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Authors

Lin, Nancy U
Borges, Virginia
Anders, Carey
et al.

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Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, PhD[12]; Volkmar Mueller, MD[13]; Amelia Zelnak, MD[14]; Michael P. DiGiovanna, MD, PhD[15]; Thomas Bachelot, MD[16]; A. Jo Chien, MD[17]; Ruth O'Regan, MD[5]; Andrew Wardley, MBChB, MSc, MD[18]; Alison Conlin, MD, MPH[19]; David Cameron, MD, MA[20]; Lisa Carey, MD[21]; Giuseppe Curigliano, MD, PhD[22]; Karen Gelmon, MD[23]; Sibylle Loibl, MD, PhD[24]; JoAl Mayor, PharmD[25]; Suzanne McGoldrick, MD, MPH[25]; Xuebei An, PhD[25]; and Eric P. Winer, MD[1]

abstract

PURPOSE In the HER2CLIMB study, patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer with brain metastases (BMs) showed statistically significant improvement in progression-free survival (PFS) with tucatinib. We describe exploratory analyses of intracranial efficacy and survival in participants with BMs.

PATIENTS AND METHODS Patients were randomly assigned 2:1 to tucatinib or placebo, in combination with trastuzumab and capecitabine. All patients underwent baseline brain magnetic resonance imaging; those with BMs were classified as active or stable. Efficacy analyses were performed by applying RECIST 1.1 criteria to CNS target lesions by investigator assessment. CNS-PFS (intracranial progression or death) and overall survival (OS) were evaluated in all patients with BMs. Confirmed intracranial objective response rate (ORR-IC) was evaluated in patients with measurable intracranial disease.

RESULTS There were 291 patients with BMs: 198 (48%) in the tucatinib arm and 93 (46%) in the control arm. The risk of intracranial progression or death was reduced by 68% in the tucatinib arm (hazard ratio [HR], 0.32; 95% CI, 0.22 to 0.48; $P < .0001$). Median CNS-PFS was 9.9 months in the tucatinib arm versus 4.2 months in the control arm. Risk of death was reduced by 42% in the tucatinib arm (OS HR, 0.58; 95% CI, 0.40 to 0.85; $P = .005$). Median OS was 18.1 versus 12.0 months. ORR-IC was higher in the tucatinib arm (47.3%; 95% CI, 33.7% to 61.2%) versus the control arm (20.0%; 95% CI, 5.7% to 43.7%; $P = .03$).

CONCLUSION In patients with HER2-positive breast cancer with BMs, the addition of tucatinib to trastuzumab and capecitabine doubled ORR-IC, reduced risk of intracranial progression or death by two thirds, and reduced risk of death by nearly half. To our knowledge, this is the first regimen to demonstrate improved antitumor activity against BMs in patients with HER2-positive breast cancer in a randomized, controlled trial.

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ASSOCIATED CONTENT

Appendix

Protocol

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Up to 50% of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer will develop brain metastases (BMs) during the course of their disease.[1-5] Initial therapy for BMs typically consists of locally directed therapy with surgical resection, stereotactic radiosurgery, and/or whole-brain radiation therapy.[6] Unfortunately, the rate of intracranial progression within 6 to 12 months with these therapies is high.[7-9] In the absence of randomized, prospective data demonstrating a benefit of switching systemic agents at the time of brain progression, ASCO clinical practice guidelines currently recommend that patients with stable systemic disease at the time of brain progression continue treatment with the same systemic treatment after local therapy and until further progression.[6] In patients whose BMs have progressed after radiation therapy, the limited evidence to guide further management consists primarily of nonrandomized case series describing treated-lesion control, intracranial control, and overall survival (OS), without detailed descriptions of extracranial outcomes or concurrent systemic therapy.[10-12]

Patients with untreated or treated and progressing (ie, active) BMs have traditionally been excluded from participation in most clinical trials evaluating systemic HER2-targeting regimens.[13,14] Recently reported progression-free survival (PFS) in lapatinib-naïve

CONTEXT

Key Objective

To explore the impact of tucatinib, when combined with trastuzumab and capecitabine, on intracranial efficacy and survival in patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer and brain metastases (BMs) in the randomized HER2CLIMB clinical trial.

Knowledge Generated

Among 291 enrolled patients with BMs, the addition of tucatinib to trastuzumab and capecitabine doubled the intracranial objective response rate (47.3% *v* 20.0%; $P = .03$), reduced the risk of intracranial progression or death by two thirds (hazard ratio [HR], 0.32; 95% CI, 0.22 to 0.48; $P < .0001$), and reduced the risk of death by nearly half (HR, 0.58; 95% CI, 0.40 to 0.85; $P = .005$).

Relevance

The combination of tucatinib, trastuzumab, and capecitabine is the first systemic therapy to our knowledge to demonstrate clinically meaningful benefits, including prolongation of survival, in patients with HER2-positive breast cancer who have either stable or active BMs in the context of a prospective, randomized clinical trial.

(n = 37) or lapatinib-treated patients (n = 12) with progressive CNS disease treated with neratinib plus capecitabine was 5.5 and 3.1 months, respectively,[15] similar to the 3.6 months previously reported for lapatinib plus capecitabine in patients with progressive CNS disease.[16] At the time HER2CLIMB was designed, there were no approved systemic treatments for breast cancer patients with active brain metastases.

Penetration across an intact blood-brain barrier is assumed to be limited with antibody-based anti-HER2 agents, such as trastuzumab, pertuzumab, and antibody-drug conjugates.[17] Small-molecule HER2 kinase inhibitors have the potential to penetrate the brain more effectively. Tucatinib is a small-molecule oral tyrosine kinase inhibitor (TKI) that is highly selective for HER2, with demonstrated antitumor activity alone and in combination with other HER2-targeting agents.[18] A phase Ib trial evaluating tucatinib plus trastuzumab in patients with active HER2-positive BMs provided preliminary evidence of intracranial activity (objective responses and prolonged clinical benefit), including in patients with prior lapatinib and/or neratinib exposure.[19] Another phase Ib trial reported intracranial response in 5 of 12 patients with active HER2-positive CNS disease treated with tucatinib with trastuzumab and/or capecitabine.[20]

The HER2CLIMB randomized, double-blind, placebo-controlled trial compared tucatinib versus placebo in combination with trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1.[21] The trial was unique in that it enrolled a large proportion (48%) of patients with BMs, including previously untreated, treated stable, and treated and progressing BMs. HER2CLIMB demonstrated clinically meaningful and statistically significant improvements in OS, PFS, and confirmed objective response rate (ORR) in all patients treated with tucatinib, trastuzumab, and capecitabine.[21] Based in large part on the HER2CLIMB results, tucatinib was approved by the FDA in April 2020 for use in combination with trastuzumab and capecitabine in patients with and without brain metastases who have received one or more prior anti-HER2–based regimens in the metastatic setting. Importantly, HER2CLIMB was the first randomized trial to our knowledge to demonstrate a statistically significant and clinically meaningful improvement in PFS among patients with BMs. We report exploratory analyses of the intracranial and OS outcomes in HER2CLIMB patients with BMs.

PATIENTS AND METHODS

Study Design

The design of the HER2CLIMB trial has been described previously.[21] Patients age ≥ 18 years with centrally confirmed, locally advanced or metastatic HER2-positive breast carcinoma previously treated with trastuzumab, pertuzumab, and T-DM1 were randomly assigned 2:1 by minimization to receive either tucatinib or placebo in combination with trastuzumab and capecitabine (Appendix Fig A1, online only). Patients were stratified based upon presence or absence of BM, Eastern Cooperative Oncology Group performance status score (0 or 1), and geographic region (North America [Canada, n = 32] or rest of the world). The trial was conducted in accordance with regulatory requirements and International Conference on Harmonisation Good Clinical Practice guidelines. The study protocol was approved by institutional review boards and ethics committees, and all patients provided written informed consent.

Assessment and Classification of BMs

All HER2CLIMB patients had magnetic resonance imaging (MRI) of the brain at baseline. Patients with BMs on the baseline scan had a contrast-enhanced brain MRI every 6 weeks for 24 weeks and every 9 weeks thereafter. BMs at enrollment were classified as treated and stable (prior

local treatment and no evidence of progression at baseline brain MRI, including patients treated during the screening period), treated and progressing (prior local treatment but evidence of progression of existing lesions, new lesions, or untreated lesions remaining after prior treatment at baseline brain MRI), or untreated (no prior local treatment). Patients with BMs were allowed up to 2 mg of dexamethasone per day (or equivalent) for control of BM symptoms. Patients with untreated brain lesions > 2 cm could enroll if immediate local therapy was not required per investigator assessment of factors such as size, location, and symptoms. Patients who required immediate local therapy based on new findings on the screening brain MRI could still enroll after receiving radiation therapy or surgery and completing a mandated washout period; these patients were included in the treated stable group for this analysis and were not considered to have measurable disease assessable for intracranial response. Patients with leptomeningeal disease were excluded.

Efficacy Assessments

Disease response and progression in the brain were evaluated by applying RECIST 1.1[22] to assess brain lesions in isolation from other organs based on investigator assessment. Intracranial response was derived from the change in the sum of diameters of all target brain lesion measurements as well as consideration of nontarget and new brain lesions, using RECIST 1.1 response and progression thresholds.[22]

TABLE 1. Demographic and Disease Characteristics of HER2CLIMB Patients With BMs

Characteristic	No. (%)		
	Tucatinib, Trastuzumab, and Capecitabine (n = 198)	Placebo, Trastuzumab, and Capecitabine (n = 93)	Total (N = 291)
Age, years			
Median	53	52	52
Range	22-75	25-75	22-75
< 65	166 (83.8)	77 (82.8)	243 (83.5)
≥ 65	32 (16.2)	16 (17.2)	48 (16.5)
Female sex	197 (99.5)	92 (98.9)	289 (99.3)
Geographic region			
North America (US and Canada)	116 (58.6)	61 (65.6)	177 (60.8)
Rest of the world	82 (41.4)	32 (34.4)	114 (39.2)
ECOG performance status score[a]			
0	92 (46.5)	38 (40.9)	130 (44.7)
1	106 (53.5)	55 (59.1)	161 (55.3)
Histology			
Estrogen and/or progesterone receptor positive	107 (54.0)	59 (63.4)	166 (57.0)
Estrogen and progesterone receptor negative	88 (44.4)	34 (36.6)	122 (41.9)
Metastatic at initial diagnosis	77 (38.9)	39 (41.9)	116 (39.9)
Non-CNS metastatic disease	192 (97.0)	90 (96.8)	282 (96.9)
BM treatment status at baseline			
Treated and stable[b]	80 (40.4)	37 (39.8)	117 (40.2)
Treated and progressing[c]	74 (37.4)	34 (36.6)	108 (37.1)
Untreated[d]	44 (22.2)	22 (23.7)	66 (22.7)
Prior therapy for BMs			
Radiation therapy	140 (70.7)	64 (68.8)	204 (70.1)
WBRT	77 (38.9)	45 (48.4)	122 (41.9)
Targeted radiation therapy	92 (46.5)	32 (34.4)	124 (42.6)
Surgery	33 (16.7)	13 (14.0)	46 (15.8)

Abbreviations: BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; WBRT, whole-brain radiation therapy.

[a]ECOG performance status scores range from 0 to 5, with higher score indicating greater disability.

[b]All BMs previously treated with surgery/radiation therapy, without subsequent documented progression of BMs.

[c]Previously treated with surgery/radiation therapy with any documented progression of BMs since most recent surgery/radiation therapy treatment of BMs.

[d]No prior surgery/radiation therapy for BMs.

The following end points were considered exploratory: confirmed intracranial ORR (ORR-IC) and duration of intracranial response (DOR-IC) in patients with measurable intracranial lesions at baseline and CNS-PFS, defined as time from random assignment to disease progression in the brain or death resulting from any cause, whichever occurred first. DOR-IC was defined as the time from first intracranial objective response (confirmed complete or partial) to documented intracranial disease progression or death resulting from any cause, whichever occurred first.

Analyses were performed for these exploratory end points for all patients with BMs and then separately for those with stable BMs and those with active BMs. The active BM group consisted of patients with untreated or treated and progressing BMs, consistent with the 2019 US Food and Drug Administration (FDA) guidance "Cancer Clinical Trial Eligibility Criteria: Brain Metastases—Guidance for Industry."[13] OS by treatment arm was also evaluated in these subgroups.

Patients with progressive disease per RECIST 1.1 isolated to the brain were eligible to continue study-assigned therapy after local treatment until second progression at any site. These patients were considered to have progressive disease for the purposes of the primary end point. Time from random assignment to second progression in the brain or body or death was reported for patients with isolated brain progression who continued study-assigned treatment after local treatment of BMs.

Statistical Analysis

Kaplan-Meier methodology was used to estimate CNS-PFS, OS, and time to second progression curves and their 95% CIs. For CNS-PFS and OS, a stratified Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs. For time to second progression analysis, the HR from the unstratified Cox proportional hazards model was estimated because of the small number of patients. All *P* values reported are nominal and were obtained from the stratified log-rank test.

The confirmed ORR-IC with exact 95% CI was provided for patients with measurable intracranial disease at baseline by treatment arm. Comparison of ORR-IC between treatment arms was performed using a 2-sided Cochran-Mantel-Haenszel test, controlling for the aforementioned stratification factors. Among patients who achieved a confirmed ORR-IC, Kaplan-Meier estimates of median DOR-IC (corresponding 95% CIs) were provided for each treatment arm. The same censoring scheme and methods for the primary analysis of PFS were used for the DOR-IC analysis.

RESULTS

Patient Characteristics

Of 612 patients enrolled in the HER2CLIMB trial, 291 (48%) had BMs at baseline or a history of BMs: 198 (48%) in the tucatinib arm and 93 (46%) in the control arm. Median time from diagnosis of metastatic disease to development of BMs was 13.0 months (range, < 0.1 to 100.7 months) and 9.8 months (range, < 0.1 to 172.7 months), respectively. Median time from first diagnosis of BMs to study enrollment was 15.8 months (range, 1.1 to 169.2 months) and 14.5 months (range, 0.5 to 99.3 months), respectively.

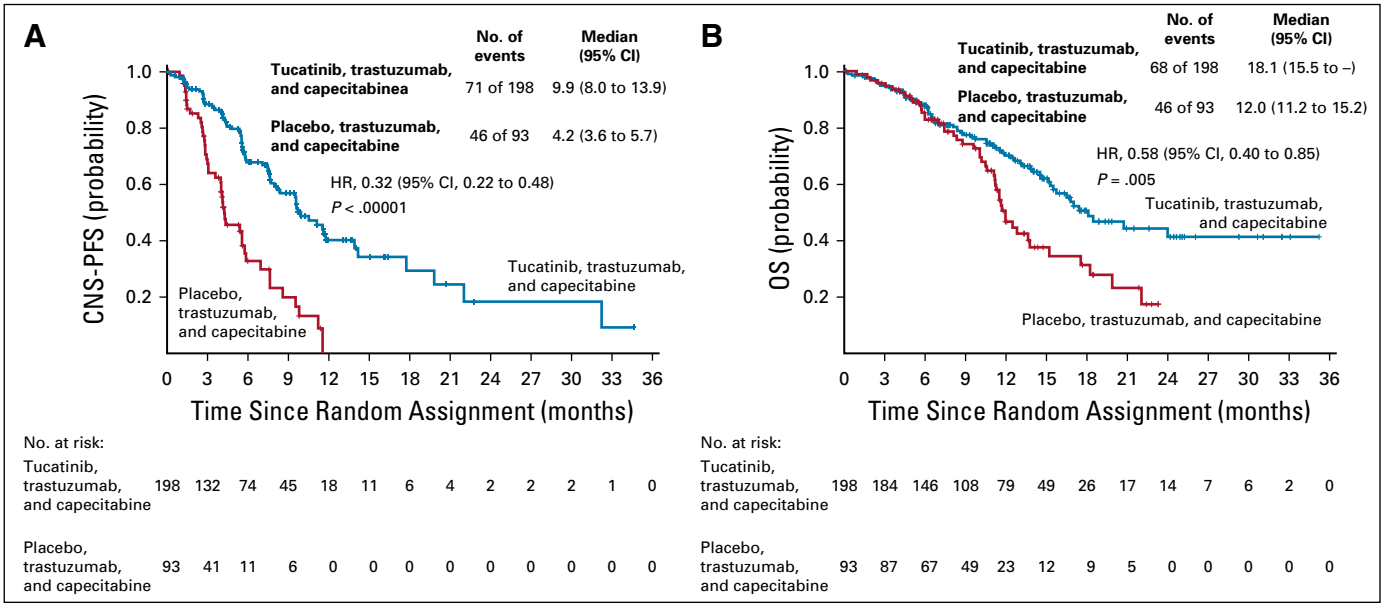

FIG 1. Kaplan-Meier curves for patients with brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

Baseline demographic and disease characteristics were well balanced between treatment arms (Table 1) and similar to the overall HER2CLIMB population.[21] Eighty patients (40.4%) in the tucatinib arm and 37 (39.8%) in the control arm had stable BMs at baseline. Active BMs (including untreated and treated progressing BMs) were identified in 118 (59.6%) and 56 patients (60.2%), respectively. Nearly all patients with BMs also had disease outside of the brain (approximately 97% in both arms).

Efficacy in All Patients With BMs

Among the 291 patients with BMs, estimated 1-year CNS-PFS was 40.2% (95% CI, 29.5% to 50.6%) in the tucatinib arm and 0% in the control arm. Risk of progression in the brain or death was reduced by 68% in the tucatinib arm versus the control arm (HR, 0.32; 95% CI, 0.22 to 0.48; $P < .0001$; Fig 1A). Median duration of CNS-PFS was 9.9 months (95% CI, 8.0 to 13.9 months) in the tucatinib arm and 4.2 months (95% CI, 3.6 to 5.7 months) in the control arm. Estimated 1-year OS was 70.1% (95% CI, 62.1% to 76.7%) in the tucatinib arm and 46.7% (95% CI, 33.9% to 58.4%) in the control arm. Risk of death was reduced by 42% in the tucatinib arm versus the control arm (HR, 0.58; 95% CI, 0.40 to 0.85; $P = .005$; Fig 1B). Median time to death resulting from any cause was 18.1 months (95% CI, 15.5 months to not estimable) in the tucatinib arm versus 12.0 months (95% CI, 11.2 to 15.2 months) in the control arm.

Efficacy in Patients With Active BMs

Among the 174 patients with active BMs, estimated 1-year CNS-PFS was 35.0% (95% CI, 23.2% to 47.0%) in the tucatinib arm and 0% in the control arm. Risk of progression in the brain or death was reduced by 64% in the tucatinib arm versus the control arm (HR, 0.36; 95% CI, 0.22 to 0.57; $P < .0001$; Fig 2A). Median duration of CNS-PFS was 9.5 months (95% CI, 7.5 to 11.1 months) in the tucatinib arm and 4.1 months (95% CI, 2.9 to 5.6 months) in the control arm. Estimated 1-year OS was 71.7% (95% CI, 61.4% to 79.7%) in the tucatinib arm and 41.1% (95% CI, 25.5% to 56.1%) in the control arm. Risk of death was reduced by 51% in the tucatinib arm versus the control arm (HR, 0.49; 95% CI, 0.30 to 0.80; $P = .004$; Fig 2B). Median duration of OS was 20.7 months (95% CI, 15.1 months to not estimable [because of the censored largest observed time]) in the tucatinib arm and 11.6 months (95% CI, 10.5 to 13.8 months) in the control arm.

Among the 75 patients with active BMs and measurable intracranial disease at baseline, the confirmed ORR-IC was 47.3% (95% CI, 33.7% to 61.2%) in the tucatinib arm versus 20.0% (95% CI, 5.7% to 43.7%) in the control arm ($P = .03$; Table 2). In these patients, median DOR-IC was 6.8 months (95% CI, 5.5 to 16.4 months) in the tucatinib arm versus 3.0 months (95% CI, 3.0 to 10.3 months) in the control arm (Table 2). Estimated proportion of patients with a response lasting 6 or 12 months was 72.7% (95% CI, 48.9% to 86.8%) and 28.3% (95% CI, 8.0% to 53.2%), respectively, in the tucatinib arm compared with 25.0% (95% CI, 0.9% to 66.5%) and 0%, respectively, in the control arm.

A subset of patients (44 in the tucatinib arm and 22 in the control arm) entered the study with active, untreated BMs and

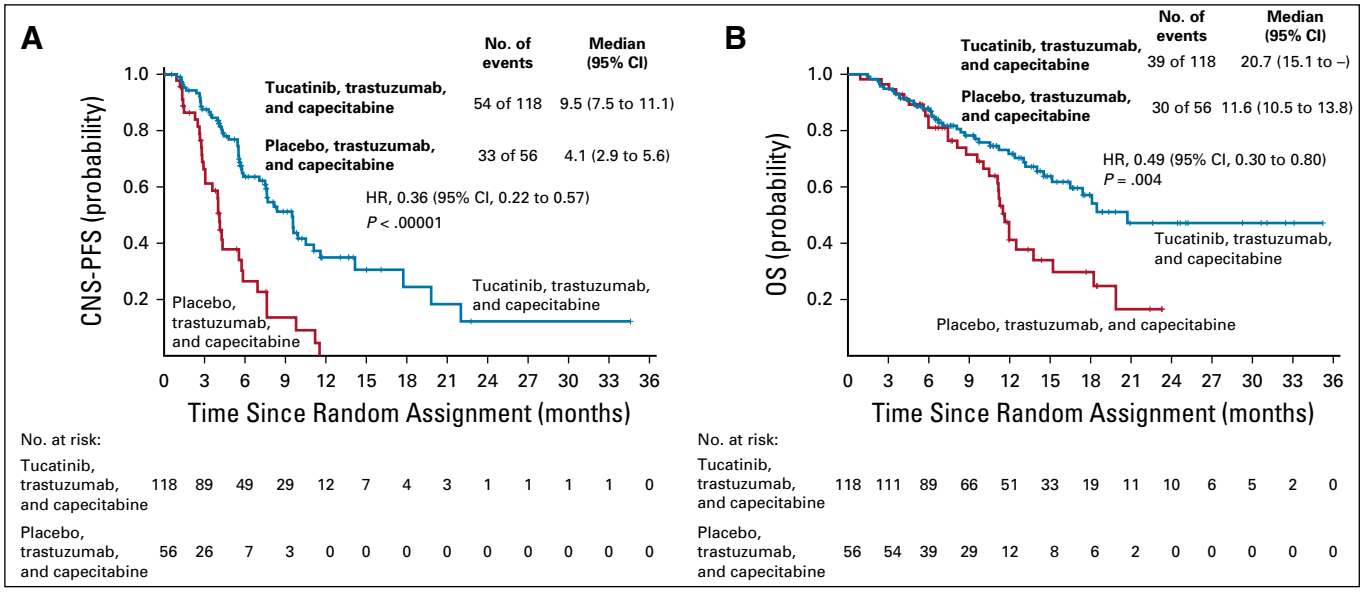

FIG 2. Kaplan-Meier curves for patients with active brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

elected to defer radiation therapy in favor of systemic therapy. Among these patients, CNS-PFS (medians, 8.1 *v* 3.1 months), ORR-IC (47.1% *v* 16.7%), and OS (median, 16.5 *v* 11.2 months) all favored the tucatinib arm (Data Supplement).

Efficacy in Patients With Stable BMs

Among the 117 patients with stable BMs, estimated 1-year CNS-PFS was 53.3% (95% CI, 31.4% to 71.0%) in the tucatinib arm and 0% in the control arm. Risk of progression in the brain or death was reduced by 69% in the tucatinib arm versus the control arm (HR, 0.31; 95% CI, 0.14 to 0.67; $P = .002$; Fig 3A). Median duration of CNS-PFS was 13.9 months (95% CI, 9.7 to 32.2 months) in the tucatinib arm and 5.6 months (95% CI, 3.0 to 9.5 months) in the control arm. Estimated 1-year OS was 67.6% (95% CI, 53.8% to 78.0%) in the tucatinib arm and 55.6% (95% CI, 34.1% to 72.6%) in the control arm. Risk of death was numerically lower in the tucatinib arm versus the control arm (HR, 0.88; 95% CI; 0.45 to 1.70; $P = .696$; Fig 3B). Median duration of OS was 15.7 months (95% CI, 13.8 months to not estimable) in the tucatinib arm and 13.6 months (95% CI, 10.2 to 22.0 months) in the control arm.

Second Progression

Thirty patients (21 in the tucatinib arm and 9 in the control arm) experienced isolated progression in the brain and underwent local therapy followed by continued study-assigned treatment (Fig 4A). In these patients, median time from random assignment to second progression (brain or body) or death was 15.9 months (95% CI, 11.7 to 28.2 months) in the tucatinib arm and 9.7 months (95% CI, 4.9 to 12.0 months) in the control arm (HR, 0.29; 95% CI, 0.11 to 0.77; $P = .009$; Fig 4B). Median time from progression in the brain to second progression (brain or body) or death in these patients was 7.6 months (95% CI, 3.9 to 11.3 months) in the tucatinib arm versus 3.1 months (95% CI, 1.2 to 4.1 months) in the control arm (HR, 0.33; 95% CI, 0.13 to 0.85; $P = .02$; Fig 4C).

DISCUSSION

To our knowledge, HER2CLIMB is the only double-blind, randomized study in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1 to demonstrate a statistically significant and clinically meaningful improvement in PFS among patients with BMs, including those with active BMs.[21] Importantly, the longer PFS with tucatinib in the overall population of patients with BMs was achieved via control of both intracranial and extracranial disease.

The brain-specific analyses presented here, although exploratory, were conducted in 291 randomly assigned

TABLE 2. Intracranial Confirmed Objective Response per Investigator in Patients With Active BMs and Measurable Intracranial Lesions at Baseline

	No. (%)	
Response	**Tucatinib, Trastuzumab, and Capecitabine (n = 55)**	**Placebo, Trastuzumab, and Capecitabine (n = 20)**
Best overall intracranial response[a]		
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not available[b]	3 (5.5)	0
Objective response of confirmed CR or PR	26	4
ORR-IC, %	47.3	20.0
95% CI[c]	33.7 to 61.2	5.7 to 43.7
Stratified P[d]	.03	
DOR-IC, months[e]	6.8	3.0
95% CI[f]	5.5 to 16.4	3.0 to 10.3

Abbreviations: CR, complete response; DOR-IC, duration of intracranial response; ORR-IC, confirmed intracranial objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Confirmed best overall response assessed per RECIST 1.1.

[b]Patients with no postbaseline response assessments.

[c]Two-sided 95% exact CI, computed using the Clopper-Pearson method.[24]

[d]Cochran-Mantel-Haenszel test controlling for stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of the world]) at random assignment.

[e]As estimated using Kaplan-Meier method.

[f]Calculated using the complementary log-log transformation method.[25]

patients with BMs and demonstrate clinically meaningful intracranial activity of tucatinib. Nearly half of patients with measurable, active BMs experienced a confirmed intracranial response, demonstrating direct activity of the tucatinib-based combination against BMs. In addition, across all enrolled patients with BMs, tucatinib significantly reduced the risk of intracranial progression or death by 68% compared with trastuzumab and capecitabine. This is the first double-blind, randomized trial of systemic therapy to our knowledge to demonstrate clinically meaningful gains in OS among patients with BMs, including those with active metastases, with a 42% reduction in the risk of death and prolongation of median OS by > 6 months. Median OS of 18.1 months in these heavily pretreated patients with BMs is notable and further supports the inclusion of patients with CNS metastases in future breast cancer trials.

A unique subset was the group of 66 patients with untreated BMs who elected to enter HER2CLIMB in lieu of radiation therapy. Although the overall numbers were small, median CNS-PFS was 8.1 months in the tucatinib arm, suggesting this strategy merits further exploration, because it may delay the need for radiation therapy.

As prespecified in the HER2CLIMB protocol, patients with isolated progression in the brain could continue study-assigned, blinded therapy after local management with radiation therapy or surgery. Although only 30 patients continued on trial after local therapy, median time from progression in the brain to second progression (brain or body) or death in these patients was 4.5 months longer in the tucatinib arm compared with the control arm, suggesting that continuation of tucatinib after cranial radiation therapy may delay subsequent disease progression. This was also seen in 2 prior phase Ib clinical trials of tucatinib, where 11 patients with isolated progression of BMs after treatment with tucatinib plus T-DM1 or tucatinib with or without trastuzumab with or without capecitabine continued study-assigned treatment after CNS-directed therapy. In those patients, median time after CNS-directed radiation therapy for isolated brain progression to any second event was 8.3 months.[23] This observation warrants further evaluation of continuing the tucatinib plus trastuzumab plus capecitabine regimen after local treatment of isolated CNS progression.

Strengths of this exploratory analysis are its sample size of nearly 300 patients with BMs and its randomized, prospective design. Because of the large number of patients with active BMs, intracranial outcomes between arms could be readily evaluated. One potential criticism is the use of RECIST 1.1 for evaluation of intracranial response. Increasingly, Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria are being incorporated into the design of BM trials. Both RECIST 1.1 and RANO-BM use unidimensional measurements of target lesions, with ≥ 30% decrease in the sum of target lesions required for partial response. The main differences are the maximum number of CNS target lesions (2 *v* 5, respectively) and incorporation of steroid use and neurologic symptoms in RANO-BM. Although future studies could retrospectively analyze archival image files and data from case report forms to compare response rates by RECIST 1.1 and RANO-BM, in the context of the statistically significant and clinically meaningful OS benefit in favor of

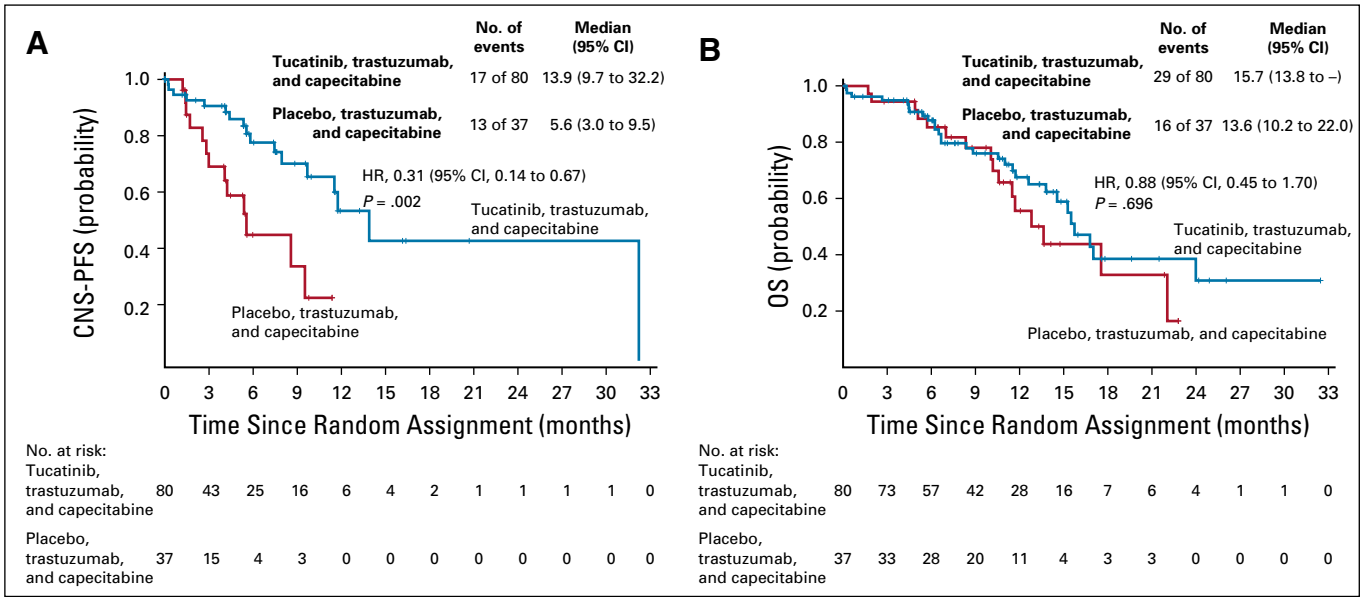

FIG 3. Kaplan-Meier curves for patients with stable brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

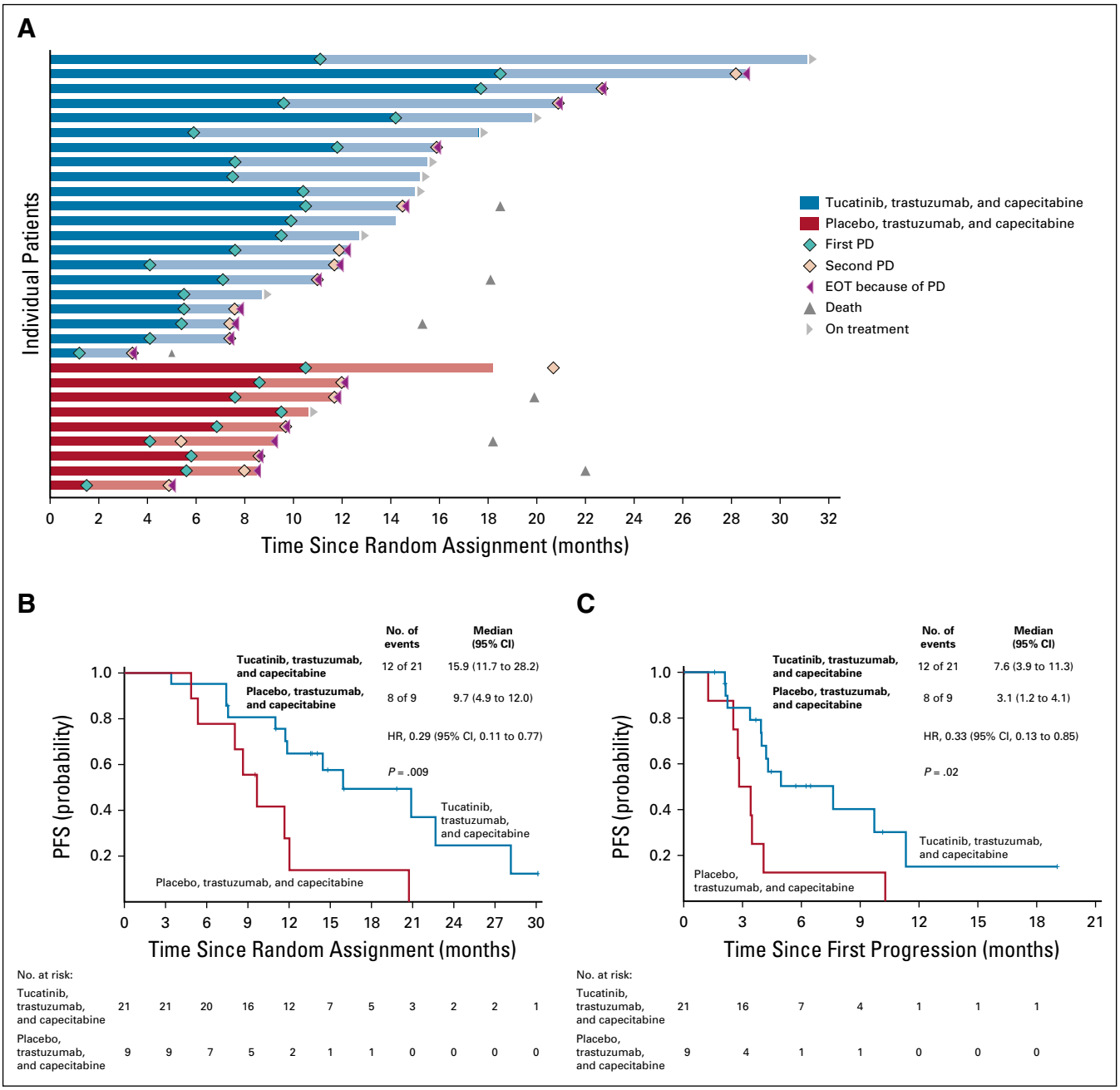

FIG 4. Outcomes in patients with isolated progression in the brain who continued with assigned study treatment. (A) Duration on treatment. (B) Time from random assignment to second disease progression (PD) by investigator assessment or death. (C) Time from first PD to second PD by investigator assessment or death. Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment.

the tucatinib arm seen in HER2CLIMB, we believe that small differences in response rates that could potentially arise using different response criteria become less critical to identify.

Of note, both the ASCO–Friends of Cancer Research Brain Metastases Working Group and the 2019 FDA "Cancer Clinical Trial Eligibility Criteria: Brain Metastases—Guidance for Industry" have recommended inclusion of patients with treated stable and active BMs in clinical trials so that results will be more applicable to this population with high unmet need.[13,14]

Together with the HER2CLIMB primary analysis, these results demonstrate that tucatinib in combination with trastuzumab and capecitabine is an active regimen for intracranial and extracranial disease in patients with HER2-positive metastatic breast cancer. To our knowledge, HER2CLIMB is the first randomized study to demonstrate

improvement in intracranial response, CNS-PFS, and OS in patients with HER2-positive breast cancer who have BMs, including active lesions. Tucatinib is the first TKI to our knowledge to demonstrate improved antitumor activity against BMs in patients with HER2-positive breast cancer in a randomized, controlled trial.

AFFILIATIONS

[1]Dana-Farber Cancer Institute, Boston, MA
[2]University of Colorado Cancer Center, Aurora, CO
[3]Duke Cancer Institute, Durham, NC
[4]MD Anderson Cancer Center, Houston, TX
[5]Carbone Cancer Center/University of Wisconsin, Madison, WI
[6]Sarah Cannon Research Institute/Tennessee Oncology–Nashville, Nashville, TN
[7]University of California Los Angeles Medical Center/Jonsson Comprehensive Cancer Center, Los Angeles, CA
[8]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[9]Royal Marsden National Health Service (NHS) Foundation Trust, London, United Kingdom
[10]Vanderbilt University Medical Center, Nashville, TN
[11]University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada
[12]Hospital Universitario Vall D'Hebron, Barcelona, Spain
[13]Universitaetsklinikum Hamburg-Eppendorf, Hamburg, Germany
[14]Northside Hospital, Atlanta, GA
[15]Yale Cancer Center/Smilow Cancer Hospital, New Haven, CT
[16]Centre Léon Bérard, Lyon, France
[17]University of California at San Francisco, San Francisco, CA
[18]Christie NHS Foundation Trust, Manchester Academic Health Science Centre & Division of Cancer Sciences, School of Medical Sciences, University of Manchester, Manchester, United Kingdom
[19]Providence Cancer Institute, Portland, OR
[20]Edinburgh Cancer Research Centre, Edinburgh, United Kingdom
[21]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[22]Istituto Europeo di Oncologia, Istituto di Ricovero e Cura a Carattere Scientifico, University of Milano, Milan, Italy
[23]British Columbia Cancer–Vancouver Centre, Vancouver, BC, Canada
[24]German Breast Group, Neu-Isenburg, Germany
[25]Seattle Genetics, Bothell, WA

CORRESPONDING AUTHOR

Nancy U. Lin, MD, 450 Brookline Ave, Dana-Farber Cancer Institute, Boston, MA 02215; e-mail: nlin@partners.org.

PRIOR PRESENTATION

Presented at the 56th ASCO Annual Meeting, Chicago, IL, May 29-June 2, 2020.

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AUTHOR CONTRIBUTIONS

Conception and design: David Cameron, Lisa Carey, Giuseppe Curigliano, Karen Gelmon, Sibylle Loibl, JoAl Mayor, Suzanne McGoldrick, Xuebei An, Eric P. Winer
Provision of study material or patients: Nancy U. Lin, Virginia Borges, Carey Anders, Rashmi Murthy, Elisavet Paplomata, Erika Hamilton, Sara Hurvitz, Sherene Loi, Alicia Okines, Vandana Abramson, Philippe L. Bedard, Mafalda Oliveira, Volkmar Mueller, Amelia Zelnak, Michael P. DiGiovanna, Thomas Bachelot, A. Jo Chien, Ruth O'Regan, Andrew Wardley, Alison Conlin
Collection and assembly of data: Nancy U. Lin, Virginia Borges, Carey Anders, Rashmi Murthy, Elisavet Paplomata, Erika Hamilton, Sara Hurvitz, Sherene Loi, Alicia Okines, Vandana Abramson, Philippe L. Bedard, Mafalda Oliveira, Volkmar Mueller, Amelia Zelnak, Michael P. DiGiovanna, Thomas Bachelot, A. Jo Chien, Ruth O'Regan, Andrew Wardley, Alison Conlin, JoAl Mayor, Suzanne McGoldrick, Xuebei An, Eric P. Winer
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

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Nancy U. Lin
Consulting or Advisory Role: Genentech/Roche, Seattle Genetics, Puma Biotechnology, Daiichi Sankyo
Research Funding: Genentech, Pfizer, Seattle Genetics, Merck
Patents, Royalties, Other Intellectual Property: Royalties for chapter in Up-to-Date regarding management of breast cancer brain metastases; royalties, Jones & Bartlett

Virginia Borges
Consulting or Advisory Role: Seattle Genetics
Research Funding: Abbott/AbbVie (Inst), Seattle Genetics (Inst), Millennium Pharmaceuticals (Inst)

Carey Anders
Honoraria: Eisai, Genentech/Roche, Ipsen, Seattle Genetics, Puma Biotechnology
Consulting or Advisory Role: Genentech/Roche, Puma Biotechnology, Eisai, Ipsen, Seattle Genetics
Research Funding: Puma Biotechnology (Inst), Lilly (Inst), Merck (Inst), Nektar (Inst), Tesaro (Inst), Seattle Genetics (Inst), G1-Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Up-to-Date.com, Jones & Bartlett
Travel, Accommodations, Expenses: Eisai

Rashmi K. Murthy
Honoraria: Puma Biotechnology, Genentech, Daiichi Sankyo, Seattle Genetics
Consulting or Advisory Role: Puma Biotechnology, Genentech/Roche, Daiichi Sankyo, Seattle Genetics
Research Funding: Genentech/Roche (Inst), Daiichi Sankyo (Inst), Pfizer (Inst), EMD Serono (Inst), Seattle Genetics (Inst)
Travel, Accommodations, Expenses: Seattle Genetics, Puma Biotechnology, Genentech, Daiichi Sankyo

Elisavet Paplomata
Honoraria: Novartis, R-Pharm, Pfizer, Mylan
Consulting or Advisory Role: Novartis, R-Pharm, Pfizer, Mylan
Research Funding: Novartis (Inst), Genentech (Inst), Corcept Therapeutics (Inst), Hoosier Cancer Research Network (Inst), Cascadian Therapeutics (Inst), AbbVie (Inst), Merck (Inst), Seattle Genetics (Inst)
Travel, Accommodations, Expenses: Novartis, Genentech, Tesaro, Merck, Amgen

Erika Hamilton
Consulting or Advisory Role: Pfizer (Inst), Genentech/Roche (Inst), Lilly (Inst), Puma Biotechnology (Inst), Daiichi Sankyo (Inst), Mersana (Inst), Boehringer Ingelheim (Inst), AstraZeneca (Inst), Novartis (Inst), Silverback Therapeutics (Inst), Black Diamond (Inst)
Research Funding: AstraZeneca (Inst), Hutchison MediPharma (Inst), OncoMed (Inst), MedImmune (Inst), Stem CentRx (Inst), Genentech/Roche (Inst), Curis (Inst), Verastem (Inst), Zymeworks (Inst), Syndax (Inst), Lycera (Inst), Rgenix (Inst), Novartis (Inst), Mersana (Inst), Millennium Pharmaceuticals (Inst), TapImmune (Inst), Lilly (Inst), BerGenBio (Inst), Medivation (Inst), Pfizer (Inst), Tesaro (Inst), Boehringer Ingelheim (Inst), Eisai (Inst), H3 Biomedicine (Inst), Radius Health (Inst), Acerta Pharma (Inst), Takeda (Inst), Macrogenics (Inst), AbbVie (Inst), Immunomedics (Inst), Fujifilm (Inst), eFFECTOR Therapeutics (Inst), Merus (Inst), Nucana (Inst), Regeneron (Inst), Leap Therapeutics (Inst), Taiho Pharmaceutical (Inst), EMD Serono (Inst), Daiichi Sankyo (Inst), ArQule (Inst), Syros Pharmaceuticals (Inst), Clovis Oncology (Inst), CytomX Therapeutics (Inst), InvestisBio (Inst), Deciphera (Inst), Unum Therapeutics (Inst), Sermonix Pharmaceuticals (Inst), Sutro (Inst), Aravive (Inst), Zenith Epigenetics (Inst), Arvinas (Inst), Torque (Inst), Harpoon (Inst), Fochon (Inst), Black Diamond (Inst), Orinove (Inst), Molecular Templates (Inst), Silverback (Inst), Seattle Genetics (Inst), Puma Biotechnology (Inst), Compugen (Inst), G1 Therapeutics (Inst), Karyopharm Therapeutics (Inst)
Travel, Accommodations, Expenses: Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Eisai, EMD Serono, Lilly, Genentech/Roche, Genzyme, Helsinn Therapeutics, Heron, Lexicon, Lilly, Medivation, Merck, Novartis, Pfizer, Roche, Sysmex, Tesaro, Guardant Health, Foundation Medicine

Sara Hurvitz
Research Funding: Genentech/Roche (Inst), Novartis (Inst), GlaxoSmithKline (Inst), Sanofi (Inst), Pfizer (Inst), Amgen (Inst), OBI Pharma (Inst), Puma Biotechnology (Inst), Dignitana (Inst), Bayer (Inst), Biomarin (Inst), Lilly (Inst), Merrimack (Inst), Cascadian Therapeutics (Inst), Seattle Genetics (Inst), Daiichi Sankyo (Inst), Macrogenics (Inst), Ambryx (Inst), Immunomedics (Inst), Pieris (Inst), Radius (Inst), Arvinas (Inst)
Other Relationship: Roche, Pfizer

Sherene Loi
Consulting or Advisory Role: AstraZeneca/MedImmune (Inst), Seattle Genetics (Inst), Bristol-Myers Squibb (Inst), Roche/Genentech (Inst), Merck Sharp & Dohme (Inst), Pfizer (Inst), Aduro Biotech (Inst), Novartis (Inst), G1 Therapeutics (Inst)
Research Funding: Roche/Genentech (Inst), Novartis (Inst), Merck (Inst), Puma Biotechnology (Inst), Bristol-Myers Squibb (Inst), Lilly (Inst), Seattle Genetics (Inst), AstraZeneca (Inst)

Alicia Okines
Stock and Other Ownership Interests: AstraZeneca (I)
Research Funding: Pfizer (Inst)
Travel, Accommodations, Expenses: LEO Pharmaceuticals

Vandana Abramson
Employment: HCA Healthcare (I)
Consulting or Advisory Role: Eisai, Daiichi Sankyo, AbbVie
Research Funding: Genentech/Roche, Astellas Pharma, Lilly

Philippe L. Bedard
Consulting or Advisory Role: Bristol-Myers Squibb (Inst), Sanofi (Inst), Pfizer (Inst)
Research Funding: Bristol-Myers Squibb (Inst), Sanofi (Inst), AstraZeneca (Inst), Genentech/Roche (Inst), Servier (Inst), GlaxoSmithKline (Inst), Novartis (Inst), SignalChem (Inst), PTC Therapeutics (Inst), Nektar (Inst), Merck (Inst), Seattle Genetics (Inst), Mersana (Inst), Immunomedics (Inst), Lilly (Inst)

Mafalda Oliveira
Honoraria: Roche, Novartis, Seattle Genetics
Consulting or Advisory Role: Roche/Genentech, GlaxoSmithKline, Puma Biotechnology, AstraZeneca, Seattle Genetics
Research Funding: Philips Healthcare (Inst), Roche/Genentech (Inst), Novartis (Inst), AstraZeneca (Inst), Immunomedics (Inst), Seattle Genetics (Inst), Boehringer Ingelheim (Inst), GlaxoSmithKline (Inst), Cascadian Therapeutics (Inst), Sanofi (Inst), Celldex (Inst), Bayer (Inst), Piqur (Inst), Puma Biotechnology (Inst), Zenith Epigenetics (Inst)
Travel, Accommodations, Expenses: Roche, Novartis, Grünenthal Group, Pierre Fabre, GP Pharm, Eisai

Volkmar Mueller
Honoraria: AstraZeneca, Amgen, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Tesaro, MSD Oncology, Pierre Fabre, Nektar, Genomic Health, Lilly, Seattle Genetics
Consulting or Advisory Role: Hexal, Roche, Amgen, Daiichi Sankyo, Nektar, Eisai, Lilly
Research Funding: Novartis (Inst), Seattle Genetics (Inst), Roche/Genentech (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, Daiichi Sankyo

Amelia Zelnak
Consulting or Advisory Role: Novartis, Pfizer
Travel, Accommodations, Expenses: Immunomedics

Michael P. DiGiovanna
Research Funding: Genentech (Inst), Cascadian Therapeutics (Inst), Seattle Genetics (Inst)
Patents, Royalties, Other Intellectual Property: Royalties from DAKO; royalties from NeoMarkers

Thomas Bachelot
Consulting or Advisory Role: Roche, Novartis, AstraZeneca, Pfizer, Seattle Genetics, MSD Oncology
Research Funding: Roche (Inst), Novartis (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, AstraZeneca

A. Jo Chien
Research Funding: Merck (Inst), Puma Biotechnology (Inst), Seattle Genetics (Inst), Amgen (Inst), Astellas Pharma (Inst)

Ruth O'Regan
Honoraria: bioTheranostics, Pfizer, Macrogenics, Immunomedics, Genomic Health, Puma Biotechnology, Novartis, Genentech, Lilly
Consulting or Advisory Role: Puma Biotechnology, bioTheranostics, Genomic Health, Novartis, Macrogenics, Immunogenics, Genentech, Lilly
Research Funding: Novartis (Inst), Eisai (Inst), Pfizer (Inst), Puma Biotechnology (Inst), Seattle Genetics (Inst)
Travel, Accommodations, Expenses: Lilly, Puma Biotechnology, Genomic Health, Macrogenics, Immunomedics

Andrew Wardley
Stock and Other Ownership Interests: Andrew Wardley Limited, Manchester Cancer Academy, Outreach Research and Innovation Group
Honoraria: Roche, Novartis, AstraZeneca, Lilly, Pfizer
Consulting or Advisory Role: Roche, Lilly, Novartis, AstraZeneca, MSD Oncology, Daiichi Sankyo, Athenex, Accord Research, Pfizer, NAPP Pharmaceuticals, Coleman Expert Network, Guidepoint Global, Gerson Lehrman Group
Speakers' Bureau: Roche, AstraZeneca, Novartis, Eisai, Lilly, Pfizer
Research Funding: Roche (Inst), Novartis (Inst), Pfizer (Inst), Most Cancer Pharma (Inst)
Travel, Accommodations, Expenses: Roche, Daiichi Sankyo
Other Relationship: MSD Oncology

Alison Conlin
Consulting or Advisory Role: Pfizer, Novartis, Seattle Genetics/Astellas Pharma, bioTheranostics

David Cameron
Consulting or Advisory Role: Lilly (Inst), Novartis (Inst), Research Triangle (Inst), Daiichi Sankyo (Inst), Prima BioMed (Inst), Merck Sharp & Dohme (Inst), Zymeworks (Inst), Eisai (Inst), Puma Biotechnology (Inst), Pfizer (Inst), Oncolytics (Inst), F. Hoffmann-La Roche (Inst), Roche (Inst), Samsung Bioepis (Korea) (Inst), Seattle Genetics (Inst), Synthon (Inst)
Research Funding: Roche (Inst), Novartis (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Novartis

Lisa Carey
Research Funding: Innocrin Pharma (Inst), Syndax (Inst), Immunomedics (Inst), Novartis (Inst)
Patents, Royalties, Other Intellectual Property: Royalty-sharing agreement, investorship interest in licensed IP to startup company, Falcon Therapeutics, that is designing neural stem cell-based therapy for glioblastoma multiforme (I)
Uncompensated Relationships: Sanofi (Inst), Novartis (Inst), G1 Therapeutics (Inst), Genentech/Roche (Inst), GlaxoSmithKline (Inst)

Giuseppe Curigliano
Honoraria: Ellipses Pharma
Consulting or Advisory Role: Roche/Genentech, Pfizer, Novartis, Lilly, Foundation Medicine, Bristol-Myers Squibb, Samsung
Speakers' Bureau: Roche/Genentech, Novartis, Pfizer, Lilly, Foundation Medicine, Samsung, Daiichi Sankyo
Travel, Accommodations, Expenses: Roche/Genentech, Pfizer

Karen Gelmon
Honoraria: AstraZeneca, Merck Sharp & Dohme
Consulting or Advisory Role: Pfizer, Novartis, AstraZeneca, Merck, Lilly, Bristol-Myers Squibb, NanoString Technologies, Genomic Health, Janssen Oncology, Roche, Mylan
Research Funding: Pfizer (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Roche (Inst)
Expert Testimony: Genentech

Sibylle Loibl
Honoraria: Chugai Pharma
Consulting or Advisory Role: Pfizer (Inst), Roche (Inst), Novartis (Inst), Seattle Genetics (Inst), Celgene (Inst), Lilly (Inst), AstraZeneca/MedImmune (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), AbbVie (Inst), Amgen (Inst)
Research Funding: AbbVie (Inst), AstraZeneca (Inst), Vifor Pharma (Inst), Amgen (Inst), Celgene (Inst), Novartis (Inst), Pfizer (Inst), Roche (Inst), Cepheid (Inst), Myriad Genetics (Inst), Immunomedics (Inst), Seattle Genetics (Inst), Daiichi Sankyo (Inst)
Patents, Royalties, Other Intellectual Property: Patent pending EP14153692.0 (Inst)

JoAl Mayor
Employment: Seattle Genetics
Stock and Other Ownership Interests: Seattle Genetics

Suzanne McGoldrick
Employment: Seattle Genetics
Stock and Other Ownership Interests: Seattle Genetics
Consulting or Advisory Role: AbbVie (I), Near Future Allergan (I)
Research Funding: AbbVie (I), Janssen (I), Takeda (I)
Travel, Accommodations, Expenses: Seattle Genetics

Xuebei An
Employment: Seattle Genetics, Novartis
Stock and Other Ownership Interests: Seattle Genetics

Eric P. Winer
Stock and Other Ownership Interests: Verastem
Honoraria: Genentech/Roche, Genomic Health
Consulting or Advisory Role: Leap Therapeutics, Seattle Genetics, Jounce Therapeutics, GlaxoSmithKline, Carrick Therapeutics, Lilly, Genomic Health, G1 Therapeutics
Research Funding: Genentech (Inst), Novartis (Inst)

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APPENDIX

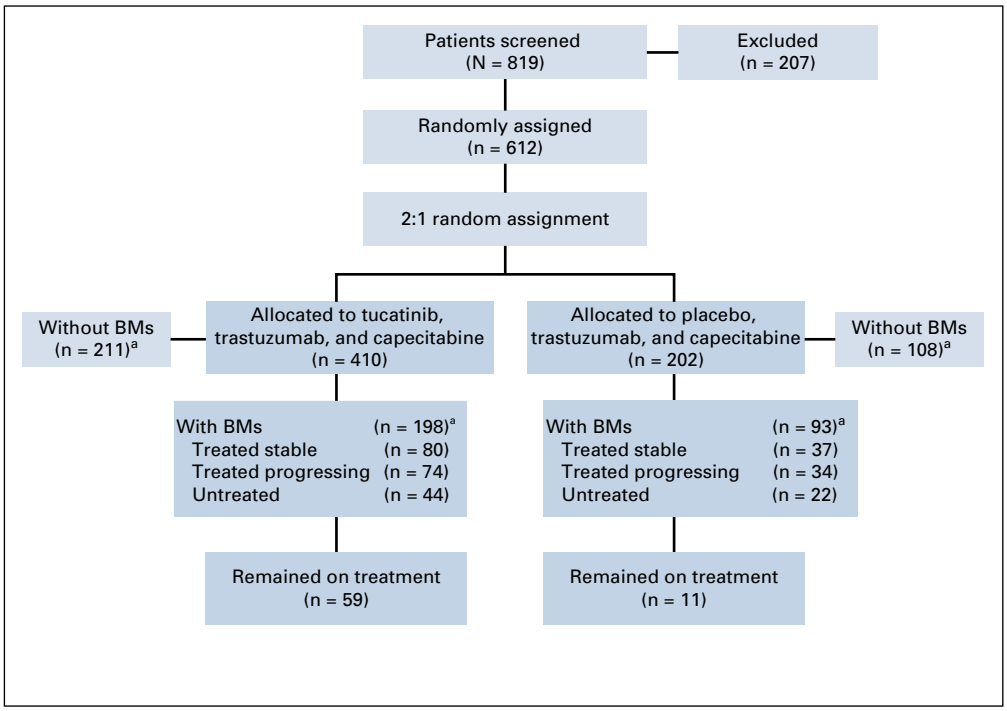

FIG A1. CONSORT diagram. BM, brain metastasis. ([a]) Two enrolled patients did not undergo baseline brain magnetic resonance imaging (1 in tucatinib arm and 1 in placebo arm).