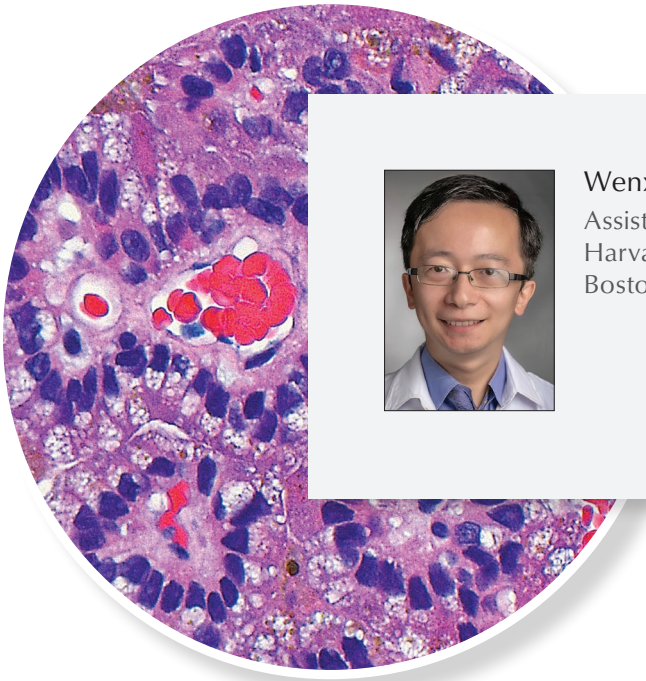
Case Study Series

Clinical Advances in Hematology & Oncology November 2026

Therapeutic Approaches in aRCC: Focus on Patient Selection for IO–IO vs IO–TKI



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Therapeutic Approaches in aRCC: Focus on Patient Selection for IO–IO vs IO–TKI

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In the Clinic . . .

Patient 1: Metastatic Recurrence 2 Years After Completing Adjuvant Pembrolizumab

DK is a 63-year-old man diagnosed with stage II clear cell renal cell carcinoma (RCC). He completes 1 year of adjuvant pembrolizumab following nephrectomy for high-risk disease. Approximately 2 years after his final dose of pembrolizumab, surveillance chest computed tomography (CT) imaging demonstrates enlarging pulmonary nodules; a bone scan reveals new bone metastases.

This patient has a prolonged 2-year interval between completion of adjuvant pembrolizumab therapy and metastatic recurrence. It is reasonable to consider rechallenging with an immunotherapy (IO)-containing regimen, as this patient's disease may still be sensitive to programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) checkpoint inhibition. Cabozantinib + nivolumab is a good option, particularly when disease burden or symptoms favor rapid tumor reduction with a tyrosine kinase inhibitor (TKI)–containing combination. Its use in this setting is based on findings from the CheckMate 9ER study in previously untreated metastatic RCC.[1]

Other good options include pembrolizumab + axitinib or pembrolizumab + lenvatinib. Lenvatinib + belzutifan offers an alternative non-IO regimen that is indicated for use following treatment with a PD-1/PD-L1 inhibitor.[2] However, data on the use of this combination for disease recurrence following adjuvant therapy are limited; just 4% of patients in the LITESPARK-011 trial were enrolled with postadjuvant therapy disease recurrence.[3] Ipilimumab + nivolumab may be considered in this patient if he has minimal cancer-related symptoms and no immediate requirement for tumor shrinkage. The efficacy of this IO–IO combination after adjuvant pembrolizumab is not established, however.

Patient 2: Disease Progression While Receiving Adjuvant Pembrolizumab + Belzutifan

SJ is a 59-year-old woman with stage III high-risk RCC with a clear cell component. After undergoing a partial nephrectomy, SJ begins adjuvant therapy with pembrolizumab + belzutifan, with abdomen/pelvis magnetic resonance imaging (MRI) and chest CT imaging planned for every 3 months. Imaging at month 6 reveals progressive pulmonary nodules and enlarging lymph nodes; she reports bone pain.

Disease progression during active adjuvant therapy requires changing treatment rather than continuing the same combination, as it can be assumed that the tumor is resistant to both adjuvant therapy mechanisms—PD-1/

On the Cover
Light micrograph of papillary renal cell carcinoma.

Credit: Ziad M. El-Zaatari/Science Source

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Table. Pivotal Trials of Approved Regimens for Adjuvant RCC.[10,11]

Trial	KEYNOTE-564	LITESPARK-022
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.

PD-L1 checkpoint inhibition and hypoxia inducible factor-2α (HIF-2α) inhibition. Additionally, given the symptomatic nature of this patient's presentation, she will likely derive clinical benefit from a regimen designed for rapid tumor shrinkage. A vascular endothelial growth factor receptor (VEGFR) TKI introduces a previously unused treatment class and is therefore a reasonable next approach.

Cabozantinib monotherapy is a good option, supported by robust activity observed in the single-agent cabozantinib arm of the CONTACT-03 study in patients with advanced RCC and prior IO exposure.[4] Single-agent axitinib is another potential VEGFR-directed option. Lenvatinib + everolimus may also be considered, but its indication requires the regimen to follow prior antiangiogenic therapy and therefore its use would be considered off label in this situation.[5]

Patient 3: Metastatic Recurrence 4 Months After Completing Adjuvant Pembrolizumab

RC is a 74-year-old man with stage II intermediate-risk clear cell RCC. He undergoes a partial nephrectomy, after which he completes 1 year of adjuvant therapy with pembrolizumab. About 4 months after completion of pembrolizumab, RC reports significant back and leg pain; a bone scan confirms metastatic disease in both locations. Additionally, chest CT reveals pulmonary lymph node enlargement.

The timing of recurrence in this patient is consistent with resistance to PD-1/PD-L1 checkpoint inhibition, given the short time interval between adjuvant therapy and disease recurrence. This, combined with the patient's symptomatic recurrence, favors initiation of a VEGFR-directed TKI regimen rather than rechallenge with further checkpoint immunotherapy.

Single-agent cabozantinib has substantial evidence supporting its efficacy in patients with prior IO exposure who were treated in the second-line metastatic RCC setting.[6] Another option is lenvatinib + belzutifan, which has shown superior progression-free survival (PFS) vs cabozantinib and is indicated for use in patients following a PD-1/PD-L1 checkpoint inhibitor.[3,5] Other potential choices include single-agent axitinib and lenvatinib + everolimus. Tivozanib as a single agent has demonstrated activity after prior checkpoint inhibitors, as shown in the TiNivo-2 study.[7] However, its indication requires at least 2 prior systemic therapies, limiting its routine use immediately after adjuvant pembrolizumab.[8]

Patterns of Recurrence After Surgery

After primary treatment (partial or radical nephrectomy), patients with resectable RCC receive adjuvant therapy that is selected based on disease stage and tumor histology.[9] In patients with clear-cell histology, recommended adjuvant therapy options include surveillance or treatment with the IO pembrolizumab, administered either as a single agent or in combination with the HIF-2α inhibitor belzutifan. For patients with a non–clear cell histology, recommended adjuvant treatment options are limited to surveillance or a clinical trial.

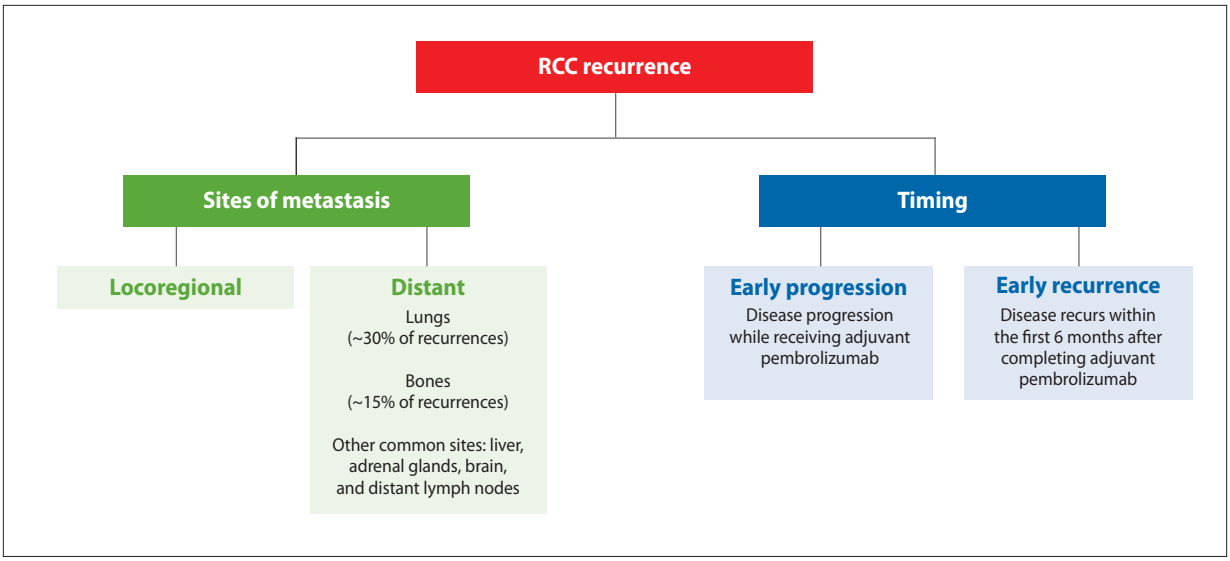


Figure 1. Classification of RCC recurrence.

RCC, renal cell carcinoma.

Despite adjuvant therapy, disease recurrence is common. This was demonstrated in the KEYNOTE-564 study, in which nearly 40% of patients experienced disease recurrence within 5 years of adjuvant pembrolizumab therapy.[10] Though only shorter follow-up data are available with pembrolizumab + belzutifan in the LITESPARK-022 study, approximately 20% of patients had experienced recurrence within the first 24 months of completing this combination.[11] Table provides key efficacy and safety data for each of these trials.

When disease recurrence occurs, it can be classified by the extent and location of disease (Figure 1). RCC recurrences most commonly occur as distant metastases, although locoregional recurrences also occur. The lungs are the most frequent site of distant metastasis, accounting for approximately 30% of recurrences, and the bones are the second most common distant site (approximately 15%).[12,13] Other common distant sites of metastasis include the liver, adrenal glands, brain, and distant lymph nodes.

Another way to classify RCC recurrence is by timing. Patients with disease progression while receiving adjuvant pembrolizumab are considered early progressors, and those whose disease recurs within the first 6 months after completing adjuvant pembrolizumab have early recurrence. Both groups of patients are considered likely to have resistance to PD-1/PD-L1 blockade and therefore an appropriate first-line therapy for these patients is a VEGFR TKI–based regimen. In contrast, patients with late recurrences (occurring >6 months after completing adjuvant pembrolizumab) may still be immune-responsive and either an IO–IO or IO–TKI standard first-line combination may be considered (Figure 2).[1,14-22]

In the Clinic…

Disease progression during active adjuvant therapy requires changing treatment rather than continuing the same combination.

Current Evidence for Treatment of Recurrence Following Adjuvant IO

In advanced RCC, VEGFR TKIs are an established treatment option following IO progression; these agents include cabozantinib, tivozanib, lenvatinib, and axitinib (Figure 3). Typically, preferred first-line treatment options for patients with advanced clear cell RCC are a combination of a TKI and IO or dual IO.

To address the question of whether IO rechallenge could improve outcomes over the TKI alone, 2 randomized, phase 3 rechallenge trials were conducted in patients with advanced RCC who experienced recurrence following IO. CONTACT-03 evaluated the addition of the IO atezolizumab to cabozantinib, whereas TiNivo-2 assessed the addition of the IO nivolumab to tivozanib.[4,7] Neither study found an improvement in PFS with the addition of an IO to a TKI in patients with prior IO use, confirming a lack of benefit with IO rechallenge. These data are particularly relevant in patients progressing on or immediately after (within 6 months) adjuvant pembrolizumab therapy.

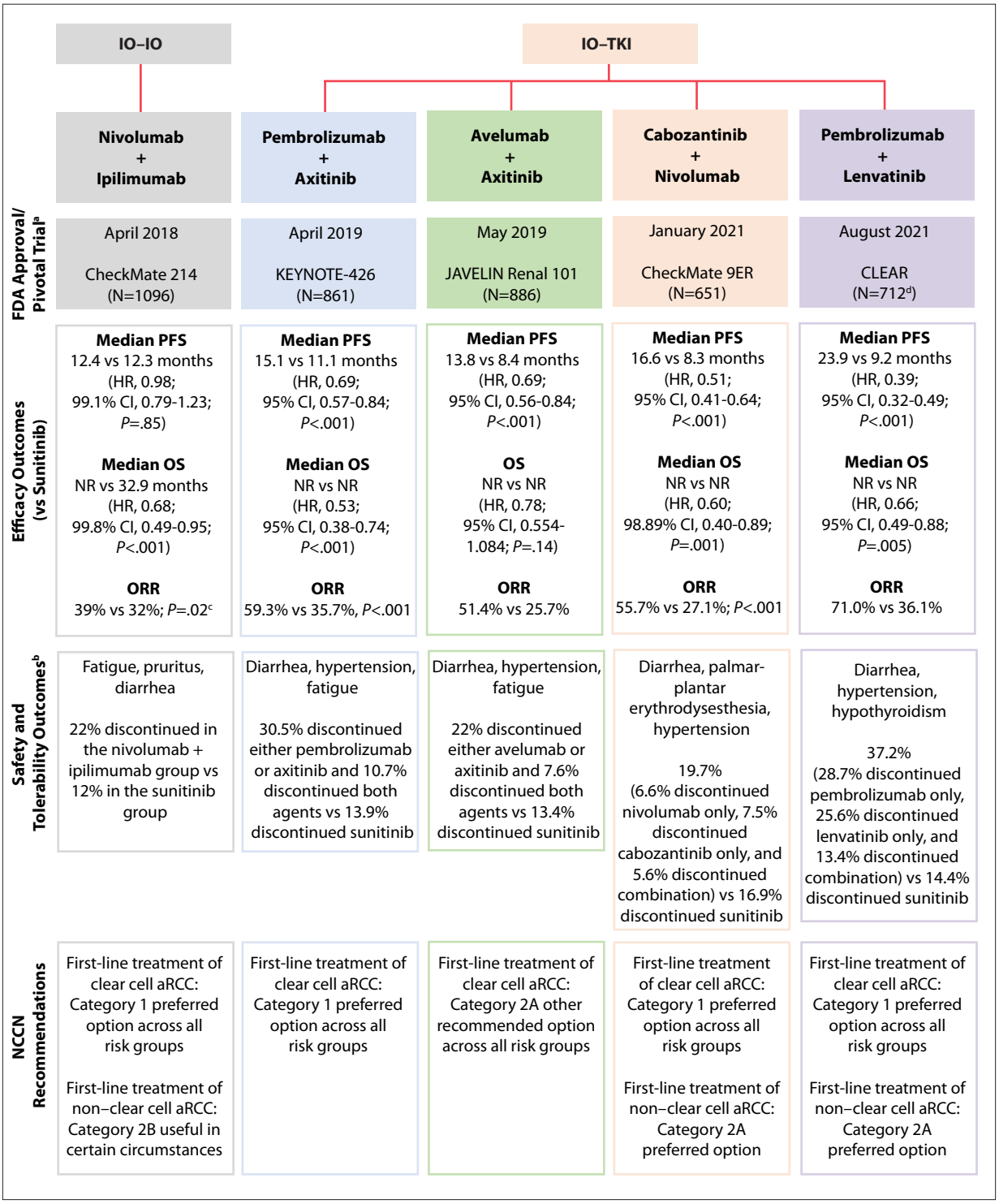


Figure 2. NCCN-recommended FDA-approved combination regimens in the first-line treatment of aRCC.[1,14-22]

[a]All patients had clear cell aRCC.
[b]Three most frequently reported adverse events in the treatment regimen arm and discontinuations due 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, US 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.

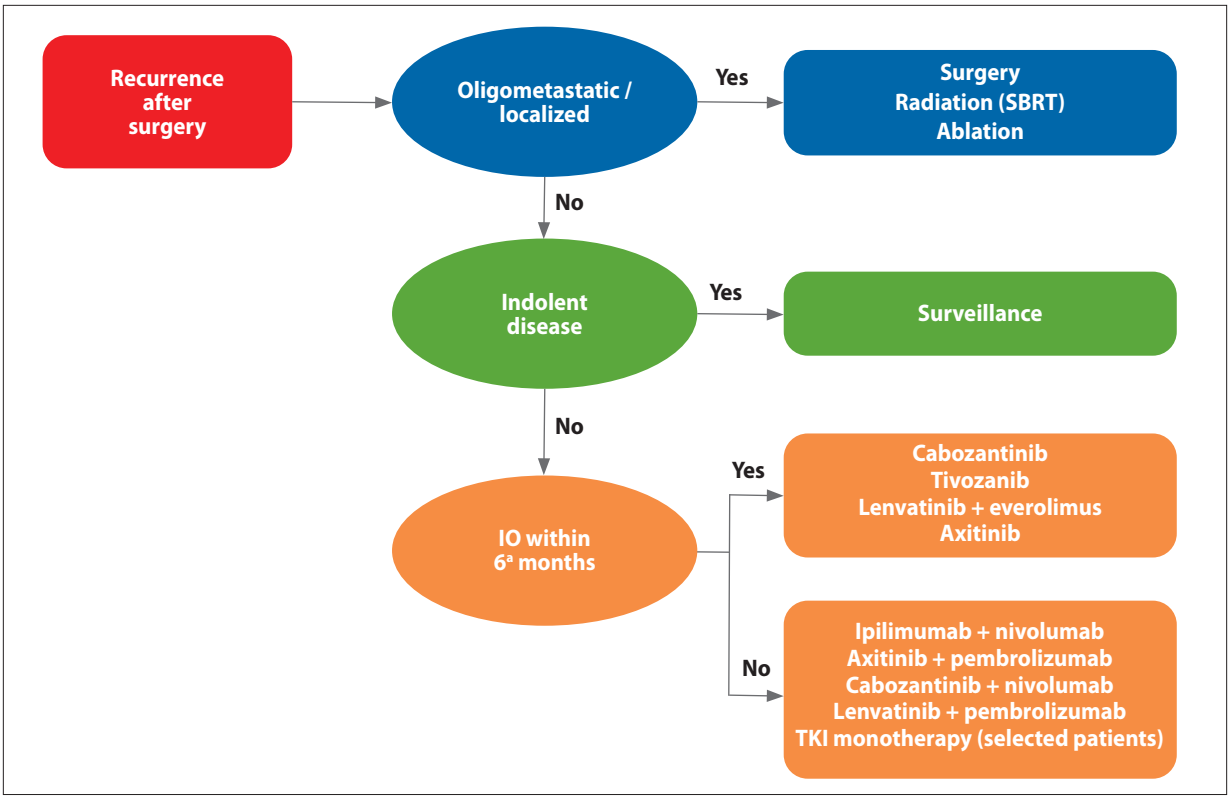


Figure 3. Treatment approach to recurrent RCC.

[a]There is not yet an established consensus in the field as to whether recurrence within the 6- to 12-month period following ICI reflects ICI-refractory disease.
IO, immunotherapy; RCC, renal cell carcinoma; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor.
Courtesy of Wenxin (Vincent) Xu, MD.

Because each of these studies included the single-agent VEGFR TKI as the control arm, these same studies provide important evidence of the activity of single-agent VEGFR TKIs when used in patients with recurrence following an IO. These data may be reasonably extrapolated to provide guidance on treatment sequencing following adjuvant IO, despite relatively low numbers of adjuvant IO patients included in the studies.

CONTACT-03

The CONTACT-03 study was an open-label, randomized, multicenter, international phase 3 trial designed to evaluate the efficacy and safety of adding the IO atezolizumab to cabozantinib compared with cabozantinib alone in patients with advanced RCC who experienced disease progression during or after prior IO therapy.[4] To be eligible, patients were required to have had tumor progression either during or after IO in the first- or second-line locally advanced or metastatic treatment settings, or during or within 6 months after the last dose of an adjuvant IO regimen. All patients had clear cell or non–clear cell advanced RCC with or without sarcomatoid features, and a Karnofsky performance status of 70 or higher. Randomized patients were treated with cabozantinib (60 mg daily) either as a single agent or in combination with atezolizumab. Treatment was continued until intolerable toxicity or loss of clinical benefit.

A total of 522 patients were randomized to treatment.[4] All patients had received IO as their most recent line of therapy—53% in the first-line setting and 46% in the second-line setting. Fewer than 1% had received IO in the adjuvant setting.

The primary analysis of the CONTACT-03 study found that IO rechallenge with atezolizumab added to cabozantinib after disease progression on an IO did not

In the Clinic…

A prolonged interval between completion of adjuvant therapy and metastatic recurrence makes it reasonable to consider rechallenging with an IO-containing regimen.

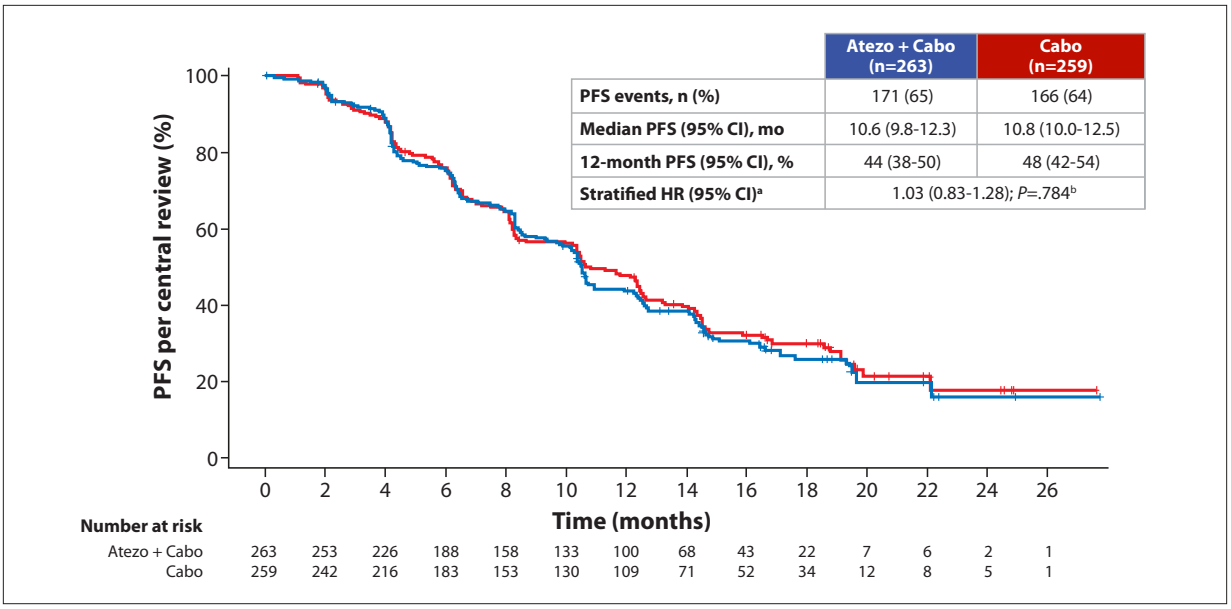


Figure 4. CONTACT-03: centrally reviewed PFS with atezolizumab + cabozantinib vs cabozantinib in patients with mRCC who progressed during or after prior ICI treatment.[4]

[a]Stratified for IMDC risk group.[4]

[b]Not significant at *P*=.002.

Atezo, atezolizumab; Cabo, cabozantinib; HR, hazard ratio; IMDC, International mRCC Database Consortium; mo, months; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; RCC, renal cell carcinoma.

In the Clinic…

Short interval between adjuvant therapy and disease recurrence favors initiation of a VEGFR-directed TKI regimen, rather than rechallenge with further checkpoint immunotherapy.

improve patient outcomes compared with cabozantinib alone (Figure 4).[4] Importantly, evaluation of the results from CONTACT-03 also showed that patients treated with single-agent cabozantinib derived clinically meaningful benefit in the post-IO setting. The independent review committee (IRC)–assessed median PFS (a coprimary endpoint) was 10.8 months with cabozantinib alone (compared with 10.6 months with cabozantinib + atezolizumab). The objective response rate was 41% in the cabozantinib alone arm, with a median duration of response (DOR) of 14.8 months. At the time of the primary analysis, the coprimary endpoint of median overall survival (OS) was not evaluable in the cabozantinib-alone arm and was 25.7 months in the cabozantinib + atezolizumab arm.

In the CONTACT-03 study, the most common any-grade adverse events (AEs) reported with cabozantinib alone were diarrhea (70.7%) and palmar-plantar erythrodysesthesia syndrome (41.0%).[4] The most frequent grade 3 or 4 AEs reported with cabozantinib monotherapy were hypertension (12.5%) and diarrhea (6.6%). All other grade 3 or 4 AEs with cabozantinib monotherapy were reported in fewer than 5% of patients. With cabozantinib monotherapy, the rate of AEs leading to dose interruption or reduction was 87%.

The CONTACT-03 study provided data confirming the benefit of cabozantinib monotherapy after prior IO therapy in patients with advanced RCC. CONTACT-03 enrolled patients who had received IO in either the first-line or second-line setting, meaning cabozantinib was administered in either the second-line or third-line setting—indeed, single-agent cabozantinib was used in the third line in nearly half (46%) of the study population. To more directly and prospectively address whether single-agent cabozantinib was beneficial as second-line therapy following disease progression on first-line IO, the CaboPoint study was conducted.

CaboPoint

The CaboPoint study was an open-label, multicenter, international phase 2 study that enrolled 127 patients with advanced RCC who had received either IO–IO or IO–TKI therapy in the first-line setting only.[6] Cabozantinib

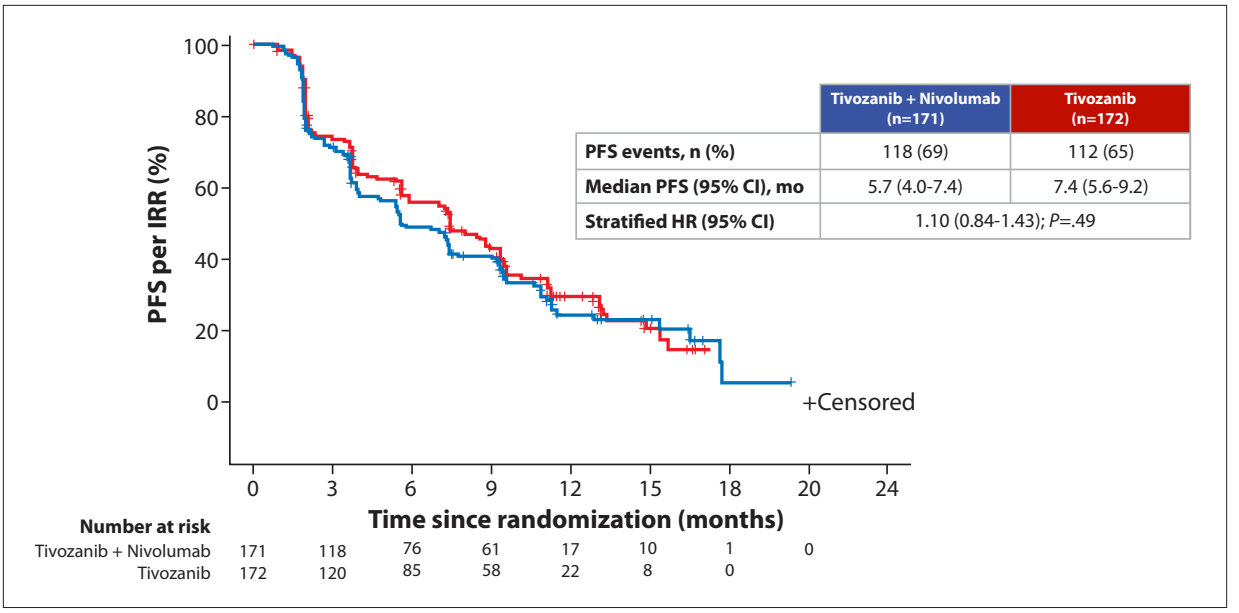


Figure 5. TiNivo-2 study: centrally reviewed PFS with tivozanib + nivolumab vs tivozanib after prior ICI therapy.[7]

HR, hazard ratio; mo, months; IRR, independent radiology review; PFS, progression-free survival.

(60 mg/day) was administered until disease progression or unacceptable toxicity, or up to a maximum of 18 months.

The objective response rate (ORR), the primary endpoint of the study, was 40.5% in patients who had received first-line IO–IO and was 27.5% in patients who had received first-line IO–TKI.[6] The overall ORR across all patients was 36.1%. Median DOR was not calculable for patients who had received first-line IO–IO, and was 8.3 months for patients who had received first-line IO–TKI. Median PFS was 10.9 months in patients who had received first-line IO–IO and was 8.3 months in patients who had received first-line IO–TKI. Median OS was 24.3 months in patients who had received first-line IO–IO and was 24.1 months in patients who had received first-line IO–TKI.

The most common grade 3 or 4 treatment-emergent AEs (TEAEs) reported in the CaboPoint study were hypertension (32.3%), diarrhea (11.0%), and pulmonary embolism (7.9%).[6] Overall, 18.9% of patients experienced a TEAE leading to discontinuation of cabozantinib, 29.1% experienced a TEAE leading to dose reduction of cabozantinib, and 84.3% experienced a TEAE leading to interruption of cabozantinib.

TiNivo-2

The TiNivo-2 study was an open-label, randomized, multicenter, international phase 3 trial comparing single-agent tivozanib vs tivozanib + the IO nivolumab in patients with advanced RCC who had progressed during or following 1 or 2 prior lines of therapy (one of which was an IO).[7] Eligible patients had advanced RCC with a clear cell component, measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In both arms, tivozanib was administered for 21 consecutive days followed by a 7-day rest period; patients were randomized to receive either standard-dose tivozanib (1.34 mg daily) alone or a reduced dose of tivozanib (0.89 mg daily) + nivolumab. Nivolumab was continued for up to 2 years, whereas tivozanib was continued until disease progression or intolerable toxicity.

Among the 343 patients randomized in the study, 14% had adjuvant therapy, 63% had received 1 line of therapy, and 37% had received 2 lines. IO was the most recent line of therapy in 70% of the patients.[7]

The primary analysis of the TiNivo-2 study demonstrated that rechallenging patients with the IO nivolumab added to tivozanib did not improve outcomes compared to tivozanib monotherapy (Figure 5), confirming similar findings from the CONTACT-03 trial.[4,7] Importantly, this analysis also showed clinically meaningful activity with single-agent tivozanib in the post-IO setting.[7] At the primary analysis of TiNivo-2, independent radiology review (IRR)–assessed median PFS (the primary endpoint) was 7.4 months in the tivozanib-alone arm, which was not improved with the addition of the IO nivolumab (IRR-assessed median PFS, 5.7 months). In a predefined analysis of those patients who had received IO as their most recent line of therapy, median PFS was 9.2 months

with tivozanib monotherapy vs 7.4 months with tivozanib + nivolumab. Objective responses occurred in 20% of patients treated with tivozanib monotherapy; the median DOR was not reached in these patients.

The final analysis of the TiNivo-2 study confirmed the long-term efficacy of tivozanib monotherapy in this setting, with a median PFS of 7.43 months in the intention-to-treat population.[23] Median OS, a key secondary endpoint, reached 22.93 months with tivozanib alone; the estimated 12-month OS was 68.9% at the final analysis.

The most common any-grade TEAEs reported in the TiNivo-2 study were hypertension (40% with tivozanib alone) and diarrhea (36% with tivozanib alone).[7] Hypertension was also the most common grade 3 or higher TEAE reported with tivozanib monotherapy, reported in 22% of patients in that arm; all other grade 3 or higher TEAEs with tivozanib monotherapy were reported in 5% or fewer patients. With tivozanib monotherapy, the rate of TEAEs leading to dose interruption or reduction was 77%. The long-term safety profile of tivozanib remained consistent at the final analysis, with any-grade hypertension reported in 54.4% of the tivozanib arm (19.3% grade 3 or 4).[23]

LenCabo

The LenCabo study was designed as the first head-to-head comparison of second-line or later TKI treatments after progression on IO combinations.[24] LenCabo was an open-label, multicenter, randomized, phase 2 trial comparing the multitargeted TKI lenvatinib + everolimus vs cabozantinib in patients who had progressive disease on an IO. All patients had advanced RCC that was either clear cell or had a clear cell component, measurable disease, and an ECOG performance status of 0, 1, or 2. All patients were required to have received 1 or 2 prior lines of systemic treatment in the metastatic setting, including an IO, or had received an IO in the adjuvant setting within the preceding 6 months prior to enrollment. Patients either had disease progression on or after their last IO regimen, or had to discontinue IO treatment owing to immune-mediated AEs. A total of 90 patients were randomized to treatment with either cabozantinib (60 mg daily) or lenvatinib (18 mg daily) + everolimus (5 mg daily).

Most patients had received 1 prior line of therapy (69.8%) and thus were receiving lenvatinib + everolimus vs cabozantinib in the second line; the remaining 30.2% had received 2 prior lines of therapy and were receiving the study treatment in the third line.[24]

Lenvatinib + everolimus resulted in a significantly prolonged median PFS compared with cabozantinib (15.7 months vs 10 months; stratified log-rank *P*=.013; unadjusted hazard ratio (HR), 0.54 [95% CI, 0.32-0.93]).[24] The lenvatinib + everolimus combination was associated with a numerically higher ORR compared with cabozantinib (52.6% vs 38.6%), but this comparison was inconclusive in an unadjusted analysis (odds ratio [OR], 1.71; 95% CI, 0.72-4.0; *P*=.22) or a multivariable analysis (OR, 1.87; 95% CI, 0.75-4.6; *P*=.17). Median DOR was longer among responding patients in the lenvatinib + everolimus arm compared with the cabozantinib arm (14.4 months vs 9.7 months, respectively). OS data were immature and inconclusive owing to a low number of events at the time of this analysis.

The most common any-grade treatment-related AEs (TRAEs) reported with lenvatinib + everolimus vs cabozantinib in the LenCabo study were diarrhea (70% vs 73.9%) and fatigue (72.5% vs 60.9%).[24] Hypertension was the most frequent grade 3 or higher TRAE reported (35% vs 15.2%). Grade 3 or higher diarrhea (12.5% vs 17.4%) and decreased lymphocyte count (12.5% vs 4.3%) were also frequently reported. In the lenvatinib + everolimus arm, the rate of TRAEs leading to dose interruption was 70% and to dose reductions was 57% (78.3% and 60.9%, respectively, in the cabozantinib arm).

Current Evidence for Treatment of Recurrence Following Adjuvant IO + Belzutifan

The randomized, phase 3 LITESPARK-022 study evaluated the addition of the HIF-2α inhibitor belzutifan to adjuvant pembrolizumab, comparing it with placebo + adjuvant pembrolizumab.[11] After a median follow-up of 28.4 months, the belzutifan + pembrolizumab combination showed a significant disease-free survival (DFS) improvement over placebo + pembrolizumab (24-month DFS, 80.7% vs 73.7%, respectively; HR, 0.72; 95% CI, 0.59-0.87; *P*<.001). Based on these results, this regimen received approval of the US Food and Drug Administration and is recommended as an adjuvant therapy option for patients with stage II disease with grade 4 tumors, or with stage III disease.[2,9]

However, it remains inevitable that recurrence will occur in a subset of patients treated with adjuvant belzutifan + pembrolizumab—even in the primary analysis of LITESPARK-022, nearly 20% of patients treated with this regimen had a recurrence by 24 months.[11] For these patients, the optimal first-line treatment remains undefined. Single-agent VEGFR TKI is the best-supported extrapolated strategy (based on the CONTACT-03 and TiNivo-2 studies[4,7]), though neither trial enrolled patients treated with a HIF-2α inhibitor. Neither belzutifan rechallenge nor belzutifan-containing combinations have data supporting either strategy after recurrence with adjuvant belzutifan + pembrolizumab.

Adding belzutifan exposes patients to a second active

drug class in the adjuvant setting, yet evidence to guide subsequent HIF-2α inhibition following recurrence remains limited. Thus, it is important to consider early-on that use of this intensified option in the adjuvant setting may therefore have implications not just for increased toxicity but also uncertainty in subsequent treatment sequencing.

Emerging Evidence

Clinical trials are evaluating the optimal treatment strategy for recurrence following adjuvant pembrolizumab.

The phase 3 LITESPARK-033 study is evaluating the combination of belzutifan + the investigational multitargeted TKI zanzalintinib in patients with advanced RCC that recurred following adjuvant IO.[25] To be eligible for enrollment, patients with advanced RCC with a clear cell component are required to have measurable disease and have received adjuvant PD-1/PD-L1 IO, experiencing recurrence within the 24 months after completing adjuvant therapy. Once enrolled, patients are randomized to treatment with either belzutifan + zanzalintinib or cabozantinib. The selection of single-agent cabozantinib as the control arm in LITESPARK-033 underscores that this agent remains a reasonable standard of care for patients with disease recurrence following adjuvant IO.

The phase 3 PEAK-1 study is comparing the investigational HIF-2α inhibitor casdatifan added to cabozantinib against placebo + cabozantinib in patients who received IO as part of the most recent regimen (either adjuvant monotherapy or first-line setting), with no more than 1 prior regimen in the metastatic setting.[26] Notably, prior treatment with an HIF-2α inhibitor or cabozantinib is considered an exclusion criterion for enrollment in this study, so these results will not be able to inform treatment sequencing decisions for patients who experience disease recurrence following adjuvant pembrolizumab + belzutifan.

In the Clinic...

Maximizing treatment across lines means implementing an effective regimen when the patient needs it while addressing and managing toxicities appropriately. Although preserving options for future lines of treatment is important, it is also critical to recognize when to balance immediate benefit with opportunities for future disease control.

Back to the Clinic . . .

Treatment sequencing for patients with recurrent clear cell RCC requires careful planning across the entire patient journey, beginning with choice of adjuvant therapy and extending through successive metastatic therapies. New options in both the adjuvant and advanced RCC settings have brought sequencing questions into focus. Patients entering their first metastatic line may have already received an IO (pembrolizumab), with or without HIF-2α inhibition (belzutifan), and therefore no longer meet the definition of treatment-naive used to define the patient population in first-line clinical trials.

Recent data have expanded these choices. LITESPARK-011 supported the FDA approval of lenvatinib + belzutifan following prior PD-1/PD-L1 checkpoint inhibition.[2,3] The combination improved PFS and response rate compared with cabozantinib, although the final OS analysis did not demonstrate a statistically significant benefit. Importantly, the trial excluded patients who had received prior cabozantinib, lenvatinib, and HIF-2α inhibitors; therefore, it does not establish the effectiveness of every sequence now being considered in practice.

Sequencing mechanisms of action is another important consideration. For recurrence during or shortly after adjuvant pembrolizumab, it is assumed that the tumor is resistant to PD-1/PD-L1 checkpoint inhibition and therefore a VEGFR TKI agent takes priority for selection. Alternatively, an IO-containing combination may be considered for patients with a prolonged treatment-free interval prior to recurrence, although PD-1/PD-L1 sensitivity remains to be proven. Following progression on adjuvant pembrolizumab + belzutifan, changing to a VEGFR TKI is reasonable, whereas retreatment with belzutifan lacks supporting evidence.

The historical inclination to "save cabozantinib for later" has consequently evolved toward using it earlier when clinically appropriate. Real-world data show attrition rates of 40% to 50% between first- and second-line therapy, and also between second- and third-line therapy. These data support using the best available therapies upfront when possible.[27] Cabozantinib monotherapy is a strong consideration for early postadjuvant therapy recurrence, whereas cabozantinib + nivolumab may be considered for selected late recurrences. One reasonable strategy among patients requiring upfront IO–TKI is cabozantinib + nivolumab followed by lenvatinib + belzutifan, thereby introducing HIF-2α inhibition after PD-1 and VEGFR exposure. Of note, this is a pragmatic clinical strategy but not a prospectively validated sequence, because LITESPARK-011 excluded prior cabozantinib.[3]

Ultimately, maximizing treatment across lines means

In the Clinic...

The historical inclination to "save cabozantinib for later" has evolved toward using it earlier when clinically appropriate. Cabozantinib monotherapy is a strong consideration for early postadjuvant therapy recurrence, whereas cabozantinib + nivolumab may be considered for selected late recurrences. One pragmatic strategy among patients requiring upfront IO–TKI is cabozantinib + nivolumab followed by lenvatinib + belzutifan, thereby introducing HIF-2α inhibition after PD-1 and VEGFR exposure.

implementing an effective regimen when the patient needs it while addressing and managing toxicities appropriately. Although preserving options for future lines of treatment is important, it is also critical to recognize when to balance immediate benefit with opportunities for future disease control.

Disclosures

Dr Xu has received research support from OncoHost, Arsenal Biosciences, and Merck; and consulting fees from Eisai, Exelixis, Xencor, Jazz Pharmaceuticals, AVEO Oncology, Merck, Celdara Medical, and Deciphera Pharmaceuticals.

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