1 NED patients as one potential risk group that may derive the greatest benefit from adjuvant ICI therapy, with an HR of 0.28. It should be noted that in KEYNOTE-564, the M1 NED subgroup only included those who had metastatic disease at the time of screening and underwent a metastatectomy either at the time of, or within 12 months of initial nephrectomy. In contrast, IMmotion 010 employed a different criterion for M1 NED, which included patients who presented with resectable metastases either at the time of screening, or a recurrence beyond 12 months after the initial nephrectomy. The M1 NED group represented 13.9% of the total study population (compared to 5.8% in KEYNOTE-564), with the majority having metachronous metastases. A DFS benefit was not observed in the IMmotion 010 subgroup, which may reflect differences in tumor biology and a more indolent course in those with late metastases. This observation is limited by the small subgroup size in both studies.

Tumor histology could also play a role in patient selection. Sarcomatoid differentiation is known to be a poor prognostic feature in RCC,[70] and historically has had poor response to chemotherapy and TKIs.[71] However, subset analyses from metastatic RCC trials suggest that sarcomatoid RCC are responsive to ICIs.[72] Interpretation of neoadjuvant/adjuvant ICI in sarcomatoid RCC is limited by the small subgroup sizes, however in KEYNOTE-564 and IMmotion 010, there were trends toward improved DFS, and in Checkmate 914, the sarcomatoid subgroup had a substantial benefit from ICIs (HR = 0.29, 95% CI: 0.09–0.91).[47,50,51] Given the poor natural history and the positive response to ICIs in multiple trials, sarcomatoid histology would be one-factor clinicians should consider when offering adjuvant ICI. With respect to other non-clear cell histologies, RAMPART and PROSPER trials were designed with broader inclusion criteria for various RCC subtypes. Trials with inclusion of non-clear cell histologies may help inform the applicability of adjuvant strategies largely studied to date in clear cell RCC.[52,54] Improvements in patient selection using biomarkers that can identify patients at high-risk of recurrence and predict response to ICIs are needed.

The use of genomic expression profiles (GEPs) in predicting recurrence after nephrectomy is an active area of research. ClearCode34 is a validated prognostic tool for clear cell RCC, which stratifies patients into low-risk (ccA) and high-risk (ccB) categories based on the expression of 34 genes.[73,74] It has been demonstrated in retrospective datasets to be superior to the UISS and SSIGN clinical models at assessing risk of death from RCC. Rini et al. developed a “recurrence score” based on a 16-gene GEP to independently predict risk of recurrence after nephrectomy.[75] This study found the combination of the recurrence score and Leibovich score improved risk differentiation. Other peripheral blood biomarkers such as circulating tumor DNA, microRNA, and long non-coding RNA are also in early stages of investigation.[76,77] Further research into incorporating GEPs and biomarkers to improve patient selection using larger, prospective studies are needed to better tailor adjuvant therapy.

Predicting the benefit from ICIs may also improve patient selection. In many immunogenic tumors, PD-L1 and tumor mutational burden are predictive of response to ICIs. In RCC, however, the evidence is inconsistent. Analyses of metastatic trials demonstrate that RCCs respond to ICIs irrespective of PD-L1 expression levels, and that higher expression of PD-L1 may not correlate with improved outcomes uniformly.[78–81] Similarly, tumor mutational burden has not been demonstrated to be a predictive marker in RCC.[78,79,81] Retrospective analyses of metastatic ICI studies have identified GEPs that are predictive of response to TKIs and/or ICIs.[75–78–81–84] These have yet to be incorporated in the adjuvant setting.

At present, many jurisdictions have approved pembrolizumab for use in the adjuvant setting.[48,53,85] Although an OS benefit has not yet been established, adjuvant treatment has been shown to reduce the risk of recurrence. In a real-world setting, eligible patients should be made aware of the option for adjuvant pembrolizumab including the benefits, toxicities, and the need for longer term OS data. These discussions may also highlight ongoing trials to further study this space. Ultimately, care plans for adjuvant therapy should remain patient-centered, taking into consideration patients' values, goals, and comorbidities.

As adjuvant ICIs become part of routine clinical practice in RCC, one question that remains unanswered is whether patients with disease recurrence should be rechallenged with ICIs in the metastatic setting. Evidence in this area is mostly retrospective and has been mostly examined in melanoma and non-small cell lung cancer where ICIs have been standards of care for over a decade.[86,87] Ideally, prospective data would inform whether there is utility for ICI rechallenge, heretofore lacking in RCC. In this void, individualized decisions may take into consideration several factors. First, the timing of progression is important: whether it was during or after completion of adjuvant treatment, and if so time since last treatment with ICI. Secondly, the expected activity with combination approaches after adjuvant monotherapy should be considered. In the mRCC setting, salvage addition of CTLA-4 agents after progression on PD-1 therapy has shown significant activity.[88] Finally, the patient's performance status and prior immune-related toxicities need to be taken into consideration. We suggest that standard first-line ICI-based combinations could be offered to those who have a recurrence 6 months beyond completion of adjuvant immunotherapy. In contrast, in patients who recur during adjuvant ICI or within 6 months of completion, next line standard therapy with TKIs should be offered. Similar approaches have been described in the literature for RCC,[89] however will require contextualizing within jurisdictional drug approval bodies globally.

In summary, the current literature provides support for the use of pembrolizumab in the adjuvant setting post-nephrectomy for those at high risk of RCC recurrence based on tumor stage, grade, and histology. ICIs hold great promise in the adjuvant treatment of RCC both as monotherapy and in combination with other agents such as TKIs, HIF 2α inhibitors, and personalized vaccines. More mature OS data from completed and ongoing trials may help reassure routine clinical utility in most patients with resected RCC. Further research into risk assessment, GEPs as well as pathomics and radiomics may help better refine patient selection for peri-operative therapy. At present, an individualized approach that takes into consideration an assessment of disease recurrence risk, other comorbidities, and patient preferences would be important in determining candidacy for adjuvant ICIs.

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