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ORIGINAL ARTICLE

Tucatinib and trastuzumab emtansine for patients with previously treated HER2-positive locally advanced and metastatic breast cancer: primary analysis of the randomized phase III trial HER2CLIMB-02☆

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Background: Trastuzumab emtansine (T-DM1) is a standard treatment option in patients with previously treated human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer (LA/MBC). Here, we report the efficacy and safety of tucatinib in combination with T-DM1 compared with T-DM1 alone from the phase III HER2CLIMB-02 study (NCT03975647).

Patients and methods: Eligible patients had HER2-positive LA/MBC that had been previously treated with trastuzumab and a taxane in any setting; these included patients with brain metastases (BMs). Patients were randomly assigned 1 : 1 to receive T-DM1 (3.6 mg/kg intravenously every 21 days) combined with either tucatinib (300 mg orally twice daily) in the tucatinib arm or placebo (orally twice daily) in the control arm.

Results: In total, 463 patients were randomly assigned. After a median follow-up duration of 24.4 months, the median progression-free survival (PFS) was 9.5 months in the tucatinib arm and 7.4 months in the control arm [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.61-0.95, $P = 0.0163$]. A PFS benefit was observed across all prespecified subgroups, including in patients with BMs. Interim overall survival analysis results were immature. The median OS was not reached in the tucatinib arm and was 38.0 months in the control arm (HR 1.23, 95% CI 0.87-1.74). The incidences of treatment-emergent adverse events (TEAEs) associated with any treatment discontinuation and of grade $\geq$3 TEAEs were higher in the tucatinib arm than in the control arm (22.1% versus 11.6% and 68.8% versus 41.2%, respectively). The most common grade $\geq$3 TEAEs in the tucatinib arm were elevated alanine aminotransferase (16.5%) and aspartate aminotransferase levels (16.5%) (versus 2.6% for both in the control arm).

Conclusion: The addition of tucatinib to T-DM1 improved PFS in patients with previously treated HER2-positive LA/MBC, including patients with BMs, and exhibited a manageable safety profile.

Key words: advanced/metastatic breast cancer, brain metastases, human epidermal growth factor receptor 2-positive, T-DM1, trastuzumab emtansine, tucatinib

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is overexpressed in ∼15%-20% of breast cancers (BCs), and HER2-overexpressing (HER2-positive) tumors have been historically associated with poor overall survival (OS).[1-3] HER2-directed therapies have led to significant survival gains in HER2-positive BC in both the early-stage and metastatic disease settings.[4-10] Despite the development and approval of multiple HER2-directed agents for metastatic BC (MBC), most patients develop therapeutic resistance and, ultimately, disease progression occurs.[11-14] Targeting HER2 with both intracellular and extracellular HER2-directed therapies (vertical receptor inhibition of HER2) may improve outcomes in patients with HER2-positive MBC.[5,9,15]

Although HER2-directed therapies have led to improved control of systemic disease, the incidence of brain metastases (BMs) in patients with HER2-positive MBC remains high, with up to half of all patients with HER2-positive MBC developing BMs.[16-18] HER2-positive MBC with BMs is associated with poorer prognosis than HER2-positive MBC without BMs, with morbidity being high among patients with BMs owing to neurological toxicities or complications caused by treatments, such as surgical resection, radiosurgery, and/or whole brain radiotherapy.[19-23] Despite the unmet need in this population, patients with BMs, particularly those with active BMs, are frequently excluded from clinical trials.[24-26]

Tucatinib is an oral tyrosine kinase inhibitor that is highly selective for HER2.[27,28] In the HER2CLIMB study, adding tucatinib to trastuzumab and capecitabine resulted in improved progression-free survival (PFS) and OS in patients with unresectable locally advanced or MBC (LA/MBC), including those with BMs, compared with trastuzumab and capecitabine alone.[6,29] These results led to the regulatory approval of tucatinib in combination with trastuzumab and capecitabine for previously treated HER2-positive LA/MBC. Trastuzumab emtansine (T-DM1) is a HER2-directed antibody—drug conjugate also approved to treat patients with previously treated HER2-positive MBC,[9] and which has demonstrated intracranial activity and efficacy in the TH3RESA and KAMILLA trials.[30,31] Preclinical findings in BC models demonstrate that combining tucatinib with T-DM1 enhances the antitumor activity of either agent alone, potentially by stabilizing HER2 surface expression followed by augmented DM1 delivery to tumor cells.[27] In a phase Ib study, the combination of tucatinib and T-DM1 resulted in encouraging antitumor activity, including intracranial responses, and manageable toxicity in patients with heavily pretreated HER2-positive MBC.[32]

Based on these encouraging results, HER2CLIMB-02 was designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 for patients with HER2-positive LA/MBC whose disease progressed following the administration of trastuzumab and a taxane. Here, we report the results from the primary analysis of the HER2CLIMB-02 study.

PATIENTS AND METHODS

Study overview

HER2CLIMB-02 (NCT03975647) is a randomized, double-blind, placebo-controlled, phase III trial assessing the efficacy and safety of tucatinib combined with T-DM1 in patients with HER2-positive LA/MBC. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. All procedures were carried out in compliance with relevant laws and institutional guidelines, and the protocol was approved by institutional review boards and ethics committees at each participating study site.

Study population

Eligible patients were ≥18 years old and had centrally confirmed HER2-positive LA/MBC with known hormone receptor status per local testing. Patients were also required to have had previous treatment with trastuzumab and a taxane in any setting, with tumor progression after or intolerance to the last systemic therapy. Prior pertuzumab therapy was allowed but not required. Prior treatment with tucatinib, afatinib, trastuzumab deruxtecan (T-DXd), pyrotinib, or investigational HER2-directed agents was not permitted. Lapatinib or neratinib treatment in the past 12 months was also not permitted, unless treatment was given for ≤21 days and discontinued for reasons other than disease progression. In Japan, there was an open-label (tucatinib arm) safety run-in before enrollment into the global study to assess the safety and tolerability of tucatinib and T-DM1 in Japanese patients.

Eligible patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with adequate cardiac, renal, hepatic, and hematological function. All patients included in the study, with the exception of two patients in the tucatinib arm, underwent baseline brain magnetic resonance imaging (MRI) to assess for BMs. Patients with BMs were eligible, including patients with untreated, previously treated stable, or progressive BMs not requiring immediate local therapy, as determined by the treating clinician. Patients with untreated brain lesions >2.0 cm in size and those using systemic corticosteroids for control of BM symptoms at a total daily dose of >2 mg of dexamethasone (or equivalent) may have been eligible with approval of the medical monitor. Those with leptomeningeal disease were not eligible. Complete eligibility criteria are provided in the protocol (https://cdn.clinicaltrials.gov/large-docs/47/NCT03975647/Prot_000.pdf).

Procedures

Patients were randomly assigned 1 : 1 to receive 21-day cycles of either tucatinib (300 mg orally twice daily) or placebo (orally twice daily), in combination with T-DM1 (3.6 mg/kg intravenously every 21 days). Patients were

stratified by line of treatment for metastatic disease (first-line versus other), hormone receptor status (positive versus negative), presence or history of BMs (yes versus no), and ECOG performance status (0 versus 1).

Disease response per RECIST v1.1 was assessed by both investigators and blinded independent central review (BICR). Patients were assessed for disease progression using radiological imaging (preferably high-quality spiral contrast computed tomography and brain MRI for assessment of BMs) and other modalities, as appropriate, every 6 weeks for the first 24 weeks and every 9 weeks thereafter.

Safety was assessed through the reporting of adverse events (AEs), changes in laboratory test results, vital signs, ECOG performance status, cardiac ejection fraction results, and physical examination findings. AEs were classified using the Medical Dictionary for Regulatory Activities version 26.0 and the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03.

Assessments

The primary endpoint was investigator-assessed PFS, defined as the time from randomization to disease progression per RECIST v1.1 or death from any cause, whichever occurred first. Multiplicity-adjusted key secondary endpoints included: OS (defined as time from randomization to death due to any cause) both in the overall patient population and in patients with BMs at baseline; investigator-assessed PFS in patients with BMs at baseline; and investigator-assessed confirmed objective response rate (defined as the proportion of patients with confirmed complete response or partial response) per RECIST v1.1. Patients without events were censored at the date of the last adequate disease assessment (PFS) or the last known date alive (OS). Other secondary endpoints included: PFS per BICR in the overall population and in patients with BMs at baseline; confirmed objective response rate per BICR; duration of response and clinical benefit rate by investigator and BICR; and safety. All efficacy endpoints were assessed in the intent-to-treat analysis set, which included all randomly assigned patients. Safety outcomes were assessed in the safety analysis set, which comprised patients who received at least one dose of study treatment, including patients in the Japan safety run-in.

Statistical analysis

For the primary endpoint, 331 PFS events in total were required for 90% power to detect a hazard ratio (HR) of 0.70 at a two-sided alpha level of 0.05 using a log-rank test. Approximately 460 patients were to be randomly assigned to receive tucatinib or placebo, in combination with T-DM1, with the aim of observing 331 PFS events in ∼30 months after the first patient had been randomly assigned, assuming 24 months of patient accrual with a 5% annual dropout rate.

To maintain strong control of the family-wise type I error rate at 0.05, a fixed sequential testing procedure was used to test the primary and key secondary endpoints. If there was a statistically significant difference between the two treatment arms for the primary endpoint, a formal statistical test of OS was to be carried out at that time. Additional subsequent OS analyses were planned. If both PFS and OS results were statistically significant, the testing sequence in the other key secondary endpoints was to be investigator-assessed PFS in patients with BMs at baseline, confirmed objective response rate, and OS in patients with BMs at baseline.

For the time-to-event endpoint, the median survival time was estimated using the Kaplan—Meier method, and the associated 95% confidence interval (CI) was calculated using the complementary log—log transformation. Clopper—Pearson methodology was used to calculate the two-sided 95% CIs for outcomes other than time-to-event endpoints. Safety outcomes were analyzed using descriptive statistics. All statistical outputs were produced using SAS version 9.4 or higher (SAS Institute, Cary, NC).

RESULTS

Patients and treatment

From 8 October 2019 to 16 June 2022, 618 patients were screened; of these, 463 patients were randomly assigned at 163 sites to the tucatinib arm ($n = 228$) and to the control arm ($n = 235$) (Figure 1). The most common reason for exclusion was failure to meet protocol criteria for HER2 positivity (10.4%). In Japan, three patients across three sites were enrolled in the tucatinib arm for the safety run-in only. At data cut-off (29 June 2023), with a median follow-up duration of 24.4 months (interquartile range 21.0-29.1 months), 40 patients in the tucatinib arm and 29 patients in the control arm remained on treatment (Figure 1).

Patient demographics and disease characteristics were balanced between the two treatment arms (Table 1). In the overall population, 204 patients (44.1%) had either the presence of or a history of BMs; of the patients with BMs, 107 (52.5%) had active BMs (untreated or treated but progressive) and 97 (47.5%) had stable BMs. For both treatment arms, patients had received a median of one line of prior systemic therapy in the metastatic setting; prior pertuzumab treatment had been received by 88.6% and 91.1% of patients in the tucatinib and control arms, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.11.005).

Efficacy

Treatment with tucatinib in combination with T-DM1 demonstrated a statistically significant improvement in PFS by investigator assessment compared with treatment with T-DM1 alone; median PFS was 9.5 months (95% CI 7.4-10.9 months) in the tucatinib arm and 7.4 months (95% CI 5.6-8.1 months) in the control arm, with an HR of 0.76 (95% CI 0.61-0.95, $P = 0.0163$; Figure 2A). PFS, as assessed by BICR, was consistent with investigator assessment, with an HR of 0.76 (95% CI 0.59-0.97; Supplementary Figure S1, available at https://doi.org/10.

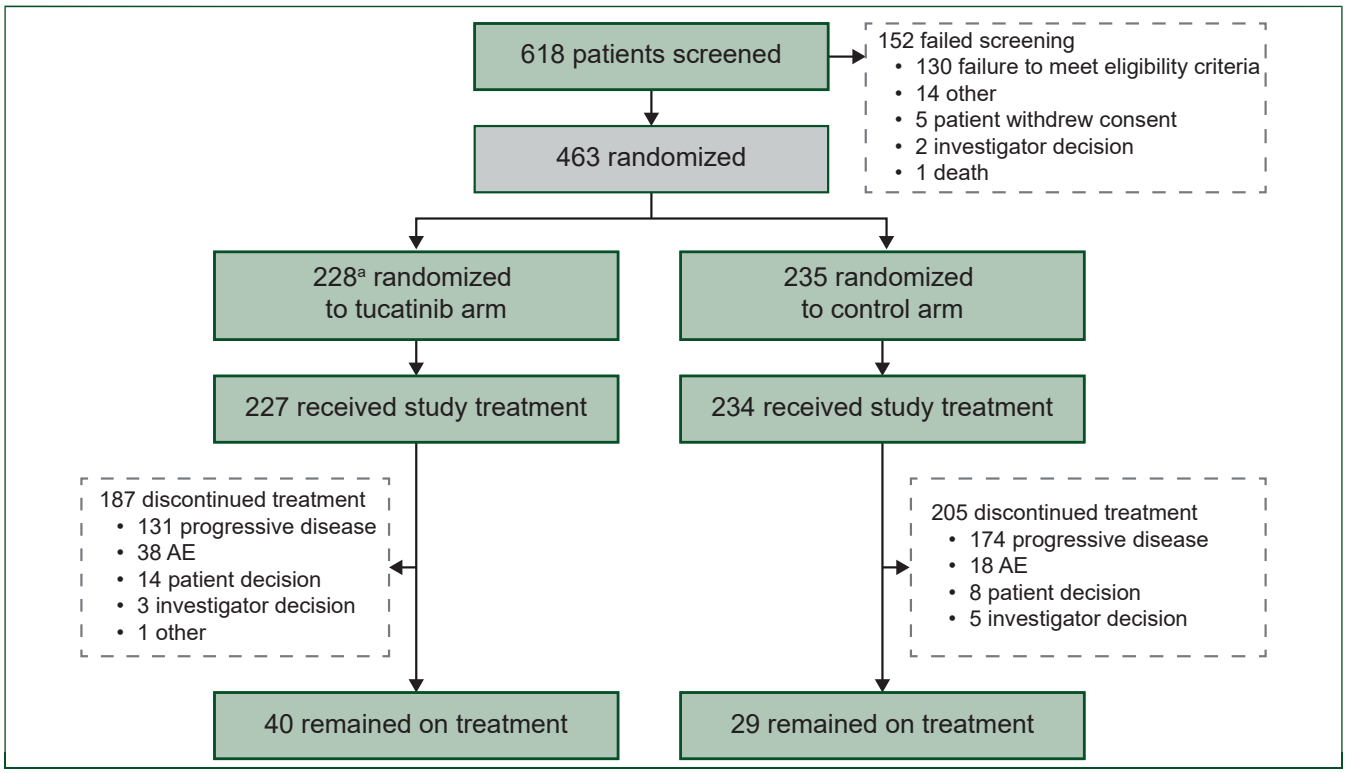


Figure 1. Patient disposition diagram.
[a]At three sites in Japan, three patients were enrolled in an open-label (tucatinib arm) safety run-in before enrollment into the global study to assess the safety and tolerability of tucatinib and T-DM1 in Japanese patients.
AE, adverse event; T-DM1, trastuzumab emtansine.

1016/j.annonc.2025.11.005). PFS benefit in the tucatinib arm was observed consistently across all prespecified subgroups (Figure 2B). In the subgroup of patients with BMs at baseline, the median investigator-assessed PFS was longer in the tucatinib arm [7.8 months (95% CI 6.7-10.0 months)] than in the control arm [5.7 months (95% CI 4.6-7.5 months), with an HR of 0.64 (95% CI 0.46-0.89); Figure 3]. Similar results were observed for BICR-assessed PFS in patients with BMs (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.11.005). Patients without a history of BMs had numerically longer median PFS in the tucatinib arm (9.7 months) compared with the control arm (8.5 months), corresponding to an HR of 0.88 (95% CI 0.65-1.19).

The interim OS results were immature, with 53% of the total required events (134 of 253) occurring, and did not meet the prespecified crossing boundary of $P \leq 0.0041$. The median OS was not reached in the tucatinib arm and was 38.0 months in the control arm, with an HR of 1.23 (95% CI 0.87-1.74) (Figure 4). No other key secondary endpoints were formally tested for statistical significance at this time. Patients with measurable disease at baseline in the tucatinib arm had a numerically higher confirmed objective response rate than those in the control arm (42.0% versus 36.1%), but had a numerically shorter median duration of response [10.4 months (95% CI 8.4-12.5 months) versus 12.5 months (95% CI 7.2-17.4 months); Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.11.005]. In the intent-to-treat analysis set, patients in the tucatinib arm had a numerically higher clinical benefit rate than those in the control arm (59.2% versus 55.7%).

Subsequent therapies

Following discontinuation of study treatment, most patients from both the tucatinib and control arms received subsequent anticancer therapy. Among those patients who had either discontinued or never received study treatment, 150 (79.8%) in the tucatinib arm and 168 (81.6%) in the control arm had been treated with at least one subsequent therapy (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.11.005). Subsequent anticancer therapies were balanced between the treatment arms, with the most common being T-DXd (49%). Other frequently used subsequent therapies included: capecitabine (30%), trastuzumab (28%), tucatinib (14%), and T-DM1 (12%).

Safety

The median treatment duration was 7.4 months (range 0.2-38.7 months) for tucatinib and 6.2 months (range 0.1-41.4 months) for placebo. The median treatment duration of T-DM1 was 7.5 months (range 0.7-38.7 months) in the tucatinib arm and 6.2 months (range 0.4-41.4 months) in the control arm.

Treatment-emergent AEs (TEAEs) of any grade were reported in 230 patients (99.6%) in the tucatinib arm and 233

Table 1. Patient demographics and baseline disease characteristics

Characteristics	Tucatinib arm (n = 228)	Control arm (n = 235)
Median age, years (range)	55.0 (26-83)	53.0 (27-82)
Female sex, *n* (%)	226 (99.1)	235 (100)
Race, *n* (%)		
Asian	66 (28.9)	65 (27.7)
Black	11 (4.8)	8 (3.4)
Other[a]	3 (1.3)	1 (0.4)
White	101 (44.3)	102 (43.4)
Unknown, multiple, or not reportable	47 (20.6)	59 (25.1)
Geographic region, *n* (%)		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
Positive hormone receptor status	137 (60.1)	140 (59.6)
ECOG performance status, *n* (%)		
0	137 (60.1)	141 (60.0)
1	91 (39.9)	94 (40.0)
Presence or history of brain metastases, *n* (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Untreated	15 (6.6)	25 (10.6)
Treated, progressive	35 (15.4)	32 (13.6)
Treated, stable	49 (21.5)	48 (20.4)
No[b]	129 (56.6)	130 (55.3)
Primary diagnosis, *n* (%)		
Invasive ductal carcinoma	208 (91.2)	216 (91.9)
Invasive ductal/lobular carcinoma	10 (4.4)	8 (3.4)
Invasive lobular carcinoma	6 (2.6)	7 (3.0)
Other	4 (1.8)	4 (1.7)
Stage IV at initial diagnosis, *n* (%)	103 (45.2)	98 (41.7)
Location of other non-CNS metastases, *n* (%)[c]		
Bone	116 (50.9)	118 (50.2)
Chest wall	68 (29.8)	66 (28.1)
Liver	76 (33.3)	82 (34.9)
Lung	95 (41.7)	85 (36.2)
Lymph node	115 (50.4)	110 (46.8)
Skin/soft tissue	33 (14.5)	30 (12.8)
Other	54 (23.7)	66 (28.1)

BM, brain metastasis; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging.
[a]Native American, Alaska Native, Native Hawaiian, or other Pacific Islander.
[b]Two patients in the tucatinib arm were missing BM status because a baseline brain MRI was not done.
[c]Includes non-CNS unresectable, locally advanced, or metastatic disease. Only occurrences >10% are shown.

patients (100%) in the control arm (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.11.005). The three most common TEAEs in the tucatinib arm were nausea (65.4%), diarrhea (56.7%), and fatigue (48.9%); in the control arm, the three most common TEAEs were nausea (49.4%), headache (39.1%), and fatigue (37.3%) (Table 2). Most of these frequently reported TEAEs in the tucatinib arm were grade 1 or 2 (percentage of patients in either category: nausea, 94.7%; diarrhea, 91.6%; fatigue, 87.6%). Similarly, the most common TEAEs in the control arm were also either grade 1 or 2 (percentage of patients in either category: nausea, 95.7%; headache, 97.8%; fatigue, 92.0%).

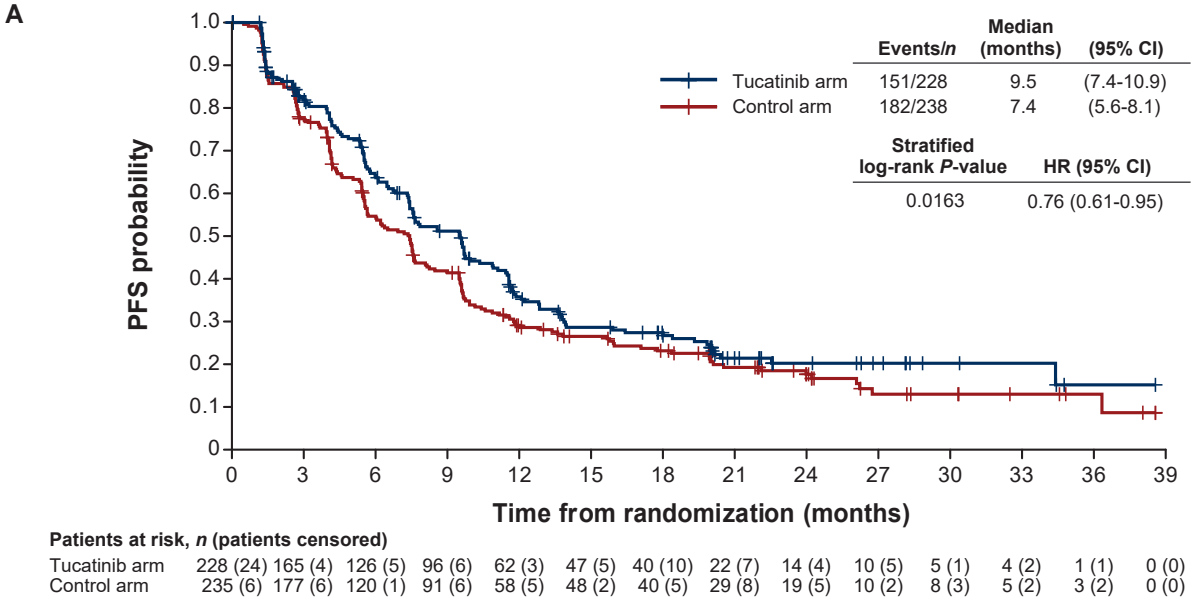
In total, 159 patients (68.8%) in the tucatinib arm and 96 patients (41.2%) in the control arm experienced a grade ≥3 TEAE. The most common grade ≥3 TEAEs in the tucatinib arm were increased alanine aminotransferase (ALT) level and increased aspartate aminotransferase (AST) level (both in 16.5% of patients in the tucatinib arm and 2.6% of patients in the control arm) (Table 2). The most common grade ≥3 TEAEs for the control arm were anemia in 4.7% of patients (versus 8.2% in the tucatinib arm) and fatigue in 3.0% of patients (versus 6.1% in the tucatinib arm).

Incidences of hepatic grade ≥3 TEAEs were higher in the tucatinib arm than in the control arm (28.6% versus 7.3%), primarily owing to AST and ALT elevations. Both tucatinib and T-DM1 were dose held and reduced (a single dose reduction for both drugs) in response to grade 3 AST/ALT elevation until improvement to grade ≤1. Dose modifications due to hepatic TEAEs are summarized in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.11.005. Of hepatic events of all grades, 85% and 75% resolved or returned to grade 1 in the tucatinib and control arms, respectively, with a median of 22 days to resolution in both arms. No Hy's law cases were identified by an independent external hepatologist.

Grade 3 diarrhea events were reported in 4.8% of patients in the tucatinib arm and 0.9% of patients in the control arm, with no grade ≥4 events being reported.

Discontinuation of all study treatment due to an AE occurred in 38 patients (16.5%) in the tucatinib arm and 18 patients (7.7%) in the control arm. Discontinuation from any study treatment due to a TEAE occurred in 22.1% of patients in the tucatinib arm and 11.6% of patients in the control arm (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.11.005). In the tucatinib and control arms, respectively, 17.3% and 6.9% of patients discontinued tucatinib or placebo due to a TEAE and 20.3% and 11.2% discontinued T-DM1 due to a TEAE. The most common TEAE resulting in discontinuation of tucatinib/placebo in the tucatinib arm was increased ALT (n = 6; 2.6%) and in the control arm, interstitial lung disease and increased blood bilirubin (both n = 3; 1.3%). The most common TEAE resulting in T-DM1 discontinuation in the tucatinib arm was increased ALT and thrombocytopenia (both n = 5; 2.2%) and in the control arm, interstitial lung disease (n = 5; 2.1%). In the tucatinib arm, 6.9% of patients discontinued tucatinib and 7.8% discontinued T-DM1 owing to hepatic TEAEs; in the control arm, 2.1% discontinued placebo and 2.1% discontinued T-DM1 owing to hepatic TEAEs (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.11.005). Of the 40 patients who discontinued tucatinib due to TEAEs, 16 (40%) were due to hepatic events with tucatinib plus T-DM1. Five of 16 (31%) patients in the control arm discontinued placebo due to hepatic TEAEs. The median time to onset of the first hepatic grade ≥3 TEAE was 35.0 days in the tucatinib arm and 95.0 days in the control arm.

Treatment-emergent serious AEs (TESAEs) were reported in 70 patients (30.3%) in the tucatinib arm and 52 patients (22.3%) in the control arm. The most common TESAEs were sepsis (n = 4; 1.7%) in the tucatinib arm and sepsis (n = 4, 1.7%) and pneumonia (n = 4; 1.7%) in the control arm. There were few TEAEs leading to death (grade 5) in either arm (n = 3; 1.3% in the tucatinib arm; n = 2; 0.9% in the control arm). No deaths were assessed as being related to



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	Tucatinib arm (*n* = 228) Events/*n*	Control arm (*n* = 235) Events/*n*	HR (95% CI)
ITT analysis	151/228	182/235	0.76 (0.61-0.95)
Baseline brain metastasis			
Yes	70/99	85/105	0.64 (0.46-0.89)
No	80/127	97/130	0.88 (0.65-1.19)
Line of treatment for metastatic disease			
First	16/26	21/28	0.51 (0.23-1.12)
Other	135/202	161/207	0.79 (0.63-1.00)
ECOG performance status			
0	86/137	109/141	0.66 (0.49-0.89)
1	65/91	73/94	0.91 (0.65-1.28)
Hormone receptor status			
Positive	85/137	107/140	0.75 (0.56-1.01)
Negative	66/91	75/95	0.82 (0.58-1.15)
Region			
North America	68/105	69/93	0.88 (0.62-1.26)
Europe/Israel	36/53	57/77	0.75 (0.46-1.20)
Asia-Pacific	47/70	56/65	0.74 (0.49-1.12)
Age			
<65 years	126/186	155/201	0.80 (0.62-1.02)
≥65 years	25/42	27/34	0.61 (0.33-1.11)
Race			
White	68/101	76/102	0.79 (0.55-1.13)
Asian	45/66	58/65	0.73 (0.49-1.11)
Other	38/61	48/68	0.79 (0.48-1.28)
Stage at initial diagnosis			
0-III	81/120	100/130	0.72 (0.53-0.99)
IV	67/103	79/98	0.77 (0.55-1.08)
Prior pertuzumab			
Yes	137/203	166/214	0.78 (0.62-0.99)
No	14/25	16/21	0.74 (0.29-1.87)

Figure 2. PFS for all patients. (A) Kaplan–Meier plot of PFS per investigator assessment for all patients. The primary analysis of PFS per investigator was conducted using the data cut-off of 29 June 2023, at which time 333 PFS events (disease progression or death) had occurred in the ITT population. Two-sided *P* value calculated from stratified log-rank test. (B) Forest plot of HR for PFS per investigator in prespecified subgroups. HR was computed from the Cox proportional hazards model using stratification factors at randomization (line of treatment for metastatic disease: first versus other; hormone receptor status: negative versus positive; presence or history of brain metastases: yes versus no; ECOG performance status: 0 versus 1). 'Other' events in the category of 'Line of treatment for metastatic disease' include patients with nonmetastatic disease and patients who received more than one line of treatment for metastatic disease.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

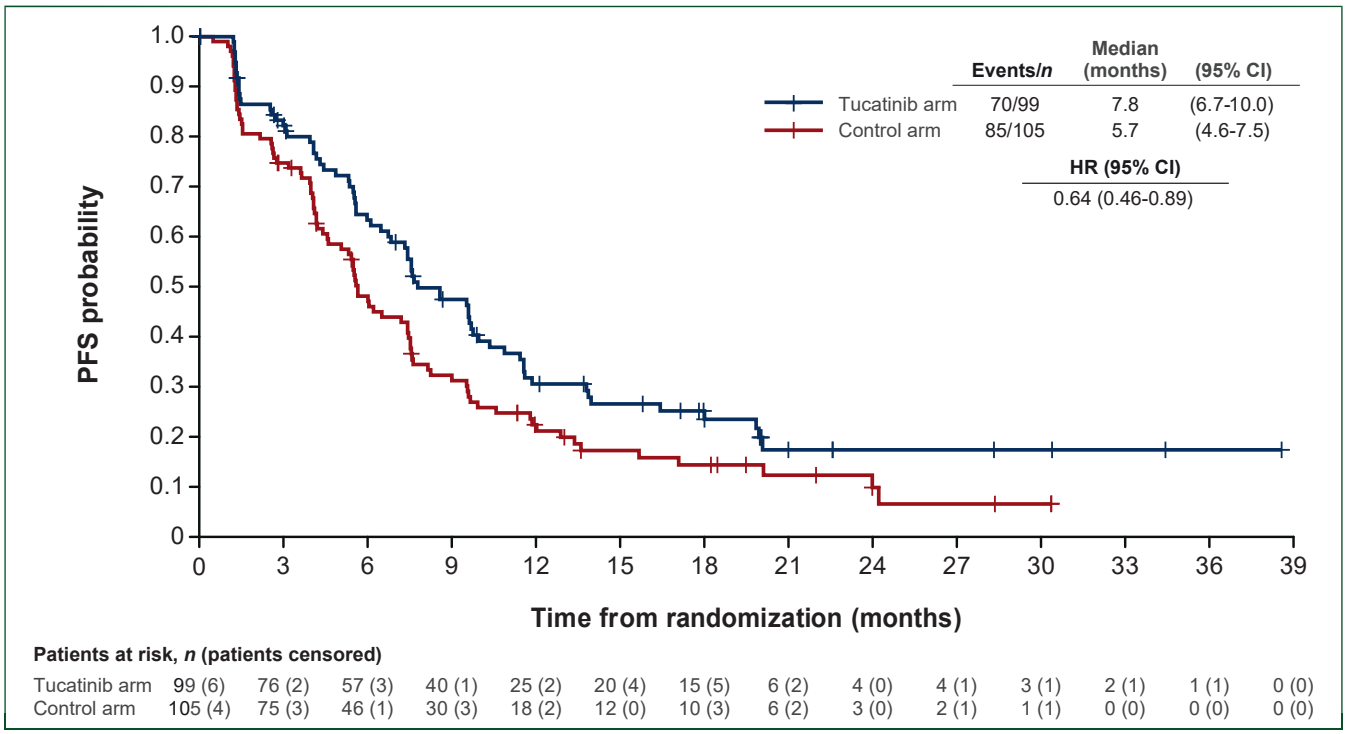

Figure 3. Kaplan–Meier plot of PFS per investigator assessment for patients with presence or history of baseline brain metastases.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

tucatinib and one death (hepatic failure) in the tucatinib arm was considered by the investigator to be possibly associated with T-DM1 infusions and/or progression of hepatic metastases. Additionally, this case was sent for review by an external hepatologist who deemed cause of death to be inconclusive but likely related to liver metastases. The three grade 5 TEAEs in the tucatinib arm were cerebrovascular accident, hepatic failure, and hypertensive

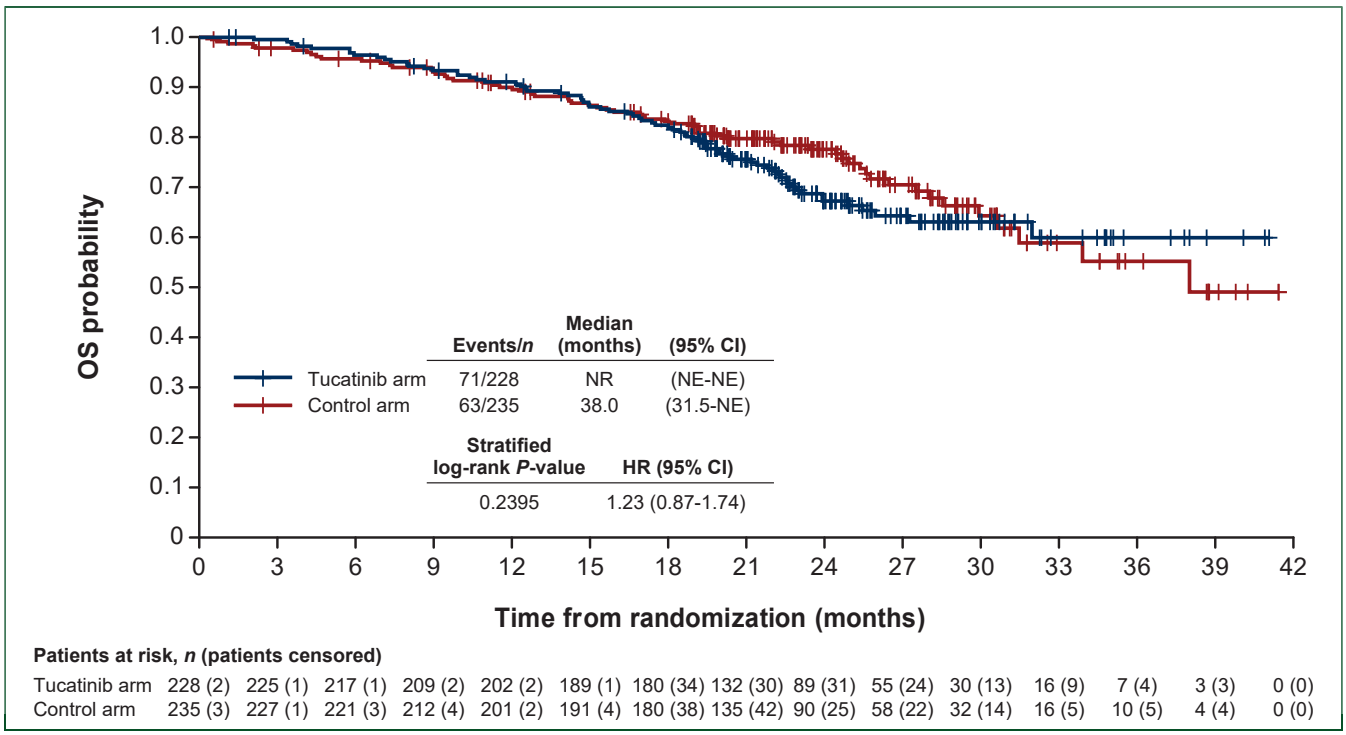

Figure 4. Kaplan–Meier plot of OS for all patients. Two-sided *P* value calculated from stratified log-rank test. The threshold for statistical significance is $P = 0.0041$.
CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival.

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Table 2. TEAEs of any grade observed in ≥20% of patients in the tucatinib arm

TEAEs, *n* (%)	Tucatinib arm (*n* = 231)		Control arm (*n* = 233)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	230 (99.6)	159 (68.8)	233 (100)	96 (41.2)
Nausea	151 (65.4)	8 (3.5)	115 (49.4)	5 (2.1)
Diarrhea	131 (56.7)	11 (4.8)	62 (26.6)	2 (0.9)
Fatigue	113 (48.9)	14 (6.1)	87 (37.3)	7 (3.0)
Vomiting	85 (36.8)	4 (1.7)	40 (17.2)	5 (2.1)
AST increased	83 (35.9)	38 (16.5)	45 (19.3)	6 (2.6)
Headache	83 (35.9)	3 (1.3)	91 (39.1)	2 (0.9)
ALT increased	80 (34.6)	38 (16.5)	40 (17.2)	6 (2.6)
Epistaxis	79 (34.2)	1 (0.4)	46 (19.7)	1 (0.4)
Decreased appetite	78 (33.8)	2 (0.9)	53 (22.7)	2 (0.9)
Constipation	62 (26.8)	2 (0.9)	77 (33.0)	1 (0.4)
Pyrexia	55 (23.8)	2 (0.9)	34 (14.6)	0
Arthralgia	54 (23.4)	1 (0.4)	63 (27.0)	5 (2.1)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

heart disease (0.4% each). For the two patients who had TEAEs leading to death in the control arm, the cause of death was brain herniation for one and death of unknown cause for the other (0.4% each).

DISCUSSION

In patients with HER2-positive LA/MBC that had been previously treated with trastuzumab and a taxane, the combination of tucatinib and T-DM1 resulted in a statistically significant 24% reduction in the risk of disease progression or death and a PFS improvement of 2.1 months compared with placebo plus T-DM1. A PFS benefit was consistently observed in all prespecified subgroups, including in patients with BMs. This study adds to the previously established data from the HER2CLIMB trial indicating that, when added to a standard-of-care (SOC) treatment option, tucatinib is clinically active in patients with HER2-positive LA/MBC, with or without BMs.

At this first interim analysis, the OS results were immature, with only 53% of the total number of required events reached at the time of data cut-off. These initial results should be interpreted with caution owing to data immaturity and heavy censoring. Longer follow-up is needed. Both arms of this study demonstrated longer OS than anticipated at the study onset; after 24.4 months of follow-up, median OS was 38.0 months in the control arm and was not reached in the tucatinib arm. The EMILIA study had shown a median OS of 30.9 months at the second interim analysis of OS with T-DM1[9]; however, longer OS may be attributed to new therapies in the treatment landscape, such as tucatinib and T-DXd, having been approved globally for the treatment of HER2-positive cancers.[33-36] Despite the relatively high-risk population with >43% of patients with BMs in this study, ∼80% received a subsequent systemic anticancer therapy (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.11.005), reflecting a lower attrition rate than expected. Almost half of patients in both arms received T-DXd as a subsequent anticancer therapy, and 15.4% of patients in the tucatinib arm and 13.6% of those in the control arm received tucatinib as a subsequent therapy (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.11.005).

Compared with patients in the control arm, a higher proportion of patients in the tucatinib arm had TEAEs, including grade ≥3 TEAEs, that led to dose modifications and discontinuations; these were primarily hepatic AEs. Hepatic AEs were generally transient, manageable, and reversible with dose modifications, with 85% and 75% of all-grade hepatic events either resolving or returning to grade 1 in the tucatinib and control arms, respectively; both arms had a median of 22 days to resolution. The percentage of patients in the tucatinib plus T-DM1 arm experiencing grade ≥3 AST/ALT elevation in this study (16.5%) was similar to the phase Ib T-DM1/tucatinib study (14%).[32] This prevalence is higher than in the tucatinib arm of HER2CLIMB (AST, 4.5% and ALT, 5.4%)[6] and the T-DM1 arm of EMILIA (AST, 4.3% and ALT, 2.9%),[9] potentially indicating a modest synergistic increase in hepatotoxicity with the tucatinib and T-DM1 combination. Although one patient died of hepatic failure in the tucatinib arm, it was determined by the investigator and an independent hepatologist to have likely resulted from progression of hepatic metastases and to be unrelated to tucatinib. Nevertheless, proactive monitoring and timely dose modifications may mitigate the risk of hepatotoxicity associated with tucatinib and T-DM1. Overall, the types of TEAEs observed in HER2CLIMB-02 were expected for the tucatinib arm, were consistent with previously reported phase Ib results of tucatinib in combination with T-DM1, and were similar to the types of TEAEs seen in the tucatinib arm of the registrational HER2CLIMB study.[6,32]

At the inception of the study, the SOC treatment of patients with HER2-positive LA/MBC was trastuzumab plus pertuzumab and a taxane as first-line therapy, and T-DM1 monotherapy as second-line therapy.[37] In accordance with guideline recommendations at the time,[37] the results of the phase Ib study,[32] and preclinical findings,[27] HER2CLIMB-02 was designed to evaluate the combination of tucatinib plus T-DM1 versus placebo plus T-DM1 in the second-line setting for treatment of HER2-positive LA/MBC. HER2CLIMB-02 did not allow for the inclusion of tucatinib or T-DXd as prior therapies because both received global approval after this study was already underway.[33-36,38] In HER2CLIMB, tucatinib in combination with trastuzumab and capecitabine improved PFS and OS in heavily pretreated patients with HER2-positive MBC, including those with BMs. In DESTINY-Breast03, T-DXd demonstrated a significant benefit in PFS and OS in patients with HER2-positive MBC compared with T-DM1 monotherapy in second- or later-line settings,[39] and T-DXd has since replaced T-DM1 as the SOC in the second-line setting.

As scientific advances are made in the HER2-positive treatment landscape, providing a variety of effective treatment options remains an unmet need for patients with HER2-positive LA/MBC who are ineligible, unable to

tolerate, or unable to access new therapies. Although T-DM1 monotherapy has been replaced by T-DXd as a SOC in the second-line setting, it remains a viable option for patients with HER2-positive LA/MBC in the third- or later-line setting.[40,41] In second- or later-line settings, tucatinib in combination with T-DM1 may become a future treatment option for patients who are not eligible for, have safety concerns with, or are unable to access T-DXd. Further, the data reported here add to existing evidence of tucatinib[29] and T-DM1[30,31] efficacy for patients with BM and combination treatment may represent a viable option for this vulnerable population. Health-related quality of life data, which is being collected during this trial, will also be important in evaluating whether tucatinib plus T-DM1 is a viable regimen. It is important to note that the data in this study do not demonstrate efficacy for patients previously treated with a tyrosine kinase inhibitor, as these patients were excluded from the HER2CLIMB-02 trial. However, a recent observational study has shown that patients, including those with BMs, can derive benefit from sequential use of tucatinib and other tyrosine kinase inhibitor-based regimens.[42] Given the rapidly evolving treatment landscape, future studies will be necessary to inform optimal treatment sequencing for patients with HER2-positive MBC.

For patients who previously received trastuzumab and a taxane (∼80% of whom had prior pertuzumab treatment), the combination of tucatinib and T-DM1 improved PFS relative to T-DM1 alone, with a manageable safety profile, including for patients with BMs.

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DATA SHARING

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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