Case Study Series

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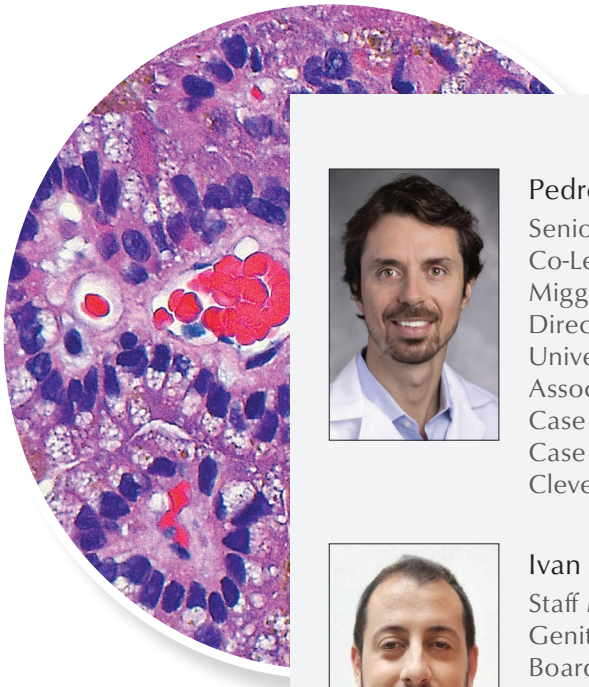
Clinical Response With Cabozantinib Plus Nivolumab, a First-Line Therapy in Advanced Renal Cell Carcinoma: A Clinical Case Report



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In the Clinic . . .

SH is a 47-year-old woman with a history of hypothyroidism and menopause who was diagnosed in March 2019 with Fuhrman grade III clear cell renal cell carcinoma (RCC), pT1b (Table 1). Her tumor was initially resected with laparoscopic right radical nephrectomy. No surveillance follow-up was performed. Her family history was notable for multiple malignancies, including gastric cancer in a sister at age 35, smoking-related lung cancer in her mother, and prostate cancer in her grandfather.

In June 2023, liver lesions were incidentally identified during laparoscopic cholecystectomy. Subsequent computed tomography (CT), fluorodeoxyglucose positron emission tomography, and magnetic resonance imaging demonstrated multiple liver metastases and a heterogeneous pancreatic body/tail mass. CT-guided liver biopsy confirmed metastatic clear cell RCC without sarcomatoid features. Laboratory evaluation showed anemia, elevated lactate dehydrogenase, normal renal and hepatic function, and normal calcium. She had an Eastern Cooperative Oncology Group performance status of 1 with mild gastrointestinal symptoms. At this point, SH was diagnosed with metastatic RCC involving the liver and pancreas, with an intermediate-risk International Metastatic RCC Database Consortium (IMDC) score based on anemia.

Given rapid progression and the need for prompt disease control, she initiated first-line nivolumab plus cabozantinib in September 2023. Imaging showed a marked response, with reduction of the liver lesion from 34 mm

On the Cover
Light micrograph of papillary renal cell carcinoma.

Credit: Ziad M. El-Zaatari/Science Source

Table 1. Patient Case Summary

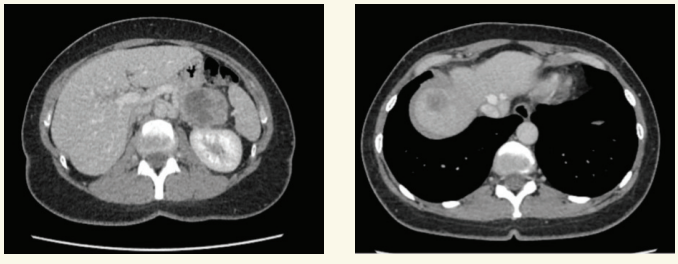
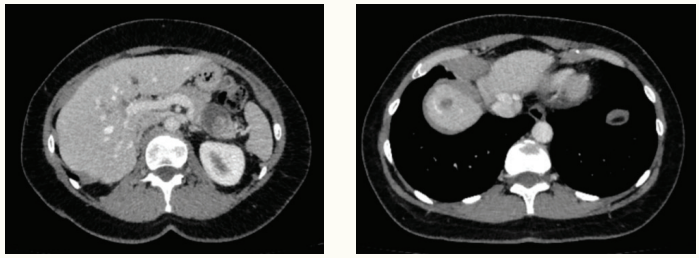
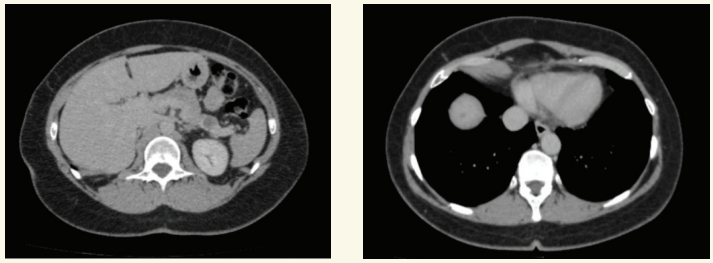
A 47-year-old woman with a past medical history significant for hypothyroidism managed with levothyroxine, and menopause. Family history was notable for malignancy in multiple first-degree relatives, including a sister who died from gastric cancer at 35 years of age, a mother with smoking-related lung cancer who died at 63 years, and a grandfather diagnosed with prostate cancer at 80 years of age.	
03/2019	• Laparoscopic right radical nephrectomy • Pathology: **clear cell renal cell carcinoma** (Fuhrman grade III), pT1b • No surveillance follow-up performed
06/22/2023	Laparoscopic cholecystectomy; incidental finding of liver lesions
07/03/2023	**CT scan** • Chest without lesions • Abdomen: solid-appearing lesion in the pancreatic tail and liver metastases
07/19/2023	**FDG PET** • Pancreas: increased uptake in pancreatic lesion • Liver: mild uptake in lesions in both lobes (SUV 2.1, 8.3, 5.7, and 6)
07/2023	**MRI** • **Liver:** multiple focal lesions in different segments, largest 34 mm in segment VIII, hypointense on T1, hyperintense on T2, with DWI restriction and persistent peripheral arterial enhancement. Findings consistent with multiple liver metastases. • **Pancreas:** mass in the body/tail measuring approximately 56 × 47 mm, heterogeneous, with cystic-necrotic areas, DWI restriction, and heterogeneous post-contrast enhancement
08/2023	CT-guided liver biopsy: clear cell carcinoma without sarcomatoid features **Laboratory** • WBC 10.1 (68%) • Platelets 353,000 • Total bilirubin: normal • Hemoglobin 10.1 • Creatinine 0.74 • LDH 324 • Hematocrit 33 • Liver enzymes: normal • Calcium: normal Patient with ECOG PS 1, occasional nausea and postprandial fullness, no diarrhea or other symptoms suggestive of neuroendocrine activity. Abdomen unremarkable, no palpable lymphadenopathy. **Relapsed clear cell renal cell carcinoma** (liver and pancreas), IMDC intermediate risk (1 point: anemia). Given the rapid disease progression and the need for a prompt response, a combination of an IO and a TKI was chosen.
09/08/2023	C1D1: initiated nivolumab 480 mg every 28 days + cabozantinib 40 mg CT scan: liver lesion 34 mm; pancreatic lesion 56 mm 
01/03/2024	C4D1: nivolumab + cabozantinib CT scan: liver lesion 11 mm; pancreatic lesion 36 mm 

Table 1. Patient Case Summary *continued*

<table>
<tr><td>05/10/2024</td><td>Toxicity: cabozantinib-associated diarrhea → dose reduction to 20 mg</td></tr>
<tr><td>08/19/2024</td><td>Toxicity: grade 2 eczematous rash</td></tr>
<tr><td>09/09/2024</td><td>C12D1: nivolumab + cabozantinib
CT scan: liver lesion 7 mm; pancreatic lesion 19 mm - PR as best response per RECIST
  </td></tr>
<tr><td>12/06/2024</td><td>Toxicity: grade 2 pneumonitis required oral corticosteroids</td></tr>
<tr><td>02/01/2025</td><td>Disease progression in lung, liver, and bone
Lung biopsy: clear cell carcinoma
NGS (Optimus 500 panel):
<table>
<tr><td>BCOR</td><td>NGS</td><td>c.4071del
S1358Pfs*11
VAF: 23,33%</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>CDKN2A</td><td>NGS</td><td>c.238C>T
R80*
VAF:14,31%</td><td>NA</td><td>NA</td><td>1</td></tr>
<tr><td>PBRM1</td><td>NGS</td><td>c.1444-2A>T
VAF:12,81%</td><td>NA</td><td>NA</td><td>1</td></tr>
<tr><td>SETD2</td><td>NGS</td><td>c.6155del
P2052Lfs*95
VAF: 11,06%</td><td>NA</td><td>NA</td><td>1</td></tr>
<tr><td>SF3B1</td><td>NGS</td><td>c.2098A>G
K700E
VAF: 9,93%</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>TMB</td><td>NGS</td><td>Alto: High</td><td>Immunotherapy</td><td>NA</td><td>NA</td></tr>
<tr><td>TP53</td><td>NGS</td><td>c.658T>C
Y220H
VAF: 13,32%</td><td>NA</td><td>NA</td><td>2</td></tr>
<tr><td>VHL</td><td>NGS</td><td>c.266_267dup
N90Sfs*70
VAF: 15,59%</td><td>Belzutifan</td><td>NA</td><td>1</td></tr>
</table></td></tr>
<tr><td>02/21/2025</td><td>Initiated axitinib 5 mg twice daily</td></tr>
<tr><td>05/2025</td><td>Partial response (cycle 3 of axitinib)</td></tr>
<tr><td>09/2025</td><td>Progression in brain and lung; hospitalization owing to seizures and clinical deterioration</td></tr>
<tr><td>11/2025</td><td>SBRT to brain lesion; initiated belzutifan 120 mg daily</td></tr>
<tr><td>01/2026</td><td>Death</td></tr>
</table>

C, cycle; D, day; DWI, diffusion-weighted imaging; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG PET, fluorodeoxyglucose positron emission tomography; CT, computed tomography; IMDC, International mRCC Database Consortium; IO, immunotherapy; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NA, not applicable; NGS, next-generation sequencing; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT, stereotactic body radiotherapy; SUV, standardized uptake value; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; VAF, variant allele frequency; WBC, white blood count.

to 7 mm and the pancreatic lesion from 56 mm to 19 mm by September 2024, consistent with partial response by Response Evaluation Criteria in Solid Tumors. The patient did experience cabozantinib-associated diarrhea that required dose reduction and grade 2 eczematous rash, as well as grade 2 pneumonitis attributed to nivolumab, which required corticosteroid treatment.

In February 2025, SH developed progression in the lung, liver, and bone; lung biopsy confirmed metastasis of the clear cell carcinoma. A next-generation sequencing panel revealed multiple alterations, including mutations in *CDKN2A* and *TP53*, and an overall high tumor mutational burden (TMB-H; 13.3 mutations/Mb). She received second-line axitinib with partial response, followed by progression in the brain and lung in September 2025. Despite hospitalization and treatment owing to seizures and clinical deterioration, SH died in January 2026.

aRCC: Disease Overview and Epidemiology

In 2026, an estimated 80,450 new cases of kidney and renal pelvis cancers are expected to be diagnosed, making it the seventh-most common cancer diagnosis in the United States.[1] Kidney cancer is more common in men than in women, with a median age at diagnosis of 65 years and 77.9% of diagnoses occurring in patients 55 years and older.

Renal cell carcinoma (RCC), the most frequently occurring kidney and renal pelvis cancer, is classified as having either clear cell histology (approximately 70%) or non-clear cell histology (including papillary RCC, chromophobe RCC, and other rare subtypes of RCC).[2] Smoking, obesity, hypertension, and exposure to certain carcinogenic chemicals have been identified as risk factors for RCC. The classic triad of flank pain, gross hematuria, and palpable abdominal mass is present in fewer than 10% of patients and typically indicates advanced disease. In the current era of widespread cross-sectional imaging, the majority of RCC is detected incidentally, with incidental diagnosis rates ranging from 37% to 61%. A subset of patients present with de novo metastatic disease in the absence of localizing symptoms.[3]

In addition, between 6% and 9% of RCC tumors are attributed to the presence of germline cancer-causing mutations.[4] The most recent revision (published in 2022) from the World Health Organization of the classification of urogenital tumors included molecular-driven groupings of RCC: *SMARCB1*-deficient medullary RCC, *TFEB*-altered RCC, *ALK*-rearranged RCC, and *ELOC*-mutated RCC.[5]

Compared with the overall RCC patient population, advanced RCC (aRCC), which includes metastatic disease, has a significantly lower 5-year relative survival (79.2% vs 20.3%).[1] RCC is marked by a high propensity for metastasis, often occurring at multiple distant metastatic sites, the most frequent being the lung (45%), bone (30%), liver (20%), and brain (8%).[6,7] Among these, bone is a particularly challenging metastatic site in aRCC and is associated with poorer clinical outcomes—reduced progression-free survival (PFS) and overall survival (OS), and increased overall burden of illness through skeletal-related events such as pathologic fractures, spinal cord or nerve root compression, and hypercalcemia.[8-10]

In aRCC, the duration of response (DOR)—how long tumor shrinkage or disappearance is maintained following treatment—is becoming increasingly important as a treatment outcome. The introduction of immunotherapy and targeted therapies has markedly improved the percentage of patients who achieve durable responses, with some lasting several years.

aRCC Treatment Landscape

The treatment of first-line aRCC has evolved from a reliance on vascular endothelial growth factor (VEGF)–targeted tyrosine kinase inhibitors (TKIs) to an increasing incorporation of immunotherapy (IO)-based combinations. These combinations include both dual immune checkpoint inhibitor (ICI)–IO regimens (nivolumab plus ipilimumab) as well as IO–TKI combinations including pembrolizumab plus axitinib, pembrolizumab plus lenvatinib, avelumab plus axitinib, and cabozantinib plus nivolumab.[11-19]

Approved over the past decade, these combination regimens (Figure 1) are now the standard of care in aRCC, with superior OS, PFS, and response rates compared with prior single-agent regimens. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Kidney Cancer (version 2.2026) include most of these ICI–IO and IO–TKI combination regimens as Category 1 preferred recommendations in the first-line setting for patients with either favorable or intermediate/poor-risk disease.[20] One exception is the combination of avelumab plus axitinib, which carries a Category 2A other recommendation in either risk group, as it is the only first-line combination that failed to demonstrate a statistically significant OS improvement.

The choice of which combination regimen to initiate is nuanced and based on considerations such as disease risk stratification, comorbidities, toxicity profiles, and patient preferences. Additional factors include the urgency of response: in patients with high disease burden or rapidly progressive disease, IO–TKI combinations may be preferred, given their higher objective response rates (ORRs) and faster depth of response (DepOR). In contrast, IO–IO combinations may be favored when a

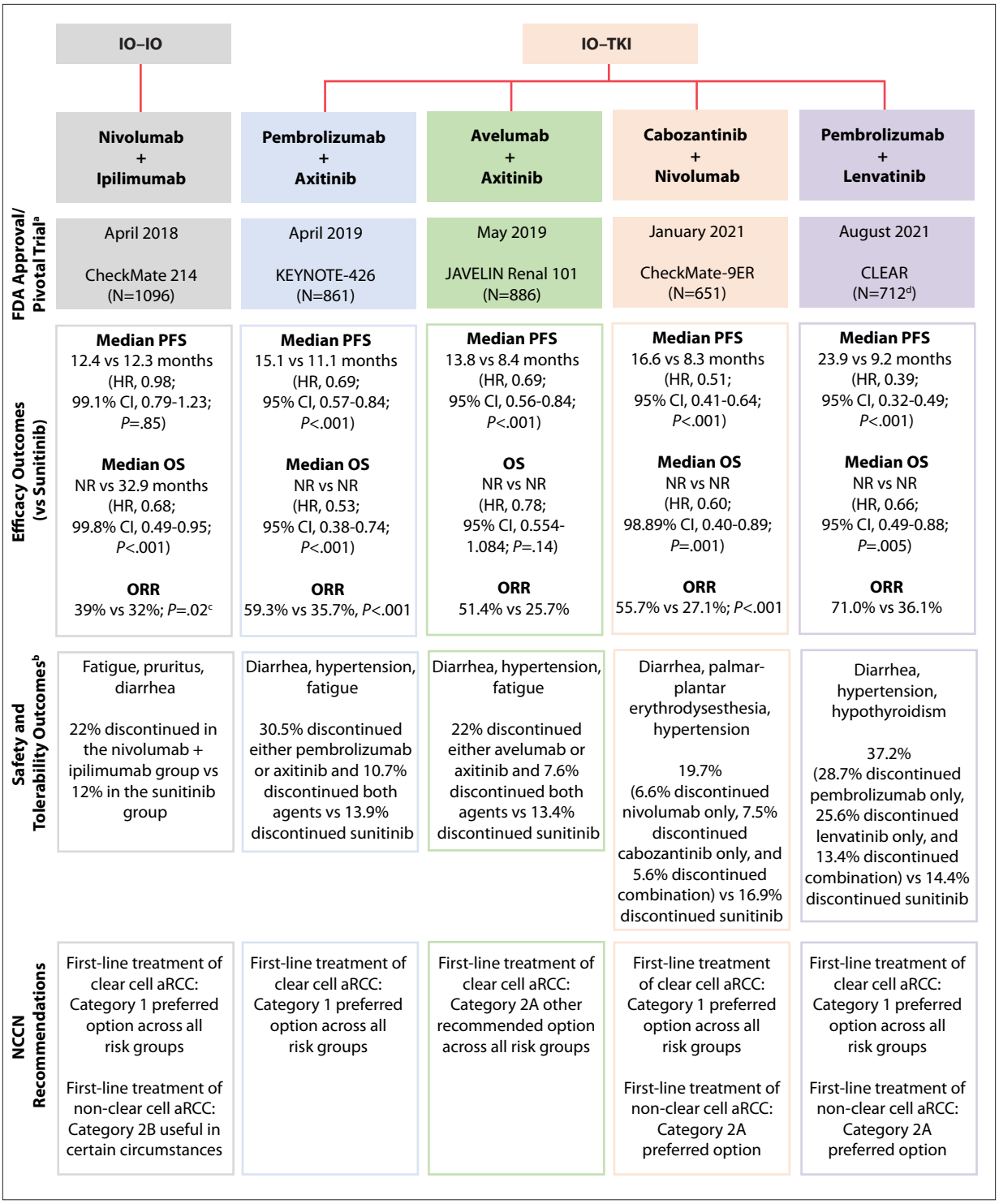


Figure 1. NCCN-preferred FDA-approved combination regimens in the first-line treatment of aRCC.[11-20]

[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.

Table 2. Summary of the Dual Mechanism of Action Attributed to Cabozantinib Plus Nivolumab[11,14,23-36]

Agent	MOA	Description	Effect
Cabozantinib[a]	TKI that inhibits MET, AXL, and VEGFR	• MET inhibition may reduce immune checkpoint expression • AXL inhibition may promote antigen presentation and tumor recognition as well as increased cytotoxic T cells • VEGFR inhibition may normalize vascularization and promote T-cell infiltration • 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, immunotherapy; MOA, mechanism of action; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

more durable response is the primary goal and immediate tumor reduction is less critical. Furthermore, in patients with sarcomatoid differentiation, IO–IO combinations—particularly nivolumab plus ipilimumab—are generally preferred, given the robust and durable responses observed in this histological subgroup. Further, the subcutaneous formulations of the IOs nivolumab and pembrolizumab are now available and indicated for use across the same solid tumor indications approved in adults as the intravenous formulations, providing patients with a potentially more flexible and convenient alternative route of administration for their IO, particularly when combined with a TKI tablet that can be taken at home.[21,22]

In SH's case, first-line cabozantinib plus nivolumab was initiated, and therefore is the focus here. This IO–TKI regimen provides an example of a combination with the potential to achieve both immune modulation and antiangiogenic activity.

Cabozantinib Plus Nivolumab as First-Line Therapy for aRCC

MOA Considerations

The TKI cabozantinib has been shown to inhibit MET, AXL, and VEGFR, tyrosine kinases overexpressed in aRCC tumor cells and important in tumor cell proliferation and metastasis, tumor angiogenesis, and immune cell regulation.[14] Although its clinical significance is unknown, this inhibition may be important for the immunomodulatory properties attributed to cabozantinib. These immunomodulatory properties may attenuate tumor-induced immunosuppression, and in this way cabozantinib may increase the nivolumab-mediated antitumor response induced by immune-checkpoint inhibition (Table 2).[23-36]

CheckMate-9ER: Efficacy Outcomes

CheckMate-9ER was a phase 3, randomized, open-label trial designed to compare the efficacy and safety of the combination of cabozantinib plus nivolumab in a head-to-head fashion with sunitinib monotherapy.[18] Patients (N=651) with previously untreated aRCC with a clear cell component were randomized to either treatment arm, stratified by 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). Treatment was continued until disease progression or unacceptable toxicity, and the primary analysis included a median follow-up of 18.1 months (range, 10.6-30.6 months).

Baseline characteristics were balanced across the treatment arms.[18] The median age was 62 years (range, 29-90) in the cabozantinib plus nivolumab arm and was 61 years (range, 28-86) in the sunitinib arm. Most patients had a Karnofsky performance status of 90 or higher (77.6% and 73.4%, respectively), and about one-half (51.7% and 52.7%, respectively) had metastatic disease. A total of 79% of the total study population had metastatic involvement of 2 or more organs, which is nearly double that seen in the real-world aRCC population (<40%).[7] The most common metastases were lung (75%), bone (23%), and liver (19%). The percentage of patients with

Table 3. PFS, OS, and ORR Outcomes at the 5-Year[a] Follow-up of the CheckMate-9ER Study[18,39]

Outcomes	Cabozantinib + Nivolumab (n=323)	Sunitinib (n=328)	HR (95% CI)
Median PFS, months	16.4	8.3	0.58 (0.49-0.70)
PFS, % 3-year 4-year 5-year	 22.2 16.3 13.6	 10.7 5.6 3.6	
Median OS, months	46.5	35.5	0.79 (0.65-0.96)
OS, % 3-year 4-year 5-year	 58.7 48.9 40.9	 49.5 39.4 35.4	
ORR[b], % (95% CI) CR, % PR, %	55.7 (50.1-61.2) 13.9 41.8	27.4 (22.7-32.6) 4.6 22.9	
SD[c], %	32.2	41.5	
PD[d], %	6.5	14.3	
Undetermined, %	5.6	16.8	
Patients with bone metastases, n	**79**	**75**	
Median PFS, months	13.8	5.3	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	0.66 (0.45-0.95)
Patients with liver metastases, n	**73**	**56**	
Median PFS, months	10.9	6.2	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	0.65 (0.43-0.97)
Patients with lung metastases, n	**241**	**251**	
Median PFS, months	16.4	8.3	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	0.75 (0.60-0.94)

[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; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 4. Median Duration of Response by DepOR Subgroup Overall and After Discontinuation of Treatment[41]

	Responders to cabozantinib plus nivolumab (n=180)[a]			
	CR (n=45)	PR1 (n=27)	PR2 (n=38)	PR3 (n=70)
Overall Median duration of response, months (95% CI)	NR (30.5-NE)	22.1 (15.1-26.0)	21.7 (14.1-30.4)	10.8 (7.0-17.3)
After treatment discontinuation Patients who discontinued treatment, n (%) Median duration of response after treatment discontinuation, months (95% CI)	23 (51) NR (24.2-NE)	8 (30) 18.4 (0.2-NE)	10 (26) NR (0.3-NE)	16 (23) 2.3 (1.2-3.5)

[a]Patients with a CR or PR1/2/3 who were alive at the 6-month time point.

CR, complete response; DepOR, depth of response; NE, not evaluable; NR, not reached; PR1/2/3, partial response and best percentage reduction in sum of diameters of target lesions by ≥80%/≥60 to <80%/<60%.

a favorable IMDC risk score was restricted, with their enrollment limited to 22% of the study population; the remaining patients had either an intermediate (58%) or a poor (20%) IMDC risk score, representing the real-world aRCC population.[37,38]

PFS was the primary endpoint of the CheckMate-9ER study (Table 3).[18] The primary analysis of the intention-to-treat population demonstrated a significant 49% reduction in the risk of progression or death with cabozantinib plus nivolumab compared with sunitinib (hazard ratio [HR], 0.51; 95% CI, 0.41-0.64; *P*<.001). Median PFS was 16.6 months in the combination arm, which was double that reached in the sunitinib arm (8.3 months). More recently, the 5-year follow-up analysis (median follow-up of 67.6 months) demonstrated that this median PFS remained consistent (16.4 vs 8.3 months; HR, 0.58; 95% CI, 0.49-0.70).[39] No formal statistical testing was conducted at the time of the updated analysis.

The ORR was doubled in the combination arm vs the sunitinib arm in the primary analysis (55.7% vs 27.1%; *P*<.001; Table 3).[18] It remained consistent at the 5-year follow-up in both arms (55.7% vs 27.4%). Furthermore, responses with cabozantinib plus nivolumab treatment deepened with time—the complete response rate of 8.0% with cabozantinib plus nivolumab at the primary analysis increased to 13.9% at the 5-year analysis, whereas that with sunitinib was the same at both analyses (4.6%).

Cabozantinib plus nivolumab combination was associated with a significant benefit in OS vs sunitinib (HR, 0.60; 98.89% CI, 0.40-0.89; *P*=.001).[18] Median OS was not reached in either treatment arm in the primary analysis, although an early and sustained separation of the treatment arms was evident in the Kaplan-Meier analysis. At the 5-year follow-up, median OS was 46.5 months with cabozantinib plus nivolumab compared with 35.5 months with sunitinib.[39]

CheckMate-9ER: Safety Outcomes

The most frequent adverse reactions of any grade reported with cabozantinib plus nivolumab vs sunitinib were diarrhea (64% vs 47%), fatigue (51% vs 50%), hepatotoxicity (44% vs 26%), palmar-plantar erythrodysesthesia (40% vs 41%), and stomatitis (37% vs 46%).[18] Grade 3 or 4 adverse reactions reported with cabozantinib plus nivolumab vs sunitinib included hypertension (13% vs 14%), hepatotoxicity (11% vs 5%), fatigue (8% vs 8%), and palmar-plantar erythrodysesthesia (8% vs 8%). Discontinuations owing to adverse reactions were 19.7% in the cabozantinib plus nivolumab arm (6.6% discontinued nivolumab only, 7.5% discontinued cabozantinib only, and 5.6% discontinued both agents) vs 16.9% in the sunitinib arm.

CheckMate-9ER: Exploratory Analysis by Metastatic Site

An exploratory analysis (conducted at the 5-year follow-up) demonstrated the efficacy of cabozantinib plus nivolumab vs sunitinib across patient subgroups with different metastatic involvement (Table 3).[39] In patients with liver metastasis, median PFS was 10.9 vs 6.9 months (HR, 0.55; 95% CI, 0.37-0.82) and in patients with bone metastases (who typically have a poor prognosis[40]), it was 13.8 months vs 5.3 months (HR, 0.43; 95% CI, 0.30-0.64).

CheckMate-9ER: Exploratory Analysis of Quality of Life

An exploratory analysis (conducted at the primary analysis) focused on quality of life (QOL) using the Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaire.[18] In the cabozantinib plus nivolumab arm, the mean FKSI-19 score was numerically maintained near baseline for more than 1.5 years, whereas in the sunitinib arm it deteriorated below baseline (in some cases over 3 points [considered a meaningful difference

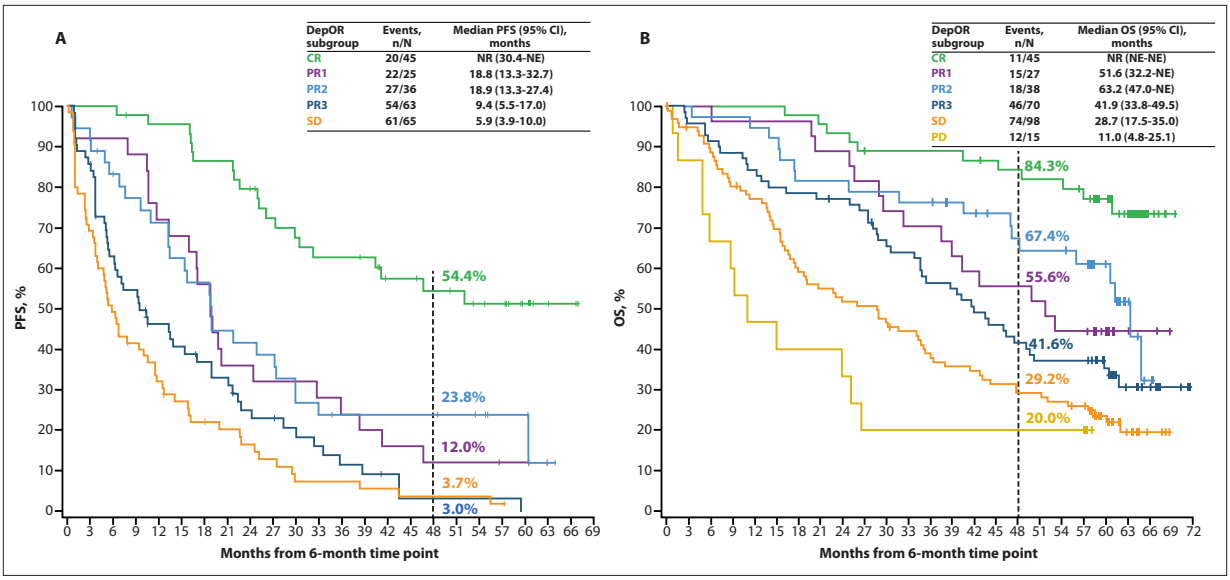


Figure 2. Kaplan-Meier estimates of (A) PFS[a] and (B) OS[b] by DepOR subgroup among patients randomized to cabozantinib plus nivolumab.[41]

[a]Among 234 patients who were alive and progression-free at the 6-month time point.

[b]Among 293 patients who were alive at the 6-month time point.

CR, complete response; DepOR, depth of response; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR1/2/3, partial response and best percentage reduction in sum of diameters of target lesions by ≥80%/≥60 to <80%/<60%; SD, stable disease.

in QOL]) over the same time period. A disease-related symptoms subscale of the FKSI-19 showed an improvement above baseline in the cabozantinib plus nivolumab arm but a decrease below baseline in the sunitinib arm.

Durability of Response With Cabozantinib Plus Nivolumab in aRCC

A post hoc analysis, using data from the final 5-year follow-up of the CheckMate-9ER study (median follow-up, 67.6 months), was conducted to characterize DepOR in patients treated with cabozantinib plus nivolumab.[41] DepOR, defined as the best percentage reduction from baseline in sum of diameters of target lesions, has been linked with improved efficacy outcomes and may be an early indicator of durable efficacy in patients receiving ICI-based regimens or targeted therapies.[42-45]

Among the 293 patients alive at a 6-month post-randomization landmark, 45 (15%) had achieved a complete response. Three subgroups of patients with partial responses were defined according to best percentage reduction in sum of diameters of target lesions—PR1: at least 80% (27 patients [9%]), PR2: at least 60% to less than 80% (38 patients [13%]), and PR3: less than 60% (70 patients [24%]). The median time to response was 2.8 to 2.9 months. Responses were observed even in patients with baseline characteristics associated with poor prognosis in aRCC, including poor IMDC prognostic risk score, sarcomatoid features, 2 or more metastatic sites, and liver metastases.

The response in patients with a complete response was durable (Table 4), as the median DOR was not yet reached at the time of analysis.[41] Among those with a partial response, the median DOR lengthened with greater tumor reduction, increasing from 10.8 months in the PR3 subgroup to 21.7 months in the PR2 subgroup and 22.1 months in the PR1 subgroup. Importantly, durable responses were maintained after patients discontinued treatment.

Greater DepOR was associated with prolonged PFS (Figure 2).[41] This was most apparent in patients with a complete response, among whom the median PFS was not reached. In patients with a partial response, the median PFS lengthened with greater tumor reduction; median PFS was 9.4 months, 18.9 months, and 18.8 months in the PR3, PR2, and PR1 subgroups, respectively. By comparison, in patients with stable disease, the median PFS was 5.9 months.

Similar trends were observed with OS, which was lengthened with greater DepOR (Figure 2).[41] The median OS was not reached in those with a complete response, and in patients with a partial response increased from 41.9 months in the PR3 subgroup to 63.2 months in the PR2 subgroup and 51.6 months in the PR1 subgroup.

The median duration of cabozantinib plus nivolumab treatment was prolonged among those patients who achieved a response as compared with patients with stable disease or progressive disease.[41] Even with this longer treatment exposure, patients with a response did not experience markedly higher rates of treatment-related adverse events (Table 5) compared with patients who did not experience a response (any grade: 99% vs 100%, respectively; grade 3 or 4: 72% vs 67%, respectively). In responding patients, the most frequently reported grade 3 or 4 treatment-related adverse events were similar to those in the overall population, and included hypertension (13%), diarrhea (9%), hyponatremia (8%), and palmar-plantar erythrodysesthesia syndrome (8%).

These post hoc exploratory analyses are descriptive in nature. No statistical procedure was employed. Results should be considered hypothesis-generating.

Table 5. Grade 3/4 TRAEs (in ≥5% of Patients) Since Start of Treatment Among Responders[41]

TRAE, n (%)	Responders to cabozantinib plus nivolumab (n=180)[a]
≥1 grade 3/4 TRAE, n (%)	**111 (62)**
Hypertension	24 (13)
Diarrhea	17 (9)
Hyponatremia	14 (8)
Palmar-plantar erythrodysesthesia syndrome	14 (8)
Increased lipase	13 (7)
Increased alanine aminotransferase	12 (7)
Hypophosphatemia	12 (7)
Increased amylase	11 (6)
Proteinuria	10 (6)

[a]Patients with a CR or PR1/2/3 who were alive at the 6-month time point. CR, complete response; PR1/2/3, partial response and best percentage reduction in sum of diameters of target lesions by ≥80%/≥60 to <80%/<60%. TRAE, treatment-related adverse event.

Cabozantinib Plus Nivolumab: Dosing and Administration in aRCC

In patients with previously untreated aRCC, the recommended starting dosage of cabozantinib is 40 mg once daily by mouth (single tablet dose), continued until disease progression or unacceptable toxicity (Table 6).[14] It is combined with nivolumab, which 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 administered for up to 2 years or until disease progression or unacceptable toxicity.

In the event of intolerable grade 2 adverse reactions, any grade 3 or 4 adverse reactions, or any-grade osteonecrosis of the jaw, it is recommended to withhold cabozantinib.[14] In some cases, prolonged exposure to cabozantinib plus nivolumab may result in chronic grade 2 toxicities that require a dose reduction for management. Following 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). Two cabozantinib tablets are available: a 40 mg tablet and a 20 mg tablet.

Back to the Clinic . . .

This patient case reflects several clinically recognizable trajectories in the management of aRCC. First, the patient experienced relapse approximately 3 years after nephrectomy, which is consistent with the known biology of RCC, where recurrence may occur even after a prolonged disease-free interval. This reinforces the importance of regular surveillance with imaging after nephrectomy, even in patients with initially localized disease.[46]

At relapse, the patient presented with visceral metastatic disease involving the liver and pancreas, a setting in which rapid disease control is clinically important. The decision to initiate first-line cabozantinib plus nivolumab was made because of the need for prompt tumor shrinkage, as was demonstrated in the CheckMate-9ER study, which showed a rapid median time to response of 2.8 months with this regimen. SH's initial response was deep and relatively rapid, with an approximately 80% reduction in target lesions, consistent with the activity expected from an IO–TKI combination.

There are also relevant mechanism of action considerations supporting cabozantinib in this setting. In addition to VEGFR inhibition, cabozantinib targets MET and AXL, pathways implicated in tumor invasiveness, metastatic progression, and resistance biology. These mechanisms may be particularly relevant in patients with aggressive or visceral metastatic phenotypes, including liver involvement.[47]

The dosing approach was consistent with standard practice. Nivolumab was administered at 480 mg every 4 weeks, which may be more convenient than every-2-

Table 6. Recommended Combination Dosing of Cabozantinib Plus Nivolumab in Patients With aRCC[14]

Dosing	Cabozantinib	Nivolumab
Starting dosage	• 40 mg once daily • 1-tablet oral administration	• 240 mg every 2 weeks or 480 mg every 4 weeks • 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 • 3- to 5-minute SC injection
First reduction	• 20 mg once daily • 1-tablet oral administration	• Same as starting dosage
Second reduction	• 20 mg once every other day • 1-tablet oral administration	• Same as starting dosage

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

week dosing, and cabozantinib was initiated at 40 mg daily. Subsequent dose reduction to cabozantinib 20 mg daily because of diarrhea was consistent with guideline-based toxicity management and the prescribing information. Importantly, the patient maintained a meaningful response despite dose reduction, illustrating that dose modification can preserve treatment exposure without necessarily compromising disease control.[48]

The durability of response was clinically meaningful, and was in line with what was expected from this combination. The patient remained on cabozantinib plus nivolumab for approximately 16 months before disease progression, which aligns with the typical PFS time frame observed in the CheckMate-9ER study (median PFS, 16.6 months with this regimen). Although the patient achieved a deep partial response, the development of acquired resistance after 1 to 2 years thus reflects a common treatment outcome.

Overall, this case highlights several practical lessons for clinical care. First-line IO–TKI therapy can produce rapid and substantial responses in patients with visceral metastatic aRCC, including liver and pancreatic disease.[49] Toxicity management is essential to maintain treatment exposure and optimize benefit. The case also demonstrates that subsequent VEGFR TKIs, such as axitinib, may retain activity after prior cabozantinib-based therapy. Finally, the later development of brain metastases underscores the growing importance of central nervous system surveillance as patients live longer and receive multiple lines of therapy.

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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References

1. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. NCI SEER Program. Accessed May 21, 2026. https://seer.cancer.gov/statfacts/html/kidrp.html
2. American Cancer Society. What is kidney cancer. Accessed May 21, 2026. https://www.cancer.org/cancer/types/kidney-cancer/about/what-is-kidney-cancer.html
3. 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.
4. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell carcinoma: 2022 update. *Eur Urol*. 2022;82(5):529-542.
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. 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.
7. 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.
8. 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.
9. 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.
10. Chen SC, Kuo PL. Bone metastasis from renal cell carcinoma. *Int J Mol Sci*. 2016;17(6):987.
11. Opdivo (nivolumab) [prescribing information]. Bristol Myers Squibb. May 2026.
12. Keytruda (pembrolizumab) [prescribing information]. Merck Sharp & Dohme. May 2026.
13. Bavencio (avelumab) [prescribing information]. EMD Serono, Inc. June 2025.
14. Cabometyx (cabozantinib) [prescribing information]. Exelixis, Inc. October 2025.
15. 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.
16. 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.
17. 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.

18. 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.
19. 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.
20. National Comprehensive Cancer Network (NCCN) Guidelines for Kidney Cancer (version 2.2026). April 14, 2026.
21. Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) [prescribing information]. Bristol Myers Squibb. May 2026.
22. Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) [prescribing information]. Merck Sharp & Dohme. May 2026.
23. 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.
24. 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):1296-1308.
25. 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.
26. Aguilera TA, Rafat M, Castellini L, et al. Reprogramming the immunological microenvironment through radiation and targeting Axl. *Nat Commun*. 2016;7:13898.
27. 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.
28. 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.
29. Hübel J, Hieronymus T. HGF/Met-signaling contributes to immune regulation by modulating tolerogenic and motogenic properties of dendritic cells. *Biomedicines*. 2015;3(1):138-148.
30. 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.
31. 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.
32. 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.
33. Hirsch L, Flippot R, Escudier B, Albiges L. Immunomodulatory roles of VEGF pathway inhibitors in renal cell carcinoma. *Drugs*. 2020;80(12):1169-1181.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. Fan Z, Huang Z, Huang X. Bone metastasis in renal cell carcinoma patients: risk and prognostic factors and nomograms. *J Oncol*. 2021;2021:5575295.
41. Suárez C, Motzer RJ, Powles T, et al. Characterization of depth and durability of response in patients with previously untreated advanced renal cell carcinoma who received cabozantinib plus nivolumab: long-term follow-up and exploratory analysis of CheckMate 9ER. Presented at: ASCO Genitourinary Cancers Symposium; San Francisco, CA, USA; February 26-28, 2026. Abstract 508.
42. Grünwald V, McKay RR, Krajewski KM, et al. Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma. *Eur Urol*. 2015;67(5):952-958.
43. Grünwald V, Lin X, Kalanovic D, Simantov R. Early tumour shrinkage: a tool for the detection of early clinical activity in metastatic renal cell carcinoma. *Eur Urol*. 2016;70(6):1006-1015.
44. Grünwald V, Powles T, Kopyltsov E, et al. Survival by depth of response and efficacy by International Metastatic Renal Cell Carcinoma Database Consortium subgroup with lenvatinib plus pembrolizumab versus sunitinib in advanced renal cell carcinoma: analysis of the phase 3 randomized CLEAR study. *Eur Urol Oncol*. 2023;6(4):437-446.
45. Grünwald V, Choueiri TK, Rini BI, et al. Association between depth of response and overall survival: exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 214. Presented at: 44th ESMO Congress (ESMO 2019); Barcelona, Spain; September 27-October 1, 2019. Abstract 950P.
46. Kucharczyk J, Mandalapu K, Satti S, Matrana MR. Outcomes of patients with late-relapse metastatic renal cell carcinoma treated with targeted therapies: a single institution experience. *Ochsner J*. 2017;17(4):331-334.
47. Vano YA, Phan L, Gravis G, et al. Cabozantinib-nivolumab sequence in metastatic renal cell carcinoma: the CABIR study. *Int J Cancer*. 2022;151(8):1335-1344.
48. Apolo AB, Motzer RJ, Powles T, et al. Exposure-response analysis of nivolumab plus cabozantinib in patients with advanced renal cell carcinoma from the phase III CheckMate 9ER trial. *Clin Cancer Res*. 2023;29(9):1662-1670.
49. Singla N, Hutchinson RC, Ghandour RA, et al. Improved survival after development of pancreatic metastasis in patients with metastatic clear cell renal cell carcinoma. *Eur Urol Oncol*. 2020;3(3):382-390.