EXPERIENCE CABOMETYX®: A TKI for patients with HCC after prior sorafenib treatment

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

DEMONSTRATED EFFICACY

Clinical benefits observed across 3 key endpoints in a pivotal trial that included patients previously treated with sorafenib.[1]

SIMPLE ONCE-DAILY DOSING

Dose reductions are recommended for adverse events which, if persistent, could become serious or intolerable.[1]

Scan the QR code for more information about CABOMETYX®.

HCC: hepatocellular carcinoma; TKI: tyrosine kinase inhibitor.

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

CABOMETYX®: Demonstrated power in aHCC vs. placebo in PFS, OS, and ORR (CELESTIAL Trial)

In a broad group of patients who all received prior treatment with sorafenib, CABOMETYX® demonstrated statistically significant clinical benefits across 3 endpoints[1]:

Overall survival

(Primary endpoint, primary analysis)
HR=0.76*† (95% CI, 0.63–0.92), p=0.0049*

Median OS:

CABOMETYX® **10.2 MONTHS** vs. placebo **8.0 MONTHS**

Progression-free survival

(Secondary endpoint, investigator assessed)
HR=0.44* (95% CI, 0.36–0.52), p<0.0001*

Median PFS:

CABOMETYX® **5.2 MONTHS** vs. placebo **1.9 MONTHS**

Objective response rate‡

(Secondary endpoint, investigator assessed)

CABOMETYX® **4%** vs. placebo **0.4%**

p=0.0086*‡

* 2-sided stratified log-rank test with etiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no) as stratification factors (per IVRS data); adjusted for stratification factors.

† Estimated using the Cox proportional-hazard model.

‡ Stratified Cochran-Mantel-Haenszel (CMH) test.

aHCC: advanced hepatocellular carcinoma; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; IVRS: Interactive Voice Response System.

CELESTIAL: A pivotal trial in aHCC

CELESTIAL was a randomized, placebo-controlled, double-blind study[1,2]

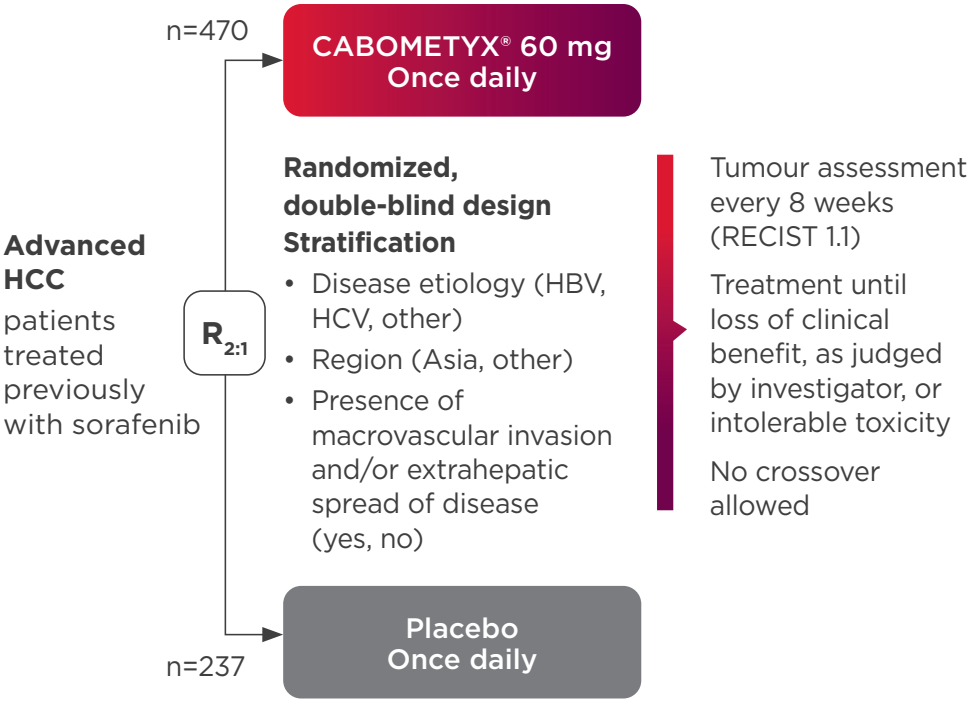


Figure adapted from the Product Monograph.[1]

Primary Endpoint:

- **Overall survival (OS)**
  The time from randomization to death from any cause

Secondary Endpoints:

- **Progression-free survival (PFS)**
  The time from randomization to radiographic progression or death from any cause, whichever occurred first
- **Objective response rate (ORR)**
  % of patients with a confirmed complete or partial response

The analysis of the primary endpoint (OS) was based on a second planned interim analysis prespecified to be performed at approximately the 75% information fraction (i.e., at approximately 466 deaths).

The median duration of follow-up was 22.9 months.

aHCC: advanced hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; RECIST: Response Evaluation Criteria in Solid Tumours.

Select baseline characteristics[1,2]*

	CABOMETYX® (n=470)	Placebo (n=237)
Age, median	64 years	64 years
Child-Pugh A Liver Disease, %	98%	99%
Etiologic factor, no. (%)†		
HBV	178 (38%)	89 (38%)
HCV	113 (24%)	55 (23%)
Dual HBV and HCV infection	8 (2%)	4 (2%)
Extrahepatic spread of disease, no. (%)	369 (79%)	182 (77%)
Prior systemic anticancer therapy, %		
Sorafenib	100%	
Two prior systemic therapy regimens	28%	

Adapted from the Product Monograph and Abou-Alfa GK, et al. 2018.[1,2]

* There were no significant differences ($p<0.05$) between the groups at baseline. Percentages may not total 100 because of rounding.

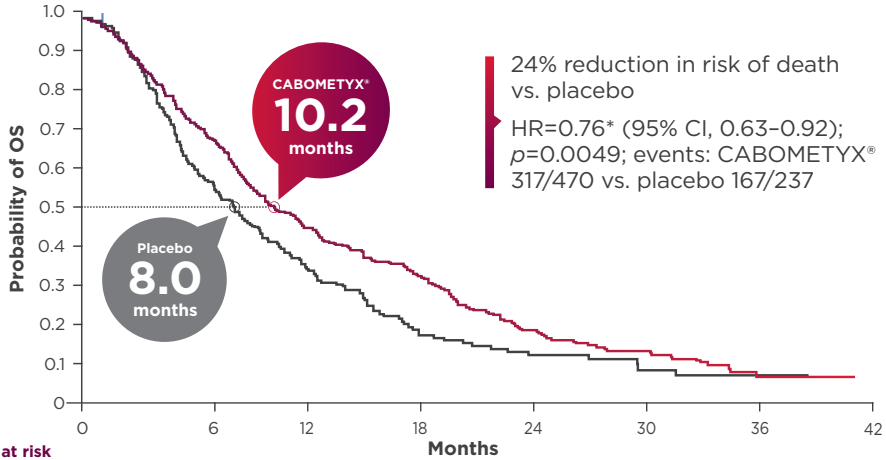
† Etiologic factors were assessed according to case-report forms. Some patients had more than one factor.

HBV: hepatitis B virus; HCV: hepatitis C virus.

CABOMETYX® extended overall survival (OS) vs. placebo[1,2]

HR=0.76*† (95% CI, 0.63–0.92), *p*=0.00498*; primary endpoint

Median OS in the ITT population (primary analysis)



24% reduction in risk of death vs. placebo

HR=0.76* (95% CI, 0.63–0.92); *p*=0.0049; events: CABOMETYX® 317/470 vs. placebo 167/237

Patients at risk

CABOMETYX®	470	281	159	93	44	22	4	0
Placebo	237	117	57	25	15	7	3	0

* 2-sided stratified log-rank test with etiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no) as stratification factors (per IVRS data).
† Estimated using the Cox proportional-hazard model.

CABOMETYX® offers the simplicity of a once-daily oral treatment

Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction, or permanent discontinuation of CABOMETYX® therapy.

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities.

Dose reductions are recommended for adverse events which, if persistent, could become serious or intolerable. Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse drug reaction, reduce the dose as follows[1]:

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

Refer to the Product Monograph for complete dosing information which includes modifications for coadministration with strong CYP3A4 inhibitors and inducers.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; ITT: intention-to-treat; IVRS: Interactive Voice Response System.

Clinical use:

CABOMETYX® is not indicated for pediatrics (<18 years of age).

Most serious warnings and precautions:

CABOMETYX® therapy: Initiated and supervised by physician experienced in anti-cancer medicines.

Patients with cardiac, severe renal and severe hepatic impairment: Not studied.

Thromboembolism, including deaths: Caution in patients at risk of venous and arterial thromboembolism. Permanently discontinue in case of acute myocardial infarction or thromboembolic complications.

Hypertension and hypertensive crisis: Monitor blood pressure prior to initiating and regularly during CABOMETYX® therapy. Do not initiate CABOMETYX® if hypertension is uncontrolled. Withhold CABOMETYX® for hypertension that is not adequately controlled with medical management; when controlled, resume with reduced dose. Permanently discontinue in severe unmanageable hypertension. Serious cases of artery dissection reported, with or without hypertension.

Gastrointestinal perforations and fistulas, including deaths: Evaluate patients with inflammatory bowel disease, tumour infiltration in GI tract, or GI surgery complications. Monitor for fistulas and perforations, including abscess and sepsis, and permanently discontinue therapy if these cannot be managed.

Hemorrhage, including deaths: Evaluate patients with a prior history of severe bleeding before initiating CABOMETYX®. Do not administer CABOMETYX® to patients with a recent history of hemorrhage, including hemoptysis, hematemesis, or melena. Permanently discontinue in the event of severe hemorrhage.

Hepatotoxicity: Monitor liver enzymes and bilirubin before and during treatment. Interrupt therapy and consider corticosteroids if liver enzymes increase. Consider dose reduction if resuming CABOMETYX®. Rare instances of vanishing bile duct syndrome have been reported. All cases occurred in patients who received immune checkpoint inhibitors either before or concurrently with CABOMETYX® treatment.

Posterior Reversible Encephalopathy Syndrome: Consider in patients with multiple symptoms, including seizures, headache, visual disturbances, confusion, or altered mental function. Permanently discontinue in patients. Posterior reversible encephalopathy syndrome was reported in one patient in the pivotal differentiated thyroid cancer study.

Wound complications: Stop therapy at least 28 days before surgery. Discontinue in patients with wound healing complications requiring medical intervention.

Other relevant warnings and precautions:

- Evaluate patients closely during the first eight weeks of treatment to determine if dose modifications are warranted, as most events can occur early in the course of treatment.
- Caution in patients on drugs that prolong QTc or at increased risk of torsade de pointes. Monitor ECG and electrolytes regularly. Discontinue in patients who develop torsade de pointes, polymorphic ventricular tachycardia or serious arrhythmia.
- Caution in patients with heart disorders. Avoid drugs that decrease heart rate and/or prolong PR interval.
- Caution when driving or operating machinery.
- Withhold therapy depending on severity of adrenal insufficiency. For Grade 2 orhigher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated.
- Monitor oral health before and during treatment. Withhold therapy if osteonecrosis of the jaw develops.
- Monitor thyroid function before and during treatment.
- Withhold therapy for intolerable Grade 2 or Grade 3-4 diarrhea until resolution to Grade 1, then resume at reduced dose. Dose interruption, reduction, or discontinuation in cases of persistent or recurrent significant GI reactions.
- Monitor platelets during treatment and dose modify according to severity of thrombocytopenia.
- Monitor for signs and symptoms of hepatic encephalopathy.
- Hypocalcemia has been observed with CABOMETYX® at a higher frequency and/or increased severity (including Grade 3 and 4) in patients with thyroid cancer compared to patients with other cancers. Monitor blood calcium levels and consider treatment with appropriate replacement therapy and/or CABOMETYX® dose modification as clinically indicated, especially in thyroid cancer patients.
- Monitor urine protein. Permanently discontinue in patients with nephrotic syndrome.
- Withhold therapy in case of intolerable Grade 2 or Grade 3 palmar-plantar erythrodysesthesia syndrome. Upon resolution to Grade 1, resume at a reduced dose.
- Do not use in pregnant women. Avoid pregnancy in women of childbearing potential and in partners of male patients taking CABOMETYX®.
- Consider fertility preservation before treatment.
- Discontinue nursing during therapy, and for at least 4 months after therapy.

For more information:

Consult the Product Monograph at **health-products.canada.ca/dpd-bdpp/**for important information relating to adverse reactions, drug interactions and dosing information. The Product Monograph is also available by calling Ipsen Medical Information at 1-855-215-2288.

ECG: electrocardiogram; GI: gastrointestinal.

References: 1. CABOMETYX® Product Monograph. Ipsen Biopharmaceuticals Canada Inc.
2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63.

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REVIEWED BY PAAB

MEMBER OF INNOVATIVE MEDICINES CANADA