Fact Sheet

CABOSUN - Phase 2 Trial

of CABOMETYX® (cabozantinib) tablets versus Sunitinib in Previously Untreated Locally Advanced or Metastatic Renal Cell Carcinoma

PHASE 2, RANDOMIZED, OPEN LABEL, ACTIVE-CONTROLLED TRIAL[1]

- Trial was conducted at 488 sites in the U.S. and included 157 participants ages 18 and older[1,2]
- Patients had previously untreated RCC with a clear cell component that was locally advanced or had metastasized to nearby tissue, lymph nodes or other places in the body and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria[1,2]
- Patients were intermediate- or poor-risk per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria[1]
  - 80.9 percent of patients were intermediate-risk per IMDC criteria and 19.1 percent were poor-risk[2]
- Patients had ECOG Performance Status (PS) 0-2[2]
  - 46 percent of patients had ECOG PS 0, 41 percent had ECOG PS 1, and 13 percent had ECOG PS 2[2]
- Patients with brain metastases were eligible if metastases were adequately treated and stable for 3 months[2]

PATIENTS WERE RANDOMLY ASSIGNED TO RECEIVE EITHER:

- Oral cabozantinib: 60 mg once daily
- Oral sunitinib: 50 mg once daily, four weeks on followed by two weeks off

Primary endpoint

- **Progression-free survival**: time until either death or disease-worsening, per investigator review

Secondary endpoints

- **Overall survival:** average length of time from randomization until death from any cause
- **Objective response rate:** percent of patients whose tumors respond to treatment (either complete or partial confirmed response)
- **Safety**

CABOSUN was conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program.

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

REFERENCES: **1.** ClinicalTrials.gov. Cabozantinib-s-malate or Sunitinib Malate in Treating Patients with Previously Untreated Locally Advanced or Metastatic Kidney Cancer. (https://clinicaltrials.gov/ct2/show/study/NCT01835158). Accessed January 2018. **2.** Choueiri T.K., Halabi, S., Sanford, Ben L., et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *Journal of Clinical Oncology.* 2017; 35:6, 591-597. Accessed January 2018 **3.** American Cancer Society. Cancer Facts & Figures 2018. (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf). Accessed January 2018. **4.** Jonasch, E., Gao, J., Rathmell, W. Renal cell carcinoma. *BMJ.* 2014; 349:g4797. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707715/) Accessed January 2018. **5.** National Cancer Institute. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. (http://seer.cancer.gov/statfacts/html/kidrp.html). Accessed January 2018. **6.** Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).

WHAT IS RCC?

- Kidney cancer is among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[3]
- Clear cell RCC is the most common type of kidney cancer in adults[4]
- In 2018, it is estimated that over 65,000 new cases will be diagnosed and approximately 15,000 people will die from kidney cancer in the U.S.[3]
- If detected while the cancer resides only within the kidney, the five-year survival rate for RCC is 93 percent[5]
- The survival rate drops to only 12 percent once RCC has spread beyond the kidney to other parts of the body, also known as advanced or metastatic disease, for which there is no identified cure[5]
- An estimated 14,000 patients in the U.S. each year are in need of first-line treatment for advanced kidney cancer[6]

CABOMETYX® (cabozantinib) is a kinase inhibitor indicated for the treatment of patients with advanced RCC.

The Prescribing Information for CABOMETYX includes Warnings and Precautions for hemorrhage, GI perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia syndrome, reversible posterior leukoencephalopathy syndrome, and embryofetal toxicity. Please see additional Important Safety Information on reverse and full Prescribing Information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Gastrointestinal (GI) Perforations and Fistulas: In RCC trials, GI perforations were reported in 1% of CABOMETYX patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, fistulas were reported in 1% of CABOMETYX patients. Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be appropriately managed.

Thrombotic Events: Thrombotic events increased with CABOMETYX. In RCC trials, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX 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: Treatment-emergent hypertension, including hypertensive crisis, increased with CABOMETYX. In RCC trials, hypertension was reported in 44% (18% Grade ≥3) of CABOMETYX 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 if there is evidence of hypertensive crisis or for severe hypertension that cannot be controlled with antihypertensive therapy or medical management.

Diarrhea: In RCC trials, diarrhea occurred in 74% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX 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.

Palmar-Plantar Erythrodysesthesia (PPE): In RCC trials, PPE occurred in 42% of CABOMETYX patients. Grade 3 PPE occurred in 8% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. 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 of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose

ADVERSE REACTIONS

The most commonly reported (≥25%) adverse reactions were: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.

Strong CYP3A4 Inducers: If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

USE IN SPECIFIC POPULATIONS

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

Hepatic Impairment: In patients with mild to 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 at https://cabometyx.com/downloads/cabometyxuspi.pdf.

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