HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER2+ Metastatic Breast Cancer

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ABSTRACT

PURPOSE The HER2CLIMB-05 study (ClinicalTrials.gov identifier: NCT05132582) is investigating the efficacy and safety of adding tucatinib to trastuzumab and pertuzumab as first-line (1L) maintenance therapy in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC).

METHODS Patients with centrally confirmed HER2+ MBC without evidence of progression post induction therapy and no or asymptomatic brain metastases (BM) were enrolled. Patients were randomly assigned 1:1 to tucatinib (300 mg) or placebo twice a day combined with trastuzumab/pertuzumab. The primary end point is investigator-assessed progression-free survival (PFS); secondary end points include overall survival (OS), PFS per blinded independent central review, CNS-PFS, and safety.

RESULTS Between March 2022 and July 2024, 654 patients were randomly assigned to tucatinib (n = 326) and placebo (n = 328) arms. All patients were female (median age, 54 years), 69.3% had de novo MBC, 52.6% were hormone receptor–positive, and 12.4% had presence/history of baseline BM. In this primary analysis, PFS was statistically significantly improved with addition of tucatinib versus placebo (hazard ratio, 0.641 [95% CI, 0.514 to 0.799]; $P < .0001$; median PFS: 24.9 *v* 16.3 months); a PFS benefit was seen regardless of the presence/absence of BM or hormone receptor status. OS data remain immature. The most common treatment-emergent adverse events (TEAEs) in the tucatinib arm were diarrhea (72.7%), nausea (33.1%), and elevated liver enzymes (ALT: 28.2%; AST: 25.8%), of which 6.1%, 0.9%, 13.5%, and 7.1%, respectively, were grade ≥3. In the tucatinib arm, 13.5% discontinued tucatinib because of TEAEs.

CONCLUSION Tucatinib addition to trastuzumab and pertuzumab demonstrated improvement in PFS with no new safety signals identified and may be an option for 1L maintenance therapy in patients with HER2+ MBC.

ACCOMPANYING CONTENT

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Appendix

Data Sharing Statement

Protocol

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View Online Article

INTRODUCTION

Globally, breast cancer is the most common form of cancer among women, with 2.3 million female patients diagnosed with breast cancer and 665,684 deaths attributed to the disease in 2022.[1] From population-based studies, 19% to 26% of patients with metastatic breast cancer (MBC) overexpress human epidermal growth factor receptor 2 (HER2-positive [HER2+]).[2,3] Tumors that overexpress HER2 occur more commonly in younger patients and have a tendency to metastasize to the brain.[4-6] The estimated 5-year survival rate of patients with HER2+ MBC is 41%-47%, depending on hormone receptor status,[7] and the majority of patients face disease progression within 2 years of initiating therapy.[8]

CONTEXT

Key Objective

Does combining the tyrosine kinase inhibitor, tucatinib, with standard of care (SOC; trastuzumab and pertuzumab) optimize first-line maintenance therapy by improving progression-free survival (PFS) compared with SOC in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC)?

Knowledge Generated

In HER2CLIMB-05, patients with HER2+ MBC receiving tucatinib had statistically significant improvement in PFS versus SOC regardless of the presence/absence of brain metastases or hormone receptor status. Diarrhea, nausea, and elevated liver enzymes, mostly of low grade, were the most common adverse events reported with tucatinib and trastuzumab/pertuzumab.

Relevance *(K.D. Miller)*

Management of patients with HER2+ metastatic disease has and continues to evolve quickly. Incorporation of tucatinib with maintenance therapy adds a valuable option, delaying disease progression and the need to resume cytotoxic therapy.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

The current standard of care (SOC) for first-line (1L) treatment of HER2+ MBC (June 2012 approval) is based on the CLEOPATRA trial[9,10] and consists of induction therapy with dual anti-HER2 monoclonal antibodies (mAbs; trastuzumab and pertuzumab) and a taxane followed by maintenance therapy with trastuzumab and pertuzumab until disease progression.[11,12] Although this regimen is associated with sustained disease control, most patients eventually experience disease progression.[9,10] The contemporary population of patients with HER2+ MBC likely differs considerably from the population included in CLEOPATRA, wherein only 11% of patients had received prior trastuzumab.[9] In both CLEOPATRA and PERUSE trials, patients who had been previously exposed to trastuzumab had worse clinical outcomes.[10,13] Thus, a more efficacious treatment strategy is warranted. Furthermore, the greater use of HER2-targeted therapy in early-stage HER2+ breast cancer and accompanying increase in overall survival (OS) has led to less recurrent disease, while the number of patients with de novo MBC is rising.[3,14]

The randomized, double-blind, phase II HER2CLIMB trial (N = 612) demonstrated that adding tucatinib, a highly selective HER2 tyrosine kinase inhibitor, versus placebo to trastuzumab and capecitabine significantly prolonged progression-free survival (PFS; median = 7.8 *v* 5.6 months, hazard ratio [HR], 0.54 [95% CI, 0.42 to 0.71]; $P < .001$) and OS (median = 24.7 *v* 19.2 months, HR, 0.73 [95% CI, 0.59 to 0.90]; $P = .004$) in heavily pretreated patients with HER2+ MBC.[15,16] Optimizing 1L maintenance therapy for patients with either HER2+ recurrent disease or de novo MBC by targeting HER2+ tumors both extracellularly, with dual anti-HER2 mAbs, and intracellularly, with tucatinib may improve patient outcomes.[17] Thus, the HER2CLIMB-05 trial was initiated to investigate the efficacy and safety of adding tucatinib to 1L maintenance therapy in a population of patients with HER2+ MBC who completed induction therapy with trastuzumab, pertuzumab, and a taxane without disease progression.

METHODS

Trial Design

HER2CLIMB-05 is a randomized, double-blind, placebo-controlled, international, phase III trial with enrollment at 219 sites in 23 countries (ClinicalTrials.gov identifier: NCT05132582).

Patients

Eligible patients were adults (18+ years) with centrally confirmed HER2+ (according to 2018 American Society of Clinical Oncologists-College of American Pathologists guidelines)[18] disease (unresectable locally advanced or MBC). If recurrent (after [neo]adjuvant therapy), ≥6-month treatment-free interval from any trastuzumab and pertuzumab received in the early breast cancer setting to diagnosis of advanced HER2+ disease was required. Patients were required to have no evidence of progression after induction therapy with 4-8 cycles of 1L trastuzumab, pertuzumab, and a taxane (patients who received <6 cycles of taxane were only eligible if the taxane was stopped because of intolerable toxicity), known hormone receptor status (hormone receptor–positive or hormone receptor–negative), Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and no or asymptomatic brain metastases (BM) confirmed by contrast-enhanced brain magnetic resonance imaging (MRI) at screening. A complete list of inclusion/exclusion criteria is provided in Appendix 1 (online only).

Random Assignment and Treatment

Patients were randomly assigned 1:1 to receive either tucatinib 300 mg or placebo twice daily, in combination with either trastuzumab (6 mg/kg intravenous [IV] or 600 mg subcutaneous [SC]) and pertuzumab (420 mg IV) or a SC fixed-dose combination of trastuzumab (600 mg), pertuzumab (600 mg), and hyaluronidase (20,000 units) administered once every 21 days. Random assignment was stratified by diagnosis (de novo or recurrent), hormone receptor status (positive or negative), and presence or history of BM (yes or no). Endocrine therapy (ET) is permitted for patients with hormone receptor–positive tumors. Study treatment continues until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. No crossover from placebo to tucatinib is allowed.

Efficacy Assessments

The intention-to-treat (ITT) analysis set included all randomly assigned patients and was used for all efficacy analyses. The primary end point was investigator-assessed PFS per RECIST v1.1. PFS was defined as the time from random assignment to documented disease progression, or death from any cause, whichever occurred first. Measurements of all known tumor sites (including at a minimum the chest, abdomen, and pelvis) were performed preferably by high-quality spiral contrast CT at baseline and every 9 weeks until progression. PFS in the ITT analysis set was also reported by patient subgroups (diagnosis [de novo or recurrent], hormone receptor status [negative or positive], presence or history of BM at baseline [yes or no], prior anti-HER2 therapy [yes or no], best response to induction therapy [complete response {CR} or partial response, stable disease or non-CR/nonprogressive disease], disease type [visceral or nonvisceral], baseline ECOG PS [0 or 1], geographic region [North America, Europe, Asia-Pacific, rest of the world], age [<65 years or ≥65 years], and race [White, Asian, African American, other]). Secondary efficacy end points included OS, PFS by blinded independent central review (BICR), and investigator-assessed CNS-PFS. OS was defined as the time from random assignment to death from any cause. CNS-PFS was defined as the time from random assignment to disease progression in the brain or death from any cause, whichever occurred first.

Contrast-enhanced brain MRI was required for all patients at screening and at the end of treatment and was repeated for patients with presence or history of BM every 9 weeks. For patients without presence or history of BM at baseline, contrast-enhanced brain MRI was repeated every 27 weeks (approximately 6 months). Additional contrast MRIs of the brain were performed as clinically appropriate.

Safety and Tolerability Assessments

The safety analysis set included all randomly assigned patients who received at least one dose of any study treatment and was used for all safety end points. Adverse events (AEs) and clinical laboratory values were assessed on day 1 of every cycle throughout treatment and approximately 30 days after the last dose of study treatment. AE and laboratory abnormality severity were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The study also assessed the frequency of discontinuations and dose modifications for tucatinib, trastuzumab, and pertuzumab.

Statistical Analyses

HER2CLIMB-05 was designed to detect a tucatinib treatment effect of ≥30% reduction in rate of PFS events. A total of 331 PFS events would provide 90% power to detect a HR of 0.70 at a two-sided significance level of .05 using a log-rank test. Further information can be found in the protocol (Appendix 1).

Descriptive statistics were used to summarize patient demographics and characteristics, AEs, and dose modifications. The Kaplan-Meier method was used to estimate time curves and median PFS and other secondary time-to-event end points with 95% CIs. HRs with 95% CIs were based on stratified Cox proportional hazards models. Comparisons between treatment arms used two-sided stratified log-rank tests. All statistical analyses were performed using SAS v.9.4 or higher (SAS Institute, Cary, NC).

Trial Oversight

The sponsor, Pfizer Inc/Seagen, designed the trial and was responsible for site monitoring and data collection in collaboration with investigators. The study protocol and other relevant documents were approved by investigator sites' ethical/institutional review boards. The study was conducted in accordance with the Consensus Framework for Ethical Collaboration derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. All participants provided written informed consent before enrollment.

RESULTS

Patient Characteristics

Between March 2022 and July 2024, 654 patients were randomly assigned to the tucatinib arm (n = 326) or the placebo (n = 328) arm (Fig 1). All patients were female with a median baseline age of 54 years (range, 24-83); 45.0% were White, 35.2% were Asian, 2.9% were Black or African American, and 19.3% were Hispanic/Latino(a)/Spanish origin (Table 1). Most patients had ECOG PS of 0 (64.1%) and de novo MBC (69.3%); 52.6% of patients had hormone receptor–positive disease. At baseline, 81 (12.4%) patients had presence or history of BM. Key patient characteristics by hormone receptor status are shown in Appendix Table A1 .

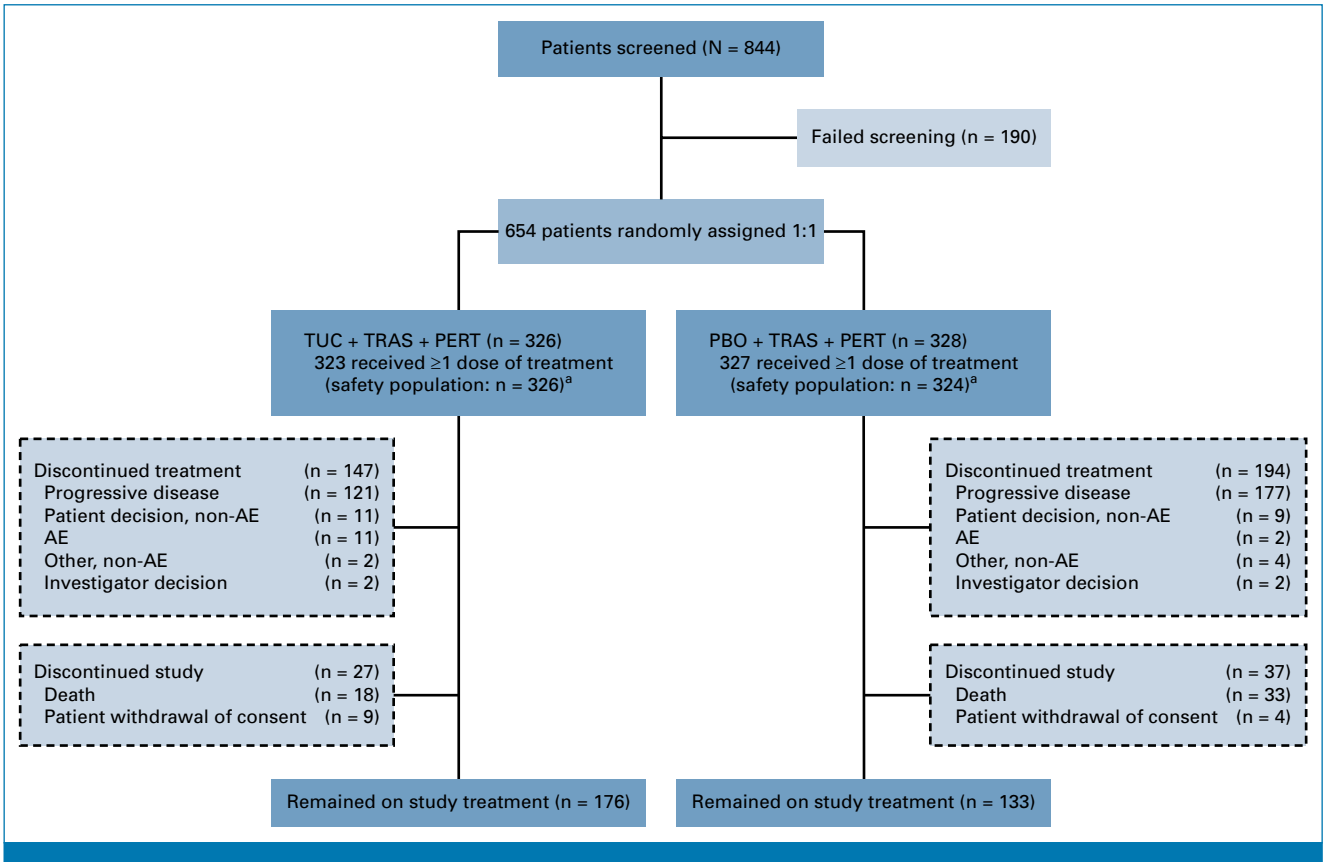

FIG 1. CONSORT diagram of the HER2CLIMB-05 study. [a]Three patients were randomly assigned to the PBO + TRAS + PERT arm but received some doses of TUC; these three patients were included in the TUC + TRAS + PERT arm for the safety analysis. AE, adverse event; PBO, placebo; PERT, pertuzumab; TRAS, trastuzumab; TUC, tucatinib.

Efficacy Assessments

At the data cutoff of September 5, 2025, the median follow-up duration for PFS was 22.6 months (95% CI, 20.8 to 22.8) in the tucatinib arm and 22.7 months (95% CI, 20.5 to 23.1) in the placebo arm. The study met its primary end point demonstrating statistically significant improvement in investigator-assessed PFS for the tucatinib arm versus the control arm (HR, 0.641 [95% CI, 0.514 to 0.799]; two-sided $P < .0001$; Fig 2A). The median PFS was 24.9 months (95% CI, 21.3 to –) in the tucatinib arm and 16.3 months (95% CI, 12.6 to 18.7) in the control arm. The results from PFS per BICR (HR, 0.654 [95% CI, 0.517 to 0.828]; median: 28.9 *v* 16.0 months; Appendix Fig A1) were consistent with those of PFS per investigator. All prespecified patient subgroups demonstrated a consistent PFS benefit with tucatinib plus trastuzumab and pertuzumab (Fig 2B), including those with hormone receptor–negative disease (HR, 0.554 [95% CI, 0.403 to 0.761]; Appendix Fig A2A) and hormone receptor–positive disease (HR, 0.725 [95% CI, 0.535 to 0.983]; Appendix Fig A2B), versus the control arm. Among those with hormone receptor–positive disease in the tucatinib and control arms, 44.0% (n = 74) and 46.0% (n = 81), respectively, received ET with their maintenance therapy.

OS at this primary analysis was not yet mature with the observed number of deaths (n = 51), representing 20.2% of the total required events (n = 252). Median OS was not reached in either treatment arm with no detrimental effect observed in the tucatinib arm versus the control arm (HR, 0.539 [95% CI, 0.303 to 0.957]; Fig 3). Subsequent anticancer therapies are shown in Appendix Table A2.

Among all patients, median CNS-PFS was not reached in either treatment arm (HR, 0.846 [95% CI, 0.616 to 1.162]; Appendix Fig A3A). Among patients with BM at baseline, the median CNS-PFS was 8.5 months (95% CI, 4.4 to 22.8) in the tucatinib arm and 4.3 months (95% CI, 2.3 to 10.6) in the control arm (HR, 0.719 [95% CI, 0.406 to 1.273]; Appendix Fig A3B).

Safety and Tolerability Assessments

Among the patients in the safety analysis set (326 in tucatinib arm and 324 in control arm), 176 and 133 were still receiving study treatment in the tucatinib and control arms, respectively (Fig 1). The median duration of tucatinib/placebo treatment was 17.1 months (range, 0.4-36.5) in the tucatinib arm and 15.5 months (range, 0.5-41.3) in the control arm. The most frequent TEAEs in the tucatinib arm were diarrhea (72.7%), nausea (33.1%), elevated ALT (28.2%), elevated AST

TABLE 1. Baseline Demographic and Clinical Characteristics of All Patients Randomly Assigned in HER2CLIMB-05

Characteristic	TUC + TRAS + PERT (n = 326)	PBO + TRAS + PERT (n = 328)	Total (N = 654)
Age, years, median (range)	54.0 (24-82)	54.0 (29-83)	54.0 (24-83)
Age group, No. (%)			
<65 years	274 (84.0)	272 (82.9)	546 (83.5)
≥65 years	52 (16.0)	56 (17.1)	108 (16.5)
Female sex, No. (%)	326 (100)	328 (100)	654 (100)
Race, No. (%)			
White	147 (45.1)	147 (44.8)	294 (45.0)
Asian	119 (36.5)	111 (33.8)	230 (35.2)
Black or African American	10 (3.1)	9 (2.7)	19 (2.9)
Multiple	5 (1.5)	1 (0.3)	6 (0.9)
American Indian or Alaska Native	0	4 (1.2)	4 (0.6)
Native Hawaiian or other Pacific Islander	0	2 (0.6)	2 (0.3)
Not reportable/other/unknown	45 (13.8)	54 (16.5)	99 (15.1)
Ethnicity, No. (%)			
Not Hispanic, Latino/a, or of Spanish origin	221 (67.8)	212 (64.6)	433 (66.2)
Hispanic, Latino/a, or of Spanish origin	55 (16.9)	71 (21.6)	126 (19.3)
Not reportable/unknown	50 (15.3)	45 (13.7)	95 (14.5)
ECOG PS,[a] No. (%)			
0	215 (66.0)	204 (62.2)	419 (64.1)
1	110 (33.7)	123 (37.5)	233 (35.6)
2	1 (0.3)	1 (0.3)	2 (0.3)
Region, No. (%)			
Asia-Pacific	121 (37.1)	113 (34.5)	234 (35.8)
Europe	116 (35.6)	114 (34.8)	230 (35.2)
Rest of world	48 (14.7)	53 (16.2)	101 (15.4)
North America	41 (12.6)	48 (14.6)	89 (13.6)
Time from disease recurrence/metastasis to random assignment, months, median (range)	6.3 (3.6-59.1)	6.3 (3.1-103.9)	6.3 (3.1-103.9)
Disease status, No. (%)			
De novo	227 (69.6)	226 (68.9)	453 (69.3)
Recurrent	99 (30.4)	102 (31.1)	201 (30.7)
Presence or history of BM, No. (%)			
Yes	41 (12.6)	40 (12.2)	81 (12.4)
Untreated	19 (5.8)	22 (6.7)	41 (6.3)
Previously treated	22 (6.7)	18 (5.5)	40 (6.1)
HER2+ testing, No. (%)			
IHC 2+, FISH+	29 (8.9)	48 (14.6)	77 (11.8)
IHC 3+	295 (90.5)	279 (85.1)	574 (87.8)
QC failure[b]	2 (0.6)	1 (0.3)	3 (0.5)
Hormone receptor status, No. (%)			
Positive	168 (51.5)	176 (53.7)	344 (52.6)
Negative	158 (48.5)	152 (46.3)	310 (47.4)
Primary tumor (T) at initial diagnosis, No. (%)			
T0	2 (0.6)	1 (0.3)	3 (0.5)
Tis	4 (1.2)	5 (1.5)	9 (1.4)
T1	47 (14.4)	48 (14.6)	95 (14.5)
T2	115 (35.3)	112 (34.1)	227 (34.7)
T3	58 (17.8)	57 (17.4)	115 (17.6)
T4	69 (21.2)	80 (24.4)	149 (22.8)
Unknown	31 (9.5)	25 (7.6)	56 (8.6)

(continued on following page)

TABLE 1. Baseline Demographic and Clinical Characteristics of All Patients Randomly Assigned in HER2CLIMB-05 (continued)

Characteristic	TUC + TRAS + PERT (n = 326)	PBO + TRAS + PERT (n = 328)	Total (N = 654)
Visceral disease,[c] No. (%)	194 (59.5)	172 (52.4)	366 (56.0)
Prior systemic therapy, No. (%)			
Any (neo)adjuvant systemic therapy	87 (26.7)	91 (27.7)	178 (27.2)
Trastuzumab[d]	60 (69.0)	67 (73.6)	127 (71.3)
Pertuzumab[d]	16 (18.4)	15 (16.5)	31 (17.4)
Induction therapy, cycles, median (range)			
Trastuzumab	6 (4-10)	6 (4-11)	6 (4-11)
Pertuzumab	6 (4-10)	6 (4-11)	6 (4-11)
Taxane	6 (4-9)	6 (3-8)	6 (3-9)
Taxane, No. (%)			
Docetaxel	198 (60.7)	189 (57.6)	387 (59.2)
Paclitaxel	116 (35.6)	129 (39.3)	245 (37.5)
Nab-paclitaxel	12 (3.7)	10 (3.0)	22 (3.4)
Best response to induction therapy, No. (%)			
Complete response	30 (9.2)	32 (9.8)	62 (9.5)
Partial response	204 (62.6)	208 (63.4)	412 (63.0)
Stable disease	77 (23.6)	75 (22.9)	152 (23.2)
Noncomplete response/nonprogressive disease	15 (4.6)	13 (4.0)	28 (4.3)

Abbreviations: BM, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HER2+, human epidermal growth factor receptor–positive; IHC, immunohistochemistry; PBO, placebo; PERT, pertuzumab; QC, quality control; TRAS, trastuzumab; TUC, tucatinib.

[a]The last nonmissing value before or on the day of the first dose of study treatment.

[b]Three samples had a HER2+ test result centrally confirmed but did not meet internal quality control criteria. Patients with IHC 3+ were counted as HER2+ per guidelines[18] regardless of FISH result.

[c]Visceral disease includes tumors located in abdomen, adrenal gland, bladder, cervix, colon, esophagus, liver, lung, ovary, pancreas, pleura, rectum, spleen, and stomach. All other locations, including BM, are classified as nonvisceral disease.

[d]Among patients who received prior systemic therapies in the (neo)adjuvant settings.

(25.8%), arthralgia (20.6%), and fatigue (20.6%); in the control arm they were diarrhea (51.2%), nausea (23.5%), and arthralgia (23.1%; Table 2). Grade ≥3 TEAEs occurred in 138 (42.3%) patients in the tucatinib arm and 79 (24.4%) patients in the control arm. The most frequent grade ≥3 TEAEs in the tucatinib arm were elevated ALT (13.5% *v* 0.6% in control arm), elevated AST (7.1% *v* 0.6% in control arm), and diarrhea (6.1% *v* 4.0% in control arm).

Serious TEAEs occurred in 55 (16.9%) patients in the tucatinib arm and 26 (8.0%) patients in the control arm (Appendix Table A3). In the tucatinib arm, the most commonly reported serious TEAEs were elevated ALT (1.5% [n = 5] *v* 0% in control arm) and drug-induced liver injury (DILI; 1.2% [n = 4] *v* 0% in control arm). TEAEs leading to any study treatment discontinuation occurred in 45 (13.8%) and 15 (4.6%) patients in the tucatinib and control arms, respectively (Appendix Table A3).

TEAEs from this study are consistent with the known safety profile of tucatinib combinations. TEAEs of diarrhea (72.7% in tucatinib arm *v* 51.2% in control arm) were primarily low grade and manageable with antidiarrheal treatment (as needed), supportive care, and dose modifications. The median time to onset of grade 3 diarrhea was 49.5 days and the median time to resolution was 8.0 days; patients with tucatinib discontinuation/dose hold/dose reduction because of diarrhea were 5 (1.5%)/28 (8.6%)/21 (6.4%), respectively. Hepatic TEAEs, with increased transaminases (AST/ALT elevations) accounting for the majority of events, were observed in 43.6% of patients in the tucatinib arm and 15.7% in the control arm. These events generally occurred early in treatment and were asymptomatic, transient, and reversible with tucatinib dose modifications. The median time to onset was 34.5 days, and the median time to resolution was 25.0 days; patients with tucatinib discontinuation/dose hold/reduction due to hepatic events were 25 (7.7%; 4.0% [n = 13] elevated ALT)/63 (19.3%)/53 (16.3%), respectively. A single grade 5 case of severe DILI was reported; however, the event was confounded by multiple concomitant medications with known hepatotoxic potential.

DISCUSSION

In this primary analysis of HER2CLIMB-05, adding tucatinib to trastuzumab and pertuzumab as 1L maintenance therapy

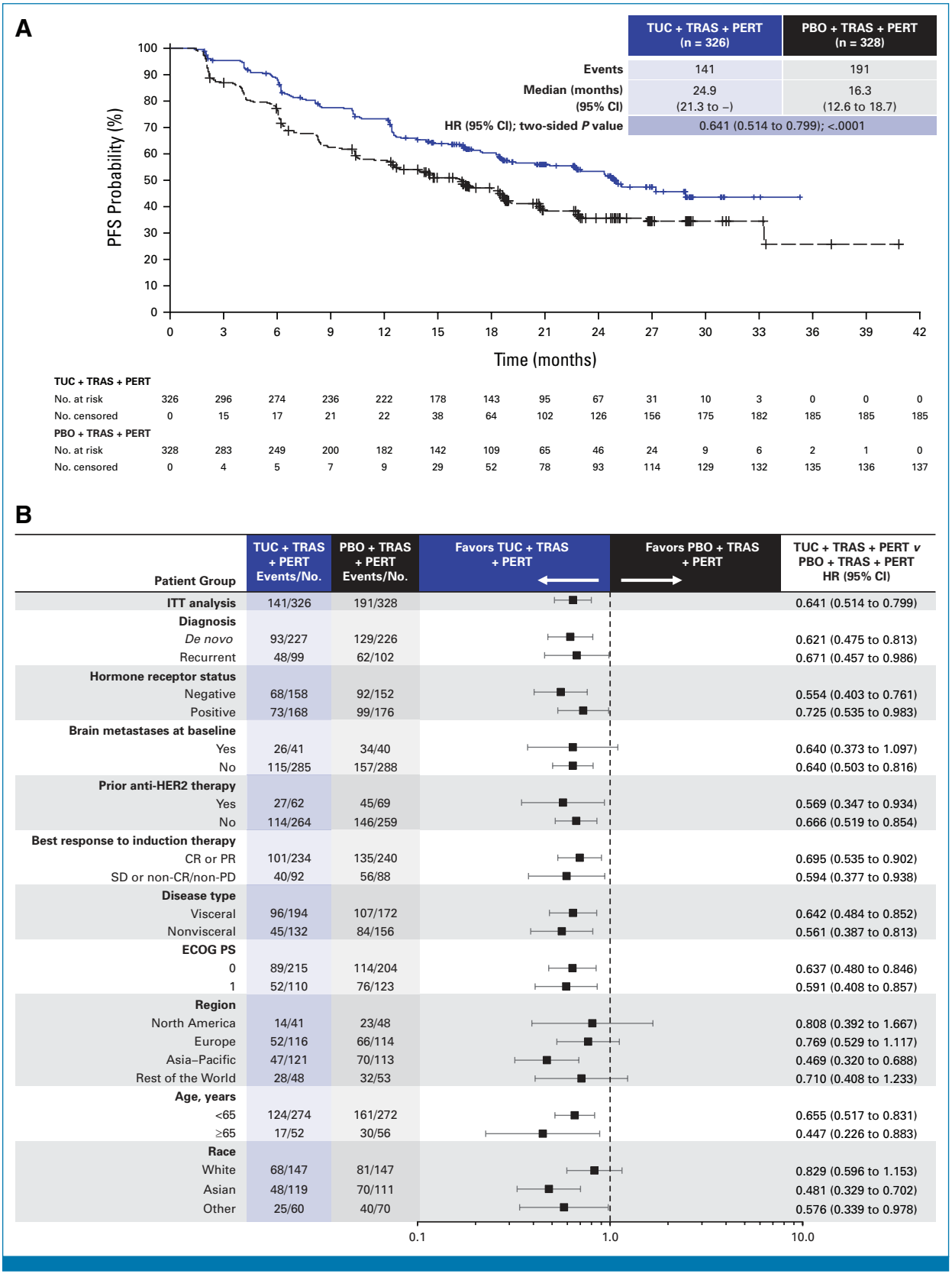

FIG 2. Kaplan–Meier estimate of (A) investigator-assessed PFS in the ITT analysis population and (B) forest plot of subgroup analyses. The random assignment stratification factors used in the Cox proportional-hazards model for computing HRs are diagnosis (de novo or recurrent), hormone receptor status (positive or negative), and presence or history of brain metastases (yes or no). If the subgroup is defined by a random assignment stratification factor, the Cox model is stratified for the random assignment stratification factors other than the one that defines the subgroup. Two-sided *P* value based on the stratified (continued on following page)

FIG 2. (Continued). log-rank test. CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; PBO, placebo; PD, progressive disease; PERT, pertuzumab; PFS, progression-free survival; PR, partial response; SD, stable disease; TRAS, trastuzumab; TUC, tucatinib.

for the treatment of patients with HER2+ MBC with no evidence of progression after completion of induction therapy with trastuzumab, pertuzumab, and a taxane resulted in statistically significant improvement in PFS, with a 36% reduced risk of disease progression or death compared with 1L trastuzumab and pertuzumab maintenance therapy (HR, 0.641 [95% CI, 0.514 to 0.799]). Following a median of six cycles of induction therapy with trastuzumab, pertuzumab, and a taxane, the median PFS was 24.9 months and 16.3 months for the tucatinib and placebo arms, respectively. The PFS benefit of the addition of tucatinib was demonstrated across all patient subgroups, regardless of the presence or absence of BM or hormone receptor status. Although CNS-PFS was numerically improved, with nearly a doubling in median CNS-PFS among patients with baseline BM treated with tucatinib versus placebo plus maintenance therapy (8.5 *v* 4.3 months), these data are preliminary (54% of patients in the tucatinib arm remain on study treatment). The safety profile of tucatinib in combination with trastuzumab and pertuzumab was generally consistent with the established safety profiles of each drug in patients with HER2+ MBC.[9,10,15,16] Diarrhea was the most common side effect in both arms, which is a known side effect of pertuzumab.[19] This primary analysis of HER2CLIMB-05 demonstrates that tucatinib addition to 1L maintenance therapy may be an effective option for HER2+ MBC with a safety profile consistent with that seen previously in tucatinib combinations.

In HER2CLIMB-05, addition of tucatinib to 1L maintenance therapy extended PFS to over 2 years, an 8.6-month improvement over SOC in this study population. In CLEOPATRA, patients with HER2+ MBC treated with 1L docetaxel combined with trastuzumab and pertuzumab had a median PFS of 18.5 months versus 12.4 months with docetaxel plus trastuzumab (HR, 0.62 [95% CI, 0.51 to 0.75]; $P < .001$).[9] In CLEOPATRA, PFS was measured from initiation of induction therapy,[9,10] whereas in HER2CLIMB-05, PFS was measured after completing induction therapy. As a result, the outcome durations between these studies are not directly comparable. Furthermore, the patient population in CLEOPATRA, with enrollment from 2008 to 2010, differed greatly from the HER2CLIMB-05 population (eg, in CLEOPATRA, 54% had de novo disease, 46.5% had received prior (neo)adjuvant chemotherapy, ET use was not allowed, few patients received prior trastuzumab [11%], and there was no previous pertuzumab use).[9]

In addition to the promising findings of this primary analysis of HER2CLIMB-05, other recent advances are expanding the treatment options for HER2+ MBC.[20,21] The phase III PATINA trial explored adding the cyclin-dependent kinase

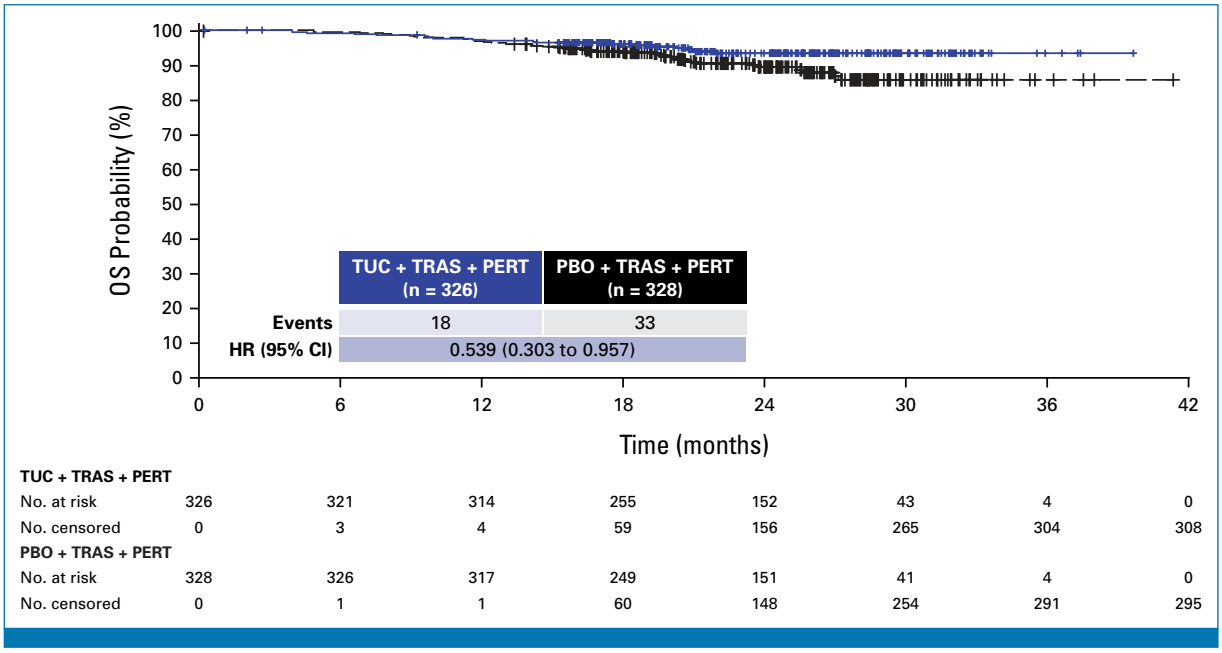

FIG 3. Kaplan–Meier estimate of OS in the ITT analysis population. HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PBO, placebo; PERT, pertuzumab; TRAS, trastuzumab; TUC, tucatinib.

TABLE 2. Treatment-Emergent Adverse Events Experienced in ≥10% of Patients in Either Treatment Arm, Regardless of Attribution

	TUC + TRAS + PERT (n = 326), No. (%)		PBO + TRAS + PERT (n = 324), No. (%)	
TEAE	All Grades	Grade ≥3	All Grades	Grade ≥3
Any	323 (99.1)	138 (42.3)	313 (96.6)	79 (24.4)
Diarrhea	237 (72.7)	20 (6.1)	166 (51.2)	13 (4.0)
Nausea	108 (33.1)	3 (0.9)	76 (23.5)	3 (0.9)
ALT increased	92 (28.2)	44 (13.5)	23 (7.1)	2 (0.6)
AST increased	84 (25.8)	23 (7.1)	29 (9.0)	2 (0.6)
Arthralgia	67 (20.6)	2 (0.6)	75 (23.1)	1 (0.3)
Fatigue	67 (20.6)	2 (0.6)	41 (12.7)	4 (1.2)
Vomiting	64 (19.6)	1 (0.3)	45 (13.9)	1 (0.3)
Pruritus	62 (19.0)	0	58 (17.9)	0
Headache	61 (18.7)	0	57 (17.6)	0
Cough	60 (18.4)	0	45 (13.9)	0
Anemia	54 (16.6)	5 (1.5)	30 (9.3)	2 (0.6)
Upper respiratory tract infection	52 (16.0)	0	27 (8.3)	1 (0.3)
Pyrexia	51 (15.6)	0	28 (8.6)	0
Decreased appetite	45 (13.8)	1 (0.3)	22 (6.8)	1 (0.3)
COVID-19	44 (13.5)	1 (0.3)	41 (12.7)	0
Muscle spasms	44 (13.5)	0	40 (12.3)	2 (0.6)
Asthenia	43 (13.2)	1 (0.3)	41 (12.7)	2 (0.6)
Nasopharyngitis	39 (12.0)	0	38 (11.7)	0
Blood creatinine increased	38 (11.7)	2 (0.6)	9 (2.8)	0
Rash	38 (11.7)	0	33 (10.2)	0
Pain in extremity	37 (11.3)	0	31 (9.6)	1 (0.3)
Weight decreased	37 (11.3)	2 (0.6)	28 (8.6)	1 (0.3)
Myalgia	36 (11.0)	2 (0.6)	31 (9.6)	0
Constipation	35 (10.7)	0	34 (10.5)	0
Back pain	34 (10.4)	0	39 (12.0)	1 (0.3)
Dizziness	32 (9.8)	0	34 (10.5)	1 (0.3)
Hypertension	16 (4.9)	6 (1.8)	36 (11.1)	14 (4.3)

NOTE. TEAEs are defined as events that are new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment. If a patient reports more than 1 AE that was coded to the preferred term, the patient was counted only once for that specific preferred term. AE and laboratory abnormality severity were graded using the NCI-CTCAE, version 5.0.

Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PBO, placebo; PERT, pertuzumab; TEAE, treatment-emergent adverse event; TRAS, trastuzumab; TUC, tucatinib.

4/6 inhibitor, palbociclib, versus placebo to trastuzumab and pertuzumab with ET in patients with HER2+/hormone receptor–positive advanced/MBC who had completed induction therapy without progression.[20] Palbociclib plus ET showed a median PFS of 44.3 months versus 29.1 months with placebo (HR, 0.75 [95% CI, 0.59 to 0.96]; $P = .02$) and was also measured from the start of maintenance therapy.[20] The patient population in PATINA differed from the HER2CLIMB-05 population, as all patients had hormone receptor–positive disease and received concomitant ET, and fewer patients had de novo disease (55%) and BM at baseline (4%).[20]

DESTINY-Breast09, a phase III trial of the antibody-drug conjugate, trastuzumab deruxtecan (T-DXd), plus pertuzumab versus 1L SOC (chemotherapy-based induction followed by maintenance with trastuzumab and pertuzumab) for HER2+ advanced/MBC, reported a median PFS of 40.7 months versus 26.9 months (HR, 0.56 [95% CI, 0.44 to 0.71]; $P < .00001$).[21] PFS was measured from the time of up-front 1L treatment initiation until progression or death, assessed by BICR.[21] The patient population in DESTINY-Breast09 included only those with a disease-free interval >6 months from last chemotherapy or HER2-targeted therapy in the (neo)adjuvant setting with no other prior systemic therapy for MBC; 52% had de novo disease at diagnosis and 54% were hormone receptor–positive. The median duration of T-DXd plus pertuzumab was 21.7 months, whereas it was 16.9 months in the control arm; at the interim analysis, 60% of patients had discontinued T-DXd (21% because of progressive disease; 21% because of AEs; 11% because of patient decision).[21]

Grade ≥3 treatment-related AEs occurred in 55% of patients who received T-DXd combination treatment and 12.1% of patients experienced treatment-related interstitial lung disease/pneumonitis with two patients having grade 5 events.[21] Cardiac toxicities (eg, decreased left ventricular ejection fraction, QT prolongation) have also been reported with T-DXd treatment.[21-23] Although T-DXd can be an effective option for patients with HER2+ MBC, some patients, such as those with lung or cardiovascular conditions, may require special consideration, especially during extended treatment periods, because of potential concerns about toxicity or prolonged AEs of a cytotoxic-containing regimen.[22]

Limitations of HER2CLIMB-05 include the exclusion of patients who progressed after induction therapy (7%-12% in CLEOPATRA and DESTINY-Breast09)[8,21]; less than half of patients with hormone receptor–positive disease received ET with maintenance therapy, a recommended SOC[11]; ET was permitted as concomitant therapy per protocol; and patients were not allowed to crossover to tucatinib. OS at this primary analysis was not yet mature, and preliminary data are shown for safety interpretation only. Potential limitations regarding the CNS-PFS analysis were the small sample size of patients with baseline presence or history of BM, difference in the frequency of brain imaging among patients with and without baseline BM, and the cessation of routine brain imaging after systemic progression, resulting in BM as a second or subsequent site of progression not being captured in this study. Study design differences make cross-study comparisons with other clinical trials difficult because not all trials measure the primary end point at the same time point: CLEOPATRA and DESTINY-Breast09 both measured PFS from the time of 1L treatment initiation, whereas both HER2CLIMB-05 and PATINA measured PFS from the time patients completed induction therapy without progression. In particular, we note that a shorter median PFS (16.3 months) was observed in our control arm compared with the trastuzumab/pertuzumab arms of CLEOPATRA (18.5 months), PATINA (29.1 months), or DESTINY-Breast09 (26.9 months); study populations also differed among trials.[9,20,21] Further analyses of HER2CLIMB-05 will report OS, CNS-PFS outcomes, patient-reported outcomes, and extended safety analyses.

The three recent phase III trials (PATINA, DESTINY-Breast-09, and HER2CLIMB-05) have all shown significant improvement in PFS in patients with HER2+ MBC,[20,21] and there is an opportunity to individualize treatment based on patient and disease characteristics, such as presence or history of BM and hormone receptor status. In HER2CLIMB-05, the addition of tucatinib to 1L maintenance therapy with trastuzumab and pertuzumab demonstrated a statistically significant 36% reduction in risk of disease progression or death compared with trastuzumab and pertuzumab maintenance therapy in patients with HER2+ MBC.

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No other potential conflicts of interest were reported.

APPENDIX 1. METHODS

Study Population

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator or sponsor and are participant to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

Inclusion Criteria

1. Have centrally confirmed human epidermal growth factor receptor 2-positive (HER2+) breast carcinoma according to the 2018 ASCO-College of American Pathologists (CAP) guidelines before random assignment (defined as a 3+ score on immunohistochemistry [IHC] and/or 2+ IHC and concurrent positive by in situ hybridization).
   a. Tissue blocks or tumor slides must be submitted and confirmed as HER2+ by a sponsor-designated central laboratory before random assignment.
2. Have unresectable locally advanced or metastatic (hereafter referred to as advanced) disease; if recurrent (after [neo]adjuvant therapy), there must be a minimum 6-month treatment-free interval from any trastuzumab and pertuzumab received in the early breast cancer setting to the diagnosis of advanced HER2+ disease. Prior standard-of-care (SOC) therapy for early breast cancer is permitted (eg, prior T-DM1); however, Exclusion Criterion 1 should be noted.
3. Have received 4-8 cycles of induction therapy including only trastuzumab, pertuzumab, and taxane as first-line (1L) of therapy for the treatment of advanced breast cancer before study enrollment. Patients are eligible provided they are without evidence of disease progression (per investigator judgment [ie, complete response, partial response, or stable disease]) following completion of induction therapy.
   a. Patients receiving <6 cycles (ie, 4-5 cycles) of taxane are only eligible if the taxane was stopped early because of intolerable toxicity (eg, documented neuropathy impacting function).
   b. Patients are permitted to receive trastuzumab and pertuzumab for two additional cycles (after completion of chemotherapy) to allow completion of screening procedures. Study treatment should begin within 6 weeks (±3 days) from the start of the last cycle of trastuzumab and pertuzumab.
   c. Patients are permitted to receive up to two cycles of carboplatin during the start of induction therapy in combination with trastuzumab, pertuzumab, and taxane (eg, to obtain confirmation of metastatic breast cancer diagnosis).
   d. Patients who received traditional medications (eg, traditional Chinese medication) and/or supplements with potential anticancer effects during induction therapy will remain eligible if they discontinue these treatments at least 4 weeks before the start of study treatment.
4. Known hormone receptor status (per local guidelines; may be hormone receptor positive or negative).
5. Be at least 18 years of age, and legally an adult at time of consent and ≥ the age of majority per regional requirements.
6. Have Eastern Cooperative Oncology Group Performance Status of 0 or 1
7. Have adequate hepatic function as defined by the following:
   a. Total bilirubin ≤1.5 × upper limit of normal (ULN), except for patients with known Gilbert disease, who may enroll if the conjugated bilirubin is ≤1.5 × ULN
   b. Transaminases (AST/serum glutamic oxaloacetic transaminase and ALT/serum glutamic pyruvic transaminase) ≤3 × ULN (≤5 × ULN if liver metastases are present)
8. Have adequate baseline hematologic parameters as defined by:
   a. Absolute neutrophil count ≥1 × $10^3/\mu L$
   b. Platelet count ≥100 × $10^3/\mu L$
   c. Hemoglobin ≥9 g/dL
   d. In patients receiving any transfusion before study entry, the above hematologic parameters must be met in absence of any transfusion for ≥14 days prior.
   e. In patients receiving growth factors before study entry, the above hematologic parameters must be met in absence of relevant growth factor use for ≥14 days prior.
9. Have a serum or plasma creatinine ≤1.5 × institutional ULN.
10. Have left ventricular ejection fraction ≥50% as assessed by echocardiogram or multiple gated acquisition scan documented within 4 weeks before the first dose of study treatment.
11. For patients of childbearing potential, the following stipulations apply:
    a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin) result within 7 days before the first dose of study treatment. A patient with a false-positive result and documented verification that the patient is not pregnant is eligible for participation. Documentation must include either an ultrasound or repeat pregnancy test to verify the false-positive nature of the pregnancy test.
    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study intervention.
    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through at least 7 months after the final dose of study intervention.
    d. If sexually active in a way that could lead to pregnancy, must consistently use at least two acceptable methods of birth control (contraception), at least one of which must be highly effective, as defined in Appendix C of the protocol, starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention.
12. For male patients, the following stipulations apply:
    a. Must agree not to donate sperm starting at the time of informed consent and continuing throughout the study period and for at least 7 months after the final dose of study intervention.
    b. If able to father children and sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use at least two acceptable methods of birth control (contraception), at least one of which must be highly effective, as defined in Appendix C, starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention.
    c. Male patients who are sexually active with a person who is pregnant or breastfeeding, must consistently use a male condom, starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention.
13. Provide signed informed consent per a consent document that has been approved by an institutional review board or independent ethics committee before initiation of any study-related tests or procedures that are not part of the SOC for the patient's disease.
14. Be willing and able to comply with study procedures.
15. ***CNS Inclusion***—Based on screening contrast-enhanced brain magnetic resonance imaging (MRI), patients may have any of the following:
    a. No evidence of brain metastases (BM)
    b. Untreated BM that are asymptomatic not needing immediate local treatment and, if identified on prior brain imaging, without evidence of progression since starting 1L induction therapy with trastuzumab, pertuzumab, and taxane
    c. Previously treated BM that are asymptomatic
       i. BM previously treated with local therapy must not have progressed since treatment
       ii. Time since whole brain radiation therapy is ≥14 days before the first dose of study treatment, time since stereotactic radiosurgery is ≥7 days before the first dose of study treatment, or time since surgical resection is ≥28 days before the first dose of study treatment
       iii. Relevant records of any CNS treatment must be available to allow for classification of target and nontarget lesions

Exclusion Criteria

1. Have previously been treated with any tyrosine kinase inhibitor targeting HER2 and/or epidermal growth factor receptor including pyrotinib, lapatinib, tucatinib, neratinib, and afatinib (except neratinib if given in extended adjuvant setting and at least 12 months have elapsed from the last neratinib dose to the start of study intervention) or are currently participating in another interventional clinical trial.
2. Unable for any reason to undergo contrast-enhanced MRI of the brain.
3. History of allergic reactions to trastuzumab, pertuzumab, or compounds chemically or biologically similar to tucatinib, except for grade 1 or 2 infusion-related reactions to trastuzumab or pertuzumab that were successfully managed, known allergy to one of the excipients in the study interventions, or hypersensitivity to murine proteins.
4. Are positive for hepatitis B by surface antigen expression, positive for active hepatitis C infection, or the presence of known chronic liver disease. Patients who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of at least 12 weeks, as documented per local guidelines. The latest local guidelines should be followed regarding the testing of hepatitis B DNA levels by polymerase chain reaction

(PCR). Patients with hepatitis B DNA levels by PCR that require nucleoside analog or other therapies are not eligible for the trial.

5. Patients known to be positive for HIV are excluded if they meet any of the following criteria:
   a. $CD4^+$ T-cell count of <350 cells/μL
   b. Detectable HIV viral load
   c. History of an opportunistic infection within the past 12 months
   d. On stable antiretroviral therapy for <4 weeks
6. Are pregnant, breastfeeding, or planning a pregnancy from the time of informed consent until 7 months after the final dose of study intervention.
7. Have inability to swallow pills or have significant GI disease or surgery that would preclude the adequate oral absorption of medications.
8. Have used a strong CYP2C8 inhibitor within five half-lives of the inhibitor or have used a strong CYP3A4 or CYP2C8 inducer within 5 days before the first dose of study treatment (Appendix D and Appendix E in protocol).
9. Have current conditions of symptomatic congestive heart failure, unstable angina pectoris, uncontrolled hypertension, or cardiac arrhythmia or history of myocardial infarction within 6 months before random assignment.
10. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures.
11. Have evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment.
12. Have ongoing ≥grade 2 toxicity from 1L induction therapy (ie, trastuzumab, pertuzumab, and taxane) except for alopecia, neuropathy, and nail toxicity
13. Have ongoing ≥grade 2 diarrhea.
14. ***CNS Exclusion***—Based on screening brain MRI and clinical assessment, patients must not have any of the following:
    a. Symptomatic brain metastasis after CNS-directed local therapy
    b. Progression of BM since starting 1L trastuzumab, pertuzumab, and taxane
    c. Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent). For patients requiring systemic steroids for control of comorbidities (eg, asthma or autoimmune diseases), the daily dose must not exceed 2 mg dexamethasone (or equivalent)
    d. Any untreated brain lesion in an anatomic site that may pose risk to patient (eg, brain stem lesions). Patients who successfully undergo local treatment for such lesions may be permitted to rescreen, if otherwise eligible, after discussion with, and approval by, the medical monitor
    e. Known or suspected leptomeningeal disease as documented by the investigator
    f. Poorly controlled (>1/wk) seizures, or other persistent neurologic symptoms despite CNS directed therapy for brain metastasis

Sample Size

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of progression-free survival (PFS) events (hazard ratio [HR] of 0.70; median PFS of 15 months in the control arm and 21.4 months in the experimental arm). A total of 331 PFS events will provide 90% power to detect a HR of 0.70 at a 2-sided significance level of 0.05 using a log-rank test. Approximately 650 patients will be randomly assigned in a 1:1 ratio to either the experimental arm or the control arm to observe 331 PFS events in approximately 34 months after the first patient is randomly assigned, assuming that PFS is following an exponential distribution with median of 15 months in the control arm and 21.4 months in the experimental arm, 22 months of patient accrual, and a 5% annual dropout rate.

It is planned that follow-up for overall survival (OS) will continue after the primary analysis of PFS until approximately 252 OS events have been observed. With 252 events, it will provide 80% power to detect a HR of 0.70 in OS at a two-sided significance level of 0.05 using a log-rank test. The final analysis of OS is estimated to take place when approximately 252 deaths have occurred, approximately 62 months after the first patient is randomly assigned, assuming that OS for the control arm is following an exponential distribution with a median of 56 months and a 2% annual dropout rate.

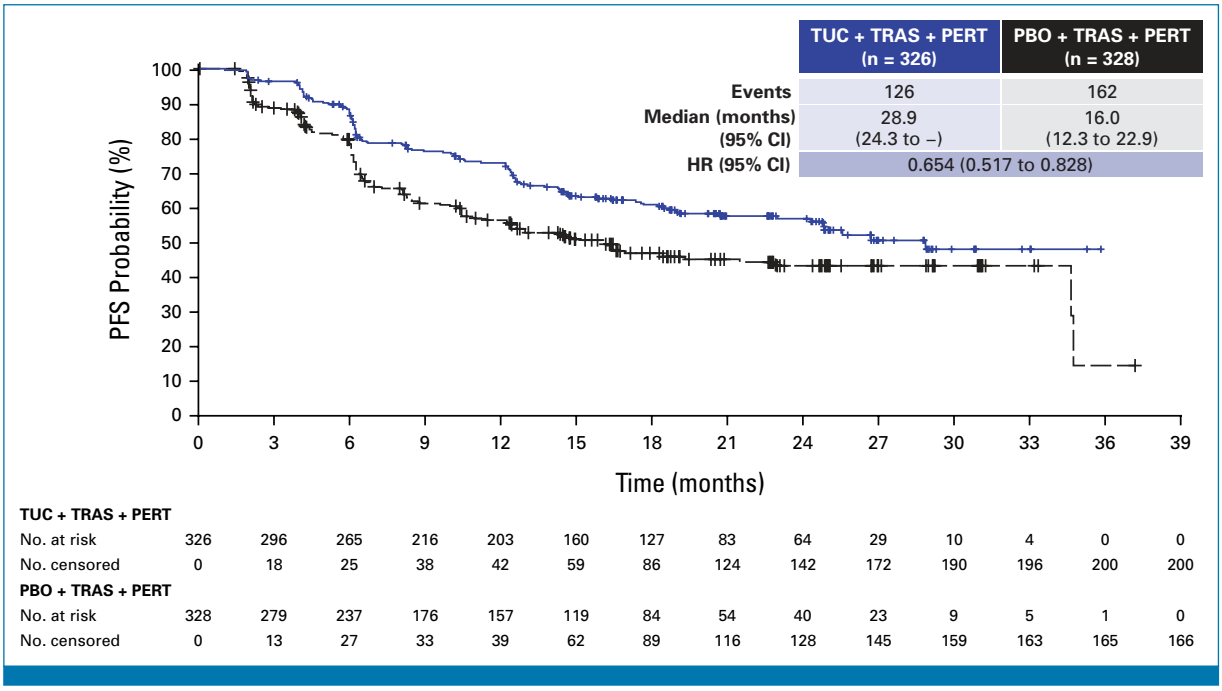

FIG A1. Kaplan-Meier estimate of PFS in the ITT analysis population assessed by blinded independent central review. HR, hazard ratio; ITT, intention-to-treat; PBO, placebo; PERT, pertuzumab; PFS, progression-free survival; TRAS, trastuzumab; TUC, tucatinib.

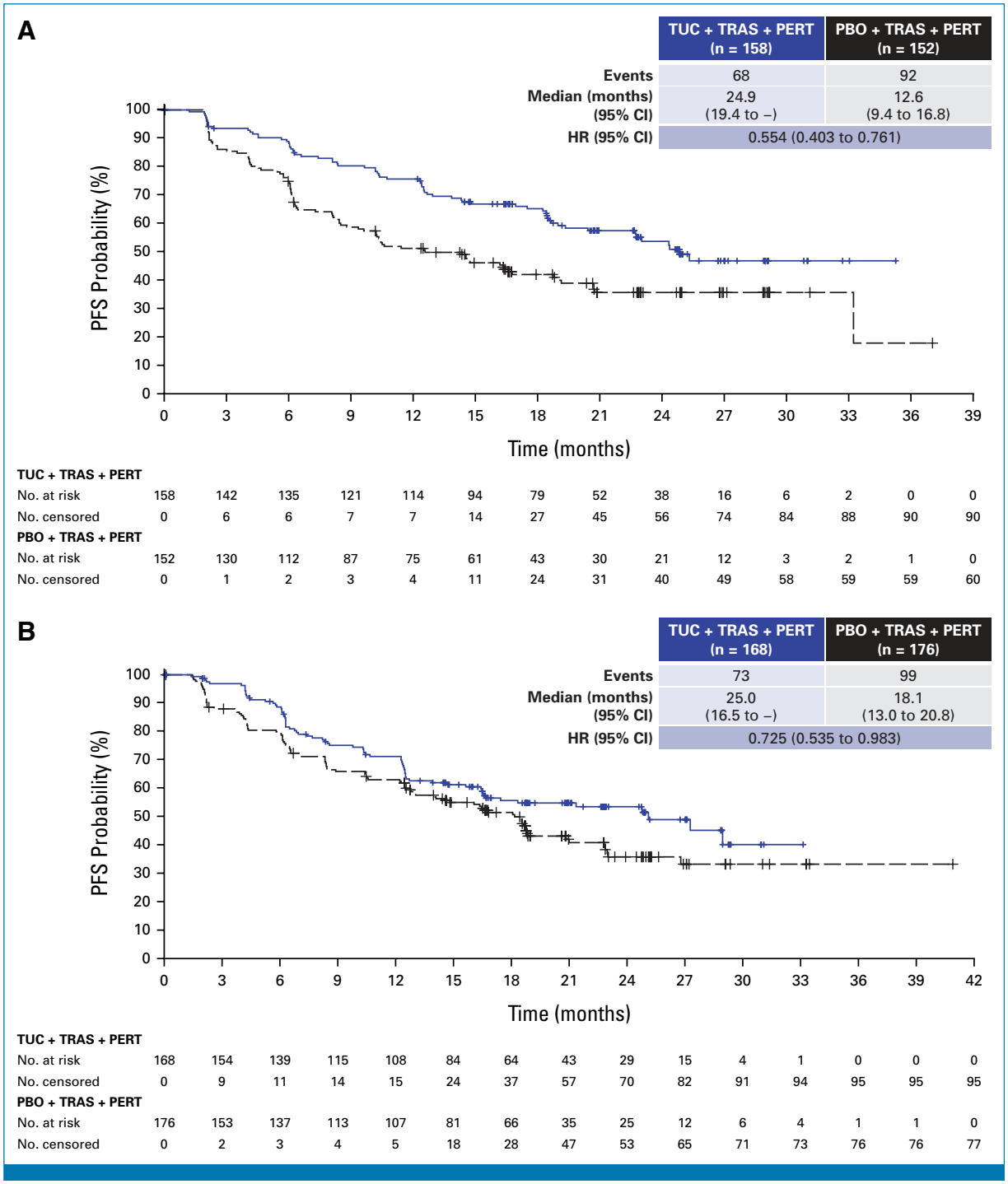

FIG A2. Kaplan-Meier estimates of investigator-assessed PFS in patients with (A) hormone receptor–negative and (B) hormone receptor–positive HER2+ MBC. HER2+, human epidermal growth factor receptor 2–positive; HR, hazard ratio; MBC, metastatic breast cancer; PBO, placebo; PERT, pertuzumab; PFS, progression-free survival; TRAS, trastuzumab; TUC, tucatinib.

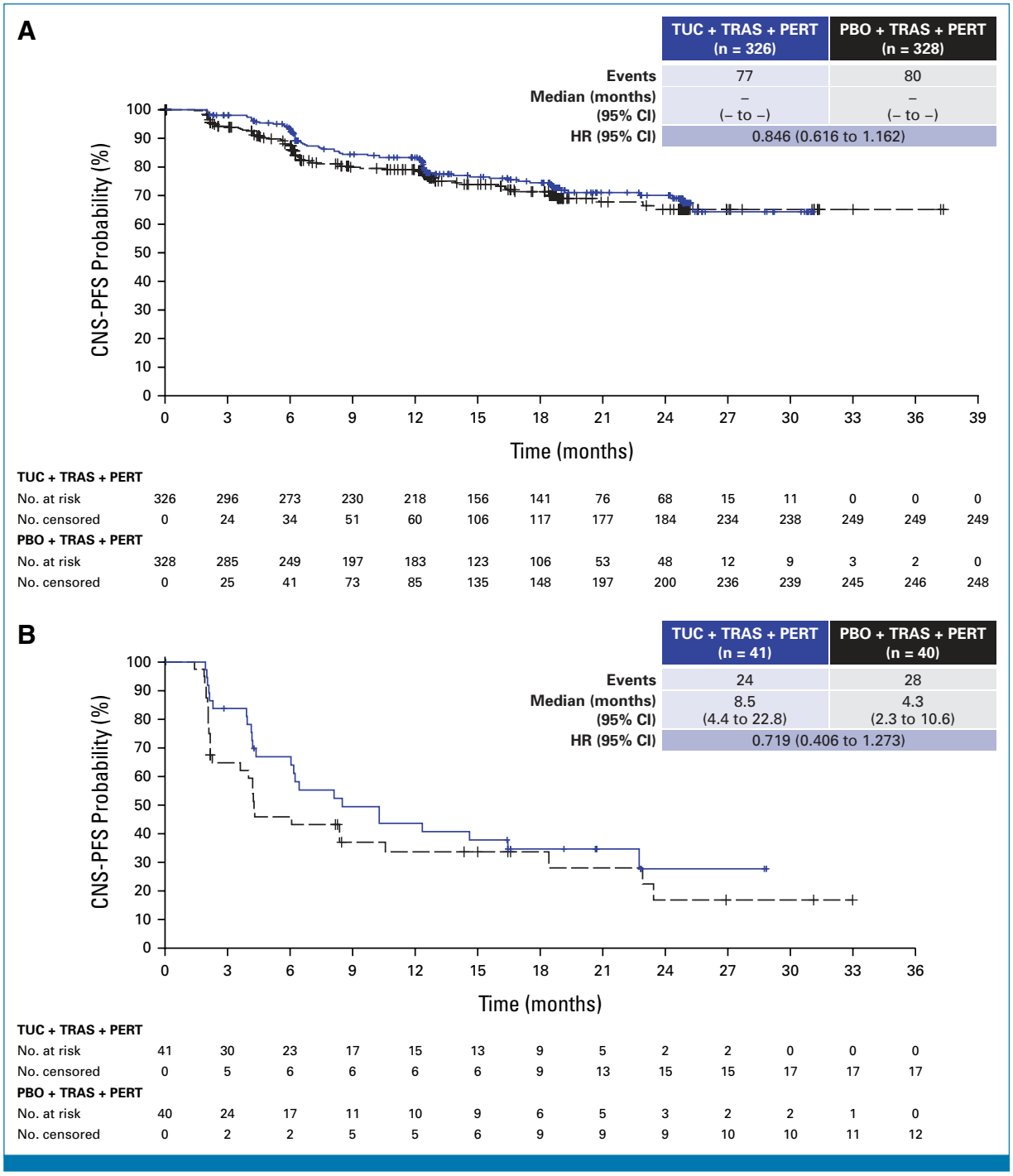

FIG A3. Kaplan-Meier estimates of (A) investigator-assessed CNS-PFS in the ITT analysis population and (B) patients with BM at baseline. BM, brain metastases; HR, hazard ratio; ITT, intention-to-treat; PBO, placebo; PERT, pertuzumab; PFS, progression-free survival; TRAS, trastuzumab; TUC, tucatinib.

TABLE A1. Baseline Demographic and Clinical Characteristics of Patients With HER2+ Metastatic Breast Cancer by Hormone Receptor Status

Characteristic	Hormone Receptor–Positive		Hormone Receptor–Negative	
	TUC + TRAS + PERT (n = 168)	PBO + TRAS + PERT (n = 176)	TUC + TRAS + PERT (n = 158)	PBO + TRAS + PERT (n = 152)
Age, years, median (range)	53.0 (24-79)	53.0 (29-83)	54.0 (29-82)	54.0 (29-80)
Disease status, No. (%)				
De novo	112 (66.7)	117 (66.5)	115 (72.8)	109 (71.7)
Recurrent	56 (33.3)	59 (33.5)	43 (27.2)	43 (28.3)
HER2+ testing, No. (%)				
IHC 2+, FISH+	24 (14.3)	37 (21.0)	5 (3.2)	11 (7.2)
IHC 3+	144 (85.7)	139 (79.0)	151 (95.6)	140 (92.1)
QC failure[a]	0	0	2 (1.3)	1 (0.7)
Visceral disease,[b] No. (%)	93 (55.4)	93 (52.8)	101 (63.9)	79 (52.0)

Abbreviations: BM, brain metastases; FISH, fluorescence in situ hybridization; HER2+, human epidermal growth factor receptor–positive; IHC, immunohistochemistry; PBO, placebo; PERT, pertuzumab; QC, quality control; TRAS, trastuzumab; TUC, tucatinib.

[a]Three samples had a HER2+ test result centrally confirmed but did not meet internal quality control criteria. Patients with IHC 3+ were counted as HER2+ per guidelines[18] regardless of FISH result.

[b]Visceral disease includes tumors located in the abdomen, adrenal gland, bladder, cervix, colon, esophagus, liver, lung, ovary, pancreas, pleura, rectum, spleen, and stomach. All other locations, including BM, are classified as nonvisceral disease.

TABLE A2. Subsequent Anticancer Therapy in the ITT Analysis Set

Subsequent Anticancer Therapy	TUC + TRAS + PERT (n = 326), No. (%)	PBO + TRAS + PERT (n = 328), No. (%)
Patients who received ≥1 subsequent anticancer therapy	114 (35.0)	178 (54.3)
Systemic therapy for progressive disease	97 (29.8)	159 (48.5)
Systemic therapy for relapsed disease	1 (0.3)	0
Maintenance	20 (6.1)	27 (8.2)
Other	2 (0.6)	3 (0.9)
Medication class		
Antineoplastic agent	27 (8.3)	46 (14.0)
Endocrine therapy	12 (3.7)	15 (4.6)
mAb/ADC	106 (32.5)	157 (47.9)
HER2 inhibitor	105 (32.2)	156 (47.6)
Pertuzumab	25 (7.7)	35 (10.7)
Pertuzumab/trastuzumab	11 (3.4)	21 (6.4)
Trastuzumab	40 (12.3)	52 (15.9)
Trastuzumab deruxtecan	53 (16.3)	81 (24.7)
Trastuzumab deruxtecan nxki	2 (0.6)	8 (2.4)
Trastuzumab emtansine	16 (4.9)	17 (5.2)
Trastuzumab mafodotin	1 (0.3)	0
Sacituzumab govitecan	1 (0.3)	0
Bevacizumab	0	1 (0.3)
CDK inhibitor	1 (0.3)	4 (1.2)
Tyrosine kinase inhibitor	11 (3.4)	19 (5.8)
Pyrotinib maleate	2 (0.6)	0
Tucatinib	4 (1.2)	10 (3.0)
Zongertinib	0	1 (0.3)
Lapatinib	1 (0.3)	0
Lapatinib ditosylate monohydrate	1 (0.3)	0
Pyrotinib	1 (0.3)	2 (0.6)
Pyrotinib maleate	2 (0.6)	6 (1.8)

Abbreviations: ADC, antibody-drug conjugate; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; mAb, monoclonal antibody; PBO, placebo; PERT, pertuzumab; TRAS, trastuzumab; TUC, tucatinib.

TABLE A3. Safety Summary in Treatment Arms

Safety Parameter	TUC + TRAS + PERT (n = 326), No. (%)	PBO + TRAS + PERT (n = 324), No. (%)
Patients with TEAE		
Any	323 (99.1)	313 (96.6)
Grade ≥3	138 (42.3)	79 (24.4)
Serious TEAE	55 (16.9)	26 (8.0)
Leading to death	1 (0.3)[a]	1 (0.3)
Discontinued from study treatment because of TEAE[b]		
Any	45 (13.8)	15 (4.6)
TUC/PBO	44 (13.5)	7 (2.2)
TRAS or PERT individually	2 (0.6)	5 (1.5)
TRAS + PERT fixed-dose combination	9 (2.8)	4 (1.2)
Most common TEAEs leading to TUC/PBO discontinuation		
Any	44 (13.5)	7 (2.2)
Hepatic events[c]	25 (7.7)	0
Diarrhea	5 (1.5)	3 (0.9)
Cardiac failure	2 (0.6)	0
Dose modification because of TEAE[d]		
Any	182 (55.8)	112 (34.6)
TUC/PBO dose hold	161 (49.4)	82 (25.3)
TUC/PBO dose reduction	95 (29.1)	36 (11.1)
TRAS dose hold	20 (6.1)	22 (6.8)
TRAS dose interruption	1 (0.3)	0
PERT dose hold	20 (6.1)	21 (6.5)
PERT dose interruption	0	0
TRAS + PERT fixed-dose combination hold	73 (22.4)	44 (13.6)
TRAS + PERT fixed-dose combination interruption	0	1 (0.3)
Patients with TRAE		
Any	302 (92.6)	268 (82.7)
Grade ≥3	101 (31.0)	41 (12.7)
Serious TRAE	25 (7.7)	6 (1.9)
Leading to death	1 (0.3)	0

Abbreviations: DILI, drug-induced liver injury; PBO, placebo; PERT, pertuzumab; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRAS, trastuzumab; TUC, tucatinib.

[a]One death occurred due to a TEAE of grade 5 DILI in the TUC arm; the patient died approximately 4.5 months after starting the study treatment and had an additional associated event of hepatic failure. The hepatic events were confounded by multiple concomitant medications with known hepatotoxic potential.

[b]If a patient discontinues TRAS or PERT, they are required to discontinue both. Patients may discontinue TUC/PBO but remain on TRAS and PERT (and vice versa).

[c]Includes (n) ALT increased (13), blood bilirubin increased (2), DILI (2), hepatic cytolysis (2), hypertransaminasemia (2), liver injury (2), AST increased (1), hepatobiliary disease (1).

[d]Dose modification includes dose hold, dose reduction, and dose interruption per investigator; dose interruption is not applicable to TUC/PBO; dose reductions were not allowed for TRAS and PERT.