A SUPPLEMENT TO
FEDERAL PRACTITIONER

A Second-Line Treatment Option for Hepatocellular Carcinoma

Including a Retrospective Exploratory Subgroup Analysis of HCC Patients with Child-Pugh B Cirrhosis

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Introduction

Liver cancer is the sixth most commonly diagnosed cancer, and the third leading cause of cancer-related deaths worldwide.[1] According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, liver cancer is the thirteenth most common cause of cancer-related death in the United States, and in 2023, 41,210 new cases and 29,300 deaths are estimated to occur.[2]

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for approximately 90% of cases.[3-5] Although HCC is clinically heterogenous,[5] the strongest risk factor for developing HCC is cirrhosis from any etiology, including chronic alcohol consumption, metabolic dysfunction associated steatotic liver disease (MASLD; formerly referred to as nonalcoholic fatty liver disease) associated with obesity or diabetes, and infection with either hepatitis B (HBV) or C virus (HCV).[3,4,6]

Although the proportion of patients with HCC with HBV or HCV infection is declining in areas with dedicated viral hepatitis elimination programs, MASLD is becoming a growing health concern, related to significant increases in the prevalence of obesity and metabolic syndrome. MASLD is currently the fastest growing cause of HCC in liver transplant (LT) candidates.[7]

HCC in US Veterans

The rate of HCC in US Veterans is approximately 5 times greater than the rate in the general population.[8] Veterans Affairs (VA) enrollees show a higher incidence of HCC because they have a higher rate of the most important risk factors: HCV and MASLD.[8] The incidence of HCC in the Veterans Health Administration (VHA) has been examined by several retrospective cohort studies. One cohort study included 21,326 patients who were diagnosed with HCC and received VA health care between 2001 and 2013.[9] Of the 7670 patients who were treated for HCC in 2013, 68% (5225) had HCV, and 61.3% with HCV-related HCC also had an alcohol-related diagnosis. Incident cases of HCC in the overall veteran population increased from 17 per 100,000 in 2002 to 45 per 100,000 in 2012, driven primarily by HCV-related HCC.[9]

A subsequent retrospective study of US Veterans from 2014 to 2016 demonstrated that despite highly successful HCV eradication efforts within the VHA, patients with established cirrhosis prior to HCV had

Disclosure

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INDICATION

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

IMPORTANT SAFETY INFORMATION

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

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Table 1. Baseline Patient and Disease Characteristics in the CELESTIAL trial[23,24]

	Patients, n (%)		Patients, n (%)	
	Overall population		Child-Pugh B subgroup	
Characteristic	**CABOMETYX (N=470)**	**Placebo (N=237)**	**CABOMETYX (N=51)**	**Placebo (N=22)**
Age (years)				
Median (range)	64 (22-86)	64 (24-86)	63.0 (22-82)	64.5 (50-85)
Sex				
Male, n (%)	379 (82)	202 (85)	45 (88)	20 (91)
Geographic region				
Asia, including Hong Kong, South Korea, Singapore, Taiwan	116 (25)	59 (25)	14 (27)	3 (14)
Europe	231 (49)	108 (46)	21 (41)	12 (55)
United States and Canada	108 (23)	59 (25)	15 (29)	6 (27)
Australia and New Zealand	15 (3)	11 (5)	1 (2)	1 (5)
ECOG performance status				
0/1/2	245 (52)/ 224 (48)/ 1 (<1)	131 (55)/ 106 (45)/0	27 (53)/ 24 (47)/0	12 (55)/ 10 (45)/0
Etiology of liver disease[a]				
HBV	178 (38)	89 (38)	18 (35)	6 (27)
HCV	113 (21)	55 (23)	16 (31)	4 (18)
HBV and HCV	8 (2)	4 (2)	NR	NR
Alcohol use	112 (24)	39 (16)	19 (37)	4 (18)
MASLD	43 (9)	23 (10)	3 (6)	2 (9)
Other	24 (5)	16 (7)	NR	NR
Unknown	75 (16)	47 (20)	-	-
Alpha-fetoprotein				
<400 ng/mL	278 (59)	136 (57)	31 (61)	16 (73)
≥400 ng/mL	192 (41)	101 (43)	20 (39)	6 (27)

a substantial residual risk of HCC for up to 10 years after achieving a sustained virologic response to HCV treatment.[10,11]

In a more recent national VA quality improvement project based on 2021 data, the most common etiologies for liver disease among patients with HCC were cured HCV (47%), followed by MASLD (31%), alcohol use (16%), and active HCV (16%).[12] Cirrhosis was documented in 77% of patients. Findings from this detailed chart review of Veterans newly diagnosed with HCC revealed that the keys to improved survival were early-stage diagnosis, diagnosis in the VA system, and receipt of curative treatment—46% of Veterans were diagnosed at a later stage. Despite the complexity of HCC treatment decision-making, including multidisciplinary tumor board discussion and the need for community care referral at many centers, the median time from diagnosis to first treatment was only 37 days. The findings suggest that the high overall mortality of HCC is driven primarily by patients diagnosed at a later stage. However, once the diagnosis was made, treatment was reasonably expeditious.[12]

> **"Findings from this detailed chart review of Veterans newly diagnosed with HCC revealed that the key to improved survival were early-stage diagnosis, diagnosis in the VA system, and receipt of curative treatment...Despite the complexity of HCC treatment decision-making, the median time from diagnosis to first treatment was only 37 days. These findings suggest that the high overall mortality of HCC is driven primarily by patients diagnosed at a later stage but that once the diagnosis was made, treatment was reasonably expeditiously."[12]**

Prognosis

Although the overall survival (OS) rate has been increasing since 1975, the 5-year relative survival rate for liver cancer and intrahepatic bile duct cancer remains poor at 21.6%, according to SEER data.[2] Several factors influence HCC

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

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Table 1. (Cont'd)

	Patients, n (%) Overall population		Patients, n (%) Child-Pugh B subgroup	
Albumin				
<35 g/L	131 (28)	60 (25)	27 (53)	11 (50)
≥35 g/L	339 (72)	177 (75)	24 (47)	11 (50)
Bilirubin				
<22.23 µmol/L	421 (90)	221 (93)	40 (78)	20 (91)
≥22.23 to <29.07 µmol/L	37 (8)	13 (5)	6 (12)	2 (9)
≥29.07 µmol/L	12 (3)	3 (1)	5 (10)	0
Child-Pugh class at baseline				
A	462 (98)	235 (99)	NR	NR
B[b]	7 (1)	2 (1)	NR	NR
BCLC stage[c]				
B (intermediate)	42 (9)	23 (10)		
C (advanced)	427 (91)	214 (90)		
Extrahepatic spread of disease and/or macrovascular invasion	398 (85)	200 (84)	47 (92)	17 (77)
Extrahepatic spread of disease	369 (79)	182 (77)	42 (82)	15 (68)
Macrovascular invasion	129 (27)	81 (34)	22 (43)	7 (32)
Number of prior systemic antIcancer reglmens for HCC				
1	335 (71)	174 (73)	34 (65)	13 (59)
2	130 (28)	62 (26)	16 (31)	9 (41)
≥3	2 (<1)	1 (<1)	1 (2)	0

AFP, alpha-fetoprotein; BCLC, Barcelona Liver Clinic Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B; HBC, hepatitis C; MASLD, metabolic dysfunction associated steatotic liver disease; NR, not reported.

[a]Etiological factors were obtained using case-report forms; some patients had more than one factor.

[b]A few patients had ECOG performance status of 2. Seven patients in the CABOMETYX group and 2 patients in the placebo group were Child-Pugh B at randomization, which was a protocol deviation.

[c]BCLC status was assigned retrospectively, using macrovascular invasion as a surrogate for portal vein invasion. One patient in the CABOMETYX group had unknown BCLC status.

prognosis, including stage at diagnosis, tumor biology, and liver function.[5]

Assessment of liver function/hepatic functional reserve traditionally uses the Child-Pugh classification, which incorporates serum albumin, bilirubin, and prothrombin time with clinical assessments of encephalopathy and ascites. This classification provides a general estimate of liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis and allows for estimating survival rates based on hepatic function in the setting of cirrhosis.[13,14]

The American Association for the Study of Liver Diseases (AASLD) recommends the use of the Barcelona Liver Clinic Cancer (BCLC) staging system to assess patients with HCC. The BCLC system incorporates objective scores on liver dysfunction and Eastern Cooperative Oncology Group (ECOG) performance status, and ranges from Stage 0 (very early stage) to Stage A through D (terminal).[7]

Treatment for HCC

Most cases of HCC are diagnosed at an advanced stage when few patients are eligible for potentially curative treatments.[15] For patients with unresectable or advanced disease who are not transplant candidates (BCLC Stage B or C), treatment options include systemic therapies as first- and second-line treatments, locoregional therapies, clinical trials, or best supportive care.[7,16]

Preferred National Comprehensive Cancer Network (NCCN) guideline-recommended first-line systemic therapies for HCC are atezolizumab plus bevacizumab or durvalumab plus tremelimumab. Other Category 1 recommended options are sorafenib, lenvatinib, or durvalumab.[7]

Several second-line therapies are NCCN Category 1 recommended following disease progression on first-line systemic therapy and are approved in patients previously treated with sorafenib which include regorafinib and cabozantinib.[17] Following is

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

more information on CABOMETYX® (cabozantinib) as a second-line therapy for HCC along with a review of a retrospective, exploratory subgroup analysis in patients who progressed from Child-Pugh A to Child-Pugh B while receiving CABOMETYX.

CABOMETYX Indication and Select Important Safety Information

CABOMETYX is indicated for the treatment of patients with HCC who have been previously treated with sorafenib.[18]

The warnings and precautions listed in the CABOMETYX prescribing information include: hemorrhage, gastrointestinal (GI) perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar–plantar erythrodysesthesia and (PPE) syndrome, proteinuria, osteonecrosis of the jaw, impaired wound healing, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, hypocalcemia, and embryo-fetal toxicity.[18] Please see additional important safety information throughout this supplement.

CABOMETYX Mechanism of Action

CABOMETYX is a multikinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, AXL, and MET based on in vitro biochemical and/or cellular assays.[19,20] Receptor tyrosine kinases have been shown to be involved in normal cellular functions and pathological processes including oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.[18] Aberrant signaling of MET and AXL has been linked to metastasis and progression.[19-21] Synergistic activation of MET and VEGFR can enhance proliferation and result in more robust tumor vasculature.[22] In addition, AXL has been shown to be a key regulator of innate immune system activity against tumors and high AXL expression in patients and has been linked to worse prognosis. Dysregulation of AXL can suppress immune-mediated destruction of cancer cells.[21,22]

CELESTIAL Trial

The CELESTIAL trial was a randomized, double-blind, placebo-controlled, phase 3 trial that evaluated the safety and efficacy of CABOMETYX in patients with HCC who were previously treated with sorafenib.[23] A total of 707 patients were randomized (2:1) to receive either CABOMETYX 60 mg once daily (n=470) or placebo (n=237) as long as they continued to receive clinical benefit from their assigned trial regimen or until they had unacceptable toxicity.

Patients were stratified based on etiological factor (presence or absence of HBV and/or HCV), geographic region (Asia or other), and evidence of extrahepatic spread of disease and/or macrovascular invasion. The primary endpoint was OS assessed from the time of randomization to the time of death from any cause. The secondary endpoints included progression-free survival (PFS) assessed from the time of randomization until radiographic progression or death from any cause, whichever occurred first, and the objective response rate, which was defined as the percentage of patients with a confirmed complete or partial response. Response evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used by investigators to assess tumor response and progression. Safety was assessed by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and the safety population comprised 704 patients.

Inclusion criteria included one prior treatment with sorafenib, but up to 2 prior systemic treatments could have been received; Child-Pugh A liver function; ECOG performance status of 0 or 1; and adequate hematologic measures and adequate renal function assessments. The study did not exclude patients based on bile duct invasion, main portal invasion, extensive liver involvement (>50%), prior immunotherapy, intolerance to prior systemic therapy, alpha-fetoprotein (AFP) level, or viral load.

Baseline patient and disease characteristics for individuals randomized per treatment arm in CELESTIAL are listed in **Table 1.** In general, the median age was 64 years (range 22-86), 81% were male, 56% were White, and 34% were Asian. HCC etiology was attributed to HBV (38%), HCV (21%), and other causes

Table 2. Child-Pugh B Scores at Week 8 in the CELESTIAL Trial[24,a]

	CABOMETYX (n)	Placebo (n)
Patients with Child-Pugh B	51	22
Patients with available BCDM-determined Child-Pugh B score points	42	21
7	26	11
8	11	3
9	3	5

[a]As Child-Pugh grading was investigator assessed and Child-Pugh scoring was determined independently by the Biostatistics and Clinical Data Management (BCDM) department at Exelixis, Inc, some discrepancies between grading and scoring results existed.[24]

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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(40%). All patients had received sorafenib previously, and 27% of the patients had received 2 prior systemic therapy regimens.[24] Patients who progressed to Child-Pugh B within the first 8 weeks of treatment remained in the trial until disease progression or unacceptable toxicity (51/470 patients in the CABOMETYX arm and 22/237 in the placebo arm) (**Table 2**).[24]

Median OS in the intent-to-treat population was 10.2 months (95% confidence interval [CI], 9.1-12.0) for the CABOMETYX group and 8.0 months (95% CI, 6.8-9.4) for the placebo group (stratified hazard ratio [HR] for death, 0.76; 95% CI, 0.63-0.92; *P*=0.0049). Median PFS was 5.2 months (95% CI, 4.0-5.5) and 1.9 months (95% CI, 1.9-1.9), respectively, (HR, 0.44, 95% CI, 0.36-0.52; *P*<0.0001).[18,23]

In a prespecified exploratory subgroup analysis, median OS for patients receiving CABOMETYX after only 1 prior therapy was 11.4 months for the CABOMETYX group and 7.7 months for the placebo group (stratified HR for death 0.74; 95% CI, 0.59-0.92) and median PFS was 5.5 months and 1.9 months, respectively (stratified HR for disease progression or death, 0.43; 95% CI, 0.35-0.52). No statistical procedure was employed for controlling type 1 error. Results should be considered hypothesis-generating.[23]

CELESTIAL: Safety Results

Adverse reactions occurring at a higher incidence in patients treated with CABOMETYX (between-arm difference of ≥5% [all grades]) included: gastrointestinal: diarrhea (54%), nausea (31%), vomiting (26%), stomatitis (13%), and dyspepsia (10%); general: fatigue (45%), asthenia (22%), and mucosal inflammation (14%); metabolism and nutrition: decreased appetite (48%); skin and subcutaneous tissue: PPE (46%), and rash (21%); vascular: hypertension (30%); investigations: weight decreased (17%); nervous system: dysgeusia (12%); endocrine: hyperthyroidism (8%), respiratory, thoracic and mediastinal: dysphonia (19%) and dyspnea (12%); and musculoskeletal and connnective tissue: pain in extremity (9%), and muscle spasms (8%).[18]

CELESTIAL: Post Hoc Retrospective Exploratory Analysis of Patients Who Progressed From Child-Pugh A to B by Week 8

It is important to note that most clinical trials on HCC do not enroll patients with poor liver function (Child-Pugh B or worse hepatic function) and that underlying cirrhosis represents a competing risk of death in these patients. For these reasons, systemic therapies supported by phase 3 clinical trials are lacking for this patient group, and data are limited for treating patients with HCC and Child-Pugh B cirrhosis.[24] Thus, a retrospective, exploratory subgroup analysis of patients enrolled in CELESTIAL was performed to explore the safety and efficacy of CABOMETYX in patients who progressed from Child-Pugh A liver cirrhosis to Child-Pugh B at week 8 of the study treatment.[24] Week 8 was the first planned assessment for liver function using Child-Pugh scoring and disease status using radiography. Patients were excluded from the retrospective analysis if they were either Child-Pugh A or Child-Pugh C at the week 8 assessment. Baseline patient and disease characteristics for this Child-Pugh B subgroup within CELESTIAL are listed in **Table 1.**

"It is important to note that most clinical trials on HCC do not enroll patients with poor liver function (Child-Pugh B or worse hepatic function) and that underlying cirrhosis represents a competing risk of death in these patients."

The most common contributors to the development of Child-Pugh B liver cirrhosis were point changes from baseline in the levels of albumin, bilirubin, and ascites. In addition, compared with the overall study population, patients in the Child-Pugh B subgroup tended to have numerically higher baseline albumin-bilirubin (ALBI) grades 2/3, microvascular invasion, and prior transarterial chemoembolization (TACE) for HCC. Additional descriptive differences for the Child-Pugh B subgroup included higher baseline rates of macrovascular invasion, extrahepatic spread, alpha-fetoprotein ≥400 ng/mL, and greater likelihood of HBV and HCV etiology in the CABOMETYX group than in the placebo group.[24]

Median OS when analyzed in the Child-Pugh B subgroup was 8.5 months for the CABOMETYX group and 3.8 months for the placebo group (HR, 0.32; 95% CI, 0.18-0.58; **Figure 1**). Median PFS was 3.7 months and 1.9 months, respectively (HR, 0.44, 95% CI, 0.25-0.76; **Figure 2**).[24] The observed outcomes of CABOMETYX treatment in patients with reduced liver function should be interpreted with caution because of the retrospective analyses and relatively small size of the Child-Pugh B subgroup. No statistical procedure was employed for controlling type 1 error, and the results are intended to be hypothesis-generating.

Discontinuation due to treatment-related adverse events (AEs) in the Child-Pugh B subgroup occurred in 9 patients (18%) in the CABOMETYX group and 1 patient (5%) in the placebo group. AEs occurring in >30% of patients who received CABOMETYX included decreased appetite, fatigue, diarrhea, nausea, and hypoalbuminemia (**Table 3**).[24]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

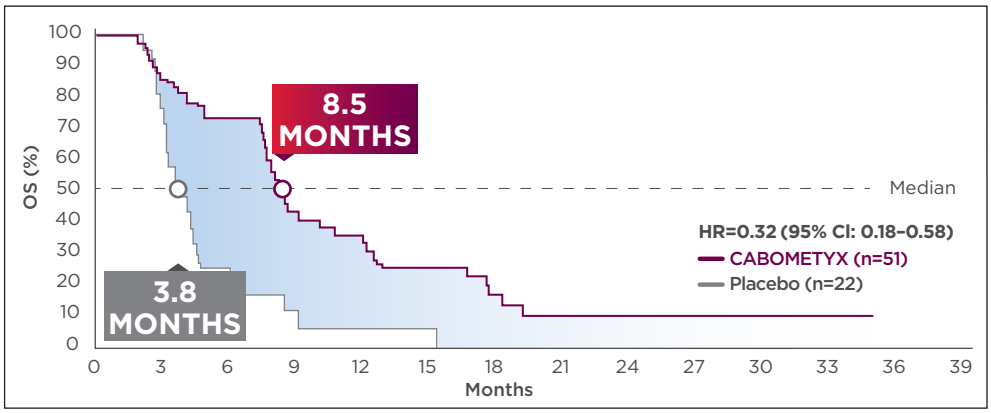
Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Retrospective exploratory subgroup analysis

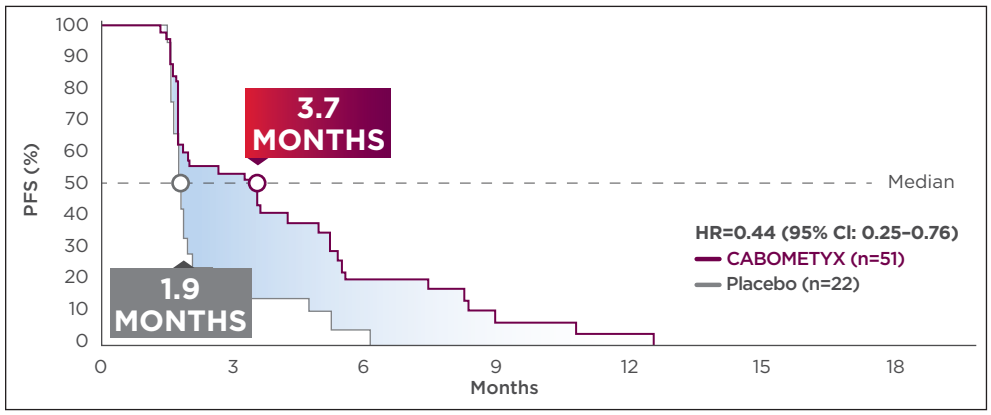
In patients whose liver cirrhosis progressed from Child-Pugh A to Child-Pugh B in CELESTIAL by Week 8[1,4]

Figure 1. Median OS in Child-Pugh B patients



Overall survival of the Child-Pugh B subgroup of CELESTIAL. OS, overall survival.

Figure 2. Median PFS in Child-Pugh B patients



Progression-free survival of the Child-Pugh B subgroup of CELESTIAL. PFS, progression-free survival.

The observed outcomes should be interpreted with caution because of the relatively small size of the Child-Pugh B subgroup. No statistical procedure was employed for controlling type I error. Results should be hypothesis-generating.

CABOMETYX Dosing

The recommended dosage of CABOMETYX is 60 mg once daily until disease progression or unacceptable toxicity.[18] It is recommended to reduce the starting dose of CABOMETYX to 40 mg once daily in patients with moderate hepatic impairment (Child-Pugh B), and to avoid the drug in those individuals with severe hepatic impairment (Child-Pugh C).[18]

The overall efficacy results of the CELESTIAL trial were achieved in the context of dose modifications. The median average daily dose was 35.8 mg for those receiving CABOMETYX in the overall population and 36.9 mg for patients receiving CABOMETYX in the Child-Pugh B subgroup.[23,24] For patients receiving CABOMETYX, the rates of dose reduction and discontinuation were 62% and 16% for the overall population and 61% and 18% for the Child-Pugh B subgroup, respectively.[23,24]

"NCCN guidelines recommend cabozantinib (CABOMETYX) as a Category 1 option for HCC following disease progression on first-line systemic therapy."

Guideline Recommendations for CABOMETYX Use

The AASLD recommends that CABOMETYX may be used as a second-line therapy in patients with preserved liver function (Child-Pugh A or well-selected Child-Pugh B cirrhosis) who develop HCC progression or intolerance with first-line systemic therapy (Level 5, Weak Recommendation).

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

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Table 3. Select Adverse Reactions Occurring in Patients (>30%) Who Progressed From Child-Pugh A to Child-Pugh B by Week 8 in the CELESTIAL Trial[24]

	CABOMETYX (n=51)		Placebo (n=22)	
All-causality AEs	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Any event	51 (100)	36 (71)	22 (100)	13 (59)
Decreased appetite	30 (59)	3 (5.9)	5 (23)	0 (0)
Fatigue	29 (57)	10 (20)	9 (41)	4 (18)
Diarrhea	24 (47)	3 (5.9)	6 (27)	1 (4.5)
Nausea	23 (45)	3 (5.9)	6 (27)	0 (0)
Ascites	17 (33)	7 (14)	12 (55)	5 (23)
Hypoalbuminemia	17 (33)	1 (2.0)	2 (9.1)	0 (0)

AEs, adverse events.

In addition, CABOMETYX is a preferred agent after sorafenib or lenvatinib if patients are not eligible for clinical trials (Level 1, Strong Recommendation).[13] The NCCN guidelines recommend cabozantinib (CABOMETYX) as a Category 1 option for Child-Pugh Class A patients, following disease progression on first-line systemic treatment.[16]

Summary

CABOMETYX is indicated for the treatment of patients with HCC who have been previously treated with sorafenib.[18] Results from the CELESTIAL trial, which demonstrated a survival benefit, supported this approval. Median OS was 10.2 months for the CABOMETYX group and 8.0 months for patients in the placebo group, and 11.4 months and 7.7 months, respectively, in a prespecified exploratory subgroup analysis of patients who only received 1 prior therapy.[23] Further, a retrospective, exploratory subgroup analysis showed patients who progressed from Child-Pugh A to Child-Pugh B at week 8 of treatment in CELESTIAL and received CABOMETYX had longer median OS than patients who received placebo (8.5 months vs 3.8 months).[24] The observed outcomes of CABOMETYX treatment in patients with reduced liver function should be interpreted with caution because of the retrospective analyses and relatively small size of the Child-Pugh B subgroup. No statistical procedure was employed for controlling type 1 error in these subgroup analyses, and, therefore, these results should be considered hypothesis-generating. The NCCN guidelines for hepatobiliary cancers include cabozantinib (CABOMETYX) as a Category 1 recommended subsequent-line treatment option for Child-Pugh A patients, following disease progression on first-line systemic treatment.[16]

References

1. World Health Organization. Globocan 2020: all cancers. Accessed June 4, 2023. https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf
2. National Cancer Institute Surveillance and End Results Program. Cancer stat facts: liver and intrahepatic bile duct cancer. 2023. Accessed June 6, 2023. https://seer.cancer.gov/statfacts/html/livibd.html
3. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers.* 2021;7(1):6.
4. Yao Z, Dai C, Yang J, et al. Time-trends in liver cancer incidence and mortality rates in the U.S. from 1975 to 2017: a study based on the surveillance, epidemiology, and end results database. *J Gastrointest Oncol.* 2023;14(1):312-324.
5. Dhanasekaran R, Bandoh S, Roberts LR. Molecular pathogenesis of hepatocellular carcinoma and impact of therapeutic advances. F1000Res. 2016;5.
6. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: Where are we? Where do we go? *Hepatology.* 2014;60(5):1767-1775.
7. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* 2023 May 22. [Online ahead of print]
8. Ju MR, Karalis JD, Chansard M, et al. Variation of hepatocellular carcinoma treatment patterns and survival across geographic regions in a Veteran population. *Ann Surg Oncol.* 2022;29(13):8413-8420.
9. Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US Veterans, 2001-2013. *Gastroenterology.* 2015;149(6):1471-1482.e1475; quiz e1417-1478.
10. Beste LA, Green P, Berry K, Belperio P, Ioannou GN. Hepatitis C–related hepatocellular carcinoma incidence in the Veterans Health Administration after introduction of direct-acting antivirals. *JAMA.* 2020;324(10):1003-1005.
11. Ioannou GN, Beste LA, Green PK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. *Gastroenterology.* 2019;157(5):1264-1278.e1264.
12. Rogal SS, Taddei T, Monto A, et al. Hepatocellular carcinoma diag-

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose

nosis and management in 2021: a national Veterans Affairs quality improvement project. *Clin Gastroenterol Hepatol.* 2023 Jul 15. [Online ahead of print]
13. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2021;19(5):541-565.
14. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open.* 2016;1(2):e000042.
15. Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: How hopeful should we be? *Oncologist.* 2006;11(7):790-800.
16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Hepatocellular Carcinoma Version 1.2023—March 10, 2023. Accessed July 20, 2023. https://www.nccn.org
17. Villarruel-Melquiades F, Mendoza-Garrido ME, García-Cuellar CM, Sánchez-Pérez Y, Pérez-Carreón JI, Camacho J. Current and novel approaches in the pharmacological treatment of hepatocellular carcinoma. *World J Gastroenterol.* 2023;29(17):2571-2599.
18. CABOMETYX (cabozantinib) Prescribing Information. Alameda, CA: Exelixis, Inc.
19. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. *Clin Cancer Res.* 2014;20(11):2959-2970.
20. Yakes FM, Chen J, Tan J, et al. Cabozantinib (xl184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther.* 2011;10(12):2298-2308.
21. Hsu CH, Huang YH, Lin SM, Hsu C. AXL and MET in hepatocellular carcinoma: a systematic literature review. *Liver Cancer.* 2022;11(2):94-112.
22. Santoni M, Iacovelli R, Colonna V, Klinz S, Mauri G, Nuti M. Antitumor effects of the multi-target tyrosine kinase inhibitor cabozantinib: a comprehensive review of the preclinical evidence. *Expert Rev Anticancer Ther.* 2021;21(9):1029-1054.
23. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018;379(1):54-63.
24. El-Khoueiry AB, Meyer T, Cheng AL, et al. Safety and efficacy of cabozantinib for patients with advanced hepatocellular carcinoma who advanced to Child-Pugh B liver function at study week 8: a retrospective analysis of the celestial randomised controlled trial. *BMC Cancer.* 2022;22(1):377.

For more information, visit: https://cabometyxhcp.com

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

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

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

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.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (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.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic 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.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-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. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. 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.

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.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

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.

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.

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.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX.

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.

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

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. 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.

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.14 Hypocalcemia
CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

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

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 embryolethality 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.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

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), in 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. 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 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 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[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 2. 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. 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 3. 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
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST[2]	3	3
Increased blood creatinine[2]	3	3
Lymphopenia[2]	1	6
Thrombocytopenia[2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[1] NCI CTCAE Version 4.0
[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values
[3] 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. 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). 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 (≥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 ≥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 4. 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			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal Pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic, and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0

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			
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] 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.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

Table 5. Laboratory Values Worsening from Baseline[a] 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 1-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] 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. 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 ≥ 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 ≥ 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 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] 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

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 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. 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 ≥ 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 ≥ 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 ≥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 (≥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 ≥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 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311[1]

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

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 5.0

[3] Includes the following terms: mucosal inflammation, stomatitis

[4] Includes the following terms: fatigue, asthenia

[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311[1]

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	Percentage (%) of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
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
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] Sponsor-defined grades for LDH were as follows: Grade 1 (> ULN to ≤ 2 × ULN), Grade 2 (> 2 × ULN to ≤ 3 × ULN), Grade 3 (> 3 × ULN).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase

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. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. 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, 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.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

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.

8.4 Pediatric Use

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

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC 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.

Physeal 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, physeal 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 ≥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, physeal 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.

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

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

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.

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.

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.

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.

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.

Thrombotic 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.

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.

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.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

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.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

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.

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.

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

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

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.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

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