

## Brain Metastases: The HER2 Paradigm

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**Abstract** Between 100,000 and 170,000 patients with cancer develop central nervous system (CNS) metastases each year in the U.S., of which ~ 20% carry a primary diagnosis of breast cancer. As a consequence of improvements in systemic therapy, which have allowed patients to live longer with advanced cancer, CNS metastases are emerging as an important sanctuary site, and the incidence may be increasing in patients with particular tumor subtypes. Unless there are improvements in the treatment of CNS disease, a growing proportion of patients may be at risk of experiencing both morbidity and mortality as a result of uncontrolled CNS progression, often at a time when their extra-CNS disease is apparently under control. This article reviews changes in the epidemiology and natural history of women with brain metastases from HER2-positive breast cancer over the last decade and presents the therapeutic challenges and opportunities that have arisen in this setting. First, the apparent increase in CNS disease among women with HER2-positive breast cancer, relative to historical controls, is discussed, followed by consideration of potential causes of this observation. Next, the implications of CNS disease, in terms of prognosis and the potential development of preventive strategies are considered. Finally, new developments in systemic approaches to the treatment of CNS disease, including cytotoxic chemotherapy and targeted therapy, are explored.

Central nervous system (CNS) metastases, including parenchymal and leptomeningeal metastases, are the most common causes of malignant disease in the brain, and are diagnosed in 100,000 to 170,000 patients per year in the U.S. alone (1, 2). Palliative radiotherapy is associated with clinical improvement or stabilization in the majority of patients, but responses are often not durable (3, 4). Historically, the lack of durability was not a problem for most patients because brain metastases occurred late in the course of illness, and progression in non-CNS sites was the dominant source of morbidity and mortality (3). Thus, the development of novel approaches to the treatment of CNS metastases has not previously been considered of high priority. However, as systemic therapies improve, there is concern that the incidence of symptomatic brain metastases will increase, and that control of CNS disease will become a more vital component of overall disease control and quality of life (5).

In women with HER2-positive breast cancer, the widespread use of HER2-directed therapy with the monoclonal antibody trastuzumab has unmasked a population in whom CNS progression is a significant source of morbidity and mortality (Figure 1; ref. 6). In contrast to the historical experience, the diagnosis of CNS metastasis frequently occurs despite excellent

systemic disease control. This "HER2 paradigm" has potentially broader implications, as similar advances in systemic therapy are being made in other subtypes of breast cancer and in other primary tumor types. The combination of a tumor type that has a high potential for CNS spread and a treatment that does not penetrate the CNS but is very effective outside of the CNS creates the opportunity for CNS disease to become a major clinical problem. Fortunately, new opportunities to improve the outcomes of patients with brain metastases are becoming increasingly available.

### Epidemiology of CNS Metastases

The incidence of CNS metastases varies by tumor site, with primary lung and breast carcinomas accounting for the bulk of patients. Barnholtz-Sloan et al. reported the incidence of brain metastases among patients diagnosed with a variety of solid tumors in the Metropolitan Detroit Cancer Surveillance System between 1973 and 2001 (7). Across five different primary sites (lung, breast, melanoma, renal, colorectal), the overall incidence of brain metastases was 9.6%. For breast cancer, the risk of developing CNS disease varied according to stage at initial diagnosis. Only 2.5% of patients who initially presented with localized disease ultimately developed CNS disease, whereas 7.6% of patients diagnosed with regional disease, and 13.4% of patients presenting with stage IV disease were eventually found to have CNS involvement. These data are consistent with historical estimates of clinically evident brain metastases among patients with advanced breast cancer, which are in the range of 10% to 16% (7–10). To date, there have not been prospective screening studies of serial computed tomography or magnetic resonance imaging to evaluate the rate of occult CNS metastasis in patients with breast cancer over time.

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However, Miller et al. described a 14.8% incidence of occult CNS involvement in heavily pretreated breast cancer patients identified as part of eligibility screening for four clinical trials, with a median time of 12 months from first distant metastasis to CNS screening study identifying CNS metastases (11). In a multivariate analysis, HER2 overexpression and the number of metastatic sites were significant predictors of CNS involvement. In contrast, at autopsy, brain metastases are found in 30% of patients with advanced breast cancer. Thus, many patients have, in the past, likely succumbed to systemic progression prior to the appearance of neurologic symptoms from coexisting and unrecognized CNS disease (12, 13).

More recent series have raised the possibility that with more effective systemic treatment, CNS disease may be seen earlier in time. For example, in a retrospective study of 768 patients treated with multimodality therapy for locally advanced or inflammatory breast cancer at M.D. Anderson Cancer Center, of the 61 patients who developed CNS metastases, the median time from initial breast cancer diagnosis to detection of CNS disease was only 2.3 years (14). Similar results were seen in a retrospective study of stage II and III patients treated at the University of North Carolina, in which the median time from diagnosis to CNS recurrence was 24 months (15). Several hypotheses have been forwarded to explain these findings: first, studies of patients with locally advanced breast cancer are likely to be skewed towards more aggressive tumor subtypes, and second, systemic chemotherapy does not adequately treat micrometastases within the CNS.

Risk factors for the development of CNS metastases from breast cancer include patient characteristics, such as young age and African-American ethnicity, and biological features of the tumor, including ER-negativity, HER2-positivity, high tumor grade, and BRCA1 phenotype (7, 8, 11, 14, 16–21). The remainder of this review will focus on the association

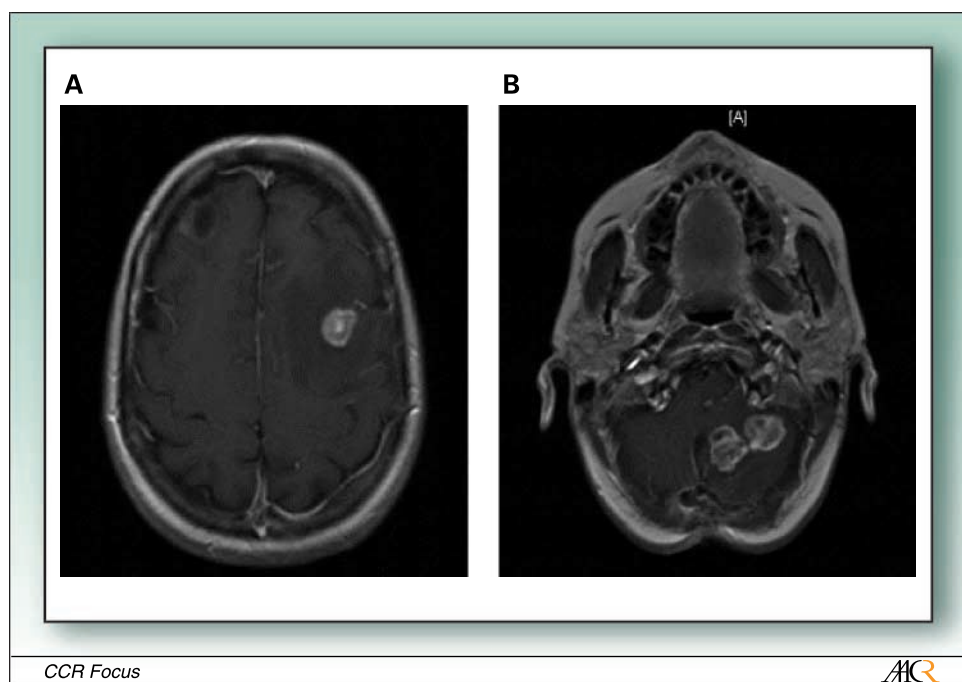
between HER2 status and CNS metastases, and explore the implications of this finding.

### Apparent Increase in CNS Metastases in HER2-Positive Breast Cancer

HER2 (Her2-/*neu*, *c-erbB-2*) is a 185-kDa transmembrane tyrosine kinase with extensive homology to the epidermal growth factor receptor (Fig. 2; refs. 22, 23). In humans, amplification of the HER2 oncogene occurs in ~25% of primary breast carcinomas, and is associated with diminished disease-free and overall survival (Fig. 3; refs. 24, 25).

Trastuzumab is a humanized, monoclonal antibody directed against the extracellular domain of HER2. Trastuzumab was approved as first-line chemotherapy in patients with HER2-positive, metastatic breast cancer based on data from the pivotal trial demonstrating that the addition of trastuzumab to cytotoxic chemotherapy improved both disease-free and overall survival (26). However, soon after the introduction of trastuzumab in the late 1990s, clinicians began to observe an apparent increase in the incidence of CNS metastases over historical estimates. This clinical observation led to a series of retrospective studies documenting an incidence of ~25% to 40% across multiple institutions (Table 1; refs. 6, 8, 21, 27–30).

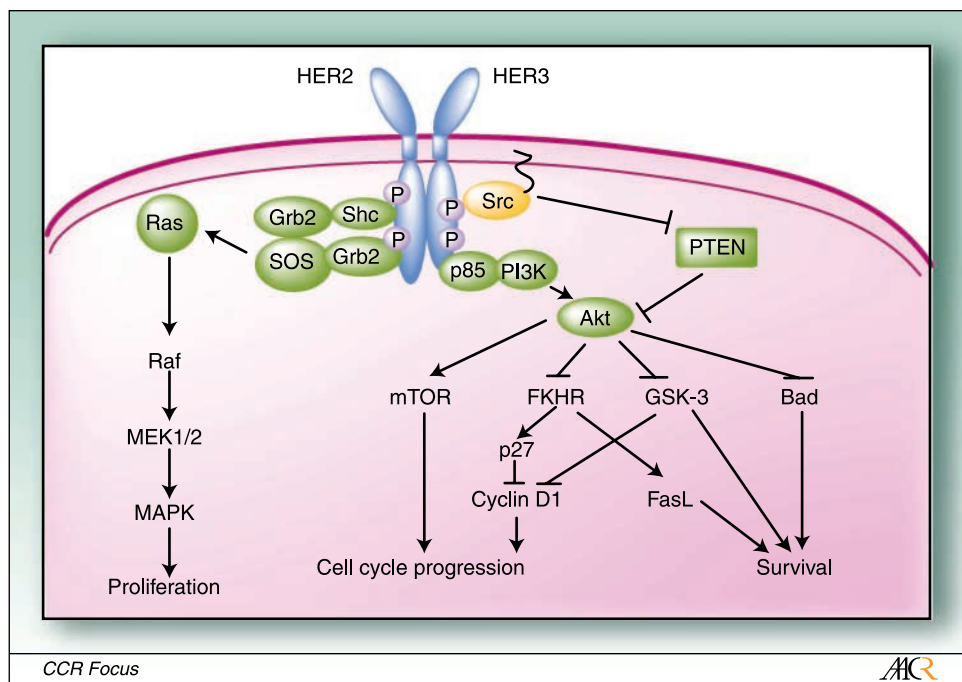
In the retrospective studies described above, the majority of patients underwent imaging examinations for clinical symptoms (i.e., evaluation of headache, focal neurologic deficits, etc.). One study evaluated the incidence of occult CNS metastases among 32 consecutive asymptomatic patients with HER2-positive breast cancer treated with trastuzumab and chemotherapy for visceral metastases and/or locoregional failure (31). In this report, 34% of patients had screen-detected brain metastases. It is yet to be determined whether early detection of CNS metastases improves outcomes, either by



**Fig. 1.** Axial MRI images (T1-weighted, post-gadolinium) showing multiple parenchymal metastases involving the left frontal lobe (A) and left cerebellum (B) in a patient with HER2-positive breast cancer.

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**Fig. 2.** The HER2 signaling pathway. Ligand binding induces dimerization, leading to activation of the intracellular tyrosine kinase. On auto- and cross-phosphorylation of the receptor complex, key downstream effectors are recruited. This figure illustrates a HER2-HER3 heterodimer, but HER2 can also form homodimers or heterodimerize with other members of the HER2 family. FKHR, forkhead in rhabdomyosarcoma; Grb2, growth factor receptor-bound protein 2; GSK-3, glycogen kinase synthase-3; MAPK, mitogen-activated protein kinase; mTOR, molecular target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; SOS, son-of-sevenless guanine nucleotide exchange factor.

improving survival, or by delaying or preventing the appearance of neurologic symptoms.

### What Accounts for the Apparent Increase in CNS Disease in Women with HER2-Positive Breast Cancer?

The apparent increase in CNS disease in women with metastatic, HER2-positive breast cancer is likely multifactorial, and could include inherent biological factors and treatment-related factors.

Two studies have examined the association between HER2 status and the risk of brain metastasis in women with operable breast cancer, treated in the pre-trastuzumab era. In a study of 319 patients, Kallioniemi et al. described a differing pattern of metastatic spread according to HER2 status, with a significantly higher risk of visceral metastases (including CNS metastases) in patients with HER2-positive tumors (32). However, the number of brain events was quite small, thus precluding any definitive conclusions. More recently, a retrospective analysis of 9,524 women with early stage breast cancer, who were enrolled in 10 adjuvant trials led by the International Breast Cancer Study Group, has identified HER2 as a risk factor for the development of CNS relapse (33). These trials were conducted between 1978 and 1999, at a time when adjuvant trastuzumab was not in use. The 10-year cumulative incidence of CNS disease as site of first relapse was 2.7% in patients with HER2-positive primary tumors, compared with 1.0% in patients with HER2-negative tumors ( $P < 0.01$ ). The 10-year cumulative incidence of CNS metastasis as either first or subsequent event was 6.8% versus 3.5% ( $P < 0.01$ ), again with a higher incidence seen in patients presenting with HER2-positive primary tumors. The

results strongly suggest that HER2-positive tumors carry a biological predisposition to metastasize to the CNS.

In addition, the available evidence suggests that trastuzumab does not penetrate the blood-brain barrier well, even in the presence of brain metastases (34, 35). In one study, the ratio of serum to cerebrospinal fluid trastuzumab level was 420:1. Even after whole brain radiotherapy, which is thought to disrupt the blood-brain barrier in and of itself, the ratio was 76:1 (35). Therefore, the CNS is a potential sanctuary site in patients with HER2-positive disease treated with trastuzumab. This hypothesis is strengthened by the observations of Burstein et al. who characterized the incidence and timing of isolated CNS metastases in patients with advanced breast cancer treated with first-line trastuzumab-based therapy (36). In the context of two multicenter trials, a 10% incidence of isolated CNS progression was identified, with CNS progression events occurring in the presence of continued control of non-CNS disease. Indeed, in several series which examined CNS progression as first or subsequent event, more than two-thirds of patients presented with CNS metastases at a time when their systemic disease remained either stable or responsive to trastuzumab. These data support the hypothesis that improvements in systemic control and overall survival associated with trastuzumab-based therapy have led to an "unmasking" of brain metastases that would otherwise have remained clinically silent prior to a patient's death (6, 30, 37).

### CNS Metastases in Adjuvant Trials of Trastuzumab

The role of trastuzumab in the treatment of patients with high risk, early-stage, HER2-positive breast cancer has been examined in four large, randomized controlled trials, and one

smaller study (38–41). In these studies, the addition of trastuzumab to standard chemotherapy unequivocally reduced the recurrence rate, including the risk of distant metastases, and represents a major advance in the care of this patient subgroup.

Because of the apparent increased risk of CNS metastases observed in women with metastatic, HER2-positive breast cancer, CNS metastasis events were separately reported in several of the adjuvant studies. In the combined analysis of NSABP B-31 and N9831, there was a numeric increase in the number of CNS metastases as first event in the trastuzumab-treated arms, compared with the control arms (Table 2). This trend was also observed in the HERA study. In NSABP B-31, subsequent recurrence events were also captured; when the data were analyzed in this manner, there was no significant difference seen in CNS metastases as first or subsequent event between arms (28 events in the trastuzumab group versus 35 events in the control group;  $P = 0.35$ ). Hence, it does not seem that trastuzumab increases the risk of CNS relapse per se; rather, these data suggest that the CNS is a sanctuary site due to the inability of trastuzumab to cross the blood-brain barrier.

### Is There a Role for Prophylactic Cranial Irradiation in Patients with Breast Cancer?

Prophylactic cranial irradiation (PCI) is considered standard-of-care in patients with small cell lung cancer who achieve complete remission (42). Without PCI, the incidence of brain metastases is 59% to 67% (43, 44). In a metaanalysis of seven randomized trials comparing PCI to observation, there was a significant reduction in the cumulative incidence of brain metastasis (relative risk, 0.46; 95% confidence interval, 0.38–0.57;  $P < 0.001$ ; absolute incidence 33.3% versus 58.6%) and in the risk of death (relative risk, 0.84;

95% confidence interval, 0.73–0.97;  $P = 0.01$ ; ref. 45). The reduction in risk of death corresponded to an improvement in 3-year survival from 15.3% to 20.7%. In terms of neuropsychologic outcomes, the published literature suggests that significant detrimental effects are relatively uncommon, but the data are limited by the small number of patients with long-term follow-up, the sensitivity of the neuropsychological assessment tools, the high rate of brain metastasis in the untreated group (which itself can lead to cognitive dysfunction), confounding effects of other treatments (such as chemotherapeutic agents), and baseline abnormalities in cognitive function (44, 46, 47).

In considering the potential role of PCI in patients with breast cancer, it is important to note that the absolute risk of CNS metastasis across the adjuvant trastuzumab trials, at a median follow-up of 1 to 2 years, has been  $<5\%$  (38, 39). Therefore, widespread screening approaches in patients with early-stage breast cancer are not likely to be cost-effective, nor is it clear that such approaches would improve survival or enhance the quality of life. Given the potential neurocognitive effects associated with PCI, even if they prove to be relatively minimal, this modality is not likely to be studied in the adjuvant setting, unless a particular group at high-risk can be identified. If, however, we are to eradicate mortality from HER2-positive breast cancer, new approaches to prevent and treat HER2-positive CNS disease are needed.

In patients with metastatic, HER2-positive breast cancer, in whom one-third will develop CNS metastases, a number of investigators have been interested in considering trials to evaluate the role of PCI. Although long-term remissions are relatively uncommon in patients with metastatic breast cancer, approximately half of patients are alive at 2 years, and a small subset of women live for many years with advanced disease (48–50). Therefore, if trials of PCI are initiated in patients with

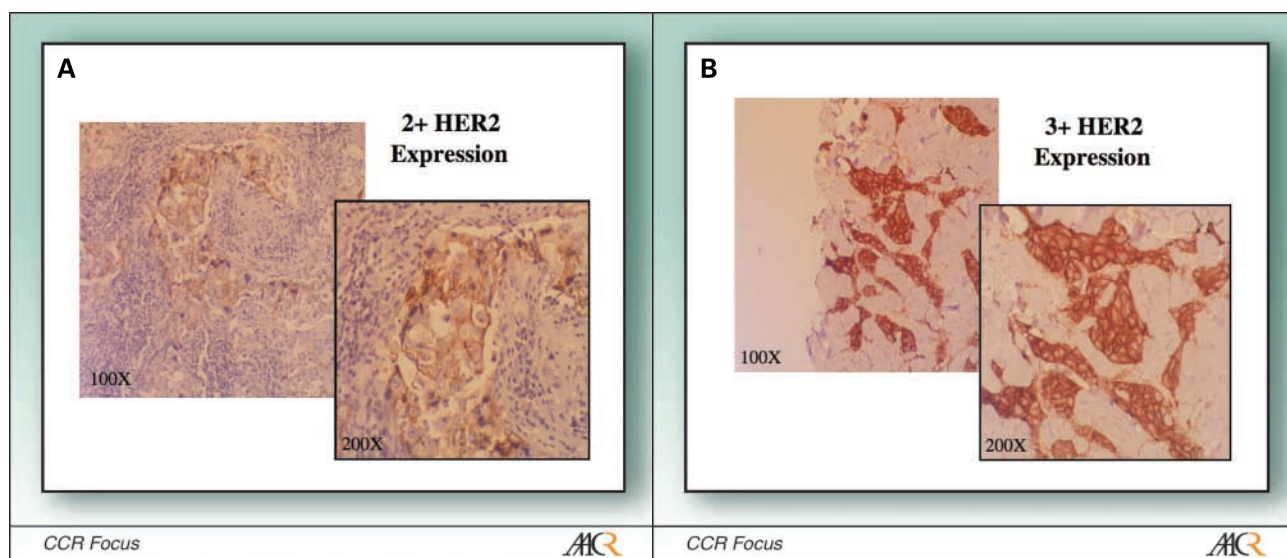


Fig. 3. Immunohistochemical staining with rabbit anti-Her2/neu antibody DAKO A0485 (magnification,  $\times 200$ ), showing (A) moderate (2+) and (B) strong (3+) expression of HER2. Courtesy of Dr. Maria Merino, National Cancer Institute, Bethesda, MD.

**Table 1.** Incidence of brain metastases among patients with HER2+ breast cancer

Study	Design	No. of patients with metastatic breast cancer	Incidence of CNS metastases (%)	Median survival from CNS diagnosis (mo)
Bendell et al. (6)	Retrospective chart review, all patients initiating trastuzumab between 1998 and 2000	122	34	13
Altaha et al. (29)	Retrospective chart review, patients with HER2-positive breast cancer diagnosed between 1998 and 2003	31	48	Not reported
Clayton et al. (30)	Retrospective chart review, all patients initiating trastuzumab between 1999 and 2002	93	25	5.4
Stemmler et al. (28)	Retrospective chart review, all patients who had received trastuzumab between 2000 and 2004	136	30.9	13
Yau et al. (27)	Retrospective chart review, all patients who had received trastuzumab between 1999 and 2003	87	30 (at 1 y)	4

breast cancer, it will be critical to include detailed neuropsychologic assessments, as late toxicity is a major concern for both patients and clinicians.

### Prognosis

Historically, the median survival of patients with breast cancer metastatic to brain has been poor, ranging from 3 to 6 months (51). Less than 20% of patients survived >1 year.

Several groups have published retrospective studies describing improved survival from time of diagnosis of brain metastases diagnoses in patients with HER2-positive, compared with HER2-negative breast cancers, although the data are not entirely consistent (52–54). For example, O'Meara et al. describe a significantly improved likelihood of 1-year survival in patients with HER2-positive breast cancer treated with stereotactic radiosurgery, compared with similar patients with HER2-negative breast cancer (78% versus 55%;  $P = 0.02$ ; ref. 52). Among patients treated at the Massachusetts General Hospital from 1998 to 2003, the median survival was also significantly longer from time of brain metastasis diagnosis in HER2-positive patients (22.4 versus 9.4 months;  $P = 0.0002$ ; ref. 55). Of interest, in this study, the difference in survival could not be explained by differential control of brain metastases, leading the authors to conclude that improvements in control of non-CNS disease was the primary driver of improved outcomes. In contrast, Tham et al. describe a shorter survival in patients with HER2-positive brain metastases, compared with patients with HER2-negative disease (56). An important difference is that the latter study spanned the years

from 1970 to 1999, prior to the trastuzumab era. We and others have hypothesized that prior to the availability of trastuzumab, control of systemic disease was the major limiting factor in the survival of women with HER2-positive, metastatic breast cancer. Since then, a number of groups, including our own, have described an apparent increase in the proportion of patients dying of CNS disease progression, compared with historical estimates. For example, in a retrospective series of 122 patients treated with trastuzumab between 1998 and 2000 at Dana-Farber/Partners Cancer Care, of the 21 patients with brain metastases who died, 52% apparently succumbed from CNS progression, in the face of stable or responsive non-CNS disease (6). It seems, then, that the improvement in survival can be largely attributed to the effects of trastuzumab on control of other sites of visceral metastasis (57).

### New Directions

Historically, few prospective trials have been conducted for the treatment of brain metastases from breast cancer. Most studies of novel agents have specifically excluded women with known CNS disease, and the majority of published trials of brain metastasis treatments have grouped together patients with a variety of solid tumors. A further challenge involves the assessment of clinical and radiographic response in the CNS, which involves complexities not present in the evaluation of non-CNS disease. However, as the survival of patients with metastatic breast cancer improves, developing novel approaches to treating CNS metastasis will become increasingly important.

**Table 2.** CNS metastasis events reported in adjuvant trastuzumab trials

Trial	Median follow-up (y)	Any distant metastasis as first event		CNS metastasis as first event		CNS metastasis at any time	
		1 Y of trastuzumab, no. (%)	No trastuzumab, no. (%)	1 Y of trastuzumab, no. events	No trastuzumab, no. events	1 Y of trastuzumab, no. events	No trastuzumab, no. events
NSABP B-31	2.4	60 (6.9)	111 (12.7)	21	11	28	35
N 9831	1.5	30 (3.7)	63 (7.8)	12	4	Not reported	Not reported
HERA	1.0	85 (5.0)	154 (9.1)	21	15	Not reported	Not reported

In contrast to the evaluation of non-CNS disease, in which Response Evaluation Criteria in Solid Tumors is a widely used standard across clinical trials, or the evaluation of primary CNS lymphoma for which unified response criteria have recently been proposed, studies of patients with CNS metastases from solid tumors have used a variety of criteria to classify response to treatment (58, 59). Variations include the imaging modalities allowed (e.g., computed tomography or magnetic resonance imaging), the method and number of dimensions of measurement, cutoffs for response, and inclusion or exclusion of neurologic symptoms and/or corticosteroid use in the definition of response. Results of studies in patients with high-grade gliomas have been somewhat conflicting, with some studies reporting good concordance between linear, bidimensional, and volumetric methods in assessing objective response and time to progression, and other studies reporting discrepancies between methods (60–62). There is a relative paucity of data comparing these approaches in metastatic brain tumors, but the limited data indicate that volumetric measurements may ultimately provide the most precise estimate of tumor size, and may also lead to earlier identification of CNS progression (63, 64). Distinguishing tumor progression from radiation necrosis is a unique challenge in patients with CNS disease, a problem compounded by the difficulty in accessing tissue for definitive diagnosis. Ultimately, we may need to turn to novel imaging techniques, which could include metabolic imaging with positron emission tomography, magnetic resonance assessment of vascular tortuosity or permeability, and/or magnetic resonance spectroscopy, each of which has promise in the evaluation of metastatic CNS lesions (65–68).

Systemic approaches to the treatment of CNS metastases include the following: (a) cytotoxic chemotherapy, (b) targeted therapies, (c) radiation sensitizers, and (d) novel drug delivery techniques. Here, we discuss chemotherapy and targeted therapies. Elsewhere in the *Focus* section, in this issue of *Clinical Cancer Research*, Patel and Mehta discuss radiation sensitizers (69) and Löscher et al. explore novel drug delivery techniques (70).

Although most cytotoxic agents do not cross the blood-brain barrier under normal conditions, there is evidence that the blood-tumor barrier is far more permissive (71, 72). Therefore, it is likely that responses in the CNS are influenced by similar considerations as systemic response, such as prior therapy and the biological characteristics of the tumor. Retrospective case series and case reports of responses to a wide variety of regimens have been published (8). A limited number of chemotherapeutic agents have also been prospectively evaluated in small phase I/II trials, including temozolomide, liposomal doxorubicin, topotecan, capecitabine, and cisplatin (73–78). Of these agents, temozolomide has been examined in multiple phase 2 studies. The results are somewhat conflicting, but in general, the rate of response has been low. This finding is not surprising given the minimal activity of temozolomide in patients with extra-CNS disease. For example, Trudeau et al. conducted a phase 2 trial which was closed after no responses were observed in the first 18 patients (76). The low response rate in the brain with temozolomide in patients with metastatic breast cancer illustrates an important point: an agent must

have activity against breast cancer if it is going to be effective in treating brain metastases from breast cancer. In contrast, clinical activity in the brain has been reported with capecitabine, an agent that is effective against breast cancer, both in case report format, and recently, in the context of a phase I trial of combined capecitabine and temozolomide (75, 79). Despite the promise of targeted therapies, it is likely that cytotoxic agents will retain an important role. Newer agents with activity in refractory breast cancer and that reach reasonable levels within brain metastases are eagerly awaited.

Because brain metastases seem to maintain the HER2 status of the primary tumor, there has been interest in evaluating HER2-targeted therapies in this setting (80, 81). Although trastuzumab does not easily penetrate the brain, the experience with gefitinib in patients with brain metastases from non-small cell lung cancer suggests that small molecule inhibitors may have activity in the brain (82). Results from a phase 2 study of lapatinib, a dual inhibitor of epidermal growth factor receptor and HER2, for patients with progressive, HER2-positive CNS metastases have recently been presented (83). Although the study did not meet its primary end point (which would have required at least four objective responses in the CNS), there was preliminary evidence of clinical activity, with two objective responses in the CNS observed among 39 patients with refractory breast cancer. There was also a numerical decrease in the number of patients experiencing CNS progression on a phase 3 trial comparing capecitabine alone versus capecitabine plus lapatinib in women with advanced breast cancer (but without active CNS disease), although the number of events was small, and the difference did not reach statistical significance (84). A larger phase 2 study in patients with active CNS metastases has recently completed accrual and results are pending. In addition to lapatinib, multiple other small molecule HER2 inhibitors (BIBW 2992, HKI-272) are in clinical development for systemic breast cancer treatment, and may also hold promise in this setting (85, 86).

Preclinical evidence in mouse models suggests that vascular endothelial growth factor expression may play an important role in the establishment of brain metastases, and that inhibition with antiangiogenic agents may decrease the risk of metastatic spread (87). Of interest, HER2 and vascular endothelial growth factor overexpression are correlated, and vascular endothelial growth factor expression adds to the prognostic information provided by HER2 alone (88). Promising activity has been observed in studies of combined trastuzumab and bevacizumab in patients with HER2-positive metastatic breast cancer, supporting the hypothesis that antiangiogenic agents may be particularly useful against HER2-positive disease (89, 90). Out of the concern for intracranial hemorrhage, patients with brain metastases have been excluded from the vast majority of studies of bevacizumab and other antiangiogenic agents. However, bevacizumab has now been studied in a phase 2 trial in combination with irinotecan in patients with recurrent malignant gliomas (91). In this study, there was encouraging preliminary safety data and an impressive response rate of 63%. These data argue for cautious evaluation of antiangiogenesis agents in patients with brain metastases, with careful attention to safety indices given the potential risks of bleeding.

## Conclusion

CNS metastases contribute to significant morbidity and mortality in patients with advanced cancers. As systemic therapies for cancer continue to improve, it is likely that CNS metastases will become increasingly prevalent, and that a greater proportion of patients will develop CNS progression after standard approaches, such as cranial radiotherapy. As an example, the introduction of trastuzumab has altered the

natural history of patients with HER2-positive breast cancer, and unmasked CNS metastases as a potential sanctuary site. It is anticipated that this HER2 paradigm is applicable across tumor types, as patients live longer with advanced cancer. At the same time, because of the relative stability of non-CNS disease in a greater proportion of patients than in the past, there is a greater need to conduct carefully designed trials of both cytotoxic chemotherapeutic agents and targeted agents, either alone, or in combination, with specific CNS end points.

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