

Clinical Trials of Lapatinib in Patients with Brain Metastases from HER2+ Breast Cancer

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Background

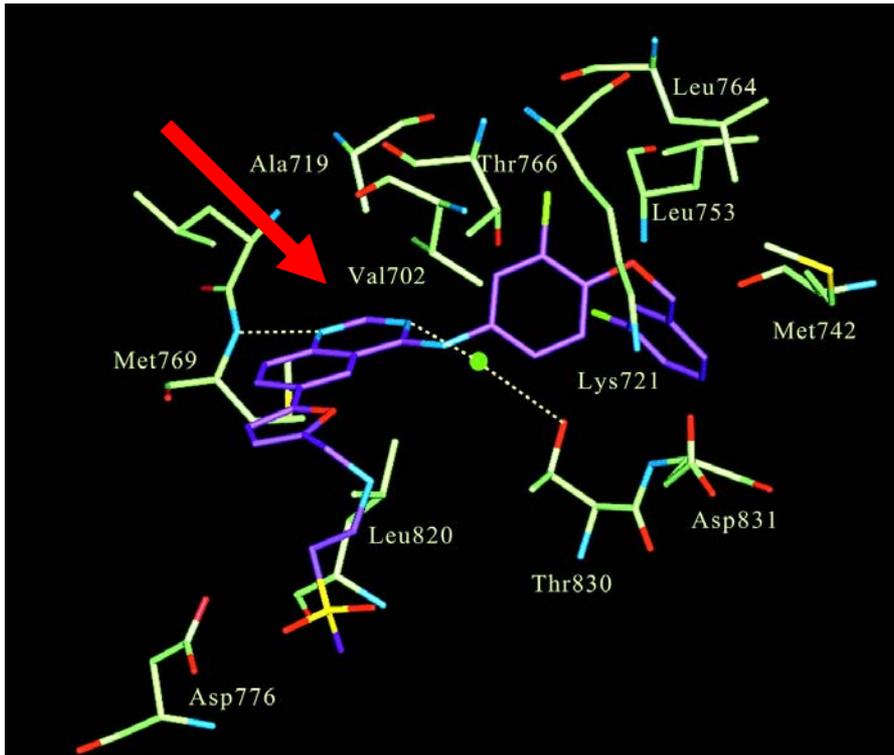
- ~1/3 of women with HER2+ MBC develop brain metastases
- For some women, the CNS has become the dominant site of disease
- Trastuzumab does not easily cross the BBB
- As women live longer, CNS progression after RT is becoming a more common problem

Background

- Median survival *after* brain met diagnosis in HER2+ pts may now exceed 1 year

Study	Median survival (mo)
Gori et al, Oncologist 2007	23
Eichler et al, Cancer 2008	17.1
Melisko et al, J Neuroonc 2008	23.1

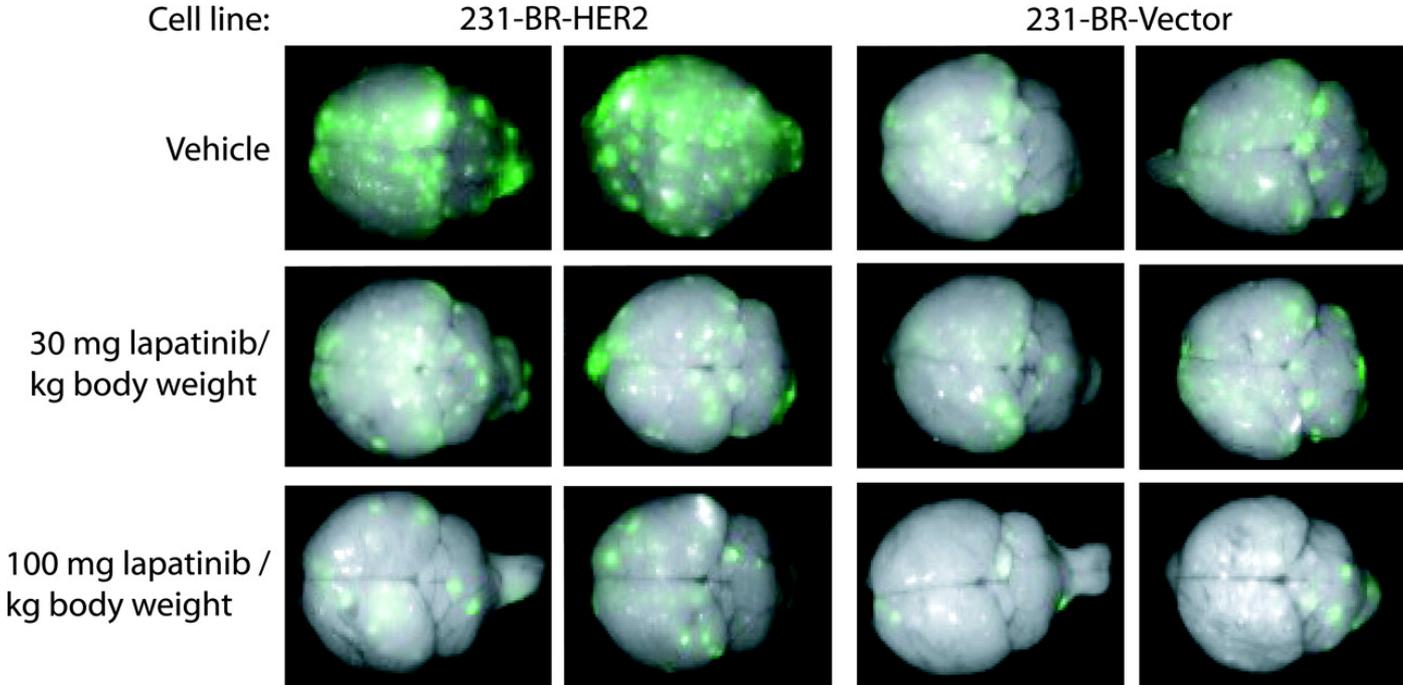
Lapatinib



- Lapatinib is an orally-bioavailable, small molecule inhibitor of EGFR and HER2
- Evidence of activity in MBC
- Gefitinib has been reported to induce regressions of CNS lesions in pts with NSCLC

Wood, E. R. et al. Cancer Res 2004;64:6652-6659

Lapatinib inhibition of metastatic colonization of mouse brain by 231-BR breast carcinoma cells



Gril, B. et al. J. Natl. Cancer Inst. 2008 100:1092-1103; doi:10.1093/jnci/djn216

Phase II Trial of Lapatinib for Brain Metastases in Patients with HER2-Positive breast cancer

NU Lin, LA Carey, MC Liu, J Younger, SE Come, M Ewend, GJ Harris, E Bullitt, A van den Abbeele, JW Henson, X Li, R Gelman, HJ Burstein, E Kasparian, DG Kirsch, A Crawford, F Hochberg, EP Winer

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Objectives

- **Primary Objective**
 - Objective response rate in the CNS
- **Secondary Objectives**
 - Objective response rate in non-CNS sites
 - Time to progression
 - Overall survival
 - Toxicity
 - Quality of life
 - Explore novel radiological predictors of response

Key Eligibility Criteria

- **Inclusion**

- Metastatic HER2+ breast cancer
- Progressive CNS metastases after WBRT and/or SRS
- --or--
- Asymptomatic CNS metastases w/o prior XRT
- ECOG PS 0-2
- At least one CNS lesion ≥ 10 mm in longest dimension

- **Exclusion**

- Cardiac ejection fraction below institutional normal limit
- Prior treatment with EGFR or HER2 inhibitor, other than trastuzumab, for MBC
- Concurrent treatment with inducers or inhibitors of CYP3A4

CNS Response Criteria

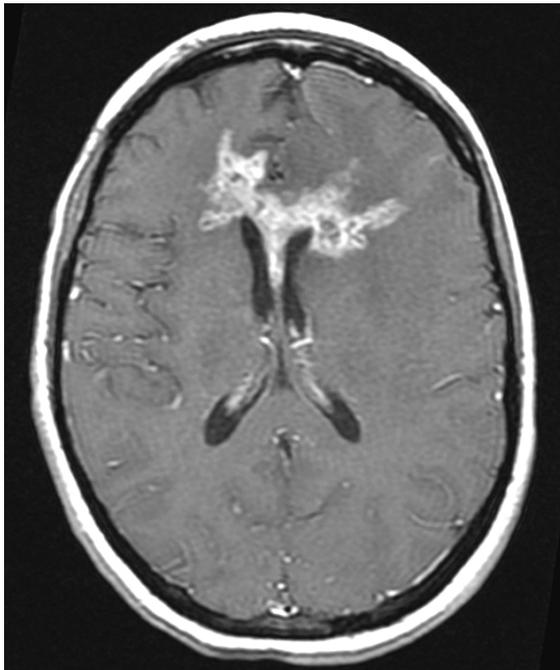
- **Complete Response (CR)**
 - Disappearance of all target lesions
- **Partial Response (PR)**
 - $\geq 30\%$ decrease in the sum of the longest dimension (LD) of target lesions, *AND, an absolute decrease of ≥ 5 mm in at least one target lesion*
- **Progressive Disease (PD)**
 - $> 20\%$ increase in sum LD of target lesions, *AND, an absolute increase ≥ 5 mm in at least one target lesion, OR, the appearance of one or more new lesions ≥ 6 mm*
- **Stable Disease (SD)**
 - Neither PD nor PR

Best CNS Response (RECIST)

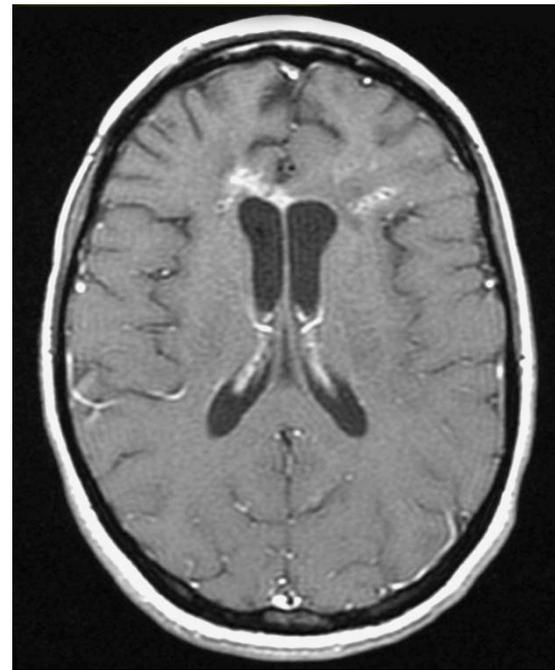
N=39

Complete Response	0 (0%)
Partial Response	1 (2.6%)
SD \geq 16 weeks (CNS+non-CNS)	6 (15.4%)

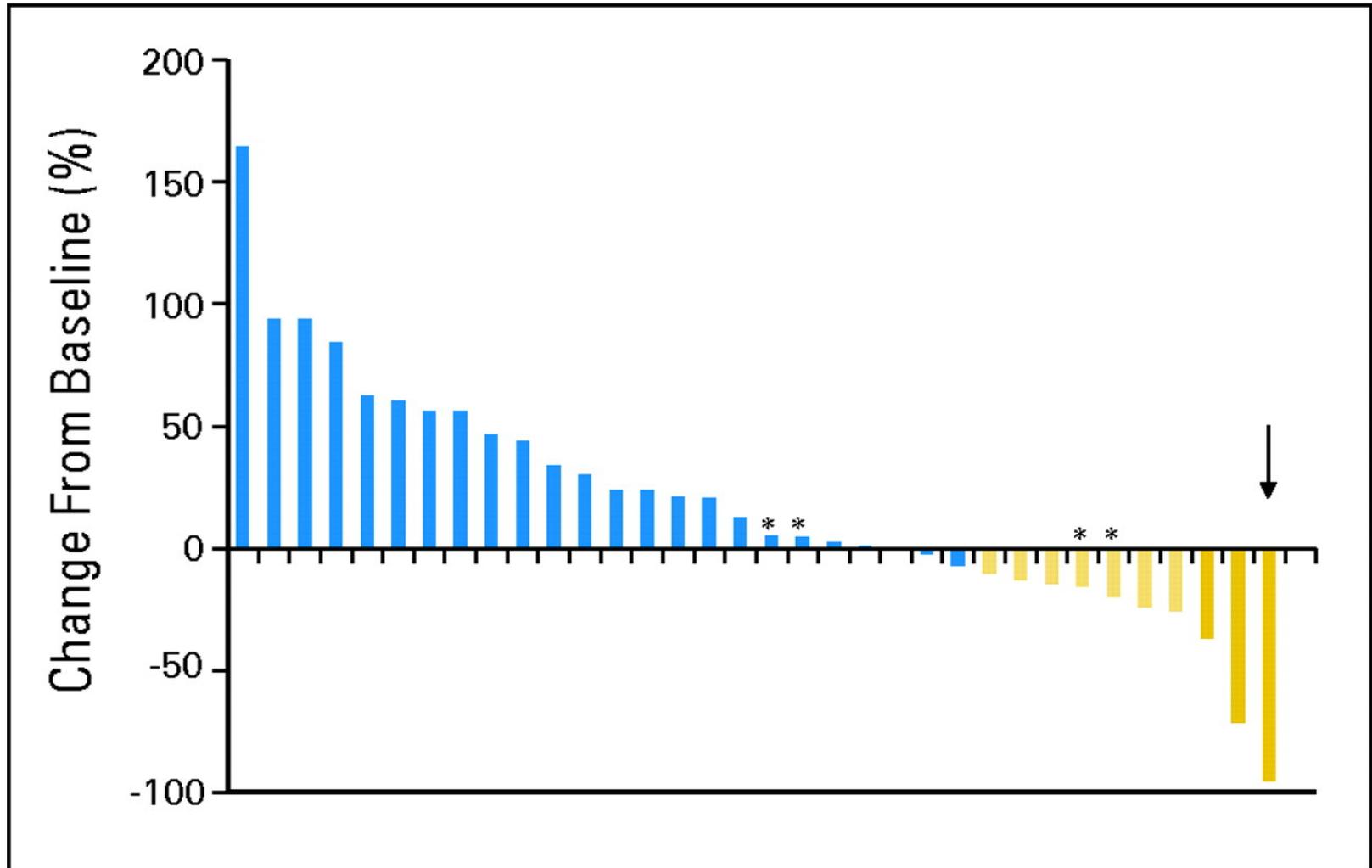
Baseline



Week 16



Best Volumetric Change in CNS Target Lesions



Volumetric Response: Exploratory Analysis

	median TTP*	p-value
$\geq 30\%$ vs $< 30\%$	1.8 vs 5.4 mo	0.16
$\geq 10\%$ vs $> 10\%$	1.8 vs 3.5 mo	0.04

Landmark method: restricted analysis to patients who had a Baseline and Week 8 MRI and no progression before or at that time point (n=27)

*from Week 8 scan

Quality of Life

- Exploratory analysis of QOL at baseline and week 8
 - EORTC QLQ C-30
 - EORTC BCM-20
- Overall, most patients reported stable symptoms at 8 weeks
 - Trend towards improved QOL in some patients with volumetric declines in CNS lesions, but numbers are small
- **Only 19/39 patients with complete data!**

Lessons Learned

- Central radiology review is key
- Volumetric data may give a better sense of activity
- Inclusion of additional parameters in definition of response
- Challenges in pt-rated QOL instruments

Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer

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Dana-Farber Cancer Institute, Boston, MA; Institut Curie, Paris, France; Institut Jules Bordet, Brussels, Belgium; Errikos Ntynan Hospital, Athens, Greece; Rocky Mountain Cancer Center, Denver, CO; Klinikum der Universität München, München, Germany; Centre Claudius Regaud, Toulouse, France; GlaxoSmithKline, Collegeville, PA

Key Eligibility Criteria

- Radiographically documented progressive CNS disease
- Prior cranial radiotherapy (WBRT and/or SRS)
- Target brain lesion (≥ 10 mm diameter)
- Prior trastuzumab
- ECOG PS 0 - 2
- Normal cardiac ejection fraction

Objectives

- **Primary**

- CNS objective response rate

- **Secondary**

- TTP (at any site)
- Overall survival
- Tolerability
- Improvement in tumor-related neurological signs and symptoms (NSS)

CNS Composite Response Criteria

	CR	PR	SD	PD
Qualifying criteria	All	All	All	Any
Brain lesions (volumetric MRI)				
Target	CR	≥ 50% ↓ vol	< 50% ↓ vol < 40% ↑ vol	≥ 40% ↑ vol
Non-target	None / CR	None / no progression		Progression
New	None			Yes
Steroids	Stable or ↓			↑ Dose
Neurological signs/symptoms	Stable or improving			New or worsening
Systemic disease (RECIST)	No progression			Progression

Neurological Signs & Symptoms

- Standardized worksheet derived from the CTCAE v3.0 covering 7 areas:
 - level of consciousness
 - neurological symptoms
 - cranial nerves
 - language
 - strength
 - sensation
 - ataxia

*"Improvement" defined as a decrease by 1 or more grade from baseline of any tumor-related NSS, with confirmation at least 4 weeks later, and no development or worsening in tumor-related NSS, radiographic disease progression, or increase in steroid requirement

Neurological Signs & Symptoms

Strength*

RUE	__ Normal	__ Abnl; specify _____
LUE	__ Normal	__ Abnl; specify _____
RLE	__ Normal	__ Abnl; specify _____
LLE	__ Normal	__ Abnl; specify _____

*If abnormal, please specify muscle group and grade according to the scale below (e.g. biceps, grade 2)

grade 1= asymptomatic with weakness on physical exam

grade 2=symptomatic and interfering w/function but not interfering with ADLs

grade 3=symptomatic and interfering with ADLs

grade 4=bedridden or disabling

CNS Composite Response

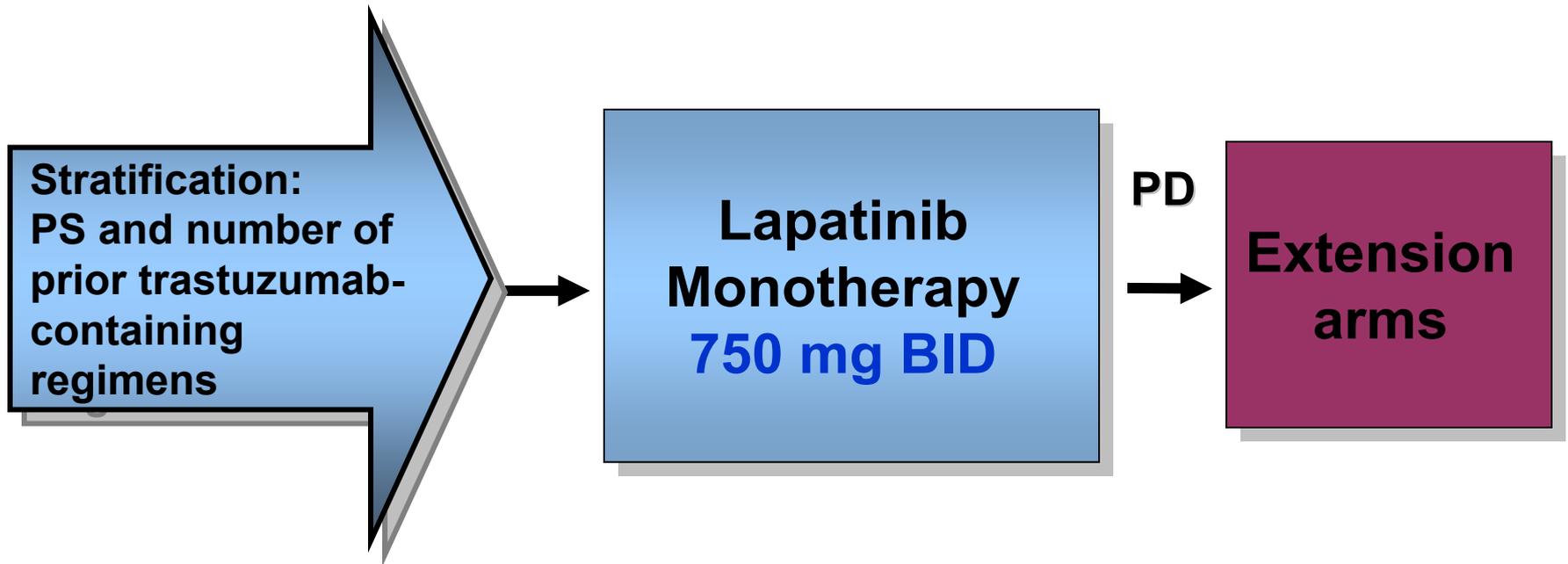
Best response	Patients, n (%)
Complete response	0 (0)
Partial response	15 (6)
Stable disease*	88 (37)

*No difference in response rate according to hormone receptor status, baseline steroid use, or time from last radiotherapy

Neurological Signs & Symptoms

- 198 patients had NSS at baseline
 - Overall, improvement reported in 11.6% of patients
 - 8/35 (23%) of patients with $\geq 20\%$ reduction in CNS tumor volume
 - 9/124 (7%) of patients without a decrease in CNS tumor volume

EGF105084: Extension Arms



CNS Composite Response: L+C Extension

Best response	Patients, n (%)
Complete response	0 (0)
Partial response	10 (20)

*20/50 patients (40%) experienced $\geq 20\%$ reduction in volume of CNS lesions

Summary of EGF105084

- EGF105084 confirms single-agent activity of lapatinib in patients with recurrent brain metastases from HER2+ breast cancer
- Although overall lapatinib activity was modest and target response rate was not reached, some patients derived durable volumetric reductions in brain tumor burden, with improvement or stabilization of CNS symptoms
- Early data suggests that lapatinib + capecitabine has CNS activity, future lapatinib-based combination studies would be of interest

Lessons Learned

- Central radiology review is feasible
- Provision of guidelines for clinical decision making in absence of “real-time” central radiology reads vs requiring imaging prior to clinic visit with rapid turn-around time
- NSS Worksheet feasible to systematically capture signs/symptoms

Ongoing Trials

- Phase I Lapatinib + WBRT (Lin)
- Phase I Lapatinib + TMZ (de Azambuja)

Concepts in Development: HER2+

- Vallow et al: Lapatinib/bevacizumab
- Lin et al: Lapatinib/pazopanib

Other HER2 TKIs....

Other combinations....