Treatment Management Guide

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

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

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

CABOMETYX® (cabozantinib) tablets

ADVANCED RENAL CELL CARCINOMA (aRCC)
CABOMETYX is indicated for the treatment of patients with advanced RCC.

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

DIFFERENTIATED THYROID CANCER (DTC)
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.

VEGFR=vascular endothelial growth factor receptor.

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, 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.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® + OPDIVO® demonstrated superior efficacy vs sunitinib in 1L aRCC across OS, PFS, and ORR in the primary analysis[1]

Primary analysis in the ITT population (median follow-up time of **18.1 months**; range: 10.6-30.6 months)[2]

Double median PFS[1,*]

16.6 months CABOMETYX + OPDIVO (95% CI: 12.5-24.9; n=323)

vs

HR=0.51 (95% CI: 0.41-0.64) *P*<.0001

8.3 months sunitinib (95% CI: 7.0-9.7; n=328)

Double ORR[1,2,*]

55.7% CABOMETYX + OPDIVO (95% CI: 50.1-61.2; n=323)

vs

P<.0001

27.1% sunitinib (95% CI: 22.4-32.3; n=328)

CR

8.0% (n=26/323) CABOMETYX + OPDIVO vs **4.6%** (n=15/328) sunitinib

PR

47.6% (n=154/323) CABOMETYX + OPDIVO vs **22.5%** (n=74/328) sunitinib

Only 5.6% of patients had PD† with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib

Superior median OS[1]

40% reduction in risk of death with CABOMETYX + OPDIVO (n=323) vs sunitinib (n=328)

(HR=0.60; 98.89% CI: 0.40-0.89; *P*=.001)

Median OS not reached in either treatment arm

44-month follow-up analysis (median follow-up time of **44.0 months**; range: 36.5-56.5 months)[3]

Median PFS*

16.6 months CABOMETYX + OPDIVO (95% CI: 12.8-19.5; n=323)

vs

HR=0.59 (95% CI: 0.49-0.71)

8.4 months sunitinib (95% CI: 7.0-9.7; n=328)

ORR*

56.0% CABOMETYX + OPDIVO (95% CI: 50.4-61.5; n=323)

vs

28.0% sunitinib (95% CI: 23.3-33.2; n=328)

CR

13.3% (n=43/323) CABOMETYX + OPDIVO vs **4.9%** (n=16/328) sunitinib

PR

42.7% (n=138/323) CABOMETYX + OPDIVO vs **23.2%** (n=76/328) sunitinib

Median OS

30% reduction in risk of death with CABOMETYX + OPDIVO (n=323) vs sunitinib (n=328)

(HR=0.70; 95% CI: 0.56-0.87)

49.5 months CABOMETYX + OPDIVO (95% CI: 40.3-not estimable)

vs

35.5 months sunitinib (95% CI: 29.2-42.3)

CheckMate-9ER trial

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) orally once daily in combination with OPDIVO 240-mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) orally once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS; secondary endpoints included OS, ORR, and safety; and HRQoL was an exploratory endpoint. An updated efficacy analysis was conducted, when 271 events were observed based on the prespecified number of deaths for the preplanned final analysis of OS (32.9-month median follow-up data [range: 25.4-45.4 months]).[1,4,5,*]

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

†PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more new lesions is also considered progression.)[6]

1L=first-line; BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; HRQoL=health-related quality of life; ITT=intention-to-treat; IV=intravenous; ORR=objective response rate; OS=overall survival; PD=progressive disease; 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.

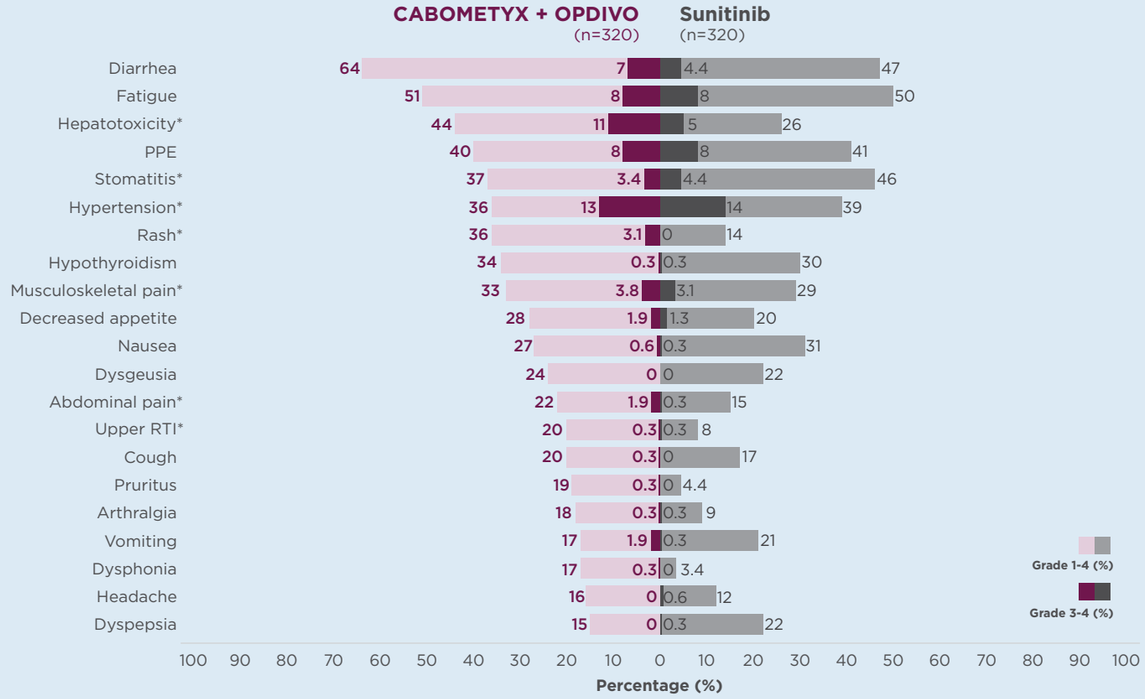
Please see additional Important Safety Information and full Prescribing Information.

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

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

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

Primary analysis (median follow-up time of 18.1 months; range: 10.6-30.6 months)[2]



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

- IMAEs occurred in patients receiving CABOMETYX + OPDIVO[2,7,8]
  - 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.

Primary analysis laboratory values worsening from baseline occurring in >20% of patients receiving CABOMETYX + OPDIVO[1,†]

	Patients (%)			
	CABOMETYX + OPDIVO		Sunitinib	
Laboratory abnormality	**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 rates due to ARs in the CABOMETYX + OPDIVO arm were low[1]

	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[7]	**16.9%**	**72.5%**

The discontinuation rate of CABOMETYX alone was 8%[1]

†Each test incidence is based on the number of patients who had both baseline and at least 1 on-study laboratory measurement available.[1]
‡OPDIVO could only be interrupted, not dose reduced.[6]
§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]

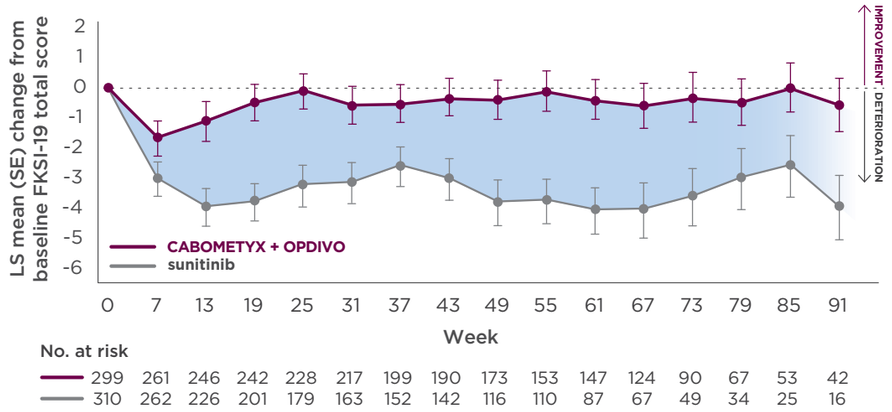
CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

FKSI-19 patient-reported quality of life

Exploratory analysis

Mean score numerically maintained near baseline with CABOMETYX + OPDIVO for over 1.5 years[8]

Total score



The clinical significance is unknown.[8]

Patients responded to statements on 7 domains[9,10]:

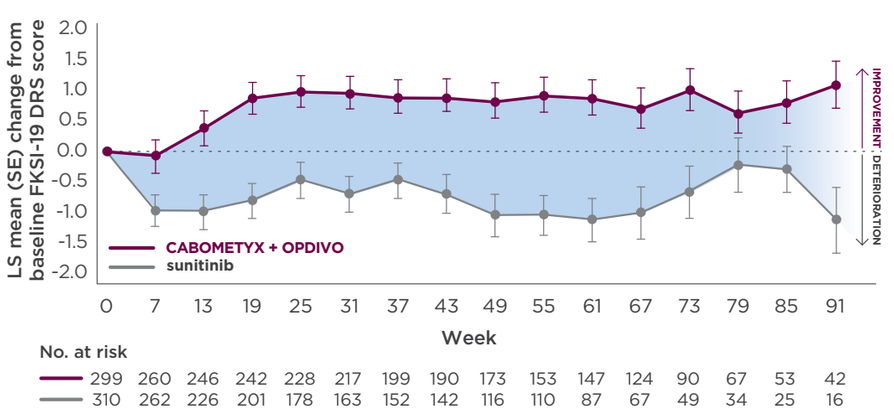
- Pain
- Fatigue
- Pulmonary symptoms
- Bowel/bladder symptoms
- Nutritional health
- Psychosocial functioning
- Treatment side effects

FKSI-19 disease-related symptoms (DRS) subscale

Exploratory analysis

Mean score numerically improved above baseline after Week 7 with CABOMETYX + OPDIVO for over 1.5 years[8]

DRS subscale



The clinical significance is unknown.[8]

Patients responded to statements about disease-related symptoms[11]:

- I have a lack of energy
- I have pain
- I am losing weight
- I have bone pain
- I feel fatigued
- I have been short of breath
- I have been coughing
- I am bothered by fevers (episodes of high body temperature)
- I have blood in my urine

Mean changes from baseline for FKSI-19 and subscales were prespecified. Least squares mean used above was done post hoc.
The FKSI-19 total score scale and 3 subscales (disease-related symptoms, treatment side effects, and functional well-being) were collected to measure tumor-specific HRQoL. Change from baseline was assessed with the use of descriptive statistics, based on a linear-regression model for repeated measures that controlled for treatment group, time point, baseline patient-reported outcomes score, and the stratification factors (IMDC prognostic risk score, tumor PD-L1 expression, and geographic region) are reported. No. at risk denotes intention-to-treat patients with baseline plus at least 1 postbaseline HRQoL assessment with nonmissing, patient-reported outcome data. Time 0 indicates baseline.[2,8]

FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; IMDC=International Metastatic RCC Database Consortium; LS=least squares; PD-L1=programmed cell death ligand 1.

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.

Please see additional Important Safety Information and full Prescribing Information.

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

CABOMETYX® is 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,*]

PRIMARY ENDPOINT: PFS[†,‡]	SECONDARY ENDPOINT: OS	SECONDARY ENDPOINT: ORR[§]
MEDIAN	MEDIAN	
7.4 months CABOMETYX (95% CI: 5.6-9.1; n=187)	**21.4 months** CABOMETYX (95% CI: 18.7-not evaluable; n=330)	**17%** CABOMETYX (95% CI: 13%-22%; n=330)
VS	VS	VS
3.8 months everolimus (95% CI: 3.7-5.4; n=188)	**16.5 months** everolimus (95% CI: 14.7-18.8; n=328)	**3%** everolimus (95% CI: 2%-6%; n=328)
HR=0.58 (95% CI: 0.45-0.74); *P*<.0001	HR=0.66 (95% CI: 0.53-0.83); *P*=.0003	*P*<.0001; partial responses only

***After at least 1 prior antiangiogenic 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.[12]

METEOR trial

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 antiangiogenic 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. The primary endpoint was PFS, and was conducted in the first 375 subjects randomized to treatment. The ITT population included all 658 patients. Secondary endpoints included OS and ORR.[1,12]

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

PRIMARY ENDPOINT: PFS[#]			
MEDIAN			
8.6 months CABOMETYX (95% CI: 6.8-14.0; n=79)	VS	**5.3 months** sunitinib (95% CI: 3.0-8.2; n=78)	**52%** reduction in risk of progression or death HR=0.48 (95% CI: 0.31-0.74); *P*=.0008

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

CABOSUN trial

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.[1,13]

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

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 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. 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 full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® safety in the METEOR trial[1]

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

Patients (%)

Adverse reaction	CABOMETYX (n=331)* All grades†	CABOMETYX (n=331)* Grade 3-4	Everolimus (n=322) All grades†	Everolimus (n=322) 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]

Patients (%)

Laboratory abnormality	CABOMETYX (n=331) All grades†	CABOMETYX (n=331) Grade 3-4	Everolimus (n=322) All grades†	Everolimus (n=322) 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, dose 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%

*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,*]

	Patients (%)	
Adverse reaction	**CABOMETYX (n=78)**	**Sunitinib (n=72)**
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,*,‡]

	Patients (%)	
Laboratory abnormality	**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, dose 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%**

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® single agent resulted in superior OS and PFS in 2L HCC[1]

vs placebo in post-sorafenib–treated patients who had progressed on at least 1 prior systemic therapy, including sorafenib

- 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 1 prior therapy (HR=0.76; 95% CI: 0.63-0.92; *P*=.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 1 prior therapy (HR=0.44; 95% CI: 0.36-0.52; *P*<.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 (second-line)[14]

SUBGROUP ANALYSIS: MEDIAN OS[7,*]

11.4 months CABOMETYX (n=335) **VS** 7.7 months Placebo (n=174)

26% reduction in risk

HR=0.74 (95% CI: 0.59-0.92)

SUBGROUP ANALYSIS: MEDIAN PFS[7,*]

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.[14]

Patients who progressed from Child-Pugh A to Child-Pugh B within the first 8 weeks of treatment remained in the trial until disease progression or unacceptable toxicity (51/470 patients in the CABOMETYX arm and 22/237 in the placebo arm)[16,†]

CELESTIAL trial

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. All patients received prior sorafenib, and 28% of patients received more than 1 prior systemic regimen. The starting dose for CABOMETYX was 60 mg, administered orally once daily. Treatment continued as long as patients had clinical benefit or until unacceptable toxicity. 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 tumor marker level, or viral load. The primary endpoint was OS. Secondary endpoints included PFS and ORR.[14,15]

†Child-Pugh scores were assessed by the investigator at the time of each radiographic disease assessment every 8 weeks.[16]

AFP=alpha-fetoprotein.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% 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.

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]

	Patients (%)			
	CABOMETYX (n=467)		Placebo (n=237)	
Adverse reaction	**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				
Pain in extremity	**9**	**<1**	4	1
Muscle spasms	**8**	**<1**	2	0

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]

	Patients (%)			
	CABOMETYX (n=467)		Placebo (n=237)	
Laboratory abnormality	**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, dose reductions, and discontinuations in the CELESTIAL trial[1,7,14]

	CABOMETYX (n=467)	Placebo (n=237)
Dose withholds	**84%**	37%
Dose reductions	**62%**	13%
Discontinuations	**16%**	3%

In an exploratory, small subgroup of CELESTIAL, patients who progressed from Child-Pugh A to Child-Pugh B: 61% had dose reductions with CABOMETYX (14% with placebo) and 18% discontinued CABOMETYX due to treatment-related ARs (5% with placebo).

*NCI-CTCAE Version 4.0.

†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.

LDH=lactate dehydrogenase.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® single agent delivered a significant benefit in 2L DTC in the primary PFS analysis[1,17]

vs placebo in patients who had progressed following prior VEGFR-targeted therapy and were RAI-R or ineligible

PFS

Median PFS was not reached in the primary analysis (n=125, 95% CI: 5.7-NE) vs PFS of 1.9 months with placebo (n=62, 95% CI: 1.8-3.6); HR=0.22, 95% CI: 0.14-0.35, *P*<.0001

78% reduction in risk of progression or death in both primary and updated analyses

Updated analysis*: Median PFS

11.0 months CABOMETYX (n=170) (95% CI: 7.4-13.8)	VS	**1.9 months** Placebo (n=88) (95% CI: 1.9-3.7)

HR=0.22 (95% CI: 0.15-0.31)

*No formal statistical testing was conducted at the time of the updated analysis.[1]

ORR

ORR†

15% CABOMETYX (n=67) (95% CI: 7-26)	VS	**0%** Placebo (n=33) (95% CI: 0-11)

In the COSMIC-311 trial, the ORR did not reach a prespecified endpoint for statistical significance (critical *P* value=.01). Data shown cover tumor response information collected, inclusive of ORR.[1,17]

†*P*=.0281. All responses confirmed were PRs.[1,17]

Stable disease‡

69% CABOMETYX (n=46/67)	VS	**42%** Placebo (n=14/33)

Disease control rate§

84% CABOMETYX (n=56/67)	VS	**42%** Placebo (n=14/33)

COSMIC-311 trial

COSMIC-311 was a phase 3, multicenter, randomized (2:1), double-blind, placebo-controlled trial in 258 RAI-R or ineligible patients with locally advanced or metastatic DTC who had progressed after prior systemic treatment. Patients were randomized to receive CABOMETYX 60 mg orally once daily or placebo with best supportive care until disease progression or unacceptable toxicity. Eligible placebo patients were allowed to cross over to receive open-label CABOMETYX after BIRC-confirmed PD per RECIST v1.1. **The multiple primary efficacy outcome measures were PFS in the ITT population (n=187) and ORR in the first 100 randomized patients.**[1,17,¶]

‡Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.[18] Stable disease may reflect the natural history of disease rather than effect of the drug.

§Disease control rate is defined as the percentage of patients with a CR, PR, or SD, as measured by RECIST v1.1.[17]

¶The multiple primary efficacy outcome measures assessed ORR in the first 100 patients (OITT) after 6 months of enrollment and PFS in all patients randomly assigned (ITT). Median follow-up was 6.2 months (IQR: 3.4-9.2) for the ITT population and 8.9 months (IQR: 7.1-10.5) for the OITT population. Median duration of treatment exposure in the safety population was 4.4 months (IQR: 2.1-7.3) for the CABOMETYX patients and 2.3 months (IQR: 1.6-5.6) for the placebo group. An updated analysis, with a median follow-up of 10.1 months, evaluated a total of 258 randomized patients.[1,17,19]

BIRC=blinded independent radiology committee; IQR=interquartile range; OITT=objective response rate intention-to-treat; RAI-R=radioactive iodine-refractory; SD=stable disease.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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. Withhold and resume at a reduced dose based on severity.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX® safety in the COSMIC-311 trial

Treatment-emergent ARs in the primary analysis (between-arm difference of ≥5% [all grades] or ≥2% [Grade 3-4])[1]

Patients (%)

	CABOMETYX (n=125)		Placebo (n=62)	
Adverse reaction	**All grades***	**Grade 3-4**	All grades*	Grade 3-4
Gastrointestinal				
Diarrhea	**51**	**7**	3	0
Nausea	**24**	**3**	2	0
Vomiting	**14**	**1**	8	0
Stomatitis†	**26**	**5**	3	0
Dry mouth	**10**	**1**	2	0
General				
Fatigue‡	**42**	**10**	23	0
Metabolism and nutrition				
Decreased appetite	**23**	**3**	16	0
Skin and subcutaneous tissue				
PPE	**46**	**10**	0	0
Vascular				
Hypertension§	**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

*NCI-CTCAE Version 5.0.
†Includes the following terms: mucosal inflammation, stomatitis.
‡Includes the following terms: fatigue, asthenia.
§Includes the following terms: hypertension, blood pressure increased, hypertensive crisis.

Laboratory abnormalities occurring in ≥10% of CABOMETYX-treated patients in the primary analysis (between-arm difference of ≥5% [all grades] or ≥2% [Grade 3-4])[1]

Patients (%)

	CABOMETYX (n=125)		Placebo (n=62)	
Laboratory abnormality	**All grades**	**Grade 3-4**	All grades	Grade 3-4
Chemistry				
Increased LDH¶	**90**	**10**	32	3
Increased AST	**77**	**1**	18	0
Increased ALT	**66**	**2**	11	0
Hypocalcemia	**36**	**9**	10	2
Increased ALP	**34**	**0**	15	0
Increased GGT	**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				
Decreased leukocytes	**38**	**2**	7	2
Decreased neutrophils	**31**	**2**	5	2
Decreased platelets	**26**	**0**	5	0

¶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).[1]

ULN=upper limit of normal.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX®: Once-daily oral starting dose as combination therapy or monotherapy[1]

COMBINATION THERAPY

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

CABOMETYX 40-mg recommended starting dose—optimized for combination treatment with OPDIVO® in 1L aRCC

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)**

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.

MONOTHERAPY

CABOMETYX® (cabozantinib) tablets

CABOMETYX 60-mg recommended starting dose for single-agent treatment in aRCC, HCC*, or DTC†,‡

CABOMETYX

60 mg once daily

*For patients with HCC who have been previously treated with sorafenib.

†For 2L patients with DTC who have progressed following prior VEGFR-targeted therapy and who are RAI-R or ineligible.

‡For adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m^2. For pediatric patients with DTC ≥12 years of age with BSA <1.2 m^2, start at 40 mg once daily.

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, including dental surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed[1]
- Do not substitute CABOMETYX tablets with cabozantinib capsules[1]
- Do not administer CABOMETYX with food. Administer at least 1 hour before or at least 2 hours after eating[1]
- Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets[1]
- Do not take a missed dose within 12 hours of the next dose[1]
- Modify the dose for certain patients with hepatic impairment and patients taking drugs known to strongly induce or inhibit CYP3A4[1]
- When administering CABOMETYX in combination with OPDIVO for the treatment of aRCC, refer to the OPDIVO Prescribing Information

Reduce starting dose of CABOMETYX for patients with hepatic impairment[1]

- **Child-Pugh B:** Reduce the starting dose of CABOMETYX 60 mg daily to 40 mg daily in patients with moderate hepatic impairment. For pediatric patients with DTC and BSA less than 1.2 m^2, reduce the starting dose from 40 mg daily to 20 mg daily
- **Child-Pugh C:** Avoid CABOMETYX in patients with severe hepatic impairment, since it has not been studied in this population

BSA=body surface area; CYP3A4=cytochrome P450 3A4.

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 AR)

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*
CABOMETYX® (cabozantinib) tablets	For pediatric patients with DTC ≥12 years of age and BSA <1.2 m²: 40 mg once daily	20 mg once daily	20 mg once every other day*

Tablets shown are not actual size.

*If previously receiving the lowest dose, resume at same dose. If not tolerated, discontinue CABOMETYX.
†For DTC, in adult and pediatric patients ≥12 years of age with BSA ≥1.2 m².

Permanently discontinue CABOMETYX for Grade 3 or 4 hemorrhage, development of a GI perforation or Grade 4 fistula, acute myocardial infarction or Grade 2 or higher cerebral infarction, Grade 3 or 4 arterial thromboembolic events or Grade 4 venous thromboembolic events, Grade 4 hypertension/hypertensive crisis or Grade 3 hypertension/hypertensive crisis that cannot be controlled, nephrotic syndrome, or reversible posterior leukoencephalopathy syndrome.

For patients being treated with CABOMETYX in combination with OPDIVO®:

- If ALT or AST >3 × ULN but ≤10 × ULN with concurrent total bilirubin <2 × 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 × ULN or >3 × ULN with concurrent total bilirubin ≥2 × ULN, both CABOMETYX and OPDIVO should be permanently discontinued

Dose Exchange Program

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

†Additional restrictions and eligibility rules apply.
§Patients are required to return any unused product.

To learn more, **contact your sales representative,**

call EASE at **1-844-900-EASE(3273)**,

or visit **www.EASE.US**

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® + OPDIVO® combination treatment in the phase 3 CheckMate-9ER trial[1,2]

SELECT COMMON ARs IN THE CHECKMATE-9ER TRIAL: GRADE 1-4 INCIDENCE (GRADE 3-4 INCIDENCE)

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

Diarrhea	PPE/HFS	Hypertension	Increased ALT
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**.

HFS=hand-foot syndrome.

Please see additional Important Safety Information and full Prescribing Information.

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

Select adverse reactions with CABOMETYX® in phase 3, single-agent trials[1,12,14,17]

SELECT COMMON ARs IN THE METEOR, CELESTIAL, AND COSMIC-311 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%)
COSMIC-311 (DTC) CABOMETYX (n=125)	51% (7%)	46% (10%)	42% (10%)	30% (10%)	77% (1%)

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**, **CELESTIAL**, and **COSMIC-311** trials.

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

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Diarrhea

Withhold[1]

CABOMETYX® for Grade 2-4 diarrhea

Monitor and manage patients using antidiarrheals as indicated

Wait[1]

Until improvement to ≤Grade 1

Restart[1]

CABOMETYX at a reduced dose; reduce by 20 mg daily

CABOMETYX + OPDIVO®:
If previously receiving 20 mg daily, reduce to 20 mg every other day. Lowest dose is 20 mg every other day

CABOMETYX monotherapy: RCC, HCC, and in adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m²:
Lowest dose is 20 mg daily

DTC in pediatric patients ≥12 years of age with BSA <1.2 m²:
Lowest dose is 20 mg every other day

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

NCI-CTCAE v5.0 Grading Identification: Diarrhea[20]

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

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

ADL=activities of daily living.

Management tips for diarrhea

Advise patients to notify their health care provider at the first signs of loose stool or an increased frequency of bowel movements[1]

- Patients should also be instructed to contact their health care provider immediately for any of the following: loose bowel movements several times a day or for 1 to 4 days, blood around the anal area or in stool, new stomach pain or cramps, lack of urination for 12 or more hours, distended stomach[21]

Supportive measures for diarrhea[22]

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

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]	Median time to first occurrence (weeks)[7]	Dose interruptions or reductions[7,†]	Discontinuations[7,†]
CheckMate-9ER (aRCC) CABOMETYX® + OPDIVO® (n=320)	**64%**	**7%**	**12.4***	**24.4%**	**0.6%**

*Time to onset data are for gastrointestinal drug-related select ARs.
†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.

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

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[7]	Dose interruptions[7,*]	Dose reductions[7,*]	Discontinuations[7,*]
METEOR (aRCC) CABOMETYX® (n=331)	74%	11%	5	22%	16%	<1%
CELESTIAL (HCC) CABOMETYX (n=467)	54%	10%	4.1	15%	10%	1.1%
COSMIC-311 (DTC) CABOMETYX (n=125)	51%	7%	NA	16%	10%	0.8%

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

See full safety results from the **METEOR**, **CELESTIAL**, and **COSMIC-311** trials.

NA=not available.

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 or Grade 3 PPE

Wait[1]

Until improvement to ≤Grade 1

Restart[1]

CABOMETYX at a reduced dose; reduce by 20 mg daily

CABOMETYX + OPDIVO®:
If previously receiving 20 mg daily, reduce to 20 mg every other day. Lowest dose is 20 mg every other day

CABOMETYX monotherapy: RCC, HCC, and in adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m²:
Lowest dose is 20 mg daily

DTC in pediatric patients ≥12 years of age with BSA <1.2 m²:
Lowest dose is 20 mg every other day

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

NCI-CTCAE v5.0 Grading Identification: PPE[20]

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

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

Management tips for PPE/HFS

Advise patients to tell their health care provider, if they experience any of the following early signs and manifestations of PPE/HFS[22]:

- 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 measures for PPE[22]:

- 20% urea cream twice daily and 0.05% clobetasol cream once daily
- Analgesics for pain control if needed for Grade 2 or above

All patients should be advised on prophylactic skin care, including[22]:

- Use of hypoallergenic moisturizing creams or ointments
- Sunscreen with 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
- Careful monitoring of patients with skin disorders for signs of infection (eg, abscess, cellulitis, or impetigo)

Early and adequate interventions are recommended to prevent worsening of skin symptoms such as blisters, desquamation, ulcerations, or necrosis of affected areas, including early referral to a dermatologist.[22]

SPF=sun protection factor.

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)[7]	Dose interruptions or reductions[7,*]	Discontinuations[7,*]
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.

Please see additional Important Safety Information and full Prescribing Information.

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

PPE/HFS: clinical experience in phase 3, single-agent trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[7]	Dose interruptions[7,*]	Dose reductions[7,*]	Discontinuations[7,*]
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%
COSMIC-311 (DTC) CABOMETYX (n=125)	46%	10%	4.0	16%	19%	0%

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

See full safety results from the **METEOR**, **CELESTIAL**, and **COSMIC-311** trials.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Fatigue

Withhold[1]

CABOMETYX® for intolerable Grade 2 or Grade 3-4 fatigue

Wait[1]

Until improvement to baseline or ≤Grade 1

Restart[1]

CABOMETYX at a reduced dose; reduce by 20 mg daily

CABOMETYX + OPDIVO®:
If previously receiving 20 mg daily, reduce to 20 mg every other day. Lowest dose is 20 mg every other day

CABOMETYX monotherapy:

RCC, HCC, and in adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m^2:
Lowest dose is 20 mg daily

DTC in pediatric patients ≥12 years of age with BSA <1.2 m^2:
Lowest dose is 20 mg every other day

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

Management tips for fatigue

Advise patients to notify their health care provider immediately for any of the following[23]:

- Too tired to get out of bed for 24-hour period
- Feel confused, dizzy, lose balance or fall
- Trouble waking up
- Trouble catching breath
- Fatigue seems to be worsening

Supportive measures for fatigue[22]

- 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

NCI-CTCAE v5.0 Grading Identification: Fatigue[20]

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

Fatigue: clinical experience in phase 3, single-agent trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Dose interruptions[7,*]	Dose reductions[7,*]	Discontinuations[7,*]
METEOR (aRCC) CABOMETYX® (n=331)	56%	9%	12%	10%	1.2%
CELESTIAL (HCC) CABOMETYX (n=467)	45%	10%	13%	7.5%	1.3%
COSMIC-311 (DTC) CABOMETYX (n=125)	42%	10%	NA	7.2%	1.6%

*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**, **CELESTIAL**, and **COSMIC-311** trials.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Hypertension*

Withhold[1]

CABOMETYX® for Grade 3 hypertension that is not adequately controlled

Wait[1]

Until adequately controlled to ≤Grade 2

Restart[1]

CABOMETYX at a reduced dose; reduce by 20 mg daily

CABOMETYX + OPDIVO®:
If previously receiving 20 mg daily, reduce to 20 mg every other day.
Lowest dose is 20 mg every other day

CABOMETYX monotherapy: RCC, HCC, and in adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m²:
Lowest dose is 20 mg daily

DTC in pediatric patients ≥12 years of age with BSA <1.2 m²:
Lowest dose is 20 mg every other day

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

Permanently discontinue[1]

CABOMETYX for Grade 3 hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis and Grade 4 hypertension

*Grouped term. Includes hypertension, BP increased, hypertensive crisis, and BP fluctuation.[1]

Management tips for hypertension

Advise patients to notify their health care provider if they develop[1]: severe headaches, nosebleeds, tiredness or confusion, vision changes, chest pain, trouble breathing, irregular heartbeat, blood in the urine

Supportive measures for hypertension[1]

- Monitor blood pressure before initiation and regularly during treatment
- If needed, prescribe medication to treat hypertension

NCI-CTCAE v5.0 Grading Identification: Hypertension[20]

Grade 1	• SBP 120-139 mm Hg or DBP 80-89 mm Hg
Grade 2	• SBP 140-159 mm Hg or DBP 90-99 mm Hg if previously within normal limit • Change in baseline medical intervention indicated • Recurrent or persistent (≥24 h) • Symptomatic increase by >20 mm Hg (DBP) or to >140/90 mm Hg • Antihypertensive monotherapy indicated
Grade 3	• SBP ≥160 mm Hg or DBP ≥100 mm Hg • Medical intervention indicated • More than 1 drug or more intensive therapy than previously used 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.

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)[7]	Dose interruptions or reductions[7,*]
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.

Hypertension: clinical experience in phase 3, single-agent trials

	All-grade incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[7]	Dose interruptions[7,*]	Dose reductions[7,*]	Discontinuations[7,*]
METEOR (aRCC) CABOMETYX® (n=331)	39%	16%	3.0	5.1%	7.6%	0%
CELESTIAL (HCC) CABOMETYX (n=467)	30%	16%	2.1	6.6%	7.5%	0.9%
COSMIC-311 (DTC) CABOMETYX (n=125)	30%	10%	2.1	7.2%	NA	0.8%

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

See full safety results from the **METEOR**, **CELESTIAL**, and **COSMIC-311** trials.

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 >3 × ULN but ≤10 × ULN with concurrent total bilirubin <2 × ULN

Wait[1]

Until hepatic AR recovers to Grades 0 or 1

Restart[1]

Rechallenge with one or both may be considered. If rechallenging with OPDIVO with or without CABOMETYX, refer to the 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

Permanently discontinue[1]

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

NCI-CTCAE v5.0 Grading Identification: Increased ALT or AST[20]

Grade 1	• >ULN-3.0 x ULN if baseline was normal • 1.5-3.0 x baseline if baseline was abnormal
Grade 2	• >3.0-5.0 x ULN
Grade 3	• >5.0-20 x ULN
Grade 4	• >20 x ULN

Management tips for elevated liver enzymes

Advise patients to notify their health care provider right away if they develop symptoms of liver problems including[1]: yellowing of skin or whites of eyes, severe nausea or vomiting, pain on the right side of stomach area (abdomen), dark urine, bleeding or bruising more easily than normal

Supportive measures for elevated liver enzymes[16]

- Frequent monitoring of transaminases should be considered
- Treatment should be held until the etiology is determined and abnormalities are corrected or stabilized at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in patients who develop increased values of ALT, AST, or bilirubin
- Evaluation of patients with elevated transaminases or 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[7,*] 10%	**Discontinuations[7,*]** 1.9%

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

Please see additional Important Safety Information and full Prescribing Information.

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

Elevated liver enzymes: CABOMETYX® single agent

For patients receiving CABOMETYX single-agent treatment

Withhold[1]

CABOMETYX for intolerable Grade 2 or Grade 3-4 elevated liver enzymes

Wait[1]

Until improvement to baseline or ≤Grade 1

Restart[1]

CABOMETYX at a reduced dose; reduce by 20 mg daily

RCC, HCC, and in adult and pediatric patients with DTC ≥12 years of age with BSA ≥1.2 m^2:
Lowest dose is 20 mg daily

DTC in pediatric patients ≥12 years of age with BSA <1.2 m^2:
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[22]

For aRCC and HCC:

CABOMETYX for irreversible hepatic dysfunction if hepatic dysfunction is not reversible despite temporary interruption of treatment, or for elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin with no other explanation

For DTC:

CABOMETYX if lab abnormalities are not reversed despite temporary interruption of treatment, for elevations >8 × ULN of ALT or AST, or for >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin with no other explanation

NCI-CTCAE v5.0 Grading Identification: Increased ALT or AST[20]

Grade 1	• >ULN-3.0 x ULN if baseline was normal • 1.5-3.0 x baseline if baseline was abnormal
Grade 2	• >3.0-5.0 x ULN
Grade 3	• >5.0-20 x ULN
Grade 4	• >20 x ULN

Management tips for elevated liver enzymes

Advise patients to notify their health care provider right away if they develop symptoms of liver problems including[1]: yellowing of skin or whites of eyes, severe nausea or vomiting, pain on the right side of stomach area (abdomen), dark urine, bleeding or bruising more easily than normal

Supportive measures for elevated liver enzymes[22]

- Frequent monitoring of transaminases should be considered
- Treatment should be held until the etiology is determined and abnormalities are corrected or stabilized at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in patients who develop increased values of ALT, AST, or bilirubin
- Evaluation of patients with elevated transaminases or 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] **73%**	Grade 3-4 incidence[1] **24%**	
Dose interruptions[7,*] **9.4%**	Dose reductions[7,*] **5.6%**	Discontinuations[7,†] **0.9%**

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

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 start treatment quickly. EASE can help 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)

30-Day Free Trial Program

Provides a free trial to help new CABOMETYX patients start treatment quickly, regardless of insurance type, with a 30-day additional supply available for patients with a payer decision delay of 5 days or more.*,†

Co-Pay Program

Eligible, commercially insured patients **may pay as little as $0 per month.** Annual and transaction limits apply.‡

Dose Exchange Program

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

Patient Assistance Program

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**
- **Prior authorization 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.
‡The Co-Pay Program is not available to patients receiving prescription reimbursement under any federal, state, or government-funded insurance programs or where prohibited by law. Additional Terms and Conditions apply.
§Patients are required to return any unused product.

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 the 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
cabometyx.com/be-connected

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

*Limit one Patient Care Kit per patient. US residents only. Additional restrictions and eligibility rules apply. Exelixis may at its sole option modify these items and conditions without notice.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

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.

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.

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, 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.

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 37% (16% 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. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% 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. Withhold and resume at a reduced dose based on severity.

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.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. 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.

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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, resume at a reduced dose.

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.

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.

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.

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.

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, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

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.

Pediatric Use: Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Physeal and longitudinal growth monitoring is recommended in children (12 years and older with DTC) with open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur.

Please see accompanying full Prescribing Information by clicking here.

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.

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CABOMETYX® (cabozantinib) tablets

Recommended dosing for CABOMETYX®: combination therapy and monotherapy[1]

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

Recommended combination starting dose in 1L aRCC*:

40 mg once daily

CABOMETYX® (cabozantinib) tablets

Recommended starting dose for aRCC or appropriate patients in HCC and DTC†:

60 mg once daily

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

†CABOMETYX is indicated for the treatment of patients with aRCC, for the treatment of patients with HCC who have been previously treated with sorafenib, and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. **For pediatric patients with DTC ≥12 years of age with BSA <1.2 m², start at 40 mg once daily.**

Visit CABOMETYXhcp.com/resources to download helpful resources for patients, including:

Patient Handbook • Side Effect Tip Cards • Treatment Journal for Patients

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Please see additional Important Safety Information and full Prescribing Information.

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