# Changing Natural History of HER2–Positive Breast Cancer Metastatic to the Brain in the Era of New Targeted Therapies

Louisa A. Mounsey,[1] Allison M. Deal,[2] Kevin C. Keith,[2] Julia M. Benbow,[2] Shlomit S. Shachar,[2,6] Timothy Zagar,[2,3,5] E. Claire Dees,[2,4] Lisa A. Carey,[2,4] Matthew G. Ewend,[2,5] Carey K. Anders[2,4]

## Abstract

**Patients with breast cancer brain metastases historically have a poor prognosis. In this single-institution cohort study of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases, we found no improvement in survival after brain recurrence over time despite wide adoption of HER2–targeted therapies. This highlights the importance of continued development of novel brain penetrant therapies for patients with HER2–positive metastatic disease to extend survival and improve quality of life.**

**Background:** Given the wide adoption of human epidermal growth factor receptor 2 (HER2)-targeted therapies for advanced HER2–positive breast cancer, we studied the natural history of patients with HER2–positive breast cancer brain metastases (BCBM) over time. **Patients and Methods:** Patients with HER2–positive BCBM identified from a prospectively maintained database at the University of North Carolina were divided into 3 cohorts by year of BCBM diagnosis. Cohorts were selected by year of HER2–targeted therapy US Food and Drug Administration approval. Overall survival (OS), time to first metastasis, time to BCBM, and BCBM survival were estimated by the Kaplan-Meier method. Associations between OS after BCBM and clinical variables were assessed by Cox proportional hazards regression models. **Results:** One hundred twenty-three patients were identified. Median age was 51 years, and 58% were white and 31% African American. OS from initial breast cancer diagnosis improved over time: 3.6 years (95% confidence interval [CI], 2.8-6.1) in the 1998-2007 cohort, 6.6 years (95% CI, 4.5-8.6) in the 2008-2012 cohort, and 7.6 years (95% CI, 4.4-9.6) in the 2013-2015 cohort ($P = .05$). While time from initial diagnosis to first metastasis did not differ ($P = .12$), time to BCBM increased over time (2.6 years [95% CI, 1.3-3.5] for 1998-2007; 2.6 years [95% CI, 2.1-4.3] for 2008-2012, and 3.3 years [95% CI, 2.2-6] for 2013-2015; $P = .05$). Although OS from BCBM did not significantly differ by cohort, patients who received HER2–targeted therapy after BCBM had a prolonged OS (2.1 years [95% CI, 1.6-2.6] vs. 0.65 years [95% CI, 0.4-1.3]; $P = .001$). **Conclusion:** OS from initial breast cancer diagnosis significantly improved over time for patients with HER2–positive breast cancer who develop BCBM, now exceeding 7 years; survival from BCBM diagnosis may now exceed 2 years.

*Clinical Breast Cancer,* Vol. 18, No. 1, 29-37 

**Keywords:** Brain metastases, Lapatinib, Outcome, TDM-1, Trastuzumab

[1]University of North Carolina School of Medicine, Chapel Hill, NC
[2]Lineberger Comprehensive Cancer Center
[3]Department of Radiation Oncology
[4]Department of Medicine
[5]Department of Neurosurgery, University of North Carolina at Chapel Hill, Chapel Hill, NC
[6]Division of Oncology, Rambam Health Care Campus, Haifa, Israel

Submitted: Feb 2, 2017; Revised: Jul 6, 2017; Accepted: Jul 29, 2017; Epub: Aug 9, 2017

Address for correspondence: Carey K. Anders, MD, Associate Professor of Medicine, Division of Hematology Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599
Fax: (919) 966-6735; e-mail contact: carey_anders@med.unc.edu


http://dx.doi.org/10.1016/j.clbc.2017.07.017

## Introduction

One-third of women with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer will be diagnosed with brain metastases (BCBM) during their disease course.[1] HER2−positive breast cancer carried a poor prognosis in the pre−targeted therapy era.[2,3] Even after the approval of trastuzumab in the metastatic setting, overall survival (OS) from diagnosis of BCBM was less than 1.2 years.[1,4] Over the past 2 decades, treatment of patients with advanced HER2−positive breast cancer has evolved significantly as a result of the approval of several HER2−targeted therapies now incorporated into routine practice, which have markedly improved the prognosis of metastatic HER2−positive breast cancer. What is not yet clear is whether improved HER2−directed therapies have had the same impact among patients with BCBM. Variability in the chemical characteristics of the newer HER2−targeted therapies, and thus differing abilities to penetrate the blood−brain barrier (BBB) to either prevent BCBM or control existing metastatic lesions, suggest that these agents may have a positive impact on the recurrence rates in the brain and survival of patients with HER2−positive BCBM.

Multiple trials evaluating HER2−directed agents beyond trastuzumab have reported on brain outcomes. Although lapatinib with capecitabine has been shown to delay time to brain progression compared to trastuzumab in patients with metastatic HER2−positive disease, there was no difference in incidence of BCBM between the 2 groups.[5] Among patients with disease that progressed while receiving trastuzumab, lapatinib plus capecitabine compared to capecitabine alone is associated with a reduced risk of brain as the site of first progression.[6] In patients with radiation-naive HER2−positive BCBM, lapatinib plus capecitabine resulted in a reduction in BCBM volume from baseline in 84% of patients, suggesting it may be a reasonable first-line treatment.[7] Moving beyond lapatinib, an exploratory analysis of patients from the CLEOPATRA trial reported that in those with HER2−positive metastatic breast cancer treated with trastuzumab and docetaxel, while the addition of pertuzumab did not change the incidence of the brain as the first site of disease recurrence, it did delay the onset of and trend toward an increased OS after diagnosis of BCBM.[8] While ado-trastuzumab emtansine (TDM-1) was initially thought to have limitations to crossing the BBB similar to trastuzumab, several reports illustrate intracranial responses in the setting of HER2−positive BCBM.[9-12] The EMILIA study comparing TDM-1 with lapatinib plus capecitabine in patients with advanced HER2−positive disease pretreated with trastuzumab found that while the proportion of patients with brain progression was the same in both groups, in patients with preexisting BCBM, TDM-1 conferred a prolonged OS.[10] The TH3RESA study found that in patients with advanced HER2−positive breast cancer pretreated with 2 or more HER2−targeted agents, those in the TDM-1 group, including those with previously treated BCBM, had a longer progression-free survival than the physician's-choice group.[12]

These emerging data indicate that patients with HER2−positive metastatic disease are benefiting from therapeutic advances. In light of these advances, however, a collective analysis of BCBM outcomes in the modern era has yet to be performed. Thus, we performed a single-institution cohort study to examine the magnitude of this benefit in patients with BCBM during the era of modern HER2−targeting.

## Methods

Patients included in this study had metastatic HER2−positive breast cancer with BCBM at any point during their disease course. Informed consent was not obtained from participants included in the study because a waiver of consent and waiver of Health Insurance Portability and Accountability Act authorization were both approved by the University of North Carolina (UNC) Biomedical institutional review board on May 9, 2015.

Relevant data for this population were retrieved using 2 clinical databases at UNC. The UNC Breast Cancer Metastatic Database contains demographic, clinical, and treatment data on all metastatic breast cancer patients treated at the UNC−Chapel Hill Cancer Hospital from 2012 to the present. A second database collected information on breast cancer patients treated at UNC between 1991 and 2012. Within the databases, HER2 positivity was defined as either positive by immunohistochemistry or amplified by fluorescence in-situ hybridization. Tumors were hormone receptor positive if estrogen receptor, progesterone receptor, or both were positive, and hormone receptor negative if both estrogen receptor and progesterone receptor were negative.

A total of 123 patients were identified from both databases, yielding the cohort for this study. Patient follow-up data were available through May 2015, with a median follow-up of 1.75 years (range, 0.1-12 years) from BCBM diagnosis. UNC institutional review board approval was obtained to conduct this retrospective analysis. Of note, UNC has a dedicated BCBM clinic and research program, initiated on August 1, 2012.

### *Statistical Analysis*

Patients were divided into 3 cohorts for analysis as defined by year of BCBM diagnosis. Cohort time intervals were selected on the basis of year of HER2−targeted therapy US Food and Drug Administration (FDA) approval: 1998-2007 for trastuzumab, 2008-2012 for lapatinib, and 2013-2015 for pertuzumab and TDM-1. The Kaplan-Meier method and log-rank test were used to estimate and compare OS from initial breast cancer diagnosis, time from initial breast cancer diagnosis to first metastatic diagnosis, time from initial breast cancer diagnosis to BCBM, time from first metastatic diagnosis to BCBM, and OS from BCBM diagnosis. Subsequent pairwise log-rank tests were performed if the overall test was significant. Univariable and multivariable Cox proportional hazards regression modeling was used to evaluate associations of clinical variables with OS from BCBM. All analyses were conducted by SAS 9.4 statistical software (SAS Institute, Cary, NC).

## Results

### *Demographics and Treatment Pattern of Patient Population*

Demographic and clinical characteristics for patients in each cohort are listed in Table 1. Median age at breast cancer diagnosis was 51 years. Fifty-eight percent of the study population was white and 31% African American. Of the 123 HER2−positive BCBM patients, 30% were diagnosed with BCBM between 1998 and 2007, 37% between 2008 and 2012, and 33% between 2013 and 2015. Treatment received for early-stage I to III disease and for non−brain metastatic disease is provided in Table 1. Receipt of

**Table 1** Patient Demographics and Treatment Pattern Before HER2–Positive Breast Cancer Brain Metastasis Diagnosis (n = 123)

| Characteristic | All | Year of Diagnosis | | | *P* |
|---|---|---|---|---|---|
| | | 1998-2007 | 2008-2012 | 2013-2015 | |
| **No. of patients** | 123 | 37 (30%) | 45 (37%) | 41 (33%) | — |
| **Age at Diagnosis of Brain Metastasis** | | | | | .13 |
| Median (range), y | 51 (32-72) | 47 (32-68) | 55 (33-72) | 52 (36-71) | |
| ≤50 y | 53 (42%) | 21 (57%) | 16 (36%) | 16 (39%) | |
| >50 y | 70 (57%) | 16 (43%) | 29 (64%) | 25 (61%) | |
| **Race** | | | | | .91 |
| White | 72 (58%) | 23 (62%) | 26 (62%) | 23 (57%) | |
| African American | 38 (31%) | 12 (32%) | 12 (29%) | 14 (35%) | |
| Asian | 3 (2%) | 0 (0%) | 2 (5%) | 1 (2%) | |
| Other | 6 (5%) | 2 (5%) | 2 (5%) | 2 (5%) | |
| **AJCC Stage at Diagnosis** | | | | | .77 |
| 0 | 3 (2%) | 0 (0%) | 2 (5%) | 1 (2%) | |
| I | 10 (8%) | 4 (11%) | 4 (10%) | 2 (5%) | |
| II | 24 (19%) | 7 (19%) | 6 (15%) | 11 (27%) | |
| III | 42 (34%) | 12 (32%) | 15 (37%) | 15 (37%) | |
| IV | 40 (32%) | 14 (38%) | 14 (34%) | 12 (29%) | |
| **IHC Subtype** | | | | | .54 |
| HER2/HR negative | 68 (55%) | 19 (53%) | 28 (62%) | 21 (51%) | |
| HER2/HR positive | 54 (44%) | 17 (42%) | 17 (38%) | 20 (49%) | |
| **Breast Surgery Received** | | | | | .15 |
| Mastectomy | 77 (63%) | 27 (73%) | 28 (62%) | 22 (54%) | |
| Lumpectomy | 20 (16%) | 2 (5%) | 9 (20%) | 9 (22%) | |
| Biopsy only | 16 (13%) | 1 (3%) | 5 (11%) | 10 (24%) | |
| None performed | 10 (8%) | 7 (19%) | 3 (7%) | 0 (0%) | |
| **Therapy for Early Stage I to III Disease (n = 79, 64%)** | | | | | |
| Chemotherapy | 65 (82%) | 19 (83%) | 20 (74%) | 26 (90%) | .31 |
| Endocrine therapy | 35 (46%) | 10 (44%) | 12 (50%) | 13 (45%) | .89 |
| HER2–targeted therapy | 40 (54%) | 7 (32%) | 13 (57%) | 20 (69%) | .03 |
| Radiotherapy | 49 (71%) | 14 (78%) | 16 (73%) | 19 (66%) | .65 |
| **Presence of brain metastasis at first metastatic diagnosis** | 36 (29%) | 9 (24%) | 17 (38%) | 10 (24%) | .29 |
| **Therapy for Nonbrain Metastatic Disease (n = 87, 71%)** | | | | | |
| Chemotherapy | 71 (82%) | 26 (93%) | 18 (64%) | 27 (87%) | .01 |
| Endocrine therapy | 35 (40%) | 7 (25%) | 16 (57%) | 12 (39%) | .05 |
| HER2–targeted therapy | 72 (83%) | 22 (79%) | 24 (86%) | 26 (84%) | .76 |
| Trastuzumab | 72 (100%) | 22 (100%) | 24 (100%) | 26 (100%) | .99 |
| Lapatinib | 21 (29%) | 2 (95%) | 10 (42%) | 9 (35%) | .04 |
| Pertuzumab | 14 (19%) | 0 (0%) | 0 (0%) | 14 (54%) | <.01 |
| TDM-1 | 3 (4%) | 0 (0%) | 0 (0%) | 3 (12%) | .06 |

Abbreviations: AJCC = American Joint Committee on Cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemical; TDM-1 = ado-trastuzumab emtansine.

HER2–targeted therapy for early stage I to III disease increased over time: 32% of the 1998-2007 cohort, 57% of the 2008-2012 cohort, and 69% of the 2012-2015 cohort ($P = .03$).

Table 2 lists the treatment received for BCBM. Of these therapies, radiotherapy was the first therapeutic intervention after BCBM diagnosis in most patients across all time cohorts (79% 1998-2007, 72% 2008-2012, and 63% 2013-2015), followed by surgery (7% 1998-2007, 17% 2008-2012, and 24% 2013-2015), chemotherapy, and HER2–targeted therapy ($P = .10$). A similar proportion (approximately 80%) of patients received trastuzumab across all cohorts, while lapatinib use after BCBM varied over time (48% 1998-2007, 79% 2008-2012, and 42% 2013-2015)

**Table 2** Patient Treatment Pattern After HER2—Positive BCBM Diagnosis

| Characteristic | All | Year of Diagnosis | | | *P* |
|---|---|---|---|---|---|
| | | 1998-2007 | 2008-2012 | 2013-2015 | |
| **No. of Brain Metastases at Initial BCBM Diagnosis** | | | | | <.0001 |
| 1 | 40 | 14 (40%) | 16 (39%) | 10 (24%) | |
| 2 | 20 | 9 (26%) | 7 (17%) | 4 (10%) | |
| 3 | 24 | 12 (34%) | 10 (24%) | 2 (5%) | |
| 4 | 4 | 0 (0%) | 1 (2%) | 3 (7%) | |
| 5+ | 29 | 0 (0%) | 7 (17%) | 22 (54%) | |
| **Therapy After BCBM Diagnosis** | | | | | .65 |
| Chemotherapy | 76 | 24 (69%) | 28 (65%) | 24 (59%) | |
| Lines of Chemotherapy | | | | | .21 |
| 1 line | 32 | 10 (29%) | 10 (23%) | 12 (29%) | |
| 2 lines | 23 | 6 (17%) | 9 (21%) | 8 (19%) | |
| 3 lines | 6 | 5 (14%) | 1 (2%) | 0 (0%) | |
| 4+ lines | 15 | 3 (9%) | 8 (19%) | 4 (10%) | |
| Endocrine therapy | 20 | 7 (20%) | 10 (24%) | 3 (7%) | .11 |
| HER2—targeted therapy | 76 | 23 (62%) | 34 (76%) | 19 (46%) | .02 |
| Trastuzumab | 60 | 19 (19/23, 83%) | 26 (26/34, 76%) | 15 (15/19, 79%) | .86 |
| Lapatinib | 46 | 11 (11/23, 48%) | 27 (27/34, 79%) | 8 (9/19, 42%) | .009 |
| Pertuzumab | 11 | 0 (0%) | 2 (2/34, 6%) | 9 (9/19, 47%) | <.0001 |
| TDM-1 | 14 | 0 (0%) | 4 (4/24, 12%) | 10 (10/19, 53%) | <.0001 |
| Radiation | | | | | .17 |
| None | 17 | 8 (22%) | 5 (11%) | 4 (10%) | |
| WBRT alone | 64 | 23 (62%) | 21 (47%) | 20 (49%) | |
| SRS alone | 22 | 3 (8%) | 9 (20%) | 10 (24%) | |
| Both | 20 | 3 (8%) | 10 (22%) | 7 (17%) | |
| Surgical intervention | 33 | 9 (24%) | 13 (29%) | 11 (27%) | .90 |

Abbreviations: BCBM = breast cancer brain metastasis; HER2 = human epidermal growth factor receptor 2; SRS = stereotactic radiosurgery; TDM-1 = ado-trastuzumab emtansine; WBRT = whole brain radiotherapy.

($P = .009$). More patients received pertuzumab ($P < .0001$) and TDM-1 ($P < .0001$) over time.

### *Survival From Initial Breast Cancer Diagnosis*

Ninety-two patients (75%) are deceased. Median OS from initial breast cancer diagnosis for the entire cohort was 6.05 years (95% confidence interval [CI], 4.37-7.03) and improved over time: 3.56 years for 1998-2007 (95% CI, 2.78-6.05), 6.64 years for 2008-2012 (95% CI, 4.5-8.58), and 7.55 years for 2013-2015 (95% CI, 4.37-9.63) ($P = .05$) (Figure 1).

### *Time to First Metastatic Diagnosis and Time to Brain Recurrence*

Median time from initial breast cancer diagnosis to first metastatic diagnosis was 1.52 years (95% CI, 1.07-2.03), median time from first metastatic diagnosis to BCBM was 1.11 years (95% CI, 0.76-1.38), and median time from initial breast cancer diagnosis to BCBM was 2.88 years (95% CI, 2.22-3.42). Time from initial breast cancer diagnosis to first metastatic diagnosis numerically increased over time but was not statistically significant ($P = .12$) (Figure 2). Time from first metastatic diagnosis to BCBM diagnosis also did not significantly change over time ($P = .13$) (Figure 3).

**Figure 1** Overall Survival From Initial Breast Cancer Diagnosis by Year of Diagnosis

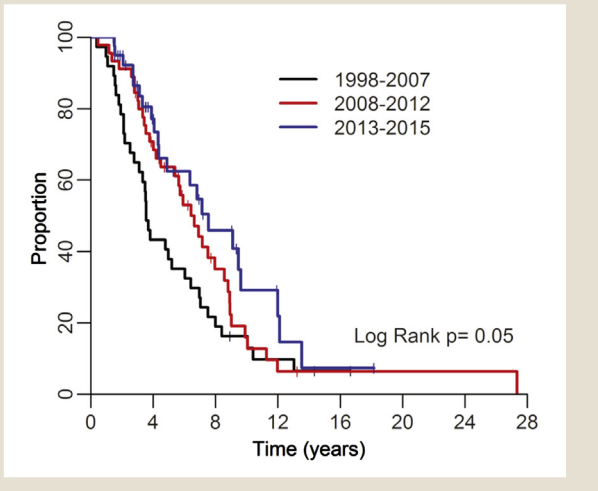
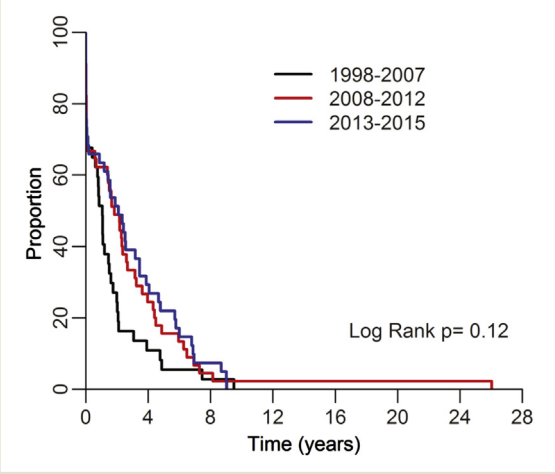


**Figure 2** Time From Initial Breast Cancer Diagnosis to First Metastatic Diagnosis by Year of Diagnosis




Time from initial breast cancer diagnosis to BCBM diagnosis, however, increased over time, with a median time to brain recurrence of 2.63 years for 1998-2007 (95% CI, 1.34-3.5), 2.61 years for 2008-2012 (95% CI, 2.11-4.31), and 3.32 years for 2013-2015 (95% CI, 2.22-6.01) ($P = .05$) (Figure 4).

### *Brain Metastasis–Specific Survival*

OS from BCBM diagnosis was 1.51 years (95% CI, 1.24-2.05) for the entire cohort and was not significantly different over time ($P = .24$) (Figure 5). Interestingly, those who received HER2–targeted therapy (62%) after BCBM diagnosis had a median OS of 2.11 years (95% CI, 1.55-2.60) compared to 0.65 years (95% CI, 0.38-1.25) in those who did not receive HER-2–targeted treatment ($P = .001$) (Figure 6).

**Figure 3** Time From First Metastatic Diagnosis to Breast Cancer Brain Metastasis Diagnosis by Year of Diagnosis

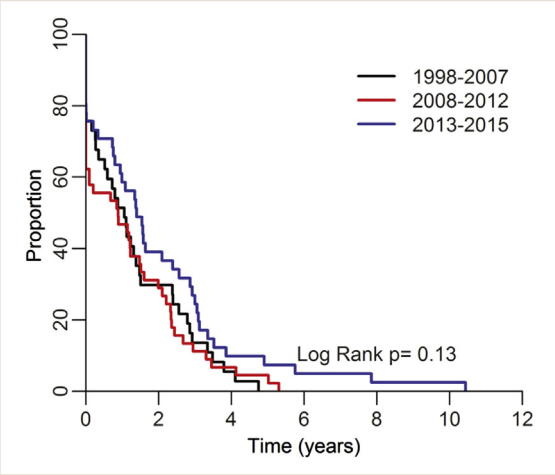
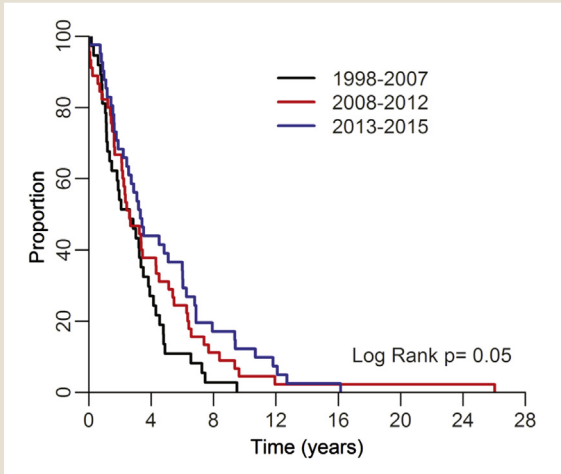



**Figure 4** Time to Breast Cancer Brain Metastasis Diagnosis From Initial Breast Cancer Diagnosis by Year of Diagnosis




Demographic and clinical characteristics of patients who received HER2–targeted therapy for BCBM compared to those who did not are listed in Table 3. A higher proportion of white subjects received HER2–targeted therapies compared to African American subjects (69% vs. 45%, $P = .03$). A higher proportion of patients in earlier cohorts received HER2–targeted therapies after BCBM than in the recent cohort (62% for 1998-2007, 76% for 2008-2012, and 46% for 2013-2015, $P = .02$).

### *Univariable and Multivariable Cox Regression Analysis*

Univariable analysis shows that receipt of HER2–targeted therapy after BCBM diagnosis was the only demographic, clinical, and treatment variable significantly associated with OS from BCBM diagnosis (hazard ratio 0.51, 95% CI 0.33-0.78) (Table 4). Given this

**Figure 5** Overall Survival After Breast Cancer Brain Metastasis Diagnosis by Year of Diagnosis

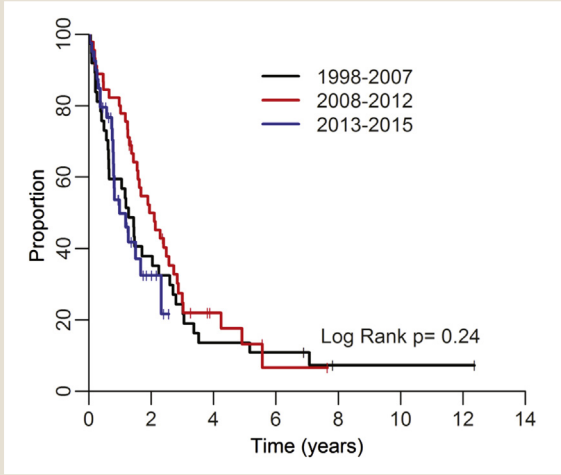
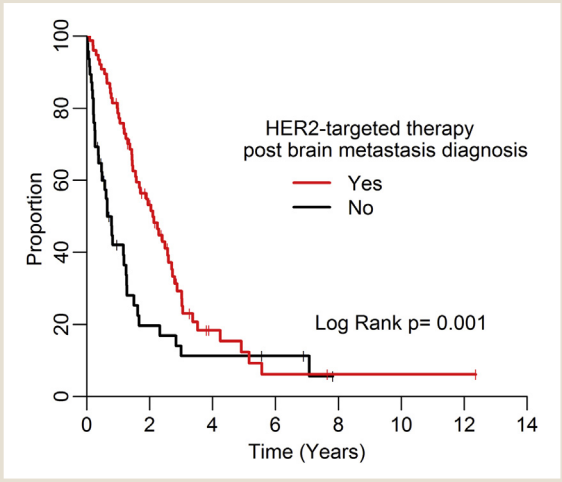


**Figure 6** Overall Survival After Breast Cancer Brain Metastasis Diagnosis by Receipt of HER2–Targeted Therapy




result, the finding that receipt of HER2–targeted therapy differs by both race and cohort, and sample size limitations, a multivariable model was fit to investigate if this relationship held after controlling for race and year of BCBM diagnosis. Receipt of HER2–targeted therapy after BCBM diagnosis remained significantly associated with longer OS from BCBM diagnosis (Table 5).

## Discussion

The purpose of this analysis was to reexamine the natural history of HER2–positive metastatic breast cancer with brain progression in the era of newer HER2–targeted therapies. Among a cohort of 123 patients with HER2–positive BCBM treated at UNC–Chapel Hill, there has been no significant change in survival after a diagnosis of BCBM over time. However, the median time to diagnosis of BCBM from initial breast cancer diagnosis appears to have increased by 9 months in the most recent era, 2013-2015, during which patients with HER2–positive disease have the benefit of multiple targeted agents. We attribute this increased time to BCBM diagnosis to both a prolonged time from initial breast cancer diagnosis to first metastatic diagnosis and from first metastatic diagnosis to BCBM diagnosis. Collectively, this leads to a delayed diagnosis of BCBM over time. These data provide a new historical control and framework for the manner in which we design novel clinical trials for this patient population, both in the prevention and active-therapy settings.

The advent of new HER2–targeted therapies contributes to a longer time from initial breast cancer diagnosis to BCBM diagnosis.[9-12] We demonstrated that patients exposed to any HER2–targeted treatment after their diagnosis of BCBM experienced a significantly longer OS than those not so exposed. Fewer patients in the 2013-2015 cohort received HER2–targeted therapy after BCBM compared to the 2 earlier cohorts. Because our survival analyses show that we are extending the time from initial diagnosis to BCBM diagnosis, we assert that in recent years, patients are diagnosed with BCBM later with more aggressive systemic disease and thus do not have the opportunity to benefit from HER2–targeted therapies. Another contributor is that many have already received newer HER2–targeted therapies before intracranial recurrence, as seen in this analysis, with over half of patients diagnosed with BCBM between 2013 and 2015 receiving pertuzumab and 12% receiving TDM-1 for non–brain metastatic disease. Furthermore, over 80% of patients received HER2–targeted therapy for non–brain metastatic disease, which was not significant across time cohorts. Thus, once brain metastases occurred, the majority of available anti–HER2–targeted therapies had already been prescribed.

A greater proportion of white subjects in our cohort received HER2–targeted therapy compared to African American subjects after BCBM diagnosis. This aligns with previous studies demonstrating racial disparity in HER2–targeted therapy throughout the disease course.[13,14] Notably, multivariable modeling did not indicate race to be significantly related to mortality after BCBM

**Table 3** Demographic and Clinical Characteristics of Patients Who Received HER2–Targeted Therapy After HER2–Positive BCBM Compared to Those Who Did Not

| Variable | Receipt of HER2–Targeted Therapy for BCBM | No HER2–Targeted Therapy for BCBM | *P* |
|---|---|---|---|
| **Age at BCBM Diagnosis** | | | |
| ≤50 y | 34 (64%) | 19 (36%) | .64 |
| >50 y | 42 (60%) | 28 (40%) | |
| **Race** | | | |
| African American | 17 (45%) | 21 (55%) | .03 |
| White | 50 (69%) | 22 (31%) | |
| Asian | 1 (33%) | 2 (67%) | |
| Other | 5 (83%) | 1 (17%) | |
| **Stage** | | | .61 |
| 0 | 2 (67%) | 1 (33%) | |
| I | 5 (50%) | 5 (50%) | |
| II | 12 (50%) | 12 (50%) | |
| III | 27 (64%) | 15 (36%) | |
| IV | 27 (67%) | 13 (32%) | |
| HER2/HR+ | 39 (57%) | 29 (43%) | .21 |
| HER2/HR- | 37 (68%) | 17 (31%) | |
| **Year of BCBM Diagnosis** | | | .02 |
| 1999-2007 | 23 (62%) | 14 (38%) | |
| 2008-2012 | 34 (76%) | 11 (24%) | |
| 2013-2015 | 19 (46%) | 22 (54%) | |
| **No. of Brain Metastatic Lesions at BCBM Diagnosis** | | | |
| 1-3 | 52 (62%) | 32 (38%) | .67 |
| >3 | 19 (58%) | 14 (42%) | |

Abbreviations: BCBM = breast cancer brain metastasis; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

**Table 4** Univariable Cox Regression Models for Mortality After HER2—Positive Breast Cancer Brain Metastasis Diagnosis

| Variable | HR (95% CI) |
|---|---|
| **Age at BCBM Diagnosis** | 1.00 (0.99-1.03) |
| ≤50 y | 1.00 |
| >50 y | 1.04 (0.69-1.58) |
| **Race** | |
| Nonwhite | 1.00 |
| White | 0.69 (0.45-1.05) |
| **No. of Brain Metastatic Lesions at BCBM Diagnosis** | 1.1 (0.96-1.26) |
| <4 | 1.00 |
| ≥4 | 1.04 (0.63-1.72) |
| **IHC Subtype** | |
| HER2/HR positive | 1.00 |
| HER2/HR negative | 0.895 (.59-1.36) |
| **Extracranial Disease at BCBM Diagnosis (n = 92)** | |
| No | 1.00 |
| Yes | 1.73 (0.77-3.89) |
| **Year of BCBM diagnosis** | |
| 1998-2007 | 1.00 |
| 2008-2012 | 0.78 (0.49-1.25) |
| 2013-2015 | 1.23 (0.7-2.18) |
| **Receipt of HER2—Targeted Therapy After BCBM Diagnosis** | |
| No | 1.00 |
| Yes | 0.51 (0.33-0.78) |

Abbreviations: BCBM = breast cancer brain metastasis; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemical; OR = odds ratio.

**Table 5** Multivariable Cox Regression Models for Mortality After HER2—Positive BCBM Diagnosis

| Variable | HR (95% CI) |
|---|---|
| **Race** | |
| Nonwhite | 1.00 |
| White | 0.74 (0.47-1.15) |
| **Year of BCBM Diagnosis** | |
| 1998-2007 | 1.00 |
| 2008-2012 | 0.92 (0.56-1.52) |
| 2013-2015 | 1.31 (0.72-2.38) |
| **Receipt of HER2—Targeted Therapy After BCBM Diagnosis** | |
| No | 1.00 |
| Yes | 0.61 (0.39-0.97) |

Abbreviations: BCBM = breast cancer brain metastasis; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; OR = odds ratio.

diagnosis, with receipt of HER2—targeted therapy being the only significant variable. This aligns with a previous study indicating no race-specific differences in survival after BCBM diagnosis.[4]

Despite the approval of 3 new HER2—targeted therapies during the course of this study, there is room for improvement in the survival of patients after a diagnosis of HER2—positive BCBM. This underscores the potential importance of new brain-penetrant therapies: COX2-MMP1/CCL7 has been identified as a targetable pathway for BCBM.[15] TPI-287, a novel brain permeable taxane, is in phase 2 clinical trials (NCT01332630).[16,17] Several clinical trials evaluating novel brain-permeable agents are ongoing: 4-demethyl-4-cholesteryloxycarbonylpenclome chemotherapy (NCT02038218)[18]; eribulin mesylate, a microtubule inhibitor (NCT02581839)[19]; cabozantinib, a tyrosine kinase and VEGFR2 inhibitor (NCT02260531)[20]; and abemaciclib, a cdk4/6 inhibitor (NCT02308020).[21] Efficacy of ANG1005, a novel formulation of paclitaxel bound to angio-pep that binds the low-density lipoprotein receptor—related protein 1 receptor on the BBB, is being investigated for recurrent brain metastases (NCT02048059).[22] Two small-molecule HER2—targeted agents are being evaluated: neratinib, an irreversible inhibitor of erbB1, HER2, and erbB4 (NCT01494662); and KD019, a tyrosine kinase inhibitor of HER2, EGFR, and VEGFR2/KDR (NCT02154529).[23-25] A phase 2 randomized trial of neratinib with paclitaxel versus trastuzumab with paclitaxel showed no difference in progression-free survival, but the combination with neratinib may delay the onset and reduce the frequency of central nervous system progression.[24] Other clinical trials are evaluating combinations of brain-permeable FDA-approved therapies: lapatinib, everolimus, and capecitabine (NCT01783756)[26]; everolimus with trastuzumab and vinorelbine (NCT01305941)[27]; and lapatinib with cabazitaxel, a brain-permeable taxane (NCT01934894).[28] We remain hopeful that these strategies will translate into improvements in the survival of patients after a diagnosis of HER2—positive BCBM.

While the number of brain metastases at initial BCBM diagnosis significantly increased over time, this did not influence survival after BCBM recurrence. We attribute this increased number of brain lesions at BCBM diagnosis to improvements in magnetic resonance imaging detection and resolution of smaller lesions that may not have been detected on older imaging platforms.

Our multivariable model shows receipt of HER2—targeted therapy after BCBM was significantly associated with prolonged OS after BCBM, even after controlling for race and time cohort. These results differ from a previous model, the Breast—Graded Prognostic Assessment of Sperduto et al,[29] intended to identify prognostic factors associated with survival in patients with BCBM, due to our focus on HER2—positive disease and the development of this prior model before wide utilization of novel HER2—targeted therapies. We hypothesize that as the therapeutic landscape of HER2—positive breast cancer evolves, and as more data are uncovered regarding the biology of brain metastases, tools such as the Breast—Graded Prognostic Assessment will likely expand and become more precise.

We recognize several limitations in our analysis. First, the UNC—Chapel Hill Cancer Hospital is a referral center with a dedicated BCBM clinic, which may attract patients with systemically different diseases. Second, a small number of patients received pertuzumab and TDM-1 due to their relatively recent FDA approval in 2012 and 2013, respectively. Thirty-one patients (25%) were still alive at the time of data extraction, and thus over time we

expect that a higher proportion of patients will be exposed to these newer therapies as results from ongoing trials comparing efficacy of existing HER2−targeted agents become available. Third, we do not have data on the presence of extracranial disease at BCBM diagnosis for the cohorts before 2012. In the univariate analysis, presence of extracranial disease at BCBM diagnosis was not significant over time, which is likely explained by the paucity of data. Finally, the retrospective nature of this analysis does not allow causation to be drawn between the natural history of the disease and the specific therapy received.

In summary, OS of patients with HER2−positive BCBM has increased, largely as a result of prolonged time between initial breast cancer diagnosis and diagnosis of BCBM over the decades. The lack of improvement in survival once BCBM are diagnosed support the continued development of novel brain-penetrant therapies for patients with HER2−positive metastatic disease to extend survival and improve quality of life.

### *Clinical Practice Points*

- One-third of women with metastatic HER2−positive breast cancer will be diagnosed with BCBM during their disease course. After approval of trastuzumab in the metastatic setting, OS from diagnosis of BCBM was less than 1.2 years. The effect of FDA approval of additional HER2−targeted agents including lapatinib, pertuzumab, and TDM-1 on the natural history of disease in these patients is less clear.
- In this cohort of patients with HER2−positive BCBM, while the OS from initial breast cancer diagnosis has increased over time, survival after diagnosis of brain recurrence has not improved. However, patients who were exposed to any HER2−targeted agent after BCBM diagnosis had a longer survival after BCBM diagnosis than those not so exposed.
- These data provide a new historical control and framework for the manner in which we design novel clinical trials for this patient population, both in the prevention and active-therapy settings. These data should encourage clinicians to utilize the available HER2−targeted agents when clinically indicated in patients with HER2−positive brain metastases.

## Acknowledgments

This work was supported by the National Cancer Institute (K23CA157728 to CKA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

This work was supported by the National Institutes of Health (T35-DK007386).

Database support was provided in part through Komen Foundation Grant SAC110044 awarded to E.C.D. REDCap support provided by the Clinical and Translational Science Award program, Division of Research Resources, National Institutes of Health (grant 1UL1TR001111).

This work was supported by University of North Carolina for a Breast Cancer Specialized Program of Research Excellence (SPORE) from the National Cancer Institute (National Institutes of Health/National Cancer Institute P50-CA58223).

This work was supported by National Cancer Institute Cancer Center support grant P30-CA16086.

## Disclosure

E.C.D. has consulted for Novartis and has received research grants from Novartis, Cerulean, Pfizer, Bayer, Roche-Genentech, Merck, and Lilly. C.K.A. has consulted for Novartis, Sanofi, toBBB, GERON, Angiochem, Merrimack, Lily, Genentech, Nektar, and Kadmon and has received funding from Novartis, Sanofi, toBBB, GERON, Angiochem, Merrimack, PUMA, Lily, Merck, Oncothyreon, Cascadian, and Nektar. The other authors have stated that they have no conflict of interest.

## References

1. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 2003; 97:2972-7.
2. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, Mcguire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; 235:177-82.
3. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Stem Cells* 1998; 16:413-28.
4. Anders CK, Deal AM, Miller CR, et al. The prognostic contribution of clinical breast cancer subtype, age, and race among patients with breast cancer brain metastases. *Cancer* 2011; 117:1602-11.
5. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2015; 33:1564-73.
6. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008; 112:533-43.
7. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol* 2013; 14:64-71.
8. Swain SM, Baselga J, Miles D, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. *Ann Oncol* 2014; 25:1116-21.
9. Kalsi R, Feigenberg S, Kwok Y, Tkaczuk K, Mehta M, Chumsri S. Brain metastasis and response to ado-trastuzumab emtansine: a case report and literature review. *Clin Breast Cancer* 2015; 15:e163-6.
10. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol* 2015; 26:113-9.
11. Bartsch R, Berghoff AS, Vogl U, et al. Activity of T-DM1 in HER2-positive breast cancer brain metastases. *Clin Exp Metastasis* 2015; 32:729-37.
12. Krop IE, Kim SB, González-Martín A, et al, Th3RESA study collaborators. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15:689-99.
13. Reeder-Hayes K, Peacock Kinton S, Meng K, Carey LA, Dusetzina SB. Disparities in use of human epidermal growth hormone receptor 2−targeted therapy for early-stage breast cancer. *J Clin Oncol* 2016; 34:2003-9.
14. Vaz-Luis I, Lin NU, Keating NL, et al. Treatment of early-stage human epidermal growth factor 2-positive cancers among medicare enrollees: age and race strongly associated with non-use of trastuzumab. *Breast Cancer Res Treat* 2016; 159:151-62.
15. Wu K, Fukuda K, Xing F, et al. Roles of the cyclooxygenase 2 matrix metalloproteinase 1 pathway in brain metastasis of breast cancer. *J Biol Chem* 2015; 290:9842-54.
16. Fitzgerald DP, Emerson DL, Qian Y, et al. TPI-287, a new taxane family member, reduces the brain metastatic colonization of breast cancer cells. *Mol Cancer Ther* 2012; 11:1959-67.
17. MD Anderson Cancer Center. TPI 287 in breast cancer metastatic to the brain, Available at: https://clinicaltrials.gov/ct2/show/NCT01332630. Accessed: June 7, 2016.
18. DEKK-TEC Inc. Study of 4-demethyl-4-cholesteryloxycarbonylpenclome in patients with brain tumors (DM-CHOC-PEN), Available at: https://clinicaltrials.gov/ct2/show/NCT02038218. Accessed: April 27, 2016.
19. Case Comprehensive Cancer Center. Treatment of brain metastases from breast cancer with eribulin mesylate, Available at: https://clinicaltrials.gov/ct2/show/study/NCT02581839. Accessed: April 27, 2016.
20. Dana-Farber Cancer Institute. Cabozantinib +/− trastuzumab in breast cancer with brain metastases, Available at: https://clinicaltrials.gov/ct2/show/study/NCT02260531. Accessed: April 27, 2016.

21. Eli Lilly and Company. A study of abemaciclib (LY2835219) in participants with breast cancer, non—small cell lung cancer, or melanoma that has spread to the brain, Available at: https://clinicaltrials.gov/ct2/show/NCT02308020. Accessed: April 27, 2016.
22. Angiochem Inc. ANG1005 in breast cancer patients with recurrent brain metastases, Available at: https://clinicaltrials.gov/ct2/show/NCT02048059. Accessed: April 27, 2016.
23. Dana-Farber Cancer Institute. HKI-272 for HER2-positive breast cancer and brain metastases, Available at: https://clinicaltrials.gov/ct2/show/NCT01494662. Accessed: April 27, 2016.
24. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel versus trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol* 2016; 2:1557-64.
25. Kadmon Corporation LLC. Study of the combination of KD019 and trastuzumab in subjects with HER2-positive metastatic breast cancer, Available at: https://clinicaltrials.gov/ct2/show/NCT02154529. Accessed: April 27, 2016.
26. Jonsson Comprehensive Cancer Center. Phase 1b/2 trial using lapatinib, everolimus, and capecitabine for treatment of HER2-positive breast cancer with CNS metastasis, Available at: https://clinicaltrials.gov/ct2/show/NCT01783756. Accessed: April 27, 2016.
27. UNC Lineberger Comprehensive Cancer Center. A study of everolimus, trastuzumab, and vinorelbine in HER2-positive breast cancer brain metastases, Available at: https://clinicaltrials.gov/ct2/show/NCT01305941. Accessed: April 27, 2016.
28. SCRI Development Innovations, LLC. Cabazitaxel plus lapatinib as therapy for HER2-positive metastatic breast cancer patients with intracranial metastases, Available at: https://clinicaltrials.gov/ct2/show/NCT01934894. Accessed: April 27, 2016.
29. Sperduto PW, Kased N, Roberge D, et al. Effect of tumor subtype on survival and the Graded Prognostic Assessment for patients with breast cancer and brain metastases. *Int J Radiat Oncol Biol Phys* 2012; 82:2111-7.