Treatment Management Guide

Strategies to help manage certain adverse reactions for your patients taking CABOMETYX® (cabozantinib) treatment

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

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

CABOMETYX® (cabozantinib) tablets

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

SECOND-LINE HCC
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

aRCC=advanced renal cell carcinoma.

IMPORTANT SAFETY INFORMATION

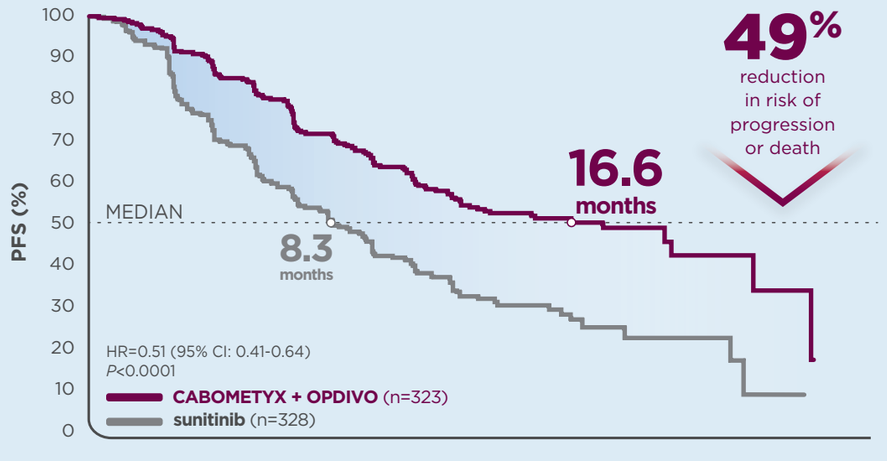
WARNINGS AND PRECAUTIONS

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.

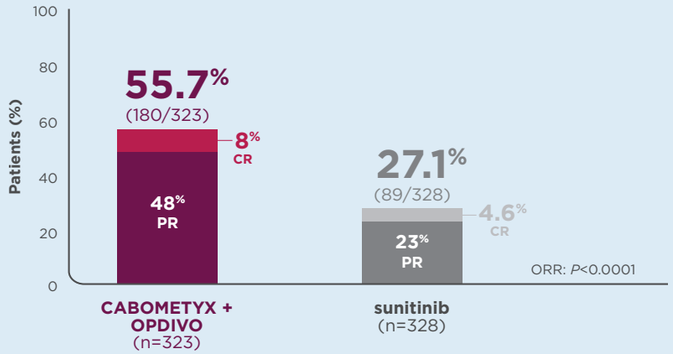
CABOMETYX® + OPDIVO®: the first and only 1L aRCC combination treatment to double PFS and ORR while delivering superior OS[1]

More than 16 months median PFS[1]*



Patients at Risk										
CABOMETYX + OPDIVO	323	279	234	196	144	77	35	11	4	0
sunitinib	328	228	159	122	79	31	10	4	1	0

More than double ORR[1]*



- **5.6% of patients had progressive disease with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib[2]**

Superior OS outcomes[1]

40%

reduction in risk of death

HR=0.60 (98.89% CI: 0.40-0.89); *P*=0.0010

- Median OS not reached in either treatment arm

CheckMate-9ER was a randomized (1:1), open-label, phase 3 trial 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 240-mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.[1,2]*

*PFS and ORR were assessed by BICR.[1]

1L=first-line; BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; IV=intravenous; ORR=objective response rate; OS=overall survival; PO=by mouth; PFS=progression-free survival; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

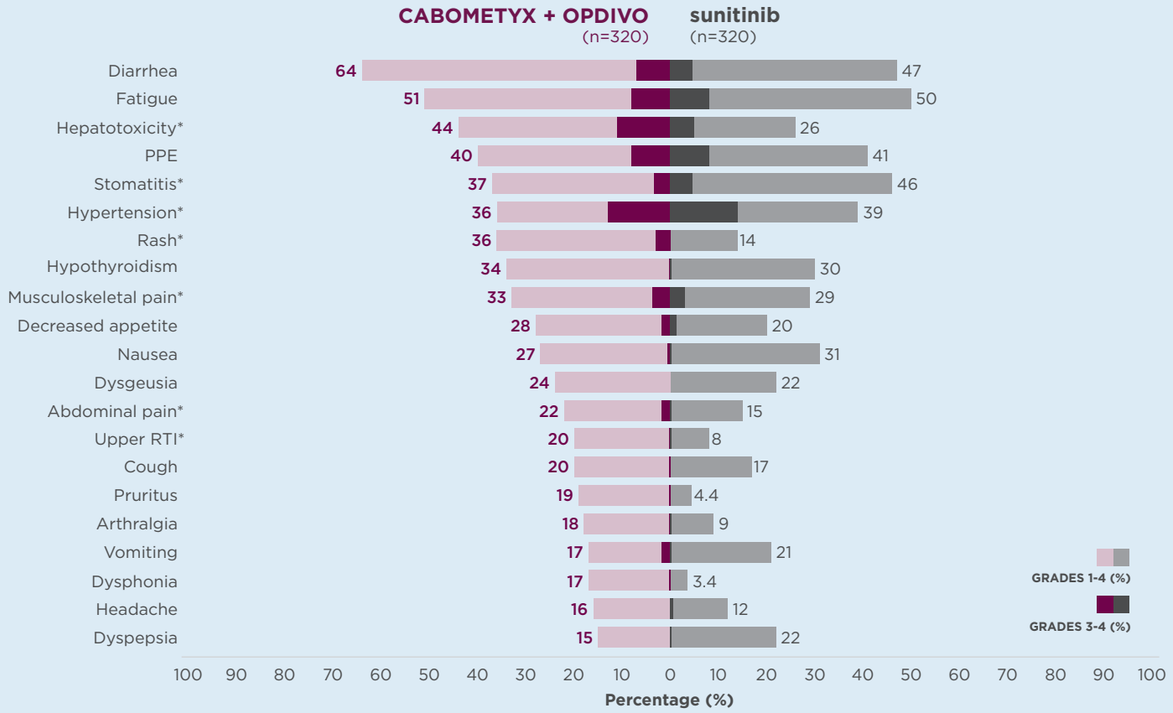
Please see additional Important Safety Information and full Prescribing Information.

CheckMate-9ER Safety

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

CABOMETYX® + OPDIVO® safety in the CheckMate-9ER trial

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.

ALT=alanine aminotransferase; AR=adverse reaction; AST=aspartate aminotransferase; 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

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%

CABOMETYX + OPDIVO Efficacy

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

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

CABOMETYX®: the only single-agent TKI with superior efficacy in both 1L and 2L aRCC[1]

The only single-agent TKI with superior OS, PFS, and ORR in 2L aRCC[1]*

SECONDARY ENDPOINT: OS	PRIMARY ENDPOINT: PFS[†‡]	SECONDARY ENDPOINT: ORR[§]
MEDIAN	MEDIAN	
21.4 months CABOMETYX (n=330)	**7.4 months** CABOMETYX (n=187)	**17%** CABOMETYX (n=330) (95% CI: 13.0%-22.0%)
VS	VS	VS
16.5 months everolimus (n=328)	3.8 months everolimus (n=188)	3% everolimus (n=328) (95% CI: 2.0%-6.0%)
HR=0.66 (95% CI: 0.53-0.83); *P*=0.0003	HR=0.58 (95% CI: 0.45-0.74); *P*<0.0001	*P*<0.0001; partial responses only

METEOR was a randomized (1:1), open-label, phase 3 trial of CABOMETYX vs everolimus in 658 patients with aRCC who had previously received at least 1 prior anti-angiogenic treatment. The starting dose for CABOMETYX was 60 mg, administered orally once daily; the starting dose for everolimus was 10 mg, administered orally once daily. Patients were required to have received at least 1 prior therapy and to have clear cell component and measurable disease.[1,3]

***After at least 1 prior anti-angiogenic therapy.**[1]
[†]In the METEOR trial, the primary PFS analysis was conducted in the first 375 subjects randomized to treatment.[1]
[‡]PFS was confirmed by blinded IRRC.[1]
[§]ORR was assessed by blinded IRRC using RECIST v1.1.[3]

The only single-agent TKI to deliver superior PFS to sunitinib in 1L aRCC[1‖]

PRIMARY ENDPOINT: PFS[¶]			
MEDIAN			
8.6 months CABOMETYX (n=79)	VS	5.3 months sunitinib (n=78)	**52%** reduction in risk of progression or death HR=0.48 (95% CI: 0.31-0.74); *P*=0.0008

CABOSUN was a randomized (1:1), open-label, multicenter, phase 2 trial of CABOMETYX vs sunitinib in 157 first-line patients with aRCC who had ≥1 IMDC risk factors. The starting dose for CABOMETYX was 60 mg, administered orally once daily; the starting dose for sunitinib was 50 mg, administered orally once daily on a schedule of 4 weeks on treatment, followed by 2 weeks off. Patients were required to have IMDC intermediate- or poor-risk disease, clear cell component, measurable disease, and ECOG PS 0-2. The primary endpoint was PFS. Secondary endpoints included OS and ORR.[1,4]

[‖]**Patients were intermediate or poor risk and had ≥1 IMDC risk factors.**[1]
[¶]PFS was assessed by a retrospective blinded IRRC.[1]

2L=second-line; ECOG PS=Eastern Cooperative Oncology Group performance status; IMDC=International Metastatic RCC Database Consortium; IRRC=independent radiology review committee; RECIST=Response Evaluation Criteria in Solid Tumors; TKI=tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

METEOR Safety › CABOSUN Safety ›

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® safety in the METEOR trial[1]

ARs occurring in ≥10% of patients in the CABOMETYX arm[1]

Percentage (%) of Patients

	CABOMETYX (n=331)*		everolimus (n=322)	
	All Grades†	Grade 3-4	All Grades†	Grade 3-4
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‡	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
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
PPE	42	8	6	<1
Rash‡	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension‡	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

Laboratory abnormalities occurring in ≥25% of patients in the CABOMETYX arm[1]

Percentage (%) of Patients

	CABOMETYX (n=331)		everolimus (n=322)	
	All Grades†	Grade 3-4	All Grades†	Grade 3-4
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§	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

Dose withholds, reductions, and discontinuations in the METEOR trial[1]

	CABOMETYX (n=331)	everolimus (n=322)
Dose withholds	70%	59%
Dose reductions	60%	24%
Discontinuations	10%	10%

◀ CABOMETYX Single-Agent Efficacy | CABOSUN Safety ▶

*One subject randomized to everolimus received CABOMETYX.
†NCI-CTCAE Version 4.0.
‡These ARs are grouped terms. For details, please see full Prescribing Information.
§Based on laboratory abnormalities.

ALP=alkaline phosphatase; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; GGT=gamma-glutamyl transferase.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® safety in the CABOSUN trial[1]

Grade 3-4 ARs occurring in >1% of patients who received CABOMETYX[1]*

	Percentage (%) of Patients	
	CABOMETYX (n=78)	**sunitinib (n=72)**
PATIENTS WITH ANY GRADE 3-4 AR	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Decreased appetite	5	1
Dehydration	4	1
Skin and Subcutaneous Tissue		
PPE	8	4
Skin ulcer	3	0
Vascular		
Hypertension†	28	21
Hypotension	5	1
Investigations		
Weight decreased	4	0
Nervous System		
Syncope	5	0
Psychiatric		
Depression	4	0
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

*NCI-CTCAE Version 4.0.
†Includes the following term: hypertension.

Laboratory-related Grade 3-4 ARs occurring in ≥1% of patients who received CABOMETYX[1]*‡

	Percentage (%) of Patients)	
	CABOMETYX (n=78)	**sunitinib (n=72)**
Metabolism and Nutrition		
Hyponatremia	9	8
Hypophosphatemia	9	7
Hypocalcemia	3	0
Hypomagnesemia	3	0
Hyperkalemia	1	3
Investigations		
Increased ALT	5	0
Increased AST	3	3
Increased blood creatinine	3	3
Lymphopenia	1	6
Thrombocytopenia	1	11

‡Laboratory abnormalities are reported as ARs and not based on shifts in laboratory values.

Dose withholds, reductions, and discontinuations in the CABOSUN trial[1]

	CABOMETYX (n=78)	**sunitinib (n=72)**
Dose withholds	**73%**	**71%**
Dose reductions	**46%**	**35%**
Discontinuations	**21%**	**22%**

CABOMETYX Single-Agent Efficacy | METEOR Safety

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® single agent: OS and PFS results in HCC

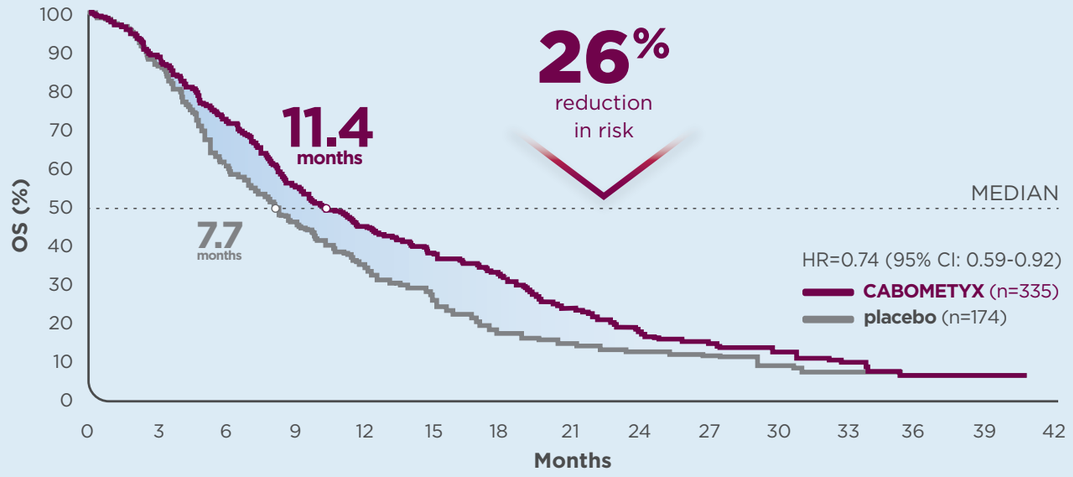
Superior OS and PFS in the treatment of 2L HCC[1]

- Primary endpoint: Median OS was 10.2 months with CABOMETYX (n=470) vs 8.0 months with placebo (n=237) in the ITT population of patients who received at least one prior therapy (HR=0.76; 95% CI: 0.63-0.92; *P*=0.0049)
- Secondary endpoint: Median PFS was 5.2 months with CABOMETYX (n=470) vs 1.9 months with placebo (n=237) in the ITT population of patients who received at least one prior therapy (HR=0.44; 95% CI: 0.36-0.52; *P*<0.0001)

In a prespecified exploratory subgroup analysis of patients who received only 1 prior systemic therapy

CABOMETYX exceeded 11 months median OS and 5 months median PFS in the second line[5,6]

SUBGROUP ANALYSIS: OS (SECOND LINE)[2]*



SUBGROUP ANALYSIS: MEDIAN PFS (SECOND LINE)[6]*

5.5 months CABOMETYX (n=335)

VS

1.9 months placebo (n=174)

57% reduction in risk
HR=0.43 (95% CI: 0.35-0.52)

*No statistical procedure was employed for controlling type I error. Results should be considered hypothesis generating.[5]

CELESTIAL was a randomized (2:1), double-blind, phase 3 trial of CABOMETYX vs placebo in 707 sorafenib-treated patients with Child-Pugh A HCC who had progressed on at least 1 prior systemic therapy. The starting dose for CABOMETYX was 60 mg, administered orally once daily. The trial had a range of patients who received 1-2 prior systemic therapies, and did not exclude patients based on main portal vein invasion, use of prior immunotherapy, >50% liver involvement, bile duct invasion, sorafenib intolerance, AFP level, or viral load. The primary endpoint was OS. Secondary endpoints included PFS and ORR.[1,2,5,6]

AFP=alpha-fetoprotein tumor marker; ITT=intent to treat.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

CELESTIAL Safety ›

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® safety in the CELESTIAL trial

ARs occurring at a higher incidence in patients treated with CABOMETYX (Between-arm difference of ≥5% [All Grades] or ≥2% [Grade 3-4])[1]

Percentage (%) of Patients

	CABOMETYX (n=467)		placebo (n=237)	
	All Grades*	Grade 3-4	All Grades*	Grade 3-4
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				
PPE	46	17	5	0
Rash†	21	2	9	<1
Vascular				
Hypertension‡	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				
Muscle spasms	8	<1	2	0
Pain in extremity	9	<1	4	1

LDH=lactate dehydrogenase.

Please see additional Important Safety Information and full Prescribing Information.

Laboratory abnormalities occurring at a higher incidence in patients treated with CABOMETYX (Between-arm difference of ≥5% [All Grades] or ≥2% [Grade 3-4])[1]

Percentage (%) of Patients

	CABOMETYX (n=467)		placebo (n=237)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
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

Dose withholds, reductions, and discontinuations in the CELESTIAL trial

	CABOMETYX (n=467)	placebo (n=237)
Dose withholds[1,2]	84%	37%
Dose reductions[1,5]	62%	13%
Discontinuations[1,5]	16%	3%

*NCI-CTCAE v4.0.
†Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected.
‡Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased.

CABOMETYX Single-Agent Efficacy

CABOMETYX® (cabozantinib) tablets

CABOMETYX®: once-daily oral starting dose as a single agent or in combination[1]

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)	CABOMETYX® (cabozantinib) tablets
CABOMETYX 40-mg recommended starting dose—optimized for combination treatment with OPDIVO® in 1L aRCC	**CABOMETYX 60-mg recommended starting dose for single-agent treatment in aRCC or HCC**
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)	**CABOMETYX** 60 mg once daily
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.	In aRCC, treatment with CABOMETYX should be continued until the patient no longer experiences clinical benefit or experiences unacceptable toxicity. In HCC, treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.

Tablets shown are not actual size.

- 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
- Do not administer CABOMETYX with food. Administer at least 1 hour before or at least 2 hours after eating
- Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets
- Do not take a missed dose within 12 hours of the next dose
- Modify the dose for patients taking drugs known to strongly induce or inhibit CYP3A4
- When administering CABOMETYX in combination with OPDIVO for the treatment of aRCC, refer to the OPDIVO Prescribing Information

Recommended dose of CABOMETYX for patients with hepatic impairment[1]

Child-Pugh B: Reduce the starting dose of CABOMETYX to **40 mg once daily** in patients with moderate hepatic impairment

- Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C)

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

You may need to adjust the CABOMETYX® dose based on individual patient safety and tolerability[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

	Recommended starting dose	First reduction	Second reduction
CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)	40 mg once daily	20 mg once daily	20 mg once every other day*
CABOMETYX® (cabozantinib) tablets	60 mg once daily	40 mg once daily	20 mg once daily*

Tablets shown are not actual size.

*If previously receiving the lowest dose, 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

Dose Exchange Program: Supporting your patients who require a dose modification during CABOMETYX treatment

- Eligible patients who require a dose reduction may receive a free 15-tablet supply of CABOMETYX in the lower dose. Additional restrictions and eligibility rules apply
- To obtain a Dose Exchange Program Form, **contact your sales representative**, call EASE at **1-844-900-EASE (3273)**, or visit **www.EASE.us**

Pharmacokinetics[1]

- The predicted terminal half-life of CABOMETYX is approximately 99 hours

GI=gastrointestinal; ONJ=osteonecrosis of the jaw.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Select adverse reactions with CABOMETYX® in the phase 3, single-agent METEOR and CELESTIAL trials[1]

SELECT COMMON ARs LEADING TO CABOMETYX DOSE REDUCTIONS IN THE METEOR AND CELESTIAL TRIALS: ALL-GRADE INCIDENCE (GRADE 3-4 INCIDENCE)

	Diarrhea	PPE/HFS	Fatigue	Hypertension	Increased AST
METEOR (aRCC) CABOMETYX (n=331)	74% (11%)	42% (8%)	56% (9%)	39% (16%)	74% (3%)
CELESTIAL (HCC) CABOMETYX (n=467)	54% (10%)	46% (17%)	45% (10%)	30% (16%)	73% (24%)

The ARs included in this guide do not represent all of the possible side effects of CABOMETYX, and not all ARs may be manageable. The following pages of this brochure focus on select ARs seen in phase 3 trials of CABOMETYX.

See full safety results from the METEOR and CELESTIAL trials.

For information on how to counsel patients with other potential ARs, please see the Patient Counseling section of the Prescribing Information.

HFS=hand-foot syndrome.

Please see additional Important Safety Information and full Prescribing Information.

Select ARs: CABOMETYX + OPDIVO®

CABOMETYX® (cabozantinib) tablets

Select adverse reactions with CABOMETYX® + OPDIVO® combination treatment in the phase 3 CheckMate-9ER trial[1]

SELECT COMMON ARs LEADING TO CABOMETYX + OPDIVO DOSE INTERRUPTIONS OR REDUCTIONS IN THE CHECKMATE-9ER TRIAL: GRADE 1-4 INCIDENCE (GRADE 3-4 INCIDENCE)[2]

	Diarrhea	PPE/HFS	Hypertension	Increased ALT
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO (n=320)	64% (7%)	40% (8%)	36% (13%)	79% (9.8%)

The ARs included in this guide do not represent all of the possible side effects of CABOMETYX, and not all ARs may be manageable. The following pages of this brochure focus on select ARs seen in phase 3 trials of CABOMETYX.

See full safety results from the **CheckMate-9ER** trial.

For information on how to counsel patients with other potential ARs, please see the Patient Counseling section of the **Prescribing Information**.

◀ Select ARs: CABOMETYX Single Agent

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Diarrhea

Withhold[1]

CABOMETYX® in patients who develop intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea

Wait[1]

Until improvement to Grade 1

Restart[1]

CABOMETYX at a reduced dose

CABOMETYX + OPDIVO®:
Reduce CABOMETYX dose by 20 mg daily (if previously receiving 20 mg daily, reduce to 20 mg every other day). Lowest dose is 20 mg every other day

CABOMETYX single agent:
Reduce dose by 20 mg daily. Lowest dose is 20 mg daily

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

Management tips for diarrhea

Implement supportive measures[8,9]

- Continuous oral hydration
- Correction of fluid and electrolyte abnormalities
- Small, frequent meals
- Avoidance of lactose-containing products, high-fat meals, and alcohol
- Administer an antidiarrheal or antimotility agent at the first sign of diarrhea (more than 1 agent may be necessary)

For patients who experience diarrhea or colitis during treatment with CABOMETYX + OPDIVO:

- Antidiarrheal agents may be considered for Grade 2 diarrhea if infection has been ruled out[10]
- For guidance around management of diarrhea or colitis with corticosteroid treatment and rechallenging with OPDIVO, refer to the OPDIVO Prescribing Information

NCI-CTCAE v4.03 grading identification: Diarrhea[7]

Grade 1	Increase of <4 stools per day over baseline
Grade 2	Increase of 4-6 stools per day over baseline
Grade 3	Increase of ≥7 stools per day over baseline Incontinence Hospitalization indicated Limiting self-care ADL*
Grade 4	Life-threatening consequences Urgent intervention indicated

*Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

ADL=activities of daily living.

Clinical Experience: CABOMETYX Single-Agent ›

Clinical Experience: CABOMETYX + OPDIVO ›

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Diarrhea: clinical experience in the phase 3, single-agent METEOR and CELESTIAL trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[2]	Dose interruptions[2]*	Dose reductions[2]*	Discontinuations[2]*
METEOR (aRCC) CABOMETYX® (n=331)	74%	11%	5	22%	16%	<1%
CELESTIAL (HCC) CABOMETYX (n=467)	54%	10%	4.1	15%	10%	1.1%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to diarrhea.

See full safety results from the METEOR and CELESTIAL trials.

◀ Management: Diarrhea

Clinical Experience: CABOMETYX + OPDIVO® ▶

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Diarrhea: clinical experience in the phase 3, combination-treatment CheckMate-9ER trial

	Grade 1-4 incidence[1]	Grade 3-4 incidence[1]	Dose interruptions or reductions[2]*	Discontinuations[2]*
CheckMate-9ER (aRCC) CABOMETYX® + OPDIVO® (n=320)	64%	7%	24.4%	0.6%

*Percentages represent the number of dose interruptions or reductions and discontinuations of any study drug due to diarrhea.

See full safety results from the CheckMate-9ER trial.

◀ Management: Diarrhea ◀ Clinical Experience: CABOMETYX Single-Agent

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Palmar-plantar erythrodysesthesia/Hand-foot syndrome (PPE/HFS)

Withhold[1]

CABOMETYX® for intolerable Grade 2 PPE or Grade 3 PPE

Wait[1]

Until improvement to Grade 1

Restart[1]

CABOMETYX at a reduced dose

CABOMETYX + OPDIVO®: Reduce CABOMETYX dose by 20 mg daily (if previously receiving 20 mg daily, reduce to 20 mg every other day). Lowest dose is 20 mg every other day

CABOMETYX single agent: Reduce dose by 20 mg daily. Lowest dose is 20 mg daily

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

NCI-CTCAE v4.03 grading identification: PPE/HFS[7]

Grade 1	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain
Grade 2	Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain Limiting instrumental ADL*
Grade 3	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain Limiting self-care ADL†

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

Management tips for PPE/HFS[8,9]

Early signs and manifestations of PPE/HFS include:

- Tingling
- Numbness
- Slight redness
- Mild hyperkeratosis
- Painful, symmetrical, red and swollen areas on palms and soles (lateral sides of fingers or periungual zones may also be affected)

Supportive care guidelines include:

- 20% urea cream twice daily and 0.05% clobetasol cream once daily
- Analgesics (NSAIDs/GABA agonists) for pain control if needed for Grade 2 or above

All patients should be advised on prophylactic skin care, including:

- Use of hypoallergenic moisturizing creams or ointments
- Sunscreen with sun protection factor (SPF) ≥30
- Avoidance of exposure of hands and feet to hot water
- Protection of pressure-sensitive areas of hands and feet
- Use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry
- Careful monitoring of patients with skin disorders for signs of infection (eg, abscess, cellulitis, or impetigo)

Adequate interventions are required to prevent worsening of skin symptoms, such as blisters, desquamations, ulcerations, or necrosis of affected areas.

Aggressive management of symptoms is recommended, including early referral to a dermatologist.

Clinical Experience: CABOMETYX Single-Agent ›

Clinical Experience: CABOMETYX + OPDIVO ›

GABA=gamma-aminobutyric acid; NSAID=nonsteroidal anti-inflammatory drug.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

PPE/HFS: clinical experience in the phase 3, single-agent METEOR and CELESTIAL trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[2]	Dose interruptions[2]*	Dose reductions[2]*	Discontinuations[2]*
METEOR (aRCC) CABOMETYX® (n=331)	42%	8%	3.4	14%	11%	<1%
CELESTIAL (HCC) CABOMETYX (n=467)	46%	17%	3.1	25%	22%	2.4%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to PPE/HFS.

See full safety results from the METEOR and CELESTIAL trials.

Management: PPE/HFS
Clinical Experience: CABOMETYX + OPDIVO®

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

PPE/HFS: clinical experience in the phase 3, combination-treatment CheckMate-9ER trial

	Grade 1-4 incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[2]	Dose interruptions or reductions[2]*	Discontinuations[2]*
CheckMate-9ER (aRCC) CABOMETYX® + OPDIVO® (n=320)	40%	8%	7.4	19.1%	0.6%

*Percentages represent the number of dose interruptions or reductions and discontinuations of any study drug due to PPE/HFS.

See full safety results from the CheckMate-9ER trial.

◀ Management: PPE/HFS ◀ Clinical Experience: CABOMETYX Single-Agent

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Fatigue

Withhold[1]

CABOMETYX® for intolerable Grade 2 fatigue and for Grade 3 fatigue

Wait[1]

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

Restart[1]

CABOMETYX at a reduced dose

CABOMETYX + OPDIVO®:
Reduce CABOMETYX dose by 20 mg daily (if previously receiving 20 mg daily, reduce to 20 mg every other day). Lowest dose is 20 mg every other day

CABOMETYX single agent:
Reduce dose by 20 mg daily. Lowest dose is 20 mg daily

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

Management tips for fatigue[8,9]

- Rule out common causes of fatigue, such as anemia, deconditioning, emotional distress, nutrition, sleep disturbance, and hypothyroidism
- Consider pharmacological management with psychostimulants, such as methylphenidate, after disease-specific morbidities have been excluded
- Dose interruption may be considered for Grade ≥3 fatigue despite optimal management, at the HCP's discretion

NCI-CTCAE v4.03 grading identification: Fatigue[7]

Grade 1	Fatigue relieved by rest
Grade 2	Fatigue not relieved by rest Limiting instrumental ADL*
Grade 3	Fatigue not relieved by rest Limiting self-care ADL†

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

Clinical Experience: CABOMETYX Single-Agent ›

Fatigue: clinical experience in the phase 3, single-agent METEOR and CELESTIAL trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Dose interruptions[2]*	Dose reductions[2]*	Discontinuations[2]*
METEOR (aRCC) CABOMETYX® (n=331)	56%	9%	12%	10%	1.2%
CELESTIAL (HCC) CABOMETYX (n=467)	45%	10%	13%	7.5%	1.5%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations of any study drug due to fatigue.

See full safety results from the **METEOR** and **CELESTIAL** trials.

Management: Fatigue

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Hypertension*: management

Withhold[1]

CABOMETYX® for hypertension that is not adequately controlled with medical management

Wait[1]

Until adequately controlled

Restart[1]

CABOMETYX at a reduced dose

CABOMETYX + OPDIVO®: Reduce CABOMETYX dose by 20 mg daily (if previously receiving 20 mg daily, reduce to 20 mg every other day). Lowest dose is 20 mg every other day

CABOMETYX single agent: Reduce dose by 20 mg daily. Lowest dose is 20 mg daily

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

Discontinue[1]

CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis

NCI-CTCAE v4.03 grading identification: Hypertension[7]

Grade 1	Pre-hypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg)
Grade 2	Stage 1 hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg) Recurrent or persistent (≥24 hours) Symptomatic increase by >20 mm Hg (DBP) or to >140/90 mm Hg if previously within normal limits Medical intervention indicated Anti-hypertensive monotherapy indicated
Grade 3	Stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) Medical intervention indicated More than 1 drug or more intensive therapy than previously used may be indicated
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurological deficit, hypertensive crisis) Urgent intervention indicated

BP=blood pressure; DBP=diastolic blood pressure; mm Hg=millimeter of mercury; SBP=systolic blood pressure.

Management tips for hypertension[8,9]

- Monitor and optimally manage BP before initiation and regularly during CABOMETYX treatment
- Other than for hypertension requiring immediate therapy, confirm the presence of new or worsened hypertension at a second visit (within 1 week) before taking therapeutic action

For SBP >150 mm Hg and <160 mm Hg or DBP >100 mm Hg and <110 mm Hg†:

- Optimize anti-hypertensive treatment by adding new or additional anti-hypertensive medications and/or increase dose of existing medications
- Reduce CABOMETYX treatment by 1 dose level if optimal anti-hypertensive therapy (usually to include 3 agents) does not result in SBP <150 mm Hg or DBP <100 mm Hg
- If symptomatic, interrupt CABOMETYX

For SBP ≥160 mm Hg or DBP ≥110 mm Hg:

- Reduce CABOMETYX treatment by 1 dose level and add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor closely for hypotension. If optimized anti-hypertensive therapy (usually to include 3 agents) does not result in SBP <150 mm Hg or DBP <100 mm Hg, CABOMETYX treatment should be dose reduced further or interrupted
- Interrupt CABOMETYX treatment if upper limits of BP (SBP ≥160 mm Hg or DBP ≥110 mm Hg) are sustained and not adequately manageable or if SBP is >180 mm Hg or DBP is >120 mm Hg or if patient is symptomatic
- Restart CABOMETYX treatment at the most tolerable dose and re-escalate CABOMETYX dose only if BP falls to and is sustained at SBP <140 mm Hg and DBP <90 mm Hg

For hypertensive crisis or hypertensive encephalopathy, discontinue CABOMETYX

*Grouped term. Includes hypertension, BP increased, hypertensive crisis, and BP fluctuation.[2]
†Or a lower threshold, based on clinical judgment.[8]

Clinical Experience: CABOMETYX Single-Agent ›

Clinical Experience: CABOMETYX + OPDIVO ›

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Hypertension: clinical experience in the phase 3, single-agent METEOR and CELESTIAL trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[2]	Dose interruptions[2]*	Dose reductions[2]*	Discontinuations[2]*
METEOR (aRCC) CABOMETYX® (n=331)	39%	16%	3	5%	7.6%	0%
CELESTIAL (HCC) CABOMETYX (n=467)	30%	16%	2.1	6.6%	7.5%	0.9%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to hypertension.

See full safety results from the **METEOR** and **CELESTIAL** trials.

◀ Management: Hypertension

Clinical Experience: CABOMETYX + OPDIVO® ▶

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Hypertension: clinical experience in the phase 3, combination-treatment CheckMate-9ER trial

	Grade 1-4 incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[2]	Dose interruptions or reductions[2]*
CheckMate-9ER (aRCC) CABOMETYX® + OPDIVO® (n=320)	36%	13%	4.1	10.6%

*Percentage represents the number of dose interruptions or reductions of any study drug due to hypertension.

See full safety results from the CheckMate-9ER trial.

◀ Management: Hypertension
◀ Clinical Experience: CABOMETYX Single-Agent

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Elevated liver enzymes: CABOMETYX® single-agent

For patients receiving CABOMETYX single-agent treatment

Withhold[8]
CABOMETYX for ≥ Grade 3 elevated ALT or AST if patients had an ALT or AST of ≥3 x ULN at baseline, or when transaminase increases are accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests

Wait[8]
Until hepatic toxicity resolves

Restart[1]
CABOMETYX at a dose reduced by 20 mg daily. Lowest dose is 20 mg daily

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

Discontinue[8]
CABOMETYX for irreversible hepatic dysfunction, or if AST elevations >3 x ULN are concurrent with >2 x ULN total bilirubin with no other explanation

NCI-CTCAE v4.03 grading identification: Increased ALT or AST[7]

Grade 1	> ULN - 3.0 x ULN
Grade 2	>3.0 - 5.0 x ULN
Grade 3	>5.0 - 20.0 x ULN
Grade 4	>20.0 x ULN

Management tips for hepatobiliary disorders[9]

- CABOMETYX should be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests (eg, International Normalized Ratio). More frequent monitoring of transaminases should be considered, and treatment should be held until the etiology is determined and abnormalities are corrected or stabilize at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in patients who develop increased values of ALT, AST, or total bilirubin
- Evaluation of patients with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors, such as illnesses that affect liver function, concomitant hepatotoxic medication, alcohol consumption, and cancer-related causes
- ARs that are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions

Increased AST: clinical experience in the phase 3 CELESTIAL trial

CELESTIAL (HCC)
CABOMETYX (n=467)

All-grade incidence[1]	Grade 3-4 incidence[1]	
73%	24%	
Dose interruptions[2]*	**Dose reductions[2]***	**Discontinuations[2]***
9.4%	5.6%	0.9%

*Percentages represent the number of dose interruptions or reductions and discontinuations of any study drug due to increased AST.

Elevated Liver Enzymes: CABOMETYX + OPDIVO® ›

ULN=upper limit of normal.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Elevated liver enzymes: CABOMETYX® + OPDIVO®

For patients receiving CABOMETYX + OPDIVO combination treatment

Withhold[1]

Both CABOMETYX and OPDIVO for ALT or AST of >3 x ULN but ≤10 x ULN with concurrent total bilirubin <2 x ULN; corticosteroid therapy may be considered

Wait[1]

Until hepatic ARs recover to Grades 0 or 1

Restart[1]

Rechallenge with a single medicine or with both medicines after recovery may be considered. If rechallenging with OPDIVO, refer to OPDIVO Prescribing Information

Reduce CABOMETYX dose by 20 mg daily (if previously receiving 20 mg daily, reduce to 20 mg every other day). Lowest dose is 20 mg every other day

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

Discontinue[1]

Both CABOMETYX and OPDIVO for ALT or AST >10 x ULN or >3 x ULN with concurrent total bilirubin ≥2 x ULN

NCI-CTCAE v4.03 grading identification: Increased ALT or AST[7]

Grade 1	> ULN - 3.0 x ULN
Grade 2	>3.0 - 5.0 x ULN
Grade 3	>5.0 - 20.0 x ULN
Grade 4	>20.0 x ULN

Management tips for hepatobiliary disorders[9]

- Frequent monitoring of transaminases should be considered, and treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in cases of increased values of ALT, AST, or total bilirubin
- Evaluation of patients with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors, such as illnesses that affect liver function, concomitant hepatotoxic medication, alcohol consumption, and cancer-related causes
- ARs that are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions
- For guidance around management of hepatobiliary disorders with corticosteroid treatment and information about rechallenging with OPDIVO, refer to the OPDIVO Prescribing Information

Increased ALT: clinical experience in the phase 3 CheckMate-9ER trial

CheckMate-9ER (aRCC)
CABOMETYX + OPDIVO
(n=320)

Grade 1-4 incidence[1] **79%**	**Grade 3-4 incidence**[1] **9.8%**
Dose interruptions or reductions[2]* **10%**	**Discontinuations**[2]* **1.9%**

*Percentages represent the number of dose interruptions or reductions and discontinuations of any study drug due to increased ALT.

Elevated Liver Enzymes: CABOMETYX Single-Agent

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

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 help 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.

Patient Education ›

Please see additional Important Safety Information and full Prescribing Information.

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

Indications and Important Safety Information

INDICATIONS

CABOMETYX® (cabozantinib) 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.

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

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

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 accompanying 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.

ISI

Recommended dosing for CABOMETYX®: combination and single-agent treatment[1]

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

Recommended combination starting dose:
40 mg once daily

CABOMETYX® (cabozantinib) tablets

Recommended starting dose:
60 mg once daily

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 at signup.CABOMETYX.com
  - 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

Visit CABOMETYXhcp.com/resources to download helpful resources for patients, including:
Patient Handbook • Side Effect Tip Cards • Treatment Journal for Patients

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2021. **2.** Data on file. Exelixis, Inc. **3.** Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(7):917-927. **4.** Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): progression-free survival by independent review and overall survival update. *Eur J Cancer*. 2018;94:115-125. **5.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63. **6.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma [supplementary appendix]. *N Engl J Med*. 2018;379(1):54-63. **7.** National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. Published June 14, 2010. Accessed September 1, 2020. evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf **8.** Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma [study protocol]. *N Engl J Med*. 2015;373(19):1814-1823. **9.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma [study protocol]. *N Engl J Med*. 2018;379(1):54-63. **10.** Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768.

Please see additional Important Safety Information and full Prescribing Information.

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