Clinical Roundtable Monograph

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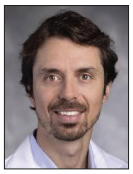
Optimizing Treatment Sequencing in Renal Cell Carcinoma in an Evolving Therapeutic Landscape

Moderator



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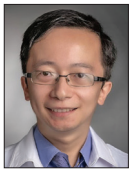

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Abstract: The management of renal cell carcinoma (RCC) continues to evolve as new combinations and therapeutic strategies are demonstrating benefit across lines of therapy. For patients with resectable clear cell RCC (ccRCC), options for adjuvant therapy now include pembrolizumab as a single agent or in combination with the hypoxia-inducible factor 2α (HIF-2α) inhibitor belzutifan. For patients with metastatic ccRCC, the preferred first-line treatment options are a combination of a tyrosine kinase inhibitor (TKI) and immunotherapy (IO) (axitinib + pembrolizumab, cabozantinib + nivolumab, or lenvatinib + pembrolizumab) or dual IO with ipilimumab + nivolumab. TKI-based therapy remains the standard treatment approach for patients with progression after IO. A single-agent TKI (cabozantinib, tivozanib, or axitinib) is an appropriate option for many patients with post-IO progression, although the more intensive combination of lenvatinib + everolimus may be considered for selected patients. Proactive management of toxicities is essential for maximizing outcomes with TKI-based therapy. Belzutifan has conventionally been used in the third-line setting, although the LITESPARK-011 trial demonstrated a progression-free survival improvement but no overall survival improvement with belzutifan + lenvatinib over single-agent cabozantinib in the post-IO setting; this regimen has been recently approved by the United States Food and Drug Administration. Novel HIF-2α inhibitors and other investigational strategies may further change the treatment landscape in the future.

Adjuvant RCC and Recurrence After Adjuvant Immunotherapy

Wenxin (Vincent) Xu, MD

For patients with resectable renal cell carcinoma (RCC) who have undergone primary treatment, the recommended approach to adjuvant therapy is based on disease histology and stage.[1] For the approximately 75% of patients who have clear cell RCC (ccRCC), options for adjuvant therapy include single-agent pembrolizumab and belzutifan + pembrolizumab; options for patients with non-clear cell histology include surveillance or a clinical trial. An overview of the pivotal trials leading to the current adjuvant regimens for ccRCC is shown in Table 1.

Evidence for Current Adjuvant Approaches

KEYNOTE-564

The role for pembrolizumab in the adjuvant treatment of patients with ccRCC was evaluated in the KEYNOTE-564 trial, which compared pembrolizumab 200 mg or placebo intravenously once every 3 weeks for 1 year in 994 patients with ccRCC at high risk for recurrence after nephrectomy. After a median follow-up of 24 months, pembrolizumab demonstrated significant improvements over placebo in the primary endpoint of disease-free survival (DFS) (24-month DFS, 77.3% vs 68.1%; hazard ratio [HR], 0.68; 95% CI, 0.53-0.87; *P*=.002).[2] The incidence of grade 3 or 4 treatment-related adverse events (AEs) was 18.6% with pembrolizumab and 1.2% with placebo. After a median follow-up of 57.2 months, pembrolizumab demonstrated a significant improvement in overall survival (OS) over placebo, with estimated 4-year OS rates of 91.2% and 86.0%, respectively (HR, 0.62; 95% CI, 0.44-0.87; *P*=.005).[3]

Based on the outcomes in KEYNOTE-564, adjuvant pembrolizumab is a standard of care option that should be discussed with all eligible patients. It is important to abide by the KEYNOTE-564 eligibility criteria, which specified patients with pathologic T2 grade 4 disease, node-positive disease, or T3 or higher disease of any grade, or with M1 resectable disease with no evidence of disease within 1 year of their original nephrectomy.

LITESPARK-022

A second standard option for adjuvant therapy approved by the United States Food and Drug Administration (FDA) on June 12, 2026, consisted of the hypoxia-inducible factor 2α (HIF-2α) inhibitor belzutifan in combination with pembrolizumab. The regimen was evaluated in the randomized, phase 3 LITESPARK-022 trial, which compared intravenous pembrolizumab 400 mg every 6 weeks (≤9 doses) + either daily oral belzutifan 120 mg or placebo for up to 1 year. After a median follow-up of 28.4 months, belzutifan + pembrolizumab demonstrated a significant DFS improvement over pembrolizumab + placebo, with 24-month DFS rates of 80.7% and 73.7%, respectively (HR, 0.72; 95% CI, 0.59-0.87; *P*<.001).[4] OS outcomes are not yet mature, and thus it is unknown whether the addition of belzutifan to pembrolizumab will provide an OS benefit. Rates of grade 3 or higher AEs were 52.1% with pembrolizumab + belzutifan and 30.2% with pembrolizumab + placebo.

Based on these outcomes, belzutifan + pembrolizumab is an option for patients with stage II disease with grade 4 tumors, or with stage III disease.[1]

Selecting Treatment Upon Recurrence

Early Recurrence

Recurrence after adjuvant pembrolizumab is common, reported

Table 1. Pivotal Trials of Approved Regimens for Adjuvant RCC

Trial	KEYNOTE-564[2,3]	LITESPARK-022[4]
Regimen	Pembrolizumab vs placebo	Belzutifan + pembrolizumab vs placebo + pembrolizumab
Patient population	ccRCC with increased risk of recurrence (N=994)	ccRCC with increased risk of recurrence (N=1841)
Efficacy vs control arm	**24-month DFS** 77.3% vs 68.1% (HR, 0.68; 95% CI, 0.53-0.87; *P*=.002) **48-month OS** 91.2% vs 86.0% (HR, 0.62; 95% CI, 0.44-0.87; *P*=.005)	**24-month DFS** 80.7% vs 73.7% (HR, 0.72; 95% CI, 0.59-0.87; *P*<.001) **24-month OS** 96.2% vs 95.7% (HR, 0.78; 95% CI, 0.51-1.19; *P*=.24)
Safety	**Serious AEs** 20.7% vs 11.5% **Grade 3/4 TRAEs** 18.6% vs 1.2%	**Grade ≥3 AEs** 52.1% vs 30.2%

AE, adverse event; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RCC, renal cell carcinoma; TRAEs, treatment-related adverse events.

in approximately 40% of patients in KEYNOTE-564 after 5 years.[5] The treatment strategy upon relapse varies based on the timing of recurrence, which reflects the likelihood of response to subsequent immune checkpoint blockade. Patients who develop recurrence during adjuvant pembrolizumab are considered early progressors, have resistance to programmed cell death protein 1 (PD-1) inhibitors, and are not likely to attain a response to subsequent PD-1/programmed death ligand 1 (PD-L1) blockade. This was demonstrated in two phase 3 trials—the TiNivo-2 trial and the CONTACT-03 trial, both of which showed that adding an immune checkpoint inhibitor (ICI) to a tyrosine kinase inhibitor (TKI) after PD-1 failure does not improve outcomes and can lead to increased toxicity.[6,7] The standard of care for these patients with early progression is a vascular endothelial growth factor receptor (VEGFR) TKI-based regimen.

Similarly, patients who develop disease progression within the first 6 months after completing adjuvant pembrolizumab also likely have PD-1 resistance, as the adjuvant PD-1 inhibitor did not prevent early recurrence. Most of these patients should also receive a TKI-based regimen in the first-line metastatic setting.

Late Recurrence

The treatment approach for patients with late recurrences—longer than 6 months after stopping pembrolizumab—is less clear. These patients may still be immune-responsive. In particular, for patients with a very late recurrence, considered a year or longer after adjuvant immunotherapy (IO), I tend to revert to my standard first-line PD-1-based combination therapies, including an IO/TKI combination or dual IO with ipilimumab and nivolumab. A single optimal sequence has not been identified.

Novel Strategies for Recurrence After Adjuvant Immunotherapy

There remains a need for more effective therapies for patients who develop RCC recurrence. The combination of lenvatinib + belzutifan has recently attained FDA approval based on progression-free survival (PFS) superiority over cabozantinib in the LITESPARK-011 trial, although OS did not reach statistical significance. Several additional phase 3 trials are evaluating novel regimens for patients with recurrence after prior IO. The PEAK-1 trial is comparing the investigational HIF-2α inhibitor casdatifan + cabozantinib against placebo + cabozantinib in patients with ccRCC with progression on or after anti-PD-1 or anti-PD-L1.[8] The LITESPARK-033 trial is comparing the multitargeted TKI zanzalintinib + belzutifan against single-agent cabozantinib in patients with advanced ccRCC who received adjuvant anti-PD-1 or anti-PD-L1 therapy after nephrectomy and developed recurrence on therapy or up to 24 months from the last dose.[9] The selection of single-agent cabozantinib as the control arm in these trials is notable as this remains a reasonable standard of care for these patients.

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First-Line Treatment of Advanced/Metastatic RCC

Ulka Vaishampayan, MD

Today the preferred first-line treatment options for patients with advanced ccRCC are a combination of a TKI and IO or dual IO (Figure 1).[1] Recommended IO/TKI regimens include axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab; the IO/IO option is ipilimumab + nivolumab. A fourth IO/TKI combination, axitinib + avelumab, is available but has not demonstrated an OS benefit and is not preferred. A single-agent TKI may be considered for selected patients.

Evidence for Current First-Line Options

An overview of the trials leading to the approval of current TKI/IO and IO/IO regimens for first-line advanced ccRCC is shown in Figure 2.[2-11]

The dual IO regimen of nivolumab + ipilimumab was approved based on results from CheckMate 214, which demonstrated significant improvements with nivolumab + ipilimumab compared with sunitinib in OS (HR, 0.68; *P*<.001) and objective response rate (ORR) in patients with intermediate-risk and poor-risk disease.[2] Grade 3 or 4 treatment-related AEs occurred in 46% of patients in the nivolumab + ipilimumab group compared with 63% in the sunitinib group; treatment-related AEs led to discontinuation in 22% and 12% of patients, respectively.[2]

The final trial update, after a median follow-up of 9.3 years, demonstrated a continued OS benefit and

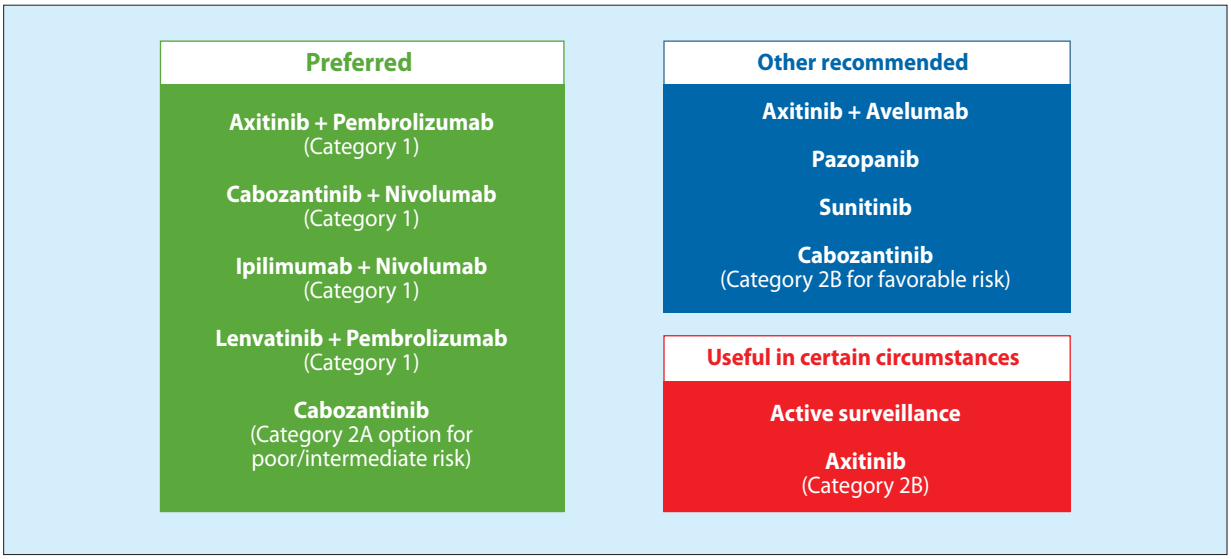

Figure 1. NCCN guideline-recommended first-line therapies for patients with ccRCC.[1]

ccRCC, clear cell renal cell carcinoma; NCCN, National Comprehensive Cancer Network.

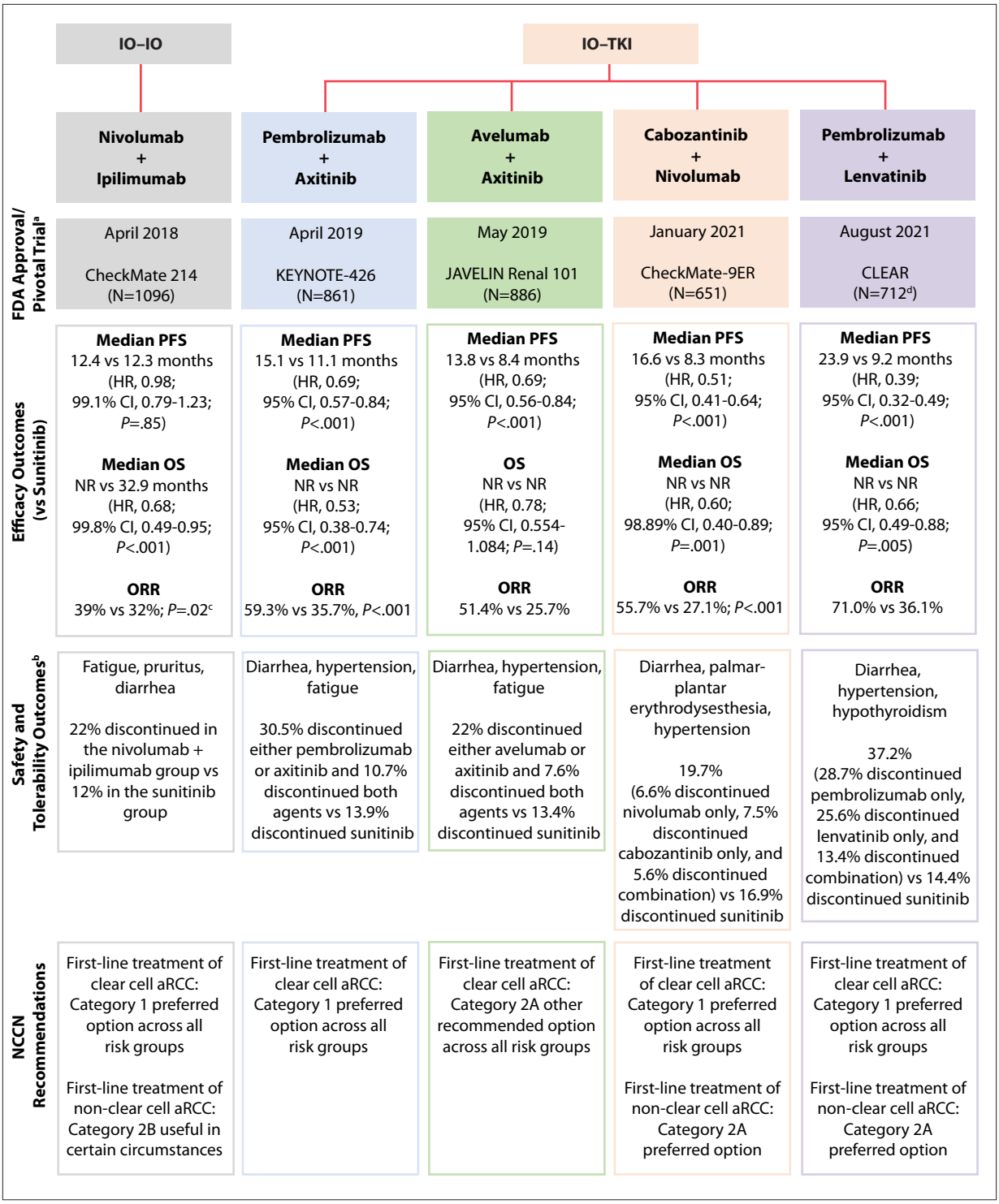

Figure 2. NCCN-preferred FDA-approved combination regimens in the first-line treatment of aRCC.[2-11]

[a]All patients had clear cell aRCC.

[b]Three most frequently reported adverse events in the treatment regimen arm and discontinuations owing to adverse reactions.

[c]Not significant per the prespecified .001 threshold.

[d]An additional 357 patients were assigned to a third arm and treated with everolimus + lenvatinib.

aRCC, advanced renal cell carcinoma; FDA, United States Food and Drug Administration; HR, hazard ratio; IO, immunotherapy; NCCN, National Comprehensive Cancer Network; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

durable responses with nivolumab + ipilimumab compared with sunitinib and an acceptable rate of grade 3 or 4 treatment-related AEs.[3] In a subgroup analysis by International Metastatic Renal Cell Carcinoma Data (IMDC) risk status, the statistically significant OS benefit with nivolumab + ipilimumab over sunitinib was observed in the intermediate/poor risk group (HR, 0.69; 95% CI, 0.59-0.81) but not in the favorable risk group (HR, 0.80; 95% CI, 0.59-1.09).

Regarding TKI/IO combinations, pembrolizumab + axitinib received FDA approval based on results from KEYNOTE-426, which reported significant improvements with pembrolizumab + axitinib vs sunitinib in OS (HR, 0.53; *P*<.0001), PFS (HR, 0.69; *P*<.001), and ORR.[4] The efficacy benefit with pembrolizumab + axitinib was observed across IMDC risk groups. Rates of grade 3 or higher AEs of any cause were 75.8% with pembrolizumab + axitinib and 70.6% with sunitinib.

Avelumab + axitinib received approval based on results of JAVELIN Renal 101, which demonstrated a significant benefit with avelumab + axitinib over sunitinib in PFS (HR, 0.69; *P*<.001) but not OS.[5]

Nivolumab + cabozantinib received approval based on results from CheckMate-9ER, which demonstrated improvements over sunitinib in OS (HR, 0.60; *P*=.001), PFS (HR, 0.51; *P*<.001), and ORR. Efficacy outcomes were consistent across subgroups. Grade 3 or higher AEs occurred in 75.3% of patients receiving nivolumab + cabozantinib and 70.6% of patients receiving sunitinib.[6]

Pembrolizumab + lenvatinib received approval based on the CLEAR trial, which showed significant improvements with pembrolizumab + lenvatinib over sunitinib in PFS (HR, 0.39; *P*<.001) and OS (HR, 0.66; *P*=.005).[7] Grade 3 or higher new or worsening AEs occurred in 82.4% and 71.8% of patients, respectively. Long-term follow-up from the IO/TKI trials showed sustained efficacy benefits with these regimens after at least 4 to 5 years.[8-11]

Selecting Among Available Options

Multiple factors are considered to select the most appropriate regimen for each patient, including disease-related factors (histology, risk based on the IMDC criteria, sites of metastases, and need for rapid response), treatment-related factors (prior treatment and toxicity profile), and patient-related factors (performance status, comorbidities, symptoms, and preferences).

In general, IO/TKI regimens are the preferred option for patients with significant symptoms, with metastases requiring a rapid response, or with risk factors that make them ineligible for ipilimumab + nivolumab. In contrast, ipilimumab + nivolumab would be preferred for eligible patients with sarcomatoid histology, which tends to be more sensitive to immune checkpoint therapy. The incorporation of IO with either approach (IO/TKI or IO/IO) has demonstrated the potential for long-term remission in some patients. An IO/TKI combination has the potential to provide both a rapid initial response followed by a long-term remission. However, if the patient does not attain a response or has later disease progression, second- and third-line options are more limited.

When considering the IO/TKI regimens, all 4 approved regimens are Category 1 preferred options in the National Comprehensive Cancer Network guidelines.[1] Clinical trial subgroup analyses have shown some differences between regimens based on disease risk. In the CLEAR trial, the OS benefit with lenvatinib + pembrolizumab over sunitinib was observed in the intermediate/poor risk group but not in the favorable-risk group.[11]

Toxicity is also a consideration with the IO/TKI regimens. TKIs generally share similar toxicity profiles, with hypertension, diarrhea, rash, and fatigue among the most frequent AEs.[4-7] However, the incidence of these AEs varies among the available agents. If significant toxicities develop during TKI therapy, these are generally rapidly reversible by holding the drug and they tend to be sensitive to dose reductions. With the current IO/TKI regimens, dose reductions are common and some permanent discontinuations should be expected.

Considerations for Patients With Synchronous Metastases

For patients with synchronous metastatic disease, typically with metastases detectable at diagnosis, available evidence suggests that patients should not proceed directly to nephrectomy. In the randomized, phase 3 CARMENA trial in patients with intermediate/poor-risk metastatic ccRCC at presentation who were candidates for nephrectomy, sunitinib alone was not inferior to nephrectomy followed by sunitinib.[12] Opting first for systemic therapy ensures patients will not miss out on systemic therapy as a result of going to surgery first.

Data from melanoma suggest that IO is more effective with the primary tumor in place.[13] Thus, unless a patient would have no clinical evidence of disease after nephrectomy, or has resectable metastases, the preferred approach is to start with systemic therapy, then assess whether to proceed to surgery. The SWOG 1931 (PROBE) trial is evaluating the role of radical nephrectomy after 12 to 15 weeks of upfront systemic therapy in patients with synchronous metastatic RCC.[14]

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Treatment After Progression and Emerging Sequencing Strategies

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Today, the preferred treatment options for patients with advanced RCC with progression after IO-containing initial therapy include a VEGF TKI, everolimus + lenvatinib, and, for patients who have already received a VEGF TKI, the HIF-2α inhibitor belzutifan (Figure 3).[1] Although other regimens may be considered in selected patients, these are the preferred approaches.

Evidence for Current Treatment Options

Axitinib demonstrated a significant PFS benefit over sorafenib (HR, 0.656; *P*<.0001) in the phase 3 AXIS trial; key grade 3 or higher AEs associated with axitinib included hypertension (17%), diarrhea (11%), and fatigue (10%).[2] Cabozantinib was evaluated in the phase 3 METEOR trial, demonstrating significant improvements over everolimus in OS (HR, 0.66; *P*=.00026), PFS (HR, 0.51; *P*<.0001), and ORR.[3] The most frequent grade 3 or 4 AEs reported with cabozantinib and everolimus, respectively, were hypertension (15% vs 4%), diarrhea (13% vs 2%), fatigue (11% vs 7%), palmar-plantar erythrodysesthesia syndrome (8% vs 1%), and anemia (6% vs 17%).

Lenvatinib + everolimus was evaluated in the phase 2 Study 205, demonstrating a PFS improvement over everolimus alone (HR, 0.40; *P*=.0005) but not over lenvatinib alone.[4] The subsequent Study 218 confirmed that the approved starting dose of lenvatinib (18 mg) is more effective than a lower starting dose.[5]

The other single-agent TKI option in previously treated RCC is tivozanib, which demonstrated a significant PFS benefit over sorafenib (HR, 0.73; *P*=.016) in the phase 3 TIVO-3 trial; the most common grade 3 or 4 treatment-related AE was hypertension, reported in 20% and 14% of patients, respectively.[6]

The next 2 trials included patients previously treated with an IO. The phase 3 LITESPARK-005 trial compared the HIF-2α inhibitor belzutifan against everolimus in patients previously treated with IO and antiangiogenic therapy (Table 2).[7] Belzutifan provided significant improvements over everolimus in PFS and ORR. Grade 3 or higher AEs of any cause occurred in 61.8% of patients receiving belzutifan (3.5% grade 5) and 62.5% of patients receiving everolimus (5.3% grade 5).

More recently, the randomized, phase 2 LenCabo trial compared lenvatinib + everolimus against single-agent cabozantinib in 86 patients with metastatic ccRCC with progression on a prior PD-1 inhibitor.[8] Lenvatinib + everolimus was associated with a significant improvement in PFS over cabozantinib (HR, 0.51; *P*=.02); discontinuation rates owing to toxicity were 20% and 10.9%, respectively.

Treatment Selection Considerations

Factors that influence the treatment decision in previously treated advanced RCC include previous regimens used and the resulting type and duration of benefit, prior regimen tolerability, disease tempo, tumor burden, and sites of disease, plus patient-related factors, including comorbidities and treatment goals.

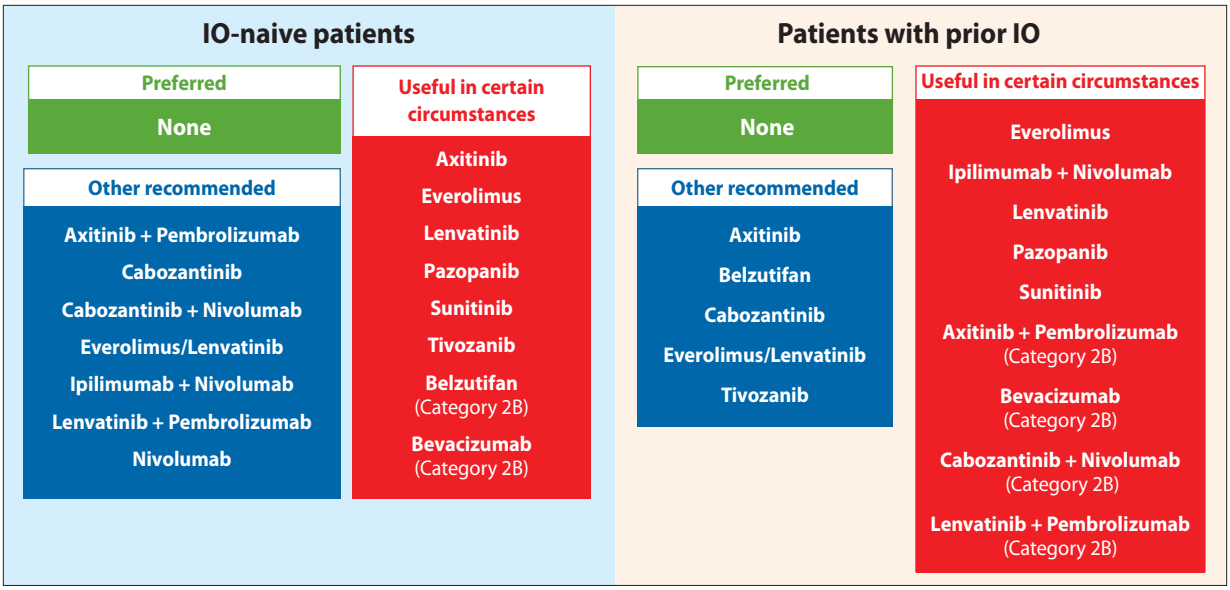

Figure 3. NCCN guideline-recommended therapies for second-line and later treatment in patients with ccRCC.[1]

IO, immunotherapy; NCCN, National Comprehensive Cancer Network; ccRCC, clear cell renal cell carcinoma.

VEGF-based therapy remains the backbone after IO; cabozantinib is an appropriate option for many patients. Tivozanib may be considered an alternative for patients with frailty in whom toxicity is a concern. On the other hand, the more intensive combination regimen of lenvatinib + everolimus may be considered for patients who are particularly fit and for whom a greater treatment response is the primary goal and patients are willing to risk greater toxicity.

Belzutifan has conventionally been used in the third-line setting; however, as evidence continues to evolve, the role of belzutifan may move earlier in some patients. Novel approaches are being evaluated in clinical trials that will hopefully continue to provide additional options for patients with previously treated ccRCC, in particular for those who have already received both an IO and a TKI.

Lack of Benefit With Immunotherapy Retreatment

Two randomized, phase 3 trials evaluated the role of IO retreatment in patients with metastatic RCC with progression after IO therapy. However, neither the TiNivo-2 study evaluating tivozanib + nivolumab nor the CONTACT-03 trial evaluating atezolizumab + cabozantinib found an improvement in PFS with the addition of IO to a TKI in patients with prior IO use.[9,10] Moreover, in the OMNIVORE trial, salvage ipilimumab in patients without a response to nivolumab also demonstrated limited benefit.[11] Thus this approach is not routinely recommended.

Emerging Strategies

Clinical trials continue to evaluate new combinations and approaches to improve outcomes for patients with metastatic RCC. Recently, findings were reported from the randomized, phase 3 LITESPARK-011 trial, which compared belzutifan + lenvatinib against single-agent cabozantinib in patients with advanced ccRCC with progression after IO with or without VEGFR TKIs (Table 2).[12] After a median follow-up of 29 months, belzutifan + lenvatinib was associated with a significant improvement over cabozantinib in PFS (median, 14.8 vs 10.7 months; HR, 0.70; 95% CI, 0.59-0.84; P<.0001). No difference in OS was noted. The most common grade 3 or higher treatment-emergent AEs were hypertension, reported in 31% of patients receiving belzutifan + lenvatinib and 29% of patients receiving cabozantinib. Fatal treatment-related AEs occurred in 2 patients in the belzutifan + lenvatinib group and 1 patient in the cabozantinib group. Recently approved by the FDA, this regimen could provide a new option for patients in the post-IO setting.

Novel HIF-2α inhibitors are also under study; the phase 3 PEAK-1 trial is evaluating the novel HIF-2a inhibitor casdatifan + cabozantinib in patients with advanced ccRCC post-IO treatment.[13]

More investigational strategies, such as bispecific antibodies and chimeric antigen receptor T-cell therapy, are also being explored. Research is also underway evaluating biomarker-driven approaches to further individualize RCC treatment selection.[14]

Table 2. Overview of the Phase 3 LITESPARK-011 Trial of Belzutifan + Lenvatinib vs Cabozantinib in Previously Treated aRCC[4]

Trial design	Phase 3 open-label, randomized trial
Patient population	Adults with advanced unresectable, locally advanced, or metastatic ccRCC with progression following anti-PD-1 or anti-PD-L1 therapy with or without previous VEGFR TKIs (N=747)
Treatment arms	Belzutifan 120 mg + lenvatinib 20 mg once daily (n=371) vs cabozantinib 60 mg orally once daily (n=376)
Efficacy outcomes	Median PFS: 14.8 vs 10.7 months; HR, 0.70; 95% CI, 0.59-0.84; *P*<.0001 Median OS: 34.9 vs 27.6 months; HR, 0.85; 95% CI, 0.68-1.05; *P*=.061
Safety outcomes	Grade ≥3 TEAEs: 84% vs 83% Most common grade ≥3 TEAE: hypertension (31% vs 29%)

aRCC, advanced renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

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Practical Approach to Optimizing Treatment Sequencing in RCC: Q&A

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H&O How does recurrence during vs after adjuvant pembrolizumab affect treatment selection?

UV This is an evidence-free zone. In the clinic, I have tended to use a single-agent TKI for patients who have progressed through pembrolizumab. If it has been at least 6 months since adjuvant pembrolizumab, we may rechallenge with an IO, depending on the sites of metastases and spread. With the FDA approval of adjuvant pembrolizumab + belzutifan, I think I would use a similar principle. I would definitely consider using cabozantinib or lenvatinib in that setting and I would consider an IO and/or belzutifan rechallenge if it has been at least 6 months.

PCB For recurrence during or shortly after adjuvant

pembrolizumab, I generally favor a VEGF TKI–based approach because the disease is behaving as IO-refractory. For later recurrence—particularly after 1 to 2 years off therapy—IO rechallenge may be reasonable in selected patients, although prospective evidence is limited. Local therapy should also be considered for oligorecurrent disease.

WX Patients with recurrence during adjuvant pembrolizumab are clearly not attaining a response to PD-1–based IO and should generally not be receiving further PD-1 or PD-L1 immune checkpoint inhibitors, given their lack of benefit.

H&O How do we choose among IO/IO and the different IO/TKI combinations in first line?

WX This is a difficult question, and it's always a challenging conversation for a patient who is starting initial treatment for metastatic RCC. These combinations are inherently different, and the best choice depends on the patient's treatment goals. Patients with symptomatic or high-risk metastases need a high immediate response rate and should receive IO/TKI combinations. The disadvantage for IO/TKI combinations is that patients generally stay on the TKI long-term, and toxicities can affect quality of life. Patients who are asymptomatic or who are perhaps younger and want a chance of durable remission in exchange for accepting a lower ORR are good candidates for combination IO with nivolumab + ipilimumab, which has some chance of prolonged disease control even after treatment is stopped.

UV I would also lean toward the IO/TKI regimen in highly symptomatic patients. I would prefer to stay away from IO/IO in patients with autoimmune diseases, whereas I would lean more toward IO/IO in sarcomatoid RCC. The IO/TKI and IO/IO approaches have not been compared head-to-head, and either is a reasonable option for patients who are otherwise healthy with a good performance status who can tolerate them. We also consider the long-term goals of the patient. CheckMate 214 was started before the IO/TKI combination studies and has the longest follow-up; the over 30% long-term remission rate at 8 and 9 years is definitely attractive.

PCB The choice between IO/IO and IO/TKI is driven by disease biology, the need for rapid disease control, comorbidities, and the patient's treatment goals. I tend to favor IO/TKI for symptomatic or high-burden disease in which an early response is important, whereas nivolumab + ipilimumab may be attractive for selected patients seeking the possibility of durable treatment-free control. Among the IO/TKI regimens, the options are more similar than different. Familiarity with the selected TKI and proactive dose management are critical.

H&O After progression on an IO/TKI, what should come next?

WX The current standard of care in the second-line setting after an IO/TKI is TKI-based therapy. Several TKIs have shown activity after a prior TKI, including cabozantinib, as demonstrated in several trials, including CONTACT-03. Lenvatinib, tivozanib, and axitinib, to some extent, also demonstrate activity in this setting. Based on LITESPARK-011, lenvatinib + belzutifan (which showed PFS benefit over cabozantinib) has received FDA approval. This is an especially good option for patients with rapid progression, who benefit from the higher response rate seen with combination therapy.

PCB After progression on IO/TKI, I generally use another TKI-based strategy. Cabozantinib is often my preferred option if it was not used in the first-line setting. Other options include lenvatinib + everolimus, tivozanib, and belzutifan. The choice depends on the prior TKI, disease tempo, need for response, comorbidities, and previous toxicities.

UV Regarding LITESPARK-011, a consideration with lenvatinib + belzutifan is the potential for increased toxicity. Although these agents have non-overlapping toxicities and the combination was generally well tolerated, the added toxicity of hypoxia and anemia are not trivial.

H&O Is there still a role for IO rechallenge?

UV There is no role for IO rechallenge at present, given the results of the TiNivo-2 and CONTACT-03 trials.

PCB Although there is no role for routine rechallenge, it could have a potential role for selected patients with a long treatment-free interval after prior IO.

WX Potentially; I may also consider rechallenge in patients who have had a long period off of IO, especially if they had an excellent initial response.

H&O Where do cabozantinib and HIF-2α–based approaches fit in the evolving sequence?

WX Both cabozantinib and HIF-2α inhibitors clearly have activity in the refractory RCC setting. The side effect profiles for these drugs are quite different. Cabozantinib has classic TKI toxicities, including hypertension, diarrhea, hand-foot syndrome, and mucositis, whereas belzutifan is associated with fatigue, anemia, and hypoxia. Oftentimes, it comes down to a conversation with the patient as to what their previous toxicities were and what toxicities they can tolerate moving forward. For someone who needs a break from the prior TKI, belzutifan can be a good option owing to the non-overlapping toxicity. However, I would note that belzutifan monotherapy has

a lower overall response rate when used as monotherapy compared with TKIs such as cabozantinib.

UV I would be a little hesitant with belzutifan in patients with less pulmonary reserve because of the hypoxia and anemia. Looking ahead, if the HIF-2α inhibitor goes into the adjuvant setting and along with pembrolizumab, then we may be using cabozantinib as our frontline TKI. The other FDA-approved options are tivozanib and lenvatinib + everolimus.

PCB Cabozantinib remains a standard post-IO option, particularly for patients who need disease control across multiple sites. Belzutifan offers a different mechanism and toxicity profile and may be attractive for patients who need a break from VEGF TKI–related toxicity, although anemia and hypoxia require careful monitoring. The use of recently approved lenvatinib + belzutifan will need to be individualized according to disease tempo, prior therapy, and tolerance for combination treatment.

H&O How do you optimize cabozantinib dosing and toxicity management in clinical practice?

UV The best approach is to anticipate toxicities and educate patients and caregivers regarding recognizing toxicities, bringing them to the attention of providers, and rapid appropriate management. It has to be a multidisciplinary team effort. You need nurses and pharmacists who are well-trained on what to expect, and can educate patients and caregivers, monitor closely for toxicities, and manage toxicities aggressively if they develop. This includes monitoring blood pressure and adjusting medications accordingly and acting quickly at the first signs of rare toxicities such as thromboembolic events or hand-foot syndrome. The sooner you can hold the drug for significant toxicities and start supportive treatment, the better. Then, depending on how they are doing, adjust the dose or restart.

PCB I emphasize education before treatment and early follow-up after cabozantinib is started. Blood pressure, diarrhea, mucositis, hand-foot syndrome, fatigue, and weight should be monitored closely. Short treatment interruptions and stepwise dose reductions are often more effective than allowing toxicity to accumulate. The goal is sustainable drug exposure over time—not maintaining the starting dose at all costs.

H&O What emerging strategies are most likely to change our sequencing approach?

WX A key question is how widely HIF-2α inhibitors will be adopted in the adjuvant setting, now that belzutifan is approved in combination with adjuvant pembrolizumab. Patients who have been exposed to belzutifan in the adjuvant setting may not have as much benefit from it in the metastatic setting. Ongoing trials will shed light on what it means to be previously exposed, and what time interval with HIF-2α inhibitors constitutes a reasonable time interval off treatment for a patient to be rechallenged. The same is true still for IO, and this will continue to be an evolving field with emerging IO and novel checkpoint options.

UV If the HIF-2α goes into the adjuvant setting, and along with pembrolizumab, then we may be potentially using cabozantinib as our frontline TKI.

PCB Looking further ahead, another strategy being evaluated in clinical trials involves modulation of the gut microbiome, which has been shown to modulate responses to IO. The bifidogenic live bacterial product CBM588 has been evaluated in early trials in combination with both nivolumab + ipilimumab and with cabozantinib + nivolumab. The phase 2 TACITO trial evaluated the potential benefit of adding fecal microbiota transplantation from donor patients with a complete response to IO to first-line treatment with pembrolizumab + axitinib. Although the trial did not meet its PFS endpoint, the strategy appeared to have potential efficacy.

Disclosures

Dr Barata has received fees from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Caris Life Sciences, Dendreon, Eisai, EMD Serono, ESSA Pharma, Exelixis, Guardant Health, Ipsen, Janssen, Merck, Merus, Myovant, Novartis, OncLive, Pfizer, Seattle Genetics, Targeted Oncology, and UroToday; and has share options in Luminate Medical.

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