Treatment Management Guide

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

aRCC, advanced renal cell carcinoma; NET, neuroendocrine tumor; VEGFR, vascular endothelial growth factor receptor.

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

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

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

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

NEUROENDOCRINE TUMORS
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET).

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extrapancreatic neuroendocrine tumors (epNET).

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

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

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]

Double median PFS[1,a]

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

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]

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

48% (n=154/323) CABOMETYX + OPDIVO vs **23%** (n=74/328) sunitinib

Only 5.6% of patients had PD[b] with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib[2]

Superior median OS[2]

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

Median PFS[3]

5-year follow-up analysis (median follow-up time of 67.6 months; range, 60.2-80.2 months)[3]

16.4 months **CABOMETYX + OPDIVO** (95% CI, 12.5-19.3; n=323)

vs

HR, 0.58 (95% CI, 0.49-0.70)

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

ORR[3,4]

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

vs

27.4% **sunitinib** (95% CI, 22.7-32.6; n=328)

CR

13.9% (n=45/323) CABOMETYX + OPDIVO vs **4.6%** (n=15/328) sunitinib

PR

41.8% (n=135/323) CABOMETYX + OPDIVO vs **22.9%** (n=75/328) sunitinib

Median OS[3]

21% reduction in risk of death with CABOMETYX + OPDIVO (n=323) vs sunitinib (n=328)

(HR, 0.79; 95% CI, 0.65-0.96)

46.5 months **CABOMETYX + OPDIVO** (95% CI, 40.6-53.8)

vs

35.5 months **sunitinib** (95% CI, 29.2-42.8)

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

CheckMate-9ER trial

CheckMate-9ER was a randomized (1:1), open-label, phase 3 trial of CABOMETYX + OPDIVO vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) 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.[1,2,a]

Preplanned final analysis of OS (median follow-up, 32.9 months; range: 25.4-45.4 months): median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI, 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI, 29.0-NR; n=328); HR, 0.70 (95% CI, 0.55-0.90).[1,5,6]

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

[b]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.)[7]

1L, first-line; BICR, blinded independent central review; CR, complete response; HR, hazard ratio; HRQOL, health-related quality of life; ITT, intention-to-treat; IV, intravenous; NR, not reported; 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, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

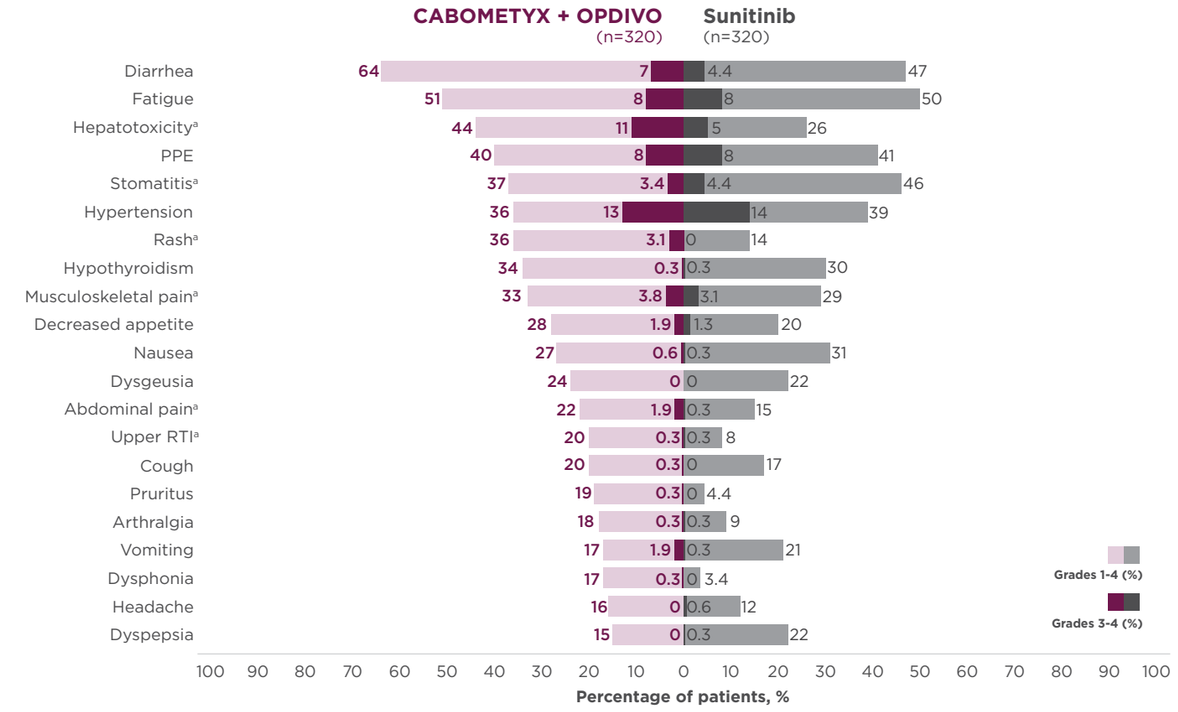
Please see additional Important Safety Information and full Prescribing Information.

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]



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

- IMAEs occurred in patients receiving CABOMETYX + OPDIVO[2,4,8]
  - 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 or OPDIVO QVANTIG 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,b]

	Percentage of patients, %			
	CABOMETYX + OPDIVO		Sunitinib	
Laboratory abnormality	**Grades 1-4**	**Grades 3-4**	**Grades 1-4**	**Grades 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 for CABOMETYX + OPDIVO was 6%[1]

	Permanent discontinuation	Dose interruption/reduction[c]
CABOMETYX or OPDIVO[1]	**20%**	**83%**
CABOMETYX only[1]	8%	46%
OPDIVO only[1]	7%	3%
CABOMETYX and OPDIVO[1]	6%[d]	21%[e]
Sunitinib[4]	**16.9%**	**72.5%**

[b]Each test incidence is based on the number of patients who had both baseline and at least 1 on-study laboratory measurement available; CABOMETYX + OPDIVO group (range: 170-317 patients) and sunitinib group (range: 173-311 patients).[1]
[c]OPDIVO could only be interrupted, not dose reduced.[7]
[d]Due to the same AR at the same time.[1]
[e]Due to the same AR at the same time; 6% for both drugs sequentially.[1]

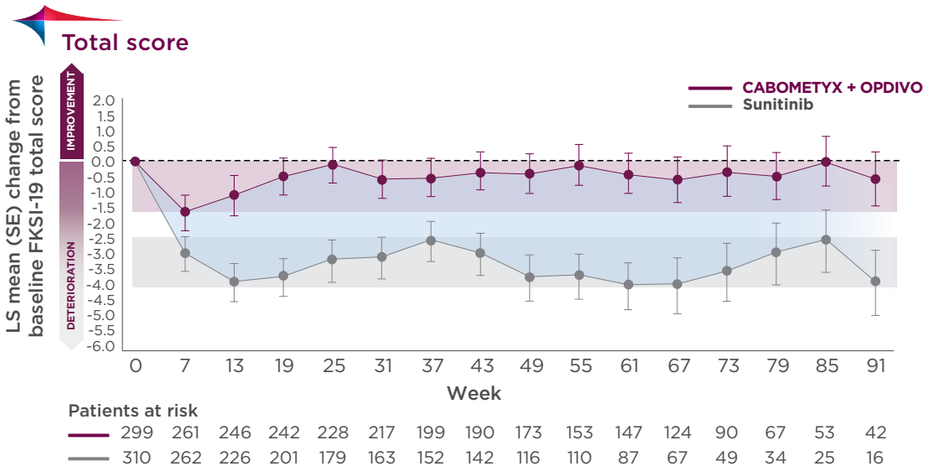
8% The discontinuation rate of CABOMETYX alone was 8%[1]

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]



The clinical significance is unknown.[8]

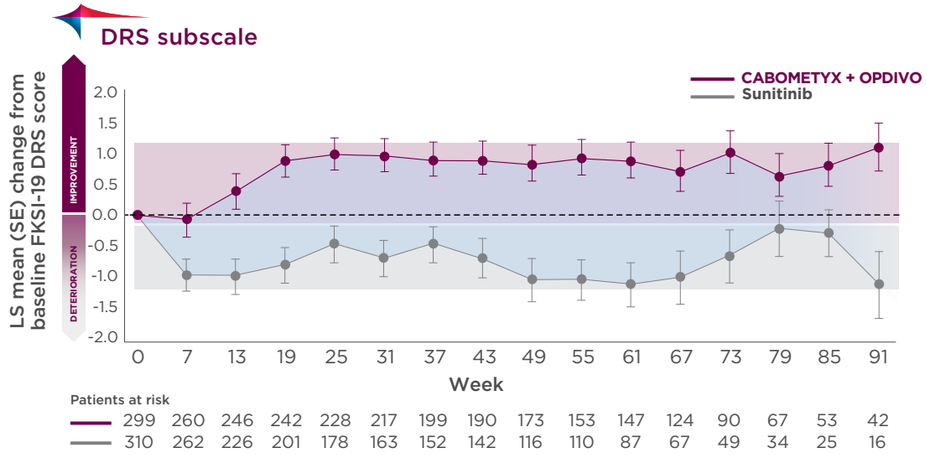
Patients responded to statements on 7 domains[9,10]:

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

FKSI-19 disease-related symptoms subscale

Exploratory analysis

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



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.[2]
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). "Patients at risk" denotes ITT patients with baseline plus at least 1 post-baseline HRQOL assessment with nonmissing, patient-reported outcome data. Time 0 indicates baseline.[2,8]

DRS, disease-related symptoms; 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; SE, standard error.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Thromboembolic Events: CABOMETYX can cause arterial or venous thromboembolic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

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 PFS, OS, and ORR in 2L aRCC[1,a]

PRIMARY ENDPOINT: MEDIAN PFS[b,c]			SECONDARY ENDPOINT: MEDIAN OS			SECONDARY ENDPOINT: ORR[d]		
7.4 months CABOMETYX (95% CI, 5.6-9.1; n=187)	VS	3.8 months everolimus (95% CI, 3.7-5.4; n=188)	**21.4 months** CABOMETYX (95% CI, 18.7-NE; n=330)	VS	16.5 months everolimus (95% CI, 14.7-18.8; n=328)	**17%** CABOMETYX (95% CI, 13%-22%; n=330)	VS	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		

[a]**After at least 1 prior antiangiogenic therapy.**[1]
[b]In the METEOR trial, the primary PFS analysis was conducted in the first 375 subjects randomized to treatment.[1]
[c]PFS was confirmed by blinded IRRC.[1]
[d]ORR was assessed by blinded IRRC using RECIST v1.1.[12]

The only single-agent TKI to deliver superior PFS vs sunitinib in 1L aRCC[1,4,e]

PRIMARY ENDPOINT: MEDIAN PFS[f]			
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

[e]**Patients were intermediate or poor risk and had ≥1 IMDC risk factors.**[1,4]
[f]PFS was assessed by a retrospective BICR.[1,4]

2L, second-line; ECOG PS, Eastern Cooperative Oncology Group performance status; IRRC, independent radiology review committee; KPS, Karnofsky Performance Status; NE, not evaluable; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

2L 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 a clear-cell component, and a KPS ≥70%. The primary endpoint was PFS and was assessed in the first 375 subjects randomized to treatment. The ITT population included all 658 patients. Secondary endpoints included OS, ORR, and safety.[1,12]

1L CABOSUN trial

CABOSUN was a randomized (1:1), open-label, multicenter, phase 2 trial of CABOMETYX vs sunitinib in 157 1L 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]

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. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) 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; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information and full Prescribing Information.

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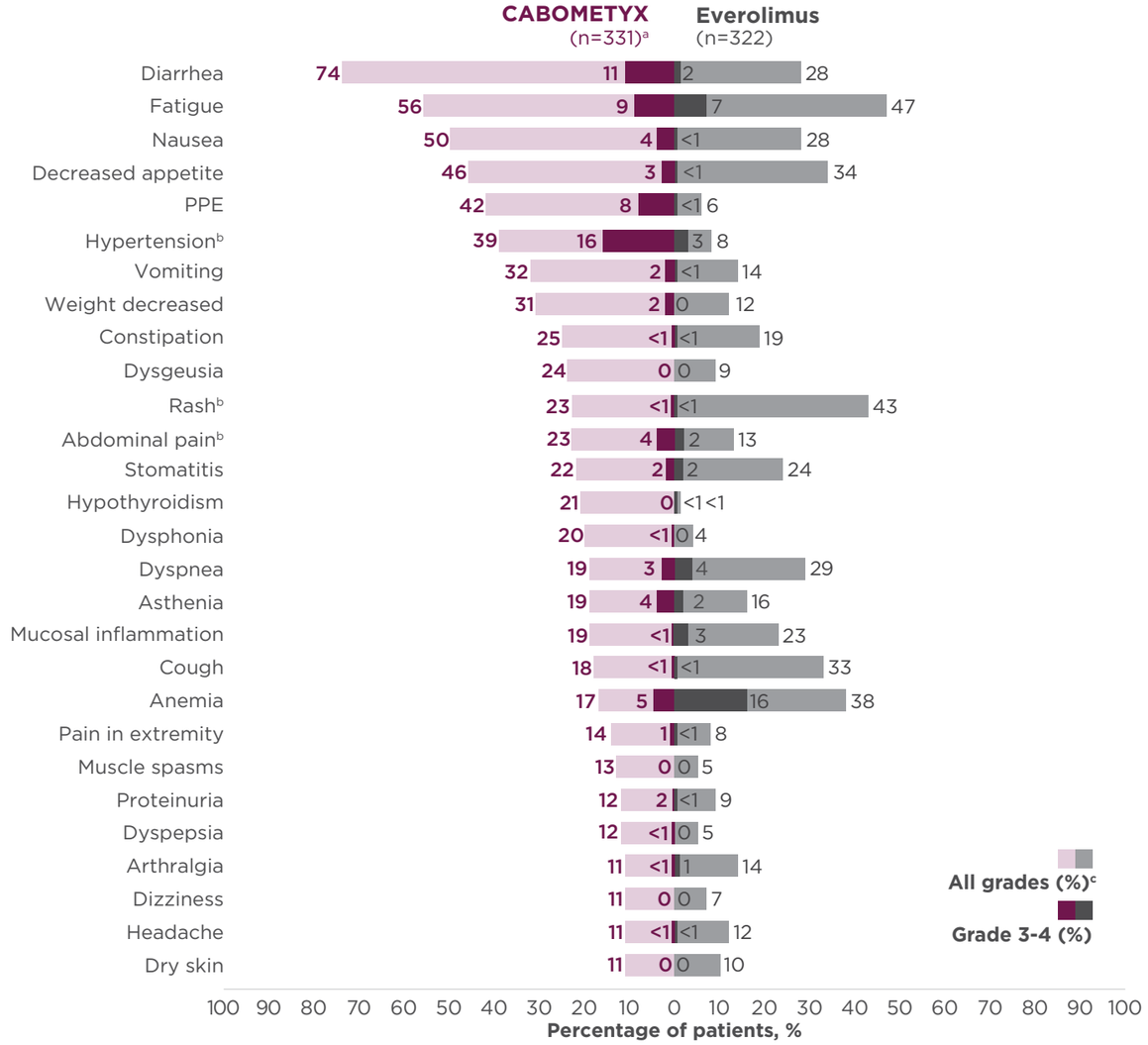
60 mg | 40 mg | 20 mg

CABOMETYX safety in the METEOR trial[1]

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



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

Percentage of patients, %

Laboratory abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All grades[c]	Grade 3-4	All grades[c]	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[b]	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%

[a]One subject randomized to everolimus received CABOMETYX.
[b]These ARs are grouped terms. For details, please see full Prescribing Information.
[c]NCI-CTCAE v4.0.
[d]Based on laboratory abnormalities.

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

Please see additional Important Safety Information and full Prescribing Information.

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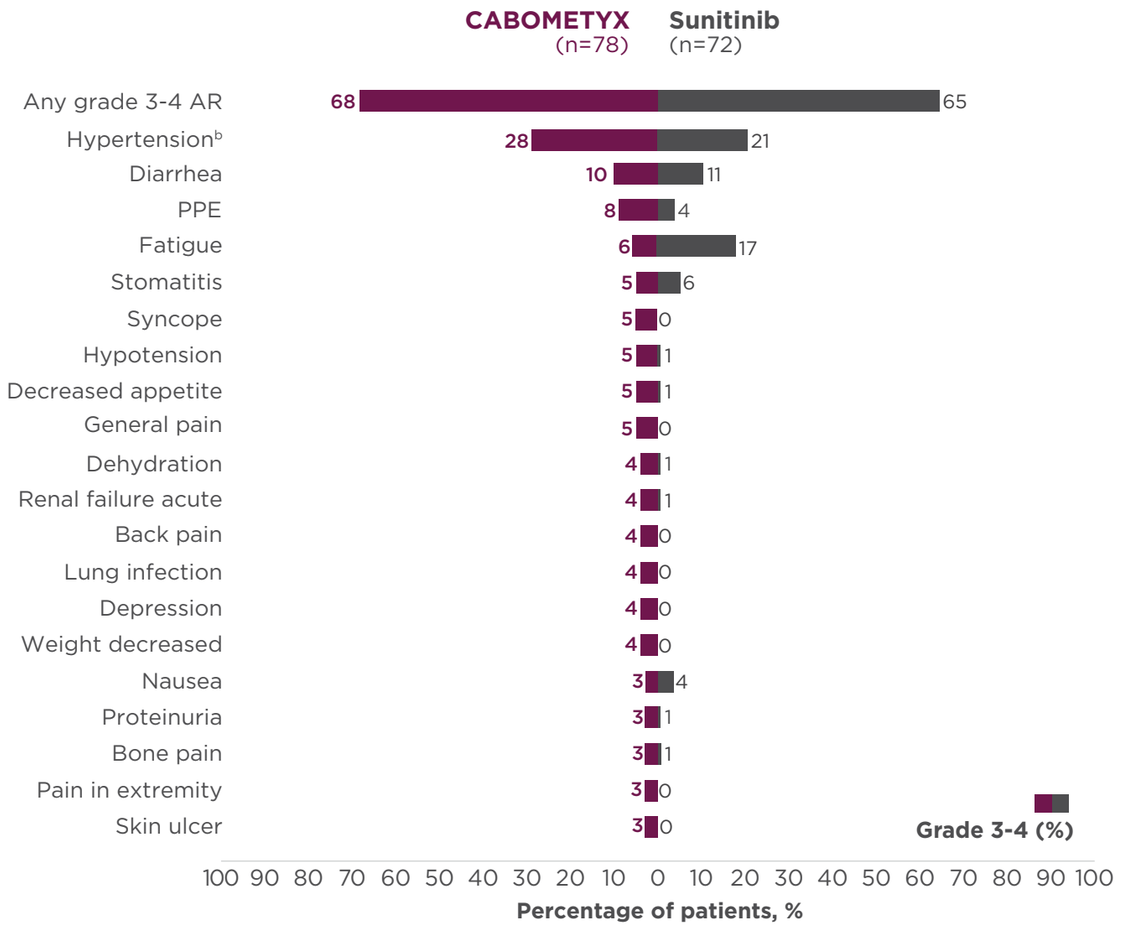
CABOMETYX safety in the CABOSUN trial[1]

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



Laboratory-related Grade 3-4 ARs occurring in ≥1% of patients who received CABOMETYX[1,a,c]

	Percentage of 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

[c]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 holds	73%	71%
Dose reductions	46%	35%
Discontinuations	21%	22%

[a]NCI-CTCAE v4.0.
[b]Includes the following term: hypertension.

Please see additional Important Safety Information and full Prescribing Information.

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Single-agent CABOMETYX resulted in superior PFS vs placebo in patients with previously treated NET that had progressed on at least 1 prior FDA-approved systemic therapy, not including SSAs[1]

PRIMARY ENDPOINT: PFS[1]

Quadrupled median PFS in pNET			Doubled median PFS in epNET		
13.8 months CABOMETYX (95% CI, 8.9-17.0; n=66)	VS **3.3** months Placebo (95% CI, 2.8-5.7; n=33)	**78%** reduction in risk HR, 0.22 (95% CI, 0.12-0.41); *P*<.0001	**8.5** months CABOMETYX (95% CI, 6.8-12.5; n=132)	VS **4.2** months Placebo (95% CI, 2.8-5.7; n=67)	**60%** reduction in risk HR, 0.40 (95% CI, 0.26-0.61); *P*<.0001

SECONDARY ENDPOINT: ORR *(Descriptive analysis)*[1,4]

pNET				epNET		
18% CABOMETYX (n=12/66)	VS	**0%** Placebo (n=33)	ORR[a]	**5%** CABOMETYX (n=7/132)	VS	**0%** Placebo (n=67)
62% CABOMETYX (n=41/66)	VS	**55%** Placebo (n=18/33)	Stable disease[b]	**64%** CABOMETYX (n=85/132)	VS	**52%** Placebo (n=35/67)
80% CABOMETYX (n=53/66)	VS	**55%** Placebo (n=18/33)	Disease control rate[c]	**69%** CABOMETYX (n=92/132)	VS	**52%** Placebo (n=35/67)

[a]All responses confirmed were partial responses.[14] [b]Stable disease is defined as neither sufficient shrinkage to qualify as partial response nor sufficient increase to qualify as PD.[15] Stable disease may reflect the natural history of disease rather than any effect of the drug.[16] [c]Disease control rate is defined as the percentage of patients with a complete response, partial response or stable disease, as measured by RECIST v1.1.[4]

FDA, US Food and Drug Administration; NCI, National Cancer Institute; SSA, somatostatin analogue.

CABINET trial

CABINET was a randomized (2:1), double-blind, placebo-controlled, phase 3, NCI-sponsored trial of CABOMETYX vs placebo in patients with advanced NET and who were previously treated with ≥1 FDA-approved systemic therapy, not including an SSA. CABINET enrolled 2 independent cohorts that evaluated patients with pNET (n=99) or epNET (n=199). The starting dose for CABOMETYX was 60 mg, administered orally once daily. The primary endpoint was PFS; ORR and OS were secondary endpoints.[1,14]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Cardiac Failure: CABOMETYX can cause severe and fatal cardiac failure. Cardiac failure occurred in 0.5% of patients treated with CABOMETYX as a single agent, including fatal cardiac failure in 0.1% of patients. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Withhold and resume at a reduced dose upon recovery or permanently discontinue depending on the severity.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Updated analysis

OS results from CABINET Trial[1]

OS data were not mature at the time of the updated analysis and may be impacted by crossover

pNET Updated OS

48% **Deaths CABOMETYX** (n=66) VS **52%** **Deaths Placebo** (n=33) (HR, 1.01; 95% CI, 0.55-1.83)

52% of placebo arm patients crossed over to open-label CABOMETYX.

epNET Updated OS

63% **Deaths CABOMETYX** (n=132) VS **60%** **Deaths Placebo** (n=67) (HR, 1.05; 95% CI, 0.71-1.54)

37% of placebo arm patients crossed over to open-label CABOMETYX.

The CABINET trial was unblinded early and patients were allowed to cross over to open-label CABOMETYX regardless of whether they had experienced progression. A later updated OS analysis was conducted when 49 deaths were observed in the pNET cohort and 123 deaths were observed in the epNET cohort.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Diarrhea: CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated 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): CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
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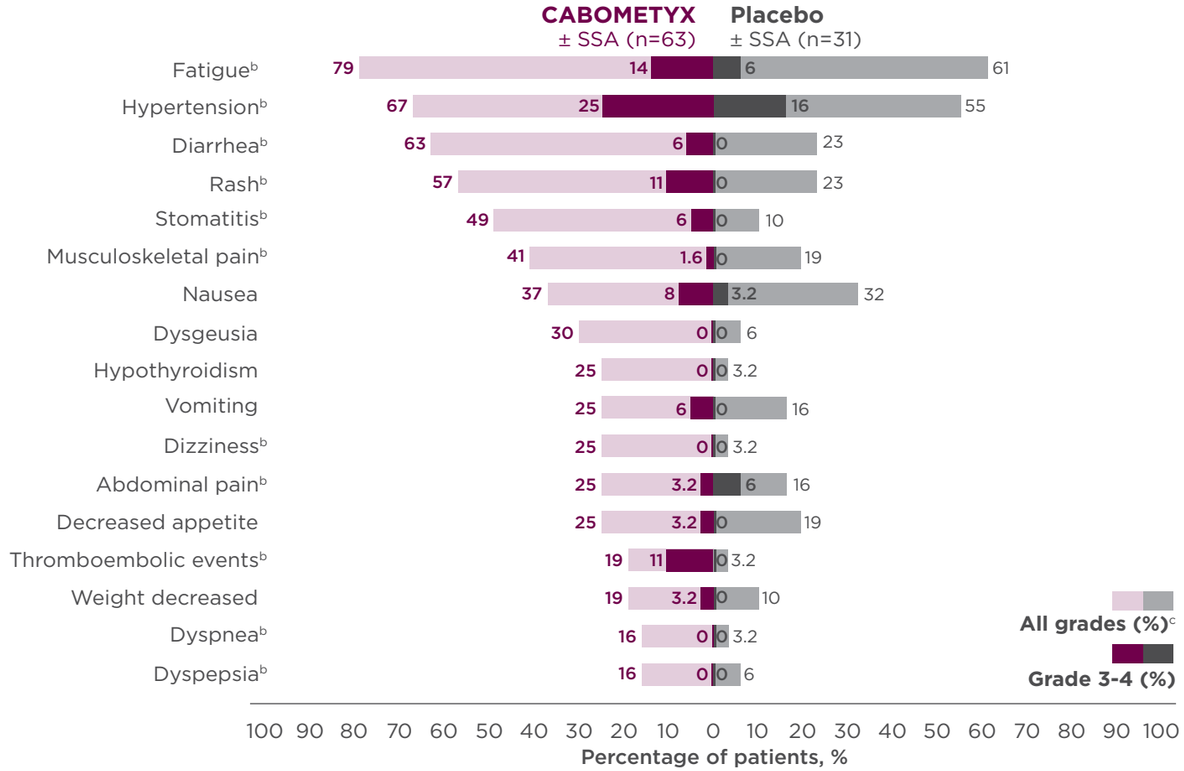
CABOMETYX safety in the CABINET trial[1,4]

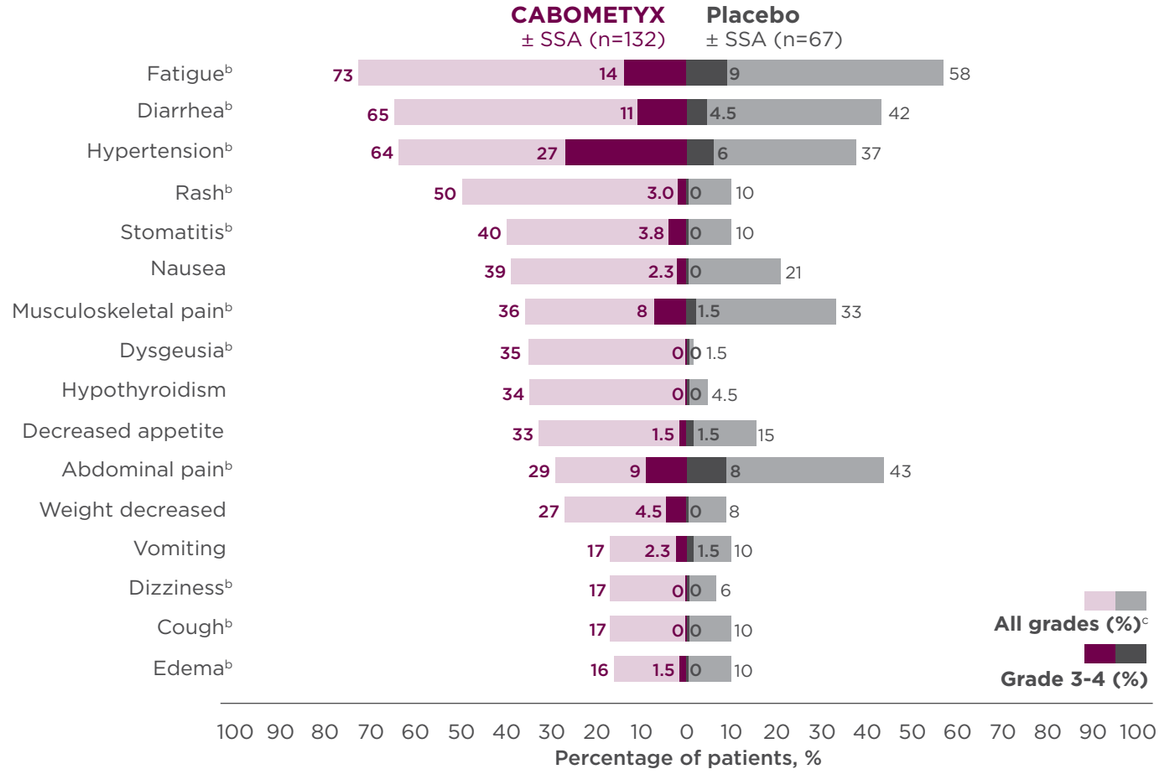
pNET Adverse reactions occurring in ≥15% of CABOMETYX patients[a]



Dose withholds, dose reductions, and discontinuations in the pNET cohort of the CABINET trial[4]

	CABOMETYX (n=66)	Placebo (n=33)
Dose withholds	83%	42%
Dose reductions	49%	16%
Discontinuations	19%	10%

epNET Adverse reactions occurring in ≥15% of CABOMETYX patients[a]



Dose withholds, dose reductions, and discontinuations in the epNET cohort of the CABINET trial[4]

	CABOMETYX (n=132)	Placebo (n=67)
Dose withholds	81%	39%
Dose reductions	38%	6%
Discontinuations	28%	19%

[a]Clinically relevant ARs in <15% of patients who received CABOMETYX included reversible peripheral neuropathy, hemorrhage, cardiac arrhythmia, hypotension, alopecia, and hair color changes.[1]
[b]These ARs are grouped terms. For details, please see full Prescribing Information.[1]
[c]NCI-CTCAE v5.0.[1]
[d]Clinically relevant ARs in <15% of patients who received CABOMETYX included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, hair color changes, and cardiac failure.[1]

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

CABOMETYX safety in the CABINET trial[1,4]

pNET Laboratory abnormalities occurring in ≥10% of CABOMETYX patients

	CABOMETYX ± SSA (n=63)		Placebo ± SSA (n=31)	
	All grades[a] (%)	Grade 3-4 (%)	All grades[a] (%)	Grade 3-4 (%)
Chemistry				
Increased AST	76	1.6	48	0
Increased ALT	75	1.6	39	3.2
Hyperglycemia[b]	37	3.2	48	3.2
Hypophosphatemia[b]	25	0	6	0
Increased ALP	22	3.2	23	0
Hypocalcemia[b]	17	0	3.2	0
Hyponatremia[b]	16	1.6	16	0
Blood bilirubin increased[b]	14	4.8	6	3.2
Hyperkalemia	14	1.6	10	0
Hypoalbuminemia[b]	14	0	10	0
Hypoglycemia[b]	11	0	6	0
Hypomagnesemia[b]	11	0	6	0
Hypokalemia[b]	10	1.6	3.2	0
Hematology				
Platelet count decreased[b]	37	0	19	0
Neutrophil count decreased[b]	27	1.6	6	0
Hemoglobin decreased[b]	25	1.6	32	0
Lymphocyte count decreased[b]	22	8	16	0
White blood cell count decreased	19	1.6	3.2	0

epNET Laboratory abnormalities occurring in ≥10% of CABOMETYX patients

	CABOMETYX ± SSA (n=132)		Placebo ± SSA (n=67)	
	All grades[a] (%)	Grade 3-4 (%)	All grades[a] (%)	Grade 3-4 (%)
Chemistry				
Increased AST	70	3.8	21	1.5
Increased ALT	63	0.8	18	1.5
Hyperglycemia[b]	30	0.8	39	1.5
Increased ALP[b]	29	4.5	30	6
Blood creatinine increased	23	0	12	1.5
Blood bilirubin increased[b]	20	3.0	10	6
Hypoalbuminemia[b]	20	0.8	9	0
Hypocalcemia[b]	20	0	4.5	0
Hypokalemia[b]	20	2.3	10	1.5
Hypomagnesemia[b]	20	0.8	4.5	0
Hypophosphatemia[b]	19	0.8	4.5	0
Hyponatremia[b]	16	2.3	7	1.5
Hematology				
Platelet count decreased[b]	55	1.5	13	1.5
White blood cell count decreased[b]	37	3.0	4.5	0
Neutrophil count decreased[b]	36	3.0	6	0
Hemoglobin decreased[b]	30	2.3	19	0
Lymphocyte count decreased[b]	28	9	18	1.5

CABINET included patients with functional disease[4]

[a]NCI-CTCAE v5.0.[1]
[b]These ARs are grouped terms. For details, please see full Prescribing Information.[1]

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Single-agent CABOMETYX 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)[17]

SUBGROUP ANALYSIS: MEDIAN OS[4,a]

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[4,a]

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)

[a]No statistical procedure was employed for controlling type I error. Results should be considered hypothesis generating.[17]

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)[18,b]

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[b] 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 to 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.[4,19]

[b]Child-Pugh scores were assessed by the investigator at the time of each radiographic disease assessment every 8 weeks.[18]

AFP, alpha-fetoprotein.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

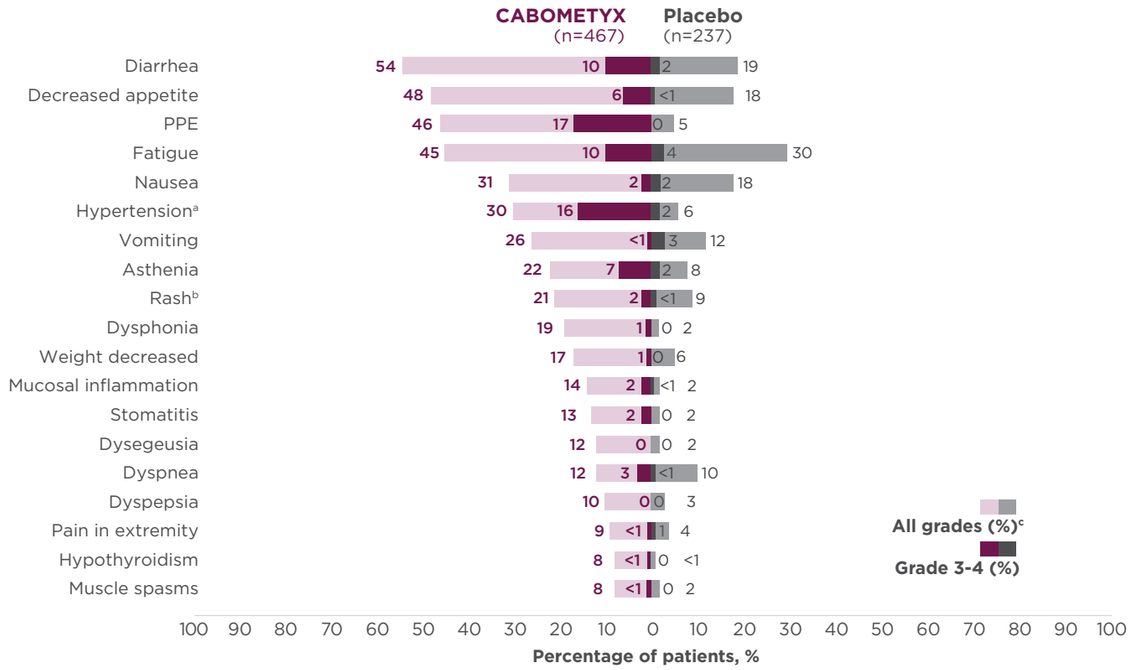
Hepatotoxicity: CABOMETYX in combination with nivolumab in RCC can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. Monitor liver enzymes before initiation of treatment and periodically. Consider more frequent monitoring as compared to when the drugs are administered as single agents. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

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]



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)	
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[1,4,17]

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

In an exploratory, small subgroup of patients in the CELESTIAL trial 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).

[a]Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased.[1]

[b]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.[1]

[c]NCI-CTCAE v4.0.[1]

LDH, lactate dehydrogenase.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Please see additional Important Safety Information and full Prescribing Information.

Single-agent CABOMETYX delivered a significant benefit in 2L DTC in the primary PFS analysis[1,20]

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[a]: 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)

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

ORR

ORR[b]

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.[1,20]

Stable disease[c]

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

Disease control rate[d]

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 patients with locally advanced or metastatic DTC who had progressed after prior VEGFR-targeted therapy and were RAI-R or ineligible. Patients were randomized to receive CABOMETYX 60 mg orally once daily or placebo with best supportive care until disease progression or unacceptable toxicity. Eligible patients in the placebo arm 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.**[1,20,e]

[b]*P*=.0281. All responses confirmed were PRs.[1,20]
[c]Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.[15] SD may reflect the natural history of disease rather than effect of the drug.
[d]Disease control rate is defined as the percentage of patients with a CR, PR, or SD, as measured by RECIST v1.1.[20]
[e]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). The study was designed such that it would be considered positive if either of the primary endpoints were met. 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.[1,20,21]

BIRC, blinded independent radiology committee; IQR, interquartile range; RAI-R, radioactive iodine-refractory.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. 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. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

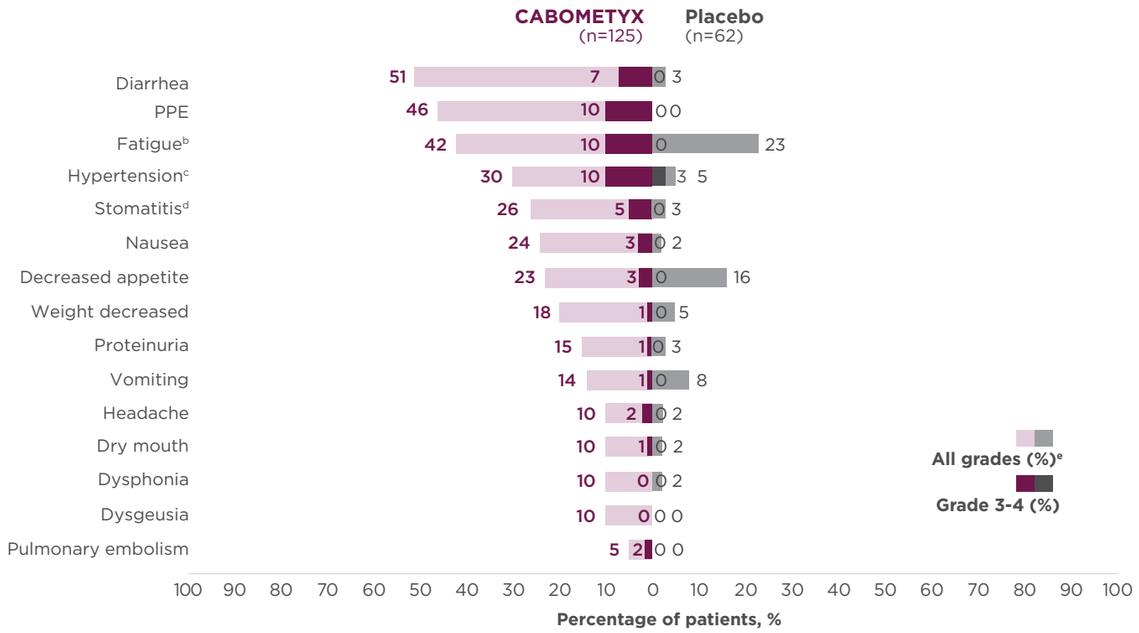
Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

CABOMETYX safety in the COSMIC-311 trial[1]

Treatment-emergent ARs in the primary analysis[a]

Any cause, occurring in ≥5% of patients in either treatment arm



Laboratory abnormalities occurring in ≥10% of patients treated with CABOMETYX in the primary analysis[f]

	Percentage of patients, %			
	CABOMETYX (n=125)		Placebo (n=62)	
Laboratory abnormality	All grades	Grade 3-4	All grades	Grade 3-4
Chemistry				
Increased LDH[g]	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

Dose withholds, dose reductions, and discontinuations in the COSMIC-311 trial[1,22]

	CABOMETYX (n=125)	Placebo (n=62)
Dose withholds	72%	27%
Dose reductions	56%	5%
Discontinuations	5%	0%

[a]Includes terms with a between-arm difference of ≥5% (any grades) or ≥2% (grade 3-4).
[b]Includes the following terms: fatigue, asthenia.
[c]Includes the following terms: hypertension, blood pressure increased, hypertensive crisis.
[d]Includes the following terms: mucosal inflammation, stomatitis.
[e]NCI-CTCAE v5.0.
[f]Includes laboratory abnormalities with a between-arm difference of ≥5% (any grades) or ≥2% (Grade 3-4).
[g]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).

ULN, upper limit of normal.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Recommended Systemic Therapy Options by the National Comprehensive Cancer Network® (NCCN®)

Cabozantinib (CABOMETYX) + nivolumab (OPDIVO)

- NCCN Category 1, preferred option across all risk groups in 1L clear cell aRCC[23,a-d]
- NCCN Category 2A, preferred option in non-clear cell aRCC[23,b-e]

Cabozantinib (CABOMETYX)

- NCCN Category 2A, preferred option in 1L intermediate-/poor-risk clear cell aRCC[23,b,e]
- NCCN Category 2A, other recommended subsequent therapy option regardless of prior IO therapy status for clear cell aRCC[23,e,f]

Cabozantinib (CABOMETYX) is a recommended systemic anti-tumor therapy for certain patients with:[24]

- Pancreatic NET (Grade 1/2)*
- Gastrointestinal tract NET (Grade 1/2)*
- Lung/thymus NET
- Grade 3 NET*

*Well-differentiated.

VIEW THE NCCN RECOMMENDATIONS

Cabozantinib (CABOMETYX)

- NCCN Category 1, subsequent-line systemic treatment option for advanced progressive HCC[25,a]

Cabozantinib (CABOMETYX)

- NCCN Category 1, option for locally recurrent, advanced, and/or metastatic RAI-R papillary thyroid cancer that has progressed following VEGFR-targeted therapy[26,a,g]

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
[a]NCCN Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
[b]Preferred designation based on superior efficacy, safety, and evidence and, when appropriate, affordability.
[c]NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d]Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[e]NCCN Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
[f]Other recommended interventions may be somewhat less efficacious, more toxic, or based on less mature data or significantly less affordable for similar outcomes.
[g]If progression after lenvatinib and/or sorafenib.
IO, immuno-oncology.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX: Once-daily starting dose as combination therapy or monotherapy[1,27]

COMBINATION THERAPY

2 WAYS TO DELIVER CABOMETYX + NIVOLUMAB IN 1L aRCC

CABOMETYX 40 mg, once-daily starting dose—optimized for **combination treatment with OPDIVO in 1L aRCC**

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

An oral and intravenous option grounded in clinical evidence

CABOMETYX 40 mg once daily

+

30 minutes

OPDIVO

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

or

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

OR

CABOMETYX® (cabozantinib) tablets + OPDIVO Qvantig™ nivolumab + hyaluronidase-nhvy SUBCUTANEOUS INJECTION | 120 mg + 2,000 units / mL

An oral and 3- to 5-minute subcutaneous option that may streamline administration for patients[a]

CABOMETYX 40 mg once daily

+

3-5 minutes

OPDIVO QVANTIG

600 mg nivolumab and **10,000 units hyaluronidase[a]** every 2 weeks (3- to 5-minute injections)

or

1200 mg nivolumab and **20,000 units hyaluronidase[a]** every 4 weeks (3- to 5-minute injections)

Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.
Treatment with OPDIVO or OPDIVO QVANTIG should be continued until disease progression or unacceptable toxicity for up to 2 years.
[a]Individual results may vary.

MONOTHERAPY

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

CABOMETYX

60 mg once daily

CABOMETYX 60-mg once-daily starting dose for single-agent treatment in aRCC, HCC[b], NET[c] or DTC[d] (for adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg)

40 mg once daily

CABOMETYX 40-mg once-daily starting dose for single-agent treatment in NET[c] and DTC[d] (for pediatric patients ≥12 years of age with bodyweight <40 kg)

[b]For patients with HCC who have been previously treated with sorafenib.
[c]For patients with previously treated, unresectable, locally advanced or metastatic, well-differentiated pNET or epNET.
[d]For patients with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-R or ineligible.

Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.

- Withhold CABOMETYX for at least 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing[1]
- Do not substitute CABOMETYX tablets with cabozantinib capsules[1]
- Administer on an empty stomach at least 1 hour before or at least 2 hours after eating
- Swallow CABOMETYX tablets whole. Do not crush, chew, or split CABOMETYX tablets[1]
- Do not take a missed dose within 12 hours of the next dose[1]
- Modify the dose for patients with moderate hepatic impairment and patients taking drugs known to moderately or strongly induce CYP3A4 or strongly inhibit CYP3A4[1]
- When administering CABOMETYX in combination with OPDIVO or OPDIVO QVANTIG for the treatment of aRCC, refer to the OPDIVO or OPDIVO QVANTIG 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 ≥12 years of age with bodyweight <40 kg, 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

Tablets shown are not actual size.
CYP3A4, cytochrome P450 3A4.

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab) OR OPDIVO Qvantig™ nivolumab + hyaluronidase-nhvy SUBCUTANEOUS INJECTION | 120 mg + 2,000 units / mL

Please see additional Important Safety Information and full Prescribing Information.

You may need to adjust the CABOMETYX dose based on individual patient safety and tolerability[1]

If ARs occur, consider supportive care and/or adjust the dose

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[a]	First reduction	Second reduction
CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab) OR OPDIVO Qvantig™ nivolumab + hyaluronidase-nhvy SUBCUTANEOUS INJECTION 120 mg + 2,000 units / mL	40 mg once daily	20 mg once daily	20 mg once every other day[b]
CABOMETYX® (cabozantinib) tablets 60 mg | 40 mg | 20 mg	60 mg once daily[c]	40 mg once daily	20 mg once daily[b]
CABOMETYX® (cabozantinib) tablets 60 mg | 40 mg | 20 mg	For pediatric patients with NET and DTC ≥12 years of age and bodyweight <40 kg: 40 mg once daily	20 mg once daily	20 mg once every other day[b]

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 or OPDIVO QVANTIG:

- If ALT or AST >3 × ULN but ≤10 × ULN without concurrent total bilirubin ≥2x ULN, both CABOMETYX and OPDIVO or OPDIVO QVANTIG 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 or OPDIVO QVANTIG, refer to OPDIVO or OPDIVO QVANTIG Prescribing Information
- If ALT or AST >10 × ULN or >3 × ULN with concurrent total bilirubin ≥2 × ULN, both CABOMETYX and OPDIVO or OPDIVO QVANTIG 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.[d,e]

[d]Additional restrictions and eligibility rules apply.
[e]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**

[a]Until disease progression or unacceptable toxicity, administer as recommended.
[b]If previously receiving the lowest dose, resume at same dose. If not tolerated, discontinue CABOMETYX.
[c]For NET and DTC, in adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg.

GI, gastrointestinal; ONJ, osteonecrosis of the jaw.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab) OR OPDIVO Qvantig™ nivolumab + hyaluronidase-nhvy SUBCUTANEOUS INJECTION 120 mg + 2,000 units / mL

Select ARs 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	Fatigue	Hypertension	Increased ALT[a]	Increased AST[a]
64% (7%)	40% (8%)	51% (8%)	36% (13%)	79% (9.8%)	77% (7.9%)

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range for CABOMETYX and OPDIVO group, 170 to 317 patients.

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 + OPDIVO

CABOMETYX Single Agent

CABOMETYX® (cabozantinib) tablets + OPDIVO (nivolumab)

Select ARs with CABOMETYX in phase 3, single-agent trials[1,12,14,17,20]

SELECT COMMON ARs IN THE METEOR, CABINET, CELESTIAL, AND COSMIC-311 TRIALS: ALL-GRADE INCIDENCE (GRADE 3-4 INCIDENCE)

		Diarrhea	PPE/HFS	Fatigue	Hypertension	Increased ALT	Increased AST
METEOR (aRCC) CABOMETYX (n=331)		74% (11%)	42% (8%)	56% (9%)	39% (16%)	68% (3%)	74% (3%)
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)	pNET	63% (6%)	43% (10%)	79% (14%)	67% (25%)	75% (1.6%)	76% (1.6%)
	epNET	65% (11%)	34% (3%)	73% (14%)	64% (27%)	63% (0.8%)	70% (3.8%)
CELESTIAL (HCC) CABOMETYX (n=467)		54% (10%)	46% (17%)	45% (10%)	30% (16%)	73% (12%)	73% (24%)
COSMIC-311 (DTC) CABOMETYX (n=125)		51% (7%)	46% (10%)	42% (10%)	30% (10%)	66% (2%)	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, CABINET, 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.

CABOMETYX + OPDIVO

CABOMETYX Single Agent

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Please see additional Important Safety Information and full Prescribing Information.

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

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

CABOMETYX monotherapy: aRCC, HCC, and in adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg:
Lowest dose is 20 mg daily

NET and DTC in pediatric patients ≥12 years of age with bodyweight <40 kg:
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[28]

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

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: diarrhea for more than 24 hours, inability to keep liquids down for more than 24 hours, blood in stool, fever[29]

Supportive measures for diarrhea[30]

- 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)

[a]Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b]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.

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

	Grade 1-4 incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[4,a]	Dose interruptions or reductions due to diarrhea[4]	Discontinuations due to diarrhea[4]
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO (n=320)	64%	7%	12.4	24.4%	0.6%

Dose interruptions and discontinuations were from any study drug. OPDIVO could not be dose reduced only interrupted.
[a]Time to onset data are for GI drug-related select ARs.

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

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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)[4]	Dose interruptions due to diarrhea[4]	Dose reductions due to diarrhea[4]	Discontinuations due to diarrhea[4]
METEOR (aRCC) CABOMETYX (n=331)	74%	11%	5	22%	16%	0.9%
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)						
pNET	63%	6%	NA	17%	3%	NA
epNET	65%	11%	NA	20%	8%	4.5%
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%

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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

NA, not available.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Palmar-plantar erythrodysesthesia/hand-foot syndrome

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

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

CABOMETYX monotherapy: aRCC, HCC, and in adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg:
Lowest dose is 20 mg daily

NET and DTC in pediatric patients ≥12 years of age with bodyweight <40 kg:
Lowest dose is 20 mg every other day

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

CTCAE v5.0 grading identification: PPE[28]

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[a]
Grade 3	• Severe skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain • Limiting self-care ADL[b]

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

SPF, sun protection factor.

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[30]:

- 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[30]:

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

All patients should be advised on prophylactic skin care, including[30]:

- 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.[30]

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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)[4]	Dose interruptions or reductions due to PPE/HFS[4]	Discontinuations due to PPE/HFS[4]
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO (n=320)	**40%**	**8%**	**7.4**	**19.1%**	**0.6%**

Dose interruptions and discontinuations were from any study drug. OPDIVO could not be dose reduced only interrupted.

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

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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)[4]	Dose interruptions due to PPE/HFS[4]	Dose reductions due to PPE/HFS[4]	Discontinuations due to PPE/HFS[4]
METEOR (aRCC) CABOMETYX (n=331)	42%	8%	3.4	14%	11%	0.3%
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)						
pNET	57%[a]	11%[a]	4.3	21%	19%	NA
epNET	50%[a]	3.0%[a]	6.3	17%	10%	NA
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%

[a]Includes rash, PPE syndrome, dermatitis acneiform, skin exfoliation, erythema multiforme, rash macular, rash maculopapular, rash pustular, dermatitis, dermatitis bullous, dermatitis contact, erythema, and dermatitis psoriasiform.

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

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

Please see additional Important Safety Information and full Prescribing Information.

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 or permanently discontinue depending on severity

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

CABOMETYX monotherapy:

aRCC, HCC, and in adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg:
Lowest dose is 20 mg daily

NET and DTC in pediatric patients ≥12 years of age with bodyweight <40 kg:
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[31]:

- Too tired to get out of bed for 24-hour period
- Trouble waking up
- Trouble catching breath
- Fatigue seems to be worsening

Supportive measures for fatigue[30]

- 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[28]

Grade 1	• Fatigue relieved by rest
Grade 2	• Fatigue not relieved by rest • Limiting instrumental ADL[a]
Grade 3	• Fatigue not relieved by rest • Limiting self-care ADL[b]

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

Fatigue: 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 due to fatigue[4]	Discontinuations due to fatigue[4]
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO (n=320)	51%	8%	NA	NA

Dose interruptions and discontinuations were from any study drug. OPDIVO could not be dose reduced only interrupted.

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

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

		All-grade incidence[1]	Grade 3-4 incidence[1]	Dose interruptions due to fatigue[4]	Dose reductions due to fatigue[4]	Discontinuations due to fatigue[4]
METEOR (aRCC) CABOMETYX (n=331)		56%	9%	12%	10%	1.2%
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)	pNET	79%	14%	16%	14%	6.5%
	epNET	73%	14%	21%	8%	3.8%
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%

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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

Please see additional Important Safety Information and full Prescribing Information.

Hypertension[a]

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

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

CABOMETYX monotherapy: aRCC, NET, HCC, and in adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg: Lowest dose is 20 mg daily

NET and DTC in pediatric patients ≥12 years of age with bodyweight <40 kg: 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

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, or 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

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

NCI-CTCAE v5.0 grading identification: hypertension[28]

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; SBP, systolic blood pressure.

Please see additional Important Safety Information and full Prescribing Information.

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)[4]	Dose interruptions or reductions due to hypertension[4]
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO (n=320)	**36%**	**13%**	**4.1**	**10.6%**

Dose interruptions and discontinuations were from any study drug. OPDIVO could not be dose reduced only interrupted.

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)[4]	Dose interruptions due to hypertension[4]	Dose reductions due to hypertension[4]	Discontinuations due to hypertension[4]
METEOR (aRCC) CABOMETYX (n=331)	39%	16%	3.0	5.1%	7.6%	0%
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)						
pNET	67%	25%	2.1	9.5%	7.9%	NA
epNET	64%	27%	2.1	14%	6.1%	NA
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%

Management

CABOMETYX + OPDIVO

CABOMETYX Single Agent

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

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Please see additional Important Safety Information and full Prescribing Information.

Elevated liver enzymes

Withhold[1]

CABOMETYX + OPDIVO or OPDIVO QVANTIG:
Both CABOMETYX and OPDIVO or OPDIVO QVANTIG for ALT or AST >3 × ULN but ≤10 × ULN with concurrent total bilirubin <2 × ULN

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

Wait[1]

CABOMETYX + OPDIVO or OPDIVO QVANTIG:
Until hepatic AR recovers to Grades 0 or 1

CABOMETYX monotherapy:
Until improvement to baseline or ≤Grade 1

Restart[1]

CABOMETYX at a reduced dose

CABOMETYX + OPDIVO or OPDIVO QVANTIG:
Rechallenge with one or both may be considered. If rechallenging with OPDIVO or OPDIVO QVANTIG with or without CABOMETYX, refer to the OPDIVO or OPDIVO QVANTIG Prescribing Information

CABOMETYX monotherapy:
aRCC, HCC, and in adult and pediatric patients with NET and DTC ≥12 years of age with bodyweight ≥40 kg: Lowest dose is 20 mg daily

NET and DTC in pediatric patients ≥12 years of age with bodyweight <40 kg:
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 + OPDIVO or OPDIVO QVANTIG:
Both CABOMETYX and OPDIVO or OPDIVO QVANTIG for ALT or AST >10 × ULN or >3 × ULN with concurrent total bilirubin ≥2 × ULN

CABOMETYX monotherapy:
Discontinue depending on severity

NCI-CTCAE v5.0 grading identification: increased ALT or AST[28]

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[30]

- 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 or OPDIVO QVANTIG, refer to the OPDIVO or OPDIVO QVANTIG Prescribing Information

Management

CABOMETYX + OPDIVO/ CABOMETYX Single Agent

Elevated liver enzymes: clinical experience in phase 3 trials[a]

		Grade 1-4 incidence[1]	Grade 3-4 incidence[1]	Median time to first occurrence (weeks)[4]	Dose interruptions or reductions due to elevated liver enzymes[4]	Discontinuations due to elevated liver enzymes[4]
CheckMate-9ER (aRCC) CABOMETYX + OPDIVO[b]	Increased ALT	79%	9.8%	10.1[c]	10%	1.9%
	Increased AST	77%	7.9%	10.1[c]	NA	1.6%

			All-grade incidence[1]	Grade 3-4 incidence[1]	Dose interruptions due to elevated liver enzymes[4]	Dose reductions due to elevated liver enzymes[4]	Discontinuations due to elevated liver enzymes[4]
CABINET (NET) CABOMETYX (pNET, n=63; epNET, n=132)	Increased ALT	pNET	75%	1.6%	9.5%	NA	NA
		epNET	63%	0.8%	4.5%	NA	NA
	Increased AST	pNET	76%	1.6%	6.3%	NA	NA
		epNET	70%	3.8%	6.8%	NA	3.0%
CELESTIAL (HCC) CABOMETYX (n=467)	Increased ALT		73%	12%	5.4%	NA	0.4%
	Increased AST		73%	24%	9.4%	5.6%	0.9%

Dose interruptions and discontinuations were from any study drug. OPDIVO could not be dose reduced only interrupted.
[a]METEOR and COSMIC trials are not included here, since median time to first occurrence, dose interruption/reduction, and discontinuation data not available for these trials.
[b]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range for CABOMETYX and OPDIVO group, 170 to 317 patients.
[c]Median time to first occurrence is for ALT and AST combined.

See full safety results from CheckMate-9ER, CABINET, and CELESTIAL trials.

Please see additional Important Safety Information and full Prescribing Information.

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)

15-Day Free Trial Program
Provides a free trial to help new CABOMETYX patients start treatment quickly, regardless of insurance type. For patients with a payer decision delay of 5 days or more, up to three additional 15-day supplies are available[a,b]

Co-Pay Program
Eligible, commercially insured patients may **pay as little as $0 per month**. Annual and transaction limits apply.[c]

Dose Exchange Program
Provides **a free 15-tablet supply in the lower dose** to help patients who require a dose reduction.[b,d]

Patient Assistance Program
Eligible patients who cannot afford their drug costs may receive CABOMETYX **free of charge**.[b]

Complete enrollment by visiting:
www.EASE.US

EASE will confirm your patient's eligibility for requested services.

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

SUPPORT FOR COVERAGE DETERMINATION

At your request, EASE can provide support with:

- **Benefits investigations**
- **Prior authorization assistance**
- **Appeals support and follow-up**

[a]Limited to on-label indications.
[b]Additional restrictions and eligibility rules apply.
[c]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.
[d]Patients are required to return any unused product.
This description of the Exelixis Access Services® program is for informational purposes only. Exelixis® makes no representation or guarantee concerning reimbursement or coverage for any service or item. Information provided through the Exelixis Access Services program does not constitute medical or legal advice and is not intended to be a substitute for a consultation with a licensed healthcare provider, legal counsel, or applicable third-party payer(s). Exelixis reserves the right to modify the program at any time without notice.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

ENCOURAGE PATIENTS AND CAREGIVERS TO SIGN UP TODAY

BE CONNECTED with CABOMETYX® (cabozantinib)

A free support program with tools and resources to help educate patients and caregivers during treatment with CABOMETYX

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

> "The CABOMETYX BE CONNECTED program is especially useful to a number of our patients. The support they provide, the education... [It] really does benefit patients in a multitude of ways."
>
> — From a doctor who encourages his patients to sign up for BE CONNECTED

SIGNING UP IS EASY

ONLINE

Go to:
cabometyx.com/be-connected

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[a]

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

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
60 mg | 40 mg | 20 mg

Indications and Important Safety Information

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

Thromboembolic Events: CABOMETYX can cause arterial or venous thromboembolic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) 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; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

Cardiac Failure: CABOMETYX can cause severe and fatal cardiac failure. Cardiac failure occurred in 0.5% of patients treated with CABOMETYX as a single agent, including fatal cardiac failure in 0.1% of patients. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Withhold and resume at a reduced dose upon recovery or permanently discontinue depending on the severity.

Diarrhea: CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated 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): CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab in RCC can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. Monitor liver enzymes before initiation of treatment and periodically. Consider more frequent monitoring as compared to when the drugs are administered as single agents. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. 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. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

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.

ISI (cont'd) ▶

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Osteonecrosis of the Jaw (ONJ): CABOMETYX can cause ONJ and it occurred in <1% of treated patients. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

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

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

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

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with CABOMETYX 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, and 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 or Moderate CYP3A4 Inducers: If coadministration with strong or moderate 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 open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

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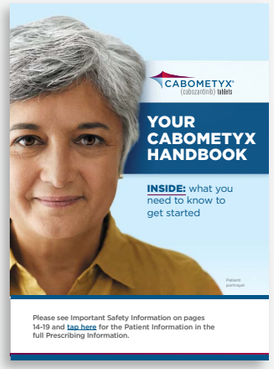
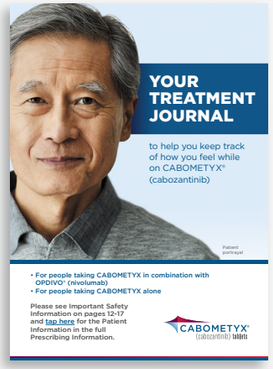
Visit CABOMETYXhcp.com/resources to download helpful resources for your patients, including:



Patient Handbook

Side Effect Tip Cards



Treatment Journal for Patients

INDICATIONS

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 advanced RCC.

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pNET.

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated epNET.

CABOMETYX is indicated for the treatment of patients with 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 DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

SELECT IMPORTANT SAFETY INFORMATION

The full Prescribing Information for CABOMETYX includes Warnings and Precautions for: hemorrhage, perforations and fistulas, thromboembolic events, hypertension and hypertensive crisis, cardiac failure, diarrhea, palmar-plantar erythrodysesthesia, hepatotoxicity, adrenal insufficiency, proteinuria, osteonecrosis of the jaw, impaired wound healing, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, hypocalcemia, and embryo-fetal toxicity.

Please see additional Important Safety Information and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
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