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FDA Approval Summary: Tucatinib with trastuzumab for advanced unresectable or metastatic, chemotherapy refractory, *HER2* positive *RAS* wild type colorectal cancer

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Abstract

On January 19, 2023, the FDA granted accelerated approval to tucatinib in combination with trastuzumab for the treatment of patients with unresectable or metastatic *RAS* wild-type, *HER2*-positive colorectal cancer who have received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Approval was based on the pooled analysis of patients receiving tucatinib in combination with trastuzumab in MOUNTAINEER (NCT03043313), an open-label, multicenter trial. The primary endpoint was overall response rate (ORR) by RECIST 1.1 as per blinded central review committee (BIRC) assessment. The main secondary endpoint was duration of response (DOR) per BIRC assessment. Eighty-four eligible patients received the combination tucatinib and trastuzumab. With a median follow-up of 16 months, the ORR was 38% (95% CI: 28, 49) and median DOR was 12.4 months (95% CI: 8.5, 20.5); 81% of responders had a response lasting more than 6 months. The most common adverse reactions observed in at least 20% of patients receiving tucatinib in combination with trastuzumab were diarrhea, fatigue, rash, nausea, abdominal pain, infusion-related reactions, and fever. FDA concluded that the magnitude of ORR and durable responses observed in patients treated with tucatinib in combination with trastuzumab in the MOUNTAINEER trial are clinically meaningful, particularly in the context of a disease with estimated survival of 6–7 months with available therapy. This is the first approval for the subset of patients with *HER2*-positive colorectal cancer. This article summarizes the FDA's thought process and review of the data supporting this accelerated approval.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the U.S., and it is estimated that 151,030 adults will be diagnosed in 2023 (1). At diagnosis, locoregional spread

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or metastases are present in 58% of patients (1). The reported 5-year survival rate is 73% for patients who are diagnosed with locoregional disease and 15% for patients with distant metastases (1). In unselected patients with advanced disease who received prior treatment with chemotherapy (i.e., fluoropyrimidines, oxaliplatin, irinotecan), with or without monoclonal antibodies, median overall survival (OS) is approximately 7 months (2,3,4).

HER2 is an oncogenic driver and an established therapeutic target in breast and gastric cancer. *HER2* overexpression or amplification in colorectal cancer is variable in different studies, ranging from 1% to 5%. This variability has been attributed to several factors, including small study populations, heterogeneity in clinicopathological characteristics, enriched populations, and different methodologies for diagnosis (5). In recent studies of colorectal cancer, *HER2* overexpression was reported in approximately 2% of patients, with an incidence of approximately 5% in patients with metastatic disease and *RAS* wild-type (WT) tumors (6,7). While *HER2* amplification or overexpression appears to be a negative prognostic factor in some trials (7,8,9,10), other studies showed no association between *HER2* amplification and clinical outcomes (7, 11,12); prognostic significance is therefore uncertain. Tucatinib, a tyrosine kinase inhibitor of *HER2*, was first approved in the US on April 17, 2020, in combination with trastuzumab and capecitabine for the treatment of patients with unresectable or metastatic *HER2*-positive (*HER2*+) breast cancer who have received one or more prior anti-*HER2*-based regimens in the metastatic setting (13).

On January 19, 2023, FDA granted accelerated approval to tucatinib in combination with trastuzumab for the treatment of adult patients with *RAS* wild-type *HER2*+ unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (refractory setting). The authors summarize the FDA's review of data and regulatory considerations supporting this approval. The Investigators' analyses and interpretation of the data have been previously published (14).

Clinical Trial Design

The MOUNTAINEER (SGNTUC-017, NCT03043313) trial provided the evidence of safety and effectiveness for the approval. MOUNTAINEER was initiated as an investigator-led, single-arm study investigating tucatinib in combination with trastuzumab (Cohort A). The trial was subsequently amended to include an industry-sponsored, randomized, open-label portion wherein patients were randomized (4:3) to receive tucatinib in combination with trastuzumab (Cohort B) or single agent tucatinib (Cohort C). Patients were required to have *HER2*+, *RAS* wild-type, unresectable or metastatic CRC and to have received prior treatment with fluoropyrimidine, oxaliplatin, irinotecan; eligible patients should have also previously received an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb) and an anti-PD1 mAb in patients with microsatellite instability-high tumors. All patients had to have measurable disease and an ECOG performance status of 0–2. Patients who received prior anti-*HER2* targeting therapy were excluded. *RAS* status was determined as standard of care prior to study entry based on expanded *RAS* testing. *HER2* positivity was defined as the presence of *HER2* overexpression or gene amplification and was prospectively determined in local laboratories using immunohistochemistry (IHC), in situ

hybridization (ISH), and/or next generation sequencing (NGS) on tumor tissue. *HER2*+ status was defined based on the following criteria: IHC 3+, IHC2+/ISH-positive assay, or *ERBB2* amplification in an NGS assay.

Overall response rate (ORR) and duration of response (DOR) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1 were the primary and key secondary endpoints, respectively. Patients in Cohort A and Cohort B received tucatinib 300 mg orally twice daily in combination with trastuzumab (loading dose 8 mg/kg intravenously followed by 6 mg/kg on Day 1 of each subsequent 3-week cycle). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to Cohort C received tucatinib 300 mg orally twice daily and were allowed to cross over to receive tucatinib and trastuzumab if they did not achieve a complete response (CR) or partial response (PR) at Week 12 or at any time upon disease progression.

Disease response assessments were conducted at baseline, every 9 weeks in Cohort A and every 6 weeks in Cohort B and Cohort C while on treatment, and every 12 weeks thereafter in all cohorts.

The primary efficacy analyses were conducted in the full analysis set (FAS) population, defined as all patients in Cohort A and Cohort B who were enrolled, had *HER2*+ tumors and received any amount of study treatment. The ORR and its exact 2-sided 95% confidence interval (CI) using the Clopper-Pearson method (15), were calculated. DOR was summarized for patients with a CR or PR. The Kaplan-Meier (16) methodology was used to calculate the median DOR and its two-sided 95% CI; the percentage of patients who remained responders at 6 months and at 12 months were summarized based on observed DOR. Safety was analyzed in patients who received at least one dose of study treatment.

Results

Efficacy

At the data cutoff date of March 28, 2022, MOUNTAINEER had enrolled 117 patients; 86 patients in Cohort A and Cohort B combined and 31 patients in Cohort C. Among the 84 efficacy evaluable patients enrolled to Cohort A and Cohort B, 69 (82%) were enrolled in the U.S. and 15 (18%) in Europe (Italy, Belgium, Spain, and France). Patient demographics and baseline disease characteristics are summarized in Table 1. The median age was 55 years. The majority of patients (84.5%) had left sided tumors. A total of 3 patients (4%) reported Black or African American race and 3 patients (4%) reported Hispanic or Latino ethnicity.

With a median follow up of 16 months, the ORR was 38% (95% CI: 28, 49), including 3 (3.6%) CRs for the 84 patients receiving the combination of tucatinib and trastuzumab. The results were consistent across various subgroups including age, performance status, primary site of disease, and geographic region. The median DOR was 12.4 months (95% CI: 8.5, 20.5); 81% and 34% of responders had a DOR of ≥ 6 and ≥ 12 months, respectively.

Safety

The safety analysis was based on 86 patients who received at least one dose of tucatinib in combination with trastuzumab. The median duration of exposure to tucatinib was 6.9 months (range: 0.7–49.3 months). Table 2 lists the most common (incidence ≥10%) treatment emergent adverse events (TEAEs). Six (7%) patients experienced Grade 4 TEAEs, including increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (2 patients), COVID-19 pneumonia (2 patients), cholangitis, acute respiratory distress, and rectal perforation (one patient each). The most common Grade 3 events included hypertension (7%), diarrhea (3.5%), abdominal pain, fatigue, and back pain (2.3% each). The most common laboratory abnormalities worsening from baseline were increased creatinine (58%), increased glucose (56%), increased ALT (46%), decreased hemoglobin (46%), decreased lymphocytes (39%), increased AST (33%), increased bilirubin (28%), increased alkaline phosphatase (25%), decreased albumin (24%), decreased leukocytes (22%), and decreased sodium (20%).

TEAEs leading to any study drug discontinuation were reported in 5 (6%) patients and included ALT increase (2 patients), fatigue, COVID19 pneumonia, and cholangitis (1 patient each). Tucatinib was held for the management of toxicity in 20 (23%) patients; the most common TEAEs leading to tucatinib being held were diarrhea/colitis in 4 patients, increased ALT in 3 patients, and infections in 3 patients. Tucatinib dosage was reduced in 8 (9%) patients; the most common TEAEs leading to dose reduction were diarrhea/colitis in 3 patients and ALT increased in 2 patients. Trastuzumab was held in 24 (28%) patients. TEAEs observed in patients in Cohort C who crossed over and received tucatinib in combination with trastuzumab were consistent with those reported in patients in Cohort A and Cohort B.

Regulatory considerations

This is the first FDA approval for the treatment of patients with unresectable or metastatic *HER2*+ *RAS* WT CRC following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Although CRC is a common disease, *HER2* overexpression or amplifications in CRC are infrequent and the incidence in modern studies is below 5% (6,7). In addition, not all patients with CRC are tested for genetic abnormalities. While randomized controlled trials are preferred to support accelerated approval – including biomarker-defined populations wherein the available therapy was not specifically studied - single arm trials may be acceptable in settings where the population is rare and there is an unmet medical need (17). In this setting, the notable response rates of significant duration in the MOUNTAINEER trial led to the accelerated approval of tucatinib in combination with trastuzumab.

Although preclinical models of *HER2*-amplified CRC tumors were sensitive to *HER2* blockade, the level of activity observed with anti-*HER2* monoclonal antibodies or tyrosine kinase inhibitors as single agents was lower than the anti-tumor activity observed with combination of these agents (18,19). Based on the preclinical data and small clinical trials supporting these findings (5), the MOUNTAINEER study combined two *HER2* inhibitors, tucatinib and trastuzumab. Single agent tucatinib activity was low with an ORR per BIRC

observed by Week 12 of 3.3% [95% CI: 0.1, 17]) among the 30 patients treated in Cohort C; 28 of these patients subsequently received tucatinib in combination with trastuzumab and 5 patients experienced a tumor response (ORR 18% [95% CI: 6, 37]) following crossover to the combination. The preclinical data and Cohort C outcomes demonstrated the contribution of tucatinib and trastuzumab to the overall effect observed, supporting the need for both agents to be used in combination.

The investigation of tucatinib in combination with trastuzumab for this indication did not reveal any new adverse event signals and the safety profile was generally consistent with the known clinical experience with tucatinib in combination with trastuzumab in patients with breast cancer. The rate of TEAEs was lower than that of the breast cancer HER2CLIMB trial, with the difference likely reflecting the use of concurrent treatment with capecitabine in the breast cancer study. The risks of the combination tucatinib and trastuzumab were deemed largely manageable with patient surveillance, treatment delays, and supportive care in most patients, and felt to be acceptable in the context of metastatic disease.

The review team concluded that the overall benefit:risk assessment supported approval of tucatinib in combination with trastuzumab for the treatment of patients with relapsed/refractory advanced or metastatic *RAS* WT, *HER2*+ CRC. The observed ORR of 38% with a median DOR of 12.4 months is clinically meaningful, particularly when compared to available treatment options. The benefit:risk assessment is summarized in Table 3.

As a condition of accelerated approval, FDA required a confirmatory study to verify clinical benefit. The ongoing randomized controlled clinical trial (MOUNTAINEER-03; NCT05253651) comparing the efficacy of tucatinib in combination with trastuzumab and mFOLFOX6 to mFOLFOX6, with or without bevacizumab or cetuximab for the first-line treatment of patients with *RAS* WT, *HER2*+ metastatic CRC was proposed as a confirmatory trial.

There is currently no FDA-approved test for assessment of *HER2* status in CRC. A post-marketing commitment was requested and agreed to by the Applicant to develop a companion diagnostic test for this indication.

This review was conducted under the FDA Oncology Center of Excellence Project Orbis (20), an initiative that provides a framework for concurrent submission and review of oncology drugs across international regulatory authorities. For this review, FDA collaborated with the Australian Therapeutic Goods Administration (TGA). The application review is ongoing at the other regulatory agency.

Conclusions

Tucatinib in combination with trastuzumab for the treatment of relapsed/refractory *RAS* WT *HER2+* CRC has a favorable risk: benefit profile. The observed ORR of 38% with a median DOR of 12.4 months is considered clinically meaningful. This approval adds to the increasing number of treatment options for biomarker selected patients with advanced CRC (21, 22, 23, 24,25).

Overall, the safety profile of tucatinib in combination with trastuzumab is acceptable given the demonstrated benefits in patients with relapsed or refractory *RAS* WT *HER2+* CRC. A randomized controlled trial to provide data to verify the benefit of tucatinib in combination with trastuzumab is underway. The Applicant agreed to FDA's request for a post marketing commitment to develop a companion diagnostic test for the selection of patients eligible for treatment with this combination.

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Table 1.

MOUNTAINEER: Demographic and Baseline Disease Characteristics

	Tucatinib and trastuzumab (Cohorts A and B) N = 84	Tucatinib (Cohort C) N= 30
Age		
– Median, years (range)	55.0 (24, 77)	59.5 (29, 75)
– ≥ 65 years old, n	12 (14%)	11 (37%)
Sex, n (%)		
– Female	33 (39%)	15 (50%)
– Male	51 (61%)	15 (50%)
Race, n (%)		
– White	65 (77%)	23 (77%)
– Asian	3 (4%)	0
– Black or African American	3 (4%)	3 (10%)
– American Indian or Alaskan native	1 (1%)	0
– Multiple	1 (1%)	0
– Unknown	11 (13%)	4 (13%)
Ethnicity, n (%)		
– Not Hispanic/Latino	64 (76%)	25 (83%)
– Hispanic/Latino	3 (4%)	1 (3%)
– Unknown	17 (20%)	4 (13%)
ECOG PS, n (%)		
– 0	50 (60%)	17 (57%)
– 1	31 (37%)	13 (43%)
– 2	3 (4%)	0
Sidedness		
– Left colon	71 (85%)	27 (90%)
– Right colon	5 (6%)	3 (10%)
– Transverse colon	7 (8%)	0
– Multiple sites	1 (1%)	0
Metastases at study entry		
– Liver	54 (64%)	15 (50%)
– Lung	59 (70%)	20 (67%)
Prior systemic therapy, n (%)		
– Fluoropyrimidine	84 (100%)	30 (100%0
– Irinotecan	83 (99%)	30 (100%)
– Oxaliplatin	84 (100%)	30 (100%)
– Anti-VEGF mAb	72 (86%)	26 (87%)
– Anti EFGR mAb	44 (52%)	17 (57%)
– Anti PD(L)1 mAb	3 (4%)	2 (7%)

Source: FDA analysis

Table 2.

MOUNTAINEER: Common Adverse Events (Incidence ≥ 10%)

	Tucatinib and trastuzumab (Cohorts A and B) N = 86; n (%)	Tucatinib (Cohort C) N= 30; n (%)
Patients with an event	82 (95%)	28 (93%)
Diarrhea	55 (64%)	10 (33%)
Fatigue	38 (44%)	6 (20%)
Rash[1]	32 (37%)	5 (17%)
Nausea	30 (35%)	5 (17%)
Infusion-related reaction	18 (21%)	0
Abdominal pain[2]	18 (21%)	10 (33%)
Pyrexia	17 (20%)	3 (10%)
Chills	16 (19%)	0
Decreased appetite	16 (19%)	4 (13%)
Back pain	15 (17%)	6 (20%)
Hypertension	15 (17%)	0
Arthralgia	14 (16%)	2 (7%)
Cough	14 (16%)	2 (7%)
Vomiting	14 (16%)	2 (7%)
Dyspnea	12 (14%)	2 (7%)
Constipation	12 (14%)	4 (13%)
Myalgia	11 (13%)	2 (7%)
Anxiety	9 (10%)	0
Anemia	9 (10%)	4 (13%)

[1]Grouped term, includes: abdominal discomfort, abdominal pain, and abdominal pain upper.

[2]Grouped term, includes: acne, dermatitis acneiform, dermatitis contact, erythema, erythema multiforme, rash, rash macular, rash maculopapular, rash papular, rash pustular, skin exfoliation, and urticaria.

Source: FDA analysis

Table 3.

FDA Benefit:Risk Analysis

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	•*HER2* overexpression or amplification is rare in CRC, and can be seen in up to an estimated 5% of patients with *RAS* WT tumors. • The prognostic role of *HER2* in CRC is unclear. • Relapsed or refractory advanced or metastatic CRC is a serious condition, with estimated median survival after treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based ± monoclonal antibodies regimens of 6–7 months	Refractory colorectal cancer is a serious and life-threatening disease
Current treatment options	•For the non-biomarker driven population, treatment after disease progression/relapse is limited to regorafenib and tipiracil/trifluridine; both drugs were approved based on improvement in overall survival-ORR was less than 2%. • No available treatment approved for *HER2+* patients.	Current treatment options for patients with *RAS* wild-type, *HER2+* refractory colorectal cancer are limited and provide a limited benefit; patients with this disease have an unmet medical need.
Benefit	•The ORR benefit in 84 patients with *RAS* WT *HER2+* advanced or metastatic CRC who received treatment with tucatinib in combination with trastuzumab in the MOUNTAINEER trial was 38% (95% CI 28, 49) • The median DoR was 12.4 months (95% CI 8.5, 20.5) • 32 patients had confirmed responses; 81% had a response duration ≥6 months.	The magnitude of ORR and durable responses observed in patients treated with tucatinib in combination with trastuzumab in the MOUNTAINEER trial are clinically meaningful, particularly in the context of a disease with estimated survival of 6–7 months with available therapy. An ongoing randomized study comparing standard of care chemotherapy in combination with tucatinib and trastuzumab for the first line treatment of patients with *RAS* WT *HER2+* metastatic CRC is ongoing.
Risk and risk management	•Among the 86 patients with *RAS* WT, *HER2+* refractory unresectable or metastatic colorectal cancer treated with tucatinib and trastuzumab in Cohorts A and B of MOUNTAINEER, the most common adverse reactions and laboratory abnormalities (incidence ≥ 20%) were diarrhea, increased creatinine increased glucose, increased ALT, decreased hemoglobin, fatigue, increased AST, rash, nausea, increased bilirubin, increased alkaline phosphatase, decrease lymphocytes, decreased albumin, decreased leukocytes, and fever	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Information in the Warnings and Precautions and Dosage and Administration sections of product labeling address these toxicities adequately.

Source: FDA analysis