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

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)

DOSAGE AND ADMINISTRATION

- Stop treatment with CABOMETYX at least 3 weeks prior to scheduled surgery, including dental surgery (2.1)
- Do NOT substitute CABOMETYX tablets with cabozantinib capsules (2.1).
- Recommended Dose:
  - 60 mg orally, once daily. (2.2, 2.3)
  - 40 mg orally, once daily, in pediatric patients with BSA less than 1.2 m^2 (2.4)
  - 40 mg orally, once daily, administered in combination with nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks (2.2)
- Administer at least 1 hour before or at least 2 hours after eating. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, 40 mg, and 60 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 ≤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 ≤ 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 (≥ 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*.

DRUG INTERACTIONS

- Strong CYP3A4 inhibitors: Reduce the CABOMETYX dosage if coadministration cannot be avoided. (2.6, 7.1)
- Strong CYP3A4 inducers: Increase the CABOMETYX dosage if coadministration cannot be avoided. (2.7, 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. (2.8, 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: 09/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

5.8 Adrenal Insufficiency

CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity *[see Dosage and Administration (2.5)]*.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 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 ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome *[see Dosage and Administration (2.5)]*.

5.10 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (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 (2.5)]*.

5.11 Impaired Wound Healing

Wound complications occurred with CABOMETYX *[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

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

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX: as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), and 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m^2 every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

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.

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 ≥ 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 ≥ 5% of patients were

Adverse Reaction	CABOMETYX (n=331) [1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] 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
[5] 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
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9

Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	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
[1] 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 (≥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[1]	**Grade 3-4[1]**
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0

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) ≥ 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.

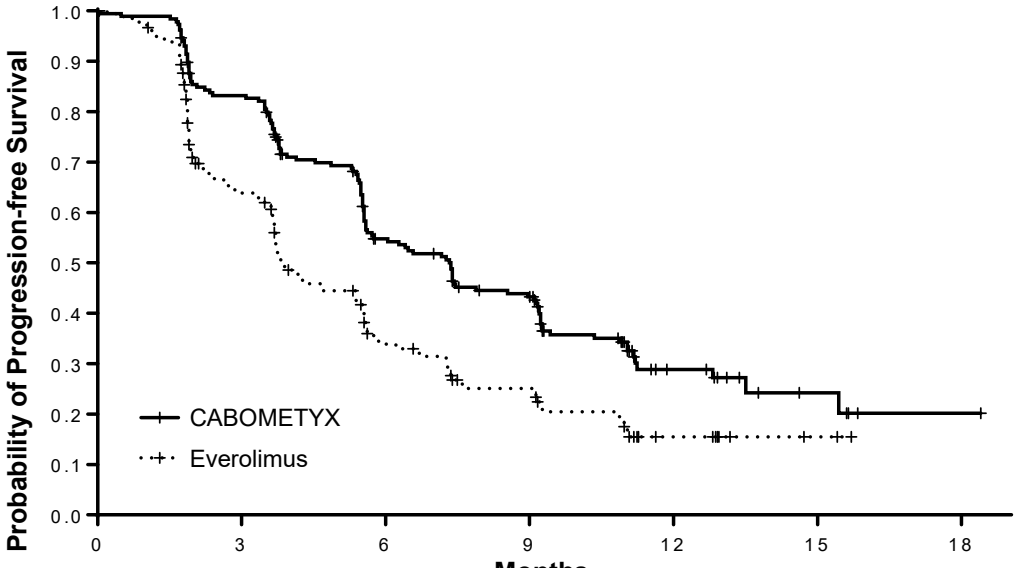
Statistically significant improvements in PFS, OS, and ORR were demonstrated for CABOMETYX compared to everolimus. Efficacy results are presented in Tables 14 and 15 and Figures 1 and 2.

Table 14: 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[1]	0.58 (0.45, 0.74), p<0.0001	

[1] 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)



Number at risk:

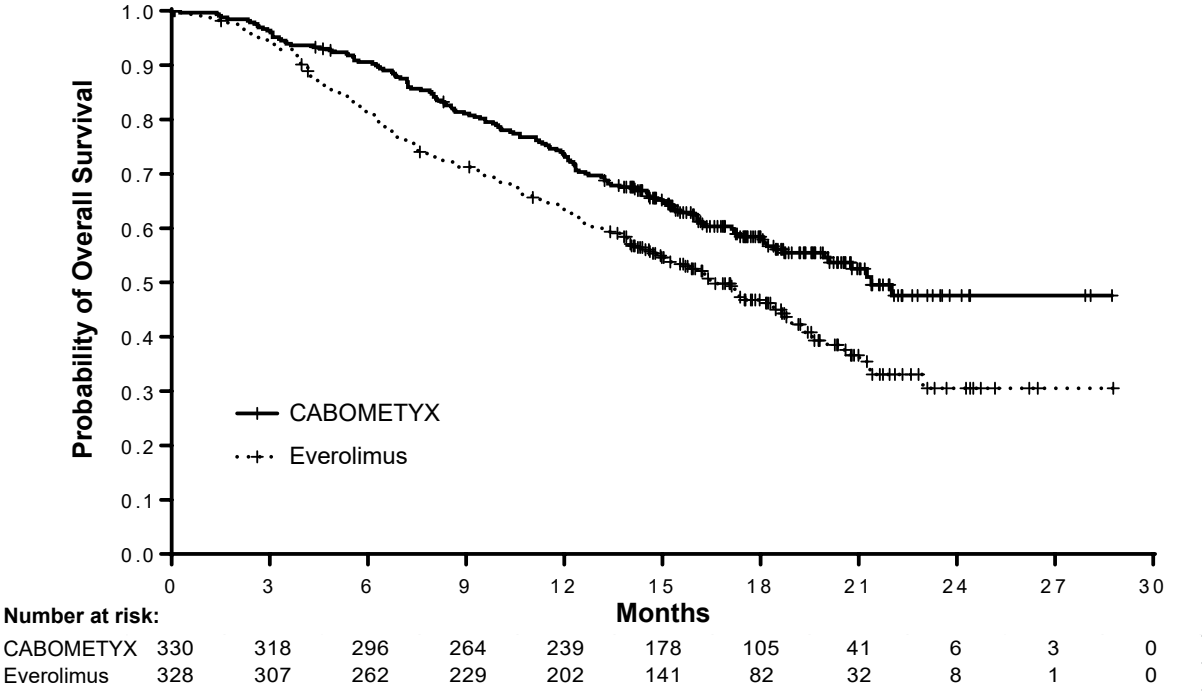
CABOMETYX	187	152	92	68	20	6	2
Everolimus	188	99	46	29	10	2	0

Table 15: 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[1]	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value[2]	p<0.0001	

[1] 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)
[2] 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 (≥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).

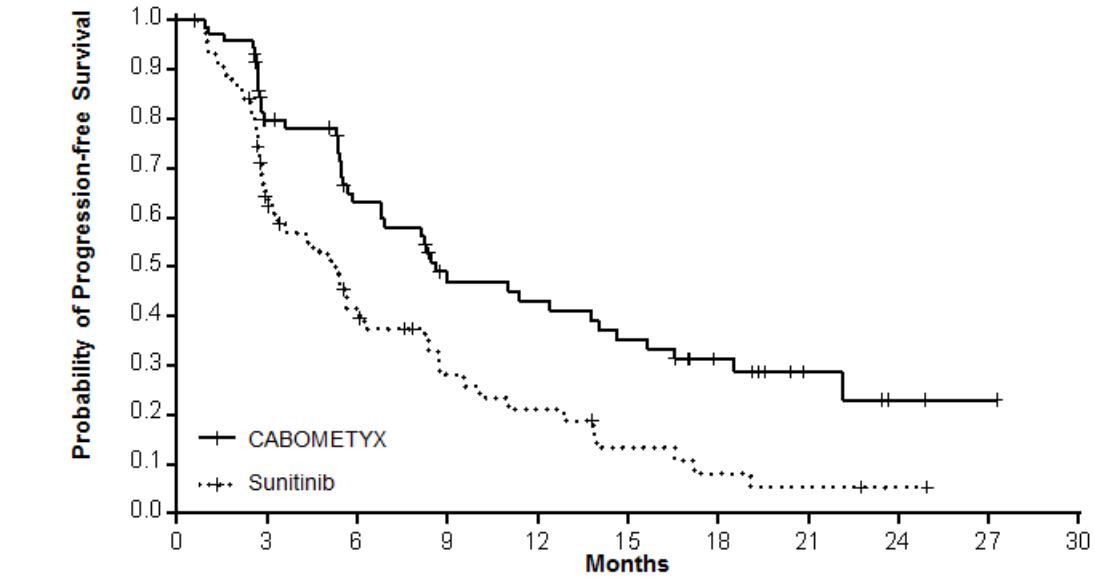
A statistically significant improvement in PFS, as assessed by a blinded independent radiology review committee, was demonstrated for CABOMETYX compared to sunitinib. Efficacy results are presented in Table 16, Figure 3, and Figure 4.

Table 16: Efficacy Results in CABOSUN

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

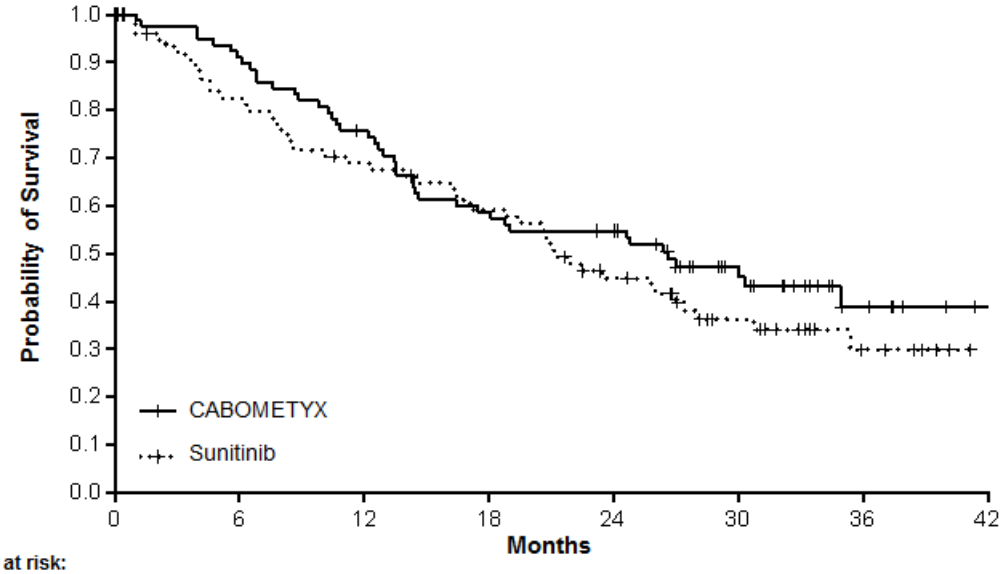
[1] as assessed by a retrospective blinded independent radiology review committee (BIRC)
[2] estimated from stratified Cox proportional hazards model with stratification factors IMDC risk group and presence of bone metastases and treatment as covariate
[3] two-sided stratified log-rank test with stratification factors IMDC risk group and presence of bone metastases
[4] no multiplicity adjustments were made for overall survival or ORR

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



Number at risk:											
CABOMETYX	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

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



Number at risk:								
CABOMETYX	79	71	58	45	41	23	8	2
Sunitinib	78	61	50	42	29	17	6	0

Important administration information

- Instruct patients to take CABOMETYX 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.

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 final 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 final 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 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
- decreased appetite
- nausea and vomiting
- weight loss
- constipation

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 or call 1-855-292-3935.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 09/2021