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## About the Patient

This case features AK, a 58-year-old female who was initially diagnosed with stage IB clear cell renal cell carcinoma (RCC) in 2018, for which she underwent a partial nephrectomy with follow-up annually. In 2022, she recurred with a distal expansile lesion in her left femur. AK underwent a left distal femur replacement in June 2022. However, in November 2022, after having recovered from that surgery, a bone scan revealed a single new bone metastasis in her manubrium. She subsequently received radiation therapy beginning in January 2023.

Follow-up workups in February and May 2023 showed no further evidence of spread of disease, until September 2023 when a computed tomography (CT) scan showed a new right iliac lesion (Figure 1). Baseline imaging demonstrated a destructive right iliac lesion with associated soft-tissue extension; the corresponding bone scan showed a subtle but discernible focus of increased uptake.

The patient was started on treatment with cabozantinib plus nivolumab, with which she quickly achieved stable disease. The patient has maintained treatment with this combination. Recently, in November 2025, stereotactic body radiation therapy was administered to the right iliac lesion, which had showed a very slight increase in size.

This case illustrates an unusual pattern of sequential, bone-only metastatic RCC, with lesions appearing in disparate skeletal sites over time (distal femur, manubrium, and right ilium). Imaging, including CT and bone scan, highlight the destructive iliac lesion used as the target lesion for monitoring.

## aRCC: Disease Overview

In 2025, kidney and renal pelvis cancers accounted for an estimated 80,980 cancer diagnoses and 14,510 deaths.[1] The median age at diagnosis of kidney and renal pelvis cancer is 65 years, with 77.8% of diagnoses in patients 55 years of age and older.

RCC, which comprises the majority of cancers of the

On the Cover
Light micrograph of papillary renal cell carcinoma.

Credit: Ziad M. El-Zaatari/Science Source

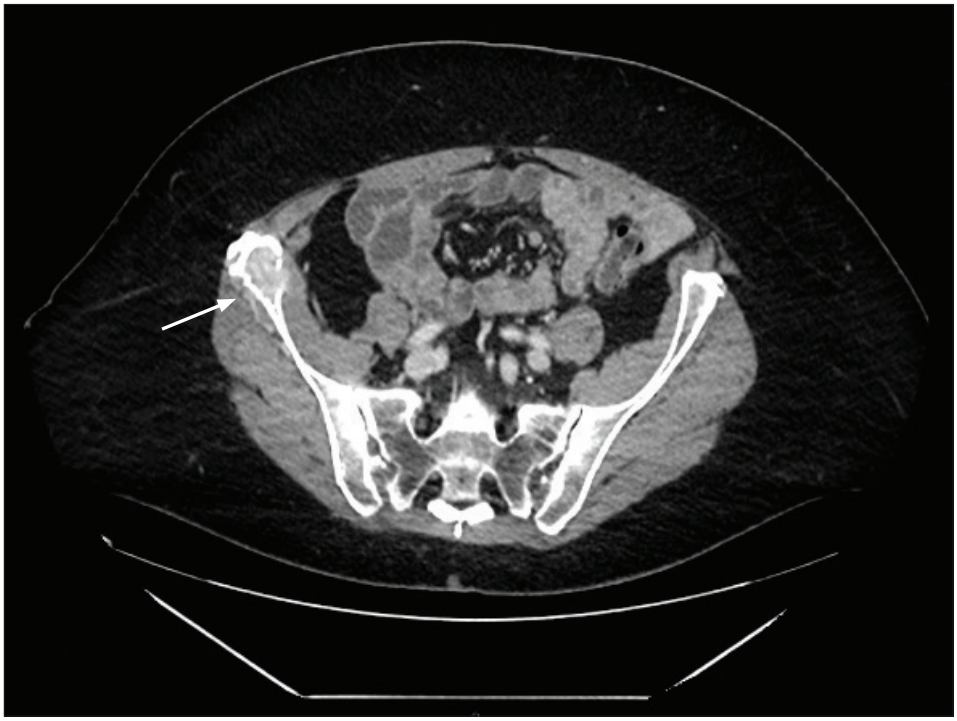

**Figure 1.** Computed tomography scan showing a new right iliac lesion in September 2023.

kidney and renal pelvis, can be classified as having either clear cell histology (approximately 70%) or non-clear cell histology, the latter of which includes papillary RCC, chromophobe RCC, and other rare subtypes.[2] Incidental detection of RCC has become increasingly common,[3] when patients present with symptoms typically described as a triad of flank pain, gross hematuria, and palpable abdominal mass.[4]

RCC risk factors include smoking, obesity, hypertension, and exposures to certain chemicals. About 6% to 9% of RCC tumors harbor germline mutations that are associated with a predisposition to cancer.[3]

In 2022, the World Health Organization (WHO) published a revised edition of the classification of urogenital tumors, which incorporated molecular-driven groupings.[5] According to the WHO, molecularly defined renal tumors show heterogeneous morphological characteristics, preventing them from being diagnosed by morphology alone. New entities defined in this WHO classification include *SMARCB1*-deficient medullary RCC, *TFEB*-altered RCC, *ALK*-rearranged RCC, and *ELOC*-mutated RCC.

Advanced RCC (aRCC), which includes metastatic disease, has a significantly lower 5-year relative survival rate compared with localized disease (19% vs 93%, respectively, for cancers of the kidney and renal pelvis).[6] aRCC is a highly vascular tumor, which facilitates its high propensity for metastasis.[7] A retrospective real-world analysis of nearly 12,000 patients with metastatic RCC showed that 60% of patients had a single metastatic site, whereas 40% had two or more metastatic sites.[8] In patients with multiple metastatic organ site involvement, the most common sites included lung, bone, liver, and brain (approximately 45%, 30%, 20%, and 8% of metastatic sites, respectively).

### *IMDC Risk Model*

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model is widely used as a clinical prognostic tool for patients with aRCC, and is considered a gold standard for predicting survival in patients.[9,10] The IMDC model evaluates 6 risk factors: time <1 year from RCC diagnosis to first-line systemic therapy, elevated platelet count, elevated absolute neutrophil count, anemia, hypercalcemia, and Karnofsky performance status <80. Based on this scoring, patients are stratified into favorable, intermediate, and poor risk groups, which exhibit median overall survival times of 43.2 months, 22.5 months, and 7.8 months, respectively. Nearly 80% of patients with RCC have intermediate or poor risk disease. Given its prognostic importance, the IMDC classification is a part of many clinical trial designs as well as clinical decision-making.

### *Focus on Bone Metastases*

Bone is a complicating metastatic site in aRCC. Bone metastases in aRCC tend to be destructive, often with an osteolytic characteristic and a soft tissue component,

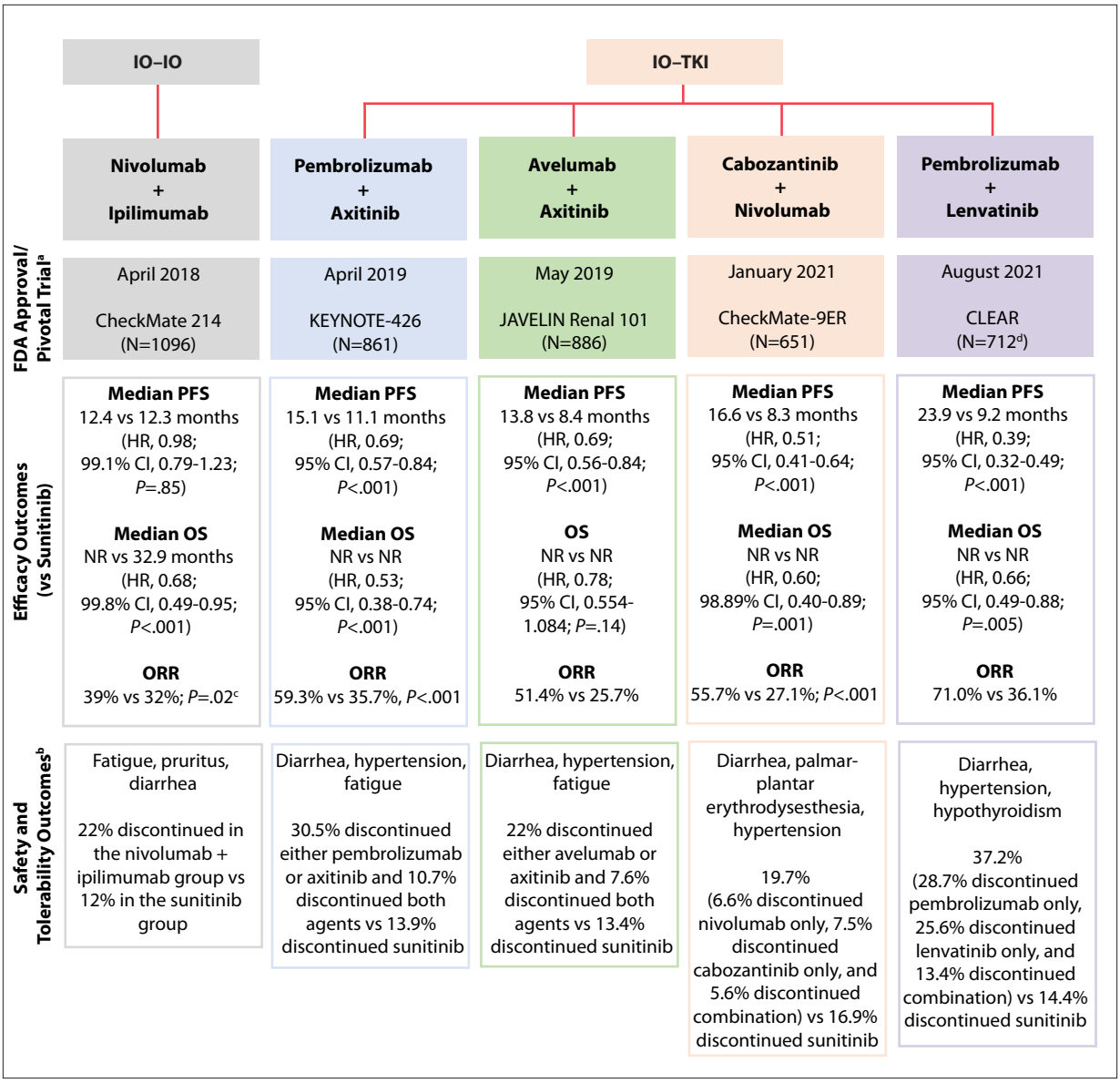


**Figure 2.** NCCN-preferred FDA-approved combination regimens in the first-line treatment of aRCC.[14-22]
[a]All patients had clear cell aRCC.
[b]Three most frequently reported adverse events in the treatment regimen arm and discontinuations owing to adverse reactions.
[c]Not significant per the prespecified .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.

which make it particularly problematic because these patients are prone to being much more symptomatic, including having a higher risk of developing pathologic fractures.

Bone metastases in aRCC are associated with a poor prognosis and worse outcomes, including reduced progression-free survival (PFS) and overall survival (OS). In addition, bone metastases add to the overall disease burden through increased risk of skeletal-related events, which may include pathological fractures, spinal cord and nerve root compression, and hypercalcemia.[11]

Prior to the introduction of newer treatment regimens, the median survival for patients with aRCC and bone metastases was between 1 and 2 years (depending on

**Table 1.** Summary of the Dual Mechanism of Action Attributed to Cabozantinib Plus Nivolumab[14,17,25-41]

| Agent | MOA | Description | Effect |
|---|---|---|---|
| Cabozantinib[a] | TKI that inhibits MET, AXL, and VEGFR | • MET inhibition may reduce immune checkpoint expression<br>• AXL inhibition may promote antigen presentation and tumor recognition as well as increased cytotoxic T cells<br>• VEGFR inhibition may normalize vascularization and promote T-cell infiltration<br>• Inhibition of MET, AXL, and VEGFR may reduce the presence of immunosuppressive cells | Counteracts tumor-induced immunosuppression |
| Nivolumab | IO that binds to PD-1 and inhibits PD-1/PD-L1 checkpoint | • PD-1/PD-L1 checkpoint inhibition may activate naive T cells and T-cell-mediated killing | Inhibits immune checkpoint to reactivate anticancer immune response |

[a]As seen in preclinical models, cabozantinib has also been shown to inhibit RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3, and TIE-2. These receptors are involved in normal and oncogenic processes such as tumor angiogenesis, cell proliferation/metastasis, and modulation of the immune response.

IO, immunothetrapy; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor 1.

whether the patient was diagnosed with bone metastases or had developed bone metastases after diagnosis).[12] However, these outcomes have significantly improved with the introduction of novel treatment combinations, extending survival to 3 or 4 years.[13]

## Treatment Landscape

First-line treatment of aRCC has grown increasingly complex over the past decade, reflecting rapid therapeutic innovation and a fundamental shift in the standard of care. Historically, treatment of aRCC was dominated by reliance on vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKIs). Approval of immunotherapy (IO)-based combinations, including dual immune checkpoint inhibitor (ICI)–IO regimens (nivolumab plus ipilimumab) and IO–TKI combinations such as pembrolizumab plus axitinib, pembrolizumab plus lenvatinib, avelumab plus axitinib, and cabozantinib plus nivolumab has transformed the first-line management of aRCC (Figure 2).[14-22] Novel subcutaneous formulations of the IOs nivolumab and pembrolizumab are also now available, indicated for use across the solid tumor indications approved in adults for the intravenous formulations.[23,24]

These approvals, largely occurring since 2017, have established combination therapy as the preferred approach for most patients with aRCC, improving OS, PFS, and response rates compared with prior monotherapy standards. However, as the number of available regimens continues to expand, clinical decision-making in aRCC has grown more nuanced, requiring careful consideration of disease risk stratification, comorbidities, toxicity profiles, and patient preferences to optimize outcomes.

The combination of cabozantinib and nivolumab is discussed here, as this regimen was utilized in the patient case presented and it represents a key example of the IO–TKI paradigm, leveraging both immune modulation and antiangiogenic activity. The approval of a subcutaneous formulation of nivolumab across its approved solid tumor indications in adults, including first-line treatment of aRCC in combination with cabozantinib, introduces an additional route of administration that may enhance treatment flexibility and patient convenience.

## Cabozantinib Plus Nivolumab as First-Line Therapy for aRCC

Cabozantinib plus nivolumab is indicated for the first-line treatment of patients with aRCC.[17] Cabozantinib is also approved in several other tumor types, including hepatocellular carcinoma, differentiated thyroid cancer, and pancreatic and extrapancreatic neuroendocrine tumors.

### *A Dual Mechanistic Approach*

The combination of the TKI cabozantinib with the IO nivolumab provides the potential for a dual mechanism of action in aRCC (Table 1). aRCC tumor cells show overexpression of MET, AXL, and VEGFR, three tyrosine kinases that have been demonstrated to be key drivers of aRCC tumorigenesis, where they are involved in tumor

**Table 2.** Summary of NCCN Guideline Recommendations for the Use of Cabozantinib Plus Nivolumab as First-Line Treatment of aRCC[42]

| Treatment setting | NCCN recommendation |
|---|---|
| First-line treatment of clear cell RCC | Category 1 preferred option across all risk groups |
| First-line treatment of non-clear cell RCC | Category 2A preferred option |

aRCC, advanced renal cell carcinoma; NCCN, National Comprehensive Cancer Network.

cell proliferation and metastasis, tumor angiogenesis, and immune cell regulation. As demonstrated with in vitro biochemical and/or cellular assays, cabozantinib is a TKI that inhibits MET, AXL, and VEGFR, although the clinical significance of this inhibition is unknown.[17]

Cabozantinib has immunomodulatory properties that attenuate tumor-induced immunosuppression, effects that may increase the antitumor response to immune-checkpoint inhibition with nivolumab. Cabozantinib-mediated immunomodulatory properties may include reduced immune checkpoint expression due to MET inhibition; increased antigen presentation, tumor recognition, and cytotoxic T cells resulting from AXL inhibition; and normalization of vascularization and increased T-cell infiltration owing to VEGFR inhibition.[25-28] Additionally, inhibition of MET, AXL, and VEGFR may reduce the presence of immunosuppressive cells.[29-38] Inhibition of PD-1 by nivolumab may activate naive T cells, triggering T-cell-mediated killing.[27,39-41]

### *Guideline Recommendations*

The National Comprehensive Cancer Network (NCCN) Guidelines for Kidney Cancer (version 1.2026)[42] designate cabozantinib plus nivolumab as an NCCN Category 1 preferred option across all risk groups as first-line treatment of clear cell RCC, and an NCCN Category 2A preferred option as first-line treatment of non-clear cell RCC. Note that cabozantinib plus nivolumab was the first IO–TKI regimen with an NCCN recommendation in both clear cell and non-clear cell aRCC (Table 2).

### *Dosing and Administration*

In patients with previously untreated aRCC, there are 2 ways to administer cabozantinib plus nivolumab therapy in the first-line setting (Table 3).[17] In both cases, cabozantinib is administered at a dosage of 40 mg once daily, continued until disease progression or unacceptable toxicity. Nivolumab may be administered either intravenously (240 mg every 2 weeks or 480 mg every 4 weeks) or subcutaneously (600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks). Both formulations of nivolumab are continued for up to 2 years or until disease progression or unacceptable toxicity.

Cabozantinib is administered as a single tablet dose, even if dose adjustments are required.[17] Two cabozantinib tablets are available—a 40 mg tablet and a 20 mg tablet. It is recommended to withhold cabozantinib in the event of intolerable grade 2 adverse reactions, any grade 3 or 4 adverse reactions, or any-grade osteonecrosis of the jaw. Upon resolution or improvement of the adverse reaction, cabozantinib is restarted at a reduced dosage (20 mg once daily for the first reduction; 20 mg once every other day for the second reduction).

Sometimes with extended use of cabozantinib plus nivolumab, chronic grade 2 level toxicities will necessitate a dose reduction. Or, in some cases, a dose interruption or treatment holiday lasting 1 or 2 weeks is sufficient to allow patients an opportunity to reset their toxicity profile. Once a patient's scans have shown evidence of an objective response, response with cabozantinib plus nivolumab tends to be durable. Thus, it is important to make sure the patient is able to tolerate the drug over long-term therapy.

## The CheckMate-9ER Study

The efficacy and safety of the cabozantinib plus nivolumab combination regimen was evaluated in CheckMate-9ER, a phase 3, randomized, open-label trial that compared the combination in a head-to-head fashion with sunitinib monotherapy.[21] A total of 651 patients with previously untreated aRCC with a clear cell component were randomized to either treatment arm; stratification factors were IMDC risk group (favorable vs intermediate vs poor), PD-L1 tumor expression (≥1% vs <1% or indeterminate), and geographic region (United States, Canada, and Western and Northern Europe vs rest of the world). Patients with autoimmune disease or other medical conditions requiring systemic immunosuppression were excluded from enrollment. Treatment was continued until disease progression or unacceptable toxicity, with tumor assessments performed at baseline, after randomization at week 12, then every 6 weeks until week 60, and every 12 weeks thereafter. Primary analysis included a median follow-up of 18.1 months (range: 10.6-30.6 months).

**Table 3.** Recommended Combination Dosing of Cabozantinib Plus Nivolumab in Patients With aRCC[17]

| Dosing | Cabozantinib | Nivolumab |
|---|---|---|
| Starting dosage | • 40 mg once daily<br>• 1-tablet oral administration | • 240 mg every 2 weeks or 480 mg every 4 weeks<br>• 30-minute IV infusion |
| | | • 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks<br>• 3- to 5-minute SC injection |
| First reduction | • 20 mg once daily<br>• 1-tablet oral administration | • Same as starting dosage |
| Second reduction | • 20 mg once every other day<br>• 1-tablet oral administration | • Same as starting dosage |

aRCC, advanced renal cell carcinoma; IV, intravenous; SC, subcutaneous.

***Baseline Characteristics***

Baseline characteristics were balanced across the 2 treatment arms.[21] A total of 40.9% of patients in the cabozantinib plus nivolumab combination arm and 36.0% in the sunitinib arm were 65 years of age and over, and most had a Karnofsky performance status of 90 or higher (77.6% and 73.4%, respectively). Most patients were within 1 year of diagnosis (65.0% and 65.2%, respectively). In this study of patients with aRCC, about one-half (51.7% and 52.7%, respectively) had metastatic disease.

The CheckMate-9ER study included patients with a broad range of characteristics, including those with a high burden of disease.[21] A total of 79% of the study population had metastatic involvement of 2 or more organs (with lung [75%], bone [23%], and liver [19%] among the most common sites), which is approximately double the proportion of patients with 2 or more metastatic sites observed in the overall aRCC population (<40%).[8] Inclusion of patients with a favorable IMDC risk score was restricted, limiting their enrollment to 22% of the study population; the majority (78%) of patients had either an intermediate (58%) or a poor (20%) IMDC risk score. This is representative of the IMDC risk groups seen in a real-world population, including a meaningful proportion of patients with poorer risk disease (intermediate or poor risk score).[43,44] The primary tumor was intact (no prior nephrectomy) in 30% of patients in the study population.

***Primary Analysis and 5-Year Follow-up***

The primary endpoint of the CheckMate-9ER study was PFS as assessed by blinded independent central review (BICR).[21] In the primary analysis in the intention-to-treat population, treatment with cabozantinib plus nivolumab resulted in a 49% reduction in the risk of progression or death (hazard ratio [HR], 0.51; 95% CI, 0.41-0.64; *P*<.001). The median PFS was doubled with the combination regimen in the primary analysis, reaching 16.6 months in the cabozantinib plus nivolumab arm compared with 8.3 months in the sunitinib arm. At a 5-year follow-up analysis (median follow-up of 67.6 months), the median PFS remained consistent (Table 4) at 16.4 months with cabozantinib plus nivolumab vs 8.3 months with sunitinib (HR, 0.58; 95% CI, 0.49-0.70).[45] Cabozantinib plus nivolumab was associated with improved PFS outcomes across most prespecified subgroups of IMDC risk categories.

BICR-assessed objective response rate, a secondary endpoint of the CheckMate-9ER study, was double in the cabozantinib plus nivolumab arm compared with the sunitinib arm at the primary analysis (55.7% vs 27.1%; *P*<.001)[21] and remained consistent at the 5-year follow-up (55.7% vs 27.4%).[45] More patients treated with cabozantinib plus nivolumab achieved a complete response than patients treated with sunitinib (8.0% vs 4.6%). Furthermore, responses with cabozantinib plus nivolumab treatment deepened with time; at the 5-year follow-up, 13.9% of patients treated with the combination regimen had achieved a complete response, compared with the same 4.6% of sunitinib-treated patients.

Tumor response in evaluable patients was a descriptive endpoint in the primary analysis of the CheckMate-9ER study. Of the 543 evaluable patients in the primary analysis, 95% experienced tumor shrinkage in the cabozantinib plus nivolumab arm compared with 85% in the sunitinib arm.

Cabozantinib plus nivolumab also had a significant benefit over sunitinib in OS, a secondary endpoint of the CheckMate-9ER study (HR, 0.60; 98.89% CI, 0.40-0.89; *P*=.001).[21] The median OS was not reached in either treatment arm, although the Kaplan-Meier analysis showed an early and sustained separation of the curves. The 5-year follow-up analysis showed median OS with

**Table 4.** PFS, OS, and ORR Outcomes at the 5-Year[a] Follow-up of the CheckMate-9ER Study[45]

| Outcomes | Cabozantinib + Nivolumab (n=323) | Sunitinib (n=328) |
|---|---|---|
| Median PFS, months | 16.4 | 8.3 |
| HR (95% CI) | 0.58 (0.49-0.70) | |
| PFS, %<br>3-year<br>4-year<br>5-year | <br>22.2<br>16.3<br>13.6 | <br>10.7<br>5.6<br>3.6 |
| Median OS, months | 46.5 | 35.5 |
| HR (95% CI) | 0.79 (0.65-0.96) | |
| OS, %<br>3-year<br>4-year<br>5-year | <br>58.7<br>48.9<br>40.9 | <br>49.5<br>39.4<br>35.4 |
| ORR[b], % (95% CI)<br>CR, %<br>PR, % | 55.7 (50.1-61.2)<br>13.9<br>41.8 | 27.4 (22.7-32.6)<br>4.6<br>22.9 |
| SD[c], % | 32.2 | 41.5 |
| PD[d], % | 6.5 | 14.3 |
| Undetermined, % | 5.6 | 16.8 |

[a]Median follow-up time of 67.6 months (range, 60.2-80.2).

[b]ORR was assessed by BICR.

[c]SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. SD may reflect the natural history of disease rather than any effect of the drug.

[d]PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more new lesions is also considered progression.)

BICR, blinded independent central review; CR, complete response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

cabozantinib plus nivolumab at 46.5 months vs 35.5 months for sunitinib.[45] No formal statistical testing was conducted at the time of the updated analysis.

In the primary analysis, the most common all-grade adverse reactions reported in the cabozantinib plus nivolumab arm included diarrhea (64% vs 47% with sunitinib), fatigue (51% vs 50%), hepatotoxicity (44% vs 26%), palmar-plantar erythrodysesthesia (40% vs 41%), and stomatitis (37% vs 46%).[21] Most adverse reactions were grade 1 or 2 in severity; the most frequently reported grade 3 or 4 adverse reactions with cabozantinib plus nivolumab vs sunitinib were hypertension (13% vs 14%), hepatotoxicity (11% vs 5%), fatigue (8% vs 8%), and palmar-plantar erythrodysesthesia (8% vs 8%). The most common laboratory values that worsened with cabozantinib plus nivolumab were increased alanine aminotransferase, increased aspartate aminotransferase, hypophosphatemia, and hypocalcemia. Most of the worsening laboratory values were grade 1 or grade 2. A total of 19.7% of the patients treated with cabozantinib plus nivolumab discontinued treatment owing to an adverse reaction (6.6% discontinued nivolumab only, 7.5% discontinued cabozantinib only, and 5.6% discontinued both nivolumab and cabozantinib) compared with 16.9% of the patients treated with sunitinib.[21]

### *Exploratory Analysis by Site of Metastases*

An exploratory analysis at the 5-year follow-up of the CheckMate-9ER study demonstrated a benefit with cabozantinib plus nivolumab vs sunitinib across patient subgroups with bone, liver, and lung metastases (Table 5). This was particularly notable for patients with bone

**Table 5.** Efficacy Outcomes in Patients According to Site of Metastasis in an Exploratory Analysis at a 5-Year[a] Follow-up of the CheckMate-9ER Study[45]

| Outcomes | Cabozantinib + Nivolumab | Sunitinib |
|---|---|---|
| **Patients with bone metastases, n** | **79** | **75** |
| Median PFS, months | 13.8 | 5.3 |
| HR (95% CI) | 0.43 (0.30-0.64) | |
| ORR, % (95% CI) | 49.4 (37.9-60.9) | 9.3 (3.8-18.3) |
| CR/PR, % | 11.4/38.0 | 0/9.3 |
| Median OS, months | 34.8 | 20.7 |
| HR (95% CI) | 0.66 (0.45-0.95) | |
| **Patients with liver metastases, n** | **73** | **56** |
| Median PFS, months | 10.9 | 6.2 |
| HR (95% CI) | 0.55 (0.37-0.82) | |
| ORR, % (95% CI) | 52.1 (40.0-63.9) | 21.4 (11.6-34.4) |
| CR/PR, % | 9.6/42.5 | 1.8/19.6 |
| Median OS, months | 37.6 | 22.1 |
| HR (95% CI) | 0.65 (0.43-0.97) | |
| **Patients with lung metastases, n** | **241** | **251** |
| Median PFS, months | 16.4 | 8.3 |
| HR (95% CI) | 0.56 (0.46-0.69) | |
| ORR, % (95% CI) | 57.3 (50.8-63.6) | 27.9 (22.4-33.9) |
| CR/PR, % | 11.2/46.1 | 4.0/23.9 |
| Median OS, months | 47.5 | 32.4 |
| HR (95% CI) | 0.75 (0.60-0.94) | |

[a]Median follow-up time of 67.6 months (range, 60.2-80.2).

CR, complete response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

metastases, as these patients typically have a poorer prognosis.[46]

For patients with bone metastases, median PFS reached 13.8 months in the cabozantinib plus nivolumab arm, compared with less than one-half that (5.3 months) in the sunitinib arm (HR, 0.43; 95% CI, 0.30-0.64). A total of 49.4% of patients with bone metastases in the cabozantinib plus nivolumab arm achieved a response, more than 5 times that in patients with bone metastases in the sunitinib arm. Among patients treated with cabozantinib plus nivolumab, several achieved a complete response (11.4%), whereas no patients in the sunitinib arm had a complete response. Median OS was 34.8 months in the cabozantinib plus nivolumab arm compared with 20.7 months in the sunitinib arm.

Note that these exploratory analyses are descriptive in nature. Subgroups were not powered to show differences between treatment arms, and results should be considered hypothesis generating. No formal statistical testing was conducted at the time of the updated analysis.

### *QOL Exploratory Analysis*

Another exploratory analysis at the primary analysis of the CheckMate-9ER study evaluated quality of life

(QOL) during treatment using the Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaire.[21] This questionnaire covers 7 QOL domains: pain, fatigue, pulmonary symptoms, bowel/bladder symptoms, nutritional health, psychosocial functioning, and treatment side effects. In patients treated with cabozantinib plus nivolumab, the mean FKSI-19 score was numerically maintained near baseline for over 1.5 years. Over the same time period, the mean FKSI-19 score among sunitinib-treated patients decreased below baseline, sometimes dropping over 3 points below baseline (a prespecified threshold determined to represent a meaningful difference in QOL). Further, the disease-related symptoms subscale (focused on bone pain, fatigue, lack of energy, overall pain, weight loss, shortness of breath, cough, fever, and blood in the urine) of the FKSI-19 improved above baseline in the cabozantinib plus nivolumab arm but deteriorated below baseline in the sunitinib arm.

## Key Considerations When Selecting an Appropriate Treatment Option

The choice for first-line aRCC treatment is based not only on key disease characteristics such as disease burden, symptom presentation, baseline physical condition, and comorbid conditions, but also on patient goals for treatment.[47]

The patient AK demonstrated multiple bone-only lesions, with no evidence of other organ involvement beyond the kidney. There were 2 primary concerns with this patient. The first was possibility of complications arising from involvement of the pelvic bone. The patient had already had a knee replacement and pathologic fracture in her left leg, and so she was likely putting significant weight on the right side. Keeping that side free from complications was critical. The second concern was her QOL. This patient was retired and active, and really enjoyed golfing. Maintaining her QOL and activity was very important to her.

Cabozantinib plus nivolumab was chosen for AK, as this combination is associated with a balance of data: superior overall survival vs sunitinib, safety and tolerability, and exploratory patient-reported QOL.[21,45] The sustained separation between the OS curves in the primary analysis of the CheckMate-9ER study can be an important factor in treatment decisions, providing patients with a significant survival advantage compared with sunitinib. Furthermore, cabozantinib plus nivolumab is effective regardless of whether the patient presents with de novo metastatic disease or they present with a late relapse in a challenging site, such as the bone. This may be attributed to the multitargeted mechanism of action of cabozantinib.

Additionally, data from the CheckMate-9ER study demonstrate that cabozantinib plus nivolumab has a well-characterized safety and tolerability profile.[21] In fact, cabozantinib plus nivolumab has been associated with probably one of the lowest rates of treatment discontinuation and major toxicities. This is an important consideration, as patients may be on these therapies for many years. Being able to dose the VEGF TKI at a submaximum dose would give AK the best chance at QOL and tolerance of therapy.

For these reasons, AK was started at 40 mg of cabozantinib in combination with nivolumab.

## Conclusion

In the current era of multiple IO–TKI combinations for aRCC, individualized treatment selection has become increasingly important to optimize patient outcomes. Among these options, the combination of cabozantinib plus nivolumab has emerged as a preferred first-line therapy, supported by evidence demonstrating superior OS compared with sunitinib in patients with previously untreated aRCC, along with a favorable safety and tolerability profile and improvements in patient-reported QOL. This regimen is particularly compelling in patients with bone metastases, where cabozantinib's multitargeted activity in the bone microenvironment may confer additional clinical benefit. The patient case presented here exemplifies evidence-based decision-making in this setting, highlighting how patient-specific disease characteristics—such as the presence of bone metastases—can inform the selection of an IO–TKI regimen with demonstrated efficacy in this subgroup.

***Disclosures***

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## References

1. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. NCI SEER Program. Accessed March 19, 2026. https://seer.cancer.gov/statfacts/html/kidrp.html
2. American Cancer Society. What is kidney cancer. Accessed March 19, 2026. https://www.cancer.org/cancer/types/kidney-cancer/about/what-is-kidney-cancer.html
3. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell carcinoma: 2022 update. *Eur Urol*. 2022;82(5):529-542.
4. Powles T, Albiges L, Bex A, et al. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(8):692-706.
5. Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs - part A: renal, penile, and testicular tumours. *Eur Urol*. 2022;82(5):458-468.

6. American Cancer Society. Survival rates for kidney cancer. Accessed March 19, 2026. https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html
7. Shuch B, Amin A, Armstrong AJ, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. *Eur Urol*. 2015;67(1):85-97.
8. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. *Ann Oncol*. 2012;23(4):973-980.
9. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141–148.
10. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009;27:5794–5799.
11. Brown J, Santini D, Charnley N, Ogareva A, Chisholm A, Jones R. Implications of bone metastasis on response to systemic therapy in patients with advanced renal cell carcinoma: a systematic literature review. *Cancer Treat Rev*. 2024;129:102792.
12. Chen SC, Kuo PL. Bone metastasis from renal cell carcinoma. *Int J Mol Sci*. 2016;17(6):987.
13. Grünwald V, Eberhardt B, Bex A, et al. An interdisciplinary consensus on the management of bone metastases from renal cell carcinoma. *Nat Rev Urol*. 2018;15(8):511-521.
14. Opdivo (nivolumab) [prescribing information]. Bristol Myers Squibb. June 2025.
15. Keytruda (pembrolizumab) [prescribing information]. Merck Sharp & Dohme. February 2026.
16. Bavencia (avelumab) [prescribing information]. EMD Serono, Inc. June 2025.
17. Cabometyx (cabozantinib) [prescribing information]. Exelixis, Inc. October 2025.
18. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290.
19. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1116-1127.
20. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103-1115.
21. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841.
22. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384(14):1289-1300.
23. Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) [prescribing information]. Bristol Myers Squibb. November 2025.
24. Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) [prescribing information]. Merck Sharp & Dohme. February 2026.
25. Balan M, Mier y Teran E, Waaga-Gasser AM, et al. Novel roles of c-Met in the survival of renal cancer cells through the regulation of HO-1 and PD-L1 expression. *J Biol Chem*. 2015;290(13):8110-8120.
26. Subramanian M, Hayes CD, Thome JJ, et al. An AXL/LRP-1/RANBP9 complex mediates DC efferocytosis and antigen cross-presentation in vivo. *J Clin Invest*. 2014;124(3):1296-308.
27. Liu H, Sun S, Wang G, et al. Tyrosine kinase inhibitor cabozantinib inhibits murine renal cancer by activating innate and adaptive immunity. *Front Oncol*. 2021;11:663517.
28. Aguilera TA, Rafat M, Castellini L, et al. Reprogramming the immunological microenvironment through radiation and targeting Axl. *Nat Commun*. 2016;7:13898.
29. Zhao GJ, Zheng JY, Bian JL, et al. Growth arrest-specific 6 enhances the suppressive function of $CD4^+CD25^+$ regulatory T cells mainly through Axl receptor. *Mediators Inflamm*. 2017;2017:6848430.
30. Yen BL, Yen ML, Hsu PJ, et al. Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. *Stem Cell Reports*. 2013;1(2):139-151.
31. Hübel J, Hieronymus T. HGF/Met-signaling contributes to immune regulation by modulating tolerogenic and motogenic properties of dendritic cells. *Biomedicines*. 2015 3;3(1):138-148.
32. Elbanna M, Orillion AR, Damayanti NP, et al. Dual inhibition of angiopoietin-TIE2 and MET alters the tumor microenvironment and prolongs survival in a metastatic model of renal cell carcinoma. *Mol Cancer Ther*. 2020;19(1):147-156.
33. Gabrilovich D, Ishida T, Oyama T, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. *Blood*. 1998;92(11):4150-4166.
34. Huang Y, Chen X, Dikov MM, et al. Distinct roles of VEGFR-1 and VEGFR-2 in the aberrant hematopoiesis associated with elevated levels of VEGF. *Blood*. 2007;110(2):624-631.
35. Hirsch L, Flippot R, Escudier B, Albiges L. Immunomodulatory roles of VEGF pathway inhibitors in renal cell carcinoma. *Drugs*. 2020;80(12):1169-1181.
36. Ning H, Shao QQ, Ding KJ, et al. Tumor-infiltrating regulatory T cells are positively correlated with angiogenic status in renal cell carcinoma. *Chin Med J (Engl)*. 2012;125(12):2120-2125.
37. Apolo AB, Nadal R, Tomita Y, et al. Cabozantinib in patients with platinum-refractory metastatic urothelial carcinoma: an open-label, single-centre, phase 2 trial. *Lancet Oncol*. 2020;21(8):1099-1109.
38. Aparicio LMA, Fernandez IP, Cassinello J. Tyrosine kinase inhibitors reprogramming immunity in renal cell carcinoma: rethinking cancer immunotherapy. *Clin Transl Oncol.* 2017;19(10):1175-1182.
39. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell*. 2014;26(5):605-622.
40. Rini BI, Rathmell WK. Biological aspects and binding strategies of vascular endothelial growth factor in renal cell carcinoma. *Clin Cancer Res*. 2007;13(2 Pt 2):741s-746s.
41. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun*. 2016;7:12624.
42. National Comprehensive Cancer Network (NCCN) Guidelines for Kidney Cancer (version 1.2026). July 24, 2025.
43. Esterberg E, Iyer S, Nagar SP, Davis KL, Tannir NM. Real-world treatment patterns and clinical outcomes among patients with advanced renal cell carcinoma. *Clin Genitourin Cancer*. 2024;22(2):115-125.e3.
44. Hall JP, Zanotti G, Kim R, et al. Treatment patterns, outcomes and clinical characteristics in advanced renal cell carcinoma: a real-world US study. *Future Oncol*. 2020;16(36):3045-3060.
45. Motzer RJ, Escudier B, Burotto M, et al. Final analysis of nivolumab plus cabozantinib for advanced renal cell carcinoma from the randomized phase III CheckMate 9ER trial. *Ann Oncol*. 2026;37(1):33-43.
46. Fan Z, Huang Z, Huang X. Bone metastasis in renal cell carcinoma patients: risk and prognostic factors and nomograms. *J Oncol*. 2021;2021:5575295.
47. Barragan-Carrillo R, Saad E, Saliby RM, et al. First and second-line treatments in metastatic renal cell carcinoma. *Eur Urol*. 2025;87(2):143-154.