

Case #6

Metastatic HER2-Positive Breast Cancer With CNS Metastases: A Clinicopathologic Discussion

All Faculty

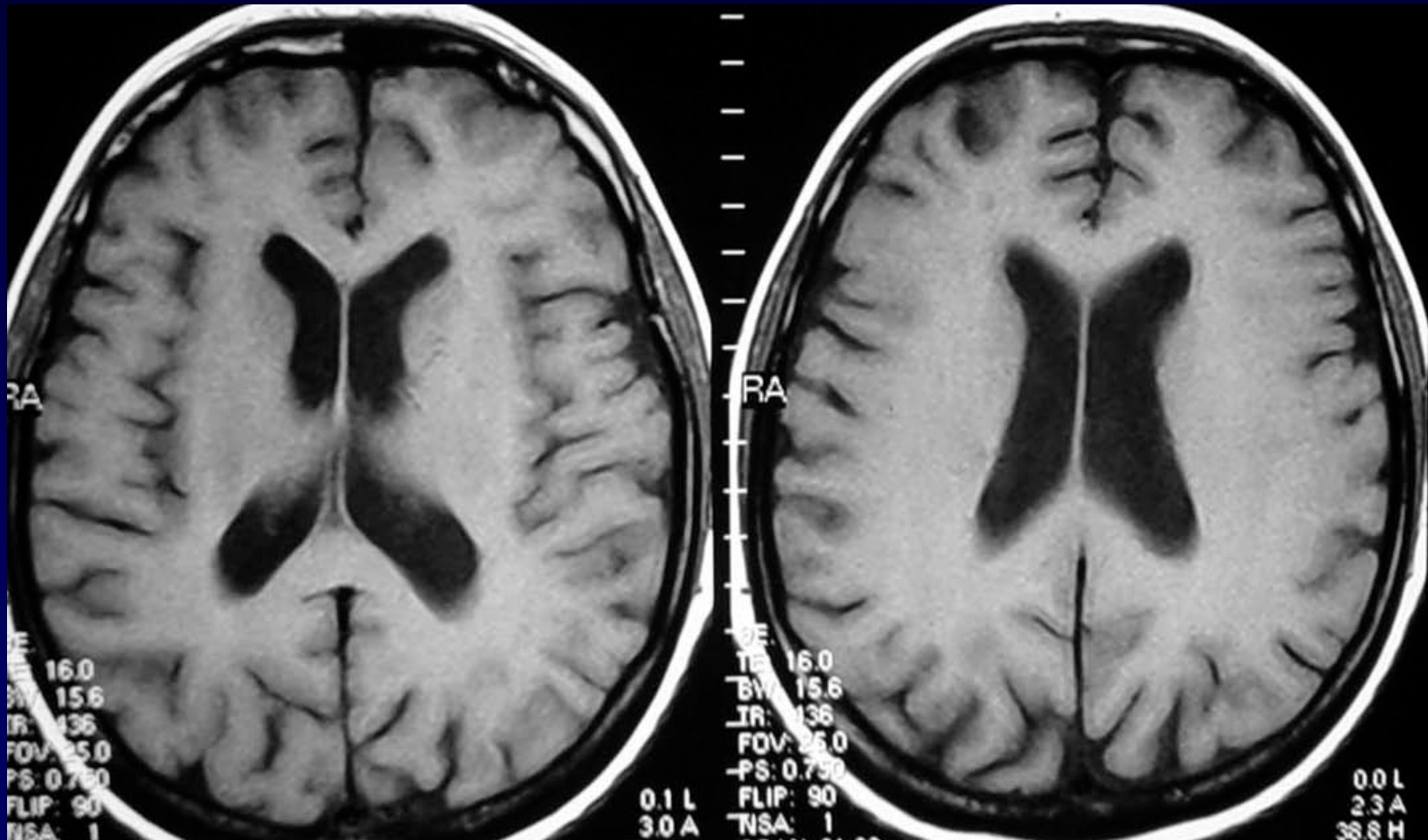
A 67-year-old artist treated for HER2-positive right breast cancer 3 years ago presents with headaches and alterations in memory.

- **HISTORY:** Stage II invasive ductal carcinoma in right breast 3 years ago. Treated with BCS, axillary lymphadenectomy, adjuvant systemic therapy, and irradiation to the involved breast and ipsilateral supraclavicular region.
- **PATHOLOGY:** Invasive ductal carcinoma, G 3, T = 2.5 cm, N = 6/18 positive, Ki67 25%, ER 40% and PR 30% HER2 3+ by IHC
- **ADJUVANT SYSTEMIC THERAPY:** AC x 4 → paclitaxel weekly x 12 + trastuzumab (1 year). After completion of paclitaxel, treatment with letrozole was also begun.

- **CLINICAL COURSE:** She did well until 2 years after completion of adjuvant trastuzumab, when she developed headaches and alterations in memory while on letrozole. No other abnormalities were found during physical examination. **Results from an MRI of her brain show multiple contrast-enhancing lesions in both hemispheres (metastases). No extracranial metastases were detected with additional imaging investigation.**
- **LABORATORY:** CBC, renal and liver function tests, and Ca⁺⁺ normal
- **LVEF: 56% by ECHO (normal)**
- **ECOG PS: 1**

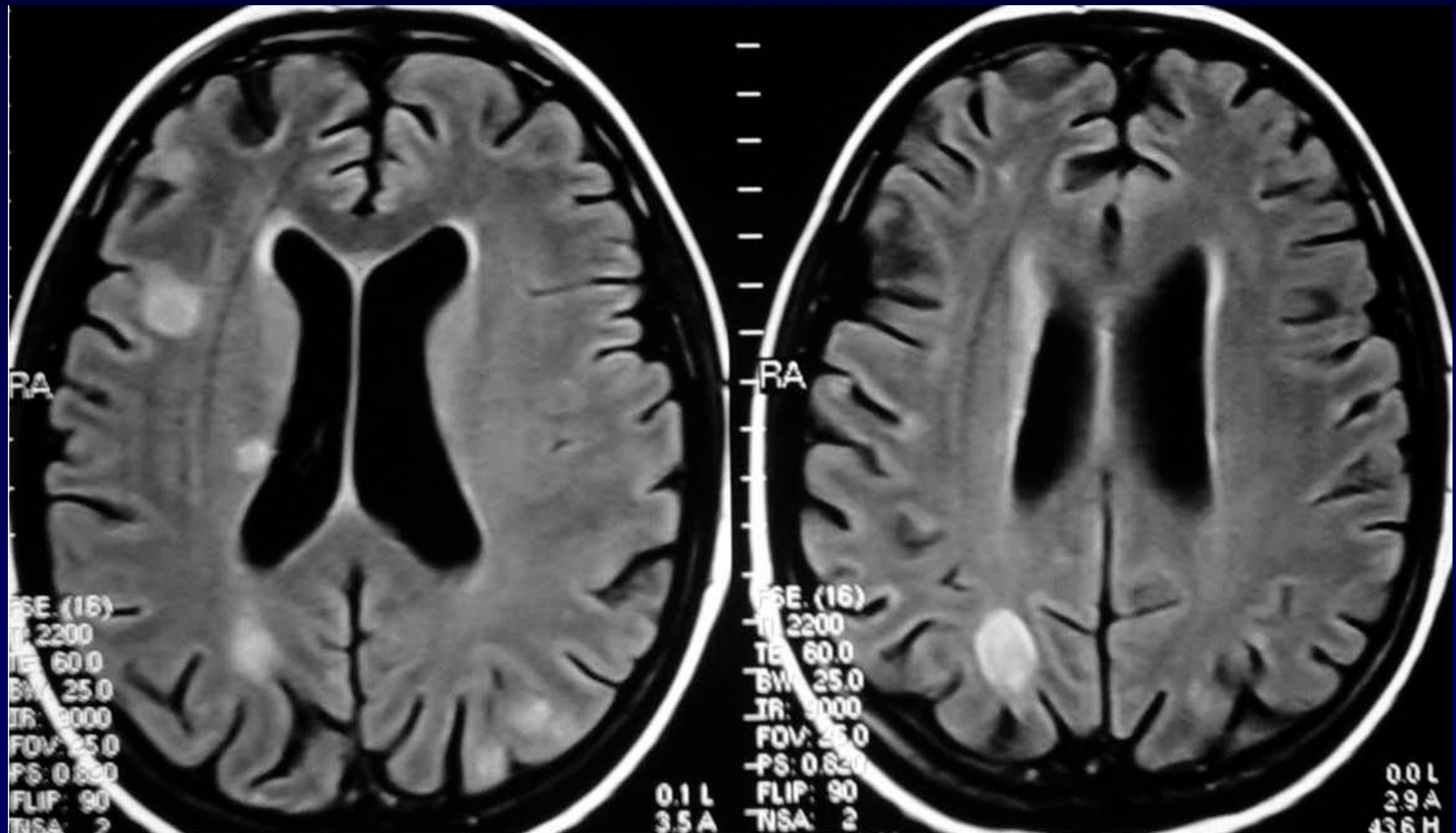
Brain MRI

Axial T1-weighted without contrast revealed no remarkable findings



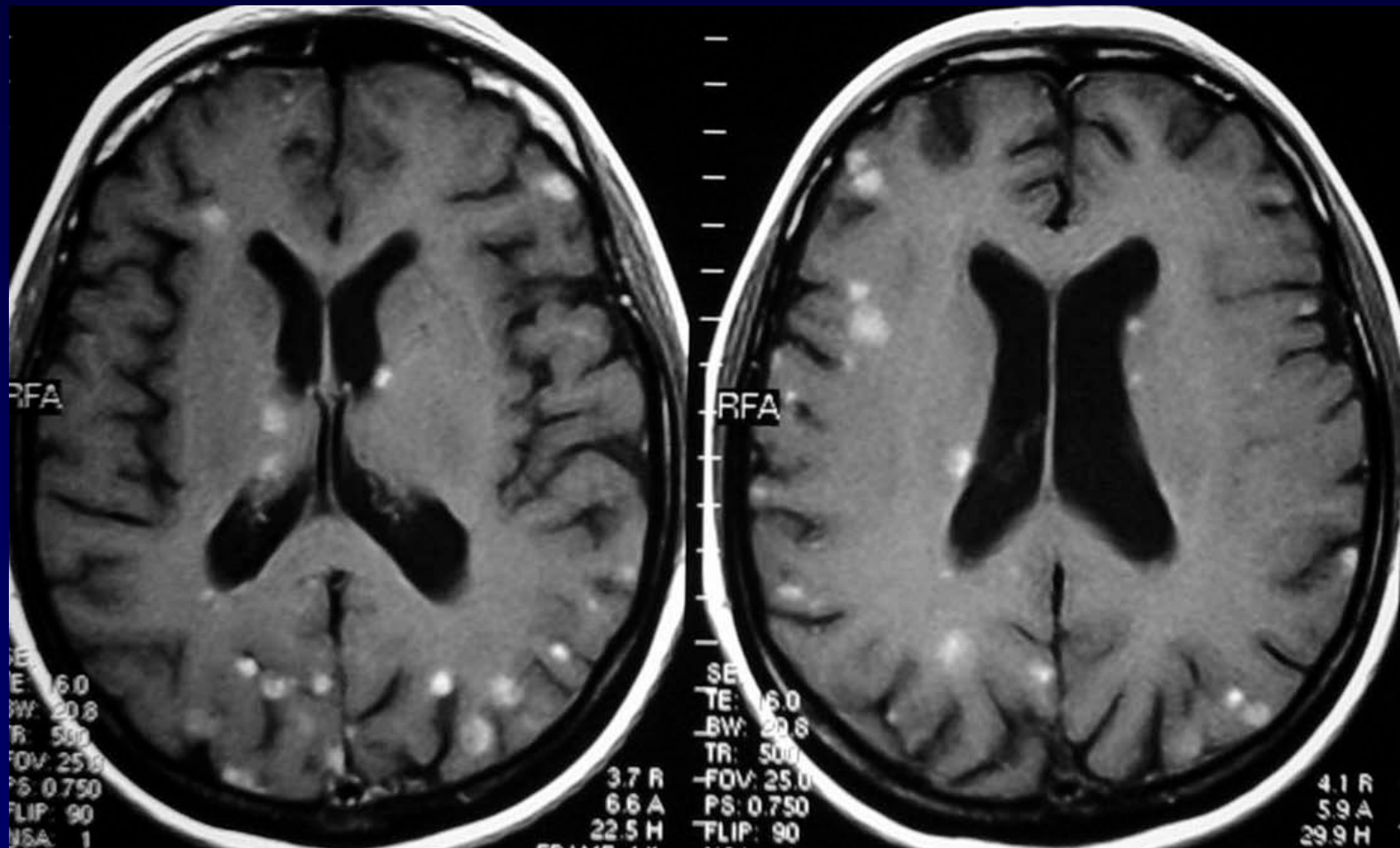
Brain MRI

FLAIR sequence in axial plane shows multiple hyperintense images in both brain hemispheres (frontal and parietal region)



Brain MRI

Axial gadolinium-enhanced, T1-weighted shows multiple nodular imaging in both brain hemispheres with cortical-subcortical and periventricular locations (BC metastasis)



Brain MRI

- **FLAIR: Fluid Attenuation Inversion Recovery**
(Sequence for tumor detection, lesions in the white matter; shows edema and inflammation produced by the lesions)

Incidence of CNS Metastases in Trastuzumab-Treated Patients

Case Series	Patient Population	#	Overall	%
Bendell et al, 2003	Trastuzumab-treated	42	123	34
Clayton et al, 2004	Trastuzumab-treated	23	93	25
Lai et al, 2004	Trastuzumab-treated	38	79	48.1
	Non-trastuzumab-treated	123	264	46.6
Lower et al, 2003	Trastuzumab-treated	22	87	26
	Non-trastuzumab-treated	58	190	31
Pinder et al, 2007	Trastuzumab-treated first-line	95	231	41
	Non-trastuzumab-treated	12	61	20
Shmueli et al, 2004	Trastuzumab-treated	10	41	21
Stemmler et al, 2006	Trastuzumab-treated	42	136	30.9
Yardley et al, 2007	HER2-positive MBC	236	768	30.7
Yau et al, 2006	Trastuzumab-treated	23	87	26.4

Part I:

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

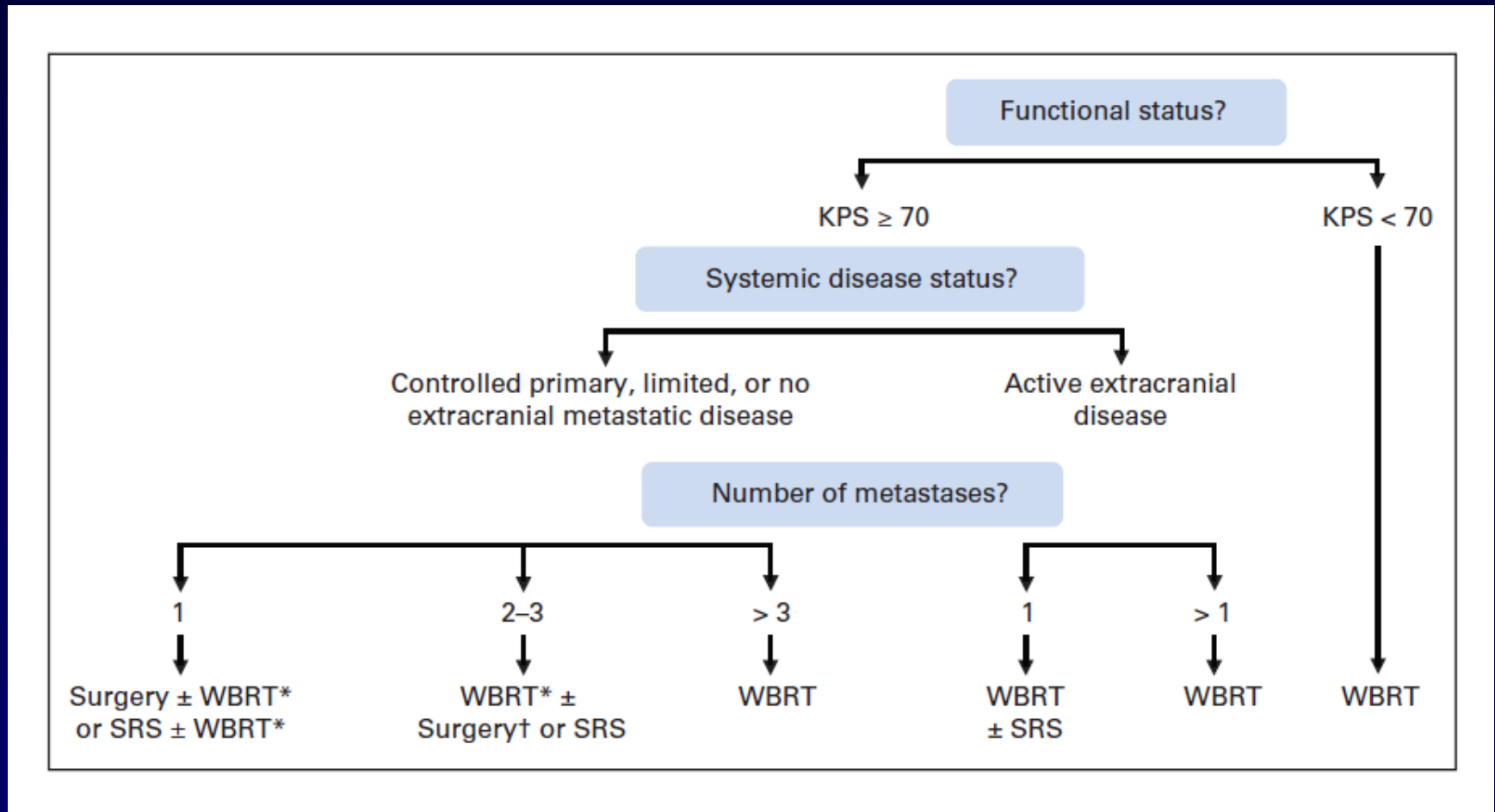
- 1. Local therapy**
- 2. Systemic therapy**
- 3. Local therapy followed by systemic therapy**
- 4. Before any therapy, I would biopsy one of the brain metastases to check hormone receptor and HER2 status**

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**
- 4. Surgery followed by WBRT**

Algorithm of Initial Treatment of Brain Metastases



Part III:

Patient received WBRT and her symptoms almost completely disappeared until the end of radiation therapy (RT). When should evaluation be performed?

- 1. 4 weeks after RT**
- 2. 6 weeks after RT**
- 3. 8 weeks after RT**

Part IV:

Results from an MRI evaluation 6 weeks after therapy of the brain 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 + chemotherapy**
- 3. I would add lapatinib to letrozole**
- 4. Lapatinib alone**
- 5. Intrathecal trastuzumab**
- 6. Other**

Capecitabine ± Lapatinib Study in HER2/*neu*+ MBC: Brain Metastases as First Site of Progression

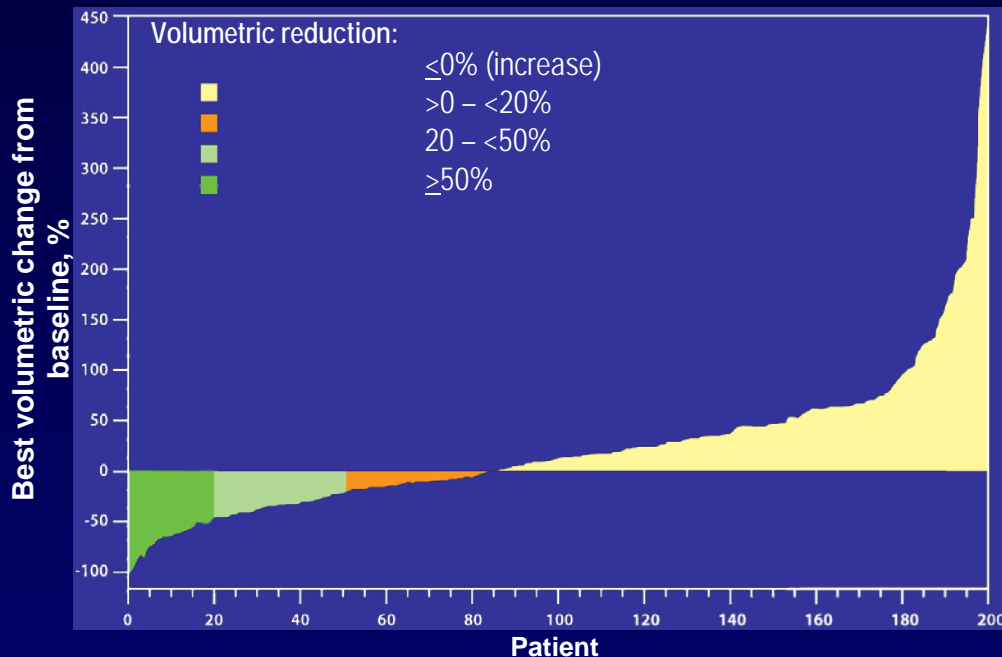
	Lapatinib + Capecitabine (n = 198)	Capecitabine (n = 201)
Patients with symptomatic CNS progression as part of their first progression event	4 (2%)	13 (6%)

P = .045

Lapatinib for Brain Metastases

EGF105084: Volumetric Reduction in CNS lesions (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)	PFS HR (95% CI)
$\geq 20\%$	3.61 (3.19-3.71)	
$\leq 20\%$	1.87 (1.84-2.14)	0.51 (0.36-0.72)
$\geq 50\%$	3.38 (2.79-5.36)	
$\leq 50\%$	2.07 (1.87-2.73)	0.61 (0.37-1.01)

EGF30008: Phase III, Randomized, Double-Blind Controlled Trial: Study Design

Patient Population:

- ER+ and/or PgR+
- Postmenopausal
- HER2+, HER-ve/Unknown
- Stage IIIb/IIIc/IV
- No prior treatment for metastatic breast cancer (MBC)

Stratification:

- Disease sites
 - Bone only/visceral or soft tissue
- Interval since adjuvant tamoxifen therapy
 - <6 mo / ≥6 mo or none

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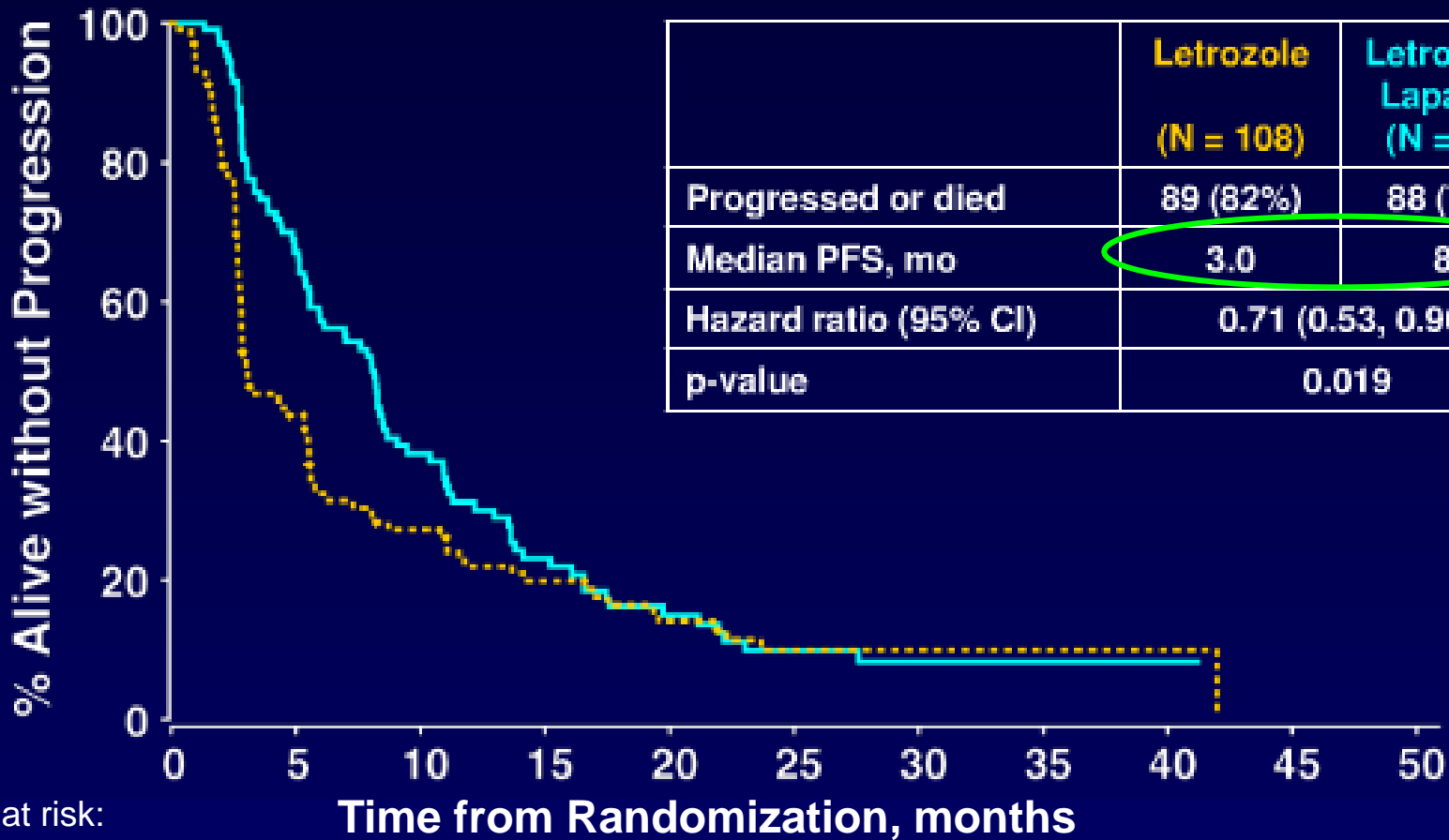
Letrozole 2.5 mg daily +
placebo

Letrozole 2.5 mg daily +
lapatinib 1500 mg daily

N = 1286

(including n = 219 HER2+)

Progression-Free Survival: HER2+ Population



Pts at risk:

	0	5	10	15	20	25	30	35	40	45	50
Let + Lap	111	69	33	20	12	8	4	1	1		
Let	108	43	26	18	12	7	5	2	2		

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

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Capecitabine 2500 mg/m² 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/m²/d
PO days 1-14 q3 weeks

- **Primary endpoint:** Incidence of CNS metastases at site of first relapse
- **Secondary endpoints:** Incidence of CNS progression at 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
EGF108919 (n = 536)	Taxane / lapatinib Taxane / trastuzumab	ErbB2+ MBC First-line No CNS mets	Start in Q2 08	1 ^o : PFS 2 ^o : ORR, OS, CBR, CNS inc
TEACH (n = 3000)	Lapatinib qd Placebo	ErbB2+ early BC Adjuvant No trastuzumab	Recruitment complete	1 ^o : DFS 2 ^o : OS, CNS RFI
<u>Design 1</u> ALTTO (n = 8000)	H→L L H H+L	ErbB2+ early BC Adjuvant	Completed accrual	1 ^o : DFS 2 ^o : 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