

Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced *ERBB2/HER2*-Positive Metastatic Breast Cancer

A Phase 1b Clinical Trial

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IMPORTANCE Treatment options for patients with disease progression after treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) are limited. Tucatinib is an oral, potent, human epidermal growth factor receptor 2 (HER2)-specific tyrosine kinase inhibitor (TKI) being developed as a novel treatment for *ERBB2/HER2*-positive breast cancer.

OBJECTIVE To determine the maximum tolerated dosage of tucatinib in combination with T-DM1 in the treatment of patients with *ERBB2/HER2*-positive metastatic breast cancer with and without brain metastases.

DESIGN, SETTING, AND PARTICIPANTS In this phase 1b open-label, multicenter, clinical trial, 57 participants enrolled between January 22, 2014, and June 22, 2015, were 18 years of age or older with *ERBB2/HER2*-positive metastatic breast cancer previously treated with trastuzumab and a taxane. Data were analyzed between January and March 2018.

INTERVENTIONS Tucatinib 300 mg or 350 mg administered orally twice per day for 21 days and T-DM1 3.6 mg/kg administered intravenously once every 21 days.

MAIN OUTCOMES AND MEASURES Safety assessments, pharmacokinetics, and response were assessed using RECIST 1.1 every 2 cycles for 6 cycles, followed by every 3 cycles.

RESULTS Fifty-seven T-DM1-naïve patients (median [IQR] 51 [44.0-63.0] years of age) who had undergone a median of 2 earlier HER2 therapies (range, 1-3) were treated. The tucatinib maximum tolerated dosage was determined to be 300 mg administered twice per day with dose-limiting toxic reactions seen at 350 mg twice per day. Pharmacokinetic analysis showed that there was no drug-drug interaction with T-DM1. Adverse events seen among the 50 patients treated at the maximum tolerated dosage regardless of causality included nausea (36 patients; 72%), diarrhea (30 patients; 60%), fatigue (28 patients; 56%), epistaxis (22 patients; 44%), headache (22 patients; 44%), vomiting (21 patients; 42%), constipation (21 patients; 42%), and decreased appetite (20 patients; 40%); the majority of adverse events were grade 1 or 2. Tucatinib-related toxic reactions that were grade 3 and above included thrombocytopenia (7 patients; 14%) and hepatic transaminitis (6 patients; 12%).

CONCLUSIONS AND RELEVANCE In this study, tucatinib in combination with T-DM1 appeared to have acceptable toxicity and to show preliminary antitumor activity among heavily pretreated patients with *ERBB2/HER2*-positive metastatic breast cancer with and without brain metastases.

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Breast cancer is the most common cancer among women worldwide and is the second leading cause of cancer-related death in the United States.^{1,2} Approximately 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2).^{3,4} Human epidermal growth factor receptor 2 (expressed by *ERBB2/HER2*) is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Cancers associated with overexpression of HER2 are more aggressive and, before the introduction of *ERBB2/HER2*-targeted agents, were associated with poorer overall survival compared with *ERBB2/HER2* negative cancers.⁵

The introduction of antibody-based *ERBB2/HER2*-targeted therapies has led to significant improvements in outcomes in the neoadjuvant, adjuvant, and metastatic settings.⁶⁻¹⁰ Lapatinib, 1 of 2 currently approved tyrosine kinase inhibitors (TKIs), has shown modest benefit in the metastatic setting but is associated with epidermal growth factor receptor (EGFR) off-target toxic reactions, including rash and diarrhea.¹¹ Similarly, neratinib, a pan-*Erb* TKI approved for use in the extended adjuvant setting, is also associated with EGFR-related toxic reactions.¹²

Treatment options for patients who experience disease progression after treatment with trastuzumab, pertuzumab, and T-DM1 are limited. Although there are no direct comparator trials, treatment guidelines currently recommend use of either lapatinib plus capecitabine, trastuzumab plus a cytotoxic chemotherapy, or lapatinib plus trastuzumab.⁴ Although lapatinib plus capecitabine is an approved regimen, it has not been studied in the setting of disease progression after earlier treatment with trastuzumab, pertuzumab, and T-DM1, nor has it been shown to improve overall survival.⁴ At this time, no single regimen is considered to be standard of care in this setting, and treatment options with better efficacy and improved tolerability for late-stage breast cancer are needed.

Tucatinib is an oral, potent, reversible HER2-specific TKI that is being developed as a novel treatment for *ERBB2/HER2*-positive breast cancer. Tucatinib selectively inhibits *ERBB2/HER2*, a feature that differentiates it from the other small-molecule *ERBB2/HER2*-targeted TKIs, all of which are dual inhibitors of both *EGFR* and *ERBB2/HER2*. Tucatinib is active as a single agent and in combination with either chemotherapy or trastuzumab in murine xenograft models of *ERBB2/HER2*-positive breast cancer, including intracranial tumor xenograft models.¹³

This study is an open-label multidose phase 1b trial of the combination of tucatinib and T-DM1 among T-DM1-naïve patients with advanced metastatic breast cancer with or without brain metastases.

Methods

Study Design and Treatment

The primary objective of this open-label phase 1b study with dose-escalation and expansion cohorts was to determine the maximum tolerated dosage of tucatinib in combination with T-DM1. Secondary objectives were to determine the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of this combination as assessed by objective response rate and progression-free survival. The institutional review boards of all participating sites

Key Points

Question What is the maximum tolerated dosage of tucatinib combined with ado-trastuzumab emtansine in the treatment of patients with *ERBB2/HER2*-positive metastatic breast cancer with and without brain metastases?

Findings In this phase 1b study of 57 patients with metastatic or unresectable locally advanced *ERBB2/HER2*-positive breast cancer treated previously with trastuzumab and a taxane, the maximum tolerated dosage of tucatinib combined with ado-trastuzumab emtansine was determined to be 300 mg administered orally twice daily; the objective response rate was 48%; and median progression-free survival was 8.2 months.

Meaning Tucatinib in combination with ado-trastuzumab emtansine had acceptable toxicity and showed preliminary antitumor activity among heavily pretreated patients with *ERBB2/HER2*-positive metastatic breast cancer with and without brain metastases.

approved the trial, which has been registered at ClinicalTrials.gov (NCT01983501). All patients provided written informed consent before the initiation of study-related treatment or procedures. The trial protocol is available in Supplement 1.

In the dose-escalation phase, a modified 3 + 3 dose-escalation design was used to determine the maximum tolerated dosage of tucatinib. On the basis of the results of the single-agent ARRAY-380-101 study, the starting dosage was selected as 300 mg twice daily using a tablet formulation.¹³ The design allowed at least 6 evaluable patients to be enrolled per tucatinib dosage level, with an expansion cohort at the maximum tolerated dosage. In addition to the maximum tolerated dosage expansion cohort, an additional brain metastases expansion cohort was enrolled that consisted of patients with either untreated or previously treated progressing brain metastases not requiring immediate central nervous system-directed therapy.

Dosage-limiting toxic reactions were defined as any adverse event during the first cycle not attributable to the patient's disease in the dosage escalation cohort. The dosage-limiting toxic reactions included hematologic toxic reactions of grade 3 or greater, neutropenia with fever, grade 4 neutropenia for more than 7 days, grade 4 thrombocytopenia, grade 3 or greater thrombocytopenia associated with significant bleeding, and grade 4 anemia; nonhematologic toxic reactions of grade 3 or greater toxicity considered related to tucatinib or the combination; interruption of dosing for more than 2 weeks if secondary to an adverse event; a dose reduction because of a toxic reaction related to tucatinib or the combination; grade 4 hypokalemia; and grade 3 or greater elevation of hepatic transaminase levels (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin levels (irrespective of transaminase levels). Events not considered to be dosage-limiting toxic reactions were grade 3 fatigue (lasting 3 days or less); nausea, diarrhea, or vomiting without optimal use of antiemetics or antidiarrheals; and grade 3 rash without maximal use of corticosteroids or anti-infective agents.

Patient Population

Patients 18 years of age or older with progressive *ERBB2/HER2*-positive metastatic breast cancer previously treated with

trastuzumab and a taxane were eligible for the study. HER2 positivity was documented by fluorescent in situ hybridization amplification or by 3+ immunohistochemistry staining using local assays. Other key inclusion criteria included evaluable lesions as defined according to RECIST 1.1, Eastern Cooperative Oncology Group performance status 0 or 1, adequate organ function, and normal left ventricular ejection fraction (LVEF). Key exclusion criteria included earlier exposure to doxorubicin at a dosage of more than 360 mg/m²; earlier treatment with T-DM1, neratinib, or afatinib; and the presence of leptomeningeal metastases. Patients with treated progressive brain metastases were excluded from the dosage escalation cohort; however, patients with treated stable brain metastases who did not require corticosteroids were included. Patients with untreated brain metastases or treated and progressive brain metastases not requiring immediate central nervous system-directed therapy were included in the brain metastases expansion cohort.

Statistical Analysis

This study was designed to assess the safety, tolerability, and maximum tolerated dosage of tucatinib given in combination with T-DM1. No formal statistical comparisons between dose cohorts were performed.

Demographic characteristics, baseline characteristics, adverse events, laboratory toxicities, and dosage-limiting toxicities were summarized among patients in the safety analysis set (ie, patients who received at least 1 dose of either tucatinib or T-DM1) using descriptive statistics. Progression-free survival, defined as the time from the date of the first dose of the study treatment to the date of documented disease progression or death from any cause, was evaluated among patients in the safety analysis set with use of Kaplan-Meier methods. Duration of response, defined as the time from the first objective response to documented disease progression, was evaluated among patients in the safety analysis set who had an objective response with use of Kaplan-Meier methods. Objective response, defined as achieving a best overall response of complete or partial response, was evaluated for assessable patients in the safety analysis set (ie, patients who had at least 1 identifiable target and/or nontarget lesion at baseline and had at least 1 postbaseline disease assessment). Patients were not followed-up to determine overall survival after completion of the study treatment.

Safety Assessments

Safety was monitored throughout the study, and assessments included all adverse events, dosage-limiting toxic reactions (in cycle 1 for dose escalation cohorts only), clinical laboratory parameters, electrocardiogram findings, Eastern Cooperative Oncology Group performance status, vital signs, physical examination findings, and LVEF. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Efficacy Assessments

Contrast computed tomography or magnetic resonance imaging scans of all areas of known disease were obtained at baseline, every 2 treatment cycles through cycle 6, and every 3 treatment cycles thereafter until disease progression, initia-

tion of a new therapy, or withdrawal of consent. All patients underwent screening brain magnetic resonance imaging before the first study dose. Scans were locally assessed with RECIST 1.1 to determine the objective response rate. For patients with brain metastases, exploratory assessments that considered only lesions in the brain with use of modified RECIST 1.1 criteria were performed.¹⁴

Pharmacokinetic Assessments

Plasma and serum samples were collected to assess the association between combination treatment and the pharmacokinetics of both tucatinib and T-DM1. Levels of tucatinib and its metabolite as well as of the T-DM1 metabolite, DM1, were measured.¹⁵ On binding to HER2, T-DM1 is internalized intracellularly, and DM1 is presumably cleaved from the antibody by lysosomal enzymes. The DM1 can also be released from the antibody-drug conjugate by plasma proteases. Tucatinib pharmacokinetics were assessed at the start of treatment (cycle 1, day 1) and again at the beginning of cycle 2 (cycle 2, day 1). Trough tucatinib samples were collected on the first day of cycles 3 through 6. Samples to evaluate DM1 levels were collected before and after T-DM1 administration for the first 2 cycles, starting on cycle 1, day 2. In addition, samples were collected to assess DM1 levels on a weekly basis for the first 6 weeks.

Results

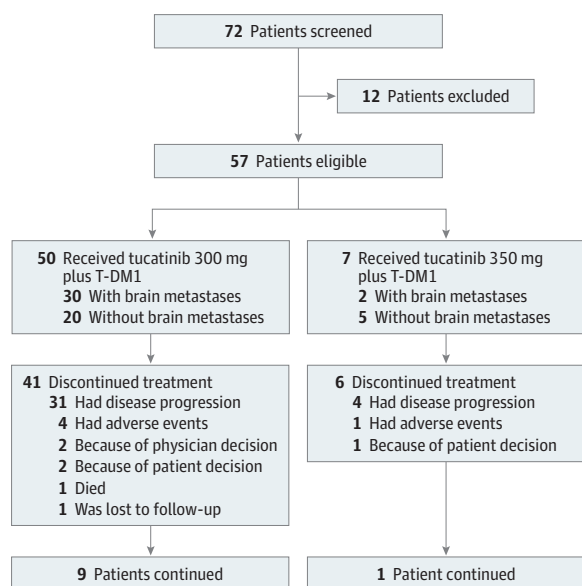
Patient Characteristics

Between January 22, 2014, and July 22, 2015, 57 patients (median age, 51 years [interquartile range, 44.0-63.0 years]; all patients were female) were enrolled at 11 sites in the United States and Canada. Data cutoff for the analysis was September 30, 2017, and data analysis was performed between January and March 2018. Fifty patients were treated at a dosage of 300 mg twice daily (including 8 patients treated in the initial dosage escalation cohort of 300 mg twice daily), 23 in the maximum tolerated dosage expansion cohort, and 19 in the brain metastases expansion cohort (Figure 1). Sixty percent of the patients (30 of 50 patients) treated at the combination maximum tolerated dosage had baseline brain metastases. Seven additional patients were enrolled and treated in the 350 mg twice daily dosage escalation cohort before that dosage level was declared dosage limiting. All patients received earlier trastuzumab, 46% (23 of 50 patients) received earlier pertuzumab, and 20% (10 of 50 patients) received earlier lapatinib. Patient characteristics are summarized in Table 1. Only a single patient treated in the 300-mg tucatinib arm had metastatic disease only in the bones.

Dosage Escalation, Dosage-Limiting Toxicities, and Maximum Tolerated Dosage

The initial dosage level for tucatinib was 300 mg administered orally twice daily (tablet formulation), which is 50% of the maximum tolerated dosage for the tucatinib powder in capsule formulation.¹³ Additional dosage escalation cohorts were originally planned with 450 and 600 mg administered orally twice daily. However, pharmacokinetic data from the 300-mg cohort demonstrated that the maximum concentration (C_{max})

Figure 1. Maximum Tolerated Dosage of Tucatinib Combined With Ado-Trastuzumab Emtansine (T-DM1) Trial Profile



A flow diagram showing the progress of patients throughout the trial.

and area under the curve (AUC) of the tablet formulation of tucatinib were indistinguishable from those of the powder in capsule formulation at the maximum tolerated dosage of 600 mg twice daily.¹³ Consequently, the dosage escalation schema was amended to include the dosages of 300, 350, and 400 mg twice daily of tucatinib.

A total of 4 patients experienced dosage-limiting toxic reactions (all grade 3) in the dose-finding phase (1 of 8 patients at the 300-mg dose level; 3 of 7 patients at the 350-mg dose level) (Table 2). Because of 3 dosage-limiting toxic reactions (drug hypersensitivity, fatigue, and vomiting) observed in 7 patients at the 350-mg dose level, the 300 mg administered orally twice daily dosage level was determined to be the maximum tolerated dosage.

Safety and Tolerability

Treatment-emergent adverse events and tucatinib-related adverse events are summarized in eTable 1 in Supplement 2. The most commonly reported treatment-emergent adverse events (all grades) at the maximum tolerated dosage were nausea (36 of 50 patients [72%]), diarrhea (30 patients [60%]), fatigue (28 patients [56%]), epistaxis (22 patients [44%]), headache (22 patients [44%]), constipation (21 patients [42%]), thrombocytopenia (7 patients [14%]), vomiting (21 patients [42%]), and decreased appetite (20 patients [40%]). Adverse events assessed by the investigator to be related to tucatinib and reported for 20% or more patients receiving the maximum tolerated dosage were (in decreasing frequency) nausea, diarrhea, fatigue, increased AST levels, vomiting, decreased appetite, increased ALT levels, and hypokalemia.

eTable 1 in Supplement 2 shows the incidence of grade 3 or higher treatment-emergent adverse events and tucatinib-related adverse events. At the maximum tolerated dosage, the

Table 1. Patient Characteristics

Characteristic	Patients, No. (%)	
	300 mg Twice Daily (n = 50)	350 mg Twice Daily (n = 7)
Age, median (range), y	51 (30-72)	51 (31-66)
Sex		
Female	50 (100)	7 (100)
Race/ethnicity		
White	37 (74)	6 (86)
Black/African American	6 (12)	0
Asian	6 (12)	1 (14)
Unknown	1 (2)	0
ECOG performance status		
0	20 (40)	2 (29)
1	30 (60)	5 (71)
No. of previous HER2 agents, median (range)	2 (1-3)	1 (1-2)
Brain metastases		
Yes	30 (60)	2 (29)
No	20 (40)	5 (71)
Most recent previous radiotherapy for brain metastases		
Whole brain	10 (20)	2 (29)
Stereotactic radiosurgery	9 (18)	0
None	31 (62)	5 (71)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

grade 3 or higher treatment-emergent adverse events reported for 10% or more of the patients (in decreasing frequency) were thrombocytopenia, hypokalemia, increased ALT levels, increased AST levels, fatigue, and hypophosphatemia. The tucatinib-related adverse events of grade 3 or higher that were reported for 10% or more of the patients were thrombocytopenia, increased ALT levels, and increased AST levels.

One patient died during the study owing to drowning, and 2 additional patients (4%) died owing to disease progression within 30 days after their last dose of tucatinib. Overall, 21 of 57 patients (37%) developed serious adverse events; in 6 patients, these adverse events were considered to be related to receipt of tucatinib. These adverse events were cardiac failure in 2 patients (both grade 1; asymptomatic decrease in LVEF) and fatigue, pyrexia and drug hypersensitivity, vomiting and hypokalemia, and pneumonia in 1 patient each.

Overall, 32 of 57 patients (56%) required interruption of tucatinib treatment. Tucatinib therapy was successfully reinitiated for 22 of 32 patients (69%), 18 of whom underwent a dosage reduction. Five patients discontinued tucatinib therapy because of an adverse event.

Elevation of hepatic transaminase levels (mostly grade 1) occurred in more than 70% of patients who were treated at the maximum tolerated dosage. In instances of grade 3 or 4 elevation of AST levels (7 of 57 patients [12%]) and/or ALT levels (8 of 57 patients [14%]), all elevated levels were reversible to baseline grade after administration of study drugs was interrupted, except in 2 cases where patients were documented to have progression of hepatic metastases. Two patients discontinued tucatinib treatment because of elevated transaminase

levels: 1 patient with grade 4 elevation of AST levels discontinued the study as mandated by the protocol, and 1 patient had tucatinib administration interrupted because of grade 3 ALT level elevation and was subsequently found to have disease progression in the liver before tucatinib therapy was restarted.

Two patients experienced grade 1 cardiac failure. In 1 patient, the decrease in LVEF did not resolve on repeated testing, and the patient discontinued the study. In the second patient, the LVEF decrease resolved, and the patient restarted therapy with tucatinib but not with T-DM1 and did not have a recurrence of the event while participating in the study.

Pharmacokinetics

The mean steady state C_{max} , median time to maximum concentration (T_{max}), and median AUC over the dosing interval (AUC_{tau}) for the 300-mg twice daily dosage were 790 ng/mL (SD, 329 ng/mL), 2 hours (range, 0-6 hours), and 4540 hours × ng/mL (range, 2600-7270 hours × ng/mL), respectively (eTable 2 in Supplement 2). At 350 mg twice daily, the mean C_{max} , median T_{max} , and median AUC_{tau} were 1120 ng/mL (SD, 525 ng/mL), 1 hour (range, 1-3 hours), and 7120 hours × ng/mL (range, not calculated), respectively (eTable 2 in Supplement 2). The last time point for pharmacokinetic sampling was 6 hours, such that the AUC_{tau} value was extrapolated. Pharmacokinetic data demonstrated that the mean plasma tucatinib concentrations and AUC were higher at the 350-mg twice daily dosage but with a similar T_{max} , which suggests a

slower elimination profile for the drug at a higher dosage. The exposure to tucatinib increased after repeated dosing, with an accumulation factor of approximately 1.5. The intersubject variability in pharmacokinetic parameters ranged between 29% and 47%. The mean plasma concentration of DM1, the metabolite of T-DM1, was low and in the nanograms per milliliter range, which is consistent with findings reported in the literature and indicates no association between tucatinib and DM1 drug levels.

Efficacy

Fifty patients treated with tucatinib plus T-DM1 at the maximum tolerated dosage had a median progression-free survival of 8.2 months (95% CI, 4.8-10.3 months) (Figure 2). Among patients previously treated with both trastuzumab and pertuzumab (n = 20), the median progression-free survival was 6.5 months (95% CI, 4.1-9.2 months). Thirty-four of 50 patients (68%) treated with the maximum tolerated dosage had measurable disease and were evaluable for response with an objective response rate of 47% (1 patient with complete response, 15 patients with partial response, 14 patients with stable disease, and 4 patients with disease progression). The clinical benefit rate (patients with complete response, partial response, and stable response for >6 months) among 48 evaluable patients with post-baseline cancer scans was 58% (28 patients). Among patients whose disease responded to treatment, the median duration of response was 6.9 months (95% CI, 2.8-19.8 months).

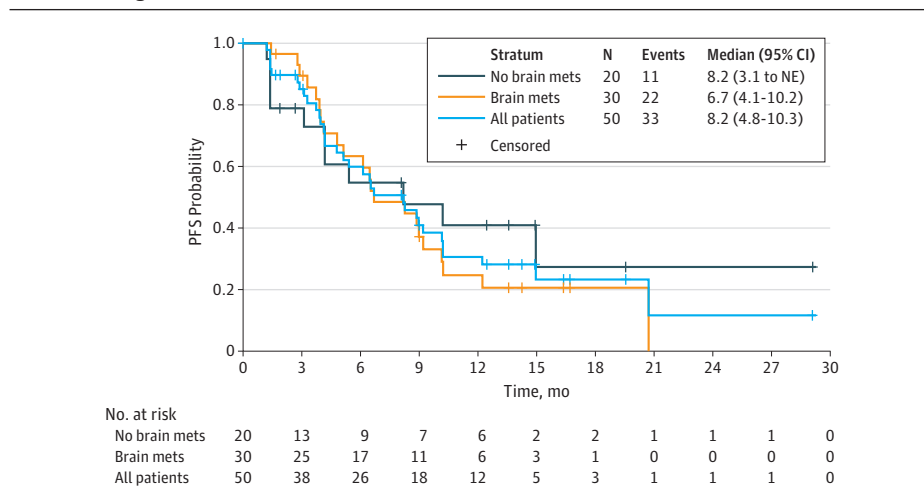
Thirty of 50 patients (60%) treated with the maximum tolerated dosage had brain metastases at study entry. Of these, 21 of 30 patients (70%) had either untreated or previously treated and progressive brain metastases. Median progression-free survival among patients with brain metastases was 6.7 months (95% CI, 4.1-10.2 months) with a median duration of overall response according to RECIST 1.1 of 6.9 months (95% CI, 1.45-19.48 months).

Activity in brain metastases was assessed using modified RECIST criteria (brain-specific criteria) considering only lesions in the brain. Brain metastases were measurable in 14 of 30 patients (47%). Among the 14 patients with measurable brain

Table 2. Dosage-Limiting Toxic Reactions Among the Dosage-Finding Cohorts

Event	Patients, No. (%)	
	300 mg Twice Daily (n = 8)	350 mg Twice Daily (n = 7)
Any dosage-limiting toxic reaction	1 (13)	3 (43)
Abnormal liver function test result	1 (13)	0
Drug hypersensitivity	0	1 (14)
Fatigue	0	1 (14)
Vomiting	0	1 (14)

Figure 2. Kaplan-Meier Plot of Progression-Free Survival (PFS) Among Patients Treated With the Maximum Tolerated Dosage of Tucatinib Combined With Ado-Trastuzumab Emtansine



Abbreviations: BM, brain metastases; Mets, metastases; NBM, no brain metastases; NE, nonevaluable.

metastases, the brain-specific objective response rate was 36% (2 patients had complete response, 3 had partial response, 7 had stable disease, and 2 were nonevaluable).

Discussion

Although the use of *ERBB2/HER2*-targeted therapy has improved the outlook for patients with *ERBB2/HER2*-positive breast cancer, almost all patients with metastatic breast cancer ultimately experience disease progression. There is evidence that dual targeting of *ERBB2/HER2*, either through the combination of 2 different *ERBB2/HER2*-targeted antibodies or through an antibody-based therapy and a TKI, can lead to further improvements in efficacy.⁸ This study, combining T-DM1 and tucatinib, demonstrated the feasibility of the combination, which provided dual inhibition of *ERBB2/HER2*, potentially improving on the efficacy of single-agent therapy with T-DM1 through use of an alternative mechanism of receptor inhibition. The greater selectivity of tucatinib compared with other *ERBB2/HER2*-targeted TKIs offers the potential to provide dual HER2 blockade with potentially fewer toxic reactions than are associated with agents that also inhibit EGFR. A *ERBB2/HER2*-targeted TKI like tucatinib with brain metastases activity may also improve the treatment of brain metastases compared with antibody-based therapy.

The study established that the tucatinib tablet formulation maximum tolerated dosage was 300 mg administered orally twice daily, and this is the recommended dosage of tucatinib to be used in subsequent and ongoing clinical trials. Furthermore, pharmacokinetic analyses indicated no drug-drug interaction between tucatinib and T-DM1.

The combination of tucatinib and T-DM1 was well tolerated at the study-derived maximum tolerated dosage and schedule. Most toxic reactions encountered were attributable to T-DM1 and were consistent with those observed in earlier studies that used T-DM1 as monotherapy.^{9,16-18} Most adverse events were manageable with supportive therapy, interruption of therapy, or dosage reduction. Of note, no significant EGFR-related adverse events were observed, which is consistent with the selectivity for HER2 of tucatinib. Despite no preventative anti-diarrheal regimen being used in this study, only 2 patients experienced grade 3 tucatinib-related diarrhea. Similarly, no cases of tucatinib-related rash were observed. The infrequency of EGFR-related toxic reactions seen with tucatinib and T-DM1 therapy makes this combination a potentially attractive treatment option.

Hepatotoxicity is observed with single-agent T-DM1 therapy as well as with tucatinib therapy. In this trial, hepatotoxicity was infrequent and reversible, which is consistent with reported single-agent studies of either agent. Cardiotoxicity, a known on-target adverse event associated with *ERBB2/*

HER2-targeted agents, was uncommon in this study, and cardiotoxicity rates in this study were consistent with historical rates of cardiotoxicity associated with these agents.

The combination of tucatinib and T-DM1 demonstrated preliminary activity in pretreated patients with *ERBB2/HER2*-positive metastatic breast cancer as reflected by a median progression-free survival of 8.2 months (95% CI, 4.8-10.3 months) among patients treated with the maximum tolerated dosage. These results compare favorably with those of retrospective trials assessing response to T-DM1 therapy after multiple lines of *ERBB2/HER2*-based therapy, among which the median progression-free survival is approximately 6 months.¹⁸⁻²¹ The median progression-free survival among patients with brain metastases was 6.7 months (95% CI, 4.1-10.2 months), which is encouraging compared with other systemic therapies used to treat a similar patient population.²²

Limitations

Nonetheless, data regarding activity among patients with brain metastases are based on a relatively small sample size. Moreover, most patients with brain metastases in the trial had either untreated brain metastases or progressive brain metastases, and such patients are typically excluded from clinical trials of systemic therapy in metastatic breast cancer. Up to 50% of patients with *ERBB2/HER2*-positive metastatic breast cancer will develop brain metastases during the course of their disease.²³⁻²⁶ The current standard therapy for brain metastases mostly uses central nervous system-directed therapy with surgery and/or radiation, both of which have the potential for treatment-related central nervous system injury that may impact cognition or elementary neurologic function, such as ambulation. There is no approved systemic regimen with significant activity in *ERBB2/HER2*-positive brain metastases. Several current *ERBB2/HER2*-targeted regimens have purported activity in brain metastases, including single-agent T-DM1; however, there are no randomized data to identify the most active systemic therapy among this patient population.²⁷⁻³⁰ A randomized trial of tucatinib in combination with T-DM1 is necessary to confirm the preliminary efficacy of this regimen among patients with brain metastases and to determine the added benefit of tucatinib in combination with T-DM1 among patients overall.

Conclusions

Tucatinib represents a promising new therapy with highly selective *ERBB2/HER2* targeting that offers a favorable adverse event profile and demonstrates preliminary systemic and brain metastases activity when used in combination with standard-dosage T-DM1 for the treatment of *ERBB2/HER2*-positive metastatic breast cancer. Additional studies with tucatinib combinations are warranted.

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Study concept and design: Borges, Ferrario.

Acquisition, analysis, or interpretation of data: All authors.

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Study supervision: Borges, Ferrario, Conlin, Chaves, Chamberlain, Hamilton.

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