A Phase II Study of Atezolizumab, Pertuzumab, and High-Dose Trastuzumab for Central Nervous System Metastases in Patients with HER2-Positive Breast Cancer

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ABSTRACT

Purpose: Patients with HER2-positive breast cancer brain metastases have few effective systemic therapy options. In a prior study, pertuzumab with high-dose trastuzumab demonstrated a high clinical benefit rate (CBR) in the central nervous system (CNS) in patients with brain metastases. The current trial evaluated whether the addition of atezolizumab to this regimen would produce further improvements in CNS response.

Patients and Methods: This was a single-arm, multicenter, phase II trial of atezolizumab, pertuzumab, and high-dose trastuzumab for patients with HER2-positive breast cancer brain metastases. Participants received atezolizumab 1,200 mg i.v. every 3 weeks, pertuzumab (loading dosage 840 mg i.v., then 420 mg i.v. every 3 weeks), and high-dose trastuzumab (6 mg/kg i.v. weekly for 24 weeks, then 6 mg/kg i.v. every 3 weeks). The primary endpoint was CNS overall response rate per Response Assessment in Neuro-Oncology Brain Metastases criteria. Key secondary endpoints included CBR, overall survival, and safety and tolerability of the combination.

Results: Among 19 enrolled participants, two had a confirmed intracranial partial response for a CNS overall response rate of 10.5% (90% confidence interval, 1.9%–29.6%). The study did not meet the prespecified efficacy threshold and was terminated early. The CBR was 42.1% at 18 weeks and 31.6% at 24 weeks. Seven patients (36.8%) required a dose delay or hold, and the most frequent any-grade adverse events were diarrhea (26.3%) and fatigue (26.3%).

Conclusions: The addition of atezolizumab to pertuzumab plus high-dose trastuzumab does not result in improved CNS responses in patients with HER2-positive breast cancer brain metastases.

Introduction

Approximately 15% to 20% of breast cancers overexpress HER2 and are classified as HER2 positive (1–3). Together with triple-negative breast cancer, HER2-positive breast tumors have the highest rates of brain metastases, with studies reporting central nervous system (CNS) involvement in up to 50% of patients with those subtypes (4–8). Although the median overall survival (OS) after a diagnosis of brain metastases now exceeds 2 years in patients with HER2-positive breast cancer with good performance status (9, 10), this outcome has resulted in patients who live long enough to have substantial morbidity from additional CNS progression post-radiation. Several systemic regimens have reported CNS activity in small trials or case series (11–15). However, only the combination of capecitabine, trastuzumab, and tucatinib has received an FDA indication specifically for the treatment of patients with brain metastases (16). Clearly, better options for the prevention and treatment of brain metastases in patients with HER2-positive breast cancer are needed.

Unfortunately, the CNS response to existing systemic anticancer therapies at standard dosages has been disappointing. For instance, large mAb are not believed to cross an intact blood-brain barrier (BBB). Therapeutic concentrations of anticancer medications in the CNS are further limited by the activity of drug efflux proteins such as P-glycoprotein, which are present in high concentrations in the luminal membranes of the brain endothelium (17). However, the BBB may be subjected to increased permeability associated with radiation effects and tumor invasion. As such, subtherapeutic trastuzumab levels achieved in the CNS may be related to insufficient dosing as opposed to the inability of trastuzumab to cross the BBB. In a preclinical model of HER2-positive breast cancer brain metastases, a dose-response curve was observed for escalating doses of trastuzumab (18). These results informed the design of the phase II PATRICIA trial, in which trastuzumab was administered at a high dose of 6 mg/kg intravenously weekly along with pertuzumab (at a standard dose and schedule) in patients with active, HER2-positive breast cancer brain metastases. At the time the current study was designed, preliminary evidence of CNS activity was available from the PATRICIA trial, though the data were not yet mature (19).

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Clin Cancer Res 2024;30:4856–65

doi: 10.1158/1078-0432.CCR-24-1161

Translational Relevance

There are few effective systemic therapies for patients with HER2-positive metastatic breast cancer with brain metastases. In a prior study, pertuzumab plus high-dose trastuzumab yielded a high central nervous system (CNS) clinical benefit rate in this population. Preclinical studies suggested that an immune checkpoint inhibitor against PD-1/PD-L1 could further improve the CNS efficacy of this regimen. To investigate this, the current single-arm trial enrolled patients with HER2-positive breast cancer brain metastases, who were treated with atezolizumab, pertuzumab, and high-dose trastuzumab. We observed a low objective response rate in the CNS (10.5%) which was not appreciably greater beyond that which would have been expected with the doublet of pertuzumab and high-dose trastuzumab without immunotherapy. Further investigations of immunotherapy combinations in patients with HER2-positive metastatic breast cancer with brain metastases should focus on novel combinations or agents other than PD-1/PD-L1 inhibitors.

Several prior studies have shown that a substantial proportion of HER2-positive breast tumors are richly infiltrated by immune cells (20–22). Of note, multiple concordant reports indicate that disease outcome in patients with HER2-positive breast cancer treated in the neo(adjuvant) setting with trastuzumab-based regimens improves when the tumor microenvironment has abundant tumor-infiltrating lymphocytes (TIL) or expresses immune-related signatures (23, 24). Single-cell analyses demonstrated that brain metastases from solid tumors are enriched by T cells and monocyte-derived macrophages and thus may have a favorable clinical response to checkpoint inhibitors (25). In addition, from a large case series of 84 breast cancer metastasis samples, the authors confirmed the high prevalence of PD-L1 positivity and observed that PD-1 and TIL were found to be higher in HER2-positive tumors (26). Furthermore, preclinical studies have demonstrated that anti–PD-1 mAb can significantly improve the therapeutic activity of trastuzumab in immunocompetent mice (27).

To date, patients with active breast cancer brain metastases have been excluded from virtually all trials of immunotherapy. However, clear CNS activity has been demonstrated with immune checkpoint inhibitors in patients with advanced melanoma or non–small cell lung cancer (28–30). Given the high prevalence of brain metastases in patients with HER2-positive breast cancer, evaluating the efficacy of immune checkpoint blockade in this patient population represents an opportunity for a major impact in this area of unmet medical need. Therefore, we hypothesized that an optimal anti-HER2 regimen designed to better penetrate the BBB, combined with an anti–PD-L1 agent, would synergize to increase efficacy against CNS metastases in patients with HER2-positive metastatic breast cancer.

Patients and Methods

Trial design

This was a single-arm, multicenter, phase II trial to evaluate the efficacy and safety of atezolizumab in combination with pertuzumab and high-dose trastuzumab for the treatment of patients with HER2-positive breast cancer brain metastases. Participants were enrolled at two sites: Dana-Farber Cancer Institute in Boston, MA, and Northwestern University Hospital in Chicago, IL. This study was conducted in accordance with the Declaration of Helsinki and after approval by the Dana-Farber/Harvard Cancer Center Institutional Review Board (and the Institutional Review Board governing Northwestern University for patients enrolled at that site). All patients provided written informed consent. The study was registered at Clinicaltrials.gov as NCT03417544. Please see Supplementary Table S1 for data on representativeness of our study population.

Patients

Patients with histologically confirmed metastatic breast cancer that was HER2 positive by the ASCO/CAP 2013 guidelines (3) by local laboratory testing were eligible for the trial. Central confirmation of HER2 status was not required. HER2 positivity was defined as IHC 3+ based on circumferential membrane staining that is complete, intense, and/or FISH positive based on one of the three following criteria: single-probe average HER2 copy number ≥6.0 signals/cell; dual-probe HER2/CEP17 ratio ≥2.0; or dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥6.0 signals/cell. Patients were required to have at least one measurable CNS lesion, defined as ≥10 mm in at least one dimension and unequivocal evidence of new and/or progressive brain metastases (active brain metastases). Patients with known leptomeningeal metastases, current use of high-dose systemic corticosteroids (defined as dexamethasone >2 mg/day or its equivalent), or prior use of immune checkpoint inhibitors were excluded.

Treatment

Patients were treated with atezolizumab 1,200 mg i.v. every 3 weeks, pertuzumab (loading dosage of 840 mg i.v., followed every 3 weeks thereafter by a dosage of 420 mg i.v.), and high-dose trastuzumab (at a dosage of 6 mg/kg i.v. weekly for the first 24 weeks and thereafter trastuzumab 6 mg/kg i.v. every 3 weeks).

Assessments

Response in the CNS and in non-CNS sites were evaluated and recorded separately. Participants were evaluated for response every 6 weeks for the first 24 weeks and then every 9 weeks thereafter. As CNS response was the primary endpoint, confirmation of partial response (PR) or complete response at least 4 weeks later was required to deem either one of the "the best overall responses" (31). Safety was assessed on the basis of the incidence of adverse events, defined according to the NCI Common Terminology Criteria for Adverse Events, version 4.0. The first six participants were assessed for dose-limiting toxicities (DLT). If two or more DLT were observed in these patients, the regimen would be declared unsafe for further study. If ≤1 DLT was observed, enrollment would continue. Changes in vital signs and laboratory results were assessed in patients who received at least one dose of any trial drug. PD-L1 status was assessed centrally by IHC using the VENTANA PD-L1 (SP142) assay (Ventana Medical Systems). PD-L1-positive disease was defined by PD-L1 expression on tumor-infiltrating immune cells for 1% or more of the tumor area. PD-L1-negative disease was defined by PD-L1 expression on immune cells for less than 1% of the tumor area.

Endpoints

The primary endpoint was CNS overall response rate (ORR) according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (32). Secondary endpoints included the following: duration of response in the CNS; bicompartmental progression-free survival (PFS), as proposed by RANO-BM guidelines and defined as either progression in the CNS according to RANO-BM criteria and/or extracranial progression according to RECIST 1.1 (32); CNS response rates according to response assessment in immunotherapy neuro-oncology brain metastases criteria (33); extracranial ORR according to RECIST 1.1 criteria (31); extracranial ORR according to immune-related response criteria (34); clinical benefit rate (CBR) at 18 and 24 weeks (defined as the proportion of participants with stable or responsive disease in both CNS and non-CNS at 18 and 24 weeks per RANO-BM criteria); PFS according to the RECIST 1.1 single-compartmental model; site of first progression (CNS vs. extracranial vs. both); OS; and safety and tolerability of the combination. DLT was defined as any of the following events occurring within 21 days of cycle 1 day 1 (C1D1) of treatment, if judged by the investigator to be possibly, probably, or definitely related to study drug: asymptomatic grade 4 neutropenia or thrombocytopenia lasting ≥7 days, grade 4 thrombocytopenia of any duration, and nonhematologic toxicity as grade 3 and above. The provider-rated neurologic function of each participant was assessed by investigators using the Neurological Assessment in Neuro-Oncology (NANO) scale (35).

Research biospecimens

Archival tissue was collected, if available, as one block or 15 4-μm-thick unstained, charged slides. Stromal TIL (sTIL) were assessed by an experienced pathologist (B.B.K). The cut sections were stored at room temperature and stained with the VENTANA PD-L1 assay (SP142). The same pathologist assessed the patient samples for evidence of viable tumor tissue before evaluating PD-L1 (SP142) staining. Tumor mutational burden (TMB) was assessed by next-generation sequencing on prior tissue biopsies. Blood samples were collected for research purposes on day 1 of cycles 1, 3, 5, and 9 and at the end of treatment. Cerebrospinal fluid samples were collected for research purposes at baseline (screening), on treatment (between C2D1 and C3D1), and at the end of treatment. Results of analyses on the cerebrospinal fluid will be reported separately.

Patient-reported outcomes

Patient-reported outcomes (PRO) were measured by the MD Anderson Symptom Inventory-Brain Tumor assessment (36) and the EQ-5D evaluation (37). PRO were completed at baseline and on day 1 of cycles 3, 5, 9, and once participants were off treatment.

Statistical analyses

This study used a Simon "optimal" two-stage design with a one-sided type I error of 0.1 and type II error of 0.1 (90% power) to detect the difference between the null (15%) and alternative (35%) CNS response rates. In the first stage, 19 patients would be enrolled. If fewer than four patients had a confirmed CNS response, the study would be discontinued after stage 1. If four or more patients had a confirmed CNS response, the study would continue to stage 2 with an additional 14 patients enrolled. If there were eight or more responses among the 33 patients, the regimen would be declared worthy of further study. If the true response rate is 15%, the chance that the regimen is declared ineffective after stage 1 is 68.4%, and the chance the regimen is declared ineffective after stage 2 is 90.4% (exact type I error = 0.096). If the true response rate is 35%, the chance that the regimen is falsely declared ineffective is 9.6% (exact power = 90.4%).

In this article, baseline patient and disease characteristics are summarized using descriptive statistics, mean and range for continuous variables, and frequency and percentage for categorical variables. CNS-ORR and CBR per RANO-BM criteria are presented with 90% confidence intervals (CI). The association between correlative endpoints (TIL, PD-L1, and TMB) and clinical response is assessed using the Fisher exact test, χ^2 test, or Wilcoxon rank-sum test, as appropriate.

Data availability

We have provided the majority of the data within this article. Given the small sample size, the supplementary data files already include most of the individual deidentified patient data. Additional data generated in this trial are available from the corresponding author upon reasonable request.

Results

Study population

From March 8, 2018, to January 21, 2020, 19 female patients with HER2-positive breast cancer with CNS metastases were enrolled across two institutions (11 at Dana-Farber Cancer Institute and eight at Northwestern University Hospital). Fourteen of 19 (73.7%) patients had received two or more lines of chemotherapy for metastatic disease. A complete list of prior regimens for each patient is reported in Supplementary Table S2. Six participants (31.6%) had prior brain surgery, nine (47.4%) had prior whole-brain radiotherapy, and 11 (57.9%) had prior stereotactic radiosurgery. The median time between CNS-directed radiation and C1D1 of study treatment was 10 months (range, 0.2–52.9 months). Notably, five participants (26.3%) had untreated brain metastases (no prior radiotherapy or surgery) at the time of study entry. Baseline patient and disease characteristics are summarized in **Table 1** and Supplementary Table S3.

At data cutoff on August 15, 2022, the median follow-up was 40.8 months (IQR, 33.61–48.62). At the time of data cutoff, all patients had discontinued study therapy; 11/19 (57.9%) had died, 7/19 (36.8%) were still alive, and 1/19 (5.3%) was lost to follow-up. Reasons for treatment discontinuation were progression of CNS disease per RANO-BM criteria in 12/19 (63.2%) patients, progression of extracranial disease per RECIST 1.1 criteria in 4/19 (21.1%) patients, clinical progression in 2/19 (10.5%) patients, and death in one patient (5.3%).

Efficacy

As shown in **Table 2**, 4/19 [21.1%; 90% CI, 7.5%–41.9%] patients evaluable for assessment of the primary endpoint had an intracranial PR, two of which were confirmed, for a confirmed CNS-ORR of 10.5% (90% CI, 1.9%–29.6%). Patient No. 7 presented with multiple (>20) lesions in both cerebral and cerebellar hemispheres as well as the brainstem, after receiving fourth-line chemotherapy with lyposomal doxorubicin and trastuzumab (neoadjuvant docetaxel, carboplatin, and trastuzumab 5 years before enrollment, received brain surgery and CyberKnife 43.6 months before enrollment, first-line therapy with capecitabine plus lapatinib, second-line with sorafenib plus whole-brain radiation therapy, and third line with T-DM1); three target lesions were identified, and ~70% reduction of target lesions was achieved after 6 weeks of treatment and resolution of the majority

Table 1. Baseline patient and disease characteristics.

Characteristic	*N* = 19 Number of patients (%)
Age at registration, years	
Median (range)	50 (35–71)
Race	
White	17 (89.5%)
Black or African American	2 (10.5%)
ECOG PS at baseline	
0	12 (63.2%)
1	7 (36.8%)
Stage at initial diagnosis	
I	1 (5.3%)
II	5 (26.3%)
III	5 (26.3%)
IV	5 (26.3%)
Not IV, but otherwise unknown	3 (15.8%)
Disease-free interval	
≤2 years	5 (26.3%)
>2 years	9 (47.4%)
Stage IV disease at diagnosis	5 (26.3%)
Hormone receptor status of primary tumor	
ER and PR positive	7 (36.8%)
ER positive/PR negative	2 (10.5%)
ER negative/PR positive	1 (5.3%)
ER and PR negative	9 (47.4%)
HER2 status of primary tumor (IHC)	
Negative (0, 1+)	2 (10.5%)
Equivocal (2+)	0 (0%)
Positive (3+)	13 (68.4%)
Not done	4 (21.1%)
HER2 status of primary tumor (FISH)	
Negative (copy number <4 and HER2/CEP17 ratio <2.0)	0 (0%)
Equivocal (4≤ copy number <6 and HER2/CEP17 ratio <2.0)	1 (5.3%)
Positive (copy number ≥6 or HER2/CEP17 ratio ≥2.0)	8 (42.1%)
Not done	10 (52.6%)
Measurable extracranial disease by RECIST 1.1 at baseline	
Yes	7 (36.8%)
No	12 (63.2%)
Tissue available at baseline	
Yes	17 (89.5%)
No	2 (10.5%)
Lines of chemotherapy for metastasis or recurrence	
None	1 (5.3%)
1 line	4 (21.1%)
2 lines	6 (31.6%)
>2 lines	8 (42.1%)
Prior brain surgery	
Yes	6 (31.6%)
No	13 (68.4%)
Prior brain radiation	
WBRT	9 (47.4%)
SRS	11 (57.9%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

of smaller lesions. Patient No. 7 experienced symptomatic progression after 49 weeks with growth of nontarget brain lesions. Patient No. 10 presented with brain lesion progression (around 10, two target lesions) while on trastuzumab/pertuzumab maintenance continued after brain resection and stereotactic radiation 14.8 months before enrollment. Trastuzumab and pertuzumab were initially started 4 years before enrollment after induction chemotherapy for *de novo* HER2+ metastatic breast cancer. Patient No. 10 experienced PR after 6 weeks (~40% reduction of target lesions) and best response at 18 weeks (~48% reduction of target lesions). Patient No. 10

Table 2. CNS best response by RANO-BM criteria.

Best response	Number of patients (%)	90% CI
ORR	2 (10.5%)[a]	1.9%–29.6%
CBR ≥ 24 weeks	6 (31.6%)	14.7%–53.0%
CBR ≥ 18 weeks	8 (42.1%)	23.0%–63.2%
CR	0 (0%)	—
PR	4 (21.1%)	7.5%–41.9%
Confirmed PR	2 (10.5%)	1.9%–29.6%
Stable disease	11 (57.9%)	36.8%–77.0%
Progression/relapse	4 (21.1%)	7.5%–41.9%

Abbreviation: CR, complete response.
[a]Two confirmed cases and two unconfirmed case (cases 5 and 12).

experienced disease progression in target and nontarget brain lesions after 31 weeks. Both patients 7 and 10 had HER2 3+ IHC primary tumors and brain metastases. Of the two unconfirmed responses, patient No. 5 received five fractions of radiation on target lesions 12 months after enrollment. Based on timing, the PR was attributed to radiation; patient No. 12 did not maintain the PR seen after 6 weeks, with progression at next the scan review (12 weeks).

The CBR was 42.1% at 18 weeks and 31.6% at 24 weeks (**Fig. 1**). When extracranial disease was evaluated by RECIST 1.1 criteria, 4/19 patients (21.1%) had clinical benefit at 24 weeks of treatment (Supplementary Fig. S1; Supplementary Table S4). The median bicompartmental PFS was 12.1 months (95% CI, 11.4–NA; Supplementary Fig. S2). The trial was discontinued after stage 1 because fewer than four patients had a confirmed CNS response.

Safety

No DLT were observed in the first six patients. Seven patients (36.8%) required a dose delay or hold (Supplementary Table S5). In one patient, atezolizumab was discontinued after cycle 16 because of diarrhea and immune-related colitis. Five experienced grade 2 to 3 diarrhea, of which four (80%) attributed to atezolizumab and pertuzumab. One patient experienced grade 3 diarrhea that was attributed to trastuzumab. The most frequent side effects reported at any grade were diarrhea (26.3%) and fatigue (26.3%). Diarrhea and fatigue required a dose reduction or hold of all study medications. Two patients

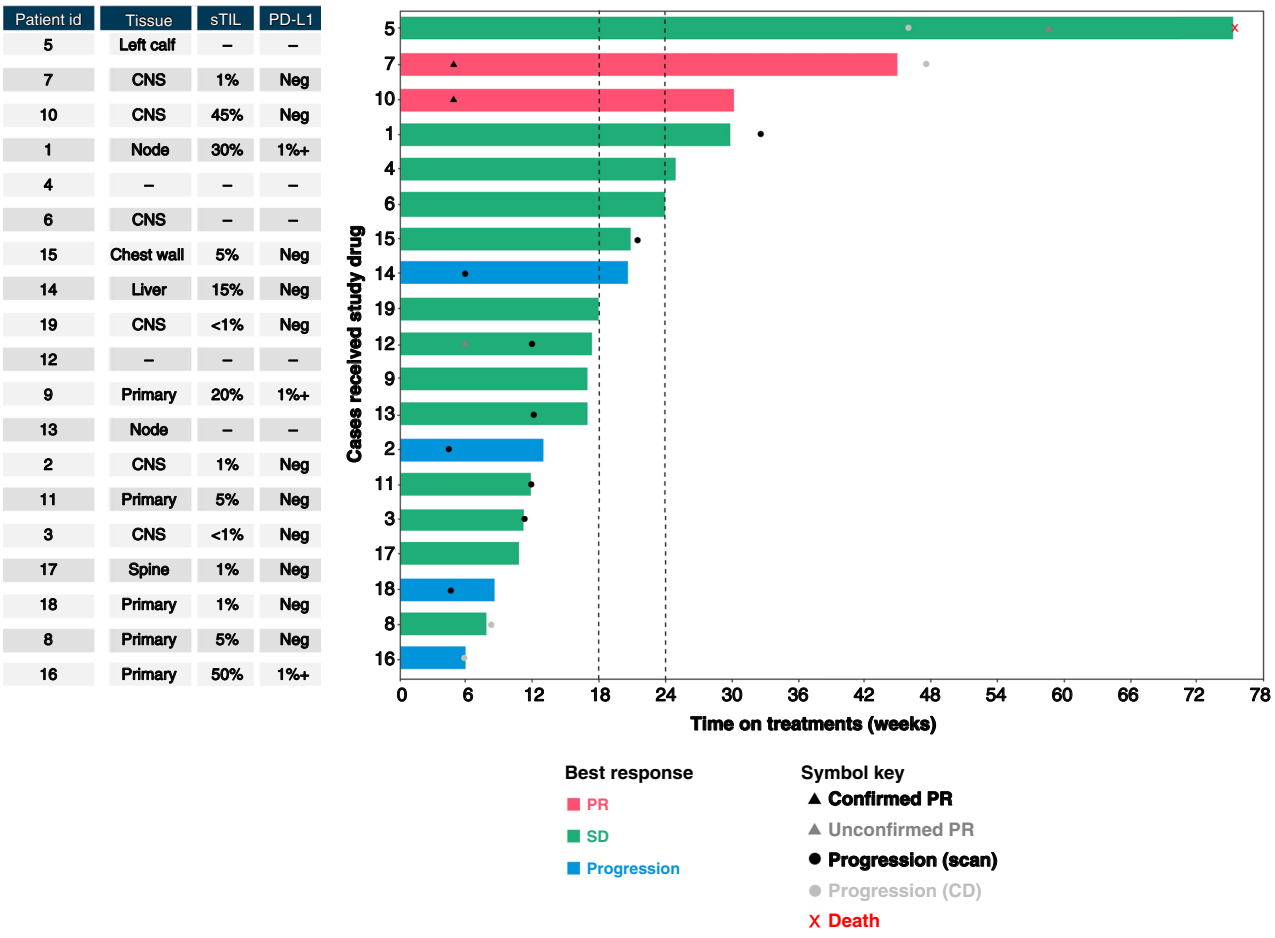

Figure 1.
Duration of clinical benefit in the CNS at 18 and 24 weeks ($n = 19$) by RANO-BM criteria. Data on response rates for patients with confirmed CR, PR, or SD. Single enrolled patients are represented including tissue origin for sTIL and PD-L1 evaluation. CR, complete response; SD, stable disease.

Table 3. AESI reported in this study.

AESI	Any-grade AESI Number of patients (%)	Grade 3/4 AESI Number of patients (%)
Immune-related hepatitis	0 (0%)	
Liver enzyme abnormalities	0 (0%)	
Hypothyroidism	2 (10.5%)	
Hyperthyroidism	0 (0%)	
Pneumonitis	0 (0%)	
Immune-related meningoencephalitis	0 (0%)	
Diarrhea	4 (21.1%)	1 (5.3%)
Immune-related adrenal insufficiency	0 (0%)	
Immune-related pancreatitis	0 (0%)	
Hyperglycemia	1 (5.3%)	1 (5.3%)
Immune-related nephritis	0 (0%)	
Other AESI occurring in ≥1% of patients		
Immune-related rash	2 (10.5%)	1 (5.3%)
Infusion-related reactions	0 (0%)	

(10.5%) experienced asymptomatic left ventricle ejection fraction (LVEF) reduction (from 61% to 47% and from 65% to 53%, respectively). For patient No. 12, an echocardiogram repeated after 5 days showed a LVEF within normal limits (57%), and treatment was resumed without further interruption. For patient No. 19, LVEF reduced from 65% (baseline) to 53% (time of treatment discontinuation). A follow-up echocardiogram 6 months after treatment discontinuation showed an LVEF of 59%. Adverse events of special interest (AESI) of any grade and related to atezolizumab were diarrhea (21.1%), hypothyroidism (10.5%), and hyperglycemia (5.3%; **Table 3**). Grade 3 AESI were diarrhea, hyperglycemia, and maculopapular rash (5.3% for each, respectively). One patient had to discontinue atezolizumab because of AESI (diarrhea). A complete list of adverse events related to study drugs and with at least 10% rate is provided in **Table 4**.

Table 4. Adverse events possibly, probably, or definitely related to study treatment.

Adverse event	*N* = 19 Any grade	Grade 2	Grade 3
Any adverse event	16 (84.2%)	10 (52.6%)	6 (31.6%)
Diarrhea	5 (26.3%)	3 (15.8%)	2 (10.5%)
Fatigue	5 (26.3%)	5 (26.3%)	0 (0%)
Anemia	2 (10.5%)	0 (0%)	2 (10.5%)
Arthralgia	2 (10.5%)	2 (10.5%)	0 (0%)
Ataxia	2 (10.5%)	2 (10.5%)	0 (0%)
Ejection fraction decreased	2 (10.5%)	2 (10.5%)	0 (0%)
Fall	2 (10.5%)	2 (10.5%)	0 (0%)
Generalized muscle weakness	2 (10.5%)	1 (5.3%)	1 (5.3%)
Headache	2 (10.5%)	2 (10.5%)	0 (0%)
Hypothyroidism	2 (10.5%)	2 (10.5%)	0 (0%)
Lymphocyte count decreased	2 (10.5%)	0 (0%)	2 (10.5%)
Nausea	2 (10.5%)	2 (10.5%)	0 (0%)
Platelet count decreased	2 (10.5%)	1 (5.3%)	1 (5.3%)
Rash maculopapular	2 (10.5%)	1 (5.3%)	1 (5.3%)
White blood cell decreased	2 (10.5%)	2 (10.5%)	0 (0%)

Only adverse events with >10% rate are shown. No adverse events of grade 4 or 5 were observed.

Correlative analyses

Archival tissue was available in 17 patients (89.5%), six of which were CNS tissues and five from primary breast tumors. In the six patients with CNS lesions assessed for receptors, five had concordant HER2 expression between the primary tumor and CNS (patients 3, 6, 7, 10, and 19), whereas one had a discordant value (HER2 positive on the primary specimen and HER2-negative in the CNS specimen, patients No. 2). Values of sTIL and PD-L1 are presented for each patient in **Fig. 1**. TMB for each sample is listed in Supplementary Table S6. Although the sample size is too small to achieve statistical significance, we did not observe any correlation between clinical responses and the presence of TIL, PD-L1, and TMB (P value = 1).

Based on provider-rated (NANO Scale) and PRO (MD Anderson Symptom Inventory-Brain Tumor or EQ-5D) evaluations, we identified a trend toward improvement of neurologic examination and symptoms (**Fig. 2A**), cancer-related symptoms (**Figs. 2B** and **C**), and general health status (**Fig. 2D**) in patients receiving clinical benefit.

Discussion

In this phase II study, we evaluated the safety and activity of atezolizumab, pertuzumab, and high-dose trastuzumab in patients with HER2-positive breast cancer with progressive brain metastases. Although 11% of patients achieved confirmed CNS responses and approximately one-third of patients achieved clinical benefit at 24 weeks, the study did not meet the prespecified efficacy threshold and was thus terminated early per protocol.

At the time the current study was designed, mature data from the phase II PATRICIA study testing the backbone of pertuzumab and high-dose trastuzumab used in the current study were not yet available (19). Since then, the final results of the PATRICIA study have been published, which reported a CNS response rate of 11% (95% CI, 3.0%–25.4%) with a median duration of response of

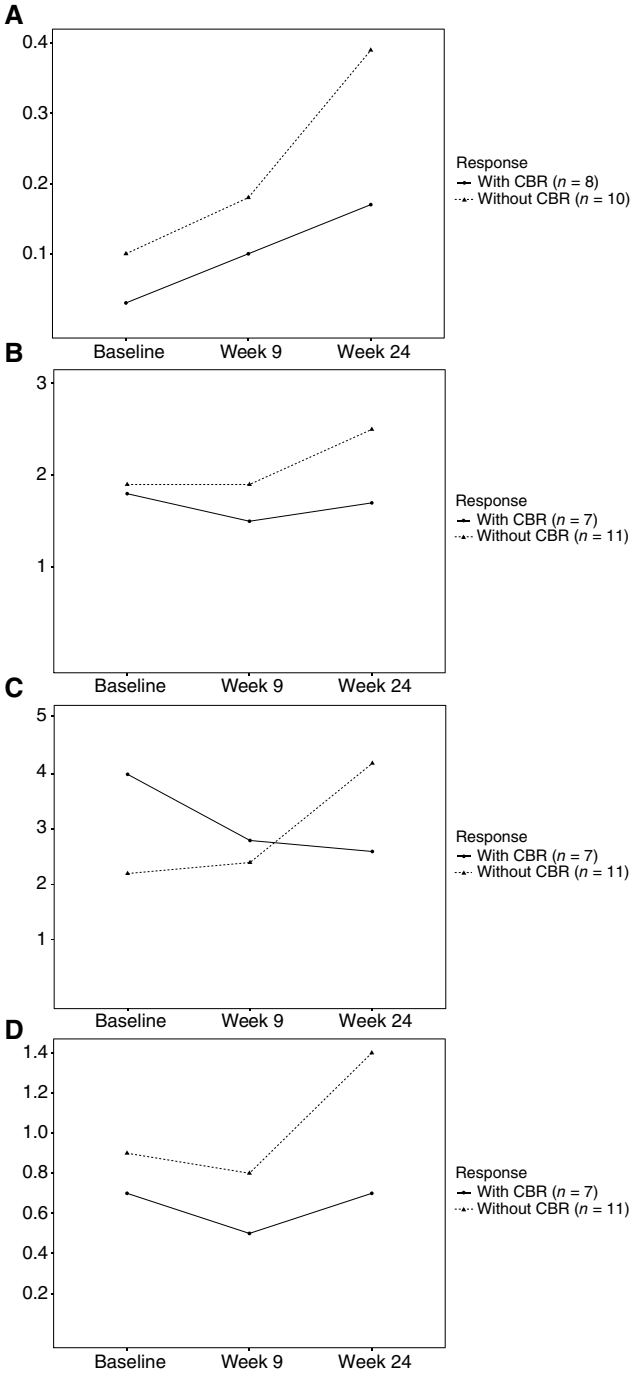

Figure 2.

Provider-rated neurological exam and PRO. **A,** NANO scale by CBR duration ≥18 weeks vs. <18 weeks. Mean scores are reported, and a higher score indicates worse neurologic function. **B,** Mean MDASI-BT scores over time by CBR duration ≥18 weeks vs. <18 weeks. Symptom severity score. Mean scores are reported, and a higher score indicates worse symptom severity. **C,** Mean MDASI-BT scores over time by CBR duration ≥18 weeks vs. <18 weeks. Symptom interference score. Mean scores are reported, and a higher score indicates greater symptom interference on daily life. **D,** General health status assessed by EQ-5D by CBR duration ≥18 weeks vs. <18 weeks. Mean scores are reported, and a higher score indicates worse health status. MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor.

4.6 months (95% CI, 3.3%–5.6%) and a 6-month CNS-CBR of 51% (95% CI, 34.4%–68.1%; ref. 38). In the absence of a randomized design, it is possible that atezolizumab contributed to the clinical benefit observed. However, the results of our study do not support a convincing additive benefit of atezolizumab to the pertuzumab/high-dose trastuzumab backbone. At the same time, we believe that results of the study provide confirmation of intracranial activity and clinical benefit of the pertuzumab/high-dose trastuzumab regimen and support the continued inclusion of this regimen in treatment guidelines (39).

To explore whether a subset of patients may have benefited from the addition of checkpoint blockade, we evaluated PD-L1 status, sTIL, and TMB on archival tissues in responders versus nonresponders and in those who achieved 24-week clinical benefit versus not, as a hypothesis-generating analysis. We did not observe any trends in favor of these biomarkers and clinical outcomes. Furthermore, we evaluated PD-L1 status and sTIL in the five patients in whom we had access to archival brain metastasis resection tissue. Unexpectedly, given prior reports of high rates of PD-L1 positivity in brain metastases (26), none of the five patients had PD-L1–positive tumors using the SP142 assay. In addition, sTIL were only found in one of five patients with CNS tissue available, and TMB was conducted from CNS only in four patients. Whether this is due to differences in prior treatment exposure, preanalytic variation in tissue handling or storage, or simply due to chance is unclear.

Importantly, the combination of atezolizumab with pertuzumab and high-dose trastuzumab did not lead to the emergence of new safety signals. No increase in the incidence of cardiotoxicity was observed with high-dose trastuzumab plus atezolizumab, supporting results of earlier studies that explored higher doses and more intensive dosing of trastuzumab versus the approved regimen (19). Two patients experienced a transient LVEF reduction that recovered without intervention and further interruptions (Supplementary Table S5). Rates of immune-related adverse events were similar to prior studies with the combination of atezolizumab and anti-HER2 therapy (40–42).

Strengths of our study were the inclusion of prospective provider-rated evaluation of the neurologic function (via the NANO scale) and inclusion of PRO instruments designed for use in people with brain tumors. We observed qualitative differences in scores between patients who achieved clinical benefit versus not, further supporting the validity of these scales to assess the clinical value of interventions in patients with breast cancer brain metastases. Similar differences in PRO trends in patients with versus without clinical benefit were observed in the PATRICIA study that tested pertuzumab with high-dose trastuzumab (38).

Although preclinical data provide a strong rationale for combining cancer immunotherapy with HER2-targeted therapy, the results of clinical trials in patients with HER2-positive breast cancer have generally been disappointing. The single-arm phase Ib/II PANACEA study evaluated trastuzumab plus pembrolizumab in patients with trastuzumab-resistant advanced HER2-positive breast cancer. During the phase II portion of the study, the ORR was 15% in patients with PD-L1–positive disease, with a 25% disease control rate at 24 weeks. Although the ORR was low, patients with PD-L1–positive disease were most likely to benefit, which inspired hope that greater efficacy could be achieved by pairing immune checkpoint inhibitors with more effective HER2-directed backbones in properly selected patients (43).

The randomized phase II KATE2 trial subsequently evaluated the combination of the PD-L1 inhibitor atezolizumab with the antibody-drug conjugate trastuzumab emtansine (T-DM1) in patients with pretreated HER2-positive metastatic breast cancer. Unfortunately, the addition of atezolizumab to T-DM1 did not result in a clinically meaningful PFS benefit in the intention-to-treat

population (41). A trend to longer OS was observed in the PD-L1–positive population, supporting ongoing evaluation of this combination in the ongoing randomized phase III KATE3 (44) and ASTEFANIA (45) trials.

For patients with high-risk early-stage HER2-positive breast cancer, the randomized, placebo-controlled, phase III IMpassion050 trial evaluated the efficacy and safety of neoadjuvant atezolizumab or placebo in combination with trastuzumab, pertuzumab, and chemotherapy. Unfortunately, the addition of atezolizumab did not increase the pathologic complete response rate versus placebo in the intention-to-treat or PD-L1–positive populations (40). In the phase III APTneo trial, the addition of atezolizumab to neoadjuvant trastuzumab plus pertuzumab and chemotherapy led to a numerical, but not statistically significant, increase in pathologic complete response versus trastuzumab plus pertuzumab/chemotherapy alone in patients with HER2-positive operable breast cancer (46). NRG-BR004 was a phase III, placebo-controlled trial designed to determine whether the addition of atezolizumab to paclitaxel, trastuzumab, and pertuzumab would improve PFS relative to paclitaxel, trastuzumab, and pertuzumab/placebo in patients with newly documented HER2-positive measurable metastatic breast cancer. The study was terminated early because of four grade 5 adverse events in the experimental arm (47). Finally, in a phase II trial of pembrolizumab in patients with brain metastases across diverse histologies, 16 patients with HER2-positive breast cancer were included. Patients were allowed to continue on trastuzumab at a standard dose and schedule (e.g., not high-dose). Although stable disease was observed, no patients with HER2-positive breast cancer achieved a confirmed intracranial response (48).

As this study was designed, several treatment regimens have shown intracranial and extracranial activities in patients with HER2-positive breast cancer brain metastases. Neratinib was evaluated in the phase II Translational Breast Cancer Research Consortium 022 clinical trial. As monotherapy, neratinib was associated with a CNS-ORR of 8% and a CBR of ~20% at 4 months; in combination with capecitabine, a CNS-ORR of 49% was observed (11, 49). 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; the CBR at 4 months in each group was 35% and 53%, respectively (50). In the randomized phase II HER2CLIMB trial, among 291 patients with brain metastases, the addition of tucatinib to trastuzumab and capecitabine significantly reduced the risk of progression in the brain or death by 68% versus placebo plus trastuzumab and capecitabine (HR, 0.32; 95% CI, 0.22%–0.48%; $P < 0.0001$). Among 75 patients with active brain metastases and measurable intracranial disease at baseline, the addition of tucatinib to trastuzumab and capecitabine significantly increased the CNS ORR versus placebo (47.3% versus 20.0%; $P = 0.03$; ref. 16). In the randomized phase III HER2CLIMB-02 trial, the combination of T-DM1 plus tucatinib resulted in a median PFS of 7.8 months versus 5.7 months with T-DM1 plus placebo among patients with brain metastases (HR, 0.64; 95% CI, 0.46%–0.89%; ref. 51). Among patients with brain metastases who enrolled in the randomized phase III TROPION-Breast01 trial, datopotamab deruxtecan produced a median PFS of 5.6 months versus 4.4 months for chemotherapy (HR, 0.73; 95% CI, 0.39%–1.42%; ref. 52). Finally, accumulating data suggest a potential intracranial efficacy of trastuzumab deruxtecan (13–15). In a pooled analysis of the DESTINY-Breast01, 02, and 03 clinical trials, trastuzumab deruxtecan consistently demonstrated superior rates of intracranial response over comparator in patients with treated/stable (45.2%) and untreated/active brain metastases (45.5%; ref. 53).

Our study had several limitations. First, we did not include a comparator arm without atezolizumab; thus, we cannot exclude its contribution to the activity of pertuzumab with high-dose trastuzumab. Second, the sample size was very small, and the trial stopped early due to lack of sufficient activity. The study was also not powered to assess subgroup analyses, and none of the correlative studies identified a biomarker of response to this regimen. In addition, the archival tissue was collected from different sites of disease, including the primary breast tumor, distant metastasis, and CNS tissue. Finally, HER2 status was not assessed centrally.

In conclusion, our phase II study showed that the addition of atezolizumab to pertuzumab and high-dose trastuzumab did not produce clear CNS benefit in patients with HER2-positive breast cancer with CNS metastases beyond that which would have been expected with pertuzumab and high-dose trastuzumab alone. However, the study was limited by the low proportion of patients with PD-L1 tumors and by the single-arm design and does not rule out the potential for immunotherapy to result in clinical benefit in biomarker-enriched populations. Further studies of immunotherapy plus anti-HER2 therapy should include distinct agents other than PD-1/PD-L1 inhibitors.

Authors' Disclosures

A. Giordano reports personal fees from Pfizer outside the submitted work. P.U. Kumthekar reports personal fees from Seagen, Belay Diagnostics, Plus Therapeutics, Servier, Telix Pharmaceuticals, Biocept, Novocure, Bioclinica, EnClear Therapeutics, Biodexa, BPGbio, and IN8bio and grants and nonfinancial support from Genentech/Roche outside the submitted work. J.P. Leone reports other support from Kazia Therapeutics, Seagen, AstraZeneca, Eli Lilly and Company, and Minerva Biotechnologies outside the submitted work. E.A. Mittendorf reports other support from AstraZeneca, BioNTech, Merck, Moderna, Bristol Myers Squibb, Roche Genentech, and Gilead; personal fees from Merck Sharp & Dohme; and grants from Roche Genentech and Komen for the Cure outside the submitted work. E.L. Mayer reports other support from Eli Lilly and Company, Novartis, and AstraZeneca outside the submitted work. S.M. Tolaney reports grants from Genentech during the conduct of the study, as well as grants and personal fees from Novartis, Merck, AstraZeneca, Genentech/Roche, Eisai, and Bristol Myers Squibb; grants, personal fees, and other support from Pfizer, Eli Lilly and Company, Gilead, and Jazz Pharmaceuticals; personal fees and other support from Sanofi, personal fees from CytomX Therapeutics, Daiichi Sankyo, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, Sumitovant Biopharma, Umoja Biopharma, Artios Pharma, Menarini/Stemline, Aadi Bioscience, Bayer, Incyte Corporation, Natera, Tango Therapeutics, SystImmune, eFFECTOR, Hengrui USA, Cullinan Oncology, Circle Pharma, Arvinas, BioNTech, and Johnson & Johnson; and grants from NanoString Technologies, Seattle Genetics, and OncoPep outside the submitted work. N.U. Lin reports grants from Roche/GNE during the conduct of the study, as well as grants and personal fees from Genentech, Pfizer/Seagen, AstraZeneca, and Olema Pharmaceuticals; grants from Zion Pharmaceuticals and Merck; and personal fees from Stemline/Menarini, Artera Inc., Daiichi Sankyo, Blueprint Medicines, Janssen, and Eisai outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

A. Giordano: Data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **P.U. Kumthekar:** Data curation, formal analysis, validation, investigation, visualization, methodology, writing–review and editing. **Q. Jin:** Data curation, formal analysis, validation, investigation, visualization, writing–review and editing. **B. Binboga Kurt:** Data curation, formal analysis, validation, investigation, visualization, writing–review and editing. **S. Ren:** Data curation, formal analysis, validation, investigation, visualization, writing–review and editing. **T. Li:** Data curation, formal analysis, validation, investigation, visualization, writing–review and editing. **J.P. Leone:** Data curation, validation, investigation, visualization, writing–review and editing. **E.A. Mittendorf:** Resources, data curation, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–review and editing. **A.M. Pereslete:** Data curation, validation, investigation, visualization, project administration, writing–review and editing. **L. Sharp:**

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Acknowledgments

Genentech, Inc. provided funding support and all doses of atezolizumab, pertuzumab, and trastuzumab used in this trial. Additional funding support was provided by the Breast Cancer Research Foundation (to N.U. Lin) and the Lili Billings Fund for Metastatic Breast Cancer Research. The authors thank Timothy K. Erick for medical writing and editing assistance and Kaitlyn T. Bifolck for editing and submission assistance. Both are full-time employees of Dana-Farber Cancer Institute.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received April 26, 2024; revised June 27, 2024; accepted August 29, 2024; published first September 3, 2024.

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