

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CABOMETYX safely and effectively. See full prescribing information for CABOMETYX.

**CABOMETYX® (cabozantinib) tablets, for oral use**  
**Initial U.S. Approval: 2012**

### RECENT MAJOR CHANGES

Dosage and Administration, Recommended Dosage for NET (2.2) 09/2025

### INDICATIONS AND USAGE

CABOMETYX is a kinase inhibitor indicated for the treatment of

- patients with advanced renal cell carcinoma (RCC). (1.1)
- patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab. (1.1)
- patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. (1.2)
- 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. (1.3)
- adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET). (1.4)
- adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET). (1.4)

### DOSAGE AND ADMINISTRATION

- Do NOT substitute CABOMETYX tablets with cabozantinib capsules. (2.1)
- Administer on an empty stomach at least 1 hour before or at least 2 hours after eating. (2.2)
- Stop treatment with CABOMETYX at least 3 weeks prior to scheduled surgery, including dental surgery. (2.1)
- Recommended Dose:
  - RCC (Single Agent): 60 mg orally, once daily. (2.2)
  - RCC (Combination Therapy): 40 mg orally, once daily with:
    - 240 mg nivolumab every 2 weeks by intravenous infusion; -OR-
    - 480 mg nivolumab every 4 weeks by intravenous infusion; -OR-
    - 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks subcutaneously; -OR-
    - 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks subcutaneously. (2.2)
  - HCC: 60 mg orally, once daily. (2.2)
  - DTC, pNET, epNET:
    - Adult patients and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg: 60 mg orally once daily. (2.2)
    - Pediatric patients 12 years of age and older with bodyweight less than 40 kg: 40 mg orally once daily. (2.2)

### DOSAGE FORMS AND STRENGTHS

Tablets: 60 mg, 40 mg, 20 mg. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Hemorrhage: Do not administer CABOMETYX if recent history of hemorrhage. (5.1)
- Perforations and Fistulas: Monitor for symptoms. Discontinue CABOMETYX for Grade 4 fistula or perforation. (5.2)
- Thrombotic Events: Discontinue CABOMETYX for myocardial infarction or serious venous or arterial thromboembolic events. (5.3)
- Hypertension and Hypertensive Crisis: Monitor blood pressure regularly. Interrupt for hypertension that is not adequately controlled with anti-hypertensive therapy. Discontinue CABOMETYX for

hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. (5.4)

- Diarrhea: May be severe. Interrupt CABOMETYX until diarrhea resolves or decreases to  $\leq$ Grade 1, resume at reduced dose. Recommend standard antidiarrheal treatments. (5.5)
- Palmar-Plantar Erythrodysesthesia (PPE): Interrupt CABOMETYX treatment until PPE resolves or decreases to Grade 1. (5.6)
- Hepatotoxicity: When used in combination with nivolumab, higher frequencies of Grade 3 and 4 ALT and AST elevation may occur than with CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity. (5.7)
- Adrenal Insufficiency: When used in combination with nivolumab, primary or secondary adrenal insufficiency may occur. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab depending on severity. (5.8)
- Proteinuria: Monitor urine protein. Interrupt CABOMETYX until proteinuria resolves to  $\leq$ Grade 1, resume CABOMETYX at a reduced dose. Discontinue for nephrotic syndrome. (5.9)
- Osteonecrosis of the jaw (ONJ): Withhold CABOMETYX for at least 3 weeks prior to invasive dental procedures and for development of ONJ. (5.10)
- Impaired Wound Healing: Withhold CABOMETYX for at least 3 weeks before elective surgery. Do not administer for at least 2 weeks following major surgery and adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established. (5.11)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue CABOMETYX. (5.12)
- Thyroid Dysfunction: Monitor thyroid function before and during treatment with CABOMETYX. (5.13)
- Hypocalcemia: Withhold CABOMETYX and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity. (5.14)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.15, 8.1, 8.3)

### ADVERSE REACTIONS

The most common ( $\geq 20\%$ ) adverse reactions are:

- **as a single agent:** diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation. (6.1)
- **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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Exelixis, Inc. at 1-855-500-3935 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Strong CYP3A4 inhibitors: Reduce the CABOMETYX dosage if coadministration cannot be avoided. (2.4, 7.1)
- Strong or moderate CYP3A4 inducers: Increase the CABOMETYX dosage if coadministration cannot be avoided. (2.5, 7.1)

### USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Reduce the CABOMETYX dosage for patients with moderate hepatic impairment. Avoid in patients with severe hepatic impairment. (2.6, 8.6)
- Lactation: Advise not to breastfeed. (8.2)
- Pediatric Use: Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2025

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

- 1.1 Renal Cell Carcinoma
- 1.2 Hepatocellular Carcinoma
- 1.3 Differentiated Thyroid Cancer
- 1.4 Neuroendocrine Tumors

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Important Dosage Information and Recommended Evaluation and Testing Before Initiating CABOMETYX
- 2.2 Recommended Dosage
- 2.3 Dosage Modifications for Adverse Reactions
- 2.4 Dosage Modifications for Coadministration with Strong CYP3A4 Inhibitors
- 2.5 Dosage Modifications for Coadministration with Strong or Moderate CYP3A4 Inducers
- 2.6 Dosage Modifications for Patients with Hepatic Impairment

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Hemorrhage
- 5.2 Perforations and Fistulas
- 5.3 Thromboembolic Events
- 5.4 Hypertension and Hypertensive Crisis
- 5.5 Diarrhea
- 5.6 Palmar-Plantar Erythrodysesthesia
- 5.7 Hepatotoxicity
- 5.8 Adrenal Insufficiency
- 5.9 Proteinuria
- 5.10 Osteonecrosis of the Jaw
- 5.11 Impaired Wound Healing
- 5.12 Reversible Posterior Leukoencephalopathy Syndrome
- 5.13 Thyroid Dysfunction

- 5.14 Hypocalcemia
- 5.15 Embryo-Fetal Toxicity

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Effects of Other Drugs on CABOMETYX

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

- 14.1 Renal Cell Carcinoma
- 14.2 Hepatocellular Carcinoma
- 14.3 Differentiated Thyroid Cancer
- 14.4 Neuroendocrine Tumors

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

**\*Sections or subsections omitted from the full prescribing information are not listed.**

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Renal Cell Carcinoma

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

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

#### 1.2 Hepatocellular Carcinoma

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

#### 1.3 Differentiated Thyroid Cancer

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

#### 1.4 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 extra-pancreatic neuroendocrine tumors (epNET).

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Dosage Information and Recommended Evaluation and Testing Before Initiating CABOMETYX

- Do not substitute CABOMETYX tablets with cabozantinib capsules.
- Stop treatment with CABOMETYX 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 [*see Warnings and Precautions (5.1, 5.10, 5.11)*].

#### 2.2 Recommended Dosage

- Administer CABOMETYX on an empty stomach. Administer at least 1 hour before or at least 2 hours after eating [*see Clinical Pharmacology (12.3)*].

- Swallow CABOMETYX tablets whole. Do not crush, chew, or split CABOMETYX tablets.
- Do not take a missed dose within 12 hours of the next dose.
- Modify the CABOMETYX dose for patients taking drugs known to moderately or strongly induce CYP3A4 or strongly inhibit CYP3A4 and for patients with moderate hepatic impairment [see *Dosage and Administration (2.4, 2.5, 2.6)*].

The recommended dosages of CABOMETYX are presented in Table 1.

<b>Table 1. Recommended Dosage for CABOMETYX</b>		
<b>Indication</b>	<b>Recommended Dosage</b>	<b>Duration</b>
<b>Renal Cell Carcinoma</b>	<u>Single Agent</u> 60 mg orally once daily	Until disease progression or unacceptable toxicity
	<u>Combination Therapy</u> 40 mg orally once daily in combination with: <ul style="list-style-type: none"> <li>• 240 mg nivolumab every 2 weeks (30- minute intravenous infusion);</li> </ul> - OR - <ul style="list-style-type: none"> <li>• 480 mg nivolumab every 4 weeks (30- minute intravenous infusion);</li> </ul> - OR- <ul style="list-style-type: none"> <li>• 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously over approximately 3-5 minutes every 2 weeks;</li> </ul> - OR- <ul style="list-style-type: none"> <li>• 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously over approximately 3-5 minutes every 4 weeks</li> </ul>	<u>CABOMETYX</u> Until disease progression or unacceptable toxicity
		<u>Nivolumab -OR- nivolumab and hyaluronidase</u> Until disease progression or unacceptable toxicity for up to 2 years
<b>Hepatocellular Carcinoma</b>	60 mg orally once daily	Until disease progression or unacceptable toxicity

<b>Differentiated Thyroid Cancer and Neuroendocrine Tumors</b>	<u>Adult Patients and Pediatric Patients 12 years of age and older with bodyweight greater than or equal to 40 kg:</u> 60 mg orally once daily  <u>Pediatric patients 12 years of age and older with bodyweight less than 40 kg:</u> 40 mg orally once daily	Until disease progression or unacceptable toxicity
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### 2.3 Dosage Modifications for Adverse Reactions

Withhold CABOMETYX for:

- Intolerable Grade 2 adverse reactions
- Grade 3 or 4 adverse reactions
- Osteonecrosis of the jaw

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

<b>Table 2. Recommended Dosage Reductions for CABOMETYX for Adverse Reactions</b>		
<b>Recommended Dosage</b>	<b>First Dosage Reduction To</b>	<b>Second Dosage Reduction To</b>
CABOMETYX 60 mg daily in adult and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg	40 mg daily	20 mg daily*
CABOMETYX 40 mg daily in pediatric patients 12 years of age and older with bodyweight less than 40 kg	20 mg daily	20 mg every other day*
CABOMETYX 40 mg daily in combination with nivolumab	20 mg daily	20 mg every other day*

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

<b>Table 3: Recommended Dosage Modifications for CABOMETYX Adverse Reactions</b>		
<b>Adverse Reaction</b>	<b>Severity*</b>	<b>CABOMETYX Dosage Modification</b>
Hemorrhage <i>[see Warnings and Precautions (5.1)]</i>	Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue CABOMETYX</li> </ul>
Perforations and Fistulas <i>[see Warnings and Precautions (5.2)]</i>	Any grade gastrointestinal perforation or  Grade 4 fistula	<ul style="list-style-type: none"> <li>• Permanently discontinue CABOMETYX</li> </ul>
Thrombotic Events <i>[see Warnings and Precautions (5.3)]</i>	Any grade acute myocardial infarction or  Grade 2 or higher cerebral infarction or  Grade 3 or 4 arterial thromboembolic events or  Grade 4 venous thromboembolic events	<ul style="list-style-type: none"> <li>• Permanently discontinue CABOMETYX</li> </ul>
Hypertension and Hypertensive Crisis <i>[see Warnings and Precautions (5.4)]</i>	Grade 3	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX until hypertension is adequately controlled to <math>\leq</math>Grade 2</li> <li>• Resume at reduced dose</li> <li>• Permanently discontinue CABOMETYX for hypertension that cannot be controlled</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue CABOMETYX</li> </ul>
Diarrhea <i>[see Warnings and Precautions (5.5)]</i>	Grade 2, Grade 3, or Grade 4	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX until <math>\leq</math>Grade 1</li> <li>• Resume at reduced dose</li> </ul>
Palmar-Plantar Erythrodysesthesia <i>[see Warnings and Precautions (5.6)]</i>	Intolerable Grade 2 or Grade 3	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX until <math>\leq</math>Grade 1</li> <li>• Resume at reduced dose</li> </ul>

<b>Table 3: Recommended Dosage Modifications for CABOMETYX Adverse Reactions</b>		
<b>Adverse Reaction</b>	<b>Severity*</b>	<b>CABOMETYX Dosage Modification</b>
Proteinuria <i>[see Warnings and Precautions (5.9)]</i>	Grade 2 or 3	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX until improvement to <math>\leq</math>Grade 1 proteinuria</li> <li>• Resume at a reduced dose</li> <li>• Permanently discontinue CABOMETYX for nephrotic syndrome</li> </ul>
Osteonecrosis of the jaw (ONJ) <i>[see Warnings and Precautions (5.10)]</i>	Any grade	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX for development of ONJ until complete resolution</li> <li>• Resume at reduced dose</li> </ul>
Reversible Posterior Leukoencephalopathy Syndrome <i>[see Warnings and Precautions (5.12)]</i>	Any grade	<ul style="list-style-type: none"> <li>• Permanently discontinue CABOMETYX</li> </ul>
Other Adverse Reactions <i>[see Adverse Reactions (6.1)]</i>	Intolerable Grade 2, or Grade 3, or Grade 4	<ul style="list-style-type: none"> <li>• Withhold CABOMETYX until improvement to baseline or <math>\leq</math>Grade 1</li> <li>• Resume at reduced dose</li> </ul>

\* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0)

The following table represents dosage modifications for the drug administered in combination that are different from those described above for CABOMETYX or in the Full Prescribing Information:

<b>Table 4. Recommended Specific Dosage Modifications for Hepatic Adverse Reactions for Combination</b>		
<b>CABOMETYX in combination with nivolumab</b>	ALT or AST $>3$ times ULN but $\leq 10$ times ULN with concurrent total bilirubin $<2$ times ULN	Withhold <sup>a</sup> both CABOMETYX and nivolumab until adverse reactions recover <sup>b</sup> to Grades 0 or 1
	ALT or AST $>10$ times ULN or $>3$ times ULN with concurrent total bilirubin $\geq 2$ times ULN	Permanently discontinue both CABOMETYX and nivolumab

<sup>a</sup> Consider corticosteroid therapy for hepatic adverse reactions if CABOMETYX is withheld or discontinued when administered in combination with nivolumab

<sup>b</sup> After recovery, rechallenge with one or both of CABOMETYX and nivolumab may be considered. If rechallenging with nivolumab with or without CABOMETYX, refer to nivolumab Prescribing Information.

When administering CABOMETYX in combination with nivolumab for the treatment of advanced RCC, refer to the nivolumab prescribing information.

## **2.4 Dosage Modifications for Coadministration with Strong CYP3A4 Inhibitors**

Reduce the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 40 mg daily or from 40 mg to 20 mg daily or from 20 mg daily to 20 mg every other day in pediatric patients 12 years of age and older with bodyweight less than 40 kg). Resume the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

## **2.5 Dosage Modifications for Coadministration with Strong or Moderate CYP3A4 Inducers**

Increase the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated. Resume the dose that was used prior to initiating the strong or moderate CYP3A4 inducer 2 to 3 days after discontinuation of the inducer. Do not exceed a daily dose of 80 mg [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

## **2.6 Dosage Modifications for Patients with Hepatic Impairment**

Reduce the starting dose of CABOMETYX 60 mg daily to 40 mg daily or 40 mg daily to 20 mg daily (for pediatric patients 12 years of age and older with bodyweight less than 40 kg) in patients with moderate hepatic impairment (Child-Pugh B) [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

## **3 DOSAGE FORMS AND STRENGTHS**

Tablets:

- 60 mg: yellow film-coated, oval shaped with no score, and debossed with “XL” on one side and “60” on the other side.
- 40 mg: yellow film-coated, triangle shaped with no score and debossed with “XL” on one side and “40” on the other side.
- 20 mg: yellow film-coated, round with no score, and debossed with “XL” on one side and “20” on the other side.

## **4 CONTRAINDICATIONS**

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hemorrhage

CABOMETYX can cause severe and fatal hemorrhages. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX-treated patients in RCC, HCC, and DTC studies [see *Adverse Reactions (6.1)*].

Withhold CABOMETYX for 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Permanently discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.10, 5.11)*].

### 5.2 Perforations and Fistulas

CABOMETYX can cause gastrointestinal (GI) perforations and fistulas.

Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients [see *Adverse Reactions (6.1)*]. GI perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation [see *Dosage and Administration (2.3)*].

### 5.3 Thromboembolic Events

CABOMETYX can cause arterial or venous thromboembolic events.

Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients [see *Adverse Reactions (6.1)*].

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention [see *Dosage and Administration (2.3)*].

### 5.4 Hypertension and Hypertensive Crisis

CABOMETYX can cause hypertension, including hypertensive crisis [see *Adverse Reactions (6.1)*]. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients. In CABINET (n=195) [see *Clinical Studies (14.4)*], hypertension was reported in 65% (26% Grade 3) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose [see *Dosage and Administration (2.3)*]. Permanently

discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis [see *Dosage and Administration (2.3)*].

## 5.5 Diarrhea

CABOMETYX can cause diarrhea. Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX [see *Adverse Reactions (6.1)*].

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to  $\leq$ Grade 1, resume CABOMETYX at a reduced dose [see *Dosage and Administration (2.3)*].

## 5.6 Palmar-Plantar Erythrodysesthesia

CABOMETYX can cause palmar-plantar erythrodysesthesia (PPE). PPE occurred in 45% of patients treated with CABOMETYX [see *Adverse Reactions (6.1)*]. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE [see *Dosage and Administration (2.3)*].

## 5.7 Hepatotoxicity

CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids [see *Dosage and Administration (2.3)*].

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients [see *Adverse Reactions (6.1)*]. ALT or AST  $>3$  times ULN (Grade  $\geq 2$ ) 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  $\geq 2$  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  $\geq 2$  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 then resume CABOMETYX at a reduced dose based on severity [see *Dosage and Administration (2.3)*].

## 5.8 Adrenal Insufficiency

CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency.

Adrenal insufficiency occurred in 4.7% (15/320) of patients treated with the combination of CABOMETYX and nivolumab including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions

[see *Adverse Reactions (6.1)*]. 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.

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 [see *Dosage and Administration (2.3)*].

## 5.9 Proteinuria

CABOMETYX can cause proteinuria.

Proteinuria was observed in 8% of patients receiving CABOMETYX [see *Adverse Reactions (6.1)*].

Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to  $\leq$ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome [see *Dosage and Administration (2.3)*].

## 5.10 Osteonecrosis of the Jaw

CABOMETYX can cause osteonecrosis of the jaw (ONJ).

ONJ occurred in <1% of patients treated with CABOMETYX [see *Adverse Reactions (6.1)*].

ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose [see *Dosage and Administration (2.3)*].

## 5.11 Impaired Wound Healing

CABOMETYX can cause impaired wound healing [see *Adverse Reactions (6.1)*]. Withhold CABOMETYX for at least 3 weeks prior to elective surgery [see *Dosage and Administration (2.1)*]. 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 [see *Dosage and Administration (2.1, 2.3)*].

## 5.12 Reversible Posterior Leukoencephalopathy Syndrome

CABOMETYX can cause reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS [see *Dosage and Administration (2.3)*].

## 5.13 Thyroid Dysfunction

CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism. Thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients [see *Adverse Reactions (6.1)*].

Assess patients for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated [see *Dosage and Administration (2.3)*].

## 5.14 Hypocalcemia

CABOMETYX can cause hypocalcemia. Hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients [see *Adverse Reactions (6.1)*]. Laboratory abnormality data were not collected in CABOSUN and CABINET.

In COSMIC-311 (n=125) [see *Clinical Studies (14.3)*], 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 [see *Dosage and Administration (2.3)*].

## 5.15 Embryo-Fetal Toxicity

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

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose [see *Use in Specific Populations (8.1, 8.3)*, *Clinical Pharmacology (12.1)*].

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Hemorrhage [see *Warnings and Precautions (5.1)*]
- Perforations and Fistulas [see *Warnings and Precautions (5.2)*]

- Thrombotic Events [see *Warnings and Precautions (5.3)*]
- Hypertension and Hypertensive Crisis [see *Warnings and Precautions (5.4)*]
- Diarrhea [see *Warnings and Precautions (5.5)*]
- Palmar-plantar Erythrodysesthesia [see *Warnings and Precautions (5.6)*]
- Hepatotoxicity [see *Warnings and Precautions (5.7)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.8)*]
- Proteinuria [see *Warnings and Precautions (5.9)*]
- Osteonecrosis of the Jaw [see *Warnings and Precautions (5.10)*]
- Impaired Wound Healing [see *Warnings and Precautions (5.11)*]
- Reversible Posterior Leukoencephalopathy Syndrome [see *Warnings and Precautions (5.12)*]
- Thyroid Dysfunction [see *Warnings and Precautions (5.13)*]
- Hypocalcemia [see *Warnings and Precautions (5.14)*]

## 6.1 Clinical Trial Experience

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

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent at 60 mg orally once daily until disease progression or unacceptable toxicity in 409 patients with RCC enrolled in a randomized, active-controlled trial (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), 195 patients with pNET or epNET enrolled in a randomized, placebo-controlled trial (CABINET), and at 40 mg CABOMETYX in combination with nivolumab 240 mg/m<sup>2</sup> every 2 weeks, in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

### Renal Cell Carcinoma

#### *METEOR*

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator [see *Clinical Studies (14.1)*]. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in  $\geq 25\%$  of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar

erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in  $\geq 5\%$  of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

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

**Table 5. Adverse Reactions Occurring in  $\geq 10\%$  Patients Who Received CABOMETYX in METEOR**

Adverse Reaction	CABOMETYX (n=331) <sup>1</sup>		Everolimus (n=322)	
	All Grades <sup>2</sup>	Grade 3-4	All Grades <sup>2</sup>	Grade 3-4
	<b>Percentage (%) of Patients</b>			
<b>Gastrointestinal</b>				
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 <sup>3</sup>	23	4	13	2
Dyspepsia	12	<1	5	0
<b>General</b>				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
<b>Metabolism and Nutrition</b>				
Decreased appetite	46	3	34	<1
<b>Skin and Subcutaneous Tissue</b>				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash <sup>4</sup>	23	<1	43	<1
Dry skin	11	0	10	0
<b>Vascular</b>				
Hypertension <sup>5</sup>	39	16	8	3
<b>Investigations</b>				
Weight decreased	31	2	12	0
<b>Nervous System</b>				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1

Adverse Reaction	CABOMETYX (n=331) <sup>1</sup>		Everolimus (n=322)	
	All Grades <sup>2</sup>	Grade 3-4	All Grades <sup>2</sup>	Grade 3-4
	<b>Percentage (%) of Patients</b>			
Dizziness	11	0	7	0
<b>Endocrine</b>				
Hypothyroidism	21	0	<1	<1
<b>Respiratory, Thoracic, and Mediastinal</b>				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
<b>Blood and Lymphatic</b>				
Anemia	17	5	38	16
<b>Musculoskeletal and Connective Tissue</b>				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
<b>Renal and Urinary</b>				
Proteinuria	12	2	9	<1
<sup>1</sup> One subject randomized to everolimus received cabozantinib. <sup>2</sup> National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 <sup>3</sup> Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower <sup>4</sup> Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform <sup>5</sup> Includes the following terms: hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation				

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

**Table 6. Laboratory Abnormalities Occurring in ≥25% Patients Who Received CABOMETYX in METEOR**

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	<b>Percentage (%) of Patients</b>			
<b>Chemistry</b>				
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
<b>Hematology</b>				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia <sup>1</sup>	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase. NCI CTCAE, Version 4.0 <sup>1</sup> Based on laboratory abnormalities				

### CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity [see *Clinical Studies (14.1)*]. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

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

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

**Table 7. Grade 3-4 Adverse Reactions Occurring in ≥1% Patients Who Received CABOMETYX in CABOSUN**

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4 <sup>1</sup>	Grade 3-4 <sup>1</sup>
	Percentage (%) of Patients	
<b>Patients with any Grade 3-4 Adverse Reaction</b>	68	65
<b>Gastrointestinal</b>		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
<b>General</b>		
Fatigue	6	17
Pain	5	0
<b>Metabolism and Nutrition</b>		
Hyponatremia <sup>2</sup>	9	8
Hypophosphatemia <sup>2</sup>	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia <sup>2</sup>	3	0
Hypomagnesemia <sup>2</sup>	3	0
Hyperkalemia <sup>2</sup>	1	3
<b>Skin and Subcutaneous Tissue</b>		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
<b>Vascular</b>		
Hypertension <sup>3</sup>	28	21
Hypotension	5	1
Angiopathy	1	1
<b>Investigations</b>		
Increased ALT <sup>2</sup>	5	0
Weight decreased	4	0
Increased AST <sup>2</sup>	3	3
Increased blood creatinine <sup>2</sup>	3	3
Lymphopenia <sup>2</sup>	1	6
Thrombocytopenia <sup>2</sup>	1	11
<b>Nervous System</b>		
Syncope	5	0
<b>Respiratory, Thoracic, and Mediastinal</b>		
Dyspnea	1	6
Dysphonia	1	0

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4 <sup>1</sup>	Grade 3-4 <sup>1</sup>
	Percentage (%) of Patients	
<b>Blood and Lymphatic</b>		
Anemia	1	3
<b>Psychiatric</b>		
Depression	4	0
Confusional state	1	1
<b>Infections</b>		
Lung infection	4	0
<b>Musculoskeletal and Connective Tissue</b>		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
<b>Renal and Urinary</b>		
Renal failure acute	4	1
Proteinuria	3	1
ALT, alanine aminotransferase; AST, aspartate aminotransferase		
<sup>1</sup> NCI CTCAE Version 4.0		
<sup>2</sup> Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values		
<sup>3</sup> Includes the following term: hypertension		

### CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC [see [Clinical Studies \(14.1\)](#)]. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) [see [Clinical Studies \(14.1\)](#)].

CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab. The most frequent ( $\geq 2\%$ ) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

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

CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

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

**Table 8. Adverse Reactions in  $>15\%$  of Patients Receiving CABOMETYX and Nivolumab - CHECKMATE-9ER**

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

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Percentage (%) of Patients				
Toxicity was graded per NCI CTCAE v4.				
<sup>a</sup> Includes abdominal discomfort, abdominal pain lower, abdominal pain upper. <sup>b</sup> Includes gastroesophageal reflux disease. <sup>c</sup> Includes asthenia. <sup>d</sup> Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure. <sup>e</sup> Includes mucosal inflammation, aphthous ulcer, mouth ulceration. <sup>f</sup> Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic. <sup>g</sup> Includes blood pressure increased, blood pressure systolic increased. <sup>h</sup> Includes primary hypothyroidism. <sup>i</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain. <sup>j</sup> Includes productive cough. <sup>k</sup> Includes nasopharyngitis, pharyngitis, rhinitis.				

**Table 9. Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >20% of Patients Receiving CABOMETYX and Nivolumab - CHECKMATE-9ER**

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Percentage (%) of Patients				
<b>Chemistry</b>				
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
<b>Hematology</b>				
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

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Neutropenia	35	3.2	67	12

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

### Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity [see *Clinical Studies (14.2)*]. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

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

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

**Table 10. Adverse Reactions Occurring in  $\geq 5\%$  of CABOMETYX-Treated Patients in CELESTIAL<sup>1</sup>**

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades <sup>2</sup>	Grade 3-4	All Grades <sup>2</sup>	Grade 3-4
	Percentage (%) of Patients			
<b>Gastrointestinal</b>				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0

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

<sup>1</sup> Includes terms with a between-arm difference of  $\geq 5\%$  (all grades) or  $\geq 2\%$  (Grade 3-4)

<sup>2</sup> NCI CTCAE Version 4.0

<sup>3</sup> Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

<sup>4</sup> Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

**Table 11. Laboratory Abnormalities Occurring in  $\geq 5\%$  of CABOMETYX-Treated Patients in CELESTIAL<sup>1</sup>**

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	<b>Percentage of Patients</b>			
<b>Chemistry</b>				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
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
<b>Hematology</b>				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

<sup>1</sup> Includes laboratory abnormalities with a between-arm difference of  $\geq 5\%$  (all grades) or  $\geq 2\%$  (Grade 3-4)

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

### Differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 187 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity [see [Clinical Studies \(14.3\)](#)]. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

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

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

**Table 12. Adverse Reactions Occurring in  $\geq 5\%$  of CABOMETYX-Treated Patients in COSMIC-311<sup>1</sup>**

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

<sup>1</sup> Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of  $\geq 5\%$  (all grades) or  $\geq 2\%$  (Grade 3-4)  
<sup>2</sup> NCI CTCAE Version 5.0  
<sup>3</sup> Includes the following terms: mucosal inflammation, stomatitis  
<sup>4</sup> Includes the following terms: fatigue, asthenia  
<sup>5</sup> Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

**Table 13. Laboratory Abnormalities Occurring in  $\geq 10\%$  of CABOMETYX-Treated Patients in COSMIC-311<sup>1</sup>**

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	<b>Percentage of Patients</b>			
<b>Chemistry</b>				
LDH increased <sup>2</sup>	90	10	32	3

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
<b>Hematology</b>				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0
<sup>1</sup> Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of $\geq 5\%$ (all grades) or $\geq 2\%$ (Grade 3-4) <sup>2</sup> Sponsor-defined grades for LDH were as follows: Grade 1 ( $> \text{ULN}$ to $\leq 2 \times \text{ULN}$ ), Grade 2 ( $> 2 \times \text{ULN}$ to $\leq 3 \times \text{ULN}$ ), Grade 3 ( $> 3 \times \text{ULN}$ ).  ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase				

## Neuroendocrine Tumors

### *Pancreatic Neuroendocrine Tumors (pNET)*

The safety of CABOMETYX was evaluated in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors in the CABINET trial [see [Clinical Studies \(14.4\)](#)]. Patients received CABOMETYX 60 mg (n=63) or placebo orally (n=31) once daily until disease progression or unacceptable toxicity. Patients with pNET were required to have disease progression after prior treatment with at least one FDA approved therapy (everolimus, sunitinib or lutetium Lu 177 dotatate), other than somatostatin analogs. The median duration of treatment was 8.3 months (range: 0.1 to 37.8) for patients receiving CABOMETYX and 2.9 months (range: 0.1 to 11.2) for patients receiving placebo.

The median age of patients who received CABOMETYX was 60 years (range: 29 to 79), 57% were male, 86% were White, 6% were Asian, 3.2% were Black, 1.6% were American Indian or Alaska Native, 1.6% were Native Hawaiian or Other Pacific Islanders, and 3.2% were Hispanic or Latino.

Serious adverse reactions occurred in 46% of patients who received CABOMETYX. Serious adverse reactions in  $\geq 2\%$  of patients included thromboembolic events (10%), vomiting (6%), sepsis (4.8%), nausea (4.8%), hypoxia (4.8%), hemorrhage (3.2%), abdominal pain (3.2%),

musculoskeletal pain (3.2%), blood bilirubin increased (3.2%), fatigue (3.2%), hyperkalemia (3.2%), and hypertension (3.2%).

Permanent discontinuation of CABOMETYX due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of CABOMETYX included thromboembolic events, acute kidney injury, rash, dyspnea, fistulas, hemorrhage, cardiac arrest, musculoskeletal pain, COVID-19 infection, Cushing’s syndrome, pneumonia, proteinuria, and myocardial infarction.

The median average daily dose was 41.4 mg for CABOMETYX. Dosage interruptions of CABOMETYX due to an adverse reaction occurred in 83% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included rash, diarrhea, fatigue, thromboembolic events, nausea, hypertension, increased ALT, blood bilirubin increased, musculoskeletal pain, stomatitis, vomiting, and increased AST.

Dose reductions of CABOMETYX due to an adverse reaction occurred in 49% of patients. Adverse reactions which required dose reductions in  $\geq 5\%$  of patients included rash, fatigue, hypertension, and stomatitis.

The most common adverse reactions occurring in  $\geq 20\%$  of CABOMETYX-treated patients were fatigue, increased AST, increased ALT, hypertension, diarrhea, rash, stomatitis, musculoskeletal pain, hyperglycemia, nausea, platelet count decreased, dysgeusia, neutrophil count decreased, abdominal pain, decreased appetite, hemoglobin decreased, dizziness, hypophosphatemia, hypothyroidism, vomiting, increased ALP, and lymphocyte count decreased.

Table 14 summarizes the adverse reactions in patients with pNET in CABINET.

**Table 14. Adverse Reactions ( $\geq 15\%$ ) in Patients with pNET Who Received CABOMETYX in CABINET**

Adverse Reaction	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades <sup>1</sup>	Grade 3 or 4	All Grades <sup>1</sup>	Grade 3 or 4
	<b>Percentage (%) of Patients</b>			
<b>General</b>				
Fatigue <sup>2</sup>	79	14	61	6
<b>Vascular</b>				
Hypertension <sup>3</sup>	67	25	55	16
Thromboembolic events <sup>4</sup>	19	11	3.2	0
<b>Gastrointestinal</b>				
Diarrhea <sup>5</sup>	63	6	23	0
Stomatitis <sup>6</sup>	49	6	10	0
Nausea	37	8	32	3.2
Abdominal pain <sup>7</sup>	25	3.2	16	6
Vomiting	25	6	16	0
Dyspepsia <sup>8</sup>	16	0	6	0
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>9</sup>	57	11	23	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				

Adverse Reaction	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades <sup>1</sup>	Grade 3 or 4	All Grades <sup>1</sup>	Grade 3 or 4
Musculoskeletal pain <sup>10</sup>	41	1.6	19	0
<b>Nervous System</b>				
Dysgeusia <sup>11</sup>	30	0	6	0
Dizziness <sup>12</sup>	25	0	3.2	0
<b>Endocrine disorders</b>				
Hypothyroidism <sup>13</sup>	25	0	3.2	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	25	3.2	19	0
<b>Investigations</b>				
Weight decreased	19	3.2	10	0
<b>Respiratory, Thoracic, and Mediastinal</b>				
Dyspnea <sup>14</sup>	16	0	3.2	0

<sup>1</sup> NCI CTCAE Version 5.0  
<sup>2</sup> Includes fatigue, asthenia  
<sup>3</sup> Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension  
<sup>4</sup> Includes thromboembolic event, pulmonary embolism, embolism, deep vein thrombosis, vena cava thrombosis, embolism venous, embolism arterial  
<sup>5</sup> Includes diarrhea, colitis  
<sup>6</sup> Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis  
<sup>7</sup> Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain  
<sup>8</sup> Includes dyspepsia, gastroesophageal reflux disease  
<sup>9</sup> Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, erythema multiforme, rash macular, rash maculo-papular, rash pustular, dermatitis, dermatitis bullous, dermatitis contact, erythema, dermatitis psoriasiform  
<sup>10</sup> Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort  
<sup>11</sup> Includes dysgeusia, taste disorder, ageusia, anosmia  
<sup>12</sup> Includes dizziness, vertigo  
<sup>13</sup> Includes hypothyroidism, blood thyroid stimulating hormone increased  
<sup>14</sup> Includes dyspnea, dyspnea exertional

Clinically relevant adverse reactions in <15% of patients who received CABOMETYX included peripheral neuropathy, hemorrhage, cardiac arrhythmia, hypotension, alopecia, and hair color changes.

Table 15 summarizes the laboratory abnormalities in patients with pNET in CABINET.

**Table 15: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with pNET Who Received CABOMETYX in CABINET**

Laboratory Abnormality	CABOMETYX (N=63)		Placebo (N=31)	
	All Grades <sup>1</sup> (%)	Grade 3 or 4 (%)	All Grades <sup>1</sup> (%)	Grade 3 or 4 (%)
<b>Chemistry</b>				
Increased AST	76	1.6	48	0
Increased ALT	75	1.6	39	3.2

Hyperglycemia <sup>2</sup>	37	3.2	48	3.2
Hypophosphatemia <sup>3</sup>	25	0	6	0
Increased ALP <sup>4</sup>	22	3.2	23	0
Hypocalcemia <sup>5</sup>	17	0	3.2	0
Hyponatremia <sup>6</sup>	16	1.6	16	0
Blood bilirubin increased <sup>7</sup>	14	4.8	6	3.2
Hyperkalemia <sup>8</sup>	14	1.6	10	0
Hypoalbuminemia <sup>9</sup>	14	0	10	0
Hypoglycemia <sup>10</sup>	11	0	6	0
Hypomagnesemia <sup>11</sup>	11	0	6	0
Hypokalemia <sup>12</sup>	10	1.6	3.2	0
<b>Hematology</b>				
Platelet count decreased <sup>13</sup>	37	0	19	0
Neutrophil count decreased <sup>14</sup>	27	1.6	6	0
Hemoglobin decreased <sup>15</sup>	25	1.6	32	0
Lymphocyte count decreased <sup>16</sup>	22	8	16	0
White blood cell count decreased <sup>17</sup>	19	1.6	3.2	0
<sup>1</sup> NCI CTCAE Version 5.0 <sup>2</sup> Includes hyperglycemia, blood glucose increased <sup>3</sup> Includes hypophosphatemia, blood phosphorus decreased <sup>4</sup> Includes blood alkaline phosphatase, blood alkaline phosphatase increased <sup>5</sup> Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased <sup>6</sup> Includes hyponatremia, blood sodium decreased <sup>7</sup> Includes blood bilirubin increased, hyperbilirubinemia <sup>8</sup> Includes hyperkalemia, blood potassium increased <sup>9</sup> Includes hypoalbuminemia, blood albumin decreased <sup>10</sup> Includes hypoglycemia, blood glucose decreased <sup>11</sup> Includes hypomagnesemia, blood magnesium decreased <sup>12</sup> Includes hypokalemia, blood potassium decreased <sup>13</sup> Includes platelet count decreased, thrombocytopenia <sup>14</sup> Includes neutrophil count decreased, neutropenia <sup>15</sup> Includes hemoglobin decreased, anemia <sup>16</sup> Includes lymphocyte count decreased, lymphopenia <sup>17</sup> Includes white blood cell count decreased, leukopenia				

### *Extra-Pancreatic Neuroendocrine Tumors (epNET)*

The safety of CABOMETYX was evaluated in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors in the CABINET trial [see [Clinical Studies \(14.4\)](#)]. Patients received CABOMETYX 60 mg (n=132) or placebo (n=67) orally once daily until disease progression or unacceptable toxicity. Patients with epNET were required to have disease progression after prior treatment with at least one FDA approved therapy (everolimus or lutetium Lu 177 dotatate), other than somatostatin analogs. The median duration of treatment was 5.4 months (range 0.1 to 32.4) for patients receiving CABOMETYX and 2.8 months (range 0.5 to 22.8) for patients receiving placebo.

The median age was 66 years (range 28 to 86), 55% were female, 86% were White, 7% were Black, 2.3% were Asian, 5% had unknown race or race not reported, and 6% were Hispanic or Latino.

Serious adverse reactions occurred in 44% of patients who received CABOMETYX. Serious adverse reactions in  $\geq 2\%$  included hypertension (6%), abdominal pain (5%), musculoskeletal pain (5%), diarrhea (3.0%), vomiting (3.0%), blood bilirubin increased (3.0%), thromboembolic events (3.0%), nausea (2.3%), hemoglobin decreased (2.3%), muscular weakness (2.3%), fatigue (2.3%), sepsis (2.3%), and syncope (2.3%). Fatal adverse reactions occurred in 4.5% of patients who received CABOMETYX, including hepatic failure, multi-organ dysfunction, gastrointestinal hemorrhage, cardiac arrest, ruptured ascending aortic aneurysm, and sudden death not otherwise specified, occurring in one patient each.

Permanent discontinuation of CABOMETYX due to an adverse reaction occurred in 28% of patients receiving CABOMETYX. Adverse reactions which resulted in permanent discontinuation of CABOMETYX included diarrhea, fatigue, increased AST, increased ALT, blood bilirubin increased, rash, thromboembolic events, hypertension, increased ALP, nausea, and stomatitis.

The median average daily dose was 42.9 mg for CABOMETYX. Dosage interruptions of CABOMETYX due to an adverse reaction occurred in 81% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included diarrhea, fatigue, rash, hypertension, nausea, stomatitis, abdominal pain, increased AST, vomiting, and musculoskeletal pain.

Dose reductions of CABOMETYX due to an adverse reaction occurred in 38% of patients. Adverse reactions which required dose reductions in  $\geq 5\%$  of patients included rash, fatigue, diarrhea, and hypertension.

The most common adverse reactions occurring in  $\geq 20\%$  of CABOMETYX-treated patients were fatigue, increased AST, diarrhea, hypertension, increased ALT, platelet count decreased, rash, stomatitis, nausea, white blood cell count decreased, neutrophil count decreased, musculoskeletal pain, dysgeusia, hypothyroidism, decreased appetite, hemoglobin decreased, hyperglycemia, abdominal pain, increased ALP, lymphocyte count decreased, weight decreased, blood creatinine increased, hypoalbuminemia, blood bilirubin increased, hypocalcemia, hypokalemia, and hypomagnesemia.

Table 16 summarizes the adverse reactions in patients with epNET in CABINET.

**Table 16. Adverse Reactions ( $\geq 15\%$ ) in Patients with epNET Who Received CABOMETYX in CABINET**

Adverse Reaction	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades <sup>1</sup>	Grade 3-4	All Grades <sup>1</sup>	Grade 3-4
	<b>Percentage (%) of Patients</b>			
<b>General</b>				
Fatigue <sup>2</sup>	73	14	58	9
Edema <sup>3</sup>	16	1.5	10	0
<b>Gastrointestinal</b>				
Diarrhea <sup>4</sup>	65	11	42	4.5
Stomatitis <sup>5</sup>	40	3.8	10	0

Adverse Reaction	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades <sup>1</sup>	Grade 3-4	All Grades <sup>1</sup>	Grade 3-4
Nausea	39	2.3	21	0
Abdominal pain <sup>6</sup>	29	9	43	8
Vomiting	17	2.3	10	1.5
<b>Vascular</b>				
Hypertension <sup>7</sup>	64	27	37	6
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>8</sup>	50	3.0	10	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal pain <sup>9</sup>	36	8	33	1.5
<b>Endocrine System</b>				
Hypothyroidism <sup>10</sup>	34	0	4.5	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	33	1.5	15	1.5
<b>Nervous System</b>				
Dysgeusia <sup>11</sup>	35	0	1.5	0
Dizziness <sup>12</sup>	17	0	6	0
<b>Investigations</b>				
Weight decreased	27	4.5	8	0
<b>Respiratory, Thoracic, and Mediastinal</b>				
Cough <sup>13</sup>	17	0	10	0

<sup>1</sup> NCI CTCAE Version 5.0

<sup>2</sup> Includes fatigue, asthenia

<sup>3</sup> Includes edema, edema peripheral, generalized edema, localized edema, periorbital edema, face edema, eye edema

<sup>4</sup> Includes diarrhea, colitis

<sup>5</sup> Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis

<sup>6</sup> Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain

<sup>7</sup> Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension

<sup>8</sup> Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, rash macular, rash pustular, dermatitis bullous, dermatitis, erythema multiforme, rash maculo-papular, dermatitis contact, erythema, dermatitis psoriasiform

<sup>9</sup> Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort

<sup>10</sup> Includes hypothyroidism, blood thyroid stimulating hormone increased

<sup>11</sup> Includes dysgeusia, taste disorder, ageusia, anosmia

<sup>12</sup> Includes dizziness, vertigo

<sup>13</sup> Includes cough, upper-airway cough syndrome, productive cough

Clinically relevant adverse reactions in <15% of patients who received CABOMETYX included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, and hair color changes.

Table 17 summarizes the laboratory abnormalities in patients with epNET in CABINET.

**Table 17: Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with epNET Who Received CABOMETYX in CABINET**

Laboratory Abnormality	CABOMETYX (N=132)		Placebo (N=67)	
	All Grades <sup>1</sup> (%)	Grade 3 or 4 (%)	All Grades <sup>1</sup> (%)	Grade 3 or 4 (%)
<b>Chemistry</b>				
Increased AST	70	3.8	21	1.5
Increased ALT	63	0.8	18	1.5
Hyperglycemia <sup>2</sup>	30	0.8	39	1.5
Increased ALP <sup>3</sup>	29	4.5	30	6
Blood creatinine increased	23	0	12	1.5
Blood bilirubin increased <sup>4</sup>	20	3	10	6
Hypoalbuminemia <sup>5</sup>	20	0.8	9	0
Hypocalcemia <sup>6</sup>	20	0	4.5	0
Hypokalemia <sup>7</sup>	20	2.3	10	1.5
Hypomagnesemia <sup>8</sup>	20	0.8	4.5	0
Hypophosphatemia <sup>9</sup>	19	0.8	4.5	0
Hyponatremia <sup>10</sup>	16	2.3	7	1.5
<b>Hematology</b>				
Platelet count decreased <sup>11</sup>	55	1.5	13	1.5
White blood cell count decreased <sup>12</sup>	37	3	4.5	0
Neutrophil count decreased <sup>13</sup>	36	3	6	0
Hemoglobin decreased <sup>14</sup>	30	2.3	19	0
Lymphocyte count decreased <sup>15</sup>	28	9	18	1.5

<sup>1</sup> NCI CTCAE Version 5.0  
<sup>2</sup> Includes hyperglycemia, blood glucose increased  
<sup>3</sup> Includes blood alkaline phosphatase, blood alkaline phosphatase increased  
<sup>4</sup> Includes blood bilirubin increased, hyperbilirubinemia  
<sup>5</sup> Includes hypoalbuminemia, blood albumin decreased  
<sup>6</sup> Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased  
<sup>7</sup> Includes hypokalemia, blood potassium decreased  
<sup>8</sup> Includes hypomagnesemia, blood magnesium decreased  
<sup>9</sup> Includes hypophosphatemia, blood phosphorus decreased  
<sup>10</sup> Includes hyponatremia, blood sodium decreased  
<sup>11</sup> Includes platelet count decreased, thrombocytopenia  
<sup>12</sup> Includes white blood cell count decreased, leukopenia  
<sup>13</sup> Includes neutrophil count decreased, neutropenia  
<sup>14</sup> Includes hemoglobin decreased, anemia  
<sup>15</sup> Includes lymphocyte count decreased, lymphopenia

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CABOMETYX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Vascular Disorders:** Arterial (including aortic) aneurysms, dissections, and rupture

## 7 DRUG INTERACTIONS

### 7.1 Effects of Other Drugs on CABOMETYX

#### Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions [see *Clinical Pharmacology (12.3)*]. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided [see *Dosage and Administration (2.4)*]. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

#### Strong or Moderate CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy [see *Clinical Pharmacology (12.3)*]. Avoid coadministration of CABOMETYX with strong or moderate CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong or moderate CYP3A4 inducers cannot be avoided [see *Dosage and Administration (2.5)*]. Avoid St. John's wort which may also decrease exposure of cabozantinib.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose (*see Data*). Advise pregnant women of the potential risk to a fetus.

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

#### Data

##### *Animal Data*

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

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

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

## 8.2 Lactation

### Risk Summary

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

## 8.3 Females and Males of Reproductive Potential

### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX [see *Use in Specific Populations (8.1)*].

### Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

### *Females*

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

### Infertility

### *Females and Males*

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

## 8.4 Pediatric Use

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

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

recommended dosages [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3, 14.4)*].

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

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

#### Juvenile Animal Toxicity Data

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

## **8.5 Geriatric Use**

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older. In CABINET, 38% of 63 patients treated with CABOMETYX were age 65 years and older, and 5% were 75 years and older in the pNET cohort, and 55% of 132 patients treated with CABOMETYX were age 65 years and older, and 13% were 75 years and older in the epNET cohort [see *Clinical Studies (14)*].

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

Of the 320 patients with RCC treated with CABOMETYX in combination with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older [see *Clinical Studies (14.1)*].

No overall difference in safety was reported between older and younger patients receiving both CABOMETYX and nivolumab.

## 8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population [see *Dosage and Administration (2.2, 2.6), Clinical Pharmacology (12.3)*].

## 8.7 Renal Impairment

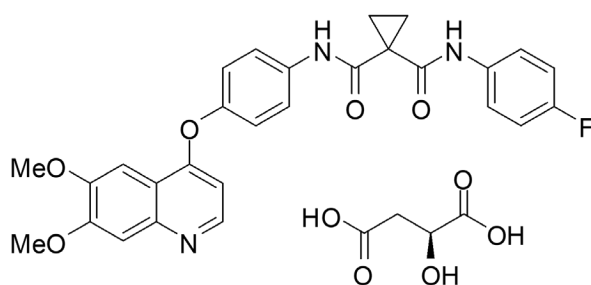
No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

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

## 11 DESCRIPTION

CABOMETYX is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is  $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$  and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is:



Cabozantinib (*S*)-malate salt is a white to off-white solid that is practically insoluble in aqueous media.

CABOMETYX (cabozantinib) tablets for oral use are supplied as film-coated tablets containing 20 mg, 40 mg, or 60 mg of cabozantinib, which is equivalent to 25 mg, 51 mg, or 76 mg of cabozantinib (*S*)-malate, respectively. CABOMETYX also contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

### 12.2 Pharmacodynamics

The exposure-response or safety relationship for cabozantinib is not fully characterized.

#### Cardiac Electrophysiology

The effect of cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled trial in patients with medullary thyroid cancer administered a cabozantinib capsule formulation. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiation. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No patients in this study had a confirmed QTcF >500 ms nor did any patients in METEOR, CABOSUN, CELESTIAL, CHECKMATE-9ER, COSMIC-311, or CABINET.

### 12.3 Pharmacokinetics

Repeat daily dosing of a cabozantinib capsule formulation for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15.

#### Absorption

Median time to peak cabozantinib concentrations ( $T_{max}$ ) ranged from 3 to 4 hours post-dose. A 19% increase in the  $C_{max}$  of CABOMETYX compared to a cabozantinib capsule formulation was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between CABOMETYX and a cabozantinib capsule formulation [*see Dosage and Administration (2.1)*].

#### *Food Effect*

Cabozantinib  $C_{max}$  and AUC increased by 41% and 57%, respectively, following a high-fat meal relative to fasted conditions in healthy subjects administered a single oral dose of a cabozantinib capsule formulation.

#### Distribution

The oral volume of distribution ( $V_z/F$ ) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma ( $\geq 99.7\%$ ).

## Elimination

The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady-state is estimated to be 2.2 L/hr.

## *Metabolism*

Cabozantinib is a substrate of CYP3A4 in vitro.

## *Excretion*

Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single dose of radiolabeled <sup>14</sup>C-cabozantinib in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72-hour collection.

## Specific Populations

The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (32-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with eGFR  $< 29$  mL/min/1.73m<sup>2</sup> as estimated by MDRD equation or requiring dialysis.

## *Pediatric Patients*

The systemic exposures to cabozantinib in pediatric patients 12 years and older at the recommended dosages are expected to be comparable to the exposure in adults at the dose of CABOMETYX 60 mg once daily.

## *Patients with Hepatic Impairment*

Based on a population pharmacokinetic analysis of cabozantinib in healthy subjects and patients with cancer, no clinically significant differences in the mean cabozantinib exposure were observed between subjects with normal liver function (total bilirubin and AST  $\leq$  ULN) and those with mild hepatic impairment (total bilirubin  $\leq$  ULN and AST  $>$  ULN or total bilirubin  $> 1$  to  $1.5 \times$  ULN and any AST value). In a dedicated pharmacokinetic study, cabozantinib exposure (AUC<sub>0-INF</sub>) increased by 63% in patients with moderate hepatic impairment (Child-Pugh B). Patients with severe hepatic impairment have not been studied [*see Dosage and Administration (2.8), Use in Specific Populations (8.6)*].

## Drug Interaction Studies

### Clinical Studies

#### *CYP3A4 Inhibitors:*

Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days), with a cabozantinib capsule formulation to healthy subjects increased single-dose cabozantinib exposure (AUC<sub>0-INF</sub>) by 38%.

#### *CYP3A4 Inducers:*

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days), with a cabozantinib capsule formulation to healthy subjects decreased single-dose cabozantinib exposure ( $AUC_{0-12h}$ ) by 77%.

#### *CYP2C8 Substrates:*

No clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) exposure ( $C_{max}$  and AUC) was observed when co-administered with a cabozantinib capsule formulation at steady-state concentrations.

#### *Gastric Acid Reducing Agents:*

No clinically-significant effect on cabozantinib exposure (AUC) was observed following co-administration of the proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single 100 mg dose of a cabozantinib capsule formulation to healthy subjects.

#### *In vitro Studies*

##### *CYP Enzymes:*

Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

Although cabozantinib is an inhibitor of CYP2C8 in vitro, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this finding, other less sensitive substrates of pathways affected by cabozantinib in vitro (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study, because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes in vitro.

Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

##### *Transporters:*

Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown.

Cabozantinib is a substrate of MRP2 in vitro and MRP2 inhibitors have the potential to increase concentrations of cabozantinib. The clinical relevance of this finding is unknown.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, once daily oral

administration of cabozantinib resulted in a statistically significant increase in the incidence of malignant/complex malignant pheochromocytoma in combination with benign pheochromocytoma or in benign pheochromocytoma alone in male rats at a dose of 1 mg/kg (approximately 5 times the human exposure by AUC at the recommended 60 mg dose). Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice at a slightly higher exposure than the intended human therapeutic exposure.

Cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* mouse micronucleus assay.

Based on nonclinical findings, male and female fertility may be impaired by treatment with CABOMETYX. In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately 13-fold of human AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (5-fold of human AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis.

## 14 CLINICAL STUDIES

### 14.1 Renal Cell Carcinoma

#### Previously Treated with Anti-angiogenic Therapy

The efficacy of CABOMETYX was evaluated in METEOR (NCT01865747), a randomized (1:1), open-label, multicenter trial of CABOMETYX versus everolimus conducted in patients with advanced RCC who had received at least 1 prior anti-angiogenic therapy. Patients had to have a Karnofsky Performance Score (KPS)  $\geq 70\%$ . Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors (TKIs) and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group.

Patients were randomized to receive CABOMETYX (N=330) 60 mg orally once daily or everolimus (N=328) 10 mg orally once daily. The majority of the patients were male (75%), with a median age of 62 years. Sixty-nine percent (69%) received only one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 46% favorable (0 risk factors), 42% intermediate (1 risk factor), and 13% poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%).

The main efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee among the first 375 subjects randomized. Other efficacy endpoints were objective response rate (ORR) and overall survival (OS) in the Intent-to-Treat (ITT) population. Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. Patients received treatment until disease progression or experiencing unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator.

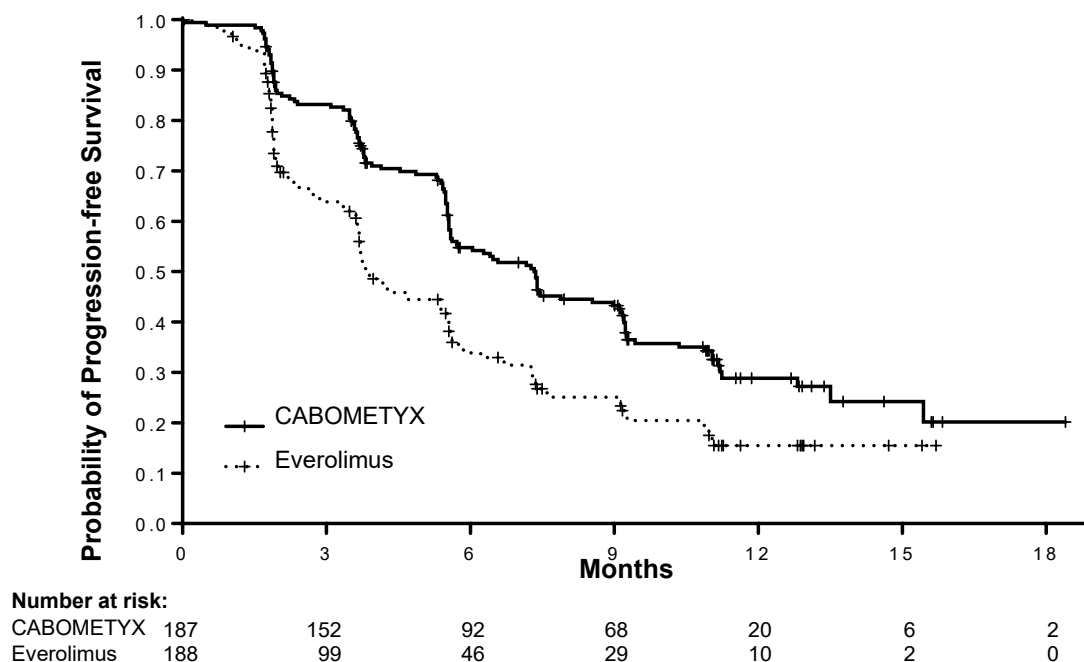
Statistically significant improvements in PFS, OS, and ORR were demonstrated for CABOMETYX compared to everolimus. Efficacy results are presented in Tables 18 and 19 and Figures 1 and 2.

**Table 18: Efficacy Results in METEOR (First 375 Randomized)**

Endpoint	CABOMETYX	Everolimus
	N = 187	N = 188
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
HR (95% CI), p-value <sup>1</sup>	0.58 (0.45, 0.74), p<0.0001	

<sup>1</sup>stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

**Figure 1: Kaplan-Meier Curves of Progression-Free Survival in METEOR (First 375 Randomized)**



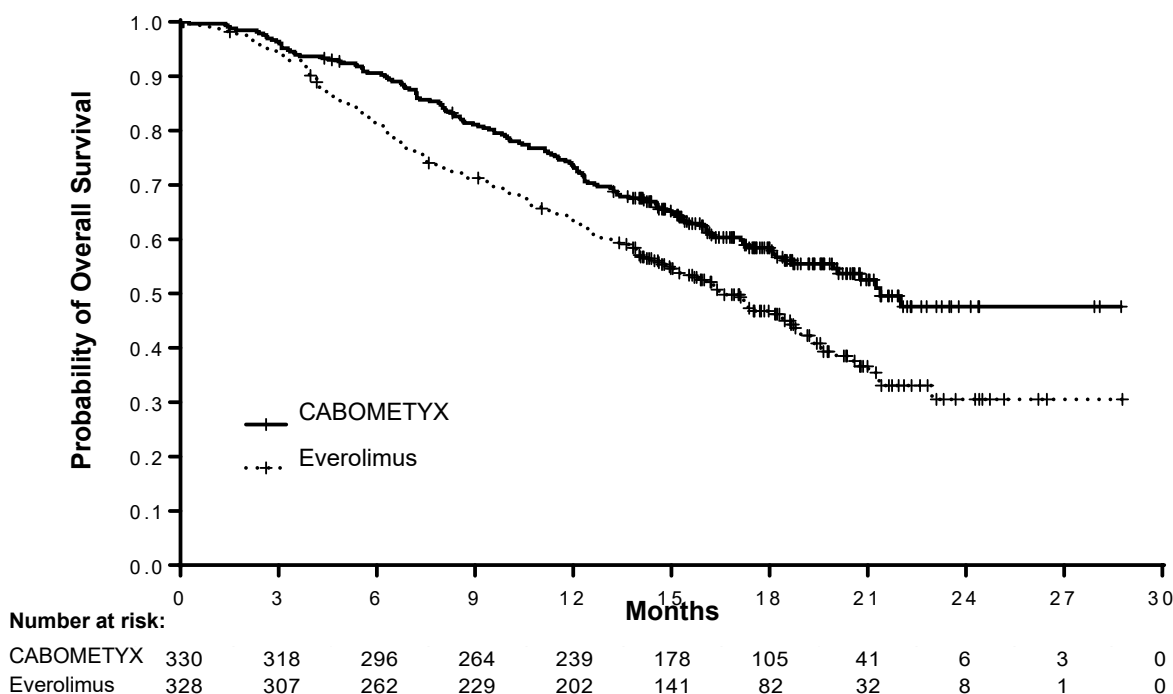
**Table 19: Efficacy Results in METEOR (ITT)**

Endpoint	CABOMETYX	Everolimus
	N = 330	N = 328
Median OS (95% CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value <sup>1</sup>	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value <sup>2</sup>	p<0.0001	

<sup>1</sup>stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

<sup>2</sup> chi-squared test

**Figure 2: Kaplan-Meier Curve of Overall Survival in METEOR (ITT)**



### First-line Treatment

#### *CABOSUN*

The efficacy of CABOMETYX was evaluated in CABOSUN (NCT01835158), a randomized (1:1), open-label, multicenter trial of CABOMETYX versus sunitinib conducted in patients with advanced RCC who had not received prior therapy. Patients were randomized to receive CABOMETYX (N=79) 60 mg orally once daily or sunitinib (N=78) 50 mg orally once daily (4 weeks on treatment followed by 2 weeks off) until disease progression or unacceptable toxicity. All patients were required to have intermediate or poor risk disease as defined by the

International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no).

The majority of patients were male (78%), with a median age of 63 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor ( $\geq 3$  risk factors).

Thirty-six percent (36%) patients had bone metastases. Forty-six percent (46%) of patients were ECOG 0, 41% ECOG 1, and 13% ECOG 2.

The major efficacy outcome measure was progression-free survival (PFS) by a retrospective blinded independent radiology review committee (BIRC).

A statistically significant improvement in PFS, as assessed by a blinded independent radiology review committee, was demonstrated for CABOMETYX compared to sunitinib. Efficacy results are presented in Table 20, Figure 3, and Figure 4.

**Table 20: Efficacy Results in CABOSUN**

<b>Endpoint</b>	<b>CABOMETYX</b>	<b>Sunitinib</b>
	N = 79	N = 78
<b>Progression-Free Survival<sup>1</sup></b>		
Events, n(%)	43 (54)	49 (63)
Median PFS (95% CI), months <sup>1</sup>	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
Hazard Ratio <sup>2</sup> (95% CI), p-value <sup>3</sup>	0.48 (0.31, 0.74), p=0.0008	
<b>Overall Survival</b>		
Events, n(%)	43 (54)	47 (60)
Hazard Ratio <sup>2,4</sup> (95% CI)	0.80 (0.53, 1.21)	
<b>Confirmed ORR, partial responses only (95% CI)<sup>1,4</sup></b>	20% (12.0, 30.8)	9% (3.7, 17.6)

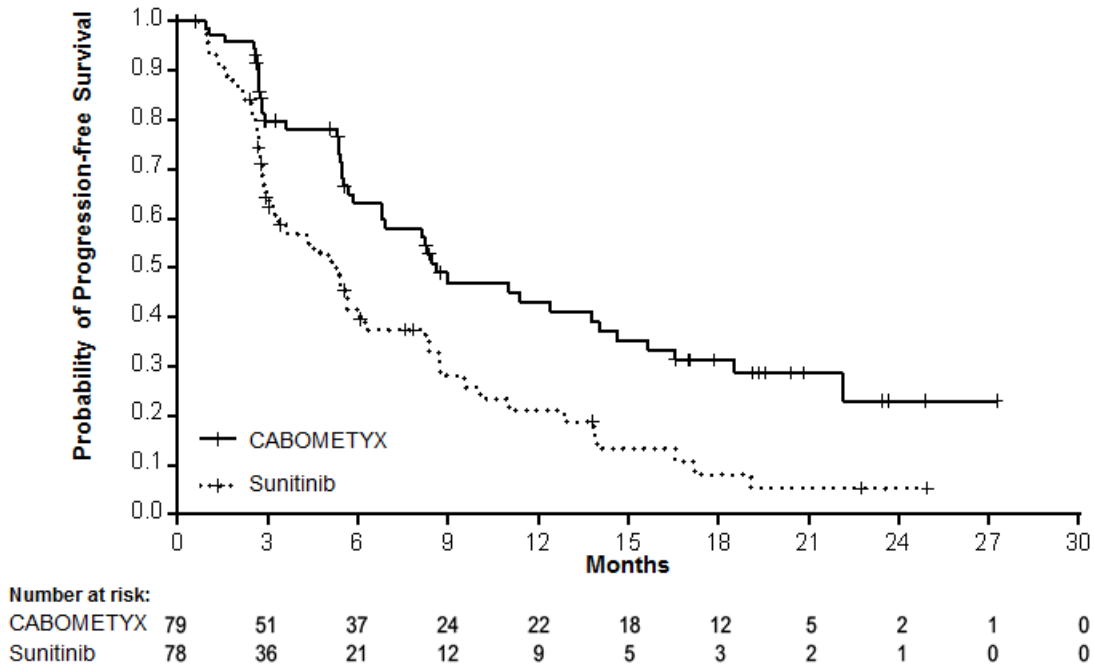
<sup>1</sup> as assessed by a retrospective blinded independent radiology review committee (BIRC)

<sup>2</sup> estimated from stratified Cox proportional hazards model with stratification factors IMDC risk group and presence of bone metastases and treatment as covariate

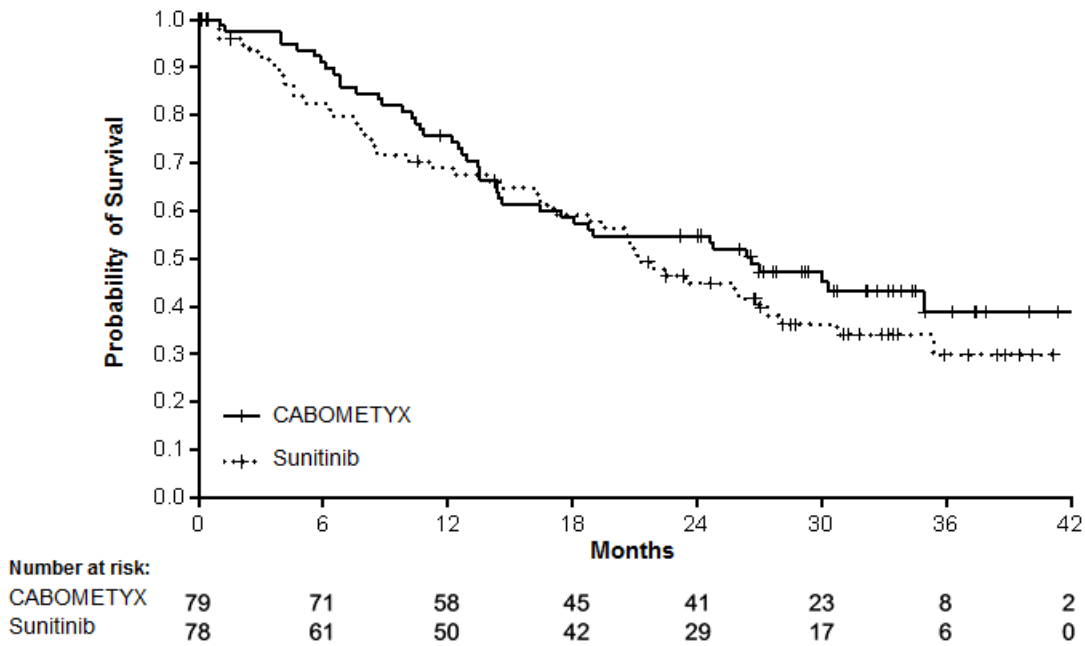
<sup>3</sup> two-sided stratified log-rank test with stratification factors IMDC risk group and presence of bone metastases

<sup>4</sup> no multiplicity adjustments were made for overall survival or ORR

**Figure 3: Kaplan-Meier Curve of Progression-Free Survival in CABOSUN**



**Figure 4: Kaplan-Meier Curve of Overall Survival in CABOSUN**



### CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of CABOMETYX combined with nivolumab versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression ( $\geq 1\%$  vs.  $< 1\%$  or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to CABOMETYX 40 mg orally daily and nivolumab 240 mg intravenously every 2 weeks (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38%  $\geq 65$  years of age and 10%  $\geq 75$  years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to CABOMETYX and nivolumab compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. An updated efficacy analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 21 and Figures 5 and 6.

**Table 21: Efficacy Results in CHECKMATE-9ER**

	<b>CABOMETYX and Nivolumab (n=323)</b>	<b>Sunitinib (n=328)</b>
<b>Progression-free Survival</b>		
Disease progression or deaths (%)	144 (45)	191 (58)
Median PFS (months) <sup>a</sup> (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI) <sup>b</sup>	0.51 (0.41, 0.64)	
p-value <sup>c,d</sup>	<0.0001	
<b>Overall Survival</b>		
Deaths (%)	67 (21)	99 (30)
Median OS (months) <sup>a</sup> (95% CI)	NR <sup>e</sup>	NR (22.6, NR <sup>e</sup> )
Hazard ratio (98.89% CI) <sup>b</sup>	0.60 (0.40, 0.89)	
p-value <sup>c,d,f</sup>	0.0010	
<b>Updated Overall Survival</b>		
Deaths (%)	121 (37)	150 (46)
Median OS (months) <sup>a</sup> (95% CI)	37.7 (35.5, NR <sup>e</sup> )	34.3 (29.0, NR <sup>e</sup> )
Hazard ratio (95% CI) <sup>b</sup>	0.70 (0.55, 0.90)	

	<b>CABOMETYX and Nivolumab (n=323)</b>	<b>Sunitinib (n=328)</b>
<b>Confirmed Objective Response Rate (95% CI)<sup>g</sup></b>	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
<b>p-value<sup>h</sup></b>	<0.0001	
Complete Response (CR)	26 (8%)	15 (4.6%)
Partial Response (PR)	154 (48%)	74 (23%)
Median duration of response in months (95% CI) <sup>a</sup>	20.2 (17.3, NR <sup>e</sup> )	11.5 (8.3, 18.4)

<sup>a</sup> Based on Kaplan-Meier estimates.

<sup>b</sup> Stratified Cox proportional hazards model.

<sup>c</sup> Based on stratified log-rank test

<sup>d</sup> 2-sided p-values from stratified log-rank test.

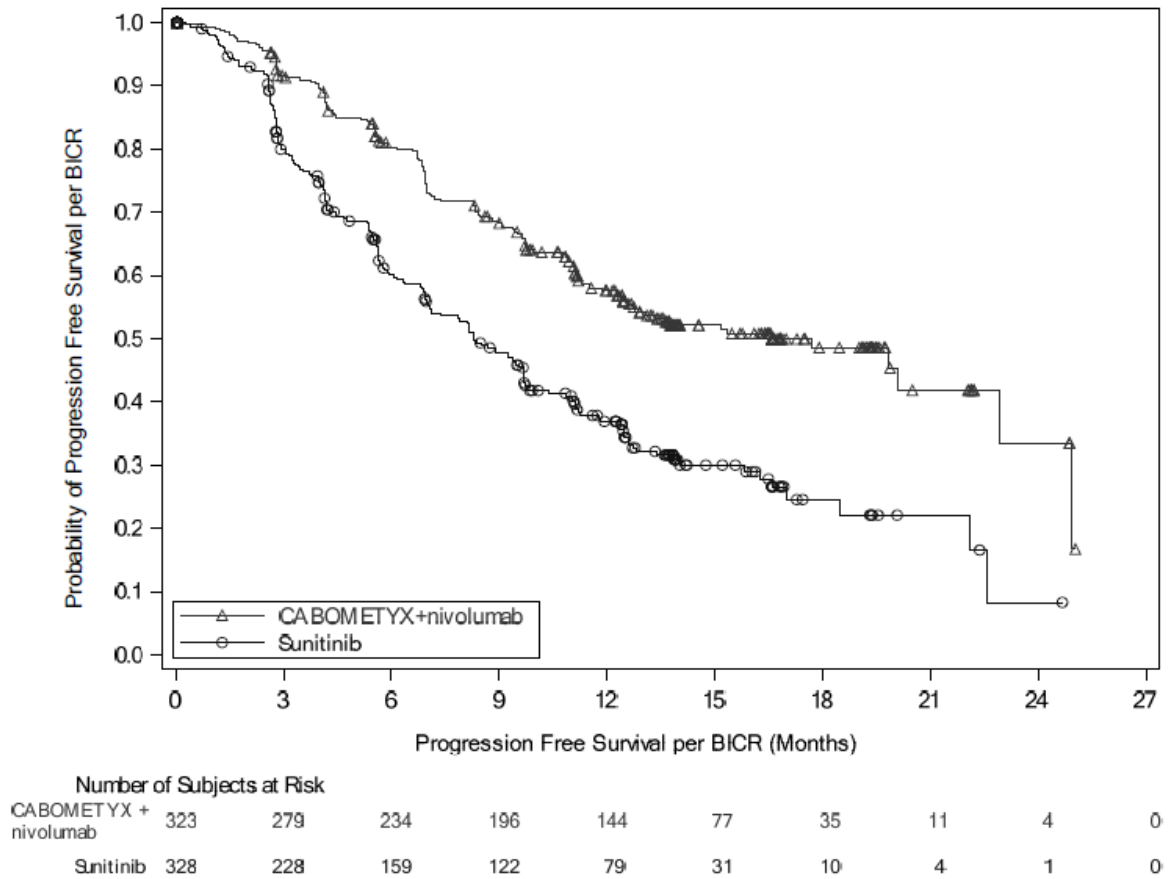
<sup>e</sup> Not Reached

<sup>f</sup> p-value is compared with the allocated alpha of 0.0111 for this interim analysis.

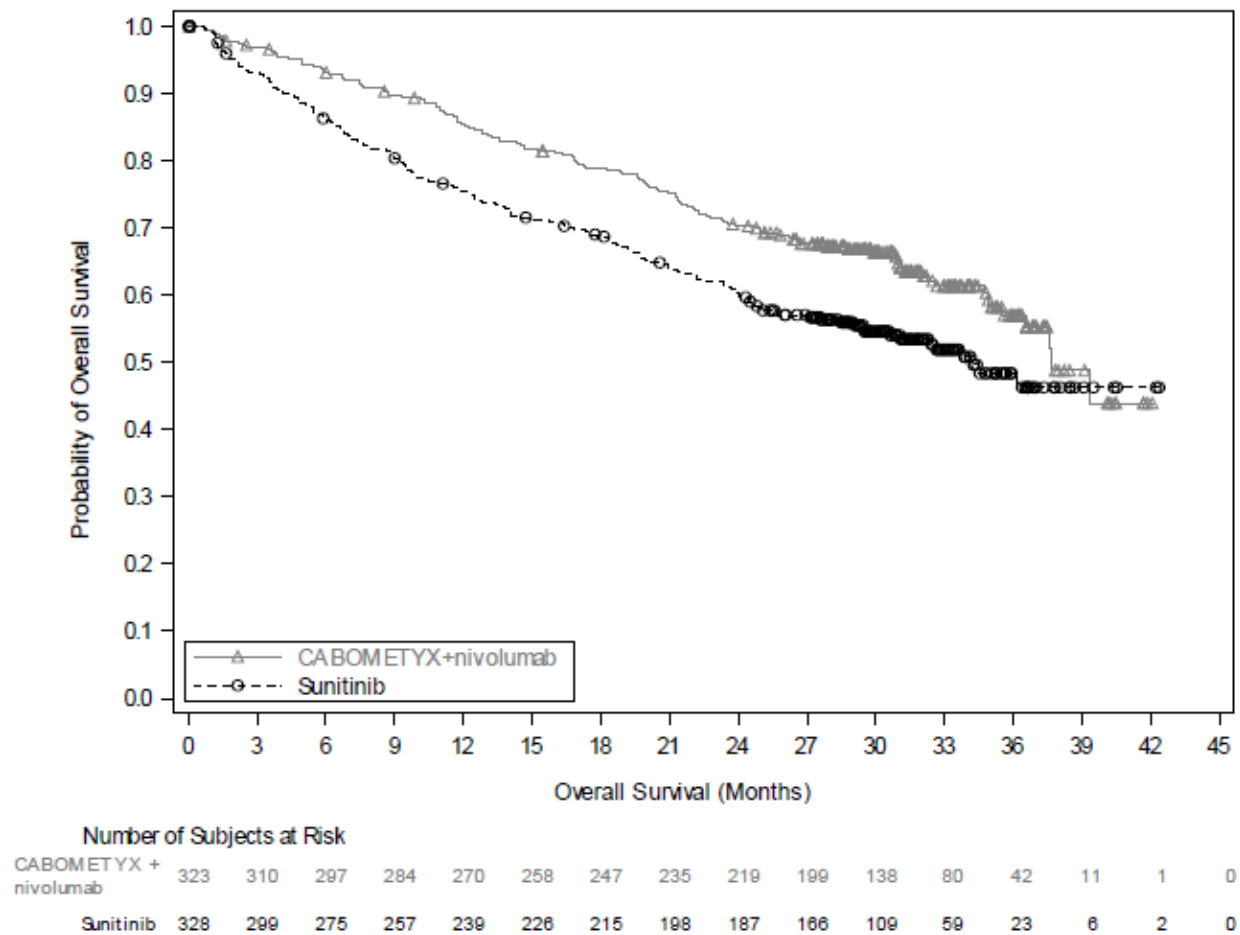
<sup>g</sup> CI based on the Clopper and Pearson method.

<sup>h</sup> 2-sided p-value from Cochran-Mantel-Haenszel test.

**Figure 5: Kaplan-Meier Curve of Progression-Free Survival in CHECKMATE-9ER**



**Figure 6: Kaplan-Meier Curve of Updated Overall Survival in CHECKMATE-9ER**



In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

## 14.2 Hepatocellular Carcinoma

The efficacy of CABOMETYX was evaluated in CELESTIAL (NCT01908426), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with hepatocellular carcinoma (HCC) who had previously received sorafenib and had Child Pugh Class A liver impairment. Patients were randomized to receive CABOMETYX 60 mg orally once daily or placebo until disease progression or unacceptable toxicity. Randomization was stratified by etiology of disease (hepatitis B virus [HBV] with or without hepatitis C virus [HCV] vs. HCV [without HBV] vs. other [without HBV and HCV]), geographic region (Asia vs. other regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes vs. no). The primary efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and objective response rate (ORR), as assessed by investigators per RECIST 1.1. Tumor assessments were conducted every 8 weeks.

In CELESTIAL, a total of 707 patients were randomized, 470 to CABOMETYX and 237 to placebo. The median age was 64 years (range 22 to 86 years), 82% were male, 56% were White and 34% were Asian. Baseline ECOG performance status was 0 (53%) or 1 (47%). The etiology of HCC was attributed to HBV in 38% of patients and HCV in 21%; etiology was attributed to causes other than HBV or HCV in 40%. Macroscopic vascular invasion or extra-hepatic tumor spread was present in 78% of patients and 41% had alpha-fetoprotein (AFP) levels  $\geq 400$  mcg/L. All patients received prior sorafenib and 27% received two prior systemic therapy regimens.

Efficacy results are summarized in Table 22, Figure 7, and Figure 8.

**Table 22: Efficacy Results from CELESTIAL**

Endpoint	CABOMETYX	Placebo
	N = 470	N = 237
<b>Overall Survival</b>		
Number of Deaths, (%)	317 (67)	167 (70)
Median OS in Months (95% CI)	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)
Hazard Ratio (95% CI) <sup>1</sup>	0.76 (0.63, 0.92)	
p-value <sup>2</sup>	p=0.0049 <sup>3</sup>	
<b>Progression-Free Survival</b>		
Number of Events, (%)	349 (74)	205 (86)
Progressive Disease	284 (60)	186 (78)
Death	65 (14)	19 (8)
Median PFS in Months (95% CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)
Hazard Ratio (95% CI) <sup>1</sup>	0.44 (0.36, 0.52)	
p-value <sup>2</sup>	p<0.0001	
<b>Overall Response Rate (ORR)</b>		
Confirmed ORR (partial responses only) (95% CI) <sup>3</sup>	4% (2.3, 6.0)	0.4% (0.0, 2.3)
p-value <sup>4</sup>	p=0.0086	

CI, confidence interval

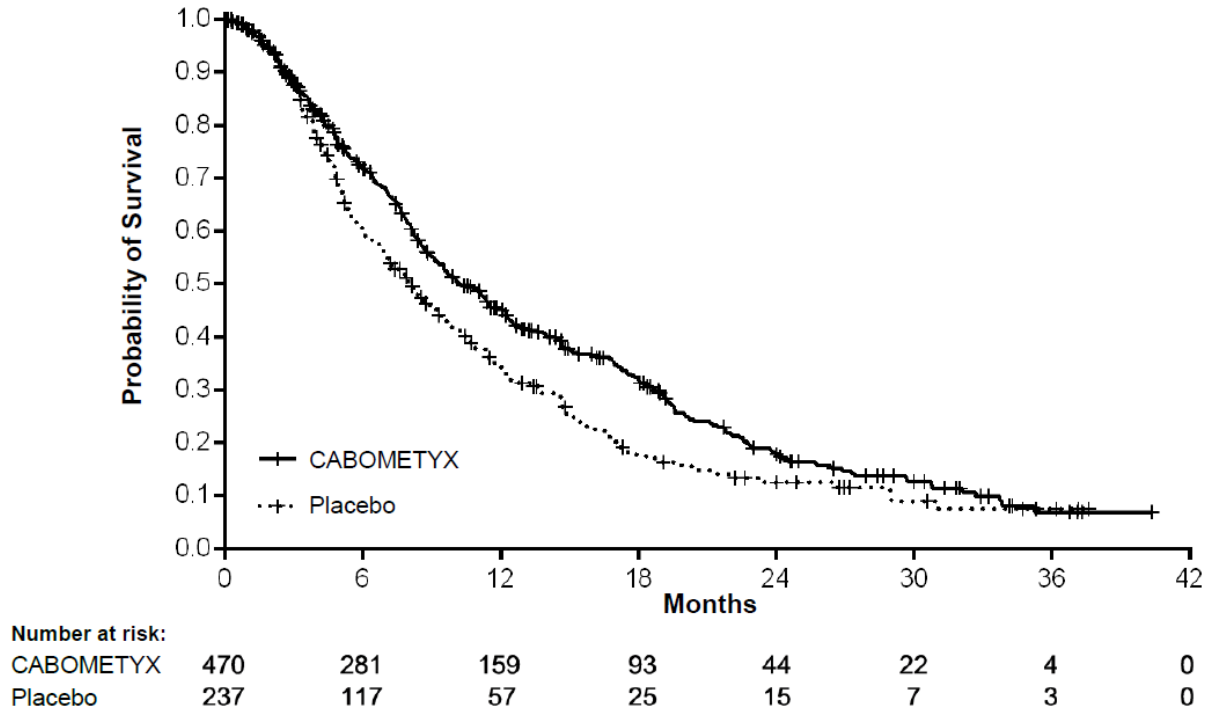
<sup>1</sup> estimated using the Cox proportional-hazard model

<sup>2</sup> log-rank test stratified by etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other), geographic region (Asia, Other Regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No) as stratification factors (per IVRS data)

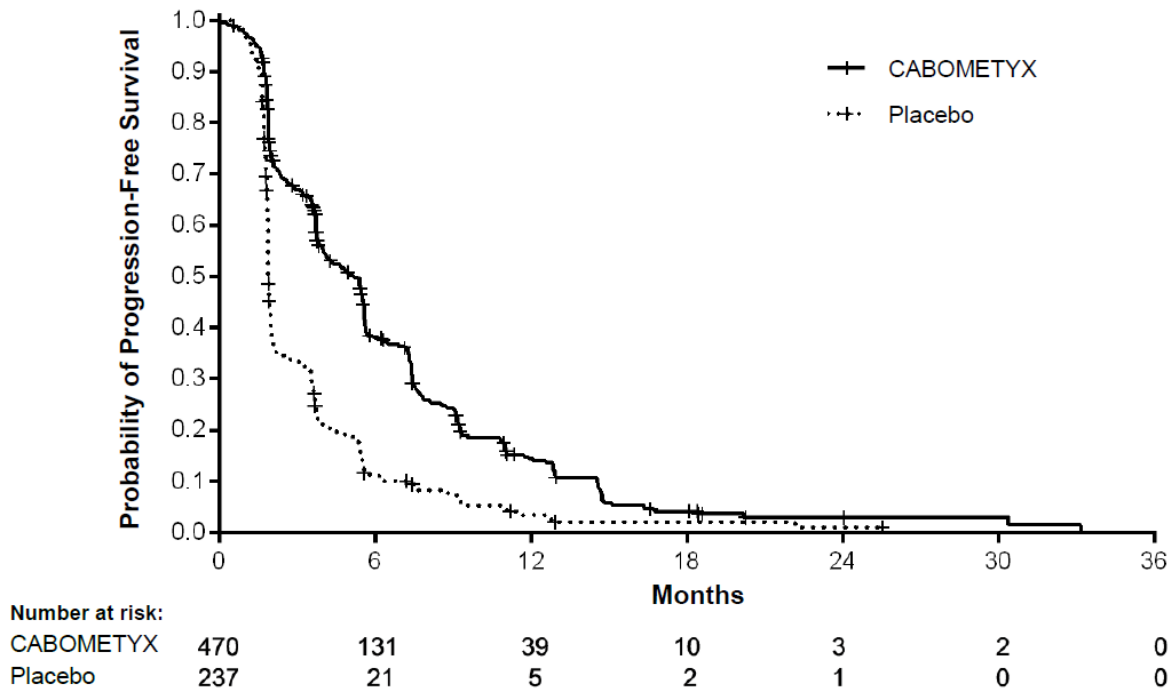
<sup>3</sup> significance level = 0.021 for 78% information (484 deaths) based on O'Brien-Fleming method

<sup>4</sup> Fisher's exact test

**Figure 7: Kaplan-Meier Curve of Overall Survival in CELESTIAL**



**Figure 8: Kaplan-Meier Curve of Progression-Free Survival in CELESTIAL**



### 14.3 Differentiated Thyroid Cancer

The efficacy of CABOMETYX was evaluated in COSMIC-311 (NCT03690388), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with locally advanced or metastatic differentiated thyroid cancer (DTC) that had progressed following prior VEGFR-targeted therapy and were radioactive iodine-refractory or ineligible. Patients were randomized to receive CABOMETYX 60 mg orally once daily or placebo with supportive care until disease progression or unacceptable toxicity. Randomization was stratified by prior receipt of lenvatinib (yes vs. no) and age ( $\leq 65$  years vs  $>65$  years). Eligible patients randomized to placebo were allowed to cross-over to CABOMETYX upon confirmation of progressive disease by blinded independent radiology review committee (BIRC). The multiple primary efficacy outcome measures were progression-free survival (PFS) in the ITT population, and overall response rate (ORR) in the first 100 randomized patients, as assessed by BIRC per RECIST 1.1. Tumor assessments were conducted every 8 weeks. Overall survival (OS) was a descriptive outcome measure.

The primary analysis of PFS included 187 randomized patients. An updated analysis of PFS was performed and included 258 randomized patients. The median age was 65 years (range 31 to 85 years), 53% were female, 70% were White, 19% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib. Baseline ECOG performance status was 0 (46%) or 1 (54%) and 93% of patients had metastatic disease.

The trial demonstrated a statistically significant improvement in PFS, while it failed to demonstrate a statistically significant improvement in ORR, for patients randomized to CABOMETYX compared with placebo. Efficacy results are summarized in Table 23 and Figure 9.

**Table 23: Efficacy Results from COSMIC-311**

	Primary Analysis		Updated Analysis <sup>1</sup>	
	CABOMETYX (n=125)	Placebo (n=62)	CABOMETYX (n=170)	Placebo (n=88)
<b>Progression-Free Survival</b>				
Number of Events, (%)	31 (25)	43 (69)	62 (36)	69 (78)
Median PFS in Months (95% CI)	NR (5.7, NE)	1.9 (1.8, 3.6)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)
Hazard Ratio (95% CI) <sup>2</sup>	0.22 (0.14, 0.35)		0.22 (0.15, 0.31)	
p-value <sup>3</sup>	<0.0001			
<b>Overall Response Rate (95% CI)</b>				
Overall Response, % (95% CI) <sup>4, 5</sup>	15% (7%, 26%)	0% (0.0%, 11%)	18% (10%, 29%)	0% (0.0%, 11%)
p-value <sup>6</sup>	0.0281			

CI, confidence interval; NR, not reached; NE, not evaluable

<sup>1</sup> No formal statistical testing was conducted at the time of the updated analysis

<sup>2</sup> Estimated using the Cox proportional-hazard model

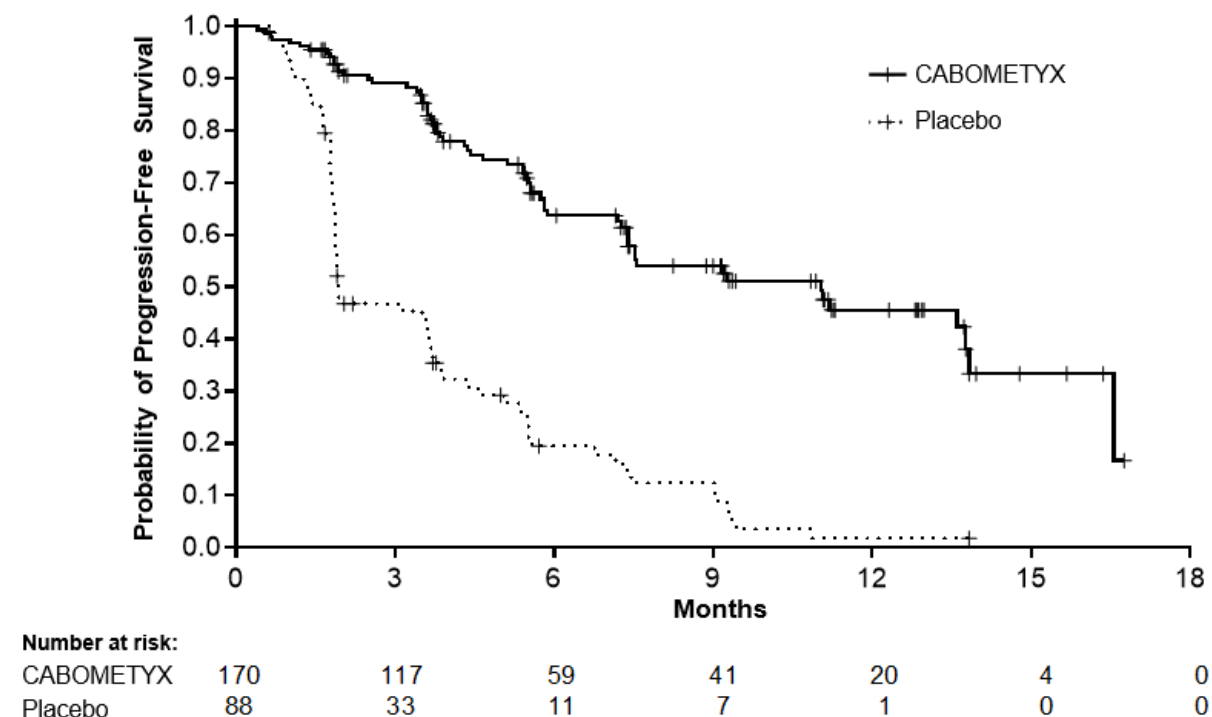
<sup>3</sup> Log-rank test stratified by receipt of prior lenvatinib (yes vs no) and age ( $\leq 65$  years vs  $>65$  years)

<sup>4</sup> All responses were partial responses

<sup>5</sup> The analysis population overall response rate was the first 100 randomized patients (67 in the CABOMETYX arm, and 33 in the placebo arm)

<sup>6</sup> Fisher's exact test compared to an alpha boundary of 0.01

**Figure 9: Kaplan-Meier Curve of Progression-Free Survival in COSMIC-311 (Updated Analysis, N=258)**



## 14.4 Neuroendocrine Tumors

### *Pancreatic Neuroendocrine Tumors*

The efficacy of CABOMETYX for the treatment of pancreatic neuroendocrine tumors (pNET) was evaluated in CABINET (NCT03375320), a randomized, double-blind, placebo-controlled, multicenter study in patients with unresectable, locally advanced or metastatic pNET that had progressed on prior therapy. Eligible patients were required to have been previously treated with at least one FDA approved therapy (everolimus, sunitinib, or lutetium Lu 177 dotatate), other than somatostatin analogs. Patients with active brain metastases or cranial epidural disease, and those who had prior treatment with cabozantinib were excluded. The study also excluded patients with clinically significant gastrointestinal (GI) bleeding, GI abnormalities, and tumor with invasion into the GI tract that may increase the risk for GI bleeding or perforation, and patients with tumor invading or encasing major blood vessels. Patients were randomized (2:1) to receive treatment with CABOMETYX 60 mg orally once daily or placebo until disease progression or unacceptable toxicity. Randomization was stratified by concurrent somatostatin analog (SSA) use (yes/no) and prior sunitinib therapy (yes/no). Tumor assessments were performed every 12 weeks. The study included patients with functional and non-functional tumors, and use of somatostatin analogs at a stable dose was permitted for symptom control. Eligible patients randomized to the placebo arm were allowed to crossover to CABOMETYX upon confirmation of progressive disease by blinded real time central review.

The major efficacy outcome measure was progression-free survival (PFS) assessed by blinded independent radiology review committee (BIRC) per RECIST 1.1. Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS).

A total of 99 pNET patients were randomized (2:1) to receive CABOMETYX 60 mg orally once daily (n=66) or placebo (n=33). The median age was 60 years (range: 29 to 79); 57% were male; 83% were White, 6% Black or African American, 4.0% Asian, 1.0% American Indian or Alaska Native, 1.0% Native Hawaiian or other Pacific Islander, 1.0% multiple races, 4.0% not reported or unknown; and 5% were Hispanic or Latino. In the 99 patients with pNET, 27% had received one prior systemic therapy, 26% had received two prior systemic therapies and 46% had received three or more prior systemic therapies.

As recommended by the Data and Safety Monitoring Board, the CABINET study was unblinded prior to the final prespecified efficacy analysis and all patients remaining on the placebo arm were permitted to crossover to treatment with cabozantinib. At the time of unblinding, the trial demonstrated a statistically significant improvement in PFS assessed by BIRC for CABOMETYX compared to placebo. An updated OS analysis was conducted when 49 deaths were observed. OS data were not mature with 32 (48%) deaths in CABOMETYX arm and 17 (52%) deaths in placebo arm (OS HR=1.01 [95% CI: 0.55, 1.83]). Fifty-two percent of placebo arm patients crossed over to open label CABOMETYX, which may impact the OS endpoint.

Efficacy results are summarized in Table 24 and Figure 10.

**Table 24: Efficacy Results in Patients with pNET in CABINET**

	<b>CABOMETYX (N=66)</b>	<b>Placebo (N=33)</b>
<b>Progression-Free Survival (PFS)</b>		
Number of events (%)	33 (50)	26 (79)
Median (95% CI) <sup>1</sup> , in months	13.8 (8.9, 17.0)	3.3 (2.8, 5.7)
Hazard Ratio (95% CI) <sup>2</sup>	0.22 (0.12, 0.41)	
p-value <sup>3</sup>	<0.0001	
<b>Overall Response Rate (ORR)</b>		
ORR (95% CI) <sup>4</sup> , %	18 (10, 30)	0 (0, 11)
<b>Duration of Response (DOR)</b>		
Median (95% CI) <sup>1</sup> , in months	11.4 (6.1, NE)	NE

CI, confidence interval; NE, not evaluable

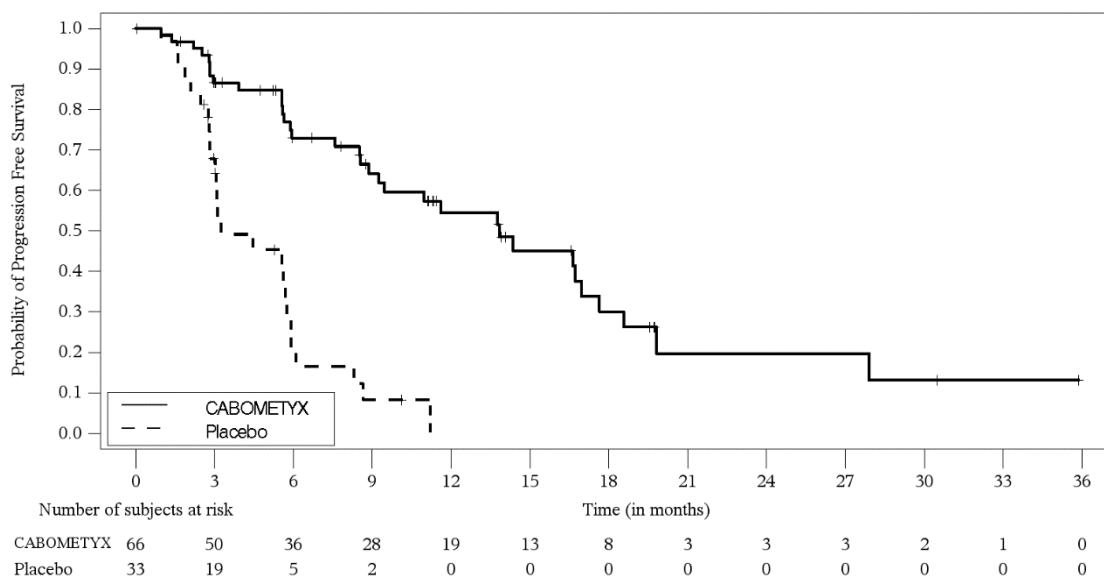
<sup>1</sup> Kaplan-Meier method

<sup>2</sup> Stratified Cox proportional hazards model stratified by concurrent somatostatin analog (SSA) use (yes/no) and prior sunitinib therapy (yes/no)

<sup>3</sup> Stratified log-rank test stratified by concurrent somatostatin analog (SSA) use (yes/no) and prior sunitinib therapy (yes/no) (compared to one-sided alpha=0.001)

<sup>4</sup> Clopper-Pearson method

**Figure 10: Kaplan-Meier Curve of Progression-Free Survival in Patients with pNET in CABINET**



### *Extra-Pancreatic Neuroendocrine Tumors*

The efficacy of CABOMETYX for the treatment of extra-pancreatic neuroendocrine tumors (epNET) was evaluated in CABINET (NCT03375320), a randomized, double-blind, placebo-controlled, multicenter study in patients with unresectable, locally advanced or metastatic epNET that had progressed on prior therapy. Eligible patients were required to have been previously treated with at least one FDA approved therapy (everolimus or lutetium Lu 177 dotatate), other than somatostatin analogs. Patients with active brain metastases or cranial epidural disease, and those who had prior treatment with cabozantinib were excluded. The study also excluded patients with clinically significant gastrointestinal (GI) bleeding, GI abnormalities, and tumor with invasion into the GI tract that may increase the risk for GI bleeding or perforation, and patients with tumor invading or encasing major blood vessels. Patients were randomized (2:1) to receive treatment with CABOMETYX 60 mg orally once daily or placebo until disease progression or unacceptable toxicity. Randomization was stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other). Tumor assessments were performed every 12 weeks. The study included patients with functional and non-functional tumors, and use of somatostatin analogs at a stable dose was permitted for symptom control. Eligible patients randomized to the placebo arm were allowed to crossover to CABOMETYX upon confirmation of progressive disease by blinded real time central review.

The major efficacy outcome measure was progression-free survival (PFS) assessed by blinded independent radiology review committee (BIRC) per RECIST 1.1. Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS).

A total of 199 epNET patients were randomized (2:1) to receive CABOMETYX 60 mg orally once daily (n=132) or placebo (n=67). The median age was 66 years (range: 28 to 86), 51% were female; 84% were White; 8% were Black or African American; 2.0% were Asian; 6% had race unknown or race not reported; and 8% were Hispanic or Latino. The primary sites of tumor were small bowel (34%) including duodenum, jejunum & ileum; lung (20%); thymus (5%); rectum (6%); cecum (2.0%); stomach (3.0%); non-cecum colon (1.0%); appendix (0.5%); others (18%); and unknown

(12%). In the 199 patients with epNET, 46% had received one prior systemic therapy, 29% had received two prior systemic therapies and 25% had received three or more prior systemic therapies.

The trial demonstrated a statistically significant improvement in PFS as assessed by BIRC, for CABOMETYX compared to placebo. An updated OS analysis was conducted when 123 deaths were observed. OS data were not mature with 83 (63%) deaths in CABOMETYX arm and 40 (60%) deaths in placebo arm (OS HR=1.05 [95% CI: 0.71, 1.54]). Thirty-seven percent of placebo arm patients crossed over to open label CABOMETYX, which may impact the OS endpoint.

Efficacy results are summarized in Table 25 and Figure 11.

**Table 25: Efficacy Results in Patients with epNET in CABINET**

	<b>CABOMETYX (N=132)</b>	<b>Placebo (N=67)</b>
<b>Progression-Free Survival (PFS)</b>		
Number of Events (%)	68 (52)	39 (58)
Median (95% CI) <sup>1</sup> , in months	8.5 (6.8, 12.5)	4.2 (3.0, 5.7)
Hazard Ratio (95% CI) <sup>2</sup>	0.40 (0.26, 0.61)	
p-value <sup>3</sup>	<0.0001	
<b>Overall Response Rate (ORR)</b>		
ORR (95% CI) <sup>4</sup> , %	5 (2.2, 11)	0 (0, 5)
<b>Duration of Response (DOR)</b>		
Median (95% CI) <sup>1</sup> , in months	8.3 (4.5, NE)	NE

CI, confidence interval; NE, not evaluable

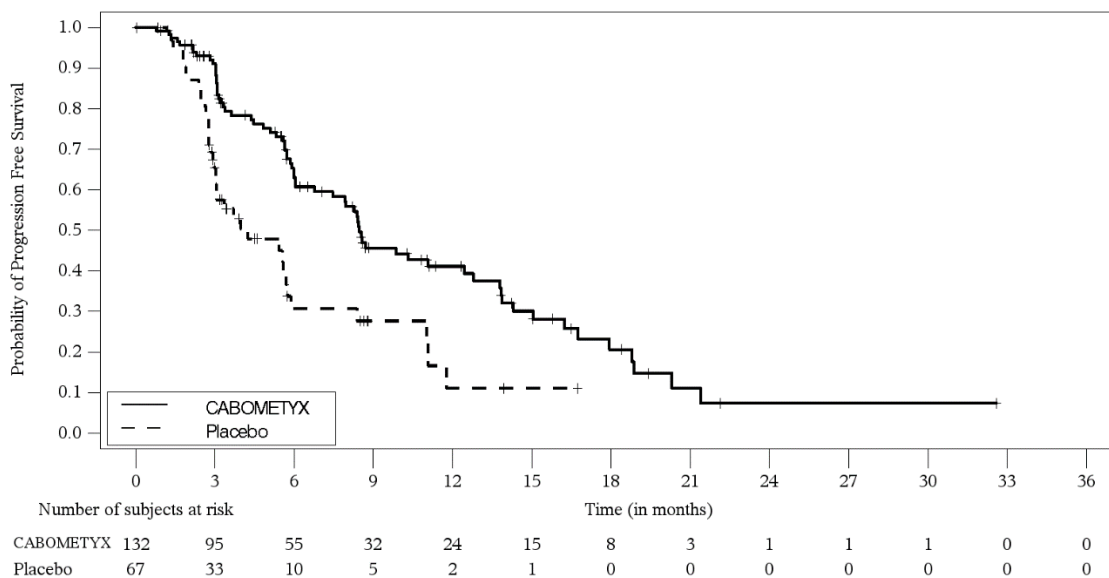
<sup>1</sup> Kaplan-Meier method

<sup>2</sup> Stratified Cox proportional hazards model stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other)

<sup>3</sup> Stratified log-rank test stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other) (compared to one-sided alpha=0.001)

<sup>4</sup> Clopper-Pearson method

**Figure 11: Kaplan-Meier Curve of Progression-Free Survival in Patients with epNET in CABINET**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

CABOMETYX tablets are supplied as follows:

60 mg tablets are yellow film-coated, oval shaped with no score, debossed with “XL” on one side and “60” on the other side of the tablet; available in:

bottle of 30 tablets:

NDC 42388-023-26

bottle of 30 tablets packaged in a carton: NDC 42388-023-46

40 mg tablets are yellow film-coated, triangle shaped with no score, debossed with “XL” on one side and “40” on the other side of the tablet; available in:

bottle of 30 tablets:

NDC 42388-025-26

bottle of 30 tablets packaged in a carton: NDC 42388-025-46

20 mg tablets are yellow film-coated, round shaped with no score, debossed with “XL” on one side and “20” on the other side of the tablet; available in:

bottle of 30 tablets:

NDC 42388-024-26

bottle of 30 tablets packaged in a carton: NDC 42388-024-46

Store CABOMETYX at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

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

- **Hemorrhage:** Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage [see *Warnings and Precautions (5.1)*].
- **Perforations and fistulas:** Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX [see *Warnings and Precautions (5.2)*].
- **Thromboembolic events:** Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs [see *Warnings and Precautions (5.3)*].
- **Hypertension and hypertensive crisis:** Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension [see *Warnings and Precautions (5.4)*].
- **Diarrhea:** Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements [see *Warnings and Precautions (5.5)*].
- **Palmar-plantar erythrodysesthesia:** Advise patients to contact their healthcare provider for progressive or intolerable rash [see *Warnings and Precautions (5.6)*].
- **Hepatotoxicity:** Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding [see *Warnings and Precautions (5.7)*].
- **Adrenal insufficiency:** Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency [see *Warnings and Precautions (5.8)*].
- **Proteinuria:** Advise patients to contact their healthcare provider for signs or symptoms of proteinuria [see *Warnings and Precautions (5.9)*].
- **Osteonecrosis of the jaw:** Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw [see *Warnings and Precautions (5.10)*].
- **Impaired wound healing:** Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see *Dosage and Administration (2.1), Warnings and Precautions (5.11)*].

- Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function [see *Warnings and Precautions (5.12)*].
- Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction [see *Warnings and Precautions (5.13)*].
- Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia [see *Warnings and Precautions (5.14)*].
- Embryo-fetal toxicity:
  - Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.15), Use in Specific Populations (8.1)*].
  - Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose [see *Use in Specific Populations (8.3)*].
- Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose [see *Use in Specific Populations (8.2)*].
- Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort [see *Drug Interactions (7.1)*].

#### Important administration information

- Instruct patients to take CABOMETYX on an empty stomach, at least 1 hour before or at least 2 hours after eating.

Manufactured for Exelixis, Inc. Alameda, CA 94502

**PATIENT INFORMATION**  
**CABOMETYX® (Ka-boe-met-iks)**  
**cabozantinib**  
**tablets**

If your healthcare provider prescribes CABOMETYX in combination with nivolumab, also read the Medication Guide that comes with nivolumab.

**What is CABOMETYX?**

CABOMETYX is a prescription medicine used to treat:

- people with kidney cancer (renal cell carcinoma). CABOMETYX may be used:
  - alone to treat people with renal cell carcinoma (RCC) that has spread (advanced RCC).
  - in combination with nivolumab when your cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
- people with liver cancer (hepatocellular carcinoma) who have been previously treated with the medicine sorafenib.
- adults and children 12 years of age and older who have a type of thyroid cancer called differentiated thyroid cancer (DTC) that has spread (locally advanced or metastatic), **and**,
  - has progressed after treatment with a VEGFR-targeted treatment, **and**
  - your DTC can no longer be treated with radioactive iodine, or you are not able to receive radioactive iodine treatment.
- adults and children 12 years of age and older who have a type of cancer called pancreatic neuroendocrine tumors (pNET) or extra-pancreatic neuroendocrine tumors (epNET) that has been previously treated, cannot be treated by surgery, and has spread (locally advanced or metastatic).

It is not known if CABOMETYX is safe and effective in children younger than 12 years of age.

**Before you take CABOMETYX**, tell your healthcare provider about all of your medical conditions, including if you:

- have had a liver problem other than liver cancer
- have a recent history of bleeding, including coughing up or vomiting blood, or black tarry stools.
- have an open or healing wound
- have high blood pressure
- have a low calcium level in your blood (hypocalcemia)
- plan to have any surgery, dental procedure, or have had a recent surgery. You should stop taking CABOMETYX at least 3 weeks before planned surgery. See **“What are the possible side effects of CABOMETYX?”**
- are pregnant, or plan to become pregnant. CABOMETYX can harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider will check your pregnancy status before you start treatment with CABOMETYX.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment and for 4 months after your last dose of CABOMETYX.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if CABOMETYX passes into your breast milk. Do not breastfeed during treatment and for 4 months after your last dose of CABOMETYX.

**Tell your healthcare provider about all the medicines you take**, including prescription or over-the-counter medicines, vitamins, and herbal supplements. CABOMETYX and certain other medicines may affect each other causing side effects.

**How should I take CABOMETYX?**

- Take CABOMETYX exactly as your healthcare provider tells you to take it.

- **Do not** take CABOMETYX with food. Take CABOMETYX at least 1 hour before or at least 2 hours after eating.
- Swallow CABOMETYX tablets whole.
- **Do not** crush, chew or split CABOMETYX tablets.
- If you miss a dose and your next scheduled dose is in less than 12 hours, take your next dose at the normal time. Do not make up the missed dose.

**What should I avoid while taking CABOMETYX?**

Avoid drinking grapefruit juice, eating grapefruit or taking supplements that contain grapefruit or St. John's wort during treatment with CABOMETYX.

**What are the possible side effects of CABOMETYX?**

**CABOMETYX may cause serious side effects, including:**

- **bleeding (hemorrhage).** CABOMETYX can cause severe bleeding that may lead to death. Tell your healthcare provider right away if you get any signs of bleeding during treatment with CABOMETYX, including:
  - coughing up blood or blood clots
  - vomiting blood or if your vomit looks like coffee-grounds
  - red or black (looks like tar) stools
  - menstrual bleeding that is heavier than normal
  - any unusual or heavy bleeding
- **a tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula).** Tell your healthcare provider right away if you get tenderness or pain in your stomach-area (abdomen) that is severe or that does not go away.
- **blood clots, stroke, heart attack, and chest pain.** Get emergency help right away if you get:
  - swelling or pain in your arms or legs
  - shortness of breath
  - feel lightheaded or faint
  - sweating more than usual
  - numbness or weakness of your face, arm or leg, especially on one side of your body
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking
  - dizziness, loss of balance or coordination
  - a sudden severe headache
- **high blood pressure (hypertension).** Hypertension is common with CABOMETYX and sometimes can be severe. Your healthcare provider will check your blood pressure before starting CABOMETYX and regularly during treatment with CABOMETYX. If needed, your healthcare provider may prescribe medicine to treat your high blood pressure. Tell your healthcare provider if you develop severe headaches, nose bleeds, tiredness or confusion, vision changes, chest pain, trouble breathing, irregular heartbeat, or blood in your urine.
- **diarrhea.** Diarrhea is common with CABOMETYX and can be severe. If needed, your healthcare provider may prescribe medicine to treat your diarrhea. Tell your healthcare provider right away if you have frequent loose, watery bowel movements.
- **a skin problem called hand-foot skin reaction.** Hand-foot skin reactions are common with CABOMETYX and can be severe. Tell your healthcare provider right away if you have rashes, redness, pain, swelling, or blisters on the palms of your hands or soles of your feet.
- **liver problems.** Liver problems may happen during treatment with CABOMETYX. When CABOMETYX is taken in combination with nivolumab, severe changes in liver function tests may happen more often than if you take CABOMETYX alone. Your healthcare provider will do blood tests to check your liver function before and during treatment with CABOMETYX. Tell your healthcare provider right away if you develop symptoms of liver problems including: yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach-area (abdomen), dark urine, bleeding or bruising more easily than normal.
- **adrenal gland problems.** Your healthcare provider will monitor you for this problem. Your healthcare provider may prescribe hormone replacement therapy or corticosteroid medicines if

needed. Tell your healthcare provider right away if you develop any of the following signs or symptoms: extreme tiredness, dizziness or fainting, weakness, nausea, or vomiting.

- **protein in your urine and possible kidney problems.** Symptoms may include swelling in your hands, arms, legs, or feet. Your healthcare provider will check you for this problem during treatment with CABOMETYX.
- **severe jaw bone problems (osteonecrosis).** Your healthcare provider should examine your mouth before you start and during treatment with CABOMETYX. Tell your dentist that you are taking CABOMETYX. It is important for you to practice good mouth care during treatment with CABOMETYX. Tell your healthcare provider right away if you develop any symptoms of jaw problems, including: jaw pain, toothache, or sores on your gums.
- **wound healing problems.** Wound healing problems have happened in people who take CABOMETYX. Tell your healthcare provider if you plan to have any surgery before or during treatment with CABOMETYX.
  - You should stop taking CABOMETYX at least 3 weeks before planned surgery.
  - Your healthcare provider should tell you when you may start taking CABOMETYX again after surgery.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen during treatment with CABOMETYX. Tell your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.
- **change in thyroid function.** CABOMETYX can cause changes in your thyroid function, including changes to thyroid hormone levels in your blood. Your healthcare provider will do blood tests to check your thyroid function before and during treatment with CABOMETYX.
- **decreased calcium level in your blood (hypocalcemia).** CABOMETYX can cause you to have a decreased amount of calcium in your blood. Your healthcare provider will do blood tests to check you for this problem and give you calcium if needed. **Tell your healthcare provider right away if you get any of the following signs or symptoms:**
  - muscle stiffness or muscle spasms
  - numbness or tingling in your fingers, toes, or around your mouth
  - seizures
  - sudden weight gain
  - swelling of your arms, hands, legs, and ankles

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with CABOMETYX if you have certain side effects.

**The most common side effects of CABOMETYX include:**

- tiredness
- nausea and vomiting
- constipation
- decreased appetite
- weight decreased

**The most common side effects of CABOMETYX when used in combination with nivolumab include:**

- tiredness
- mouth sores
- rash
- low thyroid hormone levels (hypothyroidism)
- pain in muscles, bones, and joints
- decreased appetite
- nausea
- changes in the way things taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

CABOMETYX may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of CABOMETYX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store CABOMETYX?**

- Store CABOMETYX at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep CABOMETYX and all medicines out of the reach of children.**

**General information about the safe and effective use of CABOMETYX.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CABOMETYX for a condition for which it was not prescribed. Do not give CABOMETYX to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about CABOMETYX that is written for health professionals.

**What are the ingredients in CABOMETYX?**

**Active ingredient:** cabozantinib

**Inactive ingredients:** microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

Manufactured for Exelixis, Inc. Alameda, CA 94502

For more information, go to [www.cabometyx.com](http://www.cabometyx.com) or call 1-855-292-3935.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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