RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	Tukysa™
Generic Name	tucatinib
Drug Manufacturer	Seattle Genetics, Inc

New Drug Approval

FDA Approval Date: April 1, 2020
Review Designation: Priority, Orphan
Type of Review: New Drug Application 213411

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

HER2-positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2). This protein promotes the growth of cancer cells. In about 1 of every 5 breast cancers, the cancer cells have extra copies of the gene that makes the HER2 protein. HER2-positive breast cancers tend to be more aggressive than other types of breast cancer.

Efficacy

The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in 612 patients in HER2CLIMB (NCT02614794), a randomized (2:1), double-blind, placebo-controlled trial. Patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 positivity was based on archival or fresh tissue tested with an FDA-approved test at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients received TUKYSA 300 mg or placebo orally twice daily with a trastuzumab loading dose of 8 mg/kg on Day 1 of Cycle 1 if needed and then a maintenance dose of 6 mg/kg on Day 1 of every 21-day cycle thereafter and capecitabine 1000 mg/m2 orally twice daily on Days 1 through 14 of every 21-day cycle. An alternate trastuzumab dosing regimen was 600 mg administered subcutaneously on Day 1 of every 21-day cycle. Patients were treated until disease progression or unacceptable toxicity. Tumor assessments, including brain-MRI in patients with presence or history of brain metastases at baseline, occurred every 6 weeks for the first 24 weeks and every 9 weeks thereafter. The major efficacy outcome measure was progression-free survival (PFS) in the first 480 randomized patients assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were evaluated in all randomized patients and included overall survival (OS), PFS among patients with a history or presence of brain metastases (PFSBrainMets), and confirmed objective response rate (ORR). The median age was 54 years (range: 22 - 82); 116 (19%) patients were age 65 or older. The majority were White (73%) and female (99%) and 51% had an ECOG performance status of 1. Sixty percent had estrogen and/or progesterone receptor-positive disease. Forty-eight percent had a presence or history of brain metastases; of these patients, 23% had untreated brain metastases, 40% had treated but stable brain metastases, and 37% had treated but radiographically progressing brain metastases. Seventy-four percent of patients had visceral metastases. Patients had received a median of 4 (range, 2 to 17) prior lines of systemic therapy and a median of 3 (range, 1 to 14) prior lines of systemic therapy in the metastatic setting. All patients received prior trastuzumab and T-DM1 and all but two patients had prior pertuzumab. Efficacy results are summarized in Table 9 and Figure 1

and 2. Efficacy results were consistent across patient subgroups defined by stratification factors (presence or history of brain metastases, ECOG status, region of world) and hormone receptor status.

Safety

ADVERSE EVENTS

The most common adverse reactions (≥20%) are diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

WARNINGS & PRECAUTIONS

Diarrhea: Severe diarrhea, including dehydration, acute kidney injury, and death, has been reported. Administer antidiarrheal treatment as clinically indicated. Interrupt dose, then dose reduce, or permanently discontinue TUKYSA based on severity.

Hepatotoxicity: Severe hepatotoxicity has been reported on TUKYSA. Monitor ALT, AST and bilirubin prior to starting TUKYSA, every 3 weeks during treatment and as clinically indicated. Interrupt dose, then dose reduce, or permanently discontinue TUKYSA based on severity.

Embryo-Fetal Toxicity: TUKYSA can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. Also, refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy and contraception information.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

TUKYSA is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Dose & Administration

ADULTS

Recommended dosage: 300 mg taken orally twice daily with or without food.

- For patients with severe hepatic impairment, the recommended dosage is 200 mg orally twice daily

PEDIATRICS

The safety and effectiveness of TUKYSA in pediatric patients have not been established.

GERIATRICS

In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥75 years to assess differences in effectiveness or safety.

RENAL IMPAIRMENT

The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min).

HEPATIC IMPAIRMENT

Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets:

- 50 mg: round, yellow, film-coated, debossed with “TUC” on one side and “50” on the other side.
- 150 mg: oval-shaped, yellow, film-coated, debossed with “TUC” on one side and “150” on the other side.