

CELESTIAL - Phase 3 Pivotal Trial

of CABOMETYX® (cabozantinib) in Previously Treated Advanced Hepatocellular Carcinoma



The CELESTIAL global phase 3 clinical trial tested the effects of CABOMETYX compared with placebo in patients with advanced hepatocellular carcinoma (HCC) who had already received treatment with sorafenib, the standard of care for first-line HCC treatment. The main objective of the CELESTIAL trial was to determine whether CABOMETYX can improve survival in this patient population.

▶ WHAT IS HEPATOCELLULAR CARCINOMA (HCC)?

- HCC is the most common type of liver cancer.¹
- In 2019, it is estimated that 42,000 new cases will be diagnosed and approximately 32,000 people will die from HCC in the U.S.²
- This type of liver cancer is the third leading cause of cancer-related deaths worldwide.³

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

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GLOBAL PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLINDED TRIAL

- Designed to compare CABOMETYX with placebo in 760 patients ages 18 years and older with advanced HCC whose disease had spread or grown after treatment with sorafenib, the standard of care for first-line treatment of advanced HCC.
- Patients had received up to two prior systemic cancer therapies for HCC and had adequate liver function.
- Conducted at more than 100 sites in 19 countries

PATIENTS WERE RANDOMLY ASSIGNED TO:

- Oral CABOMETYX 60 mg tablet once daily
- A placebo tablet once daily

STUDY ENDPOINTS:

Primary endpoint

- **Overall survival:** time from randomization until death from any cause in the intent-to-treat study population

Secondary endpoint

- **Objective response rate:** proportion of patients with tumor size reduction of a predefined amount and for a minimum time period
- **Progression-free survival:** time until either death or disease worsening, per investigator review

For additional information on the study, visit <https://clinicaltrials.gov>

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

Perforations and Fistulas: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

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 event requiring medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% 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. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% 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.

Proteinuria: Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

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 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.

Wound Complications: Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding 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.

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 commonly reported ($\geq 25\%$) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

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. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information <https://cabometryx.com/downloads/CABOMETRYXUSPI.pdf>.

