

# Case #4—Brain Metastases in HER2-Positive Breast Cancer: Opportunities and Challenges

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# Breast Cancer and Brain Metastases

## Incidence

- **10% to 16% (30% autopsies)**
- **Prevalent site: Supratentorial**
- **2% to 5% leptomeningeal metastases**
- **2% metastasis sincron at diagnosis**
- **Median progression-free survival (PFS) 34 months**

# Brain Metastases in Breast Cancer

- Brain metastases (BM) occur in approximately 10% to 20% of breast cancer (BC) patients (historical rates) compared with a recent increase to 25% to 34%
- Reasons for this increase in incidence are<sup>1</sup>:
  - Aging population
  - Improved detection of subclinical disease with sophisticated imaging
  - The development of improved adjuvant and palliative therapy regimens—improved survival in patients with MBC
- Contrary to lung, rarely present as first site of disease

# Risk & Prognostic Factors

## ✓ Characteristics of the patient

- **AGE**
- **PERFORMANCE STATUS**

## ✓ Characteristics of the tumor

- **Extension of brain disease**
- If primary tumor present, **locally controlled or not**
- If other systemic metastases, the **status of extracranial disease**, specially in liver/lungs (controlled vs not)
- Heavy burden of disease (↑ LDH)
- **Aggressiveness of the tumor**: ductal; **HER2+**; **HR-**;  
Short DFI (<24 months)

# 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	<u>25%</u>
Altaha et al. J Clin Oncol 2004	<u>48%</u>
Stemmler et al. SABCS 2004	31%
Yau et al. Acta Oncol 2006	30% (at 1 y)

## Incidence of CNS Metastases in Early HER2-Positive Breast Cancer

Adjuvant	Brain Mets/ HER2 Status		Brain Mets/ Trastuzumabuse	
	Positive	Negative	Yes	No
Gabos 1998–2003	27/301 (9%)	7/363 (1.9%)	–	–
Hera trial	48/3,401 (1.4%)	–	26/1703 (2%)	22/1,698 (1%)
B-31+	1,736	–	21/864 (2.4%)	11/872 (1.2%)
N9831	1,615	–	12/808 (1.2%)	04/807 (0.5%)
Pestalozzi	6.8%	3.5%	–	–
IBCSG 1979–99	2.7%	1.0%	–	–

**In 9524 EBC patients, 10-year incidence of CNS relapse was 2.7% in HER2-positive versus 1.0% in HER2-negative ( $P<.01$ ) (Pestalozzi)**

# Risk for CNS Mets in HER2-Positive MBC

**Table 4.** Risk for central nervous system metastasis development using variables found to be significant in the univariate analysis

Variable	CNS metastasis incidence	<i>p</i> -value
Menopausal status at diagnosis		
Premenopausal	50.0%	.001
Postmenopausal	21.0%	
Age at diagnosis		
≤50 years	46.4%	.003
>50 years	20.8%	
Estrogen receptor status		
Negative	43.3%	.047
Positive	25.9%	
Visceral metastases at relapse		
Yes	41.5%	.04
No	22.5%	

# Brain Metastases in HER2-Positive Disease Hypothesis

- ✓ Trastuzumab is **prolonging survival**, so the proportion of patients who develop CNS metastases increases as a function of time
- ✓ Trastuzumab is effective controlling relapses in other sites but **does not easily penetrate the blood-brain barrier**, resulting in a “sanctuary” situation in the CNS
- ✓ Patients treated with trastuzumab are ErbB2+ and thus more likely to have **more aggressive disease** (HR: 1.5 for HER2+ vs -)

# Systems of Classification

Grouping prognostic factors into comprehensive classifications

RPA	<u>R</u> ecursive <u>P</u> artitioning of <u>A</u> nalysis
SIR	<u>S</u> core <u>I</u> ndex of <u>R</u> adiosurgery
BSBM	<u>B</u> asic <u>S</u> core for <u>B</u> rain <u>M</u> etastases

Need some adaptation for breast cancer specificities: Work ongoing

# Brain Metastases & Survival

<b>No treatment</b>	<b>=</b>	<b>1 month</b>
<b>Steroids</b>	<b>=</b>	<b>2 months</b>
<b>WBRT</b>	<b>=</b>	<b>3 - 6 months</b>

# Brain Metastases Treatment Options

✓ **Supportive:** steroids, anticonvulsants

✓ **Local therapy**

- Surgery
- WBRT
- Stereotactic radiosurgery

✓ **Systemic therapy**

- Continuing trastuzumab
- Lapatinib
- Chemotherapy alone (for HER2-negative patients)

# Local Treatment for Brain Metastases

# Surgery

- For patients in whom tissue is needed for diagnosis
- For patients with lesions too large for radiosurgery (>3 cm)
- For patients with life threatening mass effect
- Specially indicated for unique lesions

# Surgery Alone vs Surgery + WBRT : Can We Omit WBRT?

61 % WBRT at recurrence

	Surgery + RT (n = 49 )	Surgery alone (n = 46 )	
Local failure	10 %	46 %	<i>P</i> <.001
Regional failure	14 %	37 %	<i>P</i> <.01
Brain failure	18 %	70 %	<i>P</i> <.001
CNS death	14 %	44 %	<i>P</i> = .003
Median survival	48 weeks	43 weeks	<i>P</i> = .39

Randomized

(Patchell RA, et al. *JAMA*. 1998;280(17):1485-1489.)

# WBRT Alone vs Surgery + WBRT

	Randomization	Median Survival, months	<i>P</i> Value Significant?
Patchell et al.	WBRT vs	3.8	Yes
	Surgery + WBRT	10	
Vecht et al.	WBRT vs	6	Yes
	Surgery + WBRT	10	
Noordijck et al.	WBRT vs	6.5	Yes
	Surgery + WBRT	11	
Mintz et al.	WBRT vs	6.3	No
	Surgery + WBRT	5.6	

# Radiosurgery + WBRT vs Radiosurgery Alone

What happens if WBRT omitted initially and RS used instead ?

- No long term toxicity of WBRT
- Identical median survival
- More frequent salvage treatment without increased neurological morbidity, if early detection of brain recurrence is detected

Confirmed in IJB series & others

Aoyama H, et al. *JAMA*. 2006;295(21):2483-2491.

De Vriendt. Presented at: EBCC-6; 15-19 April 2008; Berlin, Germany.

# Brain Metastases from Breast Cancer

	Treatment	Median Survival
Mahmoud-Ahmed et al.	WBRT	4.2 mo
Le Scodan et al.	WBRT	5 mo
Wronski et al.	Surgery +/- WBRT	14 mo
Pieper et al.	Surgery +/- WBRT	16 mo
Muacevic et al.	Radiosurgery +/- WBRT	10 mo
Firlik et al.	Radiosurgery +/- WBRT	13 mo
Devriendt et al.	Radiosurgery +/- WBRT	15.5 mo

Retrospective studies

# Recommendations

## Multiple ( >4) Brain metastases

**WBRT + / - Radiosurgery**

## Single Brain Metastasis

**Surgery + WBRT** (Patchell et al., Vecht et al., Noordijck et al.)

**Radiosurgery + WBRT** (Andrews et al.)

**? Radiosurgery alone + salvage RS** (Aoyama et al.)

## More than 1 and less than 5 Brain Metastases

**Radiosurgery + WBRT** (Andrews et al.)

**Radiosurgery alone + salvage RS** (Aoyama et al., Muacevic et al.)

# Efficacy of Chemotherapy for Breast Cancer Brain Metastases

Drug(s)	Sample size	Response rate (%)
CFP/CFP-MV/MVP/CA	100	50
CDDP + VP-16	22	55
CMF/CAF	22	59
HD IV M	32	28
CAP	7	43
TMZ + CAP	24	18
TMZ + CDDP	32	31
PTX	152	35
ED	92	68
TOP	16	38

C, cyclophosphamide; F, fluorouracil; P, prednisone; M, methotrexate; V, vincristine; A, doxorubicin; CDDP, cisplatin; VP-16, etoposide; HD, high dose; IV, intravenous; TMZ, temozolomide; CAP, capecitabine; PTX, paclitaxel; E, epirubicin; D, docetaxel; TOP, topotecan

**But NO LEVEL 1 EVIDENCE FOR ANY DRUG OVER THE OTHERS**

# Efficacy of Chemotherapy for Breast Cancer Brain Metastases

- Limited by intrinsic drug resistance and BBB BUT once blood-brain barrier is disturbed, there is at least some passage of cytotoxic agents into the brain
- BBB: P-glycoprotein is highly expressed by the brain capillary endothelium and actively mediates the efflux of some CT drugs such as doxorubicin, CTX, 5FU, taxanes, and vinorelbine
- May have a role as salvage therapy in recurrent disease
- Responsiveness of BM mirrors sensitivity of primary tumour
- **What can be recommended for HER2-neg disease: Use the same CT regimen you would choose for the same patient if metastases were somewhere else**

# Continuing Trastuzumab After Diagnosis of CNS Metastases May Extend Patients' Lives

Observational study		Median OS, Months	
		With T	Without T
Lower et al 2003 (n = 80)	From T initiation or MBC diagnosis	~53	~23 <sup>a</sup>
Kirsch et al 2005 (n = 47)	From CNS metastases diagnosis	~26	~9
Church et al 2006 (n = 22)	From CNS metastases diagnosis	12	3
Bartsch et al 2007 (n = 53)	From CNS metastases diagnosis	21	9 <sup>b</sup> and 3 <sup>c</sup>
Pinder et al 2007 (n = 292)	From MBC diagnosis	33.5	29.4
Dawood et al 2008 (n= 5 72)	From CNS metastases diagnosis	11.6	6.1

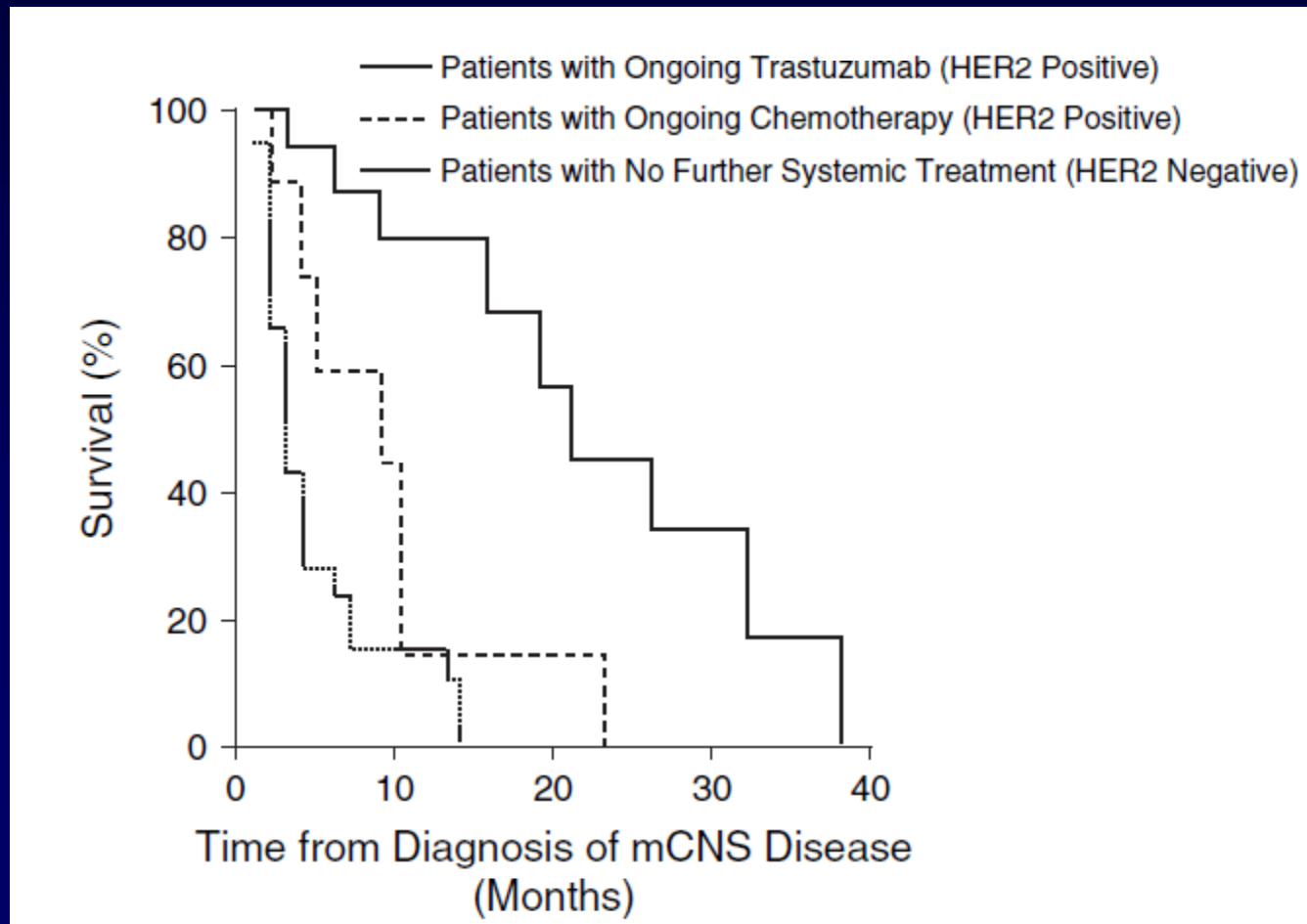
**Patients continuing trastuzumab after the diagnosis of BM have an improvement in OS (12.8 months vs 4.0 months;  $P = .0019$ )\***

<sup>a</sup>Mixed population of patients with HER2-negative and HER2-positive tumors;

<sup>b</sup>Patients received chemotherapy only; <sup>c</sup>Patients received no systemic therapy  
CNS, central nervous system

\*Nam BH et al. *Breast Cancer Res.* 2008;10:R20. doi: 10.1186/bcr1870

# Overall Survival for Patients with Brain Metastases Following WBRT and Different Treatment Strategies



Bartsch R, et al. *J Neurooncol.* 2007;85:311-317.

Pienkowski T, et al. *Ann Oncol.* 2009 Aug 28. [Epub ahead of print]

# BRAIN METASTASES

## Treatment Options

✓ **Supportive: steroids**

✓ **Local therapy**

- **Surgery**
- **WBRT**
- **Stereotactic radiosurgery**

✓ **Systemic therapy**

- **Continuing trastuzumab**
- **Lapatinib**
- **Chemotherapy alone (for HER2-neg patients)**

# Exploratory Analysis of Brain Metastases as Site of First Progression\*

Study EGF100151	Lapatinib + capecitabine (N=198)	Capecitabine (N=201)
<u>Patients with symptomatic CNS progression as part of their <u>first</u> progression event</u>	4 (2%)	13 (6%)
	<b><i>P</i> = .045</b>	

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\* As assessed by independent review committee

# EGF105084: Phase II Study of Lapatinib for Brain Metastases in ErbB2+ Breast Cancer

## Eligibility criteria:

- Women or men with stage IV disease and  $\geq 1$  measurable lesion in the brain
- IHC3+ or FISH gene amplification
- **Prior trastuzumab therapy**
- Prior treatment of brain metastases with radiation therapy or radiosurgery

## Cohorts:

1. ECOG PS 0 or 1 and 1 or 2 trastuzumab-containing regimens
2. ECOG PS 2 or  $>2$  prior trastuzumab-containing regimens

(n = 220)

Treatment:  
Lapatinib 750 mg  
bid

CNS  
progressive  
disease

Lapatinib  
1250 mg/day +  
capecitabine  
2000 mg/m<sup>2</sup>/day

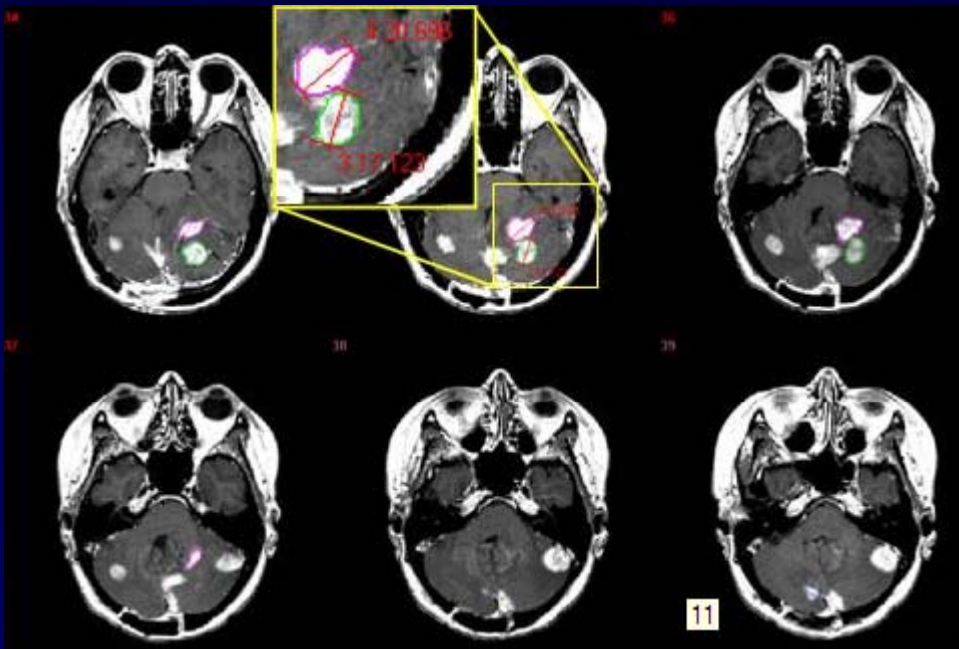
**Primary endpoint: CNS objective RR using volumetric MRI**

# CNS Response

<b>Best Response</b>	<b>Patients, n (%)</b>
<b>Complete response</b>	<b>0 (0)</b>
<b>Partial response</b>	<b>15 (6)</b>
<b>Stable disease*</b>	<b>108 (46)</b>

\* ≥8 weeks on study

# CNS Response— Importance of Volumetric Reduction in CNS Lesions

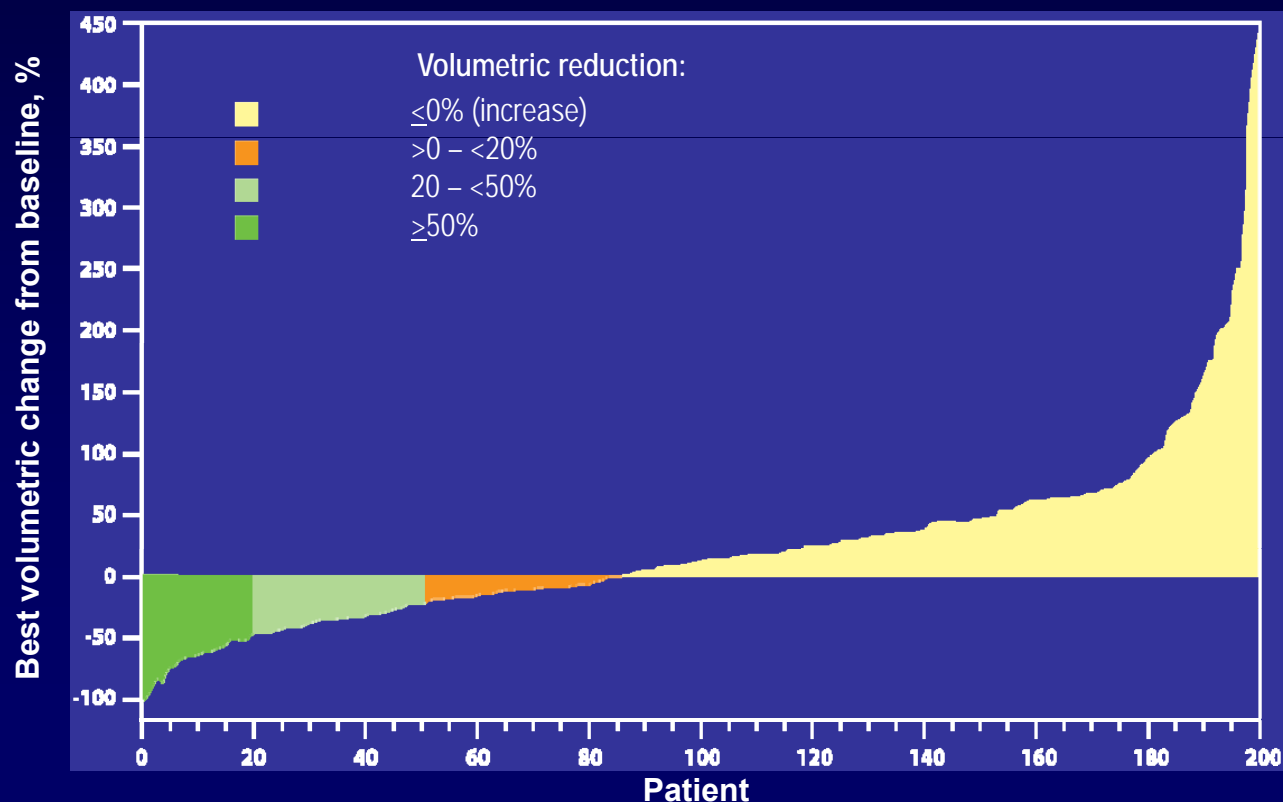


## MRI Volumetric analysis

- High resolution scans at 3 mm intervals without gaps in axial dimension

# Updated Analysis: Volumetric Reduction in EGF105084 (lapatinib monotherapy, n=200)

Overall, 29% of patients experienced volumetric reduction  
21% with a reduction  $\geq 20\%$ ; 8% with a reduction  $\geq 50\%$



volumetric reduction	median PFS mo (95%CI)
$\geq 20\%$	3.61 (3.19-3.71)
$\geq 50\%$	3.38 (2.79-5.36)

# Lapatinib + Capecitabine Extension Arm

EGF105084 amended to allow option of L+C upon radiographic disease progression in CNS and/or non-CNS

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≥50% Volumetric CNS tumor reduction, n (%)	11/50 (22)
<b>*Absolute tumor volumetric reduction, median cm<sup>3</sup> (range)</b>	<b>6.2 (3.2-12.9)</b>
Median PFS, mo, (95% CI)	6.21 (3.94- n/e)
≥20% Volumetric CNS tumor reduction (n, %)	20/50 (40)
<b>*Absolute tumor volumetric reduction, median cm<sup>3</sup> (range)</b>	<b>3.9 (0.6-12.9)</b>
Median PFS, mo, (95% CI)	4.60 (3.68-8.15)

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n/e-not estimate

Lin NU, et al. *Clin Can Res*. 2009;15(4):1452-1459.

\* Lin NU, et al. *J Clin Oncol*. 2007;25(18S): Abstract 1012.

# Lapatinib in Brain Metastases Treatment: Ongoing Trials

Study	Phase	# Patients	Treatment
NCT 00470847 (Dana Faber)	I	39	Lapatinib in combination with radiation therapy in patients with BM from HER2-positive BC
LAP111172 (Jules Bordet)	I	18	Lapatinib and temozolomide for the treatment of progressive BM in HER2-positive MBC
NCT00098605 (Dana Faber)	II	12-37	Lapatinib in patients with BM from HER2-positive BC

# CEREBEL Study: A Phase III Randomized Open-Label Study of Lapatinib plus Capecitabine vs Trastuzumab + Capecitabine in HER2-Positive Metastatic Breast Cancer

## Inclusion Criteria:

- Stage IV HER2+ breast cancer
- Prior anthracycline and a taxane
- Prior treatment with CT, trastuzumab, HT, RT is permitted
- LVEF  $\geq 50\%$ , normal organ function

## Main Exclusion Criteria:

- History and/or current evidence of CNS metastases
- prior therapy with lapatinib or ErbB2 inhibitor other than trastuzumab

No combination arm

R  
A  
N  
D  
O  
M  
I  
Z  
E

Capecitabine 2500 mg/m<sup>2</sup> bid d1-14 q21 days  
+  
Trastuzumab loading dose 8 mg/kg →  
6 mg/kg q3 weeks

Lapatinib 1250 mg PO qd continuously +  
capecitabine 2000 mg/m<sup>2</sup>/d  
PO days 1-14 q3 weeks

- Primary endpoint: Incidence of CNS metastases as site of first relapse
- Secondary endpoints: Incidence of CNS progression any time, time to first CNS progression, PFS, OS, ORR, CBR, duration of response, toxicity, pharmacogenetics and biomarker analysis

# Lapatinib in Brain Metastases Prevention: Ongoing Studies

Study	Treatment Groups	Patient Population	Status	Endpoints
<b>EGF108919</b> (n = 536)	Taxane / lapatinib Taxane / trastuzumab	ErbB2+ MBC First-line No CNS mets	Start in Q2 08	1°: PFS 2°: ORR, OS, CBR, CNS inc
<b>TEACH</b> (n = 3000)	Lapatinib qd Placebo	ErbB2+ early BC Adjuvant No trastuzumab	Recruitment complete	1°: DFS 2°: OS, CNS RFI
<u>Design 1</u>  <b>ALTTO</b> (n = 8000)	H→L L H H+L	ErbB2+ early BC Adjuvant	Recruiting since Jun 07	1°: DFS 2°: OS, TTR, TTDR, CNS inc
<u>Design 2</u>	P or TCp+H→L P or TCp+L→L P or TCp+H→H P or TCp+H+L→H+L	ErbB2+ early BC Adjuvant		

P, paclitaxel; H, trastuzumab; L, lapatinib; TCp, docetaxel + carboplatin

# My Choice

**Part I:**

**Patient received corticosteroids and her symptoms partially improved. What would be your first recommendation now?**

- 1. Local therapy**
- 2. Systemic therapy**
- 3. Local therapy followed by systemic therapy**
- 4. Before any therapy I would biopsy one of the brain metastases to check hormone receptor and HER2 status**

**Additional question: continue tamoxifen or not: YES**

# My Choice

## Part II:

Which of the following local therapy options would you recommend for this patient with multiple brain metastases?

1. Whole-brain radiation therapy (WBRT)
2. Stereotactic radiosurgery followed by WBRT
3. Stereotactic radiosurgery  
(if technically possible)
4. Surgery followed by WBRT

# My Choice

## Part III:

**Patient received WBRT and her symptoms almost completely disappeared until the end of radiation therapy. MRI evaluation 4 weeks after completion of WBRT showed partial response. If you decided to give her systemic therapy, which of the following options would you recommend?**

- 1. Rechallenge with trastuzumab + chemotherapy**
- 2. Lapatinib (Tyverb®/Tykerb®) + chemotherapy**
- 3. Lapatinib + letrozole**
- 4. Lapatinib alone**
- 5. Intrathecal trastuzumab**
- 6. Other**