FDA Approval Summary: Tucatinib for the Treatment of Patients with Advanced or Metastatic HER2-positive Breast Cancer

Mirat Shah[1], Suparna Wedam[1], Joyce Cheng[1], Mallorie H. Fiero[1], Huiming Xia[1], Fang Li[1], Jianghong Fan[1], Xinyuan Zhang[1], Jingyu Yu[1], Pengfei Song[1], Wei Chen[1], Tiffany K. Ricks[1], Xiao Hong Chen[1], Kirsten B. Goldberg[2], Yutao Gong[1], William F. Pierce[1], Shenghui Tang[1], Marc R. Theoret[2], Richard Pazdur[2], Laleh Amiri-Kordestani[1], and Julia A. Beaver[1]

ABSTRACT

On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab and capecitabine for the treatment of 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. This was the first new molecular entity evaluated under Project Orbis, an FDA Oncology Center of Excellence initiative, which supports concurrent review of oncology drugs by multiple global health authorities. Approval was based on the HER2CLIMB trial, which randomized patients to receive tucatinib or placebo with trastuzumab and capecitabine. Tucatinib demonstrated efficacy compared with placebo in progression-free survival [PFS; HR: 0.54; 95% confidence interval (CI): 0.42–0.71; $P < 0.00001$] and overall survival (OS; HR: 0.66; 95% CI, 0.50–0.87; $P = 0.00480$). Patients with either treated and stable or active brain metastases made up 48% of the study population. PFS in patients with brain metastases confirmed benefit (HR: 0.48; 95% CI, 0.34–0.69; $P < 0.00001$). The benefit in patients with brain metastases allowed for inclusion of this specific population in the indication. Important safety signals included diarrhea and hepatotoxicity which are listed under Warnings and Precautions. This article summarizes the FDA thought process and data supporting the favorable benefit–risk profile and approval of tucatinib.

Introduction

Breast cancer is the second leading cause of cancer-related death in women in the United States each year (1). Approximately 20% of patients with metastatic breast cancer (MBC) will have tumors that overexpress human epidermal growth factor receptor 2 (HER2), and these patients are often younger at diagnosis and have disease with a more aggressive phenotype (2, 3). Between 30%–55% of patients with HER2-positive MBC develop brain metastases, and patients with brain metastases have a particularly poor prognosis (4–7).

The preferred treatments for HER2-positive MBC are trastuzumab, pertuzumab, and a taxane in the first-line setting, followed by ado-trastuzumab emtansine (T-DM1) at disease progression, and both regimens have led to improved outcomes including survival (8, 9). Patients who progress on or shortly after adjuvant treatment with trastuzumab and a taxane may receive T-DM1 as first-line metastatic treatment. After progression on T-DM1, patients have several therapeutic options, but none have shown an overall survival (OS) benefit (10–14). Although brain metastases are relatively common in HER2-positive MBC, these patients have historically been excluded from clinical trials. In this article, we present the FDA rationale for approval of tucatinib for patients with HER2-positive MBC, including those with brain metastases, who have been treated with one or more prior HER2-based regimens in the metastatic setting (15).

Chemistry

The chemical name for tucatinib is (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine. The drug substance is the hemi-ethanolate form of tucatinib and is an off-white to yellow nonhygroscopic crystalline solid with low intrinsic aqueous solubility. The approved formulations of tucatinib are 50 mg and 150 mg film-coated tablets for oral administration. The recommended dosage is 300 mg twice daily.

Nonclinical pharmacology and toxicology

Tucatinib is a tyrosine kinase inhibitor of HER2. Tucatinib inhibits HER2 and HER3 phosphorylation and downstream signal transduction through the MAPK and PI3K pathways. Tucatinib inhibited cell proliferation in HER2-expressing breast cancer cell lines *in vitro* and showed antitumor activity in mouse xenograft models of HER2-expressing tumor cells. Combining tucatinib with trastuzumab demonstrated increased apoptosis of HER2-expressing breast cancer cells *in vitro* and antitumor activity in mouse models compared with either drug alone (16).

The gastrointestinal tract and liver were major target organs of toxicity in rat and monkey repeat-dose toxicology studies. This is consistent with the adverse event profile in human clinical trials.

Tucatinib can cause fetal harm when given to pregnant women and may also impair fertility in males and females based on animal findings. Tucatinib was not mutagenic in the bacterial reverse mutation assay and was not clastogenic in the *in vitro* chromosome aberration test or the *in vivo* mouse bone marrow micronucleus assay.

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. [2]Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, Maryland.

Note: This is a U.S. Government work. There are no restrictions on its use.

Corresponding Author: Mirat Shah, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, WO22 Room 2135, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 301-796-8547; Fax: 301-796-9909; E-mail: mirat.shah@fda.hhs.gov

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Clinical pharmacology

The recommended dose of tucatinib for the general population is 300 mg orally twice daily. There was an increased incidence of grade ≥ 3 AEs at the 350 mg twice daily dose (higher than that studied in the pivotal trial) during dose finding. No exposure–response relationships were identified for safety in HER2CLIMB.

Tucatinib has linear pharmacokinetics in doses ranging from 50 mg to 300 mg twice daily. Steady-state exposure is reached after approximately four days of twice daily dosing. Tucatinib's accumulation ratio is 1.7 for AUC and 1.5 for C_{max}. Tucatinib is metabolized predominantly by CYP2C8 and to a lesser extent by CYP3A. Renal elimination accounts for a small proportion of total drug clearance, with 4.1% of the total radiolabeled dose recovered in urine and 86% in feces.

Tucatinib can be taken with or without a meal. A high-fat meal increased the mean $AUC_{0-\ INF}$ by 1.5-fold and shifted the T_{max} from 1.5 hours to 4 hours; C_{max} remained unaltered. The effect of food on the pharmacokinetics of tucatinib was not considered clinically meaningful.

On the basis of drug–drug interaction studies, patients are recommended to avoid concomitant use of strong CYP2C8 inhibitors with tucatinib; the recommended dose for tucatinib is 100 mg twice daily if concomitant use of a strong CYP2C8 inhibitor is unavoidable. Concomitant use of strong CYP3A inducers or moderate CYP2C8 inducers should be avoided. Tucatinib increases the plasma concentrations of P-gp substrates. Therefore, for P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities, the dosage is recommended to be reduced when concomitantly used with tucatinib.

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/minute). Patients with severe renal impairment (creatinine clearance <30 mL/minute creatinine clearance) were not included in HER2-CLIMB, as the current capecitabine United States Prescribing Information (USPI) contains a contraindication for this population. As such, tucatinib with trastuzumab and capecitabine is not recommended in patients with severe renal impairment. No tucatinib dose adjustment is required in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The recommended starting dose for patients with severe hepatic impairment (Child-Pugh C) is 200 mg twice daily.

Clinical trial design

The approval of tucatinib was primarily based on HER2CLIMB (NCT02614794), a randomized (2:1), double-blind, placebo-controlled clinical trial of patients with HER2-positive unresectable locally advanced or metastatic breast cancer who had previously received trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting. Patients with brain metastases were eligible for this study, including patients with treated and stable brain lesions as well as patients with untreated or previously treated and progressing brain lesions. Stratification factors for randomization were presence or history of brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), and region of the world (US, Canada, or rest of world).

Study treatment was either tucatinib 300 mg or placebo orally twice daily, with trastuzumab intravenously or subcutaneously at standard

Table 1. Patient demographics and disease characteristics in the ITT-OS population of HER2CLIMB (data from FDA; ref. 15).

	Tucatinib + trastuzumab + capecitabine *n* = 410 n (%)	**Placebo + trastuzumab + capecitabine *n* = 202 n (%)**
Age, median (range)	55 (22–80)	54 (25–82)
Female	407 (99)	200 (99)
Race		
Asian	18 (4)	5 (2)
Black	41 (10)	14 (7)
White	287 (70)	157 (78)
Unknown/other	64 (16)	26 (13)
ECOG performance status		
0	204 (50)	94 (47)
1	206 (50)	108 (53)
Region		
U.S.	220 (54)	111 (55)
Canada	26 (6)	12 (6)
Rest of World	164 (40)	79 (39)
Hormone receptor status		
ER and/or PR positive	243 (59)	127 (63)
ER and PR negative	161 (39)	75 (37)
Unknown	6 (1)	0 (0)
Presence or history of brain metastases	198 (48)	93 (46)
Treated and stable	80 (20)	37 (18)
Treated and progressing	74 (18)	34 (17)
Untreated	44 (11)	22 (11)
Prior lines of systemic therapy in the metastatic setting, median (range)	3 (1–14)	3 (1–13)

Table 2. Efficacy results in HER2CLIMB (data from FDA; ref. 15).

	Tucatinib + trastuzumab + capecitabine	**Placebo + trastuzumab + capecitabine**
PFS	*N* = 320	*N* = 160
Number of events (%)	178 (55.6)	97 (60.6)
Median, months (95% CI)	7.8 (7.5–9.6)	5.6 (4.2–7.1)
HR (95% CI)[a]	0.54 (0.42–0.71)	
P[b]	<0.00001	
OS	*N* = 410	*N* = 202
Number of events (%)	130 (31.7)	85 (42.1)
Median, months (95% CI)	21.9 (18.3–31.0)	17.4 (13.6–19.9)
HR (95% CI)[a]	0.66 (0.50–0.87)	
P[b]	0.00480	
$PFS_{BrainMets}$	*N* = 198	*N* = 93
Number of events (%)	106 (53.5)	51 (54.8)
Median, months (95% CI)	7.6 (6.2–9.5)	5.4 (4.1–5.7)
HR (95% CI)[a]	0.48 (0.34–0.69)	
P[b]	<0.00001	
Confirmed ORR	*N* = 340	*N* = 171
ORR (95 % CI)[c]	40.6 (35.3–46.0)	22.8 (16.7–29.8)
P[d]	0.00008	
DOR		
Median, months (95% CI)[e]	8.3 (6.2–9.7)	6.3 (5.8–8.9)

[a]On the basis of a Cox proportional hazards regression model stratified by presence or history of brain metastases, ECOG status, and region of world.
[b]On the basis of a rerandomization procedure controlling for stratification factors at randomization (22).
[c]On the basis of the Clopper–Pearson method.
[d]On the basis of a CMH test controlling for stratification factors at randomization.
[e]Estimated by Kaplan–Meier methods with confidence intervals using the complementary log-log transform.

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doses and capecitabine 1000 mg/m2 orally twice daily on days 1–14 of every 21-day cycle. Treatment continued until unacceptable toxicity or disease progression. The primary efficacy endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR) in the initial 480 patients randomized. A protocol amendment increased the study sample size from 480 patients to 600 patients to include more patients with brain metastases. However, the primary analysis of PFS by BICR was restricted to the initial 480 patients randomized to avoid potential bias from early progression events in the overall population as a result of short follow-up. Key secondary endpoints included OS in all randomized patients, PFS in the subgroup of patients with presence or history of brain metastases at baseline ($PFS_{brainmets}$) and confirmed objective response rate (ORR) in patients with measurable disease.

The overall type-1 error rate was controlled at a two-sided level of 0.05 for the primary and key secondary endpoints using a group sequential Holm variable procedure for PFS, OS, and $PFS_{BrainMets}$, followed by a test for confirmed ORR. Planned interim analyses included one for $PFS_{BrainMets}$ and two for OS. The first interim analyses of both $PFS_{BrainMets}$ and OS were to occur at the time of the primary analysis of PFS.

Results

Efficacy

A total of 612 patients were randomized (410 to tucatinib and 202 to placebo). Patient demographics and baseline disease characteristics were generally balanced between the two arms (**Table 1**). Approximately 48% of the study population had a presence or history of brain metastases, including 19% with treated and stable brain metastases and 28% with active brain metastases (treated and progressing or untreated lesions). Patients had received a median of 3 prior lines of therapy in the metastatic setting (range 1 to 14), with 6% of patients receiving 1 prior line and 40% of patients receiving 2 prior lines. The trial demonstrated statistically significant improvements in the primary endpoint of PFS as assessed by BICR and the key secondary endpoints of OS, $PFS_{BrainMets}$, and ORR by BICR for patients in the tucatinib arm compared with the placebo arm, as shown in **Table 2** and **Figs. 1** and **2**. These results were supported by consistent findings across patient subgroups defined by stratification factors and hormone receptor (HR) status and sensitivity analyses.

Safety

The safety of tucatinib in combination with trastuzumab and capecitabine was evaluated in 601 patients who received at least one dose of study treatment on HER2CLIMB. Common adverse reactions in HER2CLIMB are summarized in **Table 3**. The most common grade ≥3 adverse reactions (≥5%) experienced by patients on the tucatinib arm were palmar–plantar erythrodysesthesia syndrome, diarrhea, and hepatotoxicity. The most frequent reasons for tucatinib discontinuation (≥1%) in patients on the tucatinib arm were hepatotoxicity (1.5%) including increased ALT (1%) and increased total bilirubin (1%), and diarrhea (1%).

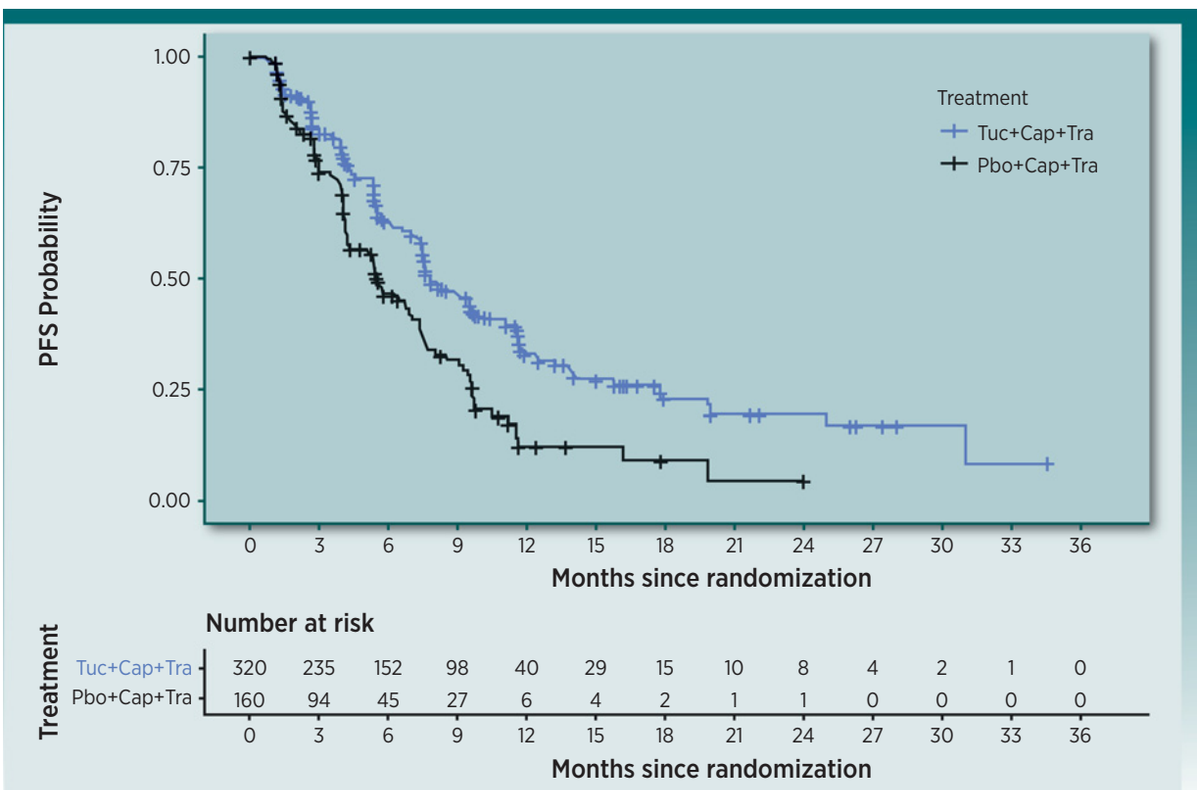

Figure 1.
Kaplan–Meier curves for PFS per BICR in the first 480 randomized patients (data from FDA; ref. 15).

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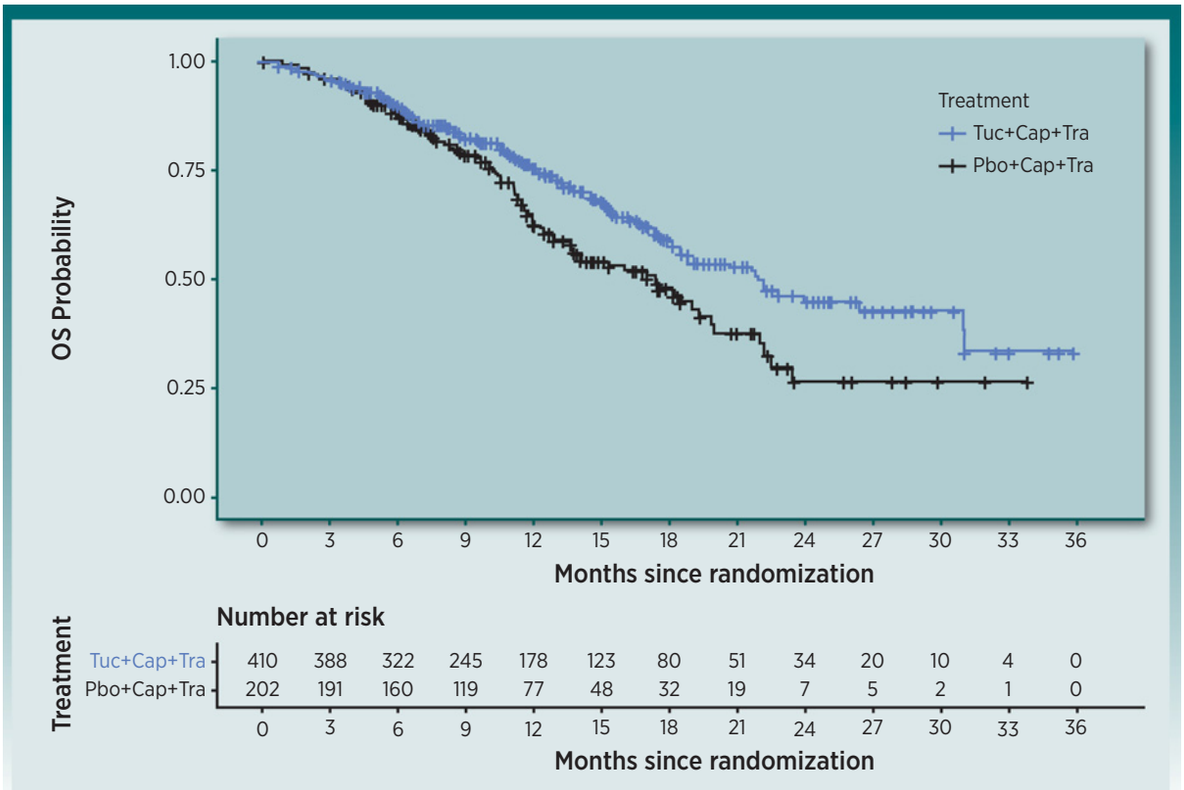

Figure 2.
Kaplan–Meier curves for OS in all randomized patients (data from FDA; ref. 15).

Diarrhea is a toxicity associated with both tucatinib and capecitabine. It was the most common adverse reaction on HER2CLIMB, experienced by 81% of patients on the tucatinib arm, compared with 53% of patients on the control arm. Twelve percent of patients on the tucatinib arm developed grade 3 diarrhea, and 0.5% of patients had grade 4 diarrhea. The 2 patients who developed grade 4 diarrhea had sequelae such as dehydration, hypotension, and acute kidney injury, and ultimately died. There was no requirement for antidiarrheal prophylaxis, but 66% of patients on the tucatinib arm used an anti-diarrheal at some point on study. The tucatinib USPI lists diarrhea under Warnings and Precautions.

Table 3. Common adverse reactions in HER2CLIMB[a] (data from FDA; ref. 15).

	Tucatinib + trastuzumab + capecitabine $N = 404$		Placebo + trastuzumab + capecitabine $N = 197$	
Adverse event	**All grades (%)**	**Grade 3–4 (%)**	**All grades (%)**	**Grade 3–4 (%)**
Diarrhea	81	13	53	9
PPE syndrome	63	13	53	9
Nausea	58	4	44	3
Hepatotoxicity	42	9	24	4
Vomiting	36	3	25	4
Stomatitis	32	3	21	1
Decreased appetite	25	1	20	0
Anemia	21	4	13	3
Rash	20	1	15	1
Arthralgia	15	1	5	1
Blood creatinine increased	14	0	2	0
Weight decreased	13	1	6	1
Neuropathy peripheral	13	1	7	1
Epistaxis	12	0	5	0

Abbreviation: PPE, palmar–plantar erythrodysesthesia.
[a]Adverse reactions displayed occurred in ≥10% of patients receiving tucatinib and were ≥5% more frequent than in patients receiving placebo.

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Table 4. FDA benefit–risk assessment of tucatinib.

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• There will be an estimated 276,000 new cases and 42,170 deaths from breast cancer in the United States in 2020. • Approximately one-fifth of patients with breast cancer have a HER2-positive subtype. • Brain metastases are common in HER2-positive MBC, occurring in between 30–55% of patients.	• HER2-positive advanced or metastatic breast cancer is incurable, serious, and life-threatening.
Current treatment options	• Standard-of-care treatments for HER2-positive MBC include trastuzumab, pertuzumab, and a taxane in the first-line metastatic setting, and T-DM1 for patients who have previously received trastuzumab and a taxane. • After T-DM1, there are a variety of treatment options, but none have shown an OS benefit in the post-T-DM1 setting. • Patients with HER2-positive MBC and brain metastases do not have specific systemic therapy options.	• Patients with HER2-positive MBC, including those with brain metastases, need therapies that improve clinical outcomes and have unmet medical need.
Benefit	• Tucatinib showed statistically significant and clinically meaningful improvements compared to placebo in median PFS (HR 0.54, 95% CI: 0.42, 0.71, $P < 0.00001$) and median OS (HR 0.66, 95% CI 0.50, 0.87, $P = 0.00480$). • Approximately half of patients on HER2CLIMB had a history or presence of brain metastases at baseline. $PFS_{brainmets}$ met its endpoint, confirming benefit in this subgroup. • Breast cancer clinical trials typically exclude those with active brain metastases, but these patients were included in HER2CLIMB.	• Tucatinib with trastuzumab and capecitabine is the first treatment combination to demonstrate an improvement in median OS in the post-T-DM1 setting. • Tucatinib is specifically labeled to indicate benefit in patients with brain metastases.
Risk and risk management	• The most common adverse reactions (≥30%) in patients receiving tucatinib were diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, hepatotoxicity, vomiting, and stomatitis. • Diarrhea, hepatotoxicity, and embryo-fetal toxicity are labeled as Warnings and Precautions. • The tucatinib label includes recommendations for dose monitoring and modification.	• Tucatinib in combination with trastuzumab and capecitabine has an acceptable safety profile for the intended population and is manageable with current labeling.

Hepatoxicity was a safety signal of concern throughout the tucatinib development program with a pattern of predominantly mild-to-moderate transaminase elevation. On HER2CLIMB, in the tucatinib compared with the control arm, ALT laboratory elevation (all grades) occurred in 46% versus 27% of patients, and AST laboratory elevation (all grades) occurred in 43% versus 25% of patients. The frequencies of grade ≥ 3 ALT and AST elevations on the tucatinib versus control arm were 8% versus 0.5%, and 6% versus 1%, respectively. There were 9 patients who met initial Hy's law criteria (ALT or AST > 3× upper limit of normal with total bilirubin > 2 x upper limit of normal) on the tucatinib arm, but upon further investigation, none of these patients represented true Hy's law cases. Increases in total bilirubin were more likely due to metastatic disease or concomitant medications including capecitabine which can be associated with an indirect hyperbilirubinemia. There were no cases of tucatinib-associated liver failure or hepatotoxicity leading to death in the safety database. The tucatinib USPI lists hepatotoxicity under Warnings and Precautions and recommends monitoring liver tests at baseline and every 3 weeks and as clinically indicated, with prompt dose modification if needed. Monitoring is particularly important as both tucatinib and capecitabine are associated with liver test abnormalities.

Regulatory Insights

Tucatinib was granted regular approval for the treatment of patients with advanced 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. In HER2CLIMB, tucatinib demonstrated statistically significant and clinically meaningful improvements in PFS, OS, and $PFS_{brainmets}$. Tucatinib with trastuzumab and capecitabine is the first treatment combination to show an improvement in OS after T-DM1.

Typically, breast cancer clinical trials exclude patients with brain metastases or only permit those with previously treated and stable CNS lesions to enroll. Inclusion of a broader population with brain metastases allows for assessment of benefit-risk in patients more representative of those who will receive the drug in practice and permits more equitable access to novel therapies (17). An FDA draft guidance outlines approaches to expand trial eligibility criteria for patients with brain metastases, and HER2CLIMB utilized some of these methods (18). Patients with active brain metastases (untreated lesions or previously treated and progressing lesions) were permitted to enroll, provided they did not require immediate surgery or radiotherapy. In addition, patients who needed local treatment to CNS lesions during the screening period could enroll after receiving it.

This is the first FDA approval which specifies patients with brain metastases in the indication statement. Description of this subgroup in the indication was appropriate for tucatinib for the following reasons: patients with brain metastases accounted for almost half of the study population; HER2CLIMB applied expanded brain metastases eligibility criteria including patients with

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progressive or untreated lesions; the alpha-allocated $PFS_{brainmets}$ endpoint showed benefit in this subgroup; and OS benefit consistent with the overall ITT population was demonstrated for patients with brain metastases. The explicit inclusion of patients with brain metastases in the indication statement highlights that tucatinib was studied in these patients who are often left out of cancer clinical trials and the clinical benefit in this group was demonstrated.

Male breast cancer is rare, representing <1% of annual U.S. cases and male patients have historically been excluded from clinical trials. The FDA released a draft guidance urging the inclusion of male patients onto breast cancer clinical trials, specifying that anticipated low enrollment is not a valid reason for exclusion (19). The guidance also details that if only a few or no men are enrolled but there are no expected differences in efficacy and safety, the FDA may extrapolate from findings in women and consider nonclinical data and/or scientific literature to expand the indication to men. Male patients were eligible and enrolled to HER2CLIMB but made up <1% of the study population. Tucatinib received approval in all adult patients including men based on extrapolation from data in women and biologic rationale that men and women would respond similarly.

The tucatinib label specifies that patients should have received one or more prior HER2-based regimens in the metastatic setting which reflects the HER2CLIMB population. The protocol required previous trastuzumab, pertuzumab, and T-DM1 but did not specify the setting (early or metastatic) and did not stipulate a number for prior lines of therapy. The enrolled population was exposed to a median of 3 (range 1–14) prior lines of systemic therapy in the metastatic setting with no patients receiving treatment as first-line therapy in the metastatic setting. The approved indication for tucatinib does not list prior therapies by name to allow for flexibility and ensure continued access if the treatment landscape for HER2-positive MBC changes in the future.

Tucatinib is the first new molecular entity (NME) reviewed under Project Orbis, an FDA Oncology Center of Excellence (OCE) initiative, which supports concurrent submission and review of oncology drugs by multiple international regulatory authorities (20). Project Orbis aims to reduce the delay between U.S. receipt of a marketing application and the application's submission to other health authorities. This may allow patients in other countries earlier access to therapies and may lead to more streamlined global drug development. The FDA collaborated with Health Canada, the Australian Therapeutic Goods Administration, and for the first time, Switzerland's Swissmedic and the Singapore Health Sciences Authority. While the authorities discussed findings jointly, the FDA conducted its own full review, and each authority generated its own label and approval decision (21). The completion of FDA review four months ahead of the goal date highlights that the Project Orbis framework can support applications for NMEs in addition to supplemental applications.

Conclusions

Tucatinib is a new targeted therapy option for patients with HER2-positive MBC. Results from HER2CLIMB demonstrate a favorable benefit-risk profile and support regular approval (**Table 4**). Safety signals include diarrhea and hepatotoxicity which are manageable through labeling. The benefit in patients with brain metastasis allowed for inclusion of this specific population in the indication statement. This was the first review of an NME under FDA OCE's Project Orbis initiative, illustrating that this framework can also support novel agents in addition to supplemental applications.

Authors' Disclosures

Y. Gong has left the FDA and started working at BeiGene in August 2020, and completed work on the submitted manuscript before leaving the FDA. No disclosures were reported by the other authors.

Disclaimer

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