

**Seattle Genetics Announces U.S. FDA Approval of TUKYSA™ (tucatinib) for People with Advanced Unresectable or Metastatic HER2-Positive Breast Cancer**

*-Approved for Patients with HER2-Positive Metastatic Breast Cancer Who Have Received One or More Prior Anti-HER2 Therapies in the Metastatic Setting-*

*-First HER-2 Tyrosine Kinase Inhibitor in Combination to Improve Overall and Progression-Free Survival in Patients with Metastatic HER2-Positive Breast Cancer With or Without Brain Metastases-*

*-Application Approved Four Months Prior to Action Date Under FDA's Real-Time Oncology Review (RTOR)-*

*-Investor Conference Call Today at 1:00 p.m. Pacific Time (PT); 4:00 p.m. Eastern Time (ET)-*

**BOTHELL, Wash., April 17, 2020** – [Seattle Genetics, Inc.](#) (Nasdaq:SGEN) today announced the U.S. Food and Drug Administration (FDA) granted approval to TUKYSA™ (tucatinib) tablets in combination with trastuzumab and capecitabine for adult patients with advanced unresectable (cannot be surgically removed) or metastatic HER2-positive breast cancer, including patients with brain metastases (disease that has spread to the brain), who have received one or more prior anti-HER2-based regimens in the metastatic setting. The FDA previously granted Breakthrough Therapy designation and Priority Review for TUKYSA and reviewed this application for approval under the Real-Time Oncology Review (RTOR) pilot program. The TUKYSA New Drug Application (NDA) is also part of Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology drugs among participating international health authorities. TUKYSA is an oral, small molecule tyrosine kinase inhibitor (TKI) of HER2, a protein that contributes to cancer cell growth.<sup>1,2</sup>

“With highly significant and clinically important results for overall and progression-free survival, the addition of TUKYSA to trastuzumab and capecitabine has the potential to become a standard of care for people with HER2-positive metastatic breast cancer after having received one or more previous anti-HER2 therapies in the metastatic setting,” said Eric P. Winer, MD, Chief of the Division of Breast Oncology, Susan F. Smith Center for Women's Cancers at Dana-Farber. “Cancer spreads to the brain in up to half of patients with HER2-positive metastatic breast cancer; and this approval is based on a unique clinical trial that included patients with active brain metastases, either untreated or progressing. TUKYSA is well tolerated by patients and is a valuable addition to the agents we have for HER2-positive metastatic breast cancer.”

“We’re pleased to have collaborated with the FDA on our second expedited real-time oncology review, enabling us to rapidly bring this new targeted medicine to patients,” said Clay Siegall, Ph.D., Chief Executive Officer at Seattle Genetics. “TUKYSA has shown impressive results in people with HER2-positive metastatic breast cancer, including in patients with active brain metastases, and offers patients an effective medicine following previous treatment with other anti-HER2 agents in the metastatic setting.”

TUKYSA, in combination with trastuzumab and capecitabine, was evaluated in the trial HER2CLIMB, a randomized (2:1), double-blind, placebo-controlled trial that enrolled 612 patients with HER2-positive unresectable locally advanced or metastatic breast cancer who had previously received, either separately or in combination, trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1).

Forty-eight percent of patients in the study had a presence or history of brain metastases. The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) in the first 480 randomized patients.<sup>1</sup> Additional efficacy outcome measures were evaluated in all randomized patients and included overall survival (OS), PFS in patients with a history or presence of brain metastases, and confirmed objective response rate (ORR).

Patients who received TUKYSA in combination with trastuzumab and capecitabine had a 46 percent reduction in the risk of cancer progression or death (PFS) compared to patients who received trastuzumab and capecitabine alone (hazard ratio (HR)=0.54 [95% Confidence Interval (CI): 0.42, 0.71];  $p < 0.00001$ ). The addition of TUKYSA reduced the risk of death (OS) by 34 percent compared to trastuzumab and capecitabine alone (HR=0.66 [95% CI: 0.50, 0.87];  $p = 0.0048$ ). Nearly twice the number of patients who received TUKYSA in combination with trastuzumab and capecitabine had a confirmed objective response compared to those who received trastuzumab and capecitabine alone (40.6 percent [95% CI: 35.3, 46.0] vs. 22.8 percent [95% CI: 16.7, 29.8];  $p = 0.00008$ ). For patients with brain metastases, the addition of TUKYSA reduced the risk of cancer progression or death (PFS) by 52 percent compared to trastuzumab and capecitabine alone (HR=0.48 [95% CI: 0.34, 0.69];  $p < 0.00001$ ).

Serious adverse reactions occurred in 26 percent of patients who received TUKYSA. Serious adverse reactions occurring in 2 percent or more of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea, abdominal pain, and seizure (2% each). The most common adverse reactions occurring in 20 percent or more of patients who received TUKYSA were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash. Adverse reactions leading to treatment discontinuation occurred in 6 percent of patients who received TUKYSA; adverse reactions leading to treatment discontinuation of TUKYSA (in 1 percent or more of patients) were hepatotoxicity (1.5%) and diarrhea (1%).

The data were published in [The New England Journal of Medicine](#) in December 2019.

### **About TUKYSA (tucatinib)**

TUKYSA is an oral medicine that is a tyrosine kinase inhibitor of the HER2 protein. In vitro (in lab studies), TUKYSA inhibited phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signaling and cell growth (proliferation), and showed anti-tumor activity in HER2-expressing tumor cells. In vivo (in living organisms), TUKYSA inhibited the growth of HER2-expressing tumors. The combination of TUKYSA and the anti-HER2 antibody trastuzumab showed increased anti-tumor activity in vitro and in vivo compared to either medicine alone.<sup>1</sup>

SeaGen Secure offers access and reimbursement support to help patients access TUKYSA. For more information, go to [SeaGenSecure.com](https://www.seagen.com/secure).

### **About HER2-Positive Breast Cancer**

Patients with HER2-positive breast cancer have tumors with high levels of a protein called human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. An estimated 279,100 new cases of breast cancer will be diagnosed in the U.S. in 2020.<sup>3</sup> Between 15 and 20 percent of breast cancer cases are HER2-positive.<sup>3</sup> Historically, HER2-positive breast cancer tends to be more aggressive and more likely to recur than HER2-negative breast cancer.<sup>4,5,6</sup> Up to 50 percent of metastatic HER2-positive breast cancer patients develop brain metastases over time.<sup>7,8,9</sup>

## Important Safety Information

### Warnings and Precautions

- **Diarrhea** – TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity** – TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase  $>5 \times$  ULN, 5% had an AST increase  $>5 \times$  ULN, and 1.5% had a bilirubin increase  $>3 \times$  ULN (Grade  $\geq 3$ ). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients.

Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity** – TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

### Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in  $\geq 2\%$  of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in  $\geq 1\%$  of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in  $\geq 2\%$  of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA ( $\geq 20\%$ ) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

### Lab Abnormalities

In HER2CLIMB, Grade  $\geq 3$  laboratory abnormalities reported in  $\geq 5\%$  of patients who received TUKYSA were: increased bilirubin, decreased phosphate, increased ALT, decreased potassium, and increased AST. The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

### Drug Interactions

- **Strong CYP3A or Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

### Use in Specific Populations

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

For more information, please see the full Prescribing Information for TUKYSA [here](#).

### Conference Call Details

Seattle Genetics' management will host a conference call and webcast to discuss the approval of TUKYSA today at 1:00 p.m. Pacific Time (PT); 4:00 p.m. Eastern Time (ET). The live event will be simultaneously webcast and available for replay from the Seattle Genetics website at [www.seattlegenetics.com](http://www.seattlegenetics.com), under the Investors section. Investors may also participate in the conference call by calling 888-220-8451 (domestic) or 323-794-2588 (international). The conference ID is 5796578. A replay of the audio only will be available by calling 888-203-1112 (domestic) or 719-457-0820

(international), using conference ID 5796578. The telephone replay will be available until 5:00 p.m. PT on April 20, 2020.

### **About Seattle Genetics**

Seattle Genetics, Inc. is a global biotechnology company that discovers, develops and commercializes transformative medicines targeting cancer to make a meaningful difference in people's lives. The company is headquartered in Bothell, Washington, and has offices in California, Switzerland and the European Union. For more information on our robust pipeline, visit [www.seattlegenetics.com](http://www.seattlegenetics.com) and follow [@SeattleGenetics](https://twitter.com/SeattleGenetics) on Twitter.

### **Forward Looking Statements**

Certain statements made in this press release are forward looking, such as those, among others, relating to the therapeutic potential of TUKYSA including its efficacy, safety and therapeutic uses and the potential of TUKYSA in combination with trastuzumab and capecitabine to become a standard of care for people with HER2-positive metastatic breast cancer who have received one or more previous anti-HER2 therapies. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. Factors that may cause such a difference include the possibility that adverse events or safety signals may occur; that utilization and adoption of TUKYSA by prescribing physicians may be limited due to impacts related to the COVID-19 pandemic, including potential difficulties associated with commercializing a new therapeutic agent during the global disruptions created by the COVID pandemic, availability and extent of reimbursement or other factors; and that adverse regulatory actions may occur. More information about the risks and uncertainties faced by Seattle Genetics is contained under the caption "Risk Factors" included in the company's Annual Report on Form 10-K for the year ended December 31, 2019 filed with the Securities and Exchange Commission. Seattle Genetics disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.