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Brain metastases in Asian HER2-positive breast cancer patients: anti-HER2 treatments and their impact on survival

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BACKGROUND: In Asia, large-scale studies on anti-HER2 treatment in HER2-positive breast cancer patients with brain metastases are limited. We studied the treatment patterns of these patients in Asia to evaluate the impact of anti-HER2 treatment on the time to occurrence of brain metastases (TTBM) and survival after brain metastasis (BM).

METHODS: A retrospective study of HER2-positive breast cancer patients diagnosed with BM between January 2006 and December 2008 in six Asian countries was conducted. Demographics, tumour characteristics, treatment details, and events dates were collected from medical records.

RESULTS: Data from 280 patients were analysed. Before BM, 63% received anti-HER2 treatment. These patients had significantly longer TTBM than those without anti-HER2 treatment (median 33 *vs* 19 months; $P<0.002$). After BM, 93% received radiotherapy, 57% received chemotherapy, and 41% received anti-HER2 treatment (trastuzumab and/or lapatinib). Use of both anti-HER2 agents, primarily sequentially, after BM demonstrated the longest survival after BM and was associated with a significant survival benefit over no anti-HER2 treatment (median 26 *vs* 6 months; hazard ratio 0.37; 95% CI 0.19–0.72).

CONCLUSION: Anti-HER2 treatment before BM was associated with longer TTBM. Anti-HER2 treatment after BM was associated with a survival benefit, especially when both trastuzumab and lapatinib were utilised.

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Brain metastases are associated with substantial morbidity and mortality in cancer (DiStefano *et al*, 1979). The incidence of metastases to the brain is particularly high in patients with human epidermal growth factor receptor 2 (HER2 or ErbB2)-positive breast cancer (Bendell *et al*, 2003; Clayton *et al*, 2004; Shmueli *et al*, 2004; Stemmler *et al*, 2006; Park *et al*, 2009a).

Trastuzumab-based treatment is regarded as standard treatment of care for HER2-positive breast cancer because of its proven survival benefits (Slamon *et al*, 2001; Vogel *et al*, 2002). Trastuzumab-based treatment has also been shown to delay the development of brain metastases (Dawood *et al*, 2008; Park *et al*, 2009b). However, consensus guidelines on systemic treatment after the development of brain metastasis (BM) in HER2-positive breast cancer are limited (NCCN, 2011). Published studies on the effect of trastuzumab-based treatment on survival after BM reported mixed results. Although some studies demonstrated significant survival benefit (Bartsch *et al*, 2007; Park *et al*, 2009b; Le Scodan *et al*, 2011), another study showed no significant benefit after having adjusted for confounders (Dawood *et al*, 2008). The observed survival benefit may also be attributed to better control of extracranial disease rather than BM, as trastuzumab penetrates the blood–brain barrier poorly (Pestalozzi and Brignoli, 2000; Altundag *et al*, 2005).

These findings highlight the need for new therapeutic approaches to effectively prevent or treat brain metastases in HER2-positive breast cancer patients. Lapatinib, a small-molecule, dual HER-1/HER-2 inhibitor, which can potentially cross the blood–brain barrier, has shown promising effects on brain metastases in both preclinical and clinical settings. In preclinical models, lapatinib showed activity in inhibiting BM and reducing the number of large HER2-transfected brain metastases (Gril *et al*, 2008). In clinical studies, lapatinib was effective in volumetric

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reduction of brain lesions as monotherapy (Lin *et al*, 2008; Lin *et al*, 2009) and in combination with capecitabine (Boccardo *et al*, 2008; Lin *et al*, 2009; Ro *et al*, 2010; Sutherland *et al*, 2010; Bachelot *et al*, 2011; Lin *et al*, 2011). Lapatinib and capecitabine combination therapy was also effective in reducing BM as the first site of recurrence (Cameron *et al*, 2008). More recently, a few observational studies have demonstrated positive impact on survival in limited numbers of HER2-positive breast cancer patients treated with lapatinib alone (Park *et al*, 2009a) or in combination with trastuzumab and chemotherapy (Metro *et al*, 2011; Bartsch *et al*, 2012) after BM.

To date, most observational studies on HER2-positive breast cancer patients with brain metastases have investigated the use of trastuzumab only, primarily in Western populations (Stemmler *et al*, 2006; Yau *et al*, 2006; Bartsch *et al*, 2007; Lichinitser *et al*, 2007; Dawood *et al*, 2008; Niwinska *et al*, 2010). In Asia, there is a paucity of large-scale studies on anti-HER2 treatment in HER2-positive breast cancer patients with brain metastases and its impact on BM-related outcomes in 'real world' clinical practice. We conducted a multicentre, retrospective study of HER2-positive breast cancer patients diagnosed with BM in six Asian countries. This report aims to: (i) describe the current treatment paradigm for brain metastases in HER2-positive breast cancer patients in Asia, with specific focus on the use of anti-HER2 treatment; and (ii) understand the potential clinical role of anti-HER2 treatments on time to BM as well as survival after the development of brain metastases.

PATIENTS AND METHODS

Study design and population

In this retrospective observational study, consecutive female HER2-positive breast cancer patients diagnosed with BM between January 2006 and December 2008 were identified from hospital medical records and databases in 23 medical centres in six Asian countries (Indonesia, Korea, Malaysia, Philippines, Singapore, and Thailand). Women who had leptomeningeal metastases only or another primary cancer diagnosed between the time of diagnosis of breast cancer and brain were excluded from this study.

HER2 positivity was defined as either HER2 immunohistochemistry (IHC) 3+ staining or positive HER2 fluorescence *in situ* hybridisation (FISH). Brain metastases were diagnosed by computed tomography and/or magnetic resonance imaging with neurological signs and symptoms.

Patient demographics, tumour characteristics at diagnosis, dates of metastatic events, treatment details, and survival status were abstracted from medical records. All patients were followed until either the date of death or the last-known physician visit on or before 30 June 2009. This study was approved by all local institutional review boards.

Statistical methods

Patient demographics and tumour characteristics were summarised overall and by receipt of anti-HER2 treatment after BM. Comparisons between groups used the χ^2, Fisher's exact or Kruskall–Wallis test, where appropriate.

Time to occurrence of brain metastases (TTBM) was defined as the time from initial diagnosis of HER2-positive breast cancer to the diagnosis of BM. Brain as first site of metastasis was defined as the presence of brain metastases in the absence of other synchronous metastases. Overall survival (OS) after BM was defined as the time from diagnosis of BM to death (event) or last follow-up visit (censor).

Kaplan–Meier estimates of median TTBM overall and stratified by anti-HER2 treatment before BM were calculated and compared using the log-rank test. As there were insufficient numbers of patients treated with individual anti-HER2 treatments before BM diagnosis, exposure before BM was reported as a binary variable (any or no anti-HER2 treatment). Brain as first site of metastasis was stratified by receipt of anti-HER2 treatment in the adjuvant setting and compared using the χ^2 test. As trastuzumab alone was the only anti-HER2 treatment received in the adjuvant setting, exposure in the adjuvant setting was reported as a binary variable (adjuvant trastuzumab or no adjuvant trastuzumab treatment).

Median OS after BM was also estimated by Kaplan–Meier method and compared using the log-rank test. Exposure to anti-HER2 treatment after BM was reported both as a binary variable (any or no anti-HER2 treatment) and as a detailed variable that separated patients into those who received either trastuzumab alone, lapatinib alone, both agents or no anti-HER2 treatment. Patients in the 'both agents' category may have received the anti-HER2 agents either sequentially or concomitantly.

Univariate and multivariate Cox regression analyses were performed to identify independent predictors of OS after BM. Adjusted Cox proportional hazard models were also developed to estimate the association between anti-HER2 treatment received after BM and OS after BM. Potential confounding variables that were significantly associated with both the likelihood of receiving anti-HER2 treatment after BM and with OS after BM were entered into a backward selection model, which retained only those variables significant with a P-value of $\leqslant 0.05$.

Sensitivity analyses of the final fully adjusted model were conducted to explore the robustness of the adjusted hazard ratios (HRs). The adjusted Cox proportional hazard models were refitted after having relaxed the proportional hazards assumption for key confounders (chemotherapy and hormonal therapy after BM) that may have a time-dependent effect on OS after BM.

RESULTS

Patient demographics and characteristics

A total of 311 patients were initially identified as potential study candidates; 31 patients were subsequently excluded either due to lack of information on HER2 testing or due to lack of FISH confirmation for tumours graded 2+ by IHC. The remaining 280 patients with confirmed HER2-postive breast cancer were included in this final analysis (Figure 1). Among these 280 patients, 239 were graded 3+ by IHC with or without confirmatory FISH, 21 were graded 2+ by IHC with FISH confirmation, and 20 were graded FISH-positive alone.

Approximately one-half (48.9%) of the patients came from Korea, while 25.4%, 13.6%, 9.6%, 1.8%, and 0.7% were from Singapore, Thailand, Malaysia, Indonesia, and Philippines, respectively. The majority of patients (75.7%) were treated in public medical centres.

Table 1 shows the demographics and clinical features at diagnosis of breast cancer and BM in the analysed population and in different anti-HER2 treatment groups. The median age at diagnosis of BM was 52 years. Three-quarters (76.8%) of patients had multiple brain lesions and 10.7% had leptomeningeal seeding. Apart from differences in frequency of various histological types and nuclear grades of primary breast cancer, and leptomeningeal seeding, the treatment groups were well balanced with regards to other characteristics.

Treatment patterns

Tables 2 and 3 show the treatments received before and after BM. Seven (2.5%) patients did not receive any treatment for BM (Table 2). Radiotherapy (92.9%) and chemotherapy (57.1%) were the most common treatment modalities received after diagnosis of BM.

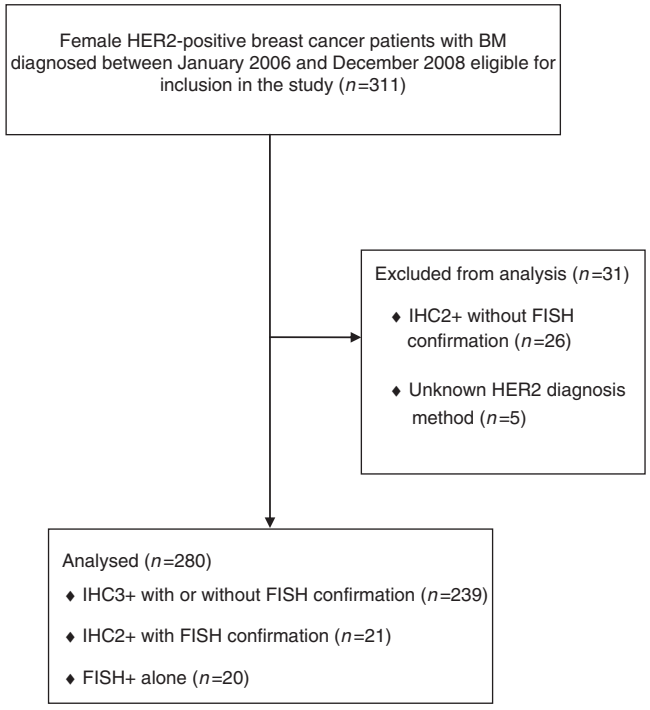

Figure 1 Patient cohort. FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry.

Sequential radiotherapy and chemotherapy was the most common treatment (54.6%) received after BM.

Anti-HER2 treatment was utilised in 62.9% of patients before BM and in 40.7% of patients after presentation with brain metastases (Table 2). Anti-HER2 treatment before diagnosis of BM was primarily trastuzumab alone (86.9%; 153 of 176) administered in the adjuvant ($n=28$) and/or metastatic setting ($n=131$) (Table 3). After the diagnosis of BM, trastuzumab alone was still the most common anti-HER2 treatment received (49.1%; 56 of 114), followed by lapatinib alone (26.3%; 30 of 114) and lapatinib in combination with trastuzumab (24.6%; 28 of 114). Among the 28 patients who received both anti-HER2 agents after BM, trastuzumab and lapatinib were primarily given sequentially in 22 patients (78.6%); 6 patients (21.4%) received both drugs concomitantly. Anti-HER2 treatment was commonly given in combination with radiotherapy (93.0%; 106 of 114) or radiotherapy and chemotherapy (80.7%; 92 of 114).

Time to brain metastasis (TTBM) and timing of brain metastasis (BM)

The median TTBM was 30.1 months (95% CI 25.0–32.7) for all patients. BM occurred significantly later in patients who received anti-HER2 treatment before BM (median TTBM 33.2 months; 95% CI 31.6–35.8) compared with those who did not (19.1 months; 95% CI 15.4–24.9; $P=0.002$) (Supplementary Table 1). Brain was the first site of metastasis in 62 (22.2%) patients. Patients who received adjuvant trastuzumab were more likely to present with brain as the first site of metastasis than those who did not (46.4%; $n=13$ *vs* 19.5%; $n=49$; $P=0.003$).

Overall survival (OS) after brain metastasis (BM)

At the end of the study period, 61.8% ($n=173$) had died, of which 54.9% ($n=95$) died due to complications of brain metastases. The median OS after BM was 10.9 months (95% CI 9.0–11.9) for all patients. OS after BM was significantly longer in patients who received anti-HER2 treatment after BM than those who did not (median 18.5 *vs* 5.7 months; $P<0.001$; Figure 2A). The greatest survival benefit (25.9 months) was observed in patients who received both trastuzumab and lapatinib, followed by lapatinib alone (21.4 months), trastuzumab alone (10.5 months), and without anti-HER2 treatment (5.7 months) ($P<0.001$) (Figure 2B).

Table 4 summarises the results of Cox regression analyses for independent prognostic factors for OS after BM. Older age at BM diagnosis, multiple brain metastases lesions, and leptomeningeal seeding were associated with poorer survival, whereas pre-menopausal status, and receipt of chemotherapy, hormonal therapy or anti-HER2 treatment after BM were predictors of prolonged survival. Of note, receipt of anti-HER2 treatment before diagnosis of BM was not significantly associated with improved OS after BM. In multivariate analysis, after controlling for age at BM, number of brain metastases lesions, receipt of chemotherapy, and receipt of hormonal therapy after BM, anti-HER2 treatment after BM remained significantly associated with improved OS after BM (38% reduction in risk of death compared with no anti-HER2 treatment; HR, 0.62; 95% CI 0.43–0.89) (Table 4).

When examining the effect of individual anti-HER2 treatment on OS after BM in multivariate analysis, use of both agents was associated with significantly greater survival benefit than no anti-HER2 treatment (63% risk reduction; HR, 0.37; 95% CI 0.19–0.72), and a non-significant trend towards improved survival over either trastuzumab alone (HR, 0.51; 95% CI 0.25–1.01) or lapatinib alone (HR, 0.60; 95% CI 0.27–1.31) (Table 5). In sensitivity analyses, treatment with both agents remained significantly associated with improved survival over no anti-HER2 treatment after relaxing the proportional hazards assumption for key confounders (HR, 0.35; 95% CI 0.18–0.69; $P=0.002$). All other comparisons also remained nearly identical, except for the HR comparing both agents to trastuzumab alone, which gained statistical significance (HR, 0.48; 95% CI 0.24–0.96; $P=0.039$).

DISCUSSION

Patients with HER2-positive breast cancer are at increased risk of developing brain metastases (Bendell *et al*, 2003; Clayton *et al*, 2004; Shmueli *et al*, 2004; Stemmler *et al*, 2006; Park *et al*, 2009a). Anti-HER2 treatments have been shown to delay the development of brain metastases and prolong survival after BM in HER2-positive breast cancer patients (Bartsch *et al*, 2007, 2012; Dawood *et al*, 2008; Park *et al*, 2009a, b; Le Scodan *et al*, 2011; Metro *et al*, 2011). However, most research has been limited to trastuzumab only and is primarily conducted in Western populations. In Asia, data on the use of anti-HER2 treatments in HER2-positive breast cancer patients with BM is limited. Our study provides a unique opportunity to understand the usage of trastuzumab and lapatinib among Asian HER2-positive breast cancer patients with brain metastases and the potential clinical role of anti-HER2 treatments on TTBM and survival after development of brain metastases in these patients.

The proportion of patients with leptomeningeal metastasis in this Asian HER2-positive breast cancer cohort (11%) was similar to other HER2-positive breast cancer populations (9–19%) (Bendell *et al*, 2003; Dawood *et al*, 2008; Park *et al*, 2009a, b) and higher than what has been observed for breast cancer patients in general (2–5%) (DeAngelis *et al*, 2000, pp 867–874). These findings suggest that HER2-positive breast cancer patients are at increased risk of leptomeningeal metastasis and may have poorer prognosis. Closer surveillance with physicians' awareness is warranted for these patients.

We found that the majority of patients (93%) in these Asian countries received radiotherapy as part of their care for BM, suggesting high level of compliance with recommended treatment guidelines and standard of care for BM (NCCN, 2011). However,

Table 1 Patient characteristics

Characteristics	All ($n=280$), *n* (%)	Anti-HER2 treatment after diagnosis of BM: Trastuzumab alone ($n=56$), *n* (%)	Lapatinib alone ($n=30$), *n* (%)	Both agents[a] ($n=28$), *n* (%)	No anti-HER2 treatment ($n=166$), *n* (%)	*P*
At primary breast cancer diagnosis						
Median age (range), years	48 (23–78)	51 (27–74)	45 (26–61)	47 (28–66)	50 (23–78)	0.089
Menopausal status						0.211
Pre-menopausal	120 (42.9)	25 (44.6)	17 (56.7)	14 (50.0)	64 (38.6)	
Post-menopausal	118 (42.1)	27 (48.2)	8 (26.7)	9 (32.1)	74 (44.6)	
Unknown	42 (15.0)	4 (7.1)	5 (16.7)	5 (17.9)	28 (16.9)	
Hormone receptor status[b]						0.409
ER+ and/or PR+	119 (42.5)	26 (46.4)	9 (30.0)	14 (50.0)	70 (42.7)	
ER− and PR−	159 (56.8)	30 (53.6)	21 (70.0)	14 (50.0)	94 (57.3)	
Both unknown or unknown and negative	2 (0.7)					
Histology[b]						0.006
Invasive ductal	266 (95.0)	51 (91.1)	30 (100.0)	24 (85.7)	161 (97.6)	
Invasive lobular	6 (2.1)	3 (5.4)	0 (0.0)	3 (10.7)	0 (0.0)	
Others	7 (2.5)	2 (3.6)	0 (0.0)	1 (3.6)	4 (2.4)	
Unknown	1 (0.4)					
AJCC stage						0.711
I	21 (7.5)	3 (5.4)	3 (10.0)	2 (7.1)	13 (7.8)	
II	73 (26.1)	16 (28.6)	11 (36.7)	4 (14.3)	42 (25.3)	
III	102 (36.4)	20 (35.7)	9 (30.0)	10 (35.7)	63 (38.0)	
IV	70 (25.0)	16 (28.6)	5 (16.7)	9 (32.1)	40 (24.1)	
Unknown	14 (5.0)	1 (1.8)	2 (6.7)	3 (10.7)	8 (4.8)	
Nuclear grade						0.017
1	7 (2.5)	3 (5.4)	0 (0.0)	0 (0.0)	4 (2.4)	
2	76 (27.1)	5 (8.9)	7 (23.3)	6 (21.4)	58 (34.9)	
3	123 (43.9)	26 (46.4)	15 (50.0)	14 (50.0)	68 (41.0)	
Unknown	74 (26.4)	22 (39.3)	8 (26.7)	8 (28.6)	36 (21.7)	
At diagnosis of BM						
Median age (range), years	52 (25–81)	54 (27–74)	49 (28–65)	49 (30–69)	52 (25–81)	0.084
Number of brain lesions						0.631
Solitary	65 (23.2)	12 (21.4)	8 (26.7)	5 (17.9)	40 (24.1)	
Multiple	215 (76.8)	44 (78.6)	22 (73.3)	23 (82.1)	126 (75.9)	
CNS involvement						0.034
Parenchymal only	240 (85.7)	44 (78.6)	30 (100.0)	26 (92.9)	140 (84.3)	
Parenchymal and leptomeningeal	30 (10.7)	11 (19.6)	0 (0.0)	2 (7.1)	17 (10.2)	
Unknown	10 (3.6)	1 (1.8)	0 (0.0)	0 (0.0)	9 (5.4)	
Site of first metastasis						0.395
Brain	63 (22.5)	16 (28.6)	4 (13.3)	5 (17.9)	38 (22.9)	
Other sites	217 (77.5)	40 (71.4)	26 (86.7)	23 (82.1)	128 (77.1)	

Abbreviations: BM = brain metastasis; ER = oestrogen receptor; PR = progesterone receptor; AJCC = American Joint Committee on Cancer; CNS = central nervous system.
[a]Trastuzumab and lapatinib given sequentially or concomitantly. [b]Patients with unknown values were not included in analysis.

anti-HER2 treatment was not as uniformly utilised, ranging from 63% before BM to only 41% after BM. Of note, a quarter of patients (25%) never received anti-HER2 treatment. Two other studies conducted in Korea also reported low usage of anti-HER2 treatment after BM. One study reported 33% of anti-HER2 treatment usage after BM (Park *et al*, 2009b) and the other reported a decrease in anti-HER2 treatment usage from 71% before BM to 37% after BM (Park *et al*, 2009a). The pattern observed in Asia is in contrast to that in Western populations where there is no marked decrease in anti-HER2 treatment usage after BM (58–60% before BM; 50–80% after BM) (Church *et al*, 2008; Eichler *et al*, 2008; Wolstenholme *et al*, 2008; Brufsky *et al*, 2011). The low usage of anti-HER2 treatment after BM observed in our Asian cohort may be largely related to the high costs associated with anti-HER2 treatment, especially in countries with no reimbursement. Further, discontinuation of anti-HER2 treatment upon the development of resistance to prior trastuzumab or lapatinib treatment may also partly explain the decline in use.

Our results showed that patients who received anti-HER2 treatment before BM, primarily trastuzumab alone, had 1.5 times significantly longer interval to the development of brain metastases than those who did not (33 *vs* 19 months). This concurs with the findings of previous studies, which reported a significant delay in the development of brain metastases with trastuzumab treatment in HER2-positive metastatic breast cancer (MBC) patients (Park *et al*, 2009a, b).

Several retrospective studies have demonstrated improved survival with trastuzumab treatment in HER2-positive breast cancer patients with brain metastases, with median survival ranging from 9 to 24 months (Bendell *et al*, 2003; Stemmler *et al*, 2006; Gori *et al*, 2007; Park *et al*, 2009b; Niwinska *et al*, 2010; Bartsch *et al*, 2012). The observed survival benefit has largely been attributed to control of the extracranial disease. Considering the promising activity of lapatinib against BM demonstrated in clinical studies (Boccardo *et al*, 2008; Lin *et al*, 2008, 2009; Ro *et al*, 2010; Sutherland *et al*, 2010; Bachelot *et al*, 2011; Lin *et al*, 2011), lapatinib may provide additional survival benefits to these patients.

In this Asian population, use of both anti-HER2 agents, primarily in a sequential manner, after BM demonstrated the greatest survival benefit (26 months *vs* 21 months for lapatinib alone *vs* 11 months for trastuzumab alone *vs* 6 months for no anti-HER2 treatment). In the adjusted analysis, although non-significant, use of both anti-HER2 agents provided a 49% risk reduction over trastuzumab alone, and a 40% risk reduction over lapatinib alone. Recent observational studies in Western

Table 2 Treatments

Treatment	All ($n=280$), *n* (%)
Prior to diagnosis of BM	
Hormonal therapy	103 (36.8)
Chemotherapy	252 (90.0)
Anti-HER2 treatment	176 (62.9)
Other targeted therapy	6 (2.1)
After diagnosis of BM	
No treatment	7 (2.5)
Local treatment	
Radiotherapy[a]	260 (92.9)
WBRT	251 (89.6)
SRS or SRT	32 (11.4)
Surgery	35 (12.5)
Intrathecal treatment	11 (3.9)
Additional systemic treatment	
Hormonal therapy	34 (12.1)
Chemotherapy	160 (57.1)
Anti-HER2 treatment	114 (40.7)
Other targeted therapy	5 (1.8)
Treatment combination	
Radiotherapy[a] + surgery	24 (8.6)
Radiotherapy[a] + surgery + chemotherapy	19 (6.8)
Radiotherapy[a] + chemotherapy	153 (54.6)
Radiotherapy[a] + chemotherapy + anti-HER2 treatment[b]	92 (32.9)
Radiotherapy[a] + Anti-HER2 treatment[b]	106 (37.9)
Radiotherapy[a] + hormonal therapy + anti-HER2 treatment[b]	17 (6.1%)
Surgery + chemotherapy	25 (8.9)

Abbreviations: BM = brain metastasis; WBRT = whole brain radiotherapy; SRS = stereotactic surgery; SRT = stereotactic therapy. [a]Includes WBRT, SRS or SRT. [b]Also includes other targeted therapy.

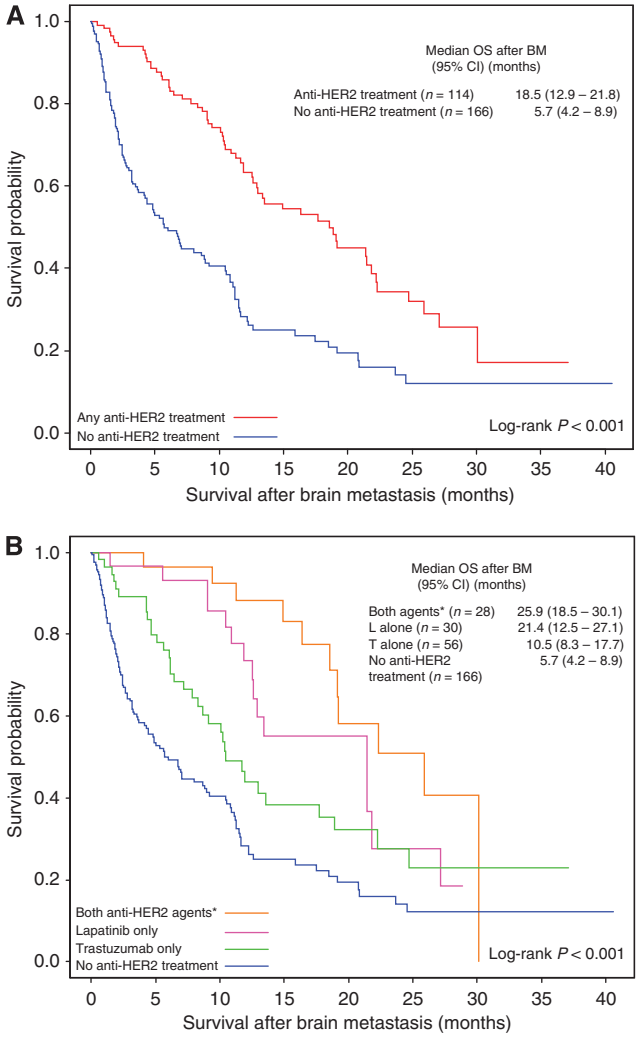

Figure 2 Overall survival (OS) after brain metastasis (BM) by anti-HER2 treatment received after diagnosis of brain metastasis (BM). (**A**) Anti-HER2 treatment *vs* no anti-HER2 treatment. Median OS after BM for all patients was 10.9 months (95% CI 9.0–11.9). (**B**) Both agents *vs* lapatinib only *vs* trastuzumab only *vs* no anti-HER2 treatment. Median OS after BM for all patients was 10.9 months (95% CI 9.0–11.9). *Trastuzumab and lapatinib given sequentially or concomitantly.

Table 3 Anti-HER2 treatment patterns

Anti-HER2 treatment before diagnosis of BM	Anti-HER2 treatment after diagnosis of BM: Trastuzumab alone ($n=56$), *n* (%)	Lapatinib alone ($n=30$), *n* (%)	Both agents[a] ($n=28$), *n* (%)	No anti-HER2 treatment ($n=166$), *n* (%)
Trastuzumab alone ($n=153$)	26 (9.3)	28 (10.0)	18 (6.4)	81 (28.9)
Lapatinib alone ($n=2$)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
Both agents[b] ($n=21$)	5 (1.8)	1 (0.4)	2 (0.7)	13 (4.6)
No anti-HER2 treatment ($n=103$)	25 (8.9)	1 (0.4)	8 (2.9)	69 (24.6)

Abbreviation: BM = brain metastasis. *Note:* Results are calculated as a percentage of the analysed population ($n=280$). [a]Trastuzumab and lapatinib given sequentially (78.6%; $n=22$) or concomitantly (21.4%; $n=6$). [b]Trastuzumab and lapatinib given sequentially (85.7%; $n=18$) or concomitantly (14.3%; $n=3$).

Table 4 Results of Cox regression analyses for independent prognostic factors for overall survival (OS) after brain metastasis (BM)

Factor	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	P[a]	Adjusted HR (95% CI)	P[a]
Menopausal status (pre- *vs* post-menopausal)	0.59 (0.43–0.81)	0.003	NS	NS
Age at BM[b] (years) (1 year increase in age)	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.03)	0.003
Number of brain metastases lesions (multiple *vs* solitary)	1.50 (1.03–2.19)	0.035	1.84 (1.25–2.72)	0.002
Leptomeningeal seeding[c] (yes *vs* no)	1.78 (1.15–2.74)	0.010	NS	NS
Chemotherapy after BM (yes *vs* no)	0.24 (0.18–0.33)	<0.001	0.27 (0.19–0.39)	<0.001
Hormonal therapy after BM (yes *vs* no)	0.56 (0.34–0.93)	0.025	0.44 (0.26–0.73)	0.001
Anti-HER2 treatment after BM (yes *vs* no)	0.41 (0.30–0.56)	<0.001	0.62 (0.43–0.89)	0.009

Abbreviations: HR = hazard ratio; CI = confidence interval; NS = not significant; BM = brain metastasis; OS = overall survival. *Note:* The following factors were not significantly associated with OS after BM in univariate analysis: medical centre type, stage or nuclear grade of primary breast tumour at diagnosis, oestrogen and progesterone receptor status of primary breast tumour at diagnosis, duration between diagnosis of breast cancer and first metastases, brain as site of first metastasis, chemotherapy before diagnosis of BM, anti-HER2 treatment before diagnosis of BM, and hormonal therapy before diagnosis of BM. [a]*P*-value from the proportional hazards model. [b]Variable modelled as a continuous variable. [c]Patients with missing or unknown value(s) for this variable were excluded.

Table 5 Crude and adjusted association between anti-HER2 treatment received after diagnosis of brain metastasis (BM) and overall survival (OS) after BM

Comparison	Crude HR (95% CI)	P[a]	Adjusted HR[b] (95% CI)	P[a]
Both[c] *vs* no anti-HER2	0.24 (0.13–0.44)	<0.001	0.37 (0.19–0.72)	0.003
Both[c] *vs* trastuzumab alone	0.41 (0.21–0.81)	0.011	0.51 (0.25–1.01)	0.055
Both[c] *vs* lapatinib alone	0.65 (0.30–1.42)	0.283	0.60 (0.27–1.31)	0.200
Trastuzumab alone *vs* no anti-HER2	0.57 (0.39–0.84)	0.005	0.73 (0.49–1.10)	0.13
Lapatinib alone *vs* no anti-HER2	0.36 (0.21–0.62)	<0.001	0.62 (0.35–1.11)	0.11
Lapatinib alone *vs* trastuzumab alone	0.63 (0.34–1.16)	0.139	0.85 (0.45–1.58)	0.605

Abbreviations: HR = hazard ratio; CI = confidence interval; BM = brain metastasis. [a]*P*-value from the proportional hazards model. [b]Model adjusted for age at diagnosis of BM, number of brain metastases lesions, receipt of hormonal treatment after diagnosis of BM, and receipt of chemotherapy after diagnosis of BM. [c]Trastuzumab and lapatinib given sequentially or concomitantly.

populations have also reported improved survival with the use of both anti-HER2 agents compared with trastuzumab alone. Metro *et al* (2011) demonstrated that patients treated with sequential combination of trastuzumab and lapatinib plus capecitabine ($n = 30$) had significantly longer survival compared with patients treated with trastuzumab-based treatments alone ($n = 23$) (28 *vs* 17 months; $P = 0.01$). Bartsch *et al* (2012) showed that among 80 patients with brain metastases from HER2-positive breast cancer, use of trastuzumab and lapatinib, either sequentially or concomitantly, with or without chemotherapy was significantly associated with a 72% reduction in risk of death compared with trastuzumab-based treatment alone ($P = 0.012$).

Our results also concur with recent data from a large prospective study in the US that reported significantly longer survival after BM in HER2-positive MBC patients who received anti-HER2 treatment with or without chemotherapy (72.5% trastuzumab alone; 27.5% trastuzumab and lapatinib) after BM than those who did not receive anti-HER2 treatment (median 17.5 *vs* 3.7 months; $P < 0.001$) (Brufsky *et al*, 2011).

Our analysis showed that chemotherapy, hormonal therapy, and anti-HER2 treatment after BM were important predictors of prolonged survival, although the overlapping usage of these treatments may contribute to a confounding effect. Recent studies have also reported survival benefits associated with the use of systemic treatments in HER2-positive breast cancer patients with brain metastases (Park *et al*, 2009a; Braccini *et al*, 2011; Kim *et al*, 2012). These findings show the potential for systemic treatments in improving the outcome of breast cancer patients even after BM diagnosis.

These findings need to be interpreted within the limitations of the study design and sample size. First, this is a retrospective, non-randomised study, and there is potential for imbalance in key prognostic factors between patients who received anti-HER2 treatment and those who did not, which may give rise to biased results. For instance, patients with better prognosis may be more likely to receive anti-HER2 treatment by virtue of living longer. Although we attempted to adjust for potential confounding factors that were known to be associated with treatment or survival, there is potential for unmeasured confounding by factors that were not collected. Nonetheless, our results were generally consistent with other retrospective studies. Second, as the sample size in each treatment group is small, further research with a larger number of patients is warranted to confirm our results. Next, there is the possibility that patients received sequential therapy with both anti-HER2 agents by virtue of living longer, which may give rise to biased results. Also, patients who received both anti-HER2 agents sequentially may have a different treatment effect from those who received them concomitantly. However, our limited sample size does not allow these groups to be analysed separately. Future studies in a larger cohort are needed to confirm if there is a different treatment effect when both the drugs are used sequentially or concomitantly. Finally, as the majority of patients were from Korea and Singapore, the treatment patterns and outcomes of patients from other Asian countries merit further study.

In conclusion, there is limited usage of anti-HER2 treatment after detection of brain metastases among our Asian cohort of patients with HER2-positive breast cancer. Anti-HER2 treatment before BM, primarily trastuzumab alone, was associated with significantly longer time to the development of brain metastases. Anti-HER2 treatment after diagnosis of BM, along with local treatment and other systemic treatments, was associated with a survival benefit, especially when both trastuzumab and lapatinib were utilised. Our results support the role of continuing systemic treatments, including anti-HER2 treatment, in improving survival even after development of brain metastases. The management

strategy for HER2-positive brain metastases should incorporate the use of systemic treatments, including anti-HER2 treatment; clinical trials on anti-HER2 treatment in this setting will help to determine the optimal regimen.

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Conflict of interest

YS Yap and N Sutandyo have received honoraria from GlaxoSmithKline. DWY Wong has received honoraria from Roche. M Kobayashi is an ex-employee of GlaxoSmithKline. SH Landis, EM Yeoh and H Moon are employees of GlaxoSmithKline. M Kobayashi, SH Landis, EM Yeoh and H Moon hold stock ownership in GlaxoSmithKline. J Ro has acted as an advisor and received honoraria from GlaxoSmithKline. The remaining authors declare no conflict of interest.

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Clinical Studies

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