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Treatment of Recurrent Metastatic Renal Cell Carcinoma After Adjuvant Immunotherapy

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ABSTRACT

The treatment of renal cell carcinoma (RCC) has evolved dramatically in the past two decades. For metastatic RCC (mRCC), first-line treatment currently consists of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI), Immune Checkpoint inhibitors (ICI), or combinations of the two. In localized RCC, a recent major advancement has been the approval of the ICI pembrolizumab for adjuvant treatment of patients with a high risk of recurrence after nephrectomy. Little is known, however, regarding the optimal treatment strategy for patients with progression of disease on adjuvant therapy or recurrence after completing adjuvant therapy. Trials to inform this topic are ongoing. In the absence of this prospective data, we provide recommendations for clinicians based on existing evidence in the form of three patient scenarios. For a patient who progresses on adjuvant ICI, we generally recommend treatment with single-agent VEGFR TKI. For a patient with metastatic recurrence after completing adjuvant pembrolizumab, treatment recommendations differ based on the time from the last ICI dose until recurrence given the persistent receptor occupancy of ICI even months after discontinuation. If recurrence occurs within 6 months of the last dose of ICI, we recommend single-agent VEGFR TKI. If recurrence occurs >12 months from the last dose of ICI, we recommend resumption of ICI in combination with VEGFR TKI or dual ICI therapy. The choice between these strategies should be based on validated risk stratification instruments, time from completion of therapy, and patient-specific factors. Patients who have a recurrence within 6-12 months provide the most challenging scenario, and we would generally recommend ICI in combination with VEGFR TKI in this setting. For patients who did not tolerate adjuvant ICI, a decision on treatment with combination ICI and VEGFR TKI versus single agent VEGFR TKI should depend on the severity of the immune-related adverse event(s) resulting in intolerance as well as the time from the last dose of therapy. Individual patient considerations must also always inform treatment decisions.

INTRODUCTION

Kidney cancer is diagnosed in more than 400,000 patients worldwide each year[1]. Among kidney cancers, greater than 90% are renal cell carcinomas (RCC), of which approximately 70% demonstrate clear cell histology[2]. Clear cell RCC accounts for the substantial majority of kidney cancer morbidity and mortality and thus has been the subject of most kidney cancer research. Clear cell RCC will be the focus of this review and designated as RCC. At the time of diagnosis, roughly 30% of patients with RCC will have advanced locoregional or metastatic disease, and up to 40% of patients initially presenting with locoregional disease will eventually develop metastases[3]. Fortunately, great progress has been made in the treatment of metastatic RCC (mRCC) over the past two decades. Median survival has increased from approximately 15 months in the early 2000s to greater than 4 years in recent trials[4,5].

The landscape of medical therapies for mRCC has evolved dramatically. Interferon (IFN) and interleukin-2 (IL-2) were introduced in the 1980s and 1990s[6,7] and

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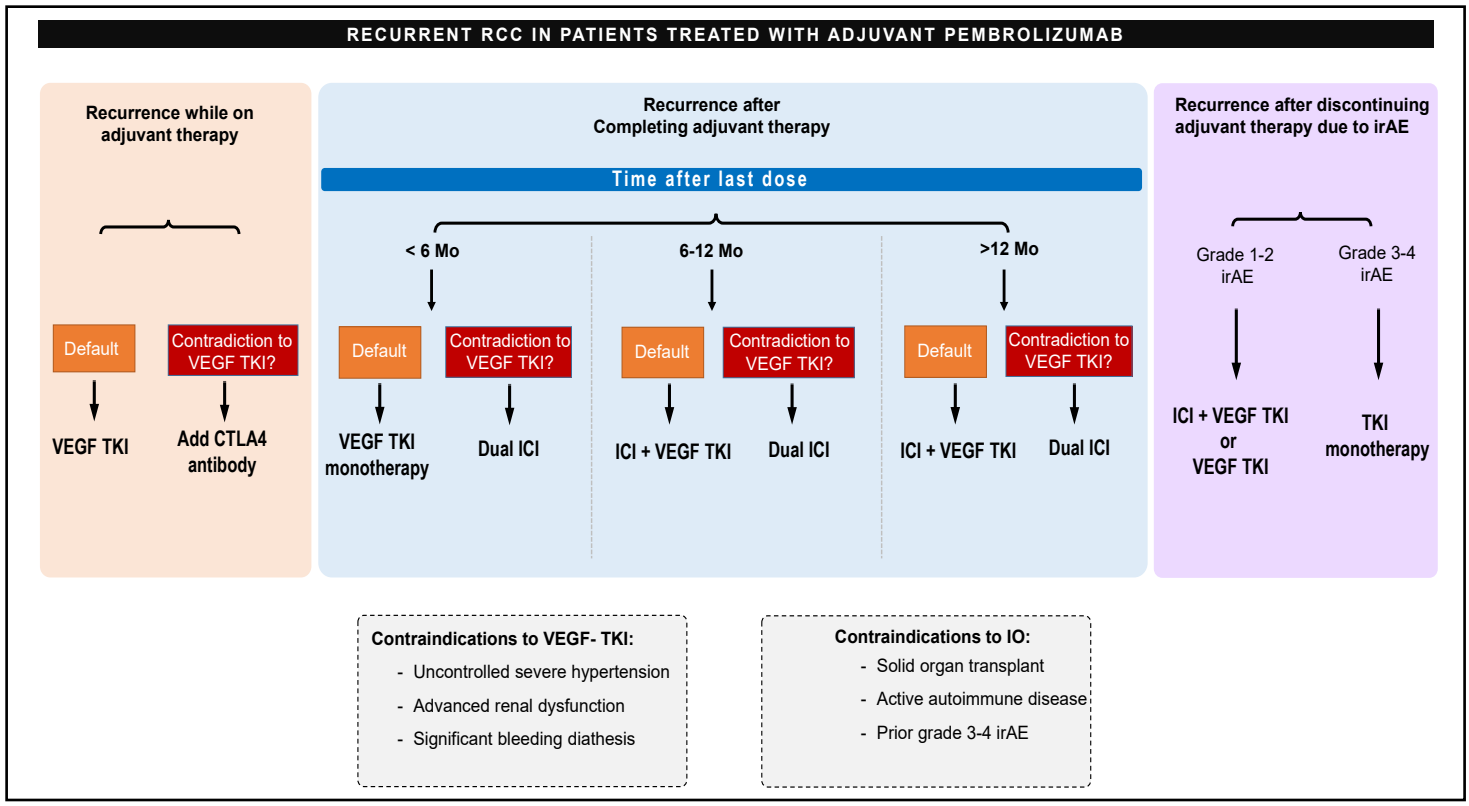

FIGURE 1. Proposed Treatment Algorithm of Metastatic Renal Cell Carcinoma Recurrence After Adjuvant Immunotherapy

remained the only proven systemic therapies for over 20 years. The VEGFR-TKI sunitinib was approved for advanced RCC in 2006[8] and revolutionized treatment. In the following years, six additional VEGFR TKIs were approved for mRCC. Agents from an additional drug class, mammalian target of rapamycin (mTOR) inhibitors, were also approved including temsirolimus[9] and everolimus[10]. Even more recently, ICIs have provided the next leap forward in mRCC. Nivolumab was the first ICI with demonstrated benefit in mRCC[11], and several subsequent single-agent ICI trials have also demonstrated efficacy. Multiple options now exist for first-line therapy in mRCC, most of which are combinations of ICI and VEGFR TKIs[12]. Important developments have also been made in surgical and ablative techniques for RCC and mRCC[13,14].

The most recent major advancement in the treatment of RCC has been the introduction of adjuvant ICI. The results of the KEYNOTE-564 trial, published in 2021, showed improved disease-free survival (DFS) in localized RCC patients treated with adjuvant pembrolizumab after nephrectomy[15]. While overall survival (OS) data are not mature, this practice is quickly becoming a standard of care. It remains unknown, however, how best to treat patients who progress on adjuvant therapy or recur after its completion. Trials that will inform management in this clinical scenario are underway (Table 1)[16-20]. We review the current evidence and propose a treatment algorithm (Figure 1) to guide clinicians in managing patients with mRCC with recurrence on or after adjuvant immunotherapy.

Adjuvant therapy for RCC

Surgical approaches including nephrectomy, partial nephrectomy, and ablation strategies are first line therapy for most patients with localized RCC[21]. Carefully selected patients with metastatic disease may even undergo resection of the primary tumor and concomitant metastasectomy to remove one or a limited number of metastases[22]. Unfortunately, greater than 35% of patients who undergo initial resection will have progression or recurrence[23]. Adjuvant treatment has been investigated extensively over the past 30 years with largely negative results. Multiple trials of adjuvant cytokines showed no benefit[24,25]. VEGFR TKIs have also been studied repeatedly, with 5 trials to date[26-30]. These have shown adjuvant VEGFR TKI therapy to be largely ineffective. While the S-TRAC trial comparing sunitinib to placebo did demonstrate a modest benefit in disease free survival (DFS), OS was unchanged and the treatment arm experienced greater toxicity. Furthermore, the ASSURE trial[26] and several other negative studies of adjuvant VEGFR TKIs were discordant with the S-TRAC results. Active surveillance, therefore, remained a standard of care after surgery, regardless of risk category.

KEYNOTE-564 was the first reported trial of ICI in the adjuvant setting for RCC. Accrual began in 2017 and results were published in 2021 with 24 months of follow up[15]. Inclusion criteria were similar to

	CONTACT-03	TiNivo-2	PDIGREE	RAMPART	Lite-Spark-011
Design	Phase III, open-label, randomized multicenter study	Phase III, open-label, randomized multicenter study	Phase III, adaptive, randomized, multicenter study	Phase III, open-label, randomized, multicenter study	Phase III, open-label, randomized multicenter study
Key Inclusion Criteria	Advanced or metastatic RCC with progression on or after ICI treatment	RCC with progression on or after ICI treatment	Intermediate or poor risk mRCC with no prior treatments	Locally advanced RCC after resection with no evidence of disease	Advanced RCC with progression on or after ICI treatment
Comparator Groups	Cabozantinib + atezolizumab vs cabozantinib alone	Tivozanib + nivolumab vs tivozanib alone	Starting treatment with ipilimumab + nivolumab, patients with CR receive nivolumab maintenance, patients with PD switch to cabozantinib, and patients without CR or PD are randomized to nivolumab vs nivolumab + cabozantinib	Active surveillance vs durvalumab vs durvalumab + tremelimumab	Pembrolizumab + lenvatinib + belzutifan vs pembrolizumab + quavonlimab + lenvatinib vs pembrolizumab+ lenvatinib
Primary Endpoints	PFS, OS	PFS	OS	OS. DFS	PFS, OS
Key Secondary Points	ORR, Duration of Response	OS, ORR, Duration of Response	PFS, CR, OR	n/a	ORR, Duration of Response
Expected Completion	12/11/2024	08/01/2025	09/15/2023	12/01/2024	10/29/2026

TABLE 1. Summary of Key Clinical Trials in the Management of Metastatic Renal Cell Carcinoma After Prior Therapy

other adjuvant trials, with eligible patients having undergone surgery (partial nephrectomy, nephrectomy, and/or metastasectomy) with negative margins but meeting investigator criteria for high risk of recurrence. This included patients who were diagnosed with tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph-node metastasis, or stage M1 (distant metastases). All patients were disease-free at the time of trial entry as assessed by site investigators. Patients were randomized to adjuvant pembrolizumab for 17 cycles (approximately 1 year) or placebo. The trial was positive, meeting the primary endpoint of improved DFS with a hazard ratio (HR) of 0.68, 95% confidence interval (CI) 0.53 – 0.87. At 24 months, 77.3% of patients in the pembrolizumab arm and 68.1% of the patients in the placebo arm were alive and recurrence free. The secondary endpoint of OS was also improved (HR 0.54, 95% CI 0.30 – 0.96), with 96.6% of patients in the pembrolizumab arm and 93.5% of patients in the placebo arm alive at 24 months. Grade 3 or higher adverse events occurred in 32.4% of patients in the pembrolizumab arm compared to 17.7% of patients in the placebo arm. There were no deaths attributable to pembrolizumab or placebo.

An additional 6 months of follow-up data for KEYNOTE-564 were presented in February 2022[31]. With a median follow-up of 30.1 months, DFS remained superior in the pembrolizumab group compared to placebo (HR 0.63, 95% CI 0.50 – 0.80). A trend toward OS benefit was maintained (HR 0.52, 95% CI 0.31 – 0.86) though statistical significance was not achieved. No new safety signals were observed. Adjuvant pembrolizumab therefore has become adopted as a standard of care in patients with RCC and increased risk of recurrence.

Notably, results of 3 different trials of adjuvant and perioperative ICI for RCC were published or presented in September 2022. The IMmotion010 trial[32] was a multicenter randomized study in which patients with increased risk of recurrence after nephrectomy were treated with atezolizumab or placebo for 1 year. The primary endpoint of increased DFS was not met (HR 0.93, 95% CI 0.75-1.15, p=0.50). The CheckMate 914 trial[33] compared adjuvant nivolumab plus ipilimumab to placebo and demonstrated no difference in the primary endpoint of DFS (HR 0.92, 95% CI 0.71-1.19, p=0.53). Lastly, the PROSPER trial compared a strategy of "perioperative" nivolumab, in which 1 dose was given prior to surgery and 9 doses were given after, to surgery alone. This open label study was stopped early due to futility, with no differences in recurrence free survival (HR 0.97, 95% CI 0.74-1.28) or OS (HR 1.48, 95% CI 0.89-2.48). Therefore, pembrolizumab remains the only proven ICI agent for adjuvant therapy.

Management of Patients with Recurrence: Existing Guidance

No consensus exists, however, regarding the optimal management of patients with recurrence during or after adjuvant ICI. This novel category of patients may be increasingly encountered by clinicians given the United States Food and Drug Administration (FDA) approval of adjuvant pembrolizumab in November of 2021[34] and ongoing trials that may expand the use of ICI in this setting[19] (19).

In the most recent guidelines from the National Comprehensive Cancer Network (NCCN), published in 2022[21], guidance is given for patients considered to have relapsed disease. However, this category is directed at patients who have progressed through first line therapy for mRCC. Given the novelty of adjuvant ICI, however, there is no data specific to patients with disease recurrence either on or after adjuvant therapy. Considerations include that adjuvant pembrolizumab is dosed for a fixed period of 1 year, not based on tolerability and clinical response as in metastatic disease, and that pembrolizumab may have a long period of receptor occupancy after discontinuation. Pharmacokinetic studies of nivolumab show that in a patient who receives at least 3 doses, the drug continues to occupy 40% of T cell PD-1 receptors for nearly 9 months[35]. Similar receptor occupancy data for pembrolizumab are not readily available, but we speculate that similar prolonged binding may occur given the similarity in their mechanisms, terminal half-life, and clearance[36]. Therefore, patients treated with pembrolizumab in the adjuvant setting may be managed differently based on the timing of their recurrence.

SCENARIO 1: Patients with Recurrence On Adjuvant Immunotherapy

For patients who have disease recurrence while receiving adjuvant ICI, we favor treatment with single agent VEGFR TKI. In the KEYNOTE-564 trial, approximately 15% of patients randomized to adjuvant therapy had recurrence during the 12 month period during which they were receiving pembrolizumab. While this scenario would appear to be relatively uncommon based on these data, clinicians may increasingly encounter such patients as use of adjuvant ICI expands and more variable populations are treated in real world settings.

Given the two mainstays of mRCC treatment are either targeting the immunogenic tumor microenvironment or angiogenesis, it is reasonable to target an alternative mechanism if patients were to progress while receiving ICI, as the ICI clearly was not controlling the disease. Prospective data supports the approach of using single agent VEGFR TKI after progressing with prior ICI. In a phase II single-arm study of axitinib for patients who had previously been treated with ICI, an overall response rate (ORR) of 38.7% was observed[37]. These were all partial responses. Among the 40 patients included in the trial, 63% had been most recently treated with nivolumab monotherapy. These patients differ from our proposed population, however, in that 71% had received two or more prior therapies before enrollment.

Additional prospective data demonstrating efficacy of VEGFR TKI after prior treatment with ICI can be found in subgroup analyses[38] of the METEOR trial[39], which randomized patients with advanced RCC after prior antiangiogenic therapy to cabozantinib vs everolimus. Among 18 patients who had also received anti-PD-1 or PD-L1 therapy and were subsequently treated with cabozantinib, an objective response was observed in 4 patients (22%). No responses were seen among the 14 patients with prior VEGFR TKI and ICI therapy who were randomized to everolimus.

Retrospective data also support that cabozantinib is effective in patients who have progressed after receiving ICI. In a retrospective analysis of 86 patients who were treated with cabozantinib monotherapy after progression on ICI[40], an ORR of 36% was observed. These were all partial responses. Of the patients included in the trial, 64% had been previously treated with ICI alone, while 36% had received combination therapy with ICI and either VEGFR TKI or another therapy. The median number of prior therapies in these patients was 2, with a range of 1-10.

Similar efficacy appears to be preserved across different agents in the VEGFR TKI class. A retrospective study of 70 patients who progressed after first-line ICI therapy included patients who were subsequently treated with axitinib, cabozantinib, pazopanib, or sunitinib[41]. An ORR of 41.2% was observed, with 1 complete response. These patients are similar to those currently being treated with adjuvant ICI in that their first systemic therapy is an ICI. Thirty-six percent of these patients, however received combination therapy with ICI + VEGFR-TKI.

There are also data to suggest that patients who receive a VEGFR TKI after progression on ICI may have better outcomes if not previously treated with a VEGFR TKI, which may be attributable to acquired TKI resistance. A retrospective analysis was conducted of 68 patients from clinical trials who received VEGFR TKI therapy after ICI with or without VEGFR TKI[42]. Patients who previously received a VEGFR TKI had an ORR of only 10% with VEGFR TKI rechallenge, while patients treated only with ICI had an ORR of 36%, a difference that was statistically

significant (P = 0.039). The insight from this study may allow for more optimistic interpretation of other data regarding patients treated with VEGFR TKI after ICI. Many of these patients had previously received a VEGFR TKI, and might have had a better response if previously treated with ICI alone, similar to the patients receiving adjuvant ICI.

It is unclear whether patients who have progressed on ICI would benefit from continued ICI in addition to VEGFR TKI. Based on pre-clinical studies, it is understood that VEGFR TKI therapy may reverse immunosuppression in the RCC tumor microenvironment, promoting an immune-permissive state and improving the efficacy of ICI[43]. Data from the phase 2 KEYNOTE-146 trial[44] show that 55.8% of patients previously treated with ICI responded to lenvatinib plus pembrolizumab, which is an impressive post-ICI ORR. However, 57% of patients had grade 3 or higher immune related adverse event (irAE). This knowledge raises the question of whether patients receiving VEGFR TKI therapy after progression on adjuvant pembrolizumab would still benefit from continuing ICI.

For patients with contraindications to VEGFR TKIs, the addition of an anti-CTLA-4 antibody to ICI can also be considered. In the TITAN-RCC trial[45], patients with intermediate and poor risk advanced RCC were initially treated with nivolumab, and those with early significant PD or non-responders at 16 weeks received "boost" cycles of nivolumab plus ipilimumab. Of 28 patients who received ipilimumab boosts for PD on first-line nivolumab, 3 (11%) had a PR and 8 (29%) achieved stable disease.

Additional insight will be gained from ongoing trials evaluating the safety and efficacy of ICI + VEGFR TKI in advanced RCC patients with progression on or after therapy containing ICI. CONTACT-03 is a randomized phase III study assessing cabozantinib plus atezolizumab versus cabozantinib monotherapy following progression on or after ICI in advanced RCC[16]. TiNivo-2 is a randomized phase III study comparing tivozanib plus nivolumab to tivozanib monotherapy in a similar patient population[17]. Estimated study completion dates are December, 2024 and August, 2025, respectively. Lastly, PDIGREE is an adaptive trial in which patients with intermediate or poor risk RCC will receive induction therapy with ipilimumab and nivolumab and if noted to have progressive disease after 3 months, will be switched to cabozantinib monotherapy. We eagerly await the results of these important trials, but until then, we recommend VEGFR TKI monotherapy for those who progress on ICI to avoid the known toxicity that comes with combination therapy in the setting of unknown benefit.

SCENARIO 2: Patients with Recurrence After Completion of Adjuvant ICI Therapy

In KEYNOTE-564, adjuvant pembrolizumab was given for a maximum of 1 year (17 cycles of doses every 3 weeks). In follow-up data published in September 2022, approximately 12% of patients who did not have recurrence while on adjuvant therapy went on to have recurrence in the next 18 months[46]. For patients that recur after the completion on adjuvant ICI therapy, we favor treatment selection based on the International Metastatic RCC Database Consortium (IMDC) risk score as outlined in the NCCN guidelines for first line treatment of mRCC as well as the time until recurrence.

In favorable risk disease, the NCCN guidelines currently list several combinations of ICI plus VEGFR TKI with category 1 recommendations (defined as being based on high level evidence with uniform consensus amongst committee members). Active surveillance can also be considered in select patients[47,48] as well as single agent TKI[8] for those with contraindications to ICI, such as uncontrolled autoimmune disease or solid organ transplant. In intermediate-to-high risk disease, dual ICI and combination ICI with VEGFR TKI are category 1 recommendations. Multi-disciplinary discussion of local treatment with repeat metastasectomy or radiation therapy can also be considered in select patients with oligometastatic disease.

Beyond IMDC risk stratification, clinicians may select the initial regimen based on the speed with which a response is needed, comorbid conditions, and toxicity profile, among other factors. For patients in whom a more rapid response is desired, such as those with impending visceral crisis or very high tumor burden, combination ICI with VEGFR TKI would be preferred over dual ICI given the generally accepted faster response observed with TKIs (49). For patients with recent hemorrhagic events, uncontrolled hypertension, or severe kidney disease, dual ICI may be favored over combination ICI with VEGFR TKI. Lastly, clinicians often prioritize the chance of a complete response and the potential of discontinuing therapy at some point in the future (with resulting improved quality of life), which may favor dual ICI therapy[50].

Another factor that will influence therapeutic decision making is the time from completion of therapy to metastatic recurrence. While the half-life of pembrolizumab has been reported at 12-26 days[35,51], indicating that most drug should be cleared within approximately 4 months, receptor occupancy data for the similar drug nivolumab suggests that PD-1/PD-L1 inhibitors may remain bound to their targets for considerably longer. In patients who received multiple doses, nivolumab appeared to occupy 70% of T-cell PD-1 receptors at 2 months, and

remained bound to 40% of receptors for nearly 9 months. No receptor occupancy was observed by 1 year after the last dose[35]. Similar receptor occupancy data for pembrolizumab is not readily available. It is also unknown to what degree receptor occupancy translates into clinical efficacy.

Furthermore, the duration of ongoing immune activation after exposure to pembrolizumab remains unknown. There have been rare reports of delayed immune related adverse events (DIRE) occurring after discontinuation of ICI, with a systematic review of such cases suggesting a median interval to diagnosis of 6 months after the last dose[52]. It is unclear whether the ICI was physiologically active at those times, or whether an autoimmune process had been initiated earlier in the treatment course. The overall absence of evidence regarding duration of ICI activity limits our recommendations to expert opinion. Based on existing data and clinical experience, we consider 12 months after the last dose to be a time point at which the ongoing effect of pembrolizumab is clinically insignificant. Therefore, in patients with recurrence 12 months or longer after completing adjuvant therapy, we recommend either ICI with VEGFR TKI or dual ICI therapy based on IMDC risk stratification and patient specific factors. For patients who have metastatic recurrence within the first 6 months of completing adjuvant therapy, we consider the patient to have recurred while checkpoint inhibition is ongoing and recommend VEGFR TKI monotherapy. For patients with recurrence 6-12 months after completing adjuvant therapy, it is unclear if the ICI remains active and thus, we generally recommend VEGFR TKI in combination with ICI, although TKI monotherapy or dual ICI could be considered based on patient specific factors. The results of CONTACT-03, TiNivo-2, and PDIGREE will further inform whether additional ICI with VEGFR TKI might benefit patients with early relapse after completing adjuvant therapy.

Although patients who have received adjuvant pembrolizumab have had exposure to the immune targeted approach, retrospective data indicates that treatment with dual ICI may still be effective in patients who have received prior ICI. Similar efficacy (ORR 20%) was observed in a retrospective study of 49 patients who received dual ICI after progression on prior ICI[53]. The time from last ICI treatment appeared to be longer in patients who responded to this "salvage" approach, which suggests a sensitization of tumor to ICI over time or may simply reflect less aggressive underlying disease. The applicability of efficacy data from these studies to the post-adjuvant setting, however, is limited by the heterogeneity of first line ICI therapies that patients received. A variety of anti-PD-1/PD-L1 antibodies were employed, and often in combination with anti-CLTA-4 antibodies or other targeted therapies.

Of note, an argument can be made for using single agent ICI at recurrence. A retrospective study evaluated the outcomes of 69 patients with mRCC who received at least 2 separate lines of ICI[54]. The ORR to a second line of ICI was 23%. Importantly, response rates did not appear to differ whether patients received second line therapy consisting of single agent ICI, dual ICI, or ICI + targeted therapy. Among the 15 patients who responded to second line therapy 7 (46%) received single agent ICI alone, compared to 5 (33%) who received dual ICI and 3 (30%) who received ICI + targeted therapy. While adverse effects were reported in total and not stratified according to the composition of second line therapy, this data suggests that rechallenge with single agent ICI may be reasonable from the perspectives of both efficacy and resource stewardship. However, this is a small study, and given the robust data for combination therapy in the first line treatment of mRCC, we still recommend combination therapy if possible based on patient factors.

SCENARIO 3: Patients Who Do Not Complete Adjuvant Immunotherapy Due to Toxicity

In KEYNOTE-564, 8.9% of patients randomized to adjuvant pembrolizumab did not complete the trial regimen, with adverse events cited as the most common reason for discontinuation (21.3%). For those who discontinue treatment and have subsequent metastatic recurrence, the decision on a treatment regimen should depend on the severity of the irAE in addition to time until recurrence, IMDC risk stratification, and patient specific factors. We agree with the NCCN guidelines regarding the management of immunotherapy-related toxicities[55]. In general, patients who have non-endocrine grade 3 or 4 irAEs should not be re-challenged with ICI and those who have return of toxicity upon ICI re-challenge should permanently discontinue ICI. In patients with grade 3 or 4 irAEs from adjuvant pembrolizumab, we favor treatment with single agent VEGFR TKI as in patients who progressed on adjuvant pembrolizumab.

For patients with contraindications to VEGFR TKIs, a retrospective study suggests that ICI rechallenge may be safe and reasonably efficacious. In 499 patients with advanced RCC who received ICI, 71% patients experienced an irAE. Of patients who were given ICI in their second line of therapy, only 45% experienced an irAE. Similarly, grade 3 or higher irAEs were observed in 26% and 16% of the patients during their first and second lines of ICI, respectively. Even patients who experience clinically significant irAEs may have a safe and efficacious ICI re-challenge therapies. Among 80 patients whose ICI treatment was interrupted due to an irAE, 36 (45%) were again

treated with ICI, and only 7 (19%) experiences a grade 3 or higher irAE (56). These data are biased in that fewer patients with irAEs leading to hospitalization or steroid treatment were later rechallenged with ICI. Among those who were retreated, however, ICI appeared to be moderately effective with an ORR of 34%.

Given the pharmacokinetics of pembrolizumab and these safety data, we would re-challenge patients with ICI if they recur 12 months or more after discontinuation. ICI plus VEGFR TKI as enumerated in the NCCN guidelines for first line treatment or mRCC would be favored, and VEGFR TKI monotherapy could also be considered. For patients with progression in less than 6 months after ICI discontinuation after an irAE, we would recommend treatment with VEGFR TKI monotherapy. For patients with recurrence between 6-12 months, the severity of the irAE, the IMDC risk, and patient specific factors would guide a more individualized approach.

CONCLUSION

With the FDA approval of pembrolizumab for adjuvant treatment of localized RCC with high recurrence risk, decision making surrounding treatment of metastatic recurrence is challenging.

In the absence of significant prospective data or treatment guidelines, we provide recommendations for clinicians based on existing evidence. In general, for patients who progress while on adjuvant ICI, we recommend treatment with single agent VEGFR TKI. For patients with recurrence after completing adjuvant pembrolizumab, we recommend resumption of ICI with either combination ICI and VEGFR TKI, or dual ICI based on IMDC risk, time from completion of therapy (<6, 6-12, or >12 months), and patient specific factors. For patients who did not tolerate adjuvant ICI, decision on treatment with combination ICI with VEGFR TKI versus single agent VEGFR TKI is dependent on the severity of the irAE and time from discontinuation of therapy. Results from ongoing clinical trials and future prospective clinical trials are necessary to determine the best treatment strategies for these patients.

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ONLINE CONTENT

Full online contents with additional information can be accessed at https://kidney-cancer-journal.com/KCJ20n4-r1.php

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