Central Nervous System Metastases in Patients with HER2-Positive Metastatic Breast Cancer: Incidence, Treatment, and Survival in Patients from registHER

Adam M. Brufsky[1], Musa Mayer[2], Hope S. Rugo[3], Peter A. Kaufman[5], Elizabeth Tan-Chiu[6], Debu Tripathy[7], Iulia Cristina Tudor[4], Lisa I. Wang[4], Melissa G. Brammer[4], Mona Shing[4], Marianne Ulcickas Yood[8], and Denise A. Yardley[9]

Abstract

Purpose: registHER is a prospective, observational study of 1,023 newly diagnosed HER2-positive metastatic breast cancer (MBC) patients.

Experimental Design: Baseline characteristics of patients with and without central nervous system (CNS) metastases were compared; incidence, time to development, treatment, and survival after CNS metastases were assessed. Associations between treatment after CNS metastases and survival were evaluated.

Results: Of the 1,012 patients who had confirmed HER2-positive tumors, 377 (37.3%) had CNS metastases. Compared with patients with no CNS metastases, those with CNS metastases were younger and more likely to have hormone receptor–negative disease and higher disease burden. Median time to CNS progression among patients without CNS disease at initial MBC diagnosis ($n = 302$) was 13.3 months. Treatment with trastuzumab, chemotherapy, or surgery after CNS diagnosis was each associated with a statistically significant improvement in median overall survival (OS) following diagnosis of CNS disease (unadjusted analysis: trastuzumab vs. no trastuzumab, 17.5 vs. 3.8 months; chemotherapy vs. no chemotherapy, 16.4 vs. 3.7 months; and surgery vs. no surgery, 20.3 vs. 11.3 months). Although treatment with radiotherapy seemed to prolong median OS (13.9 vs. 8.4 months), the difference was not significant ($P = 0.134$). Results of multivariable proportional hazards analyses confirmed the independent significant effects of trastuzumab and chemotherapy (HR = 0.33, $P < 0.001$; HR = 0.64, $P = 0.002$, respectively). The effects of surgery and radiotherapy did not reach statistical significance ($P = 0.062$ and $P = 0.898$, respectively).

Conclusions: For patients with HER2-positive MBC evaluated in registHER, the use of trastuzumab, chemotherapy, and surgery following CNS metastases were each associated with longer survival. *Clin Cancer Res; 17(14); 4834–43. ©2011 AACR.*

Authors' Affiliations: [1]University of Pittsburgh Cancer Center, Pittsburgh, Pennsylvania; [2]Patient Advocate, AdvancedBC.org, New York, New York; [3]UCSF Comprehensive Cancer Center; [4]Genentech, Inc., San Francisco, California; [5]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [6]Florida Cancer Care, Tamarac, Florida; [7]University of Southern California, Los Angeles, California; [8]EpiSource, LLC, and Yale University School of Medicine, New Haven, Connecticut; and [9]Sarah Cannon Research Institute, and Tennessee Oncology, PLLC, Nashville, Tennessee

Introduction

For women with advanced breast cancer, 10% to 16% develop central nervous system (CNS) metastases (1, 2). However, because most CNS metastases are diagnosed in response to clinical symptoms rather than by routine staging, the total incidence of CNS metastases is likely higher. In a study that required prescreening for CNS lesions, 14.8% of patients had occult lesions (3) and autopsy data have revealed that up to 30% of patients with advanced metastatic breast cancer (MBC) have CNS metastases (4). Several risk factors have been associated with the development of CNS lesions in patients with MBC, including younger age (<50 year), having more than 2 metastatic sites at MBC diagnosis, and HER2-positive disease (5). Patients with HER2-positive MBC tumors are 2 to 4 times more likely to develop CNS tumors than patients with HER2-negative disease (2, 6, 7). The recent apparent increase in the incidence of CNS metastases likely results from advances in detection of CNS lesions and from improvements in systemic treatment that allow more patients to live long enough to develop CNS metastases

American Association for **Cancer Research**

Translational Relevance

With a cohort of 1,023 patients with HER2-postive metastatic breast cancer (MBC), the observational cohort study registHER provided a unique opportunity to study the incidence, potential risk factors, and outcomes for patients with HER2-positive MBC who developed central nervous system (CNS) metastases. Approximately one third (377 of 1,012) of patients with HER2-positive MBC developed CNS metastases. Of the patients who developed CNS metastases, the majority (~80%) developed them after their initial MBC diagnosis. For all patients with CNS metastases ($n = 377$), the median time to first CNS event was 10.8 months. Analysis revealed that treatment with trastuzumab and chemotherapy independently led to a statistically significant improvement in median overall survival from the time CNS disease was diagnosed. This was not true for surgery or radiotherapy. Therefore, these data support the treatment of patients with HER2-positive MBC and CNS metastases with trastuzumab and chemotherapy.

(2); this has been observed in HER2-positive MBC patients treated with trastuzumab (1, 8).

In general, survival for breast cancer patients with CNS metastases is poor, with 1-year survival of approximately 20% (1). In one study of patients with CNS metastases from breast cancer ($n = 121$), survival rate was 8.0% at 2 years, 6.9% at 3 years, and 1.3% at 5 years (9). Although surgery can be an effective treatment option for patients with limited CNS disease burden (10), steroids and radiotherapy have been the mainstays of treatment of CNS metastases (11–14). For patients with fewer lesions, stereotactic radiosurgery is associated with longer survival (14, 15). Because an intact blood–brain barrier (BBB) prevents most chemotherapeutic agents from entering the CNS, chemotherapy is not used routinely to treat CNS metastases. For patients whose tumors overexpress HER2, there is an increased risk of developing CNS disease and a decrease in overall survival (OS; refs. 1, 8, 16). Treatment of HER2-positive patients who have CNS metastases with trastuzumab (Herceptin; Genentech, Inc.), a monoclonal antibody directed against HER2, seems to prolong survival, even compared with patients with HER2-negative disease (1, 8, 17).

As a multicenter, prospective, observational study of 1,023 patients, registHER is the largest study population of patients with recently diagnosed HER2-positive MBC. This study offers a unique opportunity to assess the incidence, potential risk factors, and outcomes for patients with HER2-positive MBC who developed CNS metastases.

Materials and Methods

Study design

registHER is a multicenter, prospective observational U.S.-based cohort study of patients from community and academic settings who have newly diagnosed HER2-positive MBC. The objectives of registHER were to describe the natural history of disease and treatment patterns for patients with HER2-positive MBC and to explore associations between specific therapies and patient outcomes. The study was approved by all local institutional review boards, and all enrolled patients provided informed consent.

Patient recruitment was conducted from December 2003 to February 2006. Eligible patients included women ($n = 1,013$) and men ($n = 10$) with breast cancer. HER2 status was determined according to institutional guidelines. Patients were eligible regardless of treatment before enrollment or during study follow-up. To minimize patient selection bias, investigators were encouraged to recruit all eligible patients at their practice.

Patients received care according to their physicians' standard practice without study-specified evaluations. Patient information [including demographics, tumor characteristics, initial metastasis sites and progressions, systemic treatment received (with start/stop dates), and response to treatment] were recorded at enrollment and updated every 3 months thereafter. Participating physicians or designated staff entered patient data into electronic case report forms (eCRF), using a Web-based electronic data capture system. Formal, prespecified, and scheduled assessments for tumor response were not required, and tumor progression was reported by physicians according to their standard practice.

Starting in January 2008, investigators following patients identified as having CNS metastases were asked to complete an additional retrospective questionnaire to gather data on diagnosis, leptomeningeal involvement, treatment, and response of CNS metastases to treatment. At that time, the eCRF was modified to prospectively capture these CNS metastases–specific data.

Prior to the approval of lapatinib in March 2007, data on use of lapatinib and other investigational drugs were incompletely captured. The study's eCRF was amended at the time of lapatinib approval to allow lapatinib use to be reported.

Statistical methods

Analyses incorporate follow-up data on registHER patients as of June 15, 2009 (database lock). Enrollment of 83 patients whose MBC diagnosis was more than 6 months (up to 9 months) prior to enrollment was permitted and these patients are included in all analyses.

Patients with CNS metastases were defined as those with either leptomeningeal metastases (LM) and/or metastases in the brain parenchyma. Time to CNS metastases was defined as the time from the date of MBC diagnosis to date of diagnosis of CNS metastases. Survival after CNS metastases was defined as the time from diagnosis of first CNS metastases to date of death from any cause or last follow-up. Overall survival was defined as the time between a patient's initial metastatic diagnosis and death from any cause or last follow-up.

Patient demographics and tumor characteristics were tabulated by CNS metastases status and comparisons

between groups used the χ^2 test, as appropriate. Time to CNS metastases and survival after CNS metastases were estimated using the Kaplan–Meier product-limit method. Data from patients with no event recorded were censored at the date of last follow-up. Kaplan–Meier curves and the log-rank test were used to compare unadjusted survival after CNS metastases in different treatment groups.

Patients were classified as receiving trastuzumab if they had received 21 total days or more (i.e., equivalent to ≥ 2 doses) of drug following their first CNS event. Patients were classified as receiving chemotherapy for treatment of CNS metastases if they had chemotherapy started after a CNS event or if chemotherapy started before a CNS event continued for 21 days or more after a CNS event. If radiation therapy or surgery was recorded either on the eCRF or on the CNS questionnaire, that patient was counted as having received radiation therapy or surgery, respectively. Radiation therapy or surgery specifically directed to sites other than the brain was not included.

Cox proportional hazards models were used to evaluate the association between survival and various treatments, adjusting for relevant baseline covariates that were considered *a priori* to be important factors for the physician's treatment decision or to be prognostic for survival. Several factors were evaluated, but the final multivariate model presented here includes as covariates age, Eastern Cooperative Oncology Group performance status (ECOG PS) at MBC diagnosis, hormone receptor status, cancer stage at diagnosis, CNS involvement at MBC diagnosis, and the main treatment options after CNS metastases (trastuzumab, chemotherapy, radiotherapy, and surgery). Although we describe the use of lapatinib as it was observed in this study, given the timing of the approval of lapatinib after completion of patient recruitment in registHER, no adjustment for the use of lapatinib was made.

Role of the funding source

Genentech, Inc., participated in design of the study; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the manuscript for publication.

Results

Patient and tumor characteristics

Of the 1,023 patients enrolled at 240 sites in the United States, 1,012 (99%) had a diagnosis of confirmed, HER2-positive tumors and enrolled within 12 months of their MBC diagnosis, permitting them to be included in this analysis. The median follow-up time from metastatic diagnosis was 29 months. Thirty-seven percent (377 of 1,012) of patients with MBC had a diagnosis of CNS metastases, 7% (75 of 1,012) at the time of their initial MBC diagnosis and 30% (302 of 1,012) as a subsequent site of disease progression (Fig. 1A).

For 106 (28.1%) patients, CNS metastases were their only site of first progression after metastatic diagnosis (Fig. 1A). For 15 (14.2% of this group, or 4.0% of all patients with

CNS metastases), the CNS was the only site of metastatic disease. Patients who developed CNS metastases were younger (<50 years old, 43% vs. 37%), more likely to have hormone receptor–negative disease (51% vs. 39%), and had a higher disease burden (62% vs. 49% had ≥ 2 metastatic sites) than patients without CNS metastases (Table 1).

Characteristics of CNS metastases

CNS-specific data were recorded for 83% (313 of 377) of patients with CNS metastases. For the 308 patients for whom neurologic symptom data were available, 81% had neurologic symptoms at the time CNS metastases were diagnosed (Table 2). Of the patients with CNS metastases and who had LM data available, 9.6% (30 of 311) were described as having LM, with or without parenchymal disease (Table 2).

Overall survival from MBC diagnosis

For patients with any CNS events ($n = 377$), the median OS from time of MBC diagnosis was 26.3 months (73.7% of patients died) compared with 44.6 months for patients with no CNS events ($n = 635$; 42.4% of patients died; Fig. 1B). Patients with CNS metastases at the time of MBC diagnosis had a median OS of 20.3 months; for the 15 patients for whom CNS was the only site of metastasis, median OS was 26.3 months. Patients who developed CNS metastases after their MBC diagnosis ($n = 302$) had a median OS of 27.0 months. Patients with LM disease had a median OS of 22.9 months.

Time from MBC diagnosis to development of CNS metastases

For all patients with CNS metastases ($n = 377$), the median time to first CNS event was 10.8 months (Fig. 2A). For the subset of 302 (80%) patients who developed CNS metastases during treatment of MBC, the median time to first CNS event was 13.3 months (range, 0.6–50.1 months). Of these patients, 8.3% (25 of 302) were receiving first-line therapy for MBC at the time; 42.1% (127 of 302) were receiving second-line therapy, and 47.7% (144 of 302) were receiving subsequent lines of therapy (Fig. 2B). In the subset of patients ($n = 106$) who had CNS metastases as their only site of first progression after metastatic diagnosis, the median time to first CNS event was 10.5 months (range, 0.6–43.5 months).

Prior to development of CNS metastases, trastuzumab was the most commonly received systemic therapy; 93% of patients had received trastuzumab before their first CNS event. For patients who received trastuzumab before their first CNS event ($n = 280$), the median time to diagnosis of CNS metastases was 13.6 months (range, 1.7–50.1 months). For the cohort ($n = 22$) who did not receive trastuzumab before CNS metastases, median time to CNS metastases was 7.1 months (range, 0.6–25.8 months).

Treatment after diagnosis of CNS metastases

Of the 377 patients with CNS disease, 71.4% received radiation therapy, 69.5% received chemotherapy, 68.4%
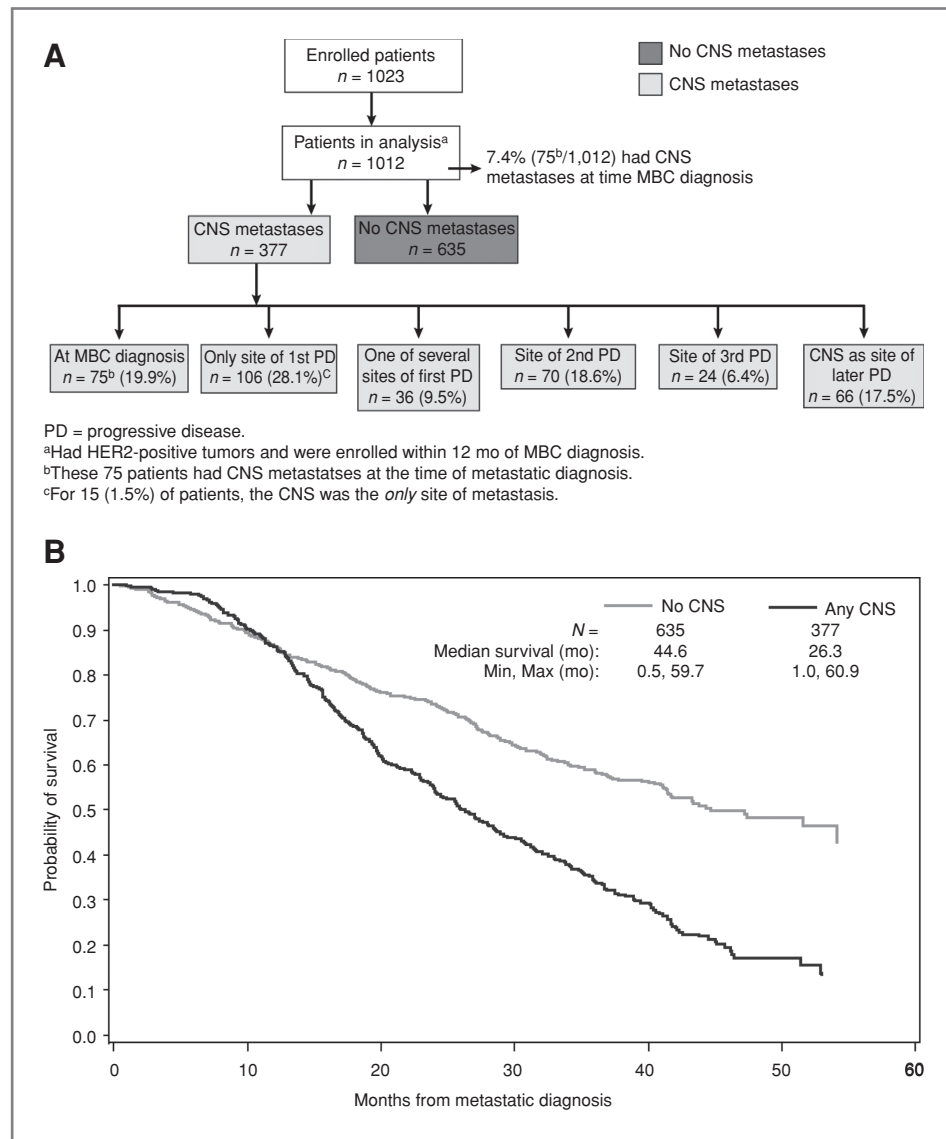
Figure 1. A, CNS metastases among patients in the registHER patient population ($n = 1,023$). B, Kaplan–Meier-estimated survival for patients with and without CNS metastases.

received trastuzumab, 24.1% received lapatinib (78% of whom also received trastuzumab), and 7.7% had surgery as part of treatment of CNS disease (Table 2). Of the 269 patients who received radiotherapy, 216 (80.3%) received whole-brain radiotherapy (WBRT), 27 (10.0%) received stereotactic radiotherapy, and 13 (4.8%) received both types (Table 3). Twenty-four (6.4%) patients did not receive any of these treatment options. A sequence or combination of radiation therapy, chemotherapy, and trastuzumab was the most common treatment after CNS metastases diagnosis, which was received by 26.5% of patients (Table 2).

For the subset of patients ($n = 302$) who developed CNS metastases after their MBC diagnosis, 71.5% received radiotherapy, 65.9% received chemotherapy, 63.3% received trastuzumab, 25.2% received lapatinib, and 5.6% had surgery. Of the 75 patients who had CNS metastases at

the time of initial MBC diagnosis, 70.7% received radiotherapy, 84.0% received chemotherapy, 89.3% received trastuzumab, 20% received lapatinib, and 16% underwent surgery.

Survival following CNS events

The median survival after first diagnosis of CNS metastases for all patients was 13.0 months (range, 0.1–55.5 months; Fig. 3A). For the patients who presented *de novo* with CNS metastases ($n = 75$), the median survival was 20.3 months (range, 1.0–55.5 months). For those diagnosed with CNS metastases subsequent to their MBC diagnosis ($n = 302$), median survival following diagnosis of CNS metastases was 9.6 months (range, 0.1–54.5 months; Fig. 3A). In all patients with CNS metastases ($n = 377$), chemotherapy and trastuzumab treatment after CNS diagnosis were each strongly associated with

Table 1. Demographic and baseline characteristics by presence of CNS metastases, n (%)

	All patients (n = 1,012)	No CNS metastases (n = 635)	Any CNS metastases (n = 377)	CNS metastases at MBC diagnosis (n = 75)	CNS metastases after MBC diagnosis (n = 302)
Age, y[a]					
<50	394 (38.9)	232 (36.5)	162 (43.0)	33 (44.0)	129 (42.7)
50–64	406 (40.1)	249 (39.2)	157 (41.6)	33 (44.0)	124 (41.1)
65+	212 (20.9)	154 (24.3)	58 (15.4)	9 (12.0)	49 (16.2)
Race					
White	799 (79.0)	496 (78.1)	303 (80.4)	60 (80.0)	243 (80.5)
Nonwhite	213 (21.0)	139 (21.9)	74 (19.6)	15 (20.0)	59 (19.5)
Hormone receptor status[a,b]					
Positive	535 (52.9)	368 (57.9)	167 (44.3)	24 (32.0)	143 (47.4)
Negative	439 (43.4)	248 (39.1)	191 (50.7)	48 (64.0)	143 (47.4)
Unknown	38 (3.8)	19 (3.0)	19 (5.0)	3 (4.0)	16 (5.3)
Number of metastatic sites[a]					
1	467 (46.1)	324 (51.0)	143 (37.9)	25 (33.3)	118 (39.1)
2+	545 (53.9)	311 (49.0)	234 (62.1)	50 (66.7)	184 (60.9)
ECOG PS at MBC diagnosis[b]					
0–1	457 (45.2)	300 (47.2)	157 (41.6)	20 (26.7)	137 (45.4)
2+	64 (6.3)	38 (6.0)	26 (6.9)	6 (8.0)	20 (6.7)
Unknown/missing	491 (48.5)	297 (46.8)	194 (51.5)	49 (65.3)	145 (48.0)
Stage at initial diagnosis					
Stage IV	277 (27.4)	181 (28.5)	96 (25.5)	17 (22.7)	79 (26.2)
Stage I–III with early relapse (≤12 mo)	137 (13.5)	88 (13.9)	49 (13.0)	11 (14.7)	38 (12.6)
Stage I–III with late relapse (>12 mo)	598 (59.1)	366 (57.6)	232 (61.5)	47 (62.7)	185 (61.3)
Prior therapy (stage I–III only)[b,c]					
Trastuzumab-based therapy without hormones	46 (4.5)	24 (3.8)	22 (5.8)	10 (13.3)	12 (4.0)
Trastuzumab-based therapy with hormones	10 (1.0)	7 (1.1)	3 (0.8)	0	3 (1.0)
Hormones only	58 (5.7)	40 (6.3)	18 (4.8)	4 (5.3)	14 (4.7)
Hormones and chemotherapy	164 (16.2)	106 (16.7)	58 (15.4)	10 (13.3)	48 (15.9)
Chemotherapy only	320 (31.6)	192 (30.2)	128 (33.9)	28 (37.3)	100 (33.1)
Other therapy	5 (0.5)	5 (0.8)	0	0	0
No prior therapy	132 (13.0)	80 (12.6)	52 (13.8)	6 (8.0)	46 (15.2)

[a]CNS metastases versus no CNS metastases (P < 0.05).
[b]CNS metastases at MBC diagnosis versus CNS metastases developed after MBC diagnosis (P < 0.05).
[c]Patients with stage IV MBC did not receive any adjuvant/neoadjuvant therapy. Percentages calculated from the total number of patients in the column. Herceptin was approved for use in the adjuvant setting in November 2006, which was after completion of enrollment into registHER (February 2006).

improved survival (log-rank test P < 0.001 for both comparisons; unadjusted; Fig. 3B and C). For patients who received trastuzumab following diagnosis of CNS disease (n = 258, 68.4%), the median survival was 17.5 months, compared with 3.7 months for patients who did not (n = 119; Fig. 3B). For patients who received chemotherapy following diagnosis of CNS disease (n = 262, 69.5%), the median survival was 16.4 months, compared with 3.7 months for patients who did not receive chemotherapy

(Fig. 3C). For patients who received surgery, the median survival was also longer (20.3 vs. 11.3 month, P = 0.013). Radiation therapy seemed to increase survival (13.9 vs. 8.4 month), but the difference was not significant (P = 0.134; Fig. 3D). For patients with reported LM disease (n = 30), the median survival from the time of CNS diagnosis was 5.8 months (range, 0.6–55.5 months).

After adjusting for the clinical characteristics of age, ECOG PS at time of MBC diagnosis, hormone receptor

Table 2. Summary of disease characteristics and treatment of patients with CNS metastatic disease ($n = 377$)

Neurologic symptoms present, n (%)	
No	59 (15.7)
Yes	249 (66.1)
Missing[a]	69 (18.3)
Method of initial diagnosis of CNS metastases[b], n (%)	
Radiologic imaging	308 (81.7)
Physical examination	74 (19.6)
Lumbar puncture	7 (1.9)
Unknown	1 (0.3)
Other	9 (2.4)
Missing[a]	64 (17.0)
Leptomeningeal involvement, n (%)	
No	281 (74.5)
Yes	30 (8.0)
Missing[a]	66 (17.5)
HER2-targeted treatment received following CNS metastases, n (%)	
Trastuzumab and other therapies,[c] but no lapatinib	179 (47.5)
Trastuzumab and lapatinib and other therapies[c]	71 (18.8)
Lapatinib and other therapies,[c] but no trastuzumab	20 (5.3)
Trastuzumab only	8 (2.1)
Trastuzumab and lapatinib only (no other therapies[c])	0
Lapatinib only	0
Other therapies[c]	69 (18.3)
Trastuzumab <21 d, but no other therapies	6 (1.6)
No therapy	24 (6.4)

[a]Patients identified as having CNS metastases on study case report forms, but who had no follow-up available on CNS-specific case report forms. No screening for CNS metastases was conducted at time of enrollment.
[b]Categories are not mutually exclusive.
[c]Includes radiation therapy, surgery, and/or chemotherapy.

status, cancer stage at initial diagnosis, and CNS involvement at metastatic diagnosis in a multivariable proportional hazards model, we found that treatment with trastuzumab (HR = 0.33; 95% CI: 0.25–0.46; $P < 0.001$) or chemotherapy (HR = 0.64; 95% CI: 0.48–0.85; $P = 0.002$) were independently associated with decreased hazard of death after CNS metastases, whereas CNS-directed radiotherapy was not ($P = 0.898$; Table 3). Although not statistically significant, there was a trend to suggest that surgery is associated with decreased hazard of death after CNS metastases (HR = 0.63, 95% CI: 0.39–1.02; $P = 0.062$). The interactions between ECOG PS and che-

motherapy or trastuzumab treatment were investigated but found to be not significant. In additional sensitivity analyses, treatment with trastuzumab continued to be associated with decreased hazard of death after CNS metastases in the multivariable proportional hazards model (HR = 0.34; 95% CI: 0.24–0.48), even after excluding potential palliative care patients [i.e., patients who survived <21 days ($n = 8$)] or who did not receive any treatment after their CNS diagnosis ($n = 47$) from the nontrastuzumab comparison group (see Supplementary Table).

Discussion

As the largest prospectively followed cohort of patients with HER2-positive MBC, registHER affords a unique opportunity to study the natural history of CNS metastases in this patient population in the context of contemporary therapies. Consistent with the incidence of CNS metastases found in retrospective analyses, approximately one third of the 1,012 patients analyzed in registHER had CNS metastases (2, 18). Potential predictive factors for the development of CNS metastases were similar to those previously noted for breast cancer patients, including younger age (<65 years), hormone receptor–negative disease, and greater disease burden. Seven percent of registHER patients had CNS metastases at the time of their initial MBC diagnosis. However, because not all patients underwent CNS screening at the time of MBC diagnosis, and not all patients with CNS metastases had neurologic symptoms, the actual incidence of CNS disease at MBC diagnosis is probably higher.

Although HER2-positive breast cancer is a relatively aggressive subtype, and it was considered that patients in registHER might have an increased incidence of LM (a particularly aggressive form of CNS disease associated with poor prognosis), we found that the incidence of LM among the HER2-positive patients in registHER (9.6% in patients with CNS disease and 2.9% overall) was comparable with previous reports (4, 13, 18, 19).

In registHER, patients who had CNS metastases at the time of MBC diagnosis survived twice as long from the time CNS disease was diagnosed (20.3 vs. 9.6 months) as did patients whose CNS disease was diagnosed after their MBC diagnosis. This raises the question of whether earlier detection of CNS lesions leads to prolonged survival post–CNS metastasis because CNS-specific therapies were administered earlier in the course of treatment (e.g., radiation therapy, or surgical resection for smaller, solitary lesions). However, the difference in survival postdetection of CNS observed in this study is likely a reflection of the difference in time to diagnosis of CNS metastases (i.e., median time to first CNS metastases was 10.8 months) rather than due to a true improvement in survival. Of note, the improved survival postdetection of CNS metastases did not correspond to improvement in OS from time of MBC diagnosis—the median OS from time of initial metastatic diagnosis was shorter in patients whose CNS metastases were noted at initial diagnosis than those whose CNS
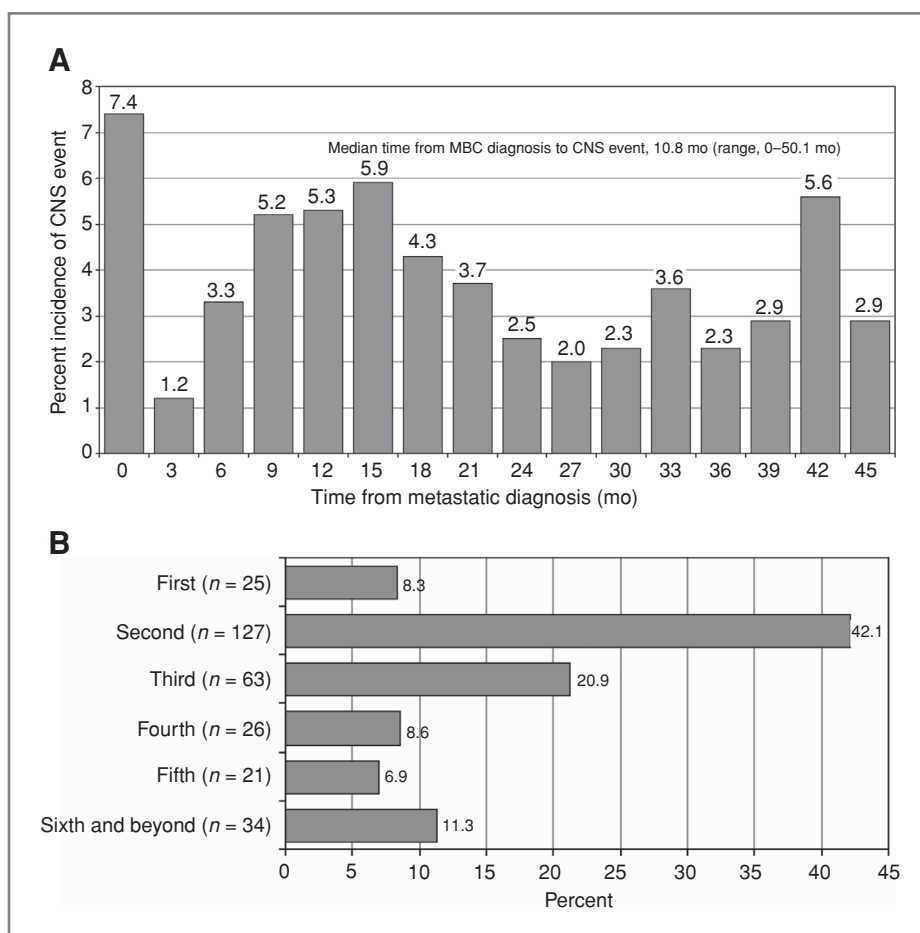
Figure 2. Progression to the CNS after initial MBC diagnosis (*n* = 302). A, incidence of CNS metastasis events by time from MBC diagnosis. Percentages represent number of patients who developed CNS metastases within the 3-month time window divided by the total number of patients at risk. B, line of treatment at first CNS progression. Line of treatment is defined as the systemic treatment patients received up until any CNS progressive disease event. Note: Because 6 (2%) patients were receiving no systemic treatment at the time of CNS metastases, they were not included in the graph.

Table 3. Multivariable proportional hazards analysis of survival after CNS metastases (*n* = 377)

	HR (95% CI)	*P*
Treatment received after first CNS event[a]		
Trastuzumab[b] (*n* = 258)	0.33 (0.25–0.46)	<0.001
Chemotherapy (*n* = 262)	0.64 (0.48–0.85)	0.002
Surgery (*n* = 29)	0.63 (0.39–1.02)	0.062
Radiation therapy (*n* = 269)	0.98 (0.75–1.30)	0.898
Cancer stage at initial dx		
Stage I–III (MBC dx ≤12 mo after initial dx) vs. stage IV	1.41 (0.95–2.10)	0.091
Stage I–III (MBC dx ≥12 mo after initial dx) vs. stage IV	0.96 (0.72–1.27)	0.767
ECOG PS at MBC diagnosis		
≥2 vs. 0 or 1	1.83 (1.14–2.96)	0.013
Unknown or missing vs. 0 or 1	1.12 (0.86–1.46)	0.405
Age, y	1.01 (1.00–1.02)	0.162
Hormone receptor status		
Positive vs. negative	0.80 (0.63–1.03)	0.088
Unknown vs. negative	1.04 (0.61–1.76)	0.888
CNS disease at MBC dx (yes vs. no)	0.50 (0.36–0.71)	<0.001

Abbreviation: dx, diagnosis.
[a]All comparisons made with patients not receiving the specified treatment; treatments not mutually exclusive.
[b]Seventy-one (27.5%) of patients who received trastuzumab after diagnosis of CNS metastases also received lapatinib (mostly after trastuzumab). No patients received only lapatinib after diagnosis of CNS metastases.
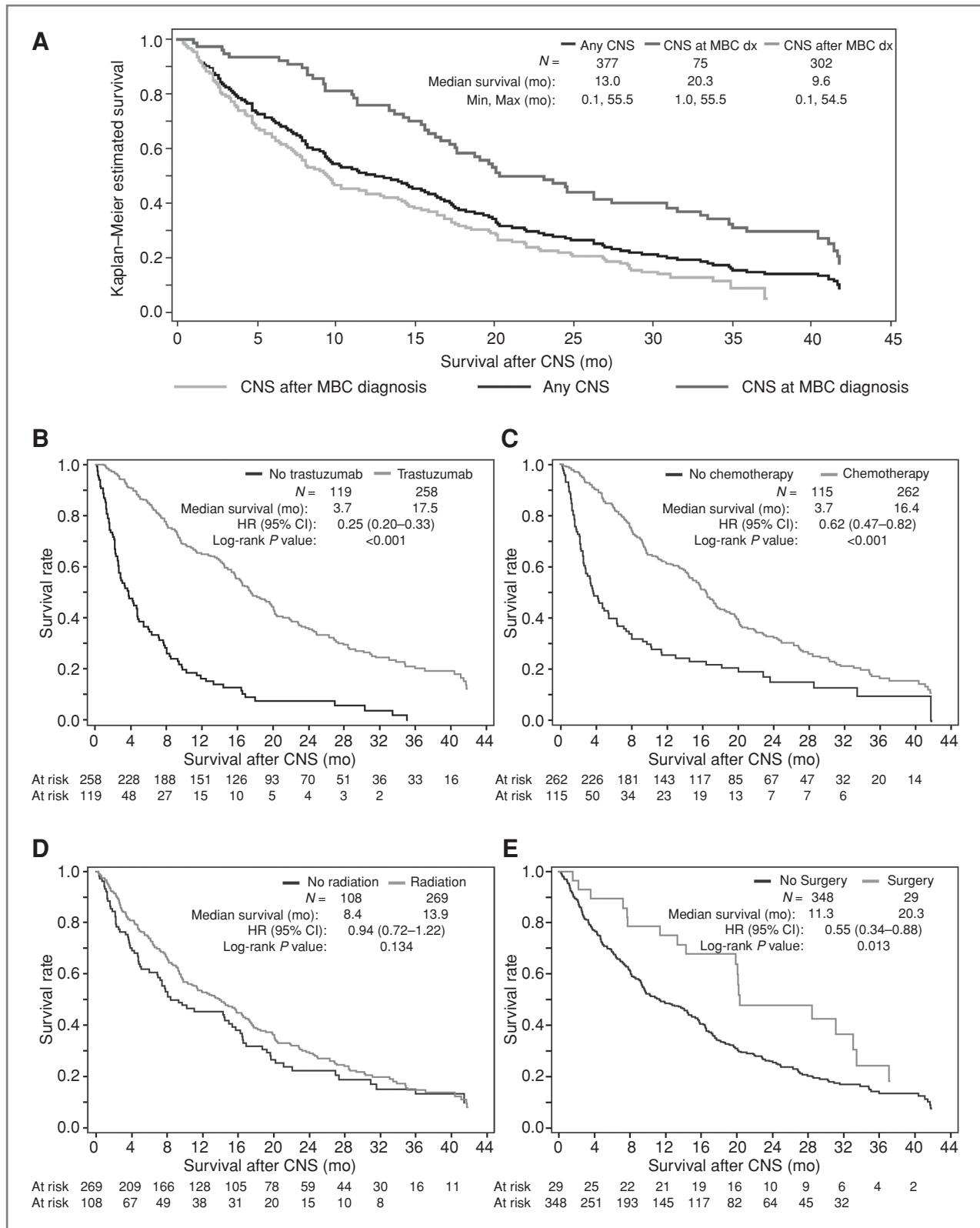
Figure 3. Post–CNS survival (unadjusted) as estimated by Kaplan–Meier methodology for all treated patients with CNS metastases. A, survival from time of CNS metastases for patients who had any CNS metastases (black), CNS metastases diagnosed after MBC diagnosis (light gray), or CNS metastases present at the time of MBC diagnosis (dark gray). dx, diagnosis. B–E, survival after first CNS event by treatment received after CNS metastasis. B, trastuzumab versus no trastuzumab. C, chemotherapy versus no chemotherapy. D, radiation therapy versus no radiation therapy. E, surgery versus no surgery. P values associated with log-rank test compare the Kaplan–Meier survival curves.

metastases were diagnosed subsequently (20.3 vs. 27.0 months). This is consistent with the possibility that patients with MBC who present with CNS metastases have a more aggressive disease.

An inherent limitation of a nonrandomized observational study results from "confounding by indication," whereby certain treatments are preferentially given to sicker patients and other treatments to healthier patients (e.g., patients who are candidates for surgical resection of their CNS tumors generally have a lower disease burden, a more favorable location of metastasis, overall better control of systemic extracranial disease, and may represent a patient population with a relatively better prognosis). Likewise, patients who received no therapy may represent a more debilitated group of patients. These results are consistent with several retrospective analyses (1, 2) and were corroborated by the multivariable analysis we conducted to adjust for clinically recognized prognostic factors and potential differences between treatment groups. In registHER, the reduction in death observed after treatment with trastuzumab, chemotherapy, and possibly surgery persisted after controlling for the key prognostic factors of age, ECOG PS, cancer stage at initial diagnosis, hormone receptor status, and CNS disease at metastatic diagnosis.

There also remains the potential for residual confounding by clinical factors that were not collected or sufficiently captured. For example, ECOG PS was missing for 52% of patients and represented ECOG PS at the time of the patient's MBC diagnosis, and not necessarily ECOG PS at the time CNS disease developed, which may have occurred months later. Therefore, the model did not fully account for this confounder. In addition, as data regarding post–CNS treatment were collected via questionnaire, those data may be incomplete. This could in part explain why patients treated with radiotherapy trended toward longer survival, yet the difference was not statistically significant. Alternatively, it may be that at the time registHER was conducted, it was not yet common practice to treat isolated CNS metastases with both WBRT and stereotactic radiotherapy, the practice now known to lead to longest survival (20). Finally, because patients may have a diagnosis of MBC up to 12 months prior to enrollment and patients with longer survival may be more likely to enroll, the OS estimates from time of MBC diagnosis in registHER may be slightly higher than expected in a general MBC patient population.

Results from registHER are consistent with recent data; for patients with MBC and CNS disease, median survival after CNS metastases was 6.1 months for patients with HER2-positive disease who received no trastuzumab ($n =$ 32) and 11.6 months for those with HER2-positive disease who did receive trastuzumab (8). Because most (78%) of the 91 patients who received lapatinib after CNS metastases also received trastuzumab, we were unable to accurately assess the independent effect of lapatinib as anti-HER2 therapy on survival after CNS metastases.

The finding that chemotherapy and trastuzumab treatment are associated with improved survival even after adjusting for relevant variables in patients after the development of CNS metastases is interesting. Because most chemotherapy agents used in the treatment of breast cancer either do not cross an intact BBB, or are pumped out of the CNS by phosphoglycoprotein in the endothelial cells comprising the BBB, they may not reach sufficient therapeutic levels to treat CNS metastases (21). Trastuzumab does not readily cross an intact BBB; in patients without CNS metastases (i.e., with an intact BBB), the ratio of trastuzumab in blood plasma to trastuzumab in the cerebral spinal fluid is greater than 300:1 (22, 23). However, in the setting of CNS lesions, the permeability of the BBB is likely increased via physical perturbation by tumors (24) and by structural changes in tumor microvessels that increase vascular permeability (25–27), including changes mediated by tumor-secreted factors such as VEGF (28). Recently, it has been shown in preclinical models that although the blood–tumor barrier (BTB) may show observable permeability changes in brain metastases, the BTB function in these models was only partly compromised and retained significant ability to impede chemotherapeutic uptake (29). Radiation therapy, which was received by 71% of the patients in registHER with CNS disease, has also been shown to increase BBB permeability (23). In addition, the finding of improved survival in patients receiving chemotherapy and trastuzumab treatment after the development of CNS metastases is a reflection of the importance of extracranial disease control with anti-HER2 therapy and chemotherapy, as a substantial proportion of patients with CNS metastases would likely die from their extracranial disease without adequate therapy (8).

A prospective study to determine which factors most affect treatment efficacy for CNS metastases of HER2-positive MBC would be of great interest.

Disclosure of Potential Conflicts of Interest

Acknowledgments

Grant Support

References

1. Pienkowski T, Zielinski CC. Trastuzumab treatment in patients with breast cancer and metastatic CNS disease. Ann Oncol 2010;21: 917–24.
2. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J Clin Oncol 2009;27:5278–86.
3. Miller KD, Weathers T, Haney LG, Timmerman R, Dickler M, Shen J, et al. Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. Ann Oncol 2003;14:1072–7.
4. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer 1983;52: 2349–54.
5. Weil RJ, Palmieri DC, Bronder JL, Stark AM, Steeg PS. Breast cancer metastasis to the central nervous system. Am J Pathol 2005;167: 913–20.
6. Kaal EC, Vecht CJ. CNS complications of breast cancer: current and emerging treatment options. CNS Drugs 2007;21:559–79.
7. Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, et al. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. J Clin Oncol 2006;24:5658–63.
8. Dawood S, Broglio K, Esteva FJ, Ibrahim NK, Kau SW, Islam R, et al. Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol 2008;19:1242–8.
9. Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17:279–86.
10. Black PM, Johnson MD. Surgical resection for patients with solid brain metastases: current status. J Neurooncol 2004;69:119–24.
11. Melisko ME, Moore DH, Sneed PK, De Franco J, Rugo HS. Brain metastases in breast cancer: clinical and pathologic characteristics associated with improvements in survival. J Neurooncol 2008;88: 359–65.
12. Mahmoud-Ahmed AS, Suh JH, Lee SY, Crownover RL, Barnett GH. Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. Int J Radiat Oncol Biol Phys 2002;54:810–7.
13. Chang EL, Lo S. Diagnosis and management of central nervous system metastases from breast cancer. Oncologist 2003;8:398–410.
14. Alexander E 3rd, Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87: 34–40.
15. O'Meara WP, Seidman AD, Yamada Y, McCormick B, Diamond S, Gutin PH, et al. Impact of HER2 status in breast cancer patients receiving stereotactic radiosurgery for brain metastases. J Clin Oncol 2005;23 Suppl:637.
16. Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer 2006;107:696–704.
17. Nam BH, Kim SY, Han HS, Kwon Y, Lee KS, Kim TH, et al. Breast cancer subtypes and survival in patients with brain metastases. Breast Cancer Res 2008;10:R20.
18. Park IH, Kwon Y, Ro JY, Lee KS, Ro J. Concordant HER2 status between metastatic breast cancer cells in CSF and primary breast cancer tissue. Breast Cancer Res Treat 2010;123:125–8.
19. Lin NU. Concordance of HER2 in primary tumor and leptomeningeal metastases: now what? Breast Cancer Res Treat 2010;123:129–31.
20. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665–72.
21. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004;22:3608–17.
22. Pestalozzi BC, Brignoli S. Trastuzumab in CSF. J Clin Oncol 2000; 18:2349–51.
23. Stemmler HJ, Heinemann V. Central nervous system metastases in HER-2-overexpressing metastatic breast cancer: a treatment challenge. Oncologist 2008;13:739–50.
24. Zhang RD, Price JE, Fujimaki T, Bucana CD, Fidler IJ. Differential permeability of the blood-brain barrier in experimental brain metastases produced by human neoplasms implanted into nude mice. Am J Pathol 1992;141:1115–24.
25. Davies D. Blood-brain barrier breakdown and oedema formation in systemic sepsis and human brain tumours. J Anat 2002;200: 528–9.
26. Papadopoulos MC, Saadoun S, Binder DK, Manley GT, Krishna S, Verkman AS. Molecular mechanisms of brain tumor edema. Neuroscience 2004;129:1011–20.
27. Gerstner ER, Fine RL. Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol 2007;25:2306–12.
28. Dobrogowska DH, Lossinsky AS, Tarnawski M, Vorbrodt AW. Increased blood-brain barrier permeability and endothelial abnormalities induced by vascular endothelial growth factor. J Neurocytol 1998;27:163–73.
29. Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA, et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. Clin Can Res 2010;16:5664–7.

Updated version	Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/17/14/4834

Cited articles	This article cites 29 articles, 8 of which you can access for free at: http://clincancerres.aacrjournals.org/content/17/14/4834.full#ref-list-1
Citing articles	This article has been cited by 19 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/17/14/4834.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/17/14/4834. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.