Addressing Brain Metastases in HER2-Positive Breast Cancer

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Conflict of Interest

- Advisory, honoraria and research support from GSK and Roche
- No financial conflicts to declare
Brain Metastases (in general)

• 1.3 million people with cancer/year in the US
  – 100-170,000 will be diagnosed with Brain Metastases
  – Most common malignancy in the brain

ACS Facts & Figures www.cancer.org

• Autopsy studies suggest that 20-40% of metastatic cancer patients have Brain Metastases

ACS Fact & Figures www.cancer.org

• Lung (1st) and Breast Cancer (2nd) are the primary tumors more frequently associated with brain metastases

Chang, Oncologist, 8:398, 2003
Lassman, Neur Clin 21:1, 2003
Brain Metastases in Breast Cancer

• Incidence of symptomatic Brain Metastases in women with breast cancer varies 10-16%.
  
  Lin, J Clin Oncol 22:3608, 2004

• Latency from initial diagnosis to development of Brain metastases is around 2-3 years
  
  Chang, Oncologist, 8:398, 2003

• In most cases Brain Metastases develop after systemic metastases (lung, liver and/or bone) have been diagnosed.
  
  Issa, J Cancer Res128:61, 2002
Figure 1. Tumor Initiation and Metastasis.

The initiation and progression of tumors depend on the acquisition of specific functions by cancer cells at both the primary and metastatic sites. Functions associated with tumor initiation are provided by oncogenic mutations and inactivation of tumor-suppressor genes. Functions associated with the initiation of metastasis include functions to which tumor cells resort for local invasion and for circumventing hypoxia and other limitations facing a growing tumor. Most functions for the initiation of both the tumor and metastasis remain essential for cancer cells to continue their metastatic development. Functions for metastasis progression provide a local advantage in a primary tumor and a distinct and sometimes organ-specific function during metastasis. Cancer cells that are endowed with these three sets of functions still depend on functions associated with metastasis virulence; these functions confer a selective advantage solely during the adaptation and takeover of a specific organ microenvironment. Genes associated with each of these functions have been identified in recent years.
A Unique Microenvironment

Structure of the blood-brain barrier (BBB)

Cerebral capillaries:
Endothelial cells sealed by tight junctions.
Close contact with pericytes
Ensheathed by astrocyte foot processes
Basal lamina

Passage of molecules is tightly regulated:
Some hydrophilic molecules enter the brain via specific transporters and carrier-mediated endocytosis, and a limited number cross the barrier via diffusion through tight junctions.

Once tumor cells penetrate the BBB, a blood:tumor barrier (BTB) is formed. Almost nothing is known about the patency of the BTB to metastases.
Frequent Genetic Alterations in EGFR- and HER2-Driven Pathways in Breast Cancer Brain Metastases

Ina Hohensee, Katrin Lamszus, Sabine Riethdorf, Sönke Meyer-Staeckling, Markus Glatzel, Jakob Matschke, Isabell Witzel, Manfred Westphal, Burkhard Brandt, Volkmar Müller, Klaus Pantel, and Harriet Wikman

From the Departments of Tumor Biology, Neurosurgery, Gynecology, and the Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg; and the Institute of Clinical Chemistry, University Medical Center Schleswig-Holstein, Kiel, Germany

Current standard systemic therapies for treating breast cancer patients with brain metastases are inefficient. Targeted therapies against human epidermal growth factor receptors are of clinical interest because of their alteration in a subset of breast cancers (BCs). We analyzed copy number, mutation status, and protein expression of epidermal growth factor receptor (EGFR), human epidermal growth factor 2 (HER2), phosphatase and tensin homologue (PTEN), and PI3K catalytic subunit (PIK3CA) in 110 ductal carcinoma in situ, primary tumor, and metastatic BC samples. Alterations in EGFR, HER2, and PTEN, alone or in combination, were found in a significantly larger fraction of breast cancer brain metastases than in primary tumors with good prognosis, bone relapse, or other distant metastases (all \( P < 0.05 \)). Primary tumor patients with a subsequent brain relapse showed almost equally high frequencies of especially EGFR and PTEN alteration as the breast cancer brain metastases patients. PIK3CA was not associated with an increased risk of brain metastases. Genetic alterations in both EGFR and PTEN were especially common in triple-negative breast cancer patients and rarely were seen among HER2-positive patients. In conclusion, we identified two independent high-risk primary BC subgroups for developing brain metastases, represented by genetic alterations in either HER2 or EGFR/PTEN-driven pathways. In contrast, none of these pathways was associated with an increased risk of bone metastasis. These findings highlight the importance of both pathways as possible targets in the treatment of brain metastases in breast cancer. (Am J Pathol 2013, 183: 83–95; http://dx.doi.org/10.1016/j.ajpath.2013.03.023)
Frequent Genetic Alterations in EGFR- and HER2-Driven Pathways in Breast Cancer Brain Metastases

**P<0.05, **P<0.01

Frequent Genetic Alterations in EGFR- and HER2-Driven Pathways in Breast Cancer Brain Metastases

RFS: EGFR Gene Copy Number

EGFR Mutation Status

Brain Metastases in Breast Cancer

• Recently: trend toward increasing CNS recurrence has been reported (from 10-16% to 25-35%).
  – Increased use of more sensitive methods of detection (CT, MRI, PET)
  – Increased index of suspicion (？)
  – Change in the natural history of the disease, i.e.
    improvement in systemic therapies leading to prolonged survival

Brain Metastases: Treatment

✓ Surgery
✓ Radiotherapy (WBRT)
✓ Stereotactic Radiosurgery (SRS)
✓ Systemic Treatment

✓ Supportive Measures
  ✓ Corticosteroids
  ✓ Anticonvulsants
<table>
<thead>
<tr>
<th>Type of CNS metastases</th>
<th>NCCN recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3 brain metastases</td>
<td>Surgery or SRS</td>
</tr>
<tr>
<td></td>
<td>Consider WBRT following surgery or SRS</td>
</tr>
<tr>
<td></td>
<td>WBRT alone if advanced systemic disease</td>
</tr>
<tr>
<td>&gt;3 brain metastases</td>
<td>Consider SRS in selected cases</td>
</tr>
<tr>
<td></td>
<td>WBRT</td>
</tr>
<tr>
<td>Leptomeningeal metastases</td>
<td>Radiation therapy for palliation of symptoms, to sites of bulky disease and for CSF flow abnormalities</td>
</tr>
<tr>
<td></td>
<td>CSF chemotherapy or high-dose methotrexate</td>
</tr>
<tr>
<td></td>
<td>May consider craniospinal irradiation</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; NCCN, National Comprehensive Cancer Network; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.
Brain Metastases: Addition of local therapy to WBRT

✓ Single Brain Metastases (only a minority of patients...):
  ✓ Randomized to Surgery + WBRT vs. WBRT alone
  ✓ Local Control: 48% vs. 80% (p<.02)
  ✓ OS: 15 weeks vs. 40 weeks (p<.01)


✓ One to Three Brain Metastases:
  ✓ Randomized to SRT + WBRT vs. WBRT alone
  ✓ Improved functional autonomy with combination
  ✓ Survival benefit for patients with single unressectable metastasis

Brain Metastases: Addition of WBRT to local therapy*

The addition of WBRT to either surgery or SRS reduces intracranial failure with no impact in survival

* No dedicated trial to address the question in breast cancer patients

Dawood S, Gonzalez-Angulo AM. Oncologist 2013;18:675
Brain Metastases: Treatment

 ✓ More than 5 Brain Metastases
   ✓ Only retrospective data
   ✓ SRS alone better than WBRT alone
   ✓ In patients treated with SRS alone the number of metastases may not predict survival
 ✓ Survey among Radiation Oncologists (2010)
   ✓ >50%: reasonable to to use SRS as initial treatment

Brain Metastases in Breast Cancer: Treatment

✓ No specific guidelines for the management of brain metastases from BC

✓ No clear data comparing different tumor types

✓ The number of brain metastases and the status of the systemic disease (if either under control or progressing) heavily influences the therapeutic selection.
CNS Metastases and HER2-positive BC

Patients with HER2-positive MBC are two to four times more likely to develop brain metastases than patients with HER2-negative disease.

HER2-positive status is a significant risk factor for CNS relapse.

Kaal EC, Vecht CJ. CNS Drugs 2007;21:559–79.
Brain Metastases: The HER2 Paradigm

✓ Historically, CNS metastases occurred late and progression in non-CNS dominant source of morbidity and mortality.

✓ As systemic therapies improve, the incidence of asymptomatic or symptomatic brain metastases will increase (management of CNS disease will become more vital).

✓ The widespread use of trastuzumab in HER2-positive breast cancer has unmasked a population in whom CNS progression is a significant source of morbidity and mortality.
Brain Metastases in HER2-positive disease: Hypothesis

✓ Patients treated with trastuzumab (HER2+) are more likely to have more aggressive disease;

✓ Trastuzumab prolongs survival, so the proportion of patients who develop CNS metastases increases as a function of time;

✓ Trastuzumab is more effective controlling relapses in other sites but does not easily penetrate the blood-brain barrier, (“sanctuary” situation in the CNS).
CNS Metastases and HER2-positive BC

Retrospective study of 9524 women with EBC enrolled in 10 clinical trials between 1978-1999, the 10-year cumulative incidences of CNS as first relapse site were 2.7% (HER2-positive) vs. 1.0% (HER2-negative) (P < 0.01).

Cumulative incidence of CNS metastases as either a first or subsequent event were greater in patients with HER2-positive compared with HER2-negative disease (6.8% vs. 3.5%; P < 0.01).

CNS Metastases and HER2-positive BC

Population-based registry with 1458 patients with EBC

CNS as first recurrence

- 0.6% HER2-negative patients
- 4% HER2-positive with Adjuvant Trastuzumab
- 1.2% HER2-positive not receiving Trastuzumab

Time to CNS as first recurrence,

- HER2-positive Adjuvant Trastuzumab (20.3 months)
- HER2-negative (19.8 months) and those
- HER2-positive no trastuzumab (10.3 months)

(P = 0.018).

## CNS Metastases events reported in adjuvant trastuzumab trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Any metastases as 1st event</th>
<th>CNS metastases as 1st event</th>
<th>CNS metastases at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. events</td>
<td>no. events</td>
</tr>
<tr>
<td><strong>NSABP B-31</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trastuzumab</td>
<td>60 (6.9)</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>no trastuzumab</td>
<td>111 (12.7)</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td><strong>NCCTG 9831</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trastuzumab</td>
<td>30 (3.7)</td>
<td>12</td>
<td>Not reported</td>
</tr>
<tr>
<td>no trastuzumab</td>
<td>63 (7.8)</td>
<td>4</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>HERA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trastuzumab</td>
<td>85 (5.0)</td>
<td>21</td>
<td>Not reported</td>
</tr>
<tr>
<td>no trastuzumab</td>
<td>154 (9.1)</td>
<td>15</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

CNS Metastases are more common in HER2-positive early breast cancer

25-50% of patients with HER2 positive MBC treated with trastuzumab develop CNS metastases


Incidence seems higher than that reported in historical (10%–15%) and some autoptic (29.6%) series

Incidence of CNS Metastases among women with MBC treated with trastuzumab

- Bendell et al. *Cancer* 2003 34%
- Weitzen et al. *ASCO* 2002 29%
- Heinrich et al. *ASCO* 2003 43%
- Clayton et al. *Br J Cancer* 2004 25%
- Altaha et al. *J Clin Oncol* 2004 48%
- Stemmler et al. *SABCS* 2004 31%
- Yau et al. *Acta Oncol* 2006 30% (at 1 y)
registHER: observational study

Enrolled patients
\(n = 1023\)

Patients in analysis\(^a\)
\(n = 1012\)

7.4\% (75\(^b\)/1,012) had CNS metastases at time MBC diagnosis

CNS metastases
\(n = 377\)

No CNS metastases
\(n = 635\)

At MBC diagnosis
\(n = 75\(^b\) (19.9\%)\)

Only site of 1st PD
\(n = 106 (28.1\%)\)^c

One of several sites of first PD
\(n = 36 (9.5\%)\)

Site of 2nd PD
\(n = 70 (18.6\%)\)

Site of 3rd PD
\(n = 24 (6.4\%)\)

CNS as site of later PD
\(n = 66 (17.5\%)\)

PD = progressive disease.

\(^a\)Had HER2-positive tumors and were enrolled within 12 mo of MBC diagnosis.

\(^b\)These 75 patients had CNS metastases at the time of metastatic diagnosis.

\(^c\)For 15 (1.5\%) of patients, the CNS was the only site of metastasis.
registHER: disease characteristics (N=377)

<table>
<thead>
<tr>
<th>Neurologic symptoms present, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>59 (15.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>249 (66.1)</td>
</tr>
<tr>
<td>Missing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69 (18.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of initial diagnosis of CNS metastases&lt;sup&gt;b&lt;/sup&gt;, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic imaging</td>
<td>308 (81.7)</td>
</tr>
<tr>
<td>Physical examination</td>
<td>74 (19.6)</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Missing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64 (17.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leptomeningeal involvement, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>281 (74.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>30 (8.0)</td>
</tr>
<tr>
<td>Missing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66 (17.5)</td>
</tr>
</tbody>
</table>

CNS Metastasis occur relatively early in the course of disease of HER2-positive MBC
registHER: observational study

registHER: observational study

registHER: treatment (N=377)

<table>
<thead>
<tr>
<th>HER2-targeted treatment received following CNS metastases, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab and other therapies, but no lapatinib</td>
<td>179 (47.5)</td>
</tr>
<tr>
<td>Trastuzumab and lapatinib and other therapies</td>
<td>71 (18.8)</td>
</tr>
<tr>
<td>Lapatinib and other therapies, but no trastuzumab</td>
<td>20 (5.3)</td>
</tr>
<tr>
<td>Trastuzumab only</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Trastuzumab and lapatinib only (no other therapies)</td>
<td>0</td>
</tr>
<tr>
<td>Lapatinib only</td>
<td>0</td>
</tr>
<tr>
<td>Other therapies</td>
<td>69 (18.3)</td>
</tr>
<tr>
<td>Trastuzumab &lt;21 d, but no other therapies</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>No therapy</td>
<td>24 (6.4)</td>
</tr>
</tbody>
</table>

registHER: observational study

### registHER: observational study

Multivariable Proportional Hazards Analysis for Survival

<table>
<thead>
<tr>
<th>Treatment received after first CNS event&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab&lt;sup&gt;b&lt;/sup&gt; (n = 258)</td>
<td>0.33 (0.25–0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy (n = 262)</td>
<td>0.64 (0.48–0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgery (n = 29)</td>
<td>0.63 (0.39–1.02)</td>
<td>0.062</td>
</tr>
<tr>
<td>Radiation therapy (n = 269)</td>
<td>0.98 (0.75–1.30)</td>
<td>0.898</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer stage at initial dx</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I–III (MBC dx ≤12 mo after initial dx) vs. stage IV</td>
<td>1.41 (0.95–2.10)</td>
<td>0.091</td>
</tr>
<tr>
<td>Stage I–III (MBC dx ≥12 mo after initial dx) vs. stage IV</td>
<td>0.96 (0.72–1.27)</td>
<td>0.767</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG PS at MBC diagnosis</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 vs. 0 or 1</td>
<td>1.83 (1.14–2.96)</td>
<td>0.013</td>
</tr>
<tr>
<td>Unknown or missing vs. 0 or 1</td>
<td>1.12 (0.86–1.46)</td>
<td>0.405</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.01 (1.00–1.02)</td>
<td>0.162</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone receptor status</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive vs. negative</td>
<td>0.80 (0.63–1.03)</td>
<td>0.088</td>
</tr>
<tr>
<td>Unknown vs. negative</td>
<td>1.04 (0.61–1.76)</td>
<td>0.888</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNS disease at MBC dx (yes vs. no)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.50 (0.36–0.71)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

registHER: observational study
Multivariable Proportional Hazards Analysis for Survival

After adjusting for age, ECOG PS at time of MBC diagnosis, HR, stage at diagnosis and CNS involvement at metastatic diagnosis in a multivariable proportional hazards model,

Trastuzumab (HR 0.33; 95% CI: 0.25–0.46; P < 0.001)
Chemotherapy (HR 0.64; 95% CI: 0.48–0.85; P=0.002)
Surgery (HR 0.63, 95% CI: 0.39–1.02; P=0.062).

CNS-directed radiotherapy HR 0.98, 95% CI: 0.75–1.30; P=0.898).

The interactions between ECOG PS and chemotherapy chemotherapy or trastuzumab treatment were investigated but found to be not significant.
## Survival with or without Trastuzumab

Median survival from diagnosis of brain metastasis in patients who did/did not continue to receive trastuzumab-based treatment.\(^3\).

<table>
<thead>
<tr>
<th>Study/design</th>
<th>N</th>
<th>Median overall survival, months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Received trastuzumab after diagnosis of brain metastasis</td>
<td>No trastuzumab following diagnosis of brain metastasis</td>
</tr>
<tr>
<td>Bartsch et al(^73)/retrospective analysis</td>
<td>53</td>
<td>21 (range: 3–38)</td>
<td>9 (range: 1–14)</td>
</tr>
<tr>
<td>Bartsch et al(^74)/retrospective analysis</td>
<td>37</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Bruksky et al(^75)/post hoc analysis of a large registry</td>
<td>377</td>
<td>17.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Church et al(^76)/retrospective analysis</td>
<td>26</td>
<td>11.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Dawood et al(^42)/retrospective analysis</td>
<td>280</td>
<td>11.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Kirsch et al(^77)/retrospective analysis</td>
<td>47</td>
<td>~26</td>
<td>~9</td>
</tr>
<tr>
<td>Le Scodan et al(^78)/retrospective analysis</td>
<td>52</td>
<td>19.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Nam et al(^79)/retrospective analysis</td>
<td>56</td>
<td>12.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Park et al(^80)/retrospective analysis</td>
<td>78</td>
<td>13.6</td>
<td>5.5</td>
</tr>
<tr>
<td>(95% CI, 9.0–18.2)</td>
<td></td>
<td>(95% CI, 0.0–13.6)</td>
<td></td>
</tr>
<tr>
<td>Park et al(^81)/retrospective analysis</td>
<td>77</td>
<td>14.9</td>
<td>4.0</td>
</tr>
<tr>
<td>(95% CI, 11.6–18.2)</td>
<td></td>
<td>(95% CI, 2.1–5.9)</td>
<td></td>
</tr>
<tr>
<td>Witzel et al(^82)/retrospective analysis</td>
<td>29</td>
<td>9.0</td>
<td>2.0</td>
</tr>
<tr>
<td>(95% CI, 7–11)</td>
<td></td>
<td>(95% CI, 0.7–3)</td>
<td></td>
</tr>
</tbody>
</table>

Trastuzumab and BBB Penetration

PET image showing brain penetration of 
89Zr-trastuzumab, (zirconium 89–labeled trastuzumab) 
in a patient with HER2-positive metastatic breast cancer

Concentrations of functional, reactive trastuzumab in serum 
and cerebrospinal fluid (CSF) of patients with metastatic 
breast cancer in relation to radiotherapy and meningeal 
carcinomatosis

Approaches to enhance drug delivery across the blood–brain barrier

(a) bradykinin analogs,
(b) receptor-mediated endocytosis,
(c) absorptive transcytosis,
(d) ultrasound.

### Table 3: Summary of key studies looking at the combination of lapatinib and capecitabine for the treatment of brain metastases among patients with HER2-positive breast cancer who had progressed following WBRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Overall CNS response rates</th>
<th>TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccardo et al. [79]</td>
<td>Lapatinib expanded access program (France)</td>
<td>138</td>
<td>18%</td>
<td>NR</td>
</tr>
<tr>
<td>Lin et al. [21]</td>
<td>Prospective</td>
<td>50</td>
<td>20%</td>
<td>3.5 mo</td>
</tr>
<tr>
<td>Sutherland et al. [80]</td>
<td>Lapatinib expanded access program (U.K.)</td>
<td>34</td>
<td>21%</td>
<td>5.1 mo</td>
</tr>
<tr>
<td>Metro et al. [81]</td>
<td>Retrospective</td>
<td>22</td>
<td>32%</td>
<td>5.1 mo</td>
</tr>
<tr>
<td>Lin et al. [82]</td>
<td>Prospective</td>
<td>13</td>
<td>38%</td>
<td>NR</td>
</tr>
<tr>
<td>Ro et al. [83]</td>
<td>Lapatinib expanded access program (Korea)</td>
<td>58</td>
<td>51.9%</td>
<td>30.4 wk</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; NR, not reported; PFS, progression free survival; TTP, time to progression of brain metastases; WBRT, whole brain radiation therapy.
CNS Metastases in asymptomatic patients

• Neuroimaging can be used to detect occult brain metastases in patients with HER2-positive breast cancer.

• Limited data suggest that OS remains the same whether WBRT is given to patients with symptomatic or non-symptomatic brain metastases identified with neuroimaging techniques…

• But, the rate of death due to progression within the brain is threefold lower when WBRT is administered to patients with asymptomatic brain metastases.

CEREBEL: Lapatinib vs. Trastuzumab

Key eligibility:
- HER2+ MBC*
- Prior anthracyclines or taxanes
- Any line therapy
- No CNS metastases*
- Evaluable systemic dx

Stratification:
- Prior trastuzumab - yes vs no
- Prior MBC tx - 0 vs ≥1

*FISH+/IHC 3+
*No CNS mets at baseline confirmed by independently reviewed MRI scan

Phase III Planned N=650

Lapatinib 1250 mg/day +
Capecitabine 2000 mg/m²/day, days 1-14 q21 days

Trastuzumab 6 mg/kg q21 days +
Capecitabine 2500 mg/m²/day, days 1-14 q21 days

Primary endpoint:
Incidence of CNS as site of first relapse
## CEREBEL: Lapatinib vs. Trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib + capecitabine (N=251)</th>
<th>Trastuzumab + capecitabine (N=250)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS as first site of relapse, n (%)</td>
<td>8 (3)</td>
<td>12 (5)</td>
<td>0.65 (0.26, 1.63)</td>
<td>0.360</td>
</tr>
<tr>
<td>Incidence of CNS progression at any time, n (%)</td>
<td>17 (7)</td>
<td>15 (6)</td>
<td>1.14 (0.52, 2.51)</td>
<td>0.8646</td>
</tr>
<tr>
<td>Time to first CNS progression, median (range)</td>
<td>5.7 (2–17)</td>
<td>4.4 (2–27)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
CEREBEL: Lapatinib vs. Trastuzumab

Investigator Assessed PFS

Pivot X, et al. ESMO 2012
CEREBEL: Lapatinib vs. Trastuzumab Overall Survival

Pivot X, et al. ESMO 2012
CEREBEL: Lapatinib vs. Trastuzumab

Conclusions

Low incidence of CNS disease as site of first relapse

First prospective data of patients screened for CNS disease showing an impressive 20% incidence of “occult” asymptomatic brain metastases in a HER2-positive

PFS favored the Trastuzumab + Capecitabine combo

Pivot X, et al. ESMO 2012
Conclusions: Breast Cancer and Brain Metastasis

• CNS metastasis affects 10-20% of patients with MBC and is associated with a poor prognosis and substantial morbidity.

• Several risk factors have been identified for the development of breast cancer brain metastases, including HER2-positive tumor status.

• Current treatment strategies utilize surgery, SRS, WBRT, and chemotherapy/targeted therapy in various combinations.
Conclusions: Anti-HER2 therapy and Brain Metastasis

• There is a substantial body of clinical evidence that trastuzumab may extend survival in patients with BC cancer brain metastases; these data support the continuation of trastuzumab therapy in these patients.

• Recognize concerns about the usefulness of systemic trastuzumab in patients with BC brain metastases, based on its theoretic inability to cross the BBB.

• There is evidence, however, that prior WBRT, or even the tumor itself, may compromise the integrity of the BBB, thereby allowing antibody penetration.
Conclusions

• Recognition of high risk populations should lead to strategies focusing at prevention and early treatment.

• CNS metastases from BC are different from those arising from other solid tumors.

• CNS metastases arising from each subtype of BC may have different natural histories.

• Treatment of patients with CNS metastases from BC should be individualized, (PS, burden of CNS and systemic disease, tumor subtype and CNS symptoms)