Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

April 2025 Volume 23, Issue 2, Supplement 4

A SPECIAL MEETING REVIEW EDITION

Highlights in Renal Cell Carcinoma From the American Society of Clinical Oncology Genitourinary Cancers Symposium

A Review of Selected Presentations From the ASCO GU Symposium • February 13-15, 2025 • San Francisco, California

Special Reporting on:

- Cabozantinib in Combination With Nivolumab and Ipilimumab in Previously Untreated Advanced Renal Cell Carcinoma: Final Results of COSMIC-313
- Nivolumab Plus Cabozantinib vs Sunitinib for Previously Untreated Advanced Renal Cell Carcinoma: Final Follow-Up Results From the CheckMate 9ER Trial
- KEYMAKER-U03 Substudy 03B: Pembrolizumab and Targeted Therapy Combinations for Advanced Clear Cell Renal Cell Carcinoma
- Lenvatinib Plus Tislelizumab as First-Line Therapy for Advanced Fumarate Hydratase-Deficient Renal Cell Carcinoma: A Single-Center, Single-Arm, Phase II Study
- Racial Disparities in Renal Cell Carcinoma Histology and Outcomes: Insights From the French Kidney Cancer Research Network (UroCCR-191)
- Casdatifan Monotherapy in Patients With Previously Treated Clear Cell Renal Cell Carcinoma: Safety, Efficacy and Subgroup Analysis Across Multiple Doses from ARC-20, a Phase 1 Open-Label Study
- Cabozantinib in Patients With Non-Locally Pretreated Brain Metastases From Renal Cell Carcinoma: Results of the Multicenter CABRAMET Phase II Trial (NCT03967522)

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Daniel J. George, MD
Eleanor Easley Distinguished Chair in the School of Medicine
Professor of Medicine, Urology, and Surgery
Member of the Duke Cancer Institute
Duke University
Durham, North Carolina

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine (PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

Cabozantinib in Combination With Nivolumab and Ipilimumab in Previously Untreated Advanced Renal Cell Carcinoma: Final Results of COSMIC-313

Combination regimens consisting of a tyrosine kinase inhibitor (TKI) and an immune checkpoint inhibitor (ICI) or 2 ICIs (ipilimumab and nivolumab) are standard approaches for the initial treatment of advanced clear cell renal cell carcinoma (ccRCC).[1] However, there remains a need for more effective regimens.

Cabozantinib is a multitargeted TKI that is approved by the US Food and Drug Administration (FDA) for use as a single agent in patients with advanced RCC (aRCC) and as first-line treatment in combination with nivolumab.[2] In an exploratory analysis of the CheckMate 9ER trial, the triplet combination of cabozantinib, nivolumab, and ipilimumab demonstrated clinical activity in patients with previously untreated aRCC, a finding supporting additional study of this regimen.[3]

The randomized, double-blind, phase 3 COSMIC-313 trial was undertaken to evaluate further the efficacy and safety of adding cabozantinib to nivolumab and ipilimumab in patients with previously untreated intermediate- or poor-risk aRCC per the International Metastatic RCC Database Consortium (IMDC) criteria. A total of 855 patients with previously untreated intermediate- or poor-prognostic-risk aRCC were randomly assigned to 40 mg of cabozantinib daily (n=428) or placebo (n=427). Either was administered with nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg once every 3 weeks for 4 cycles, followed by nivolumab maintenance (480 mg once every 4 weeks) for up to 2 years.[4]

The trial met its primary endpoint, demonstrating a significant improvement in progression-free survival (PFS) with cabozantinib, nivolumab, and ipilimumab vs placebo, nivolumab, and ipilimumab (hazard ratio [HR], 0.73; 95% CI, 0.57-0.94; *P*=.01) after a median follow-up of 14.9 months.[4] In the primary analysis, the PFS benefit in the experimental arm vs the control arm appeared to be greater in intermediate-risk disease (HR, 0.63; 95% CI, 0.47-0.85) than in poor-risk disease (HR, 1.04; 95% CI, 0.65-1.69).

Laurence Albiges, MD, PhD, presented the final results of COSMIC-313 after a median follow-up of 45 months.[5] In this update, cabozantinib, nivolumab, and ipilimumab continued to demonstrate a significant improvement in PFS in comparison with placebo, nivolumab, and ipilimumab, with median PFS of 16.6 and 11.2 months, respectively (HR, 0.82; 95% CI, 0.69-0.98) (Figure 1).

As in the primary analysis, in this update, the benefit of the triplet regimen in this update was restricted to patients in the intermediate-risk subgroup, who made up 75% of the population. Among intermediate-risk patients, the median PFS was 22.1 months with cabozantinib, nivolumab, and ipilimumab vs 11.3 months with placebo, nivolumab, and ipilimumab (HR, 0.76; 95% CI, 0.62-0.93). In the 25% of patients with poor-risk disease, the median PFS was 9.5 months with

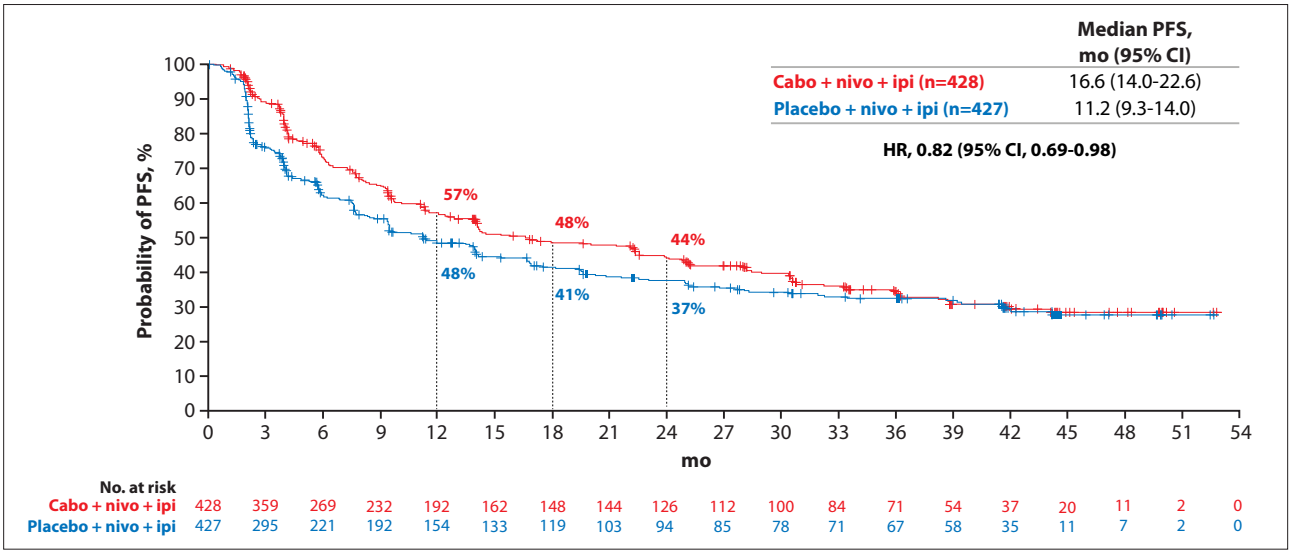


Figure 1. Updated PFS in the ITT population at a median follow-up of 45.0 months in the COSMIC-313 trial. The PFS benefit was maintained with longer follow-up. cabo, cabozantinib; HR, hazard ratio; ipi, ipilimumab; ITT, intention-to-treat; mo, months; nivo, nivolumab; PFS, progression-free survival. Adapted from Albiges L et al. ASCO GU abstract 438. *J Clin Oncol.* 2024;42(4)(suppl).[5]

continues on page 10

1L aRCC

#1 PRESCRIBED TKI+IO COMBINATION IN 1L aRCC

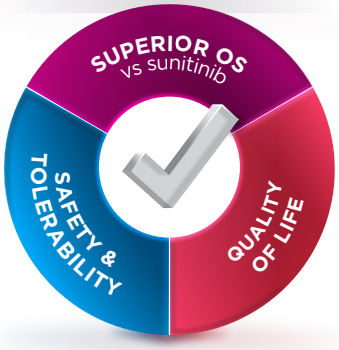
Based on IQVIA BrandImpact data as of December 2024. Subject to change without notice.[1]

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

EFFICACY IN BALANCE

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[2]

A BALANCE OF DATA*



A 1L aRCC treatment that offers a balance of data:
superior OS, safety and tolerability, and patient-reported quality of life[2-4] *

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.[2,3]

Explore the balance of data

1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; IO=immunotherapy; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

INDICATION

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, occurred in CABOMETYX patients. Monitor for signs and symptoms and discontinue in patients with Grade 4 fistulas or GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension including hypertensive crisis. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

Superior PFS and ORR results in the primary analysis[2]

Primary analysis results
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Primary endpoint, assessed by BICR
Double median PFS[2]
16.6 months with CABOMETYX + OPDIVO
(95% CI: 12.5-24.9, n=323)

vs

8.3 months with sunitinib (95% CI: 7.0-9.7, n=328)
HR=0.51 (95% CI: 0.41-0.64; *P*<0.0001)

Secondary endpoint, assessed by BICR
Double ORR[2]
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 8% (n=26/323); PR: 48% (n=154/323)

vs

27.1% with sunitinib (95% CI: 22.4-32.3; n=328);
CR: 4.6% (n=15/328); PR: 23% (n=74/328) (*P*<0.0001)

5-year minimum follow-up analysis
Median follow-up time of 67.6 months; range: 60.2-80.2 months[5]

Primary endpoint, assessed by BICR
PFS[5]
16.4 months with CABOMETYX + OPDIVO
(95% CI: 12.5-19.3; n=323)

vs

8.3 months with sunitinib (95% CI: 7.0-9.7; n=328)
HR=0.58 (95% CI: 0.49-0.70)

Secondary endpoint, assessed by BICR
ORR[5]
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 13.9% (n=45/323); PR: 41.8% (n=135/323)

vs

27.4% with sunitinib (95% CI: 22.7-32.6; n=328);
CR: 4.6% (n=15/328); PR: 22.9% (n=75/328)

No formal statistical testing was conducted at the time of the updated analysis.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) PREFERRED OPTION[6]

Cabozantinib (CABOMETYX) + nivolumab (OPDIVO) was the first TKI + IO regimen with an NCCN recommendation in both clear-cell and non–clear-cell aRCC

NCCN CATEGORY 1, PREFERRED OPTION IN CLEAR-CELL RCC

- **Category 1**, preferred option across all risk groups in 1L clear-cell RCC
- NCCN Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

NCCN PREFERRED OPTION IN NON–CLEAR-CELL RCC

- **Category 2A**, preferred option in non–clear-cell RCC
- NCCN Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

NCCN makes no representations or warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea may be severe. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Proteinuria: Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

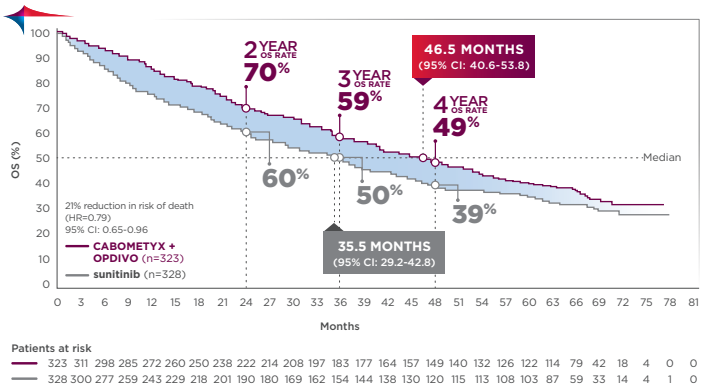
Superior OS outcomes in the primary analysis[2]

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

Primary analysis
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Secondary endpoint
Superior median OS[2]
Median OS was not reached with either CABOMETYX + OPDIVO or sunitinib
HR=0.60 (98.89% CI: 0.40-0.89, *P*=0.001)

5-year minimum follow-up analysis[5]
Median follow-up time of 67.6 months; range: 60.2-80.2 months



No formal statistical testing was conducted at the time of the updated analysis.

CheckMate-9ER was a randomized (1:1), open-label, Phase 3 trial of CABOMETYX + OPDIVO vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint; the clinical significance is unknown.[2,3,7,8]

- **Pre-planned final analysis of OS** (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90)[2,8,9]

BICR=blinded independent central review; CR=complete response; NR=not reached; PO=by mouth; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to fetus. Verify pregnancy status and advise use of effective contraception during treatment and for 4 months after last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

References: 1. Data on file. IQVIA National Prescription Audit. December 2024. Exelixis, Inc. **2.** CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc. **3.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Data on file. Exelixis, Inc. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 9, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841. **8.** Powles T, Choueiri TK, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with 2-year follow-up in CheckMate 9ER: nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. Poster presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. **9.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomized, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898.

DISCOVER MORE AT CABOMETYXhcp.com

EXELIXIS®

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thyroid Cancer
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

5.8 Adrenal Insufficiency
CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 8% of patients receiving CABOMETYX.

Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX.

ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.14 Hypocalcemia
CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

5.15 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), in 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m^2 every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Renal Cell Carcinoma

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes the following terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST[2]	3	3
Increased blood creatinine[2]	3	3
Lymphopenia[2]	1	6
Thrombocytopenia[2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[1] NCI CTCAE Version 4.0
[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values
[3] Includes the following term: hypertension

CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab.

The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal Pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic, and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

Table 5. Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 1-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX- treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

Differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 187 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, hypertension, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX. The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction of CABOMETYX were PPE, diarrhea, fatigue, proteinuria, and decreased appetite. Dose interruptions occurred in 72% patients receiving CABOMETYX. Adverse reactions requiring dosage interruption in ≥5% of patients were PPE, diarrhea, dyspnea, hypertension, decreased appetite and proteinuria. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 5% of patients.

Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311[1]

Adverse Reaction	CABOMETYX (N=125)		Placebo (N=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	51	7	3	0
Nausea	24	3	2	0
Vomiting	14	1	8	0
Stomatitis[3]	26	5	3	0
Dry mouth	10	1	2	0
General				
Fatigue[4]	42	10	23	0
Metabolism and Nutrition				
Decreased appetite	23	3	16	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	10	0	0
Vascular				
Hypertension[5]	30	10	5	3
Investigations				
Weight decreased	18	1	5	0
Nervous System				
Dysgeusia	10	0	0	0
Headache	10	2	2	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	10	0	2	0
Pulmonary embolism	5	2	0	0
Renal and Urinary				
Proteinuria	15	1	3	0

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 5.0

[3] Includes the following terms: mucosal inflammation, stomatitis

[4] Includes the following terms: fatigue, asthenia

[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311[1]

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	Percentage (%) of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] Sponsor-defined grades for LDH were as follows: Grade 1 (> ULN to ≤ 2 × ULN), Grade 2 (> 2 × ULN to ≤ 3 × ULN), Grade 3 (> 3 × ULN).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Based on the limited available data of the effects of CABOMETYX on longitudinal growth, physeal and longitudinal growth monitoring is recommended in children with open growth plates.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

- Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

Revision 10/2023

Distributed by Exelixis, Inc. Alameda, CA 94502

EXELIXIS®

Printed in USA 10/2023 CA-1121-6

continued from page 2

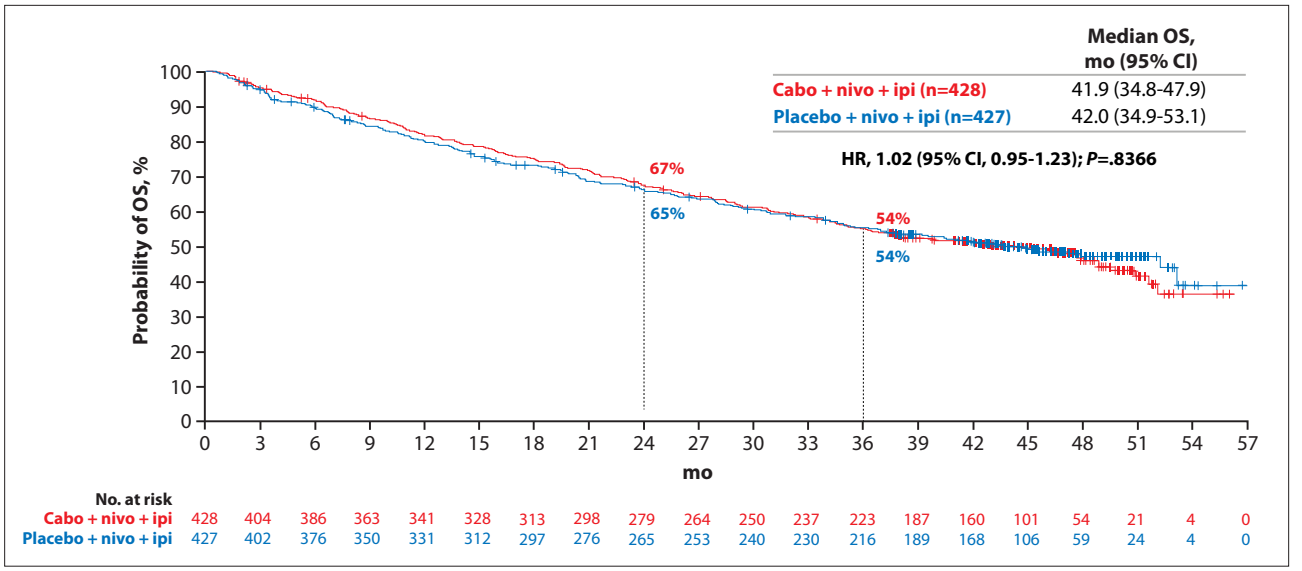


Figure 2. OS in the ITT population at a median follow-up of 45.0 months in the COSMIC-313 trial. OS was comparable between the arms. cabo, cabozantinib; HR, hazard ratio; ipi, ipilimumab; ITT, intention-to-treat; mo, months; nivo, nivolumab; OS, overall survival. Adapted from Albiges L et al. ASCO GU abstract 438. *J Clin Oncol.* 2024;42(4)(suppl).[5]

cabozantinib and 11.2 months with placebo (HR, 1.04; 95% CI, 0.73-1.48).

Overall survival (OS) outcomes were similar in the treatment arms overall and in the 2 IMDC risk groups. In the overall population, the median OS was 41.9 months with cabozantinib, nivolumab, and ipilimumab vs 42.0 months with placebo, nivolumab, and ipilimumab (Figure 2). Approximately half of the patients in each treatment arm subsequently received at least one systemic anticancer therapy. However, the median time to first subsequent systemic therapy was longer with the triplet regimen than with placebo (14.5 vs 9.7 months).

Safety outcomes were consistent with previously reported results.[1] The incidence of grade 3/4 treatment-related AEs was higher with the experimental regimen than with the control regimen (75% vs 43%). The most common grade 3/4 treatment-related AEs in the experimental and control arms were increased alanine aminotransferase (ALT; 26% and 6%, respectively), increased aspartate aminotransferase (AST; 19% and 5%), and diarrhea (5% and 3%). Treatment-related AEs led to discontinuation of at least one regimen component in 49% of patients in the triplet arm and 26% of those in the control arm. Systemic immune-modulating medications for AEs were used in 73% and 56.7% of patients, respectively.

Exploratory biomarker analyses conducted on 398 tumor samples found no clear association between any molecular subset and a PFS or OS benefit with the triplet regimen. However, small sample sizes are a potential limitation of these analyses.

Investigators did report that levels of M2-like macrophages, which are associated with suppression of immune responses and poor prognosis in different cancers,[6,7] were higher in patients with IMDC poor-risk disease than in those with intermediate-risk disease (*P*=.0005) and in patients with visceral

ABSTRACT SUMMARY Metabolic Determinants of Exceptional Response to Immune Checkpoint Inhibition in Renal Cell Carcinoma

Studies have previously reported that the enrichment of genes associated with tertiary lymphoid structures (TLSs) is associated with the development of exceptional responses to ICI therapy in patients with RCC [Hugaboom MB. *Cancer Discov.* 2025]. At ASCO GU 2025, Saliby and colleagues presented results of studies evaluating metabolic factors associated with the development of exceptional responses (Abstract 571). Pre-therapy transcriptomic data were evaluated for 434 patients with previously untreated aRCC who received an ICI plus a VEGF inhibitor in a phase 3 clinical trial. Among the patients with extreme responses to ICI-containing therapy, upregulation of metabolic pathways was more common in those with low TLS scores than in those with high TLS scores, indicating increased metabolic activity. Metabolic activity was also higher in patients with TLS-low extreme responses (n=9) than in those with intermediate responses (n=176; *P*=.00062) or those with progressive disease (n=46; *P*=.00012). In a multivariate analysis, metabolic signature was independently associated with PFS (*P*=.010). The investigators concluded that increased activity of metabolic pathways could be associated with exceptional responses to ICI-based therapy, particularly in patients with low TLS scores.

metastases at baseline (*P*=.01).

Exploratory analyses found that among patients with levels of M2-like macrophage expression in the highest 25%, the triplet regimen appeared to provide a particular benefit vs the control regimen as assessed by PFS (HR, 0.48; 95% CI, 0.29-0.81; *P*=.0058) and OS (HR, 0.51; 95% CI, 0.31-0.86; *P*=.012), suggesting that the addition of cabozantinib to nivolumab and ipilimumab may overcome M2-like macrophage–mediated immune suppression. Preclinical and clinical validation studies to explore these observations further are ongoing.

> We have learned from the COSMIC-313 study that a triplet combination of cabozantinib, nivolumab, and ipilimumab is not for everyone. There may be subsets of patients, however—based on either clinical or immunologic factors—who could in fact benefit from a triplet combination enough to justify the added toxicity of this regimen.
>
> —Daniel J. George, MD

References

1. National Comprehensive Cancer Network (NCCN) guidelines: kidney cancer. Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed March 5, 2025.
2. CABOMETYX® (cabozantinib) prescribing information. Alameda, CA: Exelixis, Inc. Revised September 2023.
3. Apolo AB, Powles T, Escudier B, et al. Nivolumab plus ipilimumab plus cabozantinib triplet combination for patients with previously untreated advanced renal cell carcinoma: results from a discontinued arm of the phase III CheckMate 9ER trial. *Eur J Cancer*. 2022;177:63-71.
4. Choueiri TK, Powles T, Albiges L, et al; COSMIC-313 Investigators. Cabozantinib plus nivolumab and ipilimumab in renal-cell carcinoma. *N Engl J Med*. 2023;388(19):1767-1778.
5. Albiges L, Motzer R, Trevino S, et al. Cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC): final results of COSMIC-313 [ASCO GU abstract 438]. *J Clin Oncol*. 2024;42(4)(suppl).
6. Qu X, Zhao X, Lin K, et al. M2-like tumor-associated macrophage-related biomarkers to construct a novel prognostic signature, reveal the immune landscape, and screen drugs in hepatocellular carcinoma. *Front Immunol*. 2022;13:994019.
7. DeRyckere D, Huelse JM, Earp HS, Graham DK. TAM family kinases as therapeutic targets at the interface of cancer and immunity. *Nat Rev Clin Oncol*. 2023;20(11):755-779.

Nivolumab Plus Cabozantinib vs Sunitinib for Previously Untreated Advanced Renal Cell Carcinoma: Final Follow-Up Results From the CheckMate 9ER Trial

The combination of nivolumab and cabozantinib received FDA approval for the first-line treatment of patients with aRCC in January 2021 on the basis of findings from the randomized, open-label, phase 3 CheckMate 9ER trial, in which nivolumab plus cabozantinib demonstrated significantly improved PFS, OS, and confirmed overall response rate (ORR) in comparison with sunitinib.[1]

The CheckMate 9ER trial randomly assigned 651 patients with previously untreated aRCC of any IMDC risk group to receive 240 mg of nivolumab intravenously every 2 weeks plus 40 mg of cabozantinib once daily (n=323) or 50 mg of sunitinib orally once daily on a 4-weeks-on/2-weeks-off schedule (n=328).[2]

In the primary analysis after a median follow-up of 18.1 months, the trial met its primary endpoint, demonstrating a significant improvement in PFS with nivolumab plus cabozantinib vs sunitinib in a blinded independent central review (BICR; median PFS, 16.6 vs 8.3 months; HR, 0.51; 95% CI, 0.41-0.64; *P*<.001). In addition, improvements were noted in 12-month OS rates (85.7% vs 75.6%; HR, 0.60; 95% CI, 0.40-0.89; *P*=.001) and ORR per BICR (55.7% vs 27.1%; *P*<.001).[2]

Robert J. Motzer, MD, presented final follow-up results from the CheckMate 9ER trial.[3] After a median follow-up of 67.6 months, nivolumab plus cabozantinib continued to show efficacy benefits vs sunitinib in PFS and OS. The median PFS per BICR in the intention-to-treat (ITT) analysis was 16.4 months with nivolumab plus cabozantinib and 8.3 months with sunitinib (HR, 0.58; 95% CI, 0.49-0.70) (Figure 3); 5-year PFS rates were 13.6% with nivolumab plus cabozantinib and 3.6% with sunitinib.

At this final analysis, the 5-year OS rates were 40.9% with nivolumab plus cabozantinib and 35.4% with sunitinib; median OS was 46.5 months with nivolumab plus cabozantinib and 35.5 months with sunitinib (HR, 0.79; 95% CI, 0.65-0.96) (Figure 4). ORR rates were 55.7% and 27.4%, respectively, and the median duration of response (DOR) was 22.0 months with nivolumab plus cabozantinib and 15.2 months with sunitinib.

Exploratory subgroup analyses found differences in the relative benefit of nivolumab plus cabozantinib by IMDC risk group. In the IMDC favorable-risk group, the HR for PFS

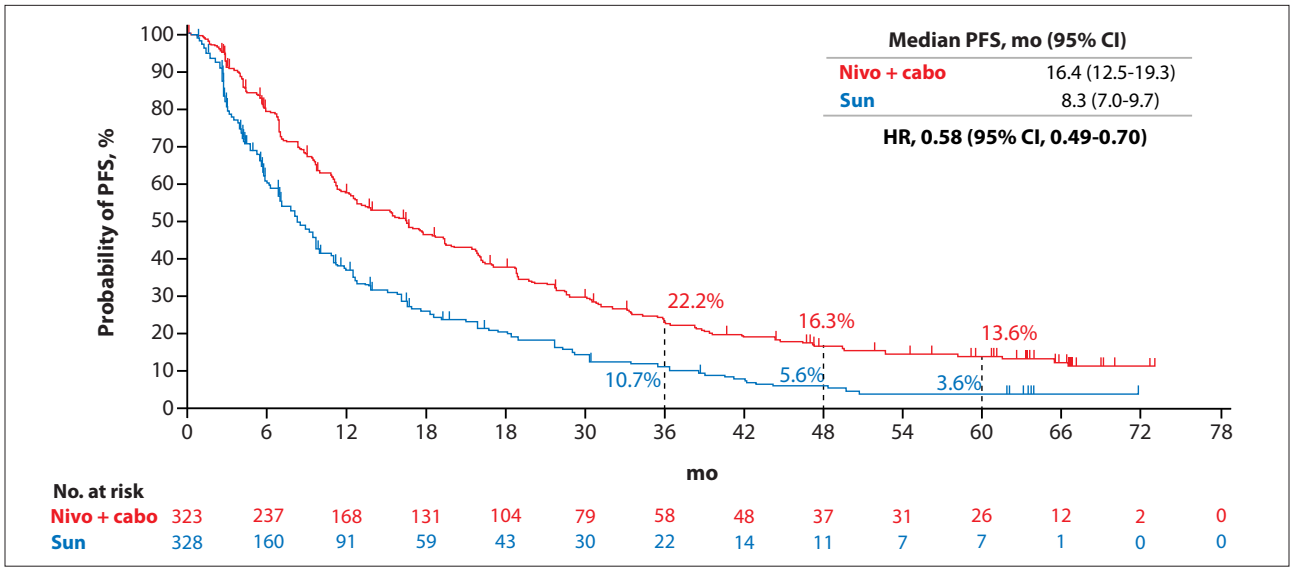


Figure 3. PFS per BICR in the ITT population at a median follow-up of 67.6 months in the CheckMate 9ER trial. A stratified Cox proportional hazards model is used for HR. BICR, blinded independent central review; cabo, cabozantinib; HR, hazard ratio; ITT, intention-to-treat; mo, months; nivo, nivolumab; PFS, progression-free survival; sun, sunitinib. Adapted from Motzer RJ et al. ASCO GU abstract 439. *J Clin Oncol.* 2024;42(4)(suppl).[3]

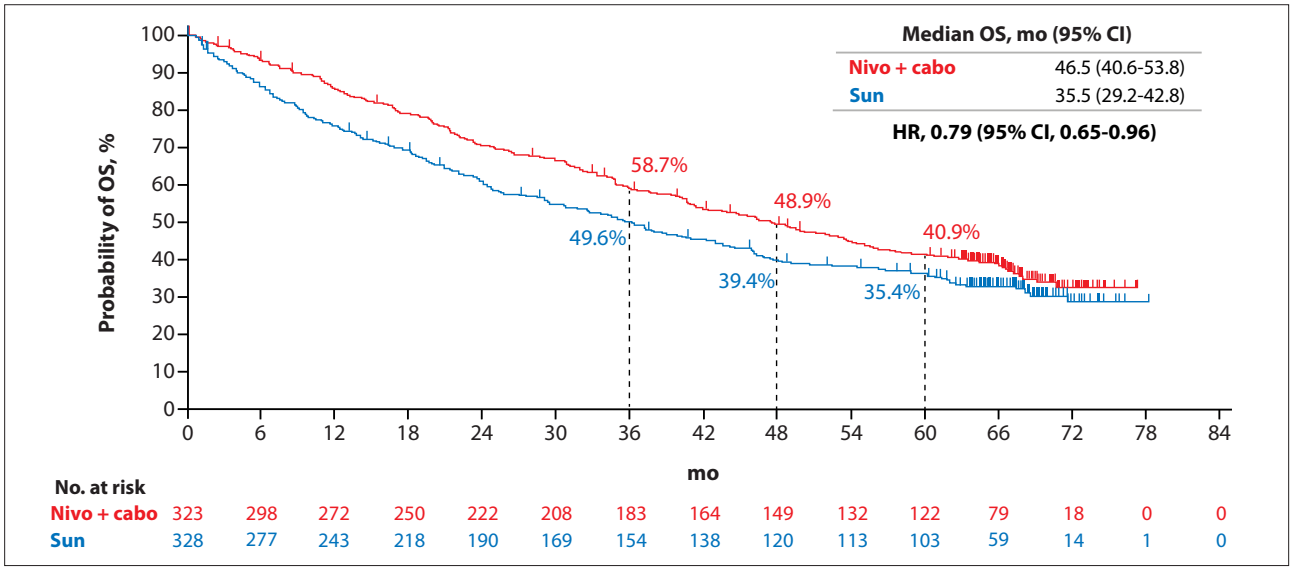


Figure 4. OS in the ITT population at a median follow-up of 67.6 months in the CheckMate 9ER trial. A stratified Cox proportional hazards model is used for HR. cabo, cabozantinib; HR, hazard ratio; ITT, intention-to-treat; mo, months; nivo, nivolumab; OS, overall survival; sun, sunitinib. Adapted from Motzer RJ et al. ASCO GU abstract 439. *J Clin Oncol.* 2024;42(4)(suppl).[3]

with nivolumab plus cabozantinib vs sunitinib was 0.67 (95% CI, 0.46-0.97) and the HR for OS was 1.08 (95% CI, 0.70-1.66). In the intermediate-/poor-risk group, the HR for PFS was 0.56 (95% CI, 0.46-0.69) and the HR for OS was 0.74 (95% CI, 0.60-0.92).

PFS, OS, and ORR all favored nivolumab plus cabozantinib over sunitinib across subgroups by organ site of metastasis, including liver, bone, and lung, at baseline. Subsequent systemic therapy was administered to 43% of patients in the nivolumab-plus-cabozantinib arm and 55% of those in the sunitinib arm.

Dose reductions were required for 62% of patients in the nivolumab-plus-cabozantinib arm and 55% of patients in the sunitinib arm; treatment-related AEs led to discontinuation of any treatment drug in 28% and 11% of patients, respectively. The most frequent grade 3/4 treatment-related AEs reported with nivolumab plus cabozantinib vs sunitinib were diarrhea (7% vs

5%), palmar-plantar erythrodysesthesia (PPE) (8% vs 8%), hypertension (13% vs 13%), fatigue (3% vs 5%), anemia (1% vs 4%), thrombocytopenia (<1% vs 5%), and increased ALT (6% vs 1%). Of 320 patients who received nivolumab plus cabozantinib, 22% required corticosteroids to manage an immune-related AE.

Investigators concluded that this updated analysis demonstrates a long-term efficacy benefit with nivolumab plus cabozantinib vs sunitinib in addition to manageable and consistent safety and tolerability of the regimen, supporting the use of nivolumab plus cabozantinib as a standard of care for patients with previously untreated aRCC.

Subcutaneous nivolumab has shown noninferiority to intravenous nivolumab on the basis of pharmacokinetic properties and ORR.[4] Accordingly, the investigators noted that subcutaneous nivolumab could be considered as an alternative to standard intravenous dosing.

> The final results of CheckMate 9ER demonstrate that this combination of nivolumab plus cabozantinib can result in meaningful long-term survival in patients with previously untreated advanced RCC. This is the first time we have seen such good results with a combination of an immune checkpoint inhibitor and a tyrosine kinase inhibitor.
>
> —Daniel J. George, MD

References

1. U.S. Food & Drug Administration. FDA approves nivolumab plus cabozantinib for advanced renal cell carcinoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma. Accessed March 5, 2025.
2. 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.
3. Motzer R, Escudier B, Burotto M, et al. Nivolumab plus cabozantinib (N+C) vs sunitinib (S) for previously untreated advanced renal cell carcinoma (aRCC): final follow-up results from the CheckMate 9ER trial [ASCO GU abstract 439]. *J Clin Oncol*. 2024;42(4)(suppl).
4. Albiges L, Bourlon MT, Chacón M, et al. Subcutaneous versus intravenous nivolumab for renal cell carcinoma. *Ann Oncol*. 2025;36(1):99-107.

KEYMAKER-U03 Substudy 03B: Pembrolizumab and Targeted Therapy Combinations for Advanced Clear Cell Renal Cell Carcinoma

In most patients with ccRCC, disease progression develops within 4 years after they have received ICI-based first-line combination therapy.[1-3] Although second-line treatment often consists of single-agent regimens,[4] combination therapy for these patients could play a role.

The open-label, rolling arm, umbrella platform, phase 1/2 KEYMAKER-U03 trial is evaluating different combination therapies for patients with locally advanced or metastatic ccRCC previously treated with a programmed death (ligand) 1 (PD-[L]1) inhibitor and a vascular endothelial growth factor (VEGF) TKI. Dr Albiges presented results from 3 arms of KEYMAKER-U03 Substudy 03B, in which 263 patients were randomly assigned to pembrolizumab plus the hypoxia-inducible factor (HIF)-2α inhibitor belzutifan (n=62), lenvatinib plus belzutifan (n=64), or pembrolizumab plus lenvatinib (n=73).[5]

The median age of enrolled patients was approximately 60 to 63 years (range, 32-86 years), 77% were male, and the majority had favorable-risk (22%) or intermediate-risk (65%)

ABSTRACT SUMMARY *FGD1* Splice Variants as Predictors of Brain and Bone Metastatic Organotropism in Clear Cell Renal Cell Carcinoma

Miller and colleagues presented results of a study evaluating associations between presence of the *FGD1*-splice variant (*FGD1*-SV) and risk of metastasis to different sites in patients with metastatic ccRCC from the ORIENT AVATAR network of National Cancer Institute–designated cancer centers (Abstract 577). The presence of *FGD1*-SV was assessed in tumor samples from 461 patients who had metastatic ccRCC with metastases to the brain (n=66), bone (n=148), bone and brain (n=19), or other sites (n=276). The overall rate of *FGD1*-SV positivity was 23% but was higher in those with brain metastases (50%) or bone metastases (44%). In a grouped analysis, the rate of *FGD1*-SV positivity was increased more than 5-fold in patients who had brain or bone metastases in comparison with patients who had metastases in all other sites (OR, 5.33; *P*=.002). *FGD1*-SV in primary tumors was associated with significantly shorter OS (*P*=.0029). However, 73 patients in the cohort had received cabozantinib, and 12 of these patients tested positive for *FGD1*-SV. In this subset, *FGD1*-SV positivity was not associated with shorter OS (HR, 1.47; *P*=.4). Finally, preclinical studies found that knockdown of *FGD1* was associated with reduced growth and migration of RCC cells in vitro.

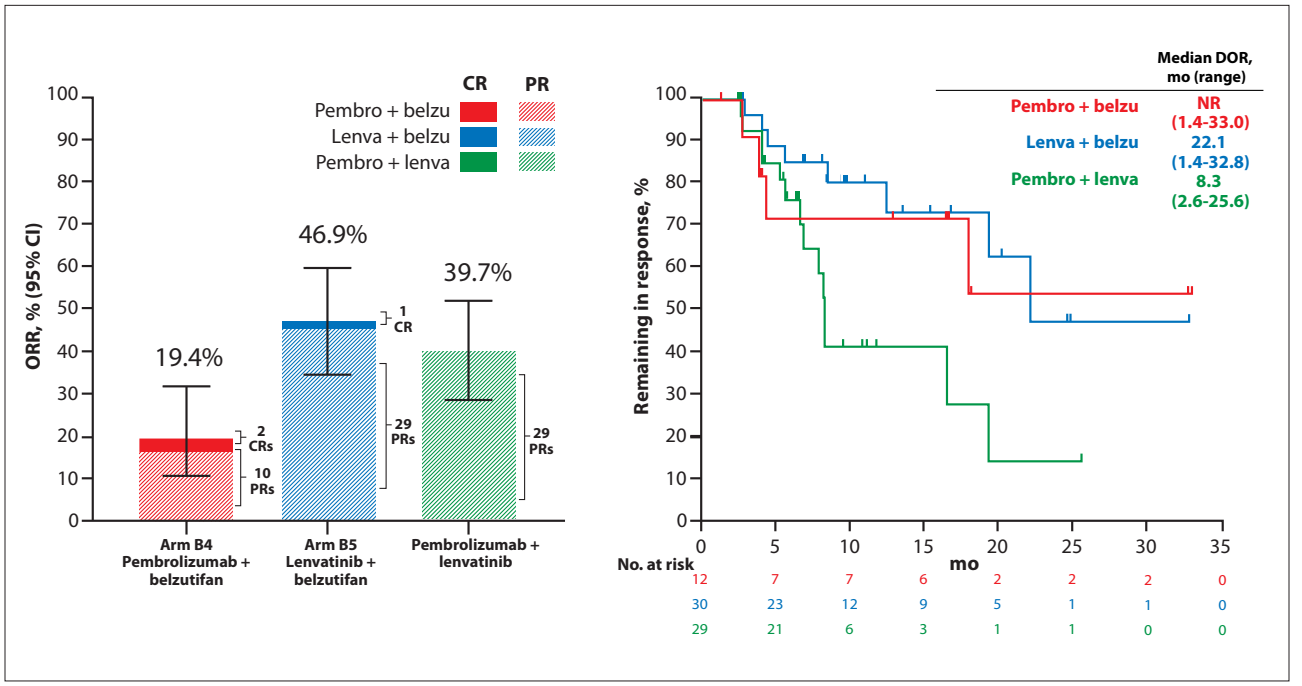


Figure 5. ORR per RECIST v1.1 by BICR in the KEYMAKER-U03 trial. The data cutoff date was March 22, 2024. belzu, belzutifan; BICR, blinded independent central review; CR, complete response; DOR, duration of response; lenva, lenvatinib; mo, months; NR, not reached; ORR, objective response rate; pembro, pembrolizumab; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1. Adapted from Albiges L et al. ASCO GU abstract 440. *J Clin Oncol.* 2024;42(4)(suppl).[5]

disease. Most patients (85%) had received at least 2 prior lines of therapy.

Lenvatinib plus belzutifan was associated with a high ORR of 46.9%, a median DOR of 22.1 months, a median PFS of 12.5 months by BICR, and an 18-month OS rate of 74.4% (Figure 5).[5] Pembrolizumab plus lenvatinib was associated with an ORR of 39.7%, a median DOR of 8.3 months, a median PFS of 9.4 months, and an 18-month OS rate of 73.2%. Pembrolizumab plus belzutifan was associated with an ORR of 19.4%, a median PFS of 5.4 months, and an 18-month OS rate of 57.6%.

The most frequent treatment-related AEs that were observed with pembrolizumab plus belzutifan were anemia (69.4%) and fatigue (24.2%). The most frequent treatment-related AEs that were observed with lenvatinib plus belzutifan were anemia (65.1%), fatigue (46.0%), diarrhea (42.9%), nausea (38.1%), hypertension (36.5%), proteinuria (36.5%), decreased appetite (27.0%), and PPE (23.8%). The most frequent treatment-related AEs that were observed with pembrolizumab plus lenvatinib were diarrhea (56.2%), hypertension (52.1%), fatigue (34.2%), proteinuria (31.5%), PPE (26.0%), and hypothyroidism (26.0%).

Investigators noted that the AEs were generally manageable, and safety profiles were consistent with the established safety profiles for each agent. The ongoing randomized, phase 3 LITESPARK-011 trial is comparing lenvatinib plus belzutifan vs cabozantinib in patients with aRCC previously treated with anti–PD-(L)1 therapy.[5]

The results of the 03B substudy demonstrate the value of a multi-arm, early-phase drug development plan to select promising regimens for further study. In this case, the combination of lenvatinib and belzutifan showed greater promise than pembrolizumab and belzutifan, supporting further development of lenvatinib plus belzutifan in this refractory patient population.
—Daniel J. George, MD

References

1. Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with

nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer*. 2022;128(11):2085-2097.
2. Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898.
3. Motzer RJ, Porta C, Eto M, et al; CLEAR Trial Investigators. Lenvatinib plus pembrolizumab versus sunitinib in first-line treatment of advanced renal cell carcinoma: final prespecified overall survival analysis of CLEAR, a phase III study. *J Clin Oncol*. 2024;42(11):1222-1228.
4. National Comprehensive Cancer Network (NCCN) guidelines: kidney cancer. Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed March 5, 2025.
5. Albiges L, Suárez C, Powles T, et al. KEYMAKER-U03 Substudy 03B: pembrolizumab (pembro) and targeted therapy combinations for advanced clear cell renal cell carcinoma (ccRCC) [ASCO GU abstract 440]. *J Clin Oncol*. 2024;42(4)(suppl).

Lenvatinib Plus Tislelizumab as First-Line Therapy for Advanced Fumarate Hydratase-Deficient Renal Cell Carcinoma: A Single-Center, Single-Arm, Phase II Study

Fumarate hydratase-deficient RCC (FH-RCC) is a rare, aggressive type of RCC that is caused by germline or sporadic mutations in the *FH* gene. These mutations lead to the accumulation of fumarate, which activates HIF, in turn promoting tumorigenesis.[1] The combination of bevacizumab and erlotinib is considered a standard therapy for FH-RCC; it demonstrated an ORR of 72.1% in patients with hereditary leiomyomatosis and RCC (HLRCC) and of 35% in patients with sporadic papillary RCC in a prospective phase 2 trial.[2,3]

In a retrospective study, response rates were comparable with bevacizumab plus erlotinib and an ICI plus a TKI (30% vs 33%), but OS on systemic treatment appeared to be longer in the ICI-plus-TKI group (HR, 0.19; 95% CI, 0.04-0.90).[4]

Wen Kong, MD, presented results of a single-center, single-arm, phase 2 study evaluating lenvatinib plus tislelizumab as first-line therapy for patients with advanced FH-RCC.[5] The trial enrolled 20 patients with previously untreated advanced FH-RCC (median age, 41.5 years; range, 24-62 years); 80% of the patients were male, and most had intermediate- (55%) or poor-risk (30%) disease by IMDC classification. Prior nephrectomy had been performed in 75% of the patients, and the median number of disease sites was 3 (range, 1-6). Most patients (75%) had germline mutations.

Patients received 200 mg of tislelizumab intravenously every 3 weeks plus 20 mg of lenvatinib orally once daily. Efficacy was assessed after a median follow-up of 9.7 months. The ORR was 90%, including a 20% complete response (CR) rate (Figure 6). The disease control rate (DCR), defined as attainment of at least stable disease (SD) at 12 weeks, was 100%, indicating no cases of primary progression during the study. Responses were observed in both hereditary and sporadic FH-RCC.

The median time to response to lenvatinib plus tislelizumab was 6 weeks. At the time of the last assessment, progressive disease (PD) had occurred in 4 patients. In this small cohort with limited follow-up, the 6-month PFS and OS rates were 85% and 100%, respectively. Three patients proceeded to undergo definitive surgery with or without radiotherapy, and 17 of 20 patients remained on treatment at the time of last follow-up.

Response	Cohort (n=20)
ORR, % (95% CI)	90 (66.9-98.3)
Best response, No. (%)	
CR	4 (20)
PR	14 (70)
SD	2 (10)
PD	0 (0)
DCR, % (95% CI)	100 (80.0-100)
CBR, % (95% CI)	85 (61.1-96.0)
Median PFS, mo	NR

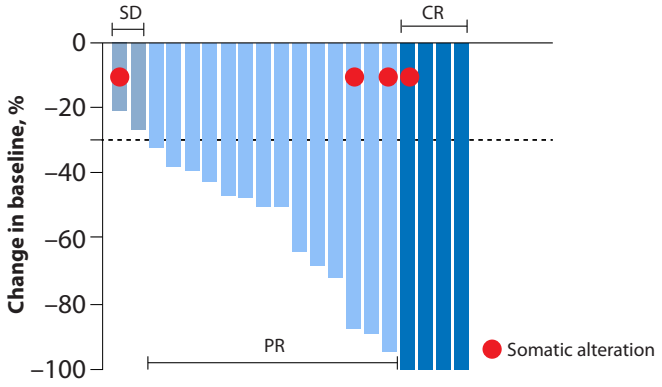


Figure 6. Efficacy in a phase 2 study of lenvatinib plus tislelizumab. The median follow-up was 9.7 (1.4-15.2) months, the ORR was 90% (18/20), and the DCR was 100%. Both hereditary and sporadic FH-RCC benefited from the treatment. CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; FH-RCC, fumarate hydratase–deficient renal cell carcinoma; mo, months; NR, not reached; ORR, objective response rate; PR, partial response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Kong W et al. ASCO GU abstract 443. *J Clin Oncol*. 2024;42(4)(suppl).[5]

ABSTRACT SUMMARY Evaluating the Efficacy of Cabozantinib in Patients With Advanced Renal Cell Carcinoma With Bone Metastasis: An Open-Label Phase 2 Study

Hongo and colleagues presented the results of an exploratory, multicenter, open-label, phase 2 study evaluating the effects of cabozantinib on bone metastases in patients with advanced ccRCC in Japan (Abstract 535). The study enrolled 31 patients with a median age of 70.0 years, 77.4% of whom had received at least one prior systemic therapy. Patients received 60 mg of cabozantinib once daily. The primary endpoint, independent review committee (IRC)-assessed ORR of bone target lesions according to the MD Anderson bone response criteria, was 6.5% (2/31); both responses were PRs. The DCR was 90.3%, and the median rate of tumor shrinkage was 5.2% (range, –42.8% to 19.2%). IRC-assessed bone-specific PFS was not evaluable owing to a short follow-up period and high rate of early censoring. Bone metastasis events occurred in 4 patients (12.9%). Radiotherapy or surgery was administered to 3 patients (9.7%) for symptomatic skeletal events. The most common treatment-emergent AEs were PPE (54.8%), malaise (45.2%), hypertension (32.3%), abnormal hepatic function (32.3%), and diarrhea (32.3%). The investigators concluded that cabozantinib may suppress the progression of bone target lesions in patients with aRCC.

Grade 3 or higher AEs occurred in 45% of patients; dose reductions of lenvatinib were required in 45% of patients, and tislelizumab was discontinued in 15%. The most frequent AEs were hypertension (80%), thyroid-stimulating hormone elevation (80%), proteinuria (65%), pharyngolaryngeal pain (45%), and hyperuricemia (40%).

Investigators concluded that the regimen showed encouraging efficacy and an acceptable safety profile. However, follow-up is limited, the data are immature, and the sample size is small for this single-center study, highlighting the need for an expanded validation study.

References

1. Lindner AK, Tulchiner G, Seeber A, Siska PJ, Thurnher M, Pichler R. Targeting strategies in the treatment of fumarate hydratase deficient renal cell carcinoma. *Front Oncol*. 2022;12:906014.
2. National Comprehensive Cancer Network (NCCN) guidelines: kidney cancer. Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed March 5, 2025.
3. Srinivasan R, Gurram S, Al Harthy M, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer [ASCO abstract 5004]. *J Clin Oncol*. 2020;38(15)(suppl).
4. Xu Y, Kong W, Cao M, et al. Genomic profiling and response to immune checkpoint inhibition plus tyrosine kinase inhibition in FH-deficient renal cell carcinoma. *Eur Urol*. 2023;83(2):163-172.
5. Kong W, Wu G, Xu Y, Wang Z, Zhang J. Lenvatinib plus tislelizumab as first-line therapy for advanced fumarate hydratase-deficient renal cell carcinoma: a single-center, single-arm, phase II study [ASCO GU abstract 443]. *J Clin Oncol*. 2024;42(4)(suppl).

This phase 2 study suggests possible efficacy with lenvatinib plus the novel PD-1 inhibitor tislelizumab. It is not clear mechanistically why this combination would be different from other combinations of tyrosine kinase inhibition plus immunotherapy, which have produced more modest results in the past, but the regimen is worthy of further investigation in a randomized controlled study. —Daniel J. George, MD

Racial Disparities in Renal Cell Carcinoma Histology and Outcomes: Insights From the French Kidney Cancer Research Network (UroCCR-191)

Racial disparities in RCC have been reported in US populations. Multiple studies have shown that papillary RCC occurs more frequently in Black than in non-Black individuals.[1-3] Moreover, among patients with ccRCC, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program have reported lower 5-year OS rates in Black than in White patients (67.1% vs 72.6%).[3]

Whereas disparities in the United States have been well documented, they have not been evaluated to the same extent in Europe, which uses a universal healthcare system. Xiaofan Lu, PhD, reported outcomes from UroCCR-191, a retrospective study conducted by the French Kidney Cancer Research Network that evaluated racial disparities among patients with RCC in France.[4]

The UroCCR database analysis included 9404 patients with data collected between 1987 and 2024. Black patients accounted for 3.6% of the cohort. The median follow-up was 28.5 months.

Investigators reported differences in the incidence of various RCC histologies by race. Among non-Black patients, 68.8% of cases were ccRCC

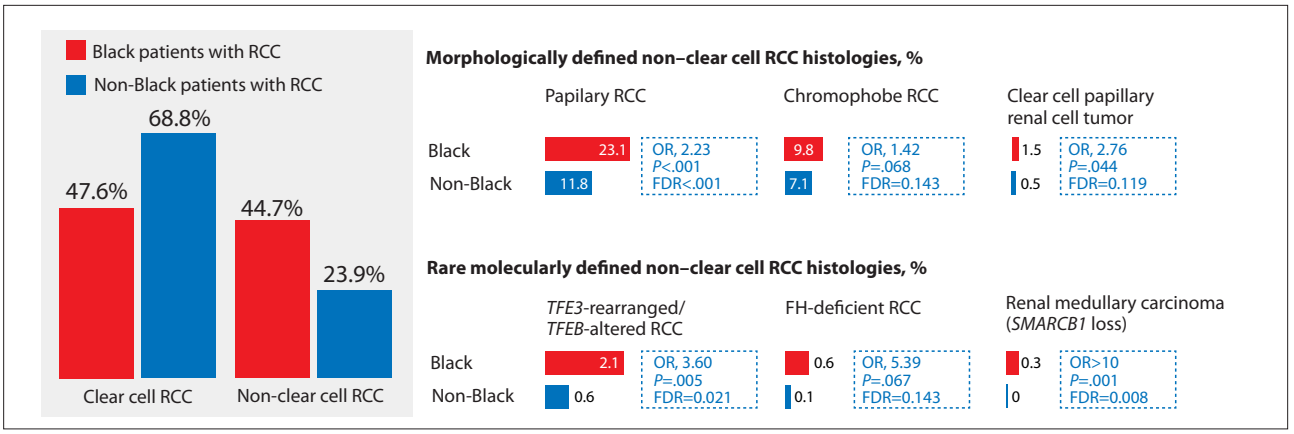


Figure 7. Results of the UroCCR-191 study comparing RCC histologies according to racial backgrounds. Bar lengths for rare molecularly defined histologies are scaled × 10 for visibility. FDR, false discovery rate; FH, fumarate hydratase; OR, odds ratio (calculated with Haldane-Anscombe correction when applicable); RCC, renal cell carcinoma. Adapted from Lu X et al. ASCO GU abstract 442. *J Clin Oncol.* 2024;42(4)(suppl).[4]

and 23.9% were non-ccRCC (Figure 7). In contrast, among Black patients, 47.6% of cases were ccRCC and 44.7% were non-ccRCC.

The most frequent morphologically defined non-ccRCC histologies were papillary RCC, accounting for 23.1% of cases in Black patients and for 11.8% of cases in non-Black patients (odds ratio [OR], 2.23; *P*<.001), chromophobe RCC (9.8% vs 7.1%; OR, 1.42; *P*=.068), and clear cell papillary renal cell tumor (1.5% vs 0.5%; OR, 2.76; *P*=.044).

Rare molecularly defined non-ccRCC histologies included *TFE3*-rearranged/*TFEB*-altered RCC, which was reported in 2.1% of Black patients and 0.6% of non-Black patients (OR, 3.60; *P*=.005), FH-deficient RCC (0.6% vs 0.1%; OR, 5.39; *P*=.067), and renal medullary carcinoma (*SMARCB1* loss; 0.3% vs 0%; OR>10; *P*=.001). The false discovery rate was below 0.15 for all subsets.

Investigators stated that Black patients were younger at diagnosis than non-Black patients, had earlier-stage tumors, and had higher rates of partial nephrectomy, although these data were not reported.

In a multivariate Cox regression analysis, distant recurrence–free survival (dRFS) was not significantly shorter in Black than in non-Black patients (adjusted HR, 0.96; 95% CI, 0.51-1.80; *P*=.894). Factors that were independently associated with dRFS outcomes included age at diagnosis, sex, nephrectomy type, tumor (T) stage, node (N) stage, and Fuhrman grade.

The investigators concluded that in France, non-ccRCC histologies, including rare molecularly defined histologies, were more common in Black than in non-Black patients with RCC. Moreover, race was not independently predictive of clinical outcomes in this analysis from a universal healthcare system.

Reported limitations include a small number of rare non-ccRCC cases, the use of binary Black vs non-Black race categories, and a short median follow-up of less than 2.5 years.

References

1. Sankin A, Cohen J, Wang H, Macchia RJ, Karaniko-

ABSTRACT SUMMARY Real-World Treatment Patterns and Clinical Outcomes in Patients With Metastatic Renal Cell Carcinoma in the US Community Setting

Brown-Bickerstaff and colleagues presented results of an analysis evaluating the use of first-line TKIs and clinical outcomes among patients with metastatic RCC receiving care in a network of US community oncology practices (Abstract 470). A total of 308 patients were matched in a 1:1:1:1 ratio by first-line treatment with ipilimumab plus nivolumab (n=77), nivolumab plus cabozantinib (n=77), pembrolizumab plus axitinib (n=77), or pembrolizumab plus lenvatinib (n=77) on the basis of IMDC risk score, sex, and age (<60 vs ≥60 years). Among patients receiving an ICI plus a TKI, the proportion of those receiving a TKI dose below the label recommendation was higher with lenvatinib (29.9%) than with cabozantinib (15.6%) or axitinib (11.7%). The median time to next treatment was significantly longer with nivolumab plus cabozantinib (8.4 months) than with pembrolizumab plus axitinib (10.0 months; HR, 1.58; 95% CI, 1.04-2.39) or pembrolizumab plus lenvatinib (9.4 months; HR, 1.57; 95% CI, 1.04-2.37) and was numerically longer than with nivolumab plus ipilimumab (8.4 months; HR, 1.45; 95% CI, 0.96-2.19). After a median follow-up of 8.8 to 14.1 months, median OS had been reached only for pembrolizumab plus lenvatinib, at 18.4 months. The 12-month OS rate was higher for nivolumab plus cabozantinib (76.8%) than for pembrolizumab plus axitinib (66.9%), ipilimumab plus nivolumab (66.3%), or pembrolizumab plus lenvatinib (64.8%).

las N. Rate of renal cell carcinoma subtypes in different races. *Int Braz J Urol*. 2011;37(1):29-32.
2. Olshan AF, Kuo TM, Meyer AM, Nielsen ME, Purdue MP, Rathmell WK. Racial difference in histologic subtype of renal cell carcinoma. *Cancer Med*. 2013;2(5):744-749.
3. Chow WH, Shuch B, Linehan WM, Devesa SS. Racial disparity in renal cell carcinoma patient survival according to demographic and clinical characteristics. *Cancer*. 2013;119(2):388-394.
4. Lu X, Bernhard JC, Audenet F, et al. Racial disparities in renal cell carcinoma histology and outcomes: insights from the French Kidney Cancer Research Network (UroCCR-191) [ASCO GU abstract 442]. *J Clin Oncol*. 2024;42(4)(suppl).

This incredibly large data set from France underscores the need for tailored RCC management that considers racial backgrounds in defining diagnosis and outcomes. At the same time, the absence of race as an independent prognostic factor highlights the potential influence of healthcare systems in modulating racial disparities.
—Daniel J. George, MD

Casdatifan Monotherapy in Patients With Previously Treated Clear Cell Renal Cell Carcinoma: Safety, Efficacy and Subgroup Analysis Across Multiple Doses from ARC-20, a Phase 1 Open-Label Study

Casdatifan is an investigational HIF-2α inhibitor that is being evaluated as monotherapy and in combination with other agents in patients with advanced RCC and other solid tumors in the phase 1 dose-escalation and dose-expansion ARC-20 study (Figure 8).[1]

Toni K. Choueiri, MD, presented results of ARC-20 in 3 cohorts of patients with previously treated ccRCC.[2] Patients received 50 mg of casdatifan as monotherapy twice daily (BID; n=33), 50 mg once daily (QD; n=31), or 100 mg QD (n=29). The primary outcomes were AEs and dose-limiting toxicities (DLTs); secondary outcomes included ORR and pharmacokinetics, and exploratory outcomes included PFS, OS, and biomarkers.

The median age of enrolled patients was 60 to 65 years across dose cohorts (range, 41-82 years); most patients (83%-94%) had received at least 2 prior regimens, and all patients had previously received a VEGF receptor TKI and a PD-(L)1 inhibitor. Outcomes were reported after median follow-up periods of 15 months with 50 mg of casdatifan BID, 12 months with 50 mg of casdatifan QD, and 5 months with 100 mg of casdatifan QD.

The incidence rates of grade 3 or higher treatment-emergent AEs (TEAEs) considered to be related to casdatifan were 49% with 50 mg of casdatifan BID, 32% with 50 mg of casdatifan QD, and 28% with 100 mg of casdatifan QD. Rates of serious TEAEs considered to be related to casdatifan were 3%, 10%, and 7%, respectively. Grade 3 or higher casdatifan-related anemia occurred in 42%, 32%, and 17% of patients, respectively, and led to discontinuation in 1 of 93 treated patients. Grade 3 or higher casdatifan-related hypoxia occurred in 9%, 7%, and 10% of patients, respectively, and led to discontinuation in 2 patients.

The confirmed ORR with casdatifan was 25% at the 50-mg BID dose (0% CR rate), 29% at the 50-mg QD dose (4% CR rate), and 33% at the 100-mg QD dose (0% CR rate). Rapid responses and a trend of decreasing tumor size were noted at the 100-mg QD dose level. Investigators concluded that the study showed promising clinical activity with casdatifan and favorable tolerability. The planned randomized, phase 3 PEAK-1 study will evaluate 100 mg of casdatifan QD plus 60 mg of cabozantinib in patients with metastatic ccRCC who

Efficacy-Evaluable Population[a]	50 mg BID (n=32)	50 mg QD (n=28)	100 mg QD (n=27)
Median follow-up, mo (range)	15 (7-19+)	12 (9-14+)	5 (2-6+)
Confirmed ORR, % (n) (95% CI)	**25 (8) (11.5-43.4)**	**29 (8) 13.2-48.7)**	**33 (9) (16.5-54.0)**
Best overall response,[b] n (%)	10 (31)	9 (32)	9 (33)
CR	0	1 (4)	0
PR	10 (31)	8 (29)	9 (33)
SD	16 (50)	15 (54)	14 (52)
PD	6 (19)	4 (14)	2[c] (7)

Figure 8. Responses to casdatifan in the ARC-20 study. Treatment showed meaningful clinical activity and disease control across doses. The data cutoff date was January 3, 2025. BID, twice a day; CR, complete response; mo, months; ORR, objective response rate; QD, every day; PR, partial response; PD, progressive disease; PR, partial response; SD, stable disease. [a]All eligible patients who received any study treatment and had at least 1 post-baseline efficacy assessment or discontinued study treatment owing to PD or death. [b]Unconfirmed best overall response. [c]In addition to the 2 patients with radiologic progressive disease, 2 patients had clinical progression before their first scan. Adapted from Choueiri T et al. ASCO GU abstract 441. *J Clin Oncol.* 2024;42(4)(suppl).[2]

previously received PD-1–targeted therapy.

References

1. ClinicalTrials.gov. A phase 1 study of AB521 monotherapy and combination therapies in renal cell carcinoma and other solid tumors (ARC-20). https://clinicaltrials.gov/study/NCT05536141. Accessed February 6, 2025.
2. Choueiri T, Lee JL, Merchan J, et al. Casdatifan (Cas) monotherapy in patients (pts) with previously treated clear cell renal cell carcinoma (ccRCC): safety, efficacy and subgroup analysis across multiple doses from ARC-20, a phase 1 open-label study [ASCO GU abstract 441]. *J Clin Oncol*. 2024;42(4)(suppl).

The results of this phase 1 dose expansion study are impressive, with encouraging objective response rates and disease control rates in patients with refractory ccRCC. They support the development of casdatifan as a single agent and in combination with FDA-approved and investigational agents, and the examination of this agent for use in earlier disease settings.

—Daniel J. George, MD

Cabozantinib in Patients With Non-Locally Pretreated Brain Metastases From Renal Cell Carcinoma: Results of the Multicenter CABRAMET Phase II Trial (NCT03967522)

The multicenter, phase 2 CABRAMET trial, presented by Sylvie Négrier, MD, PhD, was undertaken to evaluate prospectively the efficacy of cabozantinib in patients with brain metastases that have not been locally pretreated.[1] The trial enrolled patients with brain metastases larger than 5 mm (≥8 mm if solitary), including at least one metastasis that was not locally pretreated. Patients could have received up to 40 mg of corticosteroids per day and could have received up to 2 prior systemic treatments (excluding cabozantinib). Cabozantinib was administered at a dose of 60 mg/d.

The 26 patients enrolled had a median age of 67 years (range, 44-86 years); 92% of patients had ccRCC. At baseline, patients primarily had either 1 (35%) or 2 to 5 (57%) brain metastases. Prior anticancer treatments included immunotherapy (35%) and a TKI with or without immunotherapy (38%).

In the 25 evaluable patients, the 6-month brain metastasis PFS (BM-PFS) rate was 56%, according to central and investigator reviews (Table), and the median BM-PFS was 10.7 months.

The best brain metastasis response rate in the overall cohort was 61%, and all responses were partial responses (PRs). The best brain metastasis PR rate was 86% (6/7) in patients without prior treatment, 67% (6/9) in patients with prior immunotherapy, and 40% (4/10) in patients treated with a prior TKI with or without immunotherapy.

After a median follow-up of 38.8 months, the median duration of brain metastasis response had not been reached; 58.3% of responses were ongoing beyond 24 months. The median duration of treatment was 9.6 months, and in 4 patients, treatment was ongoing beyond the 24-month protocol-defined period.

The best extracranial response rate was 40% (all PRs). The median BM-PFS was 10.7 months, median PFS was 8.1 months, and median OS was 15.0 months.

Table. Efficacy in the CABRAMET Study[a]

Endpoint	Rate (%)
6-mo BM-PFS rate[b,c]:	14/25[d] (56%; 95% CI, 37.9% to NR)
PR	11/25 (44%)
SD	3/25 (12%)
PD	11/25 (44%)

6-mo BM-PFS rate, brain metastasis progression-free survival rate at 6 months; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease. [a]The median follow-up was 38.8 (28.3-52.7) months. [b]The primary endpoint. [c]According to both central review and investigators. [d]one patient was nonevaluable. Adapted from Negrier S et al. ASCO GU abstract 533. *J Clin Oncol*. 2024;42(4)(suppl).[1]

Reference

1. Négrier S, Mourey L, Blanc E, et al. Cabozantinib in patients (pts) with non-locally pretreated brain metastases (BM) from renal cell carcinoma (RCC): results of the multicenter CABRAMET phase II trial (NCT03967522) [ASCO GU abstract 533]. *J Clin Oncol*. 2024;42(4)(suppl).

The results of the phase 2 CABRAMET study are extremely promising for a patient population that historically has been difficult to manage. They strongly support the use of cabozantinib in combination with tumor-directed therapies to control brain metastases, which could minimize the need for whole-brain radiation. —Daniel J. George, MD