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CLINICAL TRIAL

Phase II study of irinotecan and temozolomide in breast cancer patients with progressing central nervous system disease

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Abstract

Purpose Breast cancer patients with progressing central nervous system (CNS) disease have limited treatment options. Few chemotherapy drugs with activity in breast cancer have well-documented CNS penetration. This phase 2 trial evaluated efficacy and safety of irinotecan 125 mg/m^2 on days 1 and 15 with temozolomide 100 mg/m^2 days 1–7 and days 15–21 of a 28 day cycle.

Methods Breast cancer patients of any biological subtype and progressing brain metastases and/or leptomeningeal disease (LMD) were eligible. The primary endpoint was CNS response rate. Secondary endpoints were clinical benefit rate (CBR), time to progression (TTP), and overall survival (OS). Imaging studies evaluating intracranial and extracranial response were performed every 8 weeks.

Results Thirty patients were evaluable for safety and efficacy. The most common hematologic and non-hematologic adverse events were neutropenia, and nausea and fatigue, respectively. There were two confirmed CNS partial responses (PR) and five patients with stable disease in the CNS $\geq$ 16 weeks, resulting in a 7% PR and 23% CBR. Median TTP was 2.3 months (range 13–444 days), and median OS from treatment initiation until death was 4.9 months (range 20–1023 days). Excluding patients with LMD, median TTP and OS were 3.1 and 5.6 months, respectively. Only one patient progressed systemically before CNS progression.

Conclusions The combination of irinotecan and temozolomide was well tolerated, demonstrated some clinical activity across multiple breast cancer subtypes with progressing CNS disease, and offers a reasonable option for patients who are not candidates for further radiation or clinical trials.

Keywords Breast cancer · Brain metastases · Chemotherapy · Clinical trial · Irinotecan · Temozolomide

Introduction

As women live longer with metastatic breast cancer, an increased prevalence of brain metastases and leptomeningeal carcinomatosis has been reported, with nearly 50% of patients with triple negative or HER2/neu positive disease developing central nervous system (CNS) metastases [1, 2]. Initial treatment of brain metastases includes whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS), and occasionally surgery. Patients whose tumors do not respond to radiation, or who develop new or recurrent metastases after WBRT or SRS have limited treatment options. Despite an increasing number of clinical trials available for this population, eligibility criteria often exclude patients with poor performance status or cytologically proven leptomeningeal disease (LMD). In addition, breast cancer patients are often heavily pretreated and concurrent progression of systemic disease further complicates treatment.

Few systemic chemotherapies with significant activity in breast cancer are documented to accumulate at similar concentrations in brain metastases as in systemic metastases such as the liver. This is in part due to the blood brain barrier, drug efflux pumps in the CNS, and potentially increased intralesional pressure in CNS disease [3]. However, systemic therapies including capecitabine, lapatinib, and neratinib

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have efficacy against both treated and untreated brain metastases, and administration of these agents may delay the need for WBRT or SRS [4–8]. Additionally there are case reports and small studies describing CNS responses to other agents including TDM-1 and everolimus [9–11]. Given the limitations and long-term toxicities of radiation, there is increasing interest in investigating systemic therapies to treat systemic and CNS disease concurrently.

Temozolomide (TMZ) is an orally administered alkylating agent that crosses the blood brain barrier and is FDA approved for the treatment of primary brain tumors. TMZ as a single agent has demonstrated modest activity, mostly stable disease, in brain metastases from melanoma, lung, and breast cancer [12]. Irinotecan has systemic activity against refractory metastatic breast cancer and represents a chemotherapy option for heavily pretreated patients [13]. Novel pegylated and liposomal formulations of irinotecan are currently being studied for breast cancer patients with CNS disease [14].

We investigated the safety and efficacy of the combination of irinotecan and temozolomide in breast cancer patients with CNS metastases and/or LMD who had progressed after WBRT and/or SRS or who declined standard therapy.

Methods

Patient selection

Patients with breast cancer and radiographically confirmed progression of previously treated CNS metastases or development of new brain metastases measuring > 5 mm after prior treatment with WBRT or SRS were eligible, unless standard therapy was declined. Patients with cerebrospinal fluid (CSF) cytology positive for carcinoma or enhancement of meninges consistent with LMD who had either progressed after radiation or intrathecal chemotherapy were also eligible. There was no limit on number of prior chemotherapy regimens for metastatic disease; prior treatment with irinotecan was not permitted, unless there was no evidence of systemic progression on irinotecan. Prior therapy with temozolomide was permitted.

Additional eligibility requirements included a life expectancy of at least 4 weeks, an ECOG performance status ≤ 2, a creatinine level ≤ 2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 times the upper limit of normal (ULN) or ≤ 5 times ULN with liver metastases, and total bilirubin ≤ 1.5 times the ULN (≤ 2 times the ULN with liver metastases). Patients were required to have adequate bone marrow function at baseline with platelets ≥ 100,000/mm^3 and absolute neutrophil count (ANC) ≥ 1000 cells/mm^3. Treatment with enzyme inducing anti-epileptic was prohibited. Patients were required to be on a stable dose of steroids within 1 week of baseline imaging.

Study design

The primary endpoints of the study were to determine the objective response rate (ORR) in the CNS to the combination of irinotecan and temozolomide, as well as to determine toxicities associated with this regimen. Secondary endpoints included clinical benefit rate (CBR), time to first progression at any site, overall survival (OS), and quantification of circulating tumor cells (CTCs) in the peripheral blood. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria v3.0 [15]. The study was approved by our institution's Committee on Human Research. Informed consent was obtained in writing from each patient before any study-specific activities occurred.

Treatment

Irinotecan was administered intravenously at 125 mg/m^2 on days 1 and 15 of a 28-day cycle, with temozolomide 100 mg/m^2 by mouth for 7 days on days 1–7 and days 15–21 every 28 days. Patients with HER2 positive breast cancer were allowed to continue trastuzumab in combination with study therapy. Treatment continued until occurrence of unacceptable toxicity or evidence of progression of brain metastases or leptomeningeal disease. Patients who experienced progression systemically, but maintained stable or responsive disease in the CNS were allowed to continue protocol therapy if it was felt to be in their best interest by the treating investigator. The irinotecan dose was reduced for toxicity including prolonged ≥ grade 3 neutropenia, ≥ grade 3 thrombocytopenia, and persistent diarrhea (≥ grade 2). Anemia was managed with red blood cell growth factors or by transfusion. Granulocyte colony-stimulating factor (G-CSF) administration was allowed at the investigator's discretion. Temozolomide dose reductions were not mandated if there were adequate blood counts with the use of G-CSF.

Evaluations

Patients underwent complete history and physical examination and evaluation of baseline symptoms, neurologic function, and performance status prior to study entry. Baseline imaging studies were performed to assess the extent of cranial and extracranial disease including MRI of the brain (and spine if the patient had LMD), computed tomography of the chest, abdomen, and pelvis, and bone scan if clinically indicated. PET/CT scan with contrast enhanced CT could be used in place of CT and bone scan.

A complete physical exam with neurological exam including level of alertness and orientation, cranial nerve

function (II-XII), extremity strength, gait, sensation, and balance was performed before study entry and every 2 weeks. Baseline laboratory studies included a complete blood cell and differential count, urinalysis, blood chemistry levels, and a serum pregnancy test in patients of childbearing potential. Complete blood cell and differential counts, electrolytes, creatinine, and liver function tests were checked every 2 weeks on study. Toxicity was assessed by the clinician on day 1 and 15 of each cycle. Compliance with temozolomide dosing was confirmed through verbal confirmation from the patient to the clinician at the time of each visit and through pill count by the experimental pharmacist when the patient returned bottles at the start of each new cycle.

Imaging assessments as described above were performed at 8-week intervals to assess response to treatment. RECIST 1.0 criteria were used to assess response systemically [16]. Response rates for patients with new or progressing parenchymal brain metastases (measuring at least 5 mm) were determined using a modified RECIST criteria in which CNS lesions < 1 cm were not considered measurable, but were considered evaluable for response. Progressive disease for patients with lesions < 1 cm was defined as follows: growth of a lesion from less than or equal to 5 mm to greater than or equal to 10 mm; or, growth of a 6–9 mm lesion by at least 5 mm in the case of non-target parenchymal brain metastases.

Patients with known or suspected LMD underwent a lumbar puncture or had CSF accessed via Ommaya to evaluate CSF cytology at baseline, week 2, week 4, and every 4 weeks thereafter. They also underwent baseline and follow-up MRIs of the brain and spine every 8 weeks. These patients were deemed to have a complete response (CR) if their CSF cytology converted to negative (if positive at baseline) and remained negative on at least one subsequent follow-up sampling, and all meningeal enhancement or nodularity on brain and/or spine MRI resolved. Patients were deemed to have progressive disease (PD) if there was extension of distribution of leptomeningeal enhancement or increase in the amount of thickness or caking at sites of known LMD. Stable disease (SD) was defined as no change in distribution of leptomeningeal enhancement or increase in the amount of thickness or caking at sites of known LMD and no progression of neurologic symptoms.

Radiographic images were evaluated through standard clinical review by radiologists not affiliated with the study. Determination of response, stable disease, or progression was determined by the investigators based on scans and reports generated for clinical care.

Circulating tumor cells (CTCs) were measured in blood at baseline and at 8 weeks using the Cellsearch® assay [17]. Seven and a half ml of blood was collected in Cell Save tubes and processed as described. Results are presented as cells per 7.5 ml.

Statistical analysis

The primary efficacy parameter was the objective response rate (ORR) in the CNS. All patients who received at least one dose of study drug and who had documented brain metastases and/or LMD were included in the safety analysis. ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR) in the CNS. Clinical benefit (CB) was defined as patients with a CR, PR, or SD in the CNS at ≥ 16 weeks. Patients who died, progressed in the CNS, progressed in non-CNS site(s), or withdrew from the study for any reason after their first dose and before CNS response was documented by MRI were considered CNS-non-responders.

This study had a two-stage design, with 12 patients entered in the first stage [18]. If at least one of the first 12 patients had CB (a response or stable disease in the CNS for ≥ 16 weeks), another 25 patients were planned be entered on study (for a total of 37). If at least 4 of these 37 had CB at 16 weeks, the combination would be deemed to be worthy of future study. With this design, the probability of stopping the trial early was 0.54 if the true CB rate was 5% and 0.07 if the true CB rate was 20%. The probability of deeming the treatment worthy of further study was 0.10 if the true CB rate was 5% and 0.90 if the true CB rate was 20%.

All comparisons on TTP and OS between biological subsets of interest and between patients with or without LMD were conducted using Kaplan–Meier methods using log-rank tests for significance. Because of the small number of patients in each group, these comparisons were completely exploratory.

Results

Thirty patients were enrolled between June 2006 and March 2012. Accrual was stopped early due to lack of funding and slow accrual (30 enrolled/37 planned). Patient demographics are listed in Table 1.

The most common non-hematologic grade serious adverse events (SAEs) were infection ($n = 4$) and hyponatremia ($n = 4$). There were no $\geq$ grade 4 non-hematologic toxicities. The most common hematologic SAEs were leukopenia [16.7% ($n = 5$) grade 3] and neutropenia [16.7% ($n = 5$) grade 3]. Table 2 summarizes adverse events occurring in at least 10% of patients and at least possibly related to study treatment.

Irinotecan dose was reduced to 100 mg/m^2 in three patients (two due to neutropenia, one due to thrombocytopenia) and reduced to 75 mg/m^2 in one patient (due to neutropenia). Temozolomide dose was also reduced to 75 mg/m^2 in two patients with concurrent irinotecan dose reductions (one due to neutropenia and one due to thrombocytopenia).

Table 1 Patient demographics

Median age	53.5 years (range 31–83)
Median number of chemo regimens in metastatic setting	2 (range 0–9)
ECOG	*n* (%)
0 or 1	20 (67)
2	10 (33)
Biological subtype	
ER+ and/or PR+	17 (57)
HER2+ (ER+ or ER−)	14 (47)
Triple negative	6 (20)
CNS sites	
Brain metastases only	20 (67)
Brain metastases with leptomeningeal disease	7 (23)
Brain metastases with intramedullary spinal cord lesions	2 (7)
Leptomeningeal disease only	1 (3)
Prior radiation	
WBRT alone	18 (60)
Prior SRS alone	4 (13)
Prior WBRT and SRS	7 (23)
No prior radiation (Patient refused)	1 (3)
Prior systemic therapies	
Prior lapatinib (among HER2+)	9 (64)
Prior temozolomide for CNS disease	2 (7)
Prior capecitabine	9 (30)

Two patients (6.7%) had a confirmed PR. In one additional patient, there was a 33% decrease in the sum of diameters of CNS lesions. However, at the subsequent 8 week scan, the decrease in diameter was 16%, not meeting criteria for confirmed CNS PR. The three responding patients had different biologic subtypes: one patient had hormone receptor positive (HR+)/HER2/neu negative disease, one had triple negative disease, and one had HR negative/HER2/neu positive disease. There were 4 additional patients with CNS SD $\geq$ 16 weeks, representing a CBR of 23%. There were no responses in patients with LMD.

Median TTP for the entire population was 2.3 months (range 13–444 days), and median OS from initiation of study treatment until death was 4.9 months (range 20–1023 days). Only one patient progressed systemically before documented CNS progression. Figure 1 demonstrates a trend towards longer TTP in patients with brain and/or spinal cord metastases compared to those with both brain metastases and LMD (3.1 vs. 2 months, $p = 0.07$, log rank). Median OS in patients without LMD was 5.6 months versus 3 months for those with LMD ($p = 0.28$, log rank). There were no statistically significant differences in TTP or OS between different biologic subsets. Median TTP was 2.3 months in patients with HR+ disease (with any HER2 status), 2.6 months in the triple negative subset, and 2.9 months in patients with HER2 positive disease (any HR status). Median OS was 3.3 months in patients with HR+ disease (with any HER2 status),

Table 2 Adverse events

AE at least possibly related	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea	17	5	1		23
Fatigue	9	6	3		18
Vomiting	12	3	2		17
Anemia	6	8	3		17
Diarrhea	14	1	1		16
Neutropenia	1	7	5		13
Leukopenia	1	6	5		12
Thrombocytopenia	6	1	1	2	10
Infection	2	3	4		9
Rash	7	2			9
Neuropathy	6	1	1		8
Hypocalcemia	7	1			8
Mucositis	6	2			8
Constipation	6	2			8
Transaminitis	5		1		6
Hypokalemia	6				6
Anorexia	6				6
Dyspepsia	6				6
Hyponatremia	1		4		5
Dizziness	4	1			5

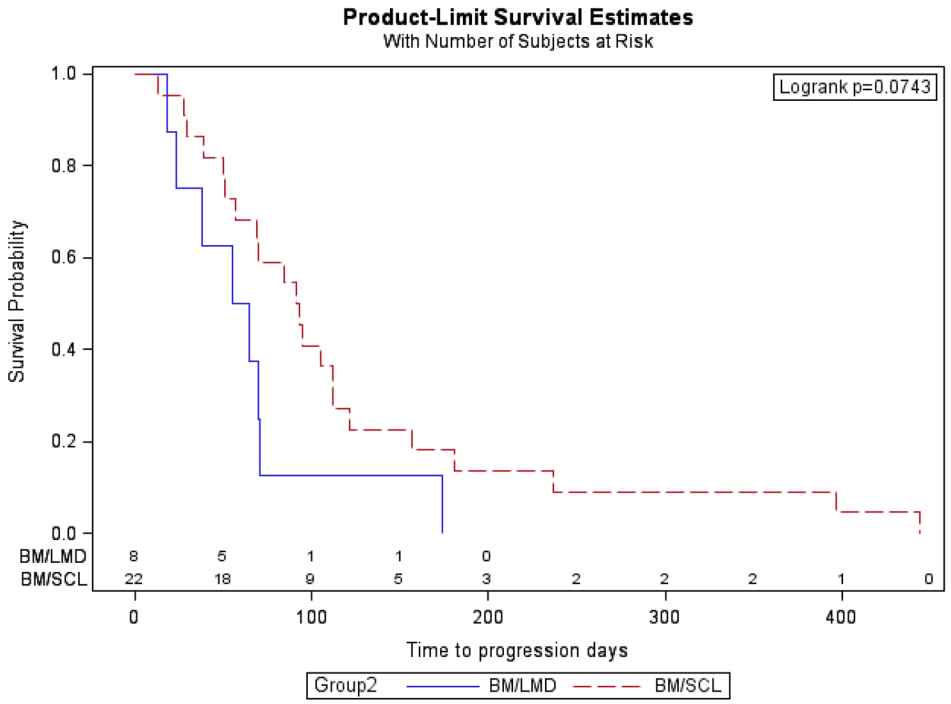

Fig. 1 Time to progression (with or without leptomeningeal disease). BM/LMD—patients with brain mets with LMD (solid line). BM/SCL—patients with brain and/or spinal cord mets without LMD (dotted line)

BM/LMD - Patients with brain mets with LMD (solid line)
BM/SCL – Patients with brain and/or spinal cord mets without LMD (dotted line)

4.6 months in the triple negative subset, and 5.0 months in patients with HER2 positive disease (any HR status).

CTCs were measured in the first 25 patients enrolled in the study; subsequent analyses were discontinued due to lack of funding. Mean and median baseline CTC values were 8.3 and 2.0 per 7.5 ml of blood, respectively. CTCs were measured in 15 patients at week 8 and mean and medians values declined to 1.0 and 0 cells per 7.5 ml of blood, respectively. There was no relationship between changes in CTC values in patients with CNS PR or SD compared to patients with CNS progression.

Discussion

The combination of irinotecan and temozolomide was well tolerated in patients with progressing brain metastases and/or LMD and demonstrated modest clinical activity across a spectrum of breast cancer biologic subtypes. This study allowed participation of patients with radiographically evident and/or cytologically positive LMD, although no responses were seen in this group. One-third of the patients had an ECOG of 2, suggesting this was a relatively ill population. We monitored CTCs in blood and observed a decrease over time in a subset of patients with serial samples. All but one patient had stable or responding systemic disease when they went off study due to CNS progression, and the decline in CTCs is consistent with systemic response to treatment. The number of CNS responses is too small to determine if decline in blood CTCs has any correlation to CNS response.

Although this trial was initiated over 11 years ago, there remains a paucity of published trials investigating systemic chemotherapies for progressing breast cancer brain metastases. Particularly rare are clinical trials enrolling patients with *all* breast cancer biological subtypes. In fact, a literature review revealed only 11 studies published since 2010 that report on CNS efficacy of systemic treatments without radiation for progressing brain metastases in advanced breast cancer (search date 5/19/19).

Pemetrexed was studied in 21 patients with solid tumors and progressive brain metastases [19]. Among 13 patients with breast cancer, a single response was seen. Median TTP and OS were 2.7 and 7.3 months, respectively. A phase II trial evaluated sagopilone, an epothilone analogue, in 15 breast cancer patients with progressive CNS disease after whole-brain radiotherapy [20]. Two PRs were observed (ORR, 13.3%), and median PFS and OS were 1.4 months and 5.3 months, respectively. The combination of irinotecan and iniparib (BSI-201) was studied in patients with triple negative breast cancer and progressing brain metastases [6]. Forty-six patients were enrolled, and 34 were evaluable for response. The intracranial PR rate was 12% and CB rate (PR or SD ≥ 6 months) was 27%. Median TTP was 2.1 months and median OS was 7.8 months.

Carboplatin and bevacizumab with or without trastuzumab was studied in patients with breast cancer (30 HER2 positive and 8 HER2 negative) and progressing brain metastases [21]. The composite CNS ORR was 63% and the CNS response rate by RECIST was 45%. Median PFS was 3.7 months among HER2 negative patients and 6.1 months in HER2 positive patients. Median OS was 12 months and 16 months, respectively. Similarly high response rates were observed in a phase 2 trial of bevacizumab given 1 day preceding cisplatin and etoposide in breast cancer patients with brain metastases refractory to whole brain radiotherapy [22]. In this study of 35 patients, the CNS ORR was 77% with 37% having a $\geq$80% volumetric reduction of CNS lesions. The median CNS PFS was 7.3 months and OS was 10.5 months.

It is interesting to note the very similar range of response and CB rates, TTP, and OS among these trials with the exception of the bevacizumab studies. There is some speculation that the effect of bevacizumab on MRI enhancement may give the appearance of imaging response, thereby explaining the dramatically higher response rates compared to other studies of similar populations, or that the observed responses included response in areas of radiation necrosis [23].

A number of trials have focused on HER2+ patients with brain metastases. In a phase 1 trial of lapatinib plus temozolomide, median PFS was 2.6 months and estimated median OS for 16 breast cancer patients was nearly 11 months [20]. In a phase Ib/II trial evaluating the combination of everolimus, lapatinib, and capecitabine in HER2-positive breast cancer with brain metastases (63% with prior radiation) the 12-week CNS ORR was 27% among 11 evaluable patients and median PFS and OS were 6.2 and 24.2 months, respectively [10]. Among 26 evaluable patients in a phase II study of everolimus, trastuzumab, and vinorelbine for progressive HER2-positive breast cancer brain metastases, ORR was 4%, CNS CBR at 6 months was 27%, median intracranial TTP was 3.9 months, and OS was 12.2 months [11]. In the TBCRC 022 trial, single agent neratinib demonstrated a CNS ORR of 8% with a median PFS of 1.9 months in HER2+ patients with progressing brain metastases [8]. In another cohort from this same trial, the combination of capecitabine and neratinib resulted in a 49% composite CNS response rate and a 24% response rate by RANO-BM in a lapatinib naïve population (cohort 3A) and a 33% composite CNS response rate in the lapatinib treated population (cohort 3B). Median PFS was 5.5 and 3.1 months in cohorts 3A and 3B, respectively, and median survival was 13.3 and 15.1 months [7].

The median OS observed in trials of HER2+ patients generally exceeds that observed in other studies, likely representing the improved prognosis observed in patients with metastatic HER2+ disease as compared to triple negative and hormone refractory advanced disease. Interestingly, in the multicenter LUX-Breast 3 trial of HER2-positive breast cancer with progressive brain metastases, afatinib alone or afatinib plus vinorelbine resulted in lower 12 week clinical benefit rates than treatment with investigator's choice (30% vs. 34.2% vs. 41.9%) [24].

In the BEACON trial investigating NKTR102, a pegylated version of irinotecan, versus treatment of physician's choice, a statistically significant improvement in overall survival was observed among patients with stable brain metastases upon study entry [14]. Although the BEACON trial did not meet its primary endpoint, the finding of better outcomes compared to other standard therapies in patients with a history of stable brain metastases is intriguing, and an ongoing phase III trial is evaluating this effect (ATTAIN trial, NCT02915744). The ATTAIN trial evaluates response and TTP systemically and in the CNS as well as OS in patients with metastatic breast cancer and stable brain metastases randomized to receive NKTR102 or chemotherapy of physician's choice [25].

This trial of irinotecan and temozolomide has several limitations, preventing direct comparison of outcomes to more recently published studies. First, the population studied was broad and heterogeneous, whereas many trials now limit enrollment to a specific biological subtype and investigate a targeted therapy for that subtype. Additionally, there was a high number (nearly one-third) of patients with LMD, who are anticipated to have a poorer prognosis and are frequently excluded from trials. Lastly, the CNS response criteria used in this trial is now outdated, as volumetric response, CNS composite response, or RANO-BM are now the more common response assessments utilized in therapeutic trials focusing on breast cancer metastatic to the CNS. In order to facilitate comparison of our results to more recent studies, we attempted to have the CNS imaging reread by an independent radiologist to generate volumetric response data. Because of the variability in scanning technique over the course of the study and the fact that some patients had scans at outside facilities, the images could not be reliably reconstructed to generate volumetric data for all patients. We were however, able to confirm, via retrospective chart review, that the patients with PRs and/or SD would have met CNS composite response criteria including no increase in steroid dose or deterioration in neurologic function.

In conclusion, the combination of irinotecan and temozolomide was found to be well tolerated and have modest clinical activity in patients with breast cancer and progressing CNS disease. Several patients experienced prolonged SD and survival after progression of their brain metastases, suggesting that the combination is worth considering in patients who are not candidates for further radiation and/or are not eligible for or cannot access a clinical trial.

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Compliance with ethical standards

Conflict of interest Michelle Melisko has received funding for clinical trials (paid to the UC Regents) from: Genentech, Merck, Astra Zeneca, Novartis, Lilly, Puma, Celldex, Galena, Nektar, and Daewha Pharmaceuticals, and honorarium from Agendia. Hope Rugo has received funding (paid to the UC Regents) from Genentech, Pfizer, Merck, Astra Zeneca, Novartis, Lilly, Nektar, Macrogenics, Immunomedics, Odonate, OBI, Seattle Genetics, Eisai, and Daiichi, and travel funding from Daiichi, Mylan, Pfizer, Amgen, Merck and Puma. John Park has stock ownership in Merrimack Pharmaceuticals and is a member of the speaker's bureau for Genentech and Pfizer. The remaining authors have no conflicts to disclose.

Ethical approval This manuscript complies with all current laws of the country in which it was performed. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained by all individual participants included in the study and all procedures were performed after obtaining informed consent.

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