

Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study

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PURPOSE Effective therapies are needed for the treatment of patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer (MBC) with brain metastases. A trastuzumab radioisotope has been shown to localize in brain metastases of patients with HER2-positive MBC, and intracranial xenograft models have demonstrated a dose-dependent response to trastuzumab.

METHODS In the phase II PATRICIA study (ClinicalTrials.gov identifier: [NCT02536339](https://clinicaltrials.gov/ct2/show/study/NCT02536339)), patients with HER2-positive MBC with CNS metastases and CNS progression despite prior radiotherapy received pertuzumab plus high-dose trastuzumab (6 mg/kg weekly) until CNS or systemic disease progression or unacceptable toxicity. The primary end point was confirmed objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases criteria. Secondary end points included duration of response, clinical benefit rate (complete response plus partial response plus stable disease ≥ 4 or ≥ 6 months) in the CNS, and safety.

RESULTS Thirty-nine patients were treated for a median (range) of 4.5 (0.3-37.3) months at clinical cutoff. Thirty-seven patients discontinued treatment, most commonly because of CNS progression ($n = 27$); two remained on treatment. CNS ORR was 11% (95% CI, 3 to 25), with four partial responses (median duration of response, 4.6 months). Clinical benefit rate at 4 months and 6 months was 68% and 51%, respectively. Two patients permanently discontinued study treatment because of adverse events (left ventricular dysfunction [treatment-related] and seizure, both grade 3). No grade 5 adverse events were reported. No new safety signals emerged with either agent.

CONCLUSION Although the CNS ORR was modest, 68% of patients experienced clinical benefit, and two patients had ongoing stable intracranial and extracranial disease for > 2 years. High-dose trastuzumab for HER2-positive CNS metastases may warrant further study.

J Clin Oncol 39:2667-2675. © 2021 by American Society of Clinical Oncology

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INTRODUCTION

Approximately 40%-50% of patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer (MBC) develop brain metastases.¹⁻³ Before approval of tucatinib by the US Food and Drug Administration in April 2020, no systemic therapy had been indicated for treatment of brain metastases in this population, prompting the search for effective and tolerable systemic therapies.

Trastuzumab improves survival in early-stage and metastatic HER2-positive breast cancer.⁴ Despite assumptions that monoclonal antibodies do not cross the blood-brain barrier, a radioisotope form of trastuzumab, ⁸⁹Zirconium-trastuzumab (⁸⁹Zr-trastuzumab), has been shown to localize in brain metastases of patients with HER2-positive MBC,⁵ and increased concentrations of trastuzumab have been detected

in the CSF of patients with HER2-positive MBC following whole-brain radiotherapy.⁶ Additionally, data from a retrospective database analysis⁷ and the observational registHER study¹ suggest that trastuzumab is associated with longer survival in patients with HER2-positive MBC presenting with CNS metastases.

Pertuzumab is a humanized monoclonal antibody targeting HER2.⁸ In an exploratory analysis of the phase III CLEOPATRA study, patients with HER2-positive MBC who received first-line pertuzumab with trastuzumab plus docetaxel experienced a delay in CNS disease onset relative to those administered trastuzumab plus docetaxel alone.⁹

Isolated CNS progression in the setting of controlled extracranial disease is common in patients with HER2-positive MBC. This suggests that subtherapeutic drug concentrations in the brain may be a driver of CNS

ASSOCIATED CONTENT

Appendix

Protocol

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

Accepted on March 4, 2021 and published at ascopubs.org/journal/jco on May 4, 2021; DOI <https://doi.org/10.1200/JCO.20.02822>

CONTEXT

Key Objective

Development of CNS metastasis is common in patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer (MBC), but systemic therapies effective against brain metastases are limited. The phase II PATRICIA study examined pertuzumab plus high-dose trastuzumab (6 mg/kg weekly) in patients with HER2-positive MBC with CNS metastases that had progressed following radiotherapy.

Knowledge Generated

Although the overall response rate in the CNS was limited, 68% of patients treated with pertuzumab plus high-dose trastuzumab experienced clinical benefit in the CNS. No new safety signals were observed.

Relevance

Despite prior assumptions that antibody treatments are unable to penetrate the CNS, we observed that pertuzumab plus high-dose trastuzumab may have clinical activity against progressive CNS metastases in some patients with HER2-positive MBC. Future studies should further investigate antibody-based regimens, including high-dose trastuzumab in combination with chemotherapy or other targeted therapies, to optimize the treatment of CNS disease.

progression rather than intrinsic tumor resistance.¹⁰ Other phase I or II studies have explored escalating or pulsatile doses of HER2-targeted tyrosine kinase inhibitors (TKIs) in an attempt to drive higher concentrations of drug into the brain and improve efficacy.^{11,12} With respect to monoclonal antibodies, in a preclinical model of HER2-positive breast cancer brain metastasis, up to three-times the dose of trastuzumab shown to be effective in mammary tumor grafts was needed to achieve similar responses in brain tumor grafts,¹³ suggesting that increased trastuzumab doses may improve CNS activity. Importantly, when administered at doses 2- or 3-times higher than the standard dose for HER2-positive MBC, trastuzumab was not associated with increased cardiotoxicity or adverse events (AEs), most likely because extracranial HER2 receptors become saturated at lower trastuzumab doses.^{14,15}

Given these preclinical and clinical findings, the phase II PATRICIA study examined pertuzumab plus high-dose trastuzumab (6 mg/kg weekly) in patients with HER2-positive MBC presenting with progressive brain metastases. We hypothesized that (1) high-dose trastuzumab would confer CNS efficacy in patients who previously progressed on standard-dose trastuzumab and (2) no increase in cardiotoxicity would be observed. This report summarizes results from the primary efficacy analysis of PATRICIA.

METHODS

Study Design

PATRICIA (ClinicalTrials.gov identifier: [NCT02536339](https://clinicaltrials.gov/ct2/show/study/NCT02536339)) was an open-label, single-arm, phase II study conducted at 16 sites in the United States (Appendix Fig A1, online only). Study participants received intravenous pertuzumab (840 mg loading dose, 420 mg every 3 weeks thereafter) and high-dose intravenous trastuzumab (6 mg/kg once

weekly) until CNS or systemic disease progression, unacceptable toxicity, withdrawal, or study termination. Dose reductions were not permitted. If pertuzumab was discontinued because of a treatment-related AE, patients were allowed to continue high-dose trastuzumab. However, if high-dose trastuzumab was discontinued because of an AE, pertuzumab was also discontinued. Patients who discontinued study treatment were followed until disease progression, and all patients were followed for 12 months after the last treatment visit for survival.

To optimize the ability to detect any incremental benefit provided by pertuzumab plus high-dose trastuzumab, no changes were allowed to existing treatment regimens for systemic disease, except for patients receiving trastuzumab emtansine (T-DM1) or lapatinib. These patients were instructed to discontinue T-DM1 or lapatinib 3 weeks and 1 week, respectively, before initiating study therapy.

PATRICIA was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable national and local regulatory requirements. The study protocol was approved by the Independent Ethics Committee or Institutional Review Board at each site. All patients provided written informed consent.

Patients

Eligible participants were adults (≥ 18 years) with confirmed HER2-positive MBC presenting with documented CNS progression, despite prior radiotherapy (stereotactic radiosurgery and/or whole-brain radiotherapy), and stable extracranial disease. Additional inclusion criteria included completion of radiotherapy > 60 days before study entry, presence of ≥ 1 measurable CNS metastasis (≥ 10 mm per Response Assessment in Neuro-Oncology Brain Metastases [RANO-BM] criteria),¹⁶ Eastern Cooperative Oncology Group performance status score of 0-1, left ventricular

TABLE 1. Baseline Demographics and Disease Characteristics

Characteristic	Patients (N = 40) ^a
Median age, years (range)	48 (34-69)
Women, No. (%)	40 (100)
Race, No. (%)	
White	36 (90)
Asian	2 (5)
Other	1 (3)
Not reported	1 (3)
ECOG PS, No. (%)	
0	13 (33)
1	26 (67)
Median LVEF, % (range)	n = 39 60 (50-75)
Breast cancer stage at initial diagnosis, No. (%)	
0	1 (3)
I	2 (5)
II	9 (23)
III	10 (25)
IV	18 (45)
Patients with extracranial disease, No. (%)	24 (60)
Measurable	8 (20)
Nonmeasurable	16 (40)
Prior CNS radiotherapy, No. (%)	n = 39
WBRT only	16 (41)
SRS only	11 (28)
Both WBRT and SRS	12 (31)
Prior craniotomy, No. (%)	6 (15)
Prior HER2-targeted treatment for MBC, No. (%) ^b	
Trastuzumab plus pertuzumab	19 (48)
Trastuzumab only (no pertuzumab)	15 (38)
T-DM1	15 (38)
Lapatinib	18 (45)
Neratinib	3 (8)
Median No. of prior chemotherapy agents, No. (range)	n = 17 3 (2-5)
Concomitant on-study systemic treatment for MBC, No. (%)	n = 11
Anastrozole	1 (9)
Capecitabine	3 (27)
Exemestane	1 (9)
Fulvestrant	1 (9)
Gemcitabine	1 (9)
Letrozole	2 (18)
Palbociclib	3 (27)
Vinorelbine	1 (9)

(continued in next column)

TABLE 1. Baseline Demographics and Disease Characteristics (continued)

Characteristic	Patients (N = 40) ^a
Median time from radiation to first study treatment, months (range)	18.6 (2.8-63.1)
Median time from onset of brain metastases to first dose of study treatment, months (range)	19.4 (3.1-65.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; PS, performance status; SRS, stereotactic radiosurgery; T-DM1, trastuzumab emtansine; WBRT, whole-brain radiotherapy.

^aData are based on all enrolled patients and include any prior exposure to the treatments.

^bPercentages sum to more than 100% because of patients having received multiple treatments.

ejection fraction (LVEF) \geq 50%, and adequate hematologic and organ function.

Exclusion criteria included presence of leptomeningeal disease, symptomatic pulmonary disease, history of intolerance (grade \geq 3) or hypersensitivity to study treatment, significant cardiac disease, or active infection. Concurrent use of nonapproved or investigational treatments (\leq 21 days before enrollment) or anthracyclines was also prohibited.

Outcomes

The primary efficacy end point was objective response rate (ORR) in the CNS, defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) per RANO-BM criteria (Appendix Table A1, online only).¹⁶ Brain responses were measured by magnetic resonance imaging at weeks 6, 12, 20, and 28, and every 12 weeks thereafter until progressive disease (PD). Secondary efficacy end points included duration of response (time from first documented CR or PR to PD or death) and clinical benefit rate (CBR; CR plus PR plus stable disease [SD] of \geq 4 or \geq 6 months) in the CNS. Duration of clinical benefit in the CNS (time from first documented CR or PR or first treatment dose for patients with SD to PD or death) was also determined. Extracranial responses were measured using computed tomography, magnetic resonance imaging, or positron-emission tomography computed tomography at weeks 8 and 16, and every 12 weeks thereafter until PD, and were assessed per RECIST version 1.1.¹⁷ AEs were coded per Medical Dictionary for Regulatory Activities version 21.1 and graded per Common Terminology Criteria for Adverse Events version 4.0. LVEF was assessed at screening, at 6 weeks, at 12 weeks, and then every 3 months during the treatment period and every 6 months during survival follow-up (12 months after the treatment discontinuation visit). Incidence of congestive heart failure (CHF) was also recorded. A preplanned interim analysis required study suspension if \geq 2 of the first 15 patients

experienced study treatment-related CHF. Pharmacokinetics of both study treatments were evaluated at week 1 (predose and within 30 minutes of completion of both infusions), week 4 (predose), week 10 (predose), and week 16 (predose and within 30 minutes of completion of both infusions).

Statistical Analyses

A total of forty patients were targeted for enrollment. Sample size was based on an assumed CNS ORR of 20%, which would result in a 95% CI of 8.4 to 36.9 in 35 efficacy-evaluable patients. The 95% CIs for ORR and CBR were calculated using the Clopper-Pearson exact method. DOR and duration of clinical benefit were estimated using the Kaplan-Meier approach, with 95% CIs for the median time-to-event calculated using the Brookmeyer-Crowley method. Patients who did not experience PD or death were censored at the last date they were known to be progression-free. AEs were summarized using descriptive statistics.

The efficacy-evaluable population comprised all treated patients who had ≥ 1 post-treatment CNS tumor assessment or who died without a follow-up tumor assessment within 30 days of the last dose of study treatment. The safety population included all patients who received any dose of study treatment. The pharmacokinetic-evaluable population included all patients who received any dose of study treatment and had ≥ 1 pharmacokinetic assessment.

The clinical cutoff date was May 1, 2019. The study is ongoing, with two patients remaining on treatment.

RESULTS

Patients

A total of forty patients were enrolled between December 15, 2015, and May 18, 2017 (Table 1). Median age was 48 years. In total, 48% (19/40) of patients were hormone receptor–positive at the time of initial breast cancer diagnosis, and 40% (16/40) were using corticosteroids at screening. Twenty-eight percent (11/40) of patients continued concomitant nonstudy systemic treatments during the study, most commonly aromatase inhibitor ($n = 4$), capecitabine ($n = 3$), or palbociclib ($n = 3$).

Thirty-nine patients received any dose of study treatment; one patient withdrew before receiving any treatment. Median (range) treatment duration was 4.8 (0.7-29.9) months for pertuzumab and 4.5 (0.5-37.4) months for trastuzumab. Patients received a median (range) of 7.0 (1-51) doses of pertuzumab and 20.0 (2-145) doses of trastuzumab. By clinical cutoff, 95% (37/39) of patients had discontinued study treatment, with 5% (2/39) still on treatment. Patients discontinued treatment because of CNS progression ($n = 27$), symptomatic deterioration ($n = 4$), withdrawal ($n = 3$), change in LVEF ($n = 1$), death ($n = 1$), and protocol deviation ($n = 1$). In total, 15% (6/40) of patients remained on study at clinical cutoff. The median (range) study duration was 16.6 (0.8-37.2) months, and the most common reason for study discontinuation was death (59% [20/34]). Causes of death were PD ($n = 16$), other with cancer being a contributing factor ($n = 3$), and unknown ($n = 1$). The safety-evaluable population comprised 39 patients, as one patient did not receive study treatment. The efficacy-evaluable population included 37 patients; two patients from the safety-evaluable population were excluded because they did not have any postbaseline assessments because of withdrawal ($n = 1$) and treatment discontinuation owing to symptomatic deterioration ($n = 1$).

Efficacy

The CNS ORR per RANO-BM criteria was 11% (4/37; 95% CI, 3 to 25), with four confirmed PRs (Table 2). DOR in these four patients was 3.2 (censored), 3.3, 4.6, and 5.6 months. DOR was censored in one patient by treatment discontinuation because of a protocol deviation (use of disallowed concomitant therapy); the other three patients experienced PD. CBR in the CNS at 4 months (CR plus PR plus SD ≥ 4 months) was 68% (25/37) (Fig 1), with a median (range) duration of 6.6 (3.2-36.8) months (Fig 2). All patients who derived clinical benefit in the CNS had stable or better extracranial disease. CBR in the CNS at 6 months (CR plus PR plus SD ≥ 6 months) was 51% (19/37), with a median (range) duration of 9.2 (3.2-36.8) months (Fig 1). One patient had ongoing SD for > 2 years, and another had ongoing SD for > 3 years. The largest percentage change in the sum of target lesion diameters is summarized in Figure 3. In a subgroup analysis of CBR at 4 months by prior HER2-targeted treatments, including

TABLE 2. Efficacy Within the CNS per RANO-BM Criteria

Response	Patients (n = 37) ^a	
	No. (%)	95% CI
ORR ^b	4 (11)	3 to 25
CBR at 4 months (CR plus PR plus SD ≥ 4 months)	25 (68) ^c	50 to 82
CBR at 6 months (CR plus PR plus SD ≥ 6 months)	19 (51) ^c	34 to 68
Confirmed best response (SD ≥ 4 months)	0	—
CR	4 (11)	—
PR	21 (57)	—
SD ≥ 4 months	12 (32)	—
Patients without clinical benefit	—	—
Confirmed best response (SD ≥ 6 months)	0	—
CR	4 (11)	—
PR	15 (41)	—
SD ≥ 6 months	18 (49)	—
Patients without clinical benefit	—	—

Abbreviations: CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease.

^aData are based on the efficacy-evaluable population.

^bPercentage of patients with confirmed CR plus confirmed PR.

^cExtracranial disease responses in these patients were also stable or better.

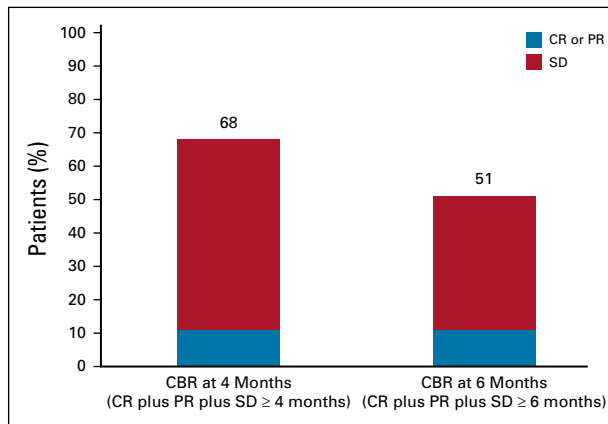


FIG 1. CBR in the CNS at 4 months (n = 25) and 6 months (n = 19). CBR, clinical benefit rate; CR, complete response; PR, partial response; SD, stable disease.

prior trastuzumab, T-DM1, lapatinib, or neratinib, patients derived clinical benefit regardless of the prior treatment received (Appendix Table A2, online only).

Safety

In a preplanned interim safety analysis (n = 15), no patients experienced treatment-related CHF; thus, the criteria to suspend the study because of CHF-related events was not met. Overall, 97% (38/39) of patients reported ≥ 1 AE, most commonly diarrhea (n = 23), fatigue (n = 17), and nausea (n = 12). All diarrhea episodes were grade 1 or 2, and none led to treatment discontinuation. In total, 44% (17/39) of patients reported ≥ 1 grade 3 (n = 14) or grade 4 (n = 3) AE (Table 3). No grade 5 AEs were reported. Thirty (77%) patients had ≥ 1 treatment-related AE, most commonly diarrhea (n = 16) and fatigue (n = 11) (Table 3). Two patients experienced a total of three treatment-related

grade 3 AEs (left ventricular dysfunction, n = 1; asthenia and fatigue, n = 1). One patient experienced treatment-related grade 4 hypertension. Only one patient experienced a treatment-related cardiac AE (grade 3 left ventricular dysfunction in a patient with prior cardiac history). The patient subsequently discontinued both study drugs; one other patient in the study also discontinued because of an AE (grade 3 seizure, not considered to be treatment-related).

Serious AEs were reported in 7 (18%) patients. Of these, one patient experienced three serious AEs (grade 3 seizure, grade 3 hydrocephalus, and grade 2 headache); the other six patients each experienced a single serious AE (seizure, n = 3; gastroenteritis viral, n = 1; hypertension, n = 1; and parainfluenza virus infection, n = 1). Hypertension (grade 4) was the only serious AE considered related to study treatment. No new safety signals emerged with either study treatment.

Pharmacokinetics

All treated patients were included in the pharmacokinetic-evaluable population (n = 39). The mean observed maximum concentration (C_{max}) of pertuzumab at steady-state (C_{max,ss}; week 16; dose 6) was 226 ± 56.2 µg/mL, and the mean observed trough concentration (C_{min}) was 102 ± 41.6 µg/mL. For trastuzumab, mean observed C_{min} increased over time and appeared to approach steady-state by week 10. Mean C_{max,ss} and C_{min,ss} for high-dose trastuzumab at steady-state (week 16; dose 6) were 394 ± 94.1 and 306 ± 90.2 µg/mL, respectively (Appendix Table A3, online only).

DISCUSSION

In the phase II PATRICIA study, we evaluated the safety and efficacy of pertuzumab plus high-dose trastuzumab

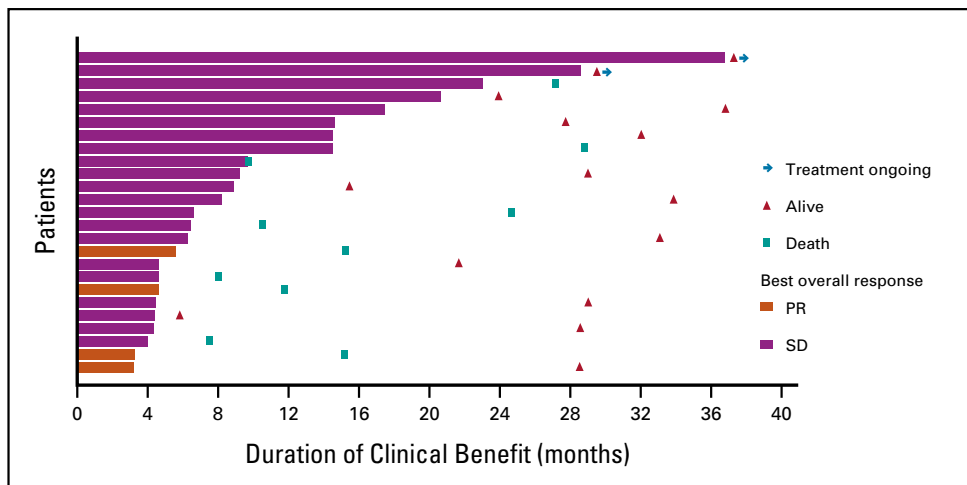


FIG 2. Duration of clinical benefit in the CNS at 4 months^a (n = 25). ^aPatients with confirmed CR, PR, or SD ≥ 4 months. CR, complete response; PR, partial response; SD, stable disease.

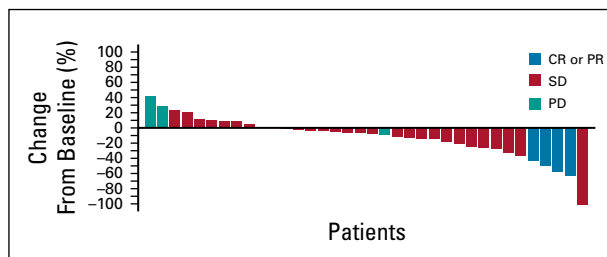


FIG 3. Largest percentage change in total sum of CNS target lesion diameters ($n = 37$). One patient without a postbaseline assessment was omitted from this analysis because of death within 30 days of last treatment, but was included in the efficacy-evaluable population. One patient was with an unconfirmed PR and was considered to have a confirmed best response of SD in the study. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

(6 mg/kg intravenous once weekly) in patients with progressive brain metastases despite prior radiotherapy. Although the observed CNS ORR per RANO-BM criteria was only 11%, CBR in the CNS was 68% at 4 months and 51% at 6 months, with two patients having SD for > 2 years. Clinical benefit was also observed in patients with prior exposure to T-DM1, lapatinib, and/or neratinib. Notably, extracranial disease responses were stable or better in patients with clinical benefit in the CNS. To our knowledge, this is the first report of a monoclonal antibody (trastuzumab) conferring CNS objective responses and clinical benefit following an increase in the systemic dose of a drug on which patients had previously progressed.

The observed efficacy signal is supported mechanistically by prior data demonstrating accumulation of ^{89}Zr -trastuzumab in brain metastases of patients with HER2-positive MBC⁵ and preclinical data suggesting a dose-dependent response to trastuzumab in the CNS.¹³ Thus, despite their size, monoclonal antibodies have the potential to enter the CNS compartment, but the extent to which they do so is likely determined by the integrity of the blood-brain barrier. Published studies describe disruption of the blood-brain barrier by tumor metastasis that increases blood-brain barrier permeability.^{18,19} The fact that monoclonal antibodies can access the CNS is further supported by multiple reports suggesting CNS activity of T-DM1, an antibody-drug conjugate composed of trastuzumab and DM1.^{20,21}

As expected, steady-state serum trastuzumab exposure was greater with the high-dose trastuzumab regimen (6 mg/kg weekly) relative to the approved regimen (4 mg/kg loading dose, 2 mg/kg weekly thereafter). Observed $C_{\max,ss}$ and $C_{\min,ss}$ in PATRICIA were 394 ± 94.1 and $306 \pm 90.2 \mu\text{g/mL}$, respectively, versus model-predicted $C_{\max,ss}$ and $C_{\min,ss}$ of 109 and $66.1 \mu\text{g/mL}$, respectively, for the approved regimen.⁴ In the phase III APHINITY study, trastuzumab was administered at the same maintenance dose as in PATRICIA (6 mg/kg), but on a 3-weekly versus weekly schedule. As expected, observed

TABLE 3. Safety Summary

AE Parameter	Patients, No. (%) ($n = 39$) ^a
AE leading to death	0
Serious AE	7 (18)
Treatment-related grade 3-4 AE	3 ^b (8)
Left ventricular dysfunction ^c	1 (3)
Asthenia	1 (3)
Fatigue	1 (3)
Hypertension	1 (3)
AE leading to treatment withdrawal	2 ^d (5)
Any treatment-related AE ^e	30 (77)
Diarrhea	16 (41)
Fatigue	11 (28)
Nausea	9 (23)
Rash	5 (13)
Constipation	2 (5)
Vomiting	2 (5)
Mucosal inflammation	2 (5)
Infusion-related reaction	2 (5)
ALT increased	2 (5)
AST increased	2 (5)
Headache	2 (5)
Pruritus	2 (5)

Abbreviations: AE, adverse event; LVEF, left ventricular ejection fraction.

^aData are based on the safety-evaluable population.

^bOne patient experienced grade 3 left ventricular dysfunction, one experienced both grade 3 fatigue and asthenia, and one experienced grade 4 hypertension.

^cPatient was a 67-year-old woman with a history of low ejection fraction and cardioembolic stroke, and concurrent hypertension. LVEF at study screening was 53%. Concomitant medications ongoing during the study included enalapril and carvedilol. Following five doses of trastuzumab and two of pertuzumab, an echocardiogram revealed an LVEF of 30% on study day 35, and the patient was diagnosed with nonserious grade 3 left ventricular dysfunction considered by the investigator to be related to the study drugs, with hypertension as another possible etiologic factor. Study treatment was permanently discontinued on study day 36. The event of left ventricular dysfunction remained unresolved as of the last safety assessment before the patient's death because of disease progression on study day 296.

^dOne patient withdrew because of grade 3 left ventricular dysfunction (treatment-related), and the other withdrew because of grade 3 seizure (not treatment-related).

^ePreferred terms reported in $\geq 5\%$ of patients are presented.

$C_{\max,ss}$ and $C_{\min,ss}$ in PATRICIA were higher than model-predicted exposures in APHINITY (225.5 ± 80 and $67.7 \pm 32 \mu\text{g/mL}$, respectively).²² Observed $C_{\max,ss}$ and $C_{\min,ss}$ values for pertuzumab in PATRICIA (226 ± 56.2 and $102 \pm 41.6 \mu\text{g/mL}$, respectively) were also comparable to model-predicted $C_{\max,ss}$ and $C_{\min,ss}$ values (184.9 [range, 124-260] and 52.1 [range, 16-97] $\mu\text{g/mL}$,

respectively) derived from a population pharmacokinetic model informed by patients with solid tumors, including HER2-positive MBC.²³

Importantly, the pertuzumab and high-dose trastuzumab combination did not lead to the emergence of new safety signals.^{4,8} No increase in the incidence of cardiotoxicity was observed with high-dose trastuzumab, supporting results of earlier studies that explored higher doses and more intensive dosing of trastuzumab versus the approved regimen.^{14,15}

When PATRICIA was being designed, phase II data on the use of lapatinib in treating patients with progressive HER2-positive brain metastases were available; however, CNS data for neratinib or tucatinib were not. In the first phase II study of patients with HER2-positive progressive brain metastases treated with single-agent lapatinib, the CNS ORR was only 3%, with a CBR at 4 months of 18%.²⁴ In a subsequent phase II study of lapatinib monotherapy, the CNS ORR was 6%, and 15% of patients were alive and progression-free at 4 months.²⁵ After the planning stages of PATRICIA, neratinib was evaluated as monotherapy in the phase II Translational Breast Cancer Research Consortium 022 study and in combination with capecitabine in the phase III NALA study, and tucatinib was explored in combination with trastuzumab in a phase Ib study and trastuzumab plus capecitabine in the HER2 CLIMB study. In Translational Breast Cancer Research Consortium 022, neratinib was associated with a CNS ORR of 8% and a CBR at 4 months of approximately 20%.²⁶ In NALA, neratinib plus capecitabine led to a delay in the time to intervention for symptomatic CNS disease versus treatment with lapatinib plus capecitabine (overall cumulative incidence 22.8% v 29.2%; $P = .043$).²⁷ In the phase Ib tucatinib plus trastuzumab study, intracranial responses were observed in 12% of patients receiving twice-daily tucatinib 300 mg plus trastuzumab and 6% of patients receiving once-daily tucatinib 750 mg plus trastuzumab; CBRs at 4 months were 35% and 53%, respectively.¹² In HER2CLIMB, tucatinib plus trastuzumab and capecitabine significantly

increased CNS ORR (47.3% v 20.0%; $P = .03$) and reduced the risk of CNS progression or death by 68% versus trastuzumab plus capecitabine alone.²⁸

In general, use of HER2-targeted TKIs combined with chemotherapy results in higher CNS ORRs relative to TKIs alone.^{25,28-30} However, patients in PATRICIA were not permitted to switch chemotherapy upon study entry; only a minority (28%) were using nonstudy systemic treatment for MBC and none of the patients with a confirmed PR received concurrent chemotherapy while on study. Thus, we believe that prior studies examining single-agent TKIs are more appropriate for placing the clinical efficacy of pertuzumab plus high-dose trastuzumab into context. Although one must be cautious with cross-trial comparisons, given possible differences in patient populations, especially as the PATRICIA study required stable extracranial disease at study baseline, the pertuzumab and high-dose trastuzumab combination yielded a CNS ORR and CBR rate at 4 months that compare favorably with the commercially available HER2-targeted TKIs when given without chemotherapy. Furthermore, although the HER2 TKI studies enrolled both patients with and without active extracranial disease, the CNS remained the most common site of disease progression.^{25,26}

In summary, although the CNS response rate observed in PATRICIA was modest (11%), the majority (68%) of patients experienced clinical benefit, and two patients had ongoing stable intracranial and extracranial disease for > 2 years. Importantly, no new safety signals were observed. These data suggest that (1) pertuzumab plus high-dose trastuzumab may have clinical utility in some patients with HER2-positive MBC and progressive CNS metastases and (2) there is potential to further optimize the dose and schedule of monoclonal antibodies to combat CNS disease. Future studies may be warranted to clarify whether additional CNS gains could be made by combining high-dose trastuzumab with chemotherapy and/or other targeted agents.

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PRIOR PRESENTATION

Presented in poster format at the 2019 San Antonio Breast Cancer Symposium (P1-18-03), San Antonio, TX, December 8-11, 2019.

SUPPORT

The PATRICIA study was sponsored by F. Hoffmann-La Roche/Genentech.

CLINICAL TRIAL INFORMATION

NCT02536339

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/jco.20.02822>.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

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ACKNOWLEDGMENT

The authors would like to thank all of the investigators and patients involved in the PATRICIA study. Editorial and medical writing support for this manuscript was provided by Tiffany DeSimone, PhD, of Ashfield Ashfield MedComms, an Ashfield Health Company, and was funded by F. Hoffmann-La Roche/Genentech (South San Francisco, CA).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study**

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Consulting or Advisory Role: Seattle Genetics, Puma Biotechnology, Daiichi Sankyo, California Institute for Regenerative Medicine (CIRM), Denali Therapeutics

Research Funding: Genentech, Pfizer, Seattle Genetics, Merck, Novartis

Patents, Royalties, Other Intellectual Property: Royalties for chapter in Up-to-Date regarding management of breast cancer brain metastases, Royalties, Jones & Bartlett

Mark Pegram

Consulting or Advisory Role: Genentech/Roche, Pfizer, Seattle Genetics, Puma, Novartis

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Research Funding: Bristol Myers Squibb, Brooklyn ImmunoTherapeutics, Merck

Travel, Accommodations, Expenses: Lilly

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Research Funding: Nektar Therapeutics

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Employment: Genentech/Roche

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Research Funding: Angiochem

No other potential conflicts of interest were reported.

APPENDIX

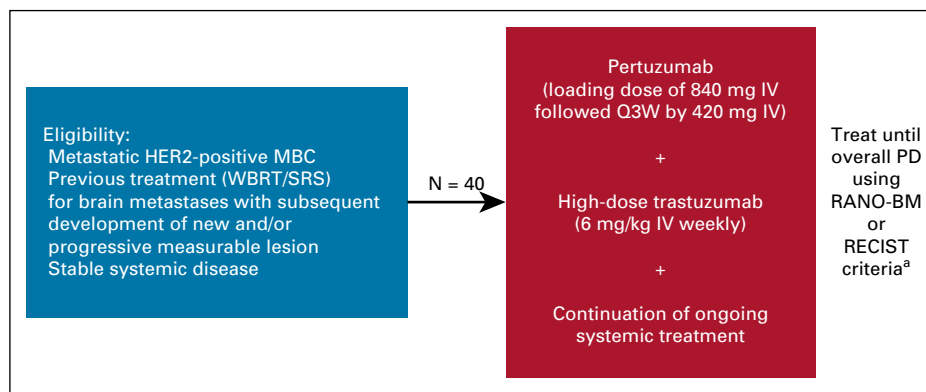


FIG A1. Study design. Primary efficacy end point: ORR in the CNS. Secondary efficacy end points: DOR in the CNS, CBR in the CNS, PFS (CNS), PFS (CNS or non-CNS), PFS (non-CNS), and OS. Safety end point: Safety of pertuzumab and trastuzumab for the treatment of HER2-positive MBC with CNS progression postradiotherapy. ^aFollowing a protocol update in October 2018, patients were followed up for 12 months post-treatment. CBR, clinical benefit rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IV, intravenous; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, once every 3 weeks; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

TABLE A1. RANO-BM Criteria

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD of CNS target lesions relative to baseline	< 30% decrease relative to baseline, but < 20% increase in sum LD of CNS target lesions relative to nadir	≥ 20% increase in sum LD of CNS target lesions relative to nadir ^a , with ≥ 1 lesion increasing by an absolute value of ≥ 5 mm
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal PD ^a
New lesion(s) ^b	None	None	None	Present ^a
Corticosteroids	None	Stable or decreased	Stable or decreased	N/A ^c
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse ^a
Requirement for response	All	All	All	Any ^a

NOTE. CNS response is scored independent of extracranial disease response (or progression).

Abbreviations: CR, complete response; LD, longest diameter; N/A, not applicable; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease.

^aProgression occurs when this criterion is met.

^bNew lesions are those not present on prior scans and visible in ≥ 2 projections. If a new lesion is equivocal, for example, because of its small size, continued therapy may be considered. Follow-up evaluation will clarify whether it represents truly new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.

^cAn increase in corticosteroids alone will not be taken into account when determining progression in the absence of persistent clinical deterioration.

TABLE A2. Clinical Benefit at 4 Months by Prior HER2-Targeted Treatment Group

Prior HER2-Targeted Treatments for MBC	n	CBR at 4 Months, No. (%)
Trastuzumab plus pertuzumab	19	9 (47)
Trastuzumab only (no pertuzumab)	15	11 (73)
T-DM1	15	7 (47)
Lapatinib	18	11 (61)
Neratinib	3	2 (67)

Abbreviations: CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

TABLE A3. Summary of Serum Concentrations of High-Dose Trastuzumab (6 mg/kg) Administered Weekly

Week	Time Point	No.	Mean Serum Concentration, μg/mL (SD)
1	Predose (C _{min}) ^a	38	57.0 ± 52.7
1	Postinfusion (C _{max})	35	181 ± 72.5
10	Predose (C _{min})	32	295 ± 70.3
16	Predose (C _{min})	22	306 ± 90.2
16	Postinfusion (C _{max})	22	394 ± 94.1

Abbreviations: C_{max}, observed maximum concentration; C_{min}, observed trough concentration; SD, standard deviation.

^aEligibility criteria did not require patients to be trastuzumab-naive. Thus, trastuzumab was detectable in some patients before study dosing at week 1.