Fact sheet

METEOR - Phase 3 Pivotal Trial

of CABOMETYX™ (cabozantinib) tablets in Advanced Renal Cell Carcinoma

What is RCC?

- Renal cell carcinoma (RCC) is a type of kidney cancer that forms in the tissues of the kidney that make urine[2]
- RCC accounts for 4% of all cancers in the United States[3]
- In the United States, approximately 62,700 new cases will be diagnosed and an estimated 14,240 people will die from RCC in 2016[4]

CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

The Prescribing Information for CABOMETYX includes Warnings and Precautions for Hemorrhage, Gastrointestinal Perforations and Fistulas, and Thrombotic Events. Please see Important Safety Information on reverse, and full Prescribing Information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

METEOR is a phase 3 pivotal trial evaluating the effect of CABOMETYX™ (cabozantinib) tablets compared with everolimus in patients with advanced renal cell carcinoma (RCC) whose disease has progressed after at least one prior anti-angiogenic therapy. The trial was conducted at 173 sites in 26 countries, and enrollment was weighted toward Western Europe, North America and Australia.

Trial Design[1]

Phase 3, open-label, randomized, event-driven, international trial

- The study included 658 patients who were 18 years of age or older with advanced or metastatic renal cell carcinoma with clear cell component
- Patients must have received prior treatment with at least one vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) and must have had radiographic progression during treatment or within 6 months after the most recent dose of the VEGFR inhibitor

Patients were randomly assigned to:

- CABOMETYX 60 mg once daily (n=330)
- Everolimus 10 mg once daily (n=328)

Patients were stratified based on prognostic risk criteria[5] and number of prior VEGFR-TKIs. No cross-over was allowed between the study arms.

Primary study endpoint	Secondary study endpoints
• **Progression-free survival**: time until either death or disease worsening, based on independent radiology review	• **Overall survival**: time following start of randomization that patients are still alive • **Objective response rate**: percent of patients whose tumors respond to treatment (either complete or partial response)

For additional information on the study refer to ClinicalTrials.gov Identifier: NCT01865747.

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1. Choueiri et. Al., Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015; 373:1814-1823. 2. National Cancer Institute. Kidney Cancer- Patient Version. (http://www.cancer.gov/types/kidney.) Accessed March 25, 2016. 3. National Cancer Institute. Genetics of Kidney Cancer. (http://www.cancer.gov/types/kidney/hp/kidney-genetics-pdq). Updated February 23, 2016. Accessed March 25, 2016. 4. National Cancer Institute. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. (http://seer.cancer.gov/statfacts/html/kidrp.html). Accessed April 24, 2016. 5. Motzer, R.J. et. al. Prognostic Factors for Survival in Previously Treated Patients With Metastatic Renal Cell Carcinoma. Journal of Clinical Oncology; Vol 22, February 1, 2004.

Important Safety Information

Hemorrhage: Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Gastrointestinal (GI) Perforations and Fistulas: Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. GI perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program. Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

Thrombotic Events: CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis: CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade ≥3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥3) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

Diarrhea: Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to diarrhea occurred in 26% of patients.

Palmar-Plantar Erythrodysesthesia Syndrome (PPES): Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. 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.

Embryo-fetal Toxicity: CABOMETYX can cause fetal harm when administered to a pregnant woman. 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.

Adverse Reactions: The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

Drug Interactions: Strong CYP3A4 inhibitors and inducers: Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

Lactation: Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

Reproductive Potential: Contraception—Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose. **Infertility** —CABOMETYX may impair fertility in females and males of reproductive potential.

Hepatic Impairment: Reduce the CABOMETYX dose in patients with mild (Child-Pugh score [C-P] A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see full Prescribing Information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

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