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ORIGINAL ARTICLE

Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis

G. Curigliano[1*], V. Mueller[2], V. Borges[3], E. Hamilton[4], S. Hurvitz[5], S. Loi[6], R. Murthy[7], A. Okines[8], E. Paplomata[9†], D. Cameron[10], L. A. Carey[11], K. Gelmon[12], G. N. Hortobagyi[7], I. Krop[13], S. Loibl[14], M. Pegram[15], D. Slamon[5], J. Ramos[16], W. Feng[16] & E. Winer[13]

[1]Istituto Europeo di Oncologia, Milan, IRCCS and University of Milano, Milan, Italy; [2]Universitaetsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]University of Colorado Hospital, Aurora; [4]Sarah Cannon Research Institute/Tennessee Oncology — Nashville, Nashville; [5]University of California, Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, USA; [6]Peter MacCallum Cancer Centre, Melbourne, Australia; [7]MD Anderson Cancer Center, Houston, USA; [8]The Royal Marsden NHS Foundation Trust, London, UK; [9]Carbone Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, USA; [10]Edinburgh Cancer Research Centre, Edinburgh, UK; [11]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, USA; [12]British Columbia Cancer — Vancouver Centre, Vancouver, Canada; [13]Dana-Farber Cancer Institute, Boston, USA; [14]German Breast Group, Neu-Isenburg, Germany; [15]Stanford Cancer Institute, Palo Alto; [16]Seagen Inc., Bothell, USA

Available online 23 December 2021

Background: In the primary analysis of the HER2CLIMB trial, tucatinib added to trastuzumab and capecitabine significantly improved overall survival (OS) and progression-free survival (PFS) in patients with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer. We report efficacy and safety outcomes, including the final OS and safety outcomes from follow-up in HER2CLIMB.

Patients and methods: HER2CLIMB is a randomized, double-blind, placebo-controlled trial in patients with locally advanced or metastatic HER2+ breast cancer, including patients with brain metastases. Patients were randomized 2 : 1 to receive tucatinib or placebo, in combination with trastuzumab and capecitabine. After the primary analysis (median follow-up of 14 months), the protocol was amended to allow for unblinding sites to treatment assignment and cross-over from the placebo combination to the tucatinib combination. Protocol prespecified descriptive analyses of OS, PFS (by investigator assessment), and safety were carried out at ∼2 years from the last patient randomized.

Results: Six hundred and twelve patients enrolled in the HER2CLIMB trial. At a median OS follow-up of 29.6 months, median duration of OS was 24.7 months for the tucatinib combination group versus 19.2 months for the placebo combination group [hazard ratio (HR) for death: 0.73, 95% confidence interval (CI): 0.59-0.90, $P = 0.004$] and OS at 2 years was 51% and 40%, respectively. HRs for OS across prespecified subgroups were consistent with the HR for the overall study population. Median duration of PFS was 7.6 months for the tucatinib combination group versus 4.9 months for the placebo combination group (HR for progression or death: 0.57, 95% CI: 0.47-0.70, $P < 0.00001$) and PFS at 1 year was 29% and 14%, respectively. The tucatinib combination was well tolerated with a low rate of discontinuation due to adverse events.

Conclusions: With additional follow-up, the tucatinib combination provided a clinically meaningful survival benefit for patients with HER2+ metastatic breast cancer.

Key words: metastatic breast cancer, human epidermal growth factor receptor 2-positive (HER2), brain metastases, tucatinib, trastuzumab, capecitabine

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) overexpression occurs in 20%-25% of all breast cancers.[1-4] HER2-positive (HER2+) breast cancer has been historically associated with a poor prognosis[5,6] and most patients with metastatic breast cancer ultimately die of their disease.[7-10] Furthermore, HER2+ breast cancer has a propensity to metastasize to the brain and there are limited treatment

*Correspondence to: Prof. Giuseppe Curigliano, Division of Early Drug Development, Istituto Europeo di Oncologia, Milan, IRCCS, Division of Medical Oncology, University of Milano, Via Ripamonti 435, 20141 Milano, Italy. Tel: +39-0257489788

E-mail: giuseppe.curigliano@ieo.it (G. Curigliano).

†Affiliation at time of analysis.

options for patients with brain metastases, as large molecules, such as monoclonal antibodies, do not easily penetrate the blood-brain barrier.

Current treatment guidelines for patients with HER2+ metastatic breast cancer recommend a taxane in combination with trastuzumab and pertuzumab, followed by trastuzumab emtansine (T-DM1) for patients who have disease progression.[11,12] Recently, small molecule tyrosine kinase inhibitors (TKIs) have shown promise in the metastatic setting.[10,13] Some HER2-directed TKIs, however, have significant off-target effects on the epidermal growth factor receptor (EGFR) leading to tolerability issues related to high incidences of diarrhea, including severe diarrhea, and skin toxicity.[10,14] Tucatinib is highly selective for the HER2 receptor and only minimally inhibits other HER family receptors, including EGFR.[15] Encouraging antitumor activity was shown in a previous phase Ib study of tucatinib in combination with trastuzumab and capecitabine in patients with HER2+ metastatic breast cancer, including those with brain metastases.[16] Similar to other regimens for patients with HER2+ metastatic breast cancer that utilize a dual blockade of HER2 (e.g. trastuzumab and pertuzumab),[17] tucatinib to date has been developed in combination with another HER2-targeting agent.

The pivotal HER2CLIMB trial (Clinical Trial Registration: NCT02614794) evaluated tucatinib compared with placebo, each in combination with trastuzumab and capecitabine, for HER2+ metastatic breast cancer after progression on trastuzumab, pertuzumab, and T-DM1 in any setting (neoadjuvant, adjuvant, and/or metastatic).[13] Patients with and without brain metastases were enrolled, including those with active (progressive and/or untreated) brain metastases. In the primary analysis (median 14.0 months of follow-up in the total study population), HER2CLIMB met all primary and alpha-controlled secondary endpoints, including a 46% reduction in the risk of progression or death in the first 480 patients, 34% reduction in risk of death in the total study population, and 52% reduction in the risk of progression or death in patients with brain metastases.[13] The benefit of tucatinib was observed across all prespecified subgroups, and secondary endpoints were met during the primary analysis.[13] Median time to first response was 1.4 months in each treatment group.

The addition of tucatinib to trastuzumab and capecitabine was well tolerated. There was a low discontinuation rate of tucatinib due to adverse events (6%). Severe diarrhea was observed in 13% of patients, and most diarrhea was manageable with short courses of antidiarrheal medications (median of 3 days per cycle) in both the tucatinib and placebo combination groups.[13] Additionally, rates of alopecia were low, there was no difference in left ventricular decline between the tucatinib and placebo combination groups, and only one case of interstitial lung disease (grade 1 pneumonitis) was reported on the tucatinib combination group.[18]

Tucatinib is approved in combination with trastuzumab and capecitabine in multiple regions of the world for patients with HER2+ metastatic breast cancer, including those with brain metastases, whose cancers have progressed on at least one prior HER2-directed treatment in the metastatic setting (United States) or two prior HER2-directed treatment regimens in any setting [European Union (EU)].

We report final efficacy and safety outcomes after an additional 15.6 months of overall survival (OS) follow-up in patients from the HER2CLIMB trial. HER2CLIMB met statistical significance for all primary and alpha-controlled secondary endpoints at the primary analysis; therefore, this follow-up analysis is descriptive only.

METHODS

Patients and treatment

The methodology of the global, randomized, double-blind HER2CLIMB trial has been described previously.[13] Patients with HER2+ metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1, in any setting, were randomly assigned 2:1 to receive either tucatinib (300 mg) or placebo orally twice daily, in combination with trastuzumab (6 mg/kg intravenously once every 21 days, with initial 8 mg/kg loading dose; subcutaneous administration was allowed) and capecitabine (1000 mg/m^2 orally twice daily on days 1-14 of each 21-day cycle). Patients with a history or presence of brain metastases at baseline, including treated stable and active (progressive and/or untreated) brain metastases, were eligible. Patients were stratified at randomization based on presence or history of brain metastases (yes or no), Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1) and region of world [USA, Canada (North America), or rest of world]. The HER2CLIMB trial was conducted in accordance with regulatory requirements and International Council for Harmonisation Good Clinical Practice guidelines. The protocol was approved by institutional review boards and ethics committees, according to the practice at each participating trial site, and informed consent was obtained for experimentation with human patients.

Assessments

In the primary analysis, disease response and progression were assessed by Blinded Independent Central Review in accordance with RECIST criteria version 1.1.[13] Protocol prespecified analyses of OS, progression-free survival (PFS), and safety in 612 patients (total population) were carried out at ~2 years from the last patient randomized in the current analysis. Disease response and progression for this analysis were assessed by the investigator in accordance with RECIST criteria version 1.1.[19] Adverse events were defined according to the Medical Dictionary for Regulatory Activities, version 22.0, and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

Kaplan–Meier methodology was used to estimate OS and PFS and the associated 95% confidence intervals (CIs). Hazard ratios (HRs) were computed from the Cox proportional hazards model using stratification factors [ECOG performance status (0 or 1), region of world (North America

or rest of world)] at random assignment. All *P* values reported are nominal and were obtained from the stratified log-rank test.

After the primary analysis, patients were unblinded and permitted to cross over from the placebo combination group to receive tucatinib in combination with trastuzumab and capecitabine (tucatinib combination group). The first patient crossed over in February 2020, and this analysis includes data up until the data cut-off on 8 February 2021. The OS analysis reported here was based on the intention-to-treat (ITT) principle, i.e. patients were analyzed per randomization regardless of cross-over. In addition, three sensitivity analyses were conducted to account for the cross-over: (i) patients who cross over were censored at the day of cross-over, (ii) inverse probability of censoring weight, and (iii) rank preserving structural failure time. The previously reported OS[13] met the prespecified criteria for significance. Herein, we report descriptive follow-up.

RESULTS

Six hundred and twelve patients enrolled in the HER2CLIMB trial. As reported previously, baseline demographic and disease characteristics were similar between treatment groups; 48% of patients had brain metastases at baseline and patients had received a median of four prior lines of therapy, three in the metastatic setting.[13] At the time of data cut-off (8 February 2021), 36 patients remained on the study treatment, of whom 35 were in the tucatinib combination group. Among patients who were randomized to receive placebo, 26 crossed over to the tucatinib combination group, of whom 9 remained on tucatinib as of data cut-off. One hundred and sixty nine patients remain in follow-up (Figure 1).

Median follow-up for OS was 29.6 months (an additional 15.6 months from the primary analysis). The median duration of OS was 24.7 months (95% CI: 21.6-28.9 months) for the tucatinib combination group versus 19.2 months (95% CI: 16.4-21.4 months) in the placebo combination group (HR for death: 0.73, 95% CI: 0.59-0.90, $P = 0.004$; Figure 2A). The estimated OS rate at 2 years was 51% (95% CI: 46% to 56%) in the tucatinib combination group and 40% (95% CI: 33% to 47%) in the placebo combination group. HRs for OS across all subgroups evaluated favored the tucatinib combination group and were consistent with the HR in the overall study population (Figure 3). The results of sensitivity analyses accounting for cross-over were similar to the ITT analysis, with estimated HRs ranging from 0.71 to 0.72.

Median duration of PFS was 7.6 months (95% CI: 6.9-8.3 months) for the tucatinib combination group versus 4.9 months (95% CI: 4.1-5.6 months) for the placebo combination group (HR for disease progression or death: 0.57, 95% CI: 0.47-0.70, $P < 0.00001$; Figure 2B). The estimated PFS rate at 1 year was 29% (95% CI: 24% to 34%) in the tucatinib combination group and 14% (95% CI: 9% to 20%)

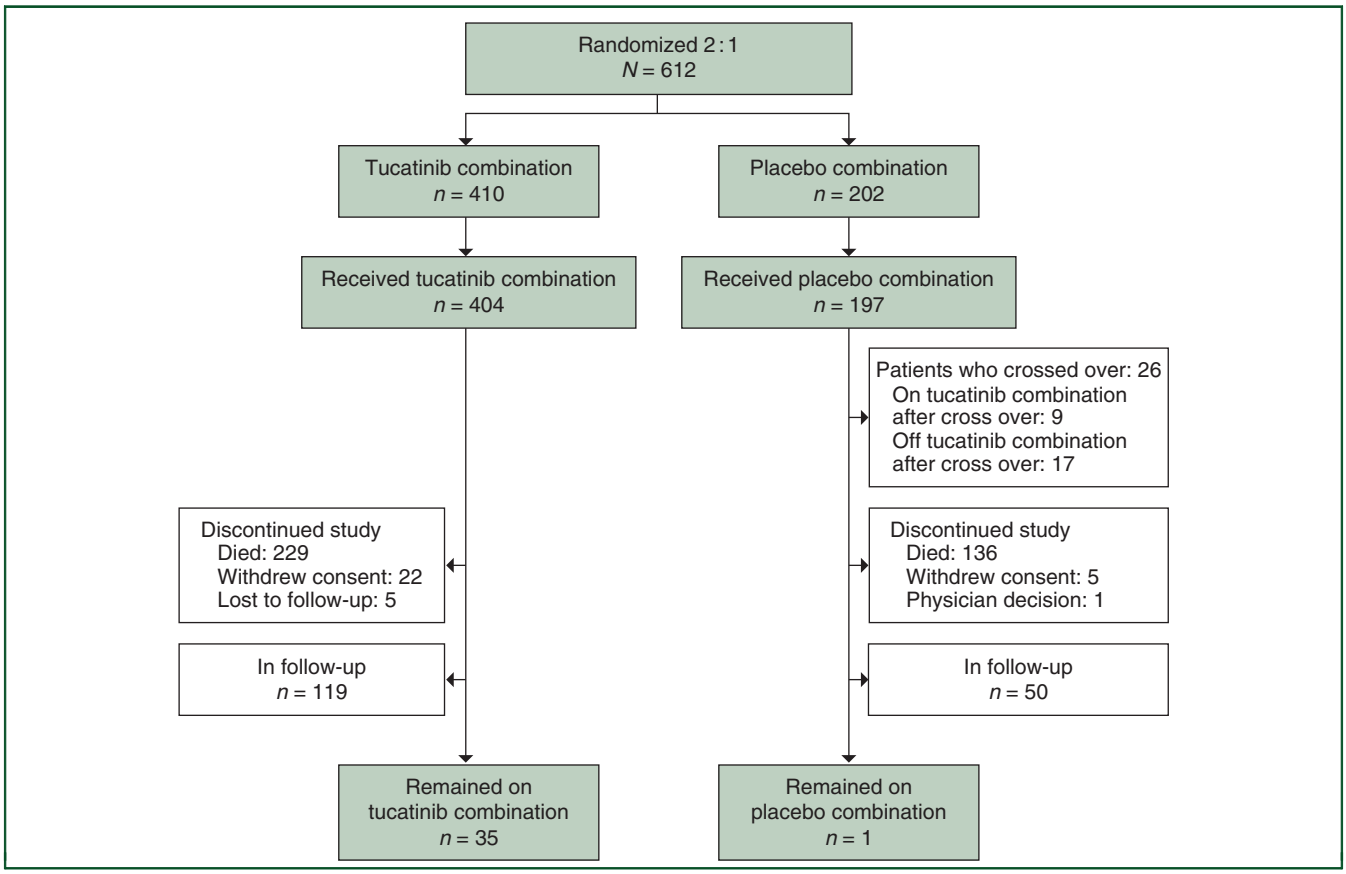

Figure 1. CONSORT diagram of HER2CLIMB study population.
Tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.

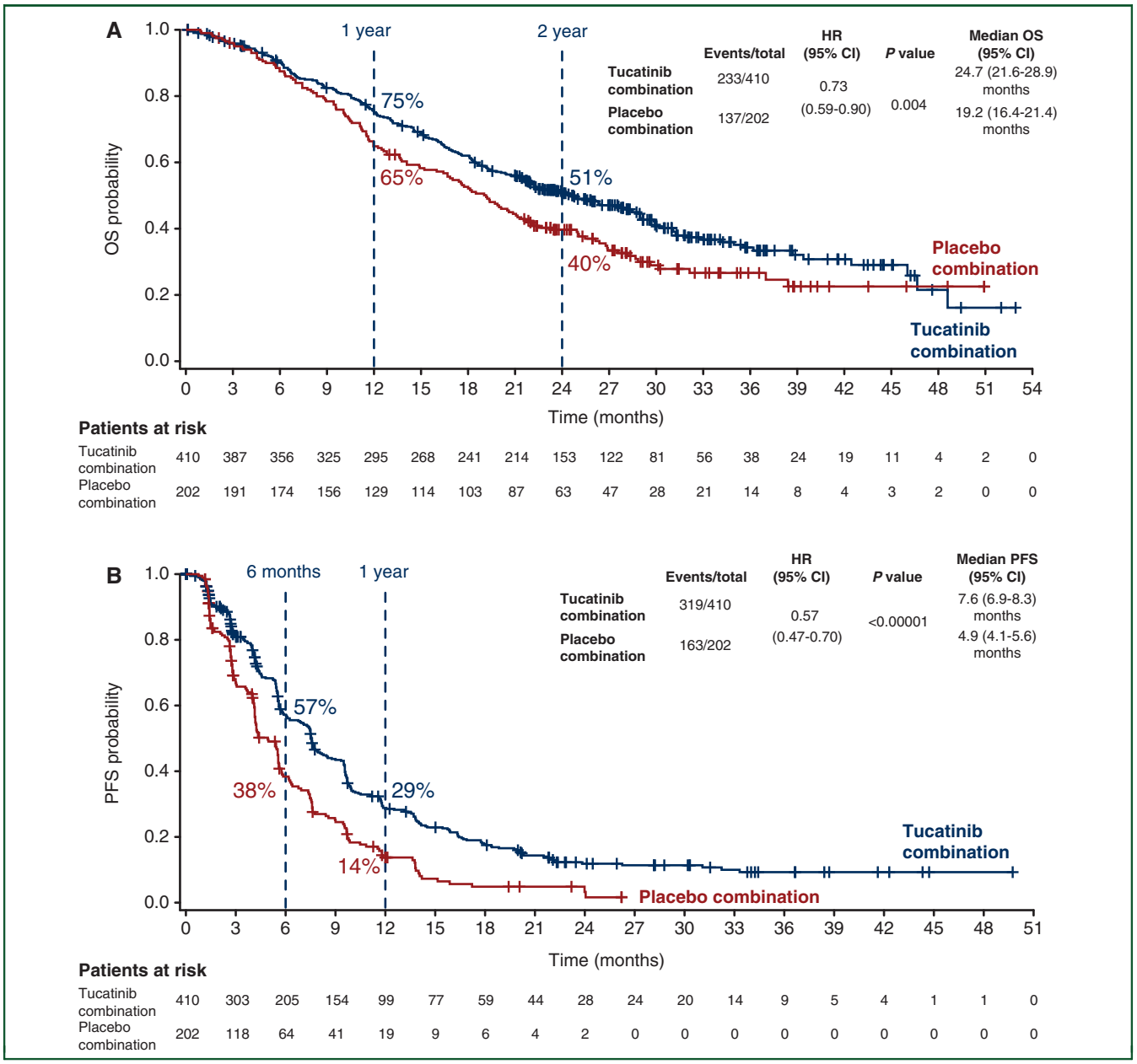

Figure 2. Kaplan–Meier estimates of (A) overall survival and (B) progression-free survival.
Tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

in the placebo combination group. After progressing on tucatinib combination, the majority of patients (77%) went on to receive additional anticancer therapies. Among these patients, 86% received ≥1 additional anti-HER2 regimens, 17% received ≥1 additional hormonal or cyclin-dependent kinase inhibitor therapies, and 8% received ≥1 additional programmed cell death protein 1/programmed death-ligand 1 inhibitor therapies. Comparable proportions of patients in the placebo combination group (82%) received additional anticancer therapies post-progression.

Patients in the tucatinib combination group completed a median (min, max) of 10 (1, 74) treatment cycles compared with 6 (1, 39) treatment cycles for patients in the placebo combination group. Median (min, max) duration of exposure was 7.4 months (<0.1, 52.0) for the tucatinib combination group and 4.4 months (<0.1, 26.9) for the placebo combination group. Rates of grade 3 or higher adverse events, serious adverse events, and treatment discontinuation due to adverse events were similar between the treatment groups (Table 1). Beyond the primary analysis, only one additional patient discontinued tucatinib due to an adverse event. With additional follow-up, the most common adverse events in patients on the tucatinib combination [diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome, nausea, fatigue, and vomiting] continued to be primarily grade 1 or 2 and their overall rates remained

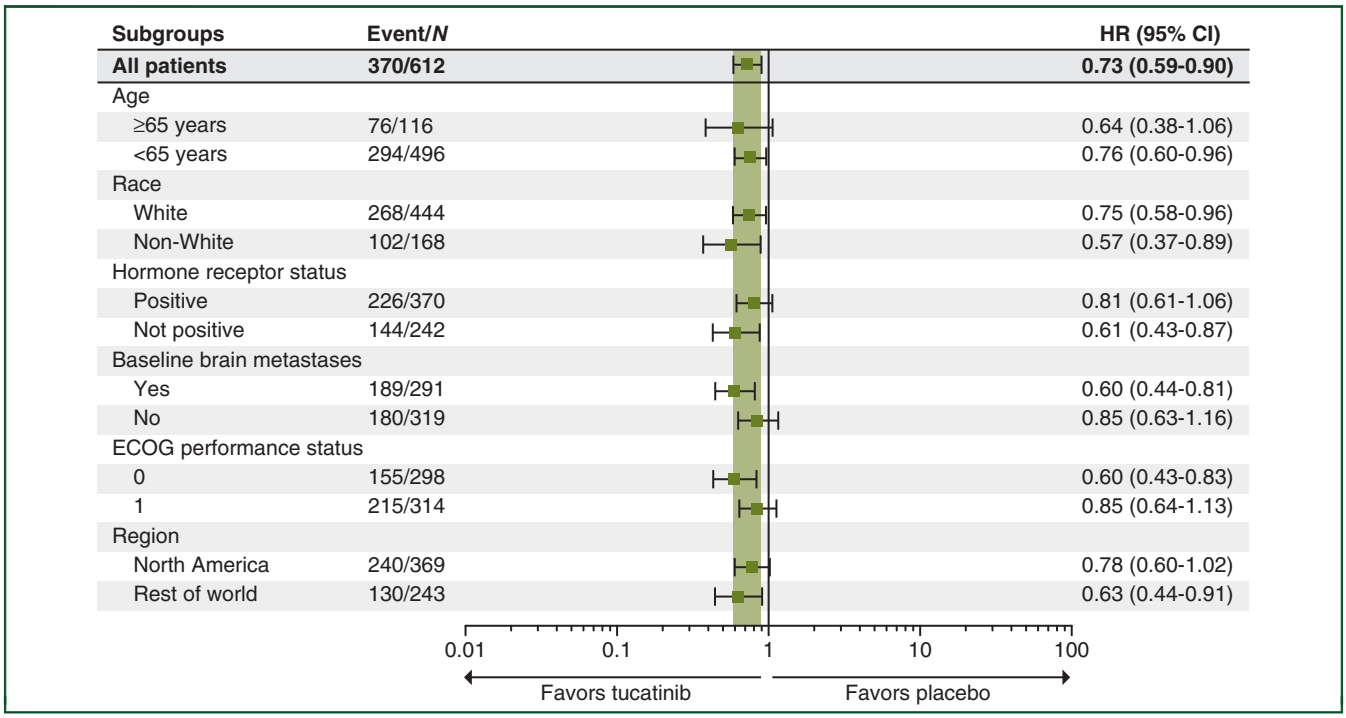

Figure 3. Forest plot of overall survival in prespecified subgroup analysis.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

stable (Table 2). Rates of the most common grade 3 or higher adverse events in patients on the tucatinib combination (PPE syndrome, diarrhea, elevations in alanine aminotransferase and aspartate aminotransferase levels, and fatigue) also remained stable with additional follow-up (Table 2).

DISCUSSION

With an additional 15.6 months of follow-up, tucatinib, added to trastuzumab and capecitabine, continues to demonstrate a significant improvement in OS, with a median survival benefit of 5.5 months. The median OS in patients treated with tucatinib combination was 24.7 months compared with 19.2 months for those treated in the placebo combination group. This final analysis showed that treatment with tucatinib combination continued to provide a robust survival benefit in a HER2+ metastatic breast cancer population that included patients with and without brain metastases whose disease had been previously treated with trastuzumab, pertuzumab, and T-DM1 in any treatment setting. To our knowledge, this is the first treatment combination to show a clinically meaningful OS benefit for patients in this disease setting. In addition, the benefit across all prespecified subgroups was consistent with the primary analysis[13] and was maintained with additional follow-up.

These survival outcomes are particularly notable given that nearly half of HER2CLIMB patients had brain metastases, including those with active brain metastases at baseline. This well represents the real-world population, where up to 50% of patients with HER2+ metastatic breast cancer will develop brain metastases at some point in their metastatic course.[20-24] In patients who undergo initial local therapy with surgical resection, stereotactic radiosurgery, and/or whole-brain radiation therapy,[25] rates of intracranial progression within 6-12 months remain high.[26-28] Even with the advances in HER2-targeted treatment, patients with brain metastases continue to have a poor prognosis.[29] Although clinical trials of treatments for HER2+ metastatic breast cancer typically have excluded patients with brain metastases, the American Society of Clinical Oncology—Friends of Cancer Research Brain Metastases Working Group and the 2019 Food and Drug Administration 'Cancer Clinical Trial Eligibility Criteria: Brain Metastases—Guidance for Industry' have called for inclusion of patients with brain metastases in clinical trials.[30,31]

In an exploratory analysis from HER2CLIMB, from an earlier data cut-off date,[32] the tucatinib combination doubled the intracranial objective response rate, reduced the risk of intracranial progression or death by two-thirds, and reduced the risk of death by nearly one in all patients with brain metastases. In this study population, the estimated 1-year intracranial PFS (CNS-PFS) was 40% in the tucatinib arm and 0% in the control arm. In patients with untreated or treated and progressing (active) brain metastases, estimated 1-year CNS-PFS was 35% in the tucatinib arm and 0% in the control arm, and in patients with treated (stable) brain metastases, it was 53% in the tucatinib arm and 0% in the control arm. Finally, among the patients who experienced isolated progression in the brain, the median time to second progression or death was 16 months in the tucatinib arm and 10 months in the control arm. These data show that systemic treatment with tucatinib in combination with trastuzumab and capecitabine provides consistent

Table 1. Adverse events summary

TEAEs	Tucatinib combination (*N* = 404) *n* (%)	placebo combination (*N* = 197) *n* (%)
Any TEAE	401 (99.3)	191 (97.0)
Grade ≥3 TEAE	245 (60.6)	101 (51.3)
Any serious TEAE	123 (30.4)	58 (29.4)
Death due to TEAE	6 (1.5)	5 (2.5)
Discontinued any study treatment due to TEAE	52 (12.9)	23 (11.7)
Discontinued tucatinib/placebo due to TEAE	24 (5.9)	8 (4.1)
Discontinued capecitabine due to TEAE	47 (11.6)	22 (11.2)
Discontinued trastuzumab due to TEAE	17 (4.2)	7 (3.6)

TEAEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up through 30 days after the last dose of study treatment (i.e. last dose of tucatinib/placebo). Tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.
TEAE, treatment-emergent adverse event.

clinical benefit to patients with and without brain metastases, which remains an area of high unmet need.

Overall, tucatinib combination was well tolerated with a low rate of discontinuation due to adverse events. Although patients in the tucatinib combination group were on treatment longer than patients in the placebo combination group, there was minimal impact of additional exposure on safety, highlighting tolerability of the tucatinib combination. The safety profile of tucatinib combination with added follow-up was consistent with the primary analysis, with no new safety signals reported and no deaths due to adverse events. Furthermore, the additional follow-up showed no notable increase in the rates of adverse events, and only one additional patient discontinued tucatinib due to an adverse event in the time since the primary analysis.

Importantly, rates of liver laboratory abnormalities and diarrhea did not increase with additional follow-up. Although overall rates of PPE were higher in the tucatinib combination group, PPE is a known side-effect of capecitabine, and the higher rates of PPE may be partially explained by a longer exposure to capecitabine in the tucatinib combination group.[18] Similarly, whereas overall rates of diarrhea were higher in the tucatinib combination group for all grades, rates of grade 3 or higher were similar between treatment groups, which could be attributed to longer duration of treatment in the tucatinib combination group.

Exploratory analysis of health-related quality of life in HER2CLIMB further supports the tolerability of the tucatinib combination. Using the EuroQol 5 Dimensions 5 Levels instrument, the tucatinib combination was found to preserve health-related quality of life throughout treatment.[33] Finally, the proportions of patients who received additional anticancer therapies post-progression in tucatinib combination and placebo combination groups were high and comparable, suggesting that tucatinib combined with trastuzumab and capecitabine is sufficiently well tolerated for patients to receive additional treatments.

This analysis had a few limitations. First, patients who crossed over and received tucatinib were included in the assessments of the placebo combination group, which introduced a bias in the ITT analysis favoring the placebo combination group. Several sensitivity analyses were carried out, however, and did not show any significant difference from the ITT analysis. Second, the primary and key secondary endpoints of the study met statistical significance at primary analysis, therefore, the analyses reported here were descriptive with no formal statistical comparisons. Lastly, because disease status was not assessed by independent central review after the primary analysis, only PFS per investigator review was reported.

Conclusions

The continued OS benefit and tolerability of tucatinib in combination with trastuzumab and capecitabine augments data from the primary analysis and further supports the use of this combination in patients with previously treated HER2+ metastatic breast cancer after progression on two HER2-targeted therapies. Tucatinib in combination with trastuzumab and capecitabine is an important treatment

Table 2. Adverse events reported in ≥20% of patients in the tucatinib arm

Adverse event	Tucatinib combination (*N* = 404) *n* (%)		Placebo combination (*N* = 197) *n* (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.

option in the rapidly evolving HER2+ metastatic treatment landscape.[34,35]

ACKNOWLEDGEMENTS

We thank the patients who participated in the HER2CLIMB trial and their families, as well as the investigators and research staff at all HER2CLIMB clinical sites; the members of the independent data and safety monitoring committee and the independent review committee; Gerald Engley, PharmD, Seagen Inc., for critical review and revision of the manuscript; and Wendi Schultz, MS, and Holly Tomlin, MPH, of Seagen Inc. and Laurie LaRusso, MS, of Chestnut Medical Communications for writing support, funded by Seagen Inc.

FUNDING

This work was supported by Seagen Inc. (Bothell, WA, USA), the manufacturer of tucatinib and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (no grant number). Writing assistance was funded by Seagen Inc. in accordance with Good Publications Practice guidelines (no grant number).

DISCLOSURE

GC: consultancy with Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Foundation Medicine, GlaxoSmithKline, Lilly, Novartis, Pfizer, Roche/Genentech, Samsung, and Seagen Inc.; honoraria from Ellipses Pharma; research funding/grants from Merck; speaker's bureau with Daiichi Sankyo, Foundation Medicine, Lilly, Novartis, Pfizer, Roche/Genentech, Samsung, and Seagen Inc.; travel from Pfizer and Roche/Genentech. VM: consultancy with Amgen, Daiichi Sankyo, Eisai, Gilead, Hexal, Lilly, Nektar, Roche, and Seagen Inc.; honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Genomic Health, Lilly, MSD Oncology, Nektar, Novartis, Onkowissen, Pfizer, Pierre Fabre, Roche, Seagen Inc., Tesaro, and Teva; speaker's bureau with Novartis, Roche, and Seagen Inc.; travel from Daiichi Sankyo, P Value Communications, and Roche. VB: consultancy with Seagen Inc.; research funding/grants from AstraZeneca, Genentech, Olema Oncology, Oncosec, Pfizer, and Seagen Inc. EH: consultancy with Genentech/Roche, Boehringer Ingelheim, Novartis, Dantari, Lilly, Merck, Puma Biotechnology, Silverback Therapeutics, CytomX, Pfizer, Mersana, Black Diamond, H3 Biomedicine, Daiichi Sankyo, AstraZeneca, Arvinas, Deciphera Pharmaceuticals, Eisai, and Seagen Inc.; research funding/grants from OncoMed, Genentech/Roche, Zymeworks, Rgenix, ArQule, Clovis, Silverback Therapeutics, Millennium, Acerta Pharma, Sermonix Pharmaceuticals, Torque, Black Diamond, Karyopharm, Infinity Pharmaceuticals, Curis, Syndax, Novartis, Boehringer Ingelheim, Immunomedics, FujiFilm, Taiho, Deciphera, Fochon, Molecular Templates, Onconova Therapeutics, Dana Farber Cancer Hospital, Hutchinson MediPharma, MedImmune, Seagen Inc., Puma Biotechnology, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Takeda, Merus, Regeneron, Arvinas, Stemcentrx, Verastem, eFFECTOR Therapeutics, CytomX, InventisBio, Lycera, Mersana, Radius Health, AbbVie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, Merck, PharmaMar, Olema, Polyphor, Immunogen, Plexxikon, Amgen, Akesobio Australia, and Shattuck Labs. SH: equity ownership in Ideal Implant, ROM Tech; research funding/grants from Ambrx, Amgen, AstraZeneca, Arvinas, Bayer, CytomX, Daiichi Sankyo, Dignitana, Genentech/Roche, Gilead, GlaxoSmithKline, Immunomedics, Eli Lilly, Macrogenics, Novartis, Pfizer, Medivation, BioMarin, OBI Pharma, Pieris, PUMA, Radius, Sanofi, Seagen Inc., Zymeworks, and Phoenix Molecular Designs, Ltd.; travel from Lilly. SL: consultancy and advisory board membership with AbbVie, Amgen, AstraZeneca, Bayer Bristol-Myers Squibb, Celgene, Daiichi Sankyo, EirGenix, G1 Therapeutics, GlaxoSmithKline, Gilead, Lilly, Novartis, Pfizer, Pierre Fabre, Prime/Medscape, Puma, Roche/Genentech, Seagen Inc., and Silverback; honoraria from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer, Pierre Fabre, Prime/Medscape, Roche/Genentech, and Samsung; research funding/grants from AbbVie, AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Novartis, Pfizer, Roche/Genentech, and Seagen Inc.; patents/royalties: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8, vm Scope GmbH; employee of GBG Forschungs GmbH; other (non-financial — medical writing) with Daiichi Sankyo, Gilead, Novartis, Pfizer, Puma, Roche/Genentech, and Seagen Inc. RM: consultancy with AstraZeneca, Genentech/Roche, Novartis, Puma, and Seagen Inc.; honoraria from AstraZeneca, Genentech, Novartis, Puma, and Seagen Inc.; research funding/grants from AstraZeneca, Daiichi Sankyo, EMD Serono, Genentech/Roche, Pfizer, and Seagen Inc.; travel from Genentech and Seagen Inc. AO: advisory board membership with AstraZeneca, Roche/Genentech, and Seagen Inc.; honoraria from Daiichi Sankyo, Lilly, Pfizer, and Seagen Inc.; research funding/grants from Pfizer and Roche/Genentech; travel from AstraZeneca, Daiichi Sankyo, LEO Pharma, and Lilly. EP: consultancy with Biotheranostics, Mylan Novartis, Pfizer, Puma, and R-pharm; honoraria from Mylan Novartis, Pfizer, Puma, and R-pharm; research funding/grants from AbbVie, Cascadian, Corcept, Genentech, Hoosier Cancer Research Network, Immunogenicity, Merck, Novartis, and Seagen Inc.; speaker's bureau with OncLive Clinical Congress Consultants; travel from Amgen, Genentech, Merck, Novartis, and Tesaro. DC: consultancy with and research funding from Novartis, Roche, and Seagen Inc. LAC: advisory board membership (all uncompensated) from Eisai, Sanofi, Novartis, G1 Therapeutics, Genentech/Roche, GlaxoSmithKline, AZ, Daiichi Sankyo, Aptitude Health, and Exact Sciences; royalty sharing agreement, investorship interest in licensed IP to startup company, Falcon Therapeutics, that is designing neural stem cell-based therapy for glioblastoma multiforme (immediate family member); research funding/grants (to institution) from AbbVie, NanoString, Novartis, Seagen Inc., Syndax, and Veracyte; other (uncompensated relationships) with Aptitude Health, AstraZeneca/Daiichi Sankyo, Exact Sciences, G1 Therapeutics, Genentech/Roche, GlaxoSmithKline, Novartis, and Sanofi. KG: consultancy with AstraZeneca, Ayala, Bristol-Myers Squibb, Genentech, Genomic Health, Gilead, Janssen, Lilly, Merck, Mylan, NanoString, Novartis, Pfizer, and Roche; honoraria

from AstraZeneca, Merck Sharp & Dohme, Pfizer, Novartis, and Lilly; research funding/grants from AstraZeneca, Bristol-Myers Squibb, Pfizer, and Roche. GNH: consultancy with, research funding/grants, and travel from Novartis. IK: advisory board membership with AMAG Pharma and Freeline Therapeutics; consultancy with AstraZeneca, Bristol-Myers Squibb, Context Therapeutics, Daiichi Sankyo, Genentech/Roche, Ionis Pharma, Macrogenics, Merck, Novartis, Seagen Inc., and Taiho; employment with AMAG Pharma and Freeline Therapeutics; equity ownership: AMAG Pharma, Freeline Therapeutics, and Vertex; honoraria from AstraZeneca, Celltrion, and Genentech/Roche; research funding/grants from Genentech and Pfizer. SL: consultancy with AbbVie, Amgen, AstraZeneca/MedImmune, Bayer, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, EirGenix, GlaxoSmithKline, Immunomedics, Lilly, Medscape, Merck, Novartis, Pfizer, Pierre Fabre, Puma, Samsung, and Seagen Inc.; honoraria from Chugai Pharma; Patent Pending EP14153692.0; research funding/grants from AbbVie, Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Immunomedics, Myriad Genetics, Novartis, Pfizer, Pierre Fabre, Roche, Seagen Inc., and Vifor Pharma. MP: consultancy and honoraria from Genentech/Roche and Seagen Inc. DS: corporate board membership with BioMarin; consultancy with Lilly, Novartis, Pfizer, and Seagen Inc.; equity ownership in Amgen, BioMarin, Merck Sharp & Dohme, Pfizer, Seagen Inc., Vertex, TORL BioTherapeutics, and 1200 Pharma; honoraria and speaker's bureau from Novartis; research funding/grants from Novartis, Pfizer, and Seagen Inc.; travel from Novartis and Pfizer. JR: employment and equity ownership with Seagen Inc. WF: employment and equity ownership with Seagen Inc. EW: Carrick Therapeutics, G1 Therapeutics, Genentech/Roche, Gilead, GlaxoSmithKline, Jounce, Leap, Lilly, Seagen Inc., Syros Pharma, and Zymeworks; honoraria from Genentech/Roche and Genomic Health; research funding/grants from AstraZeneca and Genentech; other relationship with InfiniteMD.

REFERENCES

1. Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive breast cancer tumors for early stage patients in the US. *Cancer Invest*. 2010;28(9):963-968.
2. Gong Y, Liu YR, Ji P, Hu X, Shao ZM. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. *Sci Rep*. 2017;7:45411.
3. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.
4. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med*. 2007;131(1):18-43.
5. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182.
6. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244(4905):707-712.
7. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119.
8. Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2013;14(6):461-471.
9. Rugo HS, Im SA, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 2021;7(4):573-584.
10. Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38(27):3138-3149.
11. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
12. Giordano SH, Temin S, Davidson NE. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update summary. *J Oncol Pract*. 2018;14(8):501-504.
13. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609.
14. Welslau M, Diéras V, Sohn JH, et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. *Cancer*. 2014;120(5):642-651.
15. Kulukian A, Lee P, Taylor J, et al. Preclinical activity of HER2-selective tyrosine kinase inhibitor tucatinib as a single agent or in combination with trastuzumab or docetaxel in solid tumor models. *Mol Cancer Ther*. 2020;19(4):976-987.
16. Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2018;19(7):880-888.
17. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.
18. Okines A, Paplomata E, Wahl T, et al. Management of adverse events in patients with HER2+ metastatic breast cancer treated with tucatinib, trastuzumab, and capecitabine (HER2CLIMB). Abstract no. 1043; American Society of Clinical Oncology. May 29-31, 2020, Chicago, IL; 2020.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
20. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*. 2003;97(12):2972-2977.
21. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin Cancer Res*. 2011;17(14):4834-4843.
22. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. *J Clin Oncol*. 2009;27(31):5278-5286.
23. Olson EM, Najita JS, Sohl J, et al. Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. *Breast*. 2013;22(4):525-531.
24. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol*. 2013;14(3):244-248.
25. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases:

ASCO Clinical Practice Guideline update. *J Clin Oncol*. 2018;36(27):2804-2807.
26. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485-1489.
27. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2):134-141.
28. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048.
29. Hurvitz SA, O'Shaughnessy J, Mason G, et al. Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. *Clin Cancer Res*. 2019;25(8):2433-2441.
30. Cancer Clinical Trial Eligibility Criteria. Brain Metastases Guidance for Industry. In: Oncology Center of Excellence CfDEaRC, and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration, ed. Silver Spring, MD: Food and Drug Administration; 2019.
31. Lin NU, Prowell T, Tan AR, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. *J Clin Oncol*. 2017;35(33):3760-3773.
32. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619.
33. Mueller V, Wardley A, Paplomata E, et al. Preservation of quality of life in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer treated with tucatinib or placebo when added to trastuzumab and capecitabine (HER2CLIMB trial). *Eur J Cancer*. 2021;153:223-233.
34. Martínez-Sáez O, Prat A. Current and future management of HER2-positive metastatic breast cancer. *JCO Oncol Pract*. 2021;17(10):594-604.
35. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): results of the randomized phase III DESTINY-Breast03 study. *Ann Oncol*. 2021;32:S1287-S1288.