NEW
COMBINATION STARTING DOSE
WITH OPDIVO®

A NEW APPROACH IN **1L aRCC** TREATMENT...

NOW APPROVED

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

Dosing and Administration Guide

1L=first-line; aRCC=advanced renal cell carcinoma.

INDICATIONS

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

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Please see additional Important Safety Information and full Prescribing Information.

NEW COMBINATION STARTING DOSE

CABOMETYX® 40-mg starting dose—optimized for combination treatment with OPDIVO®[1]

CABOMETYX
40 mg once daily

+

OPDIVO
240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (30-minute IV infusion)

Tablet shown is not actual size.

Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.
Treatment with OPDIVO should be continued until disease progression or unacceptable toxicity for up to 2 years.

Recommended administration of CABOMETYX[1]

DO NOT ADMINISTER CABOMETYX WITH FOOD
Administer CABOMETYX at least 1 hour before or at least 2 hours after eating

Swallow tablet whole
DO NOT CRUSH

If your patients miss a dose[1]

IF THE NEXT SCHEDULED DOSE IS:

in less than 12 hours	in 12 hours or more
Do not make up the missed dose	Take the missed dose as soon as possible
Take the next dose at the usual time	Take the next dose at the usual time

- 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 is observed
- Do not substitute CABOMETYX tablets with cabozantinib capsules
- Modify the dose for certain patients with hepatic impairment and for patients taking drugs known to strongly induce or inhibit CYP3A4
- Avoid ingesting food (eg, grapefruit or grapefruit juice) or nutritional supplements (eg, St. John's wort) that are known to strongly induce or inhibit CYP3A4 during CABOMETYX treatment
- A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively, relative to fasting conditions in healthy subjects administered a single oral dose of a cabozantinib capsule formulation
- When administering CABOMETYX in combination with OPDIVO for the treatment of aRCC, refer to the OPDIVO Prescribing Information

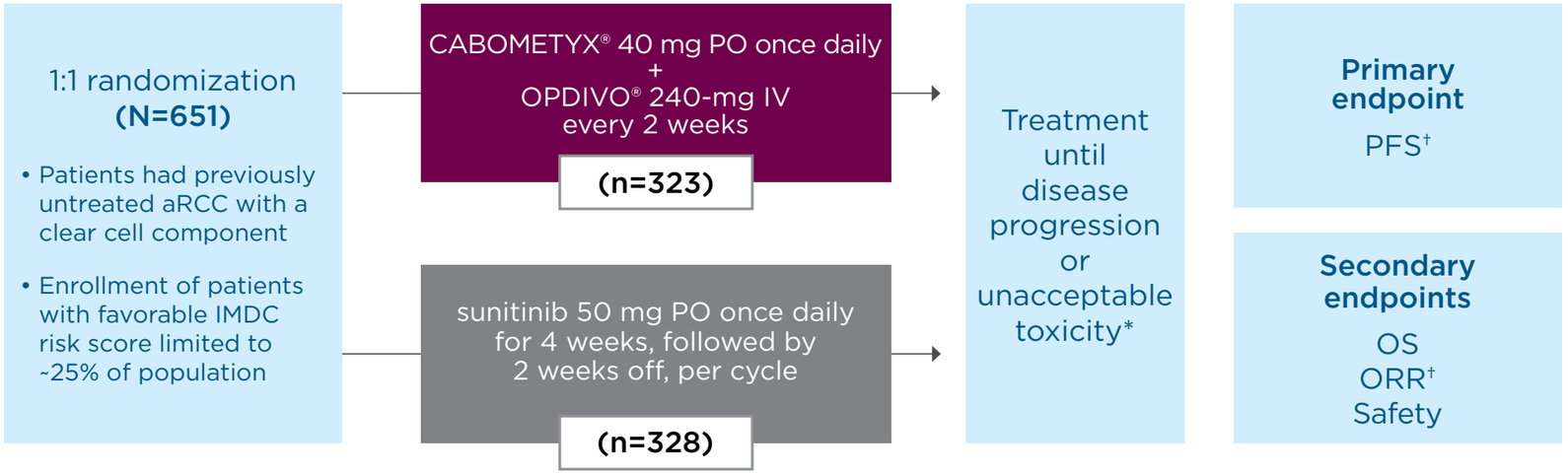
AUC=area under the curve; C_{max}=maximum concentration; IV=intravenous.

Please see additional Important Safety Information and full Prescribing Information.

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

CheckMate-9ER: a phase 3, randomized, head-to-head trial[1,2]

An open-label trial vs sunitinib in patients with previously untreated aRCC[1,2]



*Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter. Treatment beyond RECIST v1.1–defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.[1]
†PFS and ORR were assessed by BICR.[1]

The starting dose of CABOMETYX was 40 mg in CheckMate-9ER[1]

BICR=blinded independent central review; IMDC=International Metastatic RCC Database Consortium; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PO=by mouth; RECIST=Response Evaluation Criteria In Solid Tumors.

Please see additional Important Safety Information and full Prescribing Information.

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

CABOMETYX® dose modifications for adverse reactions (ARs)[1]

FOR INTOLERABLE GRADE 2 ARs, GRADE 3-4 ARs, AND ONJ

Withhold
CABOMETYX

Wait
until resolution/improvement (ie, return to baseline or resolution to Grade 1)

Reduce
the dose based on chart below

Combination starting dose	First reduction	Second reduction
40 mg once daily	20 mg once daily	20 mg once every other day*

Tablets shown are not actual size.

*If previously receiving 20 mg once every other day, resume at same dose. If not tolerated, discontinue CABOMETYX.

- Permanently discontinue CABOMETYX for severe hemorrhage, development of GI perforation or Grade 4 fistula, acute myocardial infarction or arterial/venous thromboembolic events that require medical intervention, severe hypertension that cannot be controlled with anti-hypertensive therapy or hypertensive crisis, nephrotic syndrome, or reversible posterior leukoencephalopathy syndrome

For patients being treated with CABOMETYX in combination with OPDIVO:

- If ALT or AST >3 x ULN but ≤10 x ULN with concurrent total bilirubin <2 x ULN, both CABOMETYX and OPDIVO should be withheld until hepatic ARs recover to Grades 0 or 1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with OPDIVO, refer to OPDIVO Prescribing Information
- If ALT or AST >10 x ULN or >3 x ULN with concurrent total bilirubin ≥2 x ULN, both CABOMETYX and OPDIVO should be permanently discontinued

When strong CYP3A4 inhibitors cannot be avoided:

- Reduce the daily CABOMETYX dose by 20 mg. Resume the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor

When strong CYP3A4 inducers cannot be avoided:

- Increase the daily CABOMETYX dose by 20 mg as tolerated. Resume the dose that was used prior to initiating the strong CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. Do not exceed a daily dose of 80 mg

Avoid CABOMETYX in patients with severe hepatic impairment.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; ONJ=osteonecrosis of the jaw; ULN=upper limit of normal.

Please see additional Important Safety Information and full Prescribing Information.

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

Discontinuation rate due to ARs in the CABOMETYX® + OPDIVO® arm similar to sunitinib[1,2]

	Permanent discontinuation	Dose interruption/reduction
CABOMETYX or OPDIVO[1]	**20%**	**83%**
CABOMETYX only[1]	8%	46%
OPDIVO only[1]	7%	3%
CABOMETYX and OPDIVO[1]	6%*	21%†
Sunitinib[2]	**16.9%**	**72.5%**

*Due to the same AR at the same time.[1]
†Due to the same AR at the same time; 6% for both drugs sequentially.[1]

The mean average daily dose of CABOMETYX was 30 mg/day[2]

Please see additional Important Safety Information and full Prescribing Information.

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

Indications and Important Safety Information

INDICATIONS

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

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

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

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX 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 at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement 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 more frequent monitoring of liver enzymes than 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.

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 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.

Proteinuria: Proteinuria was observed in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

ISI (cont'd) ➤

CABOMETYX®
(cabozantinib) tablets

Indications and Important Safety Information (cont'd)

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. 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 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, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

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 is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, 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.

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

ADVERSE REACTIONS

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

CABOMETYX as a single agent: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

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.

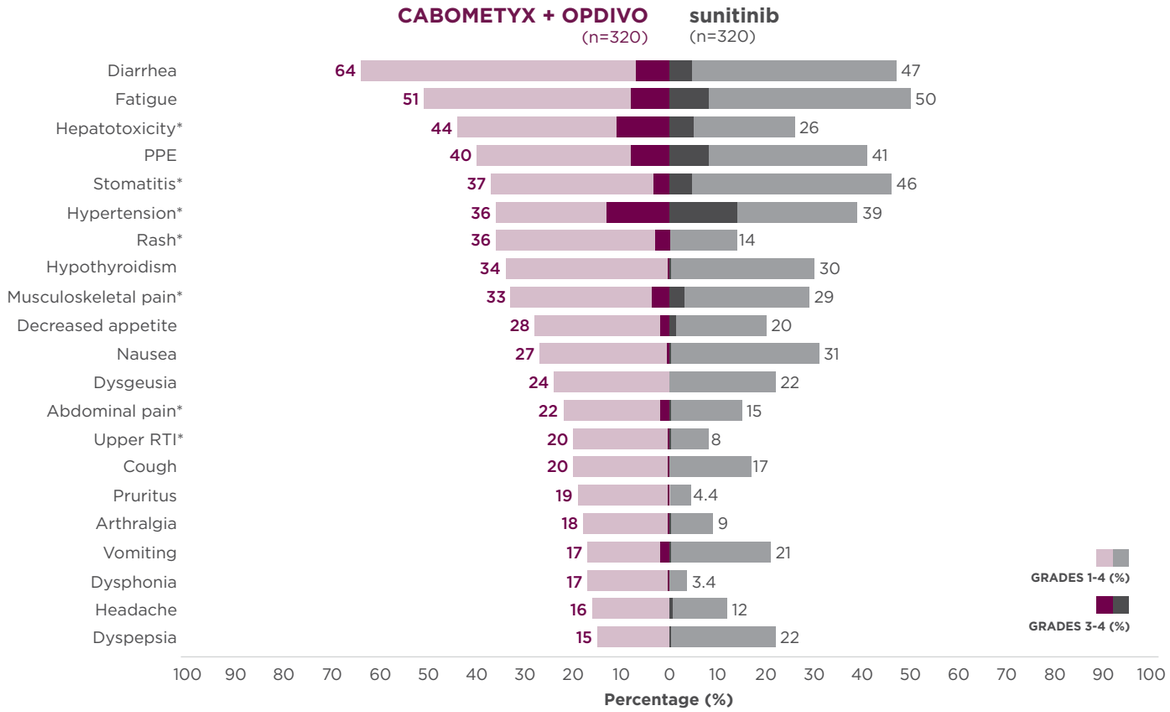
Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see full Prescribing Information.

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.

CABOMETYX® (cabozantinib) tablets

ARs occurring in >15% of patients receiving CABOMETYX® + OPDIVO®[1]



*These ARs are grouped terms. For details, please see full Prescribing Information.[1]

- IMAEs occurred in patients receiving CABOMETYX + OPDIVO[2]
  - The most common all-grade IMAEs were hypothyroidism, hyperthyroidism, rash, diarrhea, and hepatotoxicity
  - 19.1% of patients required high-dose steroids for IMAE management

For additional guidance around IMAE management, refer to the OPDIVO Prescribing Information.

IMAE=immune-mediated adverse event; PPE=palmar-plantar erythrodysesthesia; RTI=respiratory tract infection.

Please see additional Important Safety Information and full Prescribing Information.

Laboratory values worsening from baseline occurring in >20% of patients receiving CABOMETYX + OPDIVO[1†]

Percentage (%) of Patients

	CABOMETYX + OPDIVO		sunitinib	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
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

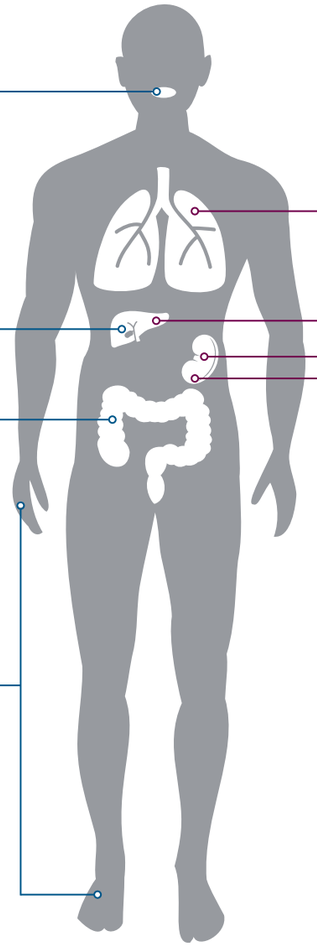
†Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.[1]

ARs and Discontinuations ›

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

ARs and discontinuations in CheckMate-9ER

Five most common ARs of any grade observed with CABOMETYX® + OPDIVO®[1]



Stomatitis
CABOMETYX + OPDIVO: 37%
sunitinib: 46%

Hepatotoxicity*
CABOMETYX + OPDIVO: 44%
sunitinib: 26%

Diarrhea
CABOMETYX + OPDIVO: 64%
sunitinib: 47%

PPE
CABOMETYX + OPDIVO: 40%
sunitinib: 41%

Fatigue
CABOMETYX + OPDIVO: 51%
sunitinib: 50%

Most common ARs leading to discontinuation of CABOMETYX and/or OPDIVO[2†]

Pneumonitis
CABOMETYX + OPDIVO: 0.9%
sunitinib: 0%

ALT increased
CABOMETYX + OPDIVO: 1.9%
sunitinib: 0.9%

AST increased
CABOMETYX + OPDIVO: 1.6%
sunitinib: 0.9%

Adrenal insufficiency
CABOMETYX + OPDIVO: 0.9%
sunitinib: 0%

Proteinuria
CABOMETYX + OPDIVO: 1.6%
sunitinib: 1.9%

Malignant neoplasm progression
CABOMETYX + OPDIVO: 0.9%
sunitinib: 2.2%

ARs and Lab Abnormalities

*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.[1]
†Includes discontinuation of CABOMETYX only, OPDIVO only, and CABOMETYX and OPDIVO.[1]

Please see additional Important Safety Information and full Prescribing Information.

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

EASE EXELIXIS ACCESS SERVICES®

Access. Assistance. Along the journey.

Exelixis Access Services® (EASE) provides a variety of support to help your patients get started on treatment as soon as possible. EASE can meet the unique needs of your patients and practice at each step along the access journey.

YOUR EASE CASE MANAGER

EASE offers regionally dedicated Case Managers as a single point of contact.

- Offers **prompt support** with payer coverage, financial assistance, and treatment coordination
- Can **provide the status** of your patients' access journey
- Provides **proactive follow-up**

HELP PATIENTS START AND STAY ON CABOMETYX® (cabozantinib)

15-Day Free Trial Program

Provides free drug to help patients start treatment quickly.*†

CABOMETYX Quick Start Program

Provides a limited supply of free drug to eligible patients who experience **a payer decision delay of 5 days or more**.*†

EASE Co-pay Program

Eligible commercially insured patients pay **$0 per month, for a maximum benefit of $25,000 per year**.†

EASE Dose Exchange Program

Provides a **free 15-tablet supply in the lower dose** to patients who require a dose reduction.†

EASE Patient Assistance Program (PAP)

Eligible patients who cannot afford their drug costs may receive CABOMETYX **free of charge**.†

SUPPORT FOR COVERAGE DETERMINATION

At your request, EASE can provide support with:

- **Benefits investigations (BIs)**
- **Prior authorization (PA) assistance**
- **Appeals support and follow-up**

covermymeds®

Enroll your patients in EASE through CoverMyMeds. EASE will confirm your patient's eligibility for requested services.

Contact your EASE Case Manager for questions or help.

CONTACT EASE FOR MORE INFORMATION AND TO ENROLL

CALL: 1-844-900-EASE (1-844-900-3273)
Monday to Friday, 8:00 AM to 8:00 PM (ET)

FAX: 1-844-901-EASE (1-844-901-3273)

VISIT: www.EASE.US

*Limited to on-label indications. Additional restrictions and eligibility rules apply.
†Additional restrictions and eligibility rules apply.

This description of the Exelixis Access Services® (EASE) program is for informational purposes only. Exelixis® makes no representation or guarantee concerning reimbursement or coverage for any service or item. Information provided through the Exelixis Access Services program does not constitute medical or legal advice and is not intended to be a substitute for a consultation with a licensed healthcare provider, legal counsel, or applicable third-party payer(s). Exelixis reserves the right to modify the program at any time without notice.

Please see additional Important Safety Information and full Prescribing Information.

Patient Education ›

CABOMETYX® (cabozantinib) tablets

BE CONNECTED
with CABOMETYX® (cabozantinib)

- The BE CONNECTED program is designed to offer educational support to patients and caregivers. Your patients may sign up to learn more about what they may expect while on treatment with CABOMETYX
  - Recognizing side effects, and working with your healthcare team
  - Lifestyle tips offering wellness support
  - Where to find useful resources
  - Information about organizations that may offer support

Encourage patients and caregivers to sign up today

There are 2 ways your patients can sign up:

1. ONLINE

Go to
signup.CABOMETYX.com

OR

2. MAIL

Complete and return the **sign-up card included in the Patient Care Kit**

To request a Patient Care Kit, contact your local CABOMETYX Sales Representative

EASE

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

NEW COMBINATION STARTING DOSE

CABOMETYX® 40-mg starting dose—optimized for combination treatment with OPDIVO®[1]

CABOMETYX

40 mg once daily

+

OPDIVO

240 mg every 2 weeks (30-minute IV infusion)

or

480 mg every 4 weeks (30-minute IV infusion)

Tablet shown is not actual size.

Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.
Treatment with OPDIVO should be continued until disease progression or unacceptable toxicity for up to 2 years.

SELECT IMPORTANT SAFETY INFORMATION

The full Prescribing Information for CABOMETYX includes Warnings and Precautions for: hemorrhage, perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, PPE, hepatotoxicity, adrenal insufficiency, proteinuria, ONJ, impaired wound healing, RPLS, and embryo-fetal toxicity.

INDICATIONS

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

CABOMETYX is indicated for the treatment of patients with advanced RCC.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2021. **2.** Data on file. Exelixis, Inc.

Please see additional Important Safety Information and full Prescribing Information.

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

Learn more at CABOMETYXhcp.com

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