

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213411Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

Division of Risk Management (DRM)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Application Type	NDA
Application Number	213411
PDUFA Goal Date	08/20/2020
OSE RCM #	2019-2388, 2019-2390
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	April 13, 2020
Subject	Evaluation of Need for a REMS
Established Name	tucatinib
Trade Name	Tukysa
Name of Applicant	Seattle Genetics, Inc.
Therapeutic Class	kinase inhibitor
Formulation(s)	50 mg and 150 mg tablet
Dosing Regimen	300 mg orally twice daily

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tukysa (tucatinib) is necessary to ensure the benefits outweigh its risks. Seattle Genetics, Inc. submitted a New Drug Application (NDA) 213411 for tucatinib with the proposed indication 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. The serious risks associated with tucatinib include diarrhea, hepatotoxicity, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 1 (DO1) agree that a REMS is not necessary to ensure the benefits of tucatinib outweigh its risks. The efficacy of tucatinib in combination with trastuzumab and capecitabine was supported by the HER2CLIMB study, in which the tucatinib group had a significantly improved progression-free survival. The serious risks associated with tucatinib of diarrhea, hepatotoxicity, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with tucatinib.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)<sup>a</sup> Tukysa (tucatinib) is necessary to ensure the benefits outweigh its risks. Seattle Genetics, Inc. submitted a New Drug Application (NDA) 213411 for tucatinib with the proposed indication 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.<sup>1</sup> This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Tukysa (tucatinib), a NME, is a kinase inhibitor, proposed 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. Tucatinib is supplied as a 50 mg and 150 mg tablet. The proposed dosing regimen is tucatinib 300 mg orally twice daily.<sup>b</sup> Tucatinib is not currently approved in any jurisdiction. Tucatinib was designated as an orphan product, received fast track designation, and breakthrough therapy.

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for tucatinib NDA 213411 relevant to this review:

- 06/24/2016: Fast track designation granted
- 06/05/2017: Orphan drug designation granted
- 12/16/2019: Breakthrough therapy designation granted
- 12/20/2019: NDA 213411 submission for 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 received
- 03/02/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tucatinib

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Breast cancer is a common cause of cancer in women worldwide.<sup>2,3</sup> The estimated number of new cases of breast cancer in the United States in women and in men is 276,480 and 2620, respectively.<sup>4,c</sup> Furthermore, the estimated number of women with metastatic breast cancer in the United States in 2017 was 154,794.<sup>5</sup> Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 27.4%.<sup>3,6,d</sup>

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment of stage IV or recurrent metastatic breast cancer increases survival and quality of life.<sup>3</sup> Guidelines for patients with advanced human epidermal growth factor receptor2 (HER2)-positive breast cancer from the American Society of Clinical Oncology (ASCO) recommend trastuzumab, pertuzumab, and taxane as first line therapy and trastuzumab emtansine as second line therapy.<sup>7</sup> In patients who have progressed during or after second line or greater therapy, trastuzumab emtansine if not previously used is recommended and pertuzumab if not previously used may be recommended. In patients who have progressed during or after second line or greater HER2 targeted therapy and received pertuzumab and trastuzumab emtansine, lapatinib and capecitabine, chemotherapy and trastuzumab, lapatinib and trastuzumab, or hormone therapy (estrogen receptor and/or progesterone receptor positive disease) is recommended as third line or greater therapy.

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<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, and capecitabine have a boxed warning but did not require a REMS for approval.<sup>8,9,10,11,12</sup> Trastuzumab, pertuzumab, and ado-trastuzumab emtansine have a boxed warning for cardiac toxicity (cardiomyopathy for trastuzumab, left ventricular dysfunction for pertuzumab and ado-trastuzumab emtansine) and embryo-fetal toxicity. In addition, trastuzumab has a boxed warning for infusion reactions and pulmonary toxicity and ado-trastuzumab emtansine has a boxed warning for hepatotoxicity. Lapatinib has a boxed warning for hepatotoxicity. Furthermore, capecitabine has a boxed warning for capecitabine warfarin interaction.

Recently, fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-directed antibody and topoisomerase inhibitor conjugate, was approved by the FDA in 2019 for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.<sup>13</sup> Fam-trastuzumab deruxtecan-nxki did not require a REMS for approval, but has a boxed warning for interstitial lung disease/pneumonitis and embryo-fetal toxicity. The other serious risks include neutropenia and left ventricular dysfunction.

None of the aforementioned drugs required a REMS to ensure the benefits outweighed their risks.

## 4 Benefit Assessment

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The pivotal trial NCT 02614794 (HER2CLIMB) supporting this application for efficacy and safety consisted of a Phase 2, double-blind, randomized, placebo-controlled study which evaluated tucatinib in combination with trastuzumab and capecitabine in patients with HER2-positive unresectable locally advanced or metastatic breast cancer, with or without brain metastases, that had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine separately or in combination in the neoadjuvant, adjuvant, or metastatic setting.<sup>1</sup> Patients (N=612) were randomized to tucatinib 300 mg orally twice daily, trastuzumab, and capecitabine (N=320) or placebo, trastuzumab, and capecitabine (N=160). The dosing regimen for trastuzumab was 8 mg/kg IV on day 1 of cycle 1 if needed, then 6 mg/kg IV on day 1 of every 21 day cycle or trastuzumab 600 mg subcutaneously on day 1 of every 21 day cycle. The dosing regimen for capecitabine was 1000 mg/m<sup>2</sup> orally twice daily on days 1 through 14 of every 21 day cycle. The primary endpoint was progression-free survival (PFS) in the first 480 randomized patients. The median PFS was 7.8 months in the tucatinib, trastuzumab, and capecitabine group (95% CI 7.5 to 9.6) and 5.6 months in the placebo, trastuzumab, and capecitabine group (95% CI 4.2 to 7.1), hazard ratio 0.54 (95% CI 0.42 to 0.71), p < 0.00001. One of the secondary endpoints was PFS in patients with brain metastases at baseline. The median PFS was 7.6 months in the tucatinib, trastuzumab, and capecitabine group (95% CI 6.2 to 9.5) and 5.4 months in the placebo, trastuzumab, and capecitabine group (95% CI 4.1 to 5.7), hazard ratio 0.48 (95% CI 0.34 to 0.69), p < 0.00001. The FDA clinical reviewer concluded the tucatinib was effective in HER2 positive metastatic breast cancer and significantly improved PFS.<sup>14,e</sup>

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<sup>e</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

## 5 Risk Assessment & Safe-Use Conditions<sup>f</sup>

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The safety of tucatinib in combination with trastuzumab and capecitabine was evaluated in a Phase 2 clinical trial NCT 02614794 (HER2CLIMB).<sup>1</sup> In the safety population, 404 patients received tucatinib, trastuzumab, and capecitabine and 197 patients received placebo, trastuzumab, and capecitabine. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 23/404 (6%) in the tucatinib, trastuzumab, and capecitabine group and 6/197 (3%) in the placebo, trastuzumab, and capecitabine group.<sup>14</sup> Common adverse reactions reported with tucatinib in combination with trastuzumab and capecitabine included diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

In study HER2CLIMB, 8 deaths were due to TEAE in the tucatinib, trastuzumab, and capecitabine group and 6 deaths were due to TEAE in the placebo, trastuzumab, and capecitabine group.<sup>14</sup> In the tucatinib, trastuzumab, and capecitabine group, 3 deaths were due to sudden death, 2 deaths were due to sepsis, 2 death were due to dehydration, and 1 death was due to cardiogenic shock. The FDA clinical reviewer concluded that the 2 deaths due to sepsis and 2 death due to dehydration (from diarrhea) were attributed to the study drug.

The serious risks<sup>g</sup> associated with tucatinib which include diarrhea, hepatotoxicity, and embryo-fetal toxicity are summarized in the sections below.

### 5.1 DIARRHEA

An adverse reaction of diarrhea occurred in 81% of patients in the tucatinib, trastuzumab, and capecitabine group, with Grade 3 diarrhea reported in 12% of patients and Grade 4 diarrhea reported in 0.5% of patients. Two deaths were potentially due to dehydration from diarrhea in study HER2CLIMB.<sup>14</sup> The proposed label contains recommendations for supportive care of diarrhea including administering antidiarrheal treatment as clinically indicated. If approved, this risk will be communicated in the warnings and precautions section of the label.

### 5.2 HEPATOTOXICITY

Hepatotoxicity has been reported with tucatinib in combination with trastuzumab and capecitabine. An adverse event of increased alanine aminotransferase > 5 times ULN (Grade  $\geq$  3) occurred in 8%, increased aspartate aminotransferase > 5 times ULN (Grade  $\geq$  3) occurred in 6%, and increased bilirubin > 3 times ULN (Grade  $\geq$  3) occurred in 1.5% of the tucatinib, trastuzumab, and capecitabine group.

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<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

<sup>g</sup> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

However, a Division of Hepatology and Nutrition consult indicated that in the HER2CLIMB study there was no Hy's law signal with tucatinib.<sup>15</sup> If approved, this risk will be communicated in the warnings and precautions section of the label.

### **5.3 EMBRYO-FETAL TOXICITY**

Tucatinib may cause fetal harm based on animal studies and the mechanism of action of the drug. The proposed label advises patients of the potential risk of embryo-fetal harm. The proposed label recommends in females of reproductive potential [REDACTED] (b) (4) [REDACTED] effective contraception be used during treatment and for at least 1 week after the last dose. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for at least 1 week after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

## **6 Expected Postmarket Use**

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If approved, tucatinib will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists.

## **7 Risk Management Activities Proposed by the Applicant**

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The Applicant did not propose any risk management activities for tucatinib beyond routine pharmacovigilance and labeling.

## **8 Discussion of Need for a REMS**

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The FDA clinical reviewer recommends approval of tucatinib on the basis of the efficacy and safety information currently available. Tucatinib is a kinase inhibitor and is a treatment option, in combination with trastuzumab and capecitabine, for 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. The efficacy of tucatinib in combination with trastuzumab and capecitabine was supported by the HER2CLIMB study, in which the tucatinib group had a significantly improved PFS. The serious risks associated with tucatinib of diarrhea, hepatotoxicity, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label.

Breast cancer is a common cause of cancer in women worldwide. The estimated number of women with metastatic breast cancer in the United States in 2017 was 154,794. Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 27.4%. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with tucatinib. Based on the efficacy and risk associated with tucatinib 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, the DRM and DO1 recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

## 9 Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable, therefore a REMS is not necessary for tucatinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 Appendices

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### 10.1 REFERENCES

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- <sup>1</sup> Proposed prescribing information for tucatinib as currently edited by FDA, April 7, 2020.
- <sup>2</sup> Waks AG, Winer EP. Breast Cancer Treatment: A Review. *JAMA*. 2019;321(3):288-300.
- <sup>3</sup> National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast cancer (version 3.2020 – March 6, 2020). [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) (accessed 2020 March 30).
- <sup>4</sup> Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
- <sup>5</sup> Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(6):809-815.
- <sup>6</sup> Cancer Stat Facts: Female Breast Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. <https://seer.cancer.gov/statfacts/html/breast.html> (accessed 2019 November 26)
- <sup>7</sup> Giordano SH, Temin S, Chandarlapaty S, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(26):2736-2740.
- <sup>8</sup> Herceptin (trastuzumab) package insert. South San Francisco, CA: Genentech, Inc.; 2018 November.
- <sup>9</sup> Perjeta (pertuzumab) package insert. South San Francisco, CA: Genentech, Inc.; 2020 January.
- <sup>10</sup> Kadcyla (ado-trastuzumab emtansine) package insert. South San Francisco, CA: Genentech, Inc.; 2019 May.
- <sup>11</sup> Tykerb (lapatinib) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018 December.
- <sup>12</sup> Xeloda (capecitabine) package insert. South San Francisco, CA: Genentech USA, Inc.; 2019 February.

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<sup>13</sup> Enhertu (fam-trastuzumab deruxtecan-nxki) package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2019 December.

<sup>14</sup> Shah M, Cheng J, Fiero M, Gong Y, Wedam S. Division of Oncology 1 (DO1). Tucatinib. Mid-Cycle Meeting, clinical and statistics reviewer slides. February 26, 2020.

<sup>15</sup> Division of Hepatology and Nutrition consult to NDA 213411. March 17, 2020.

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/s/  
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I concur.

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