

Optimal Treatment of Recurrent HER2 Amplified Breast Cancer (One Year Following Completion of Adjuvant Trastuzumab) Should Be Rechallenge with Trastuzumab-based Therapy

Contra

Véronique Diéras

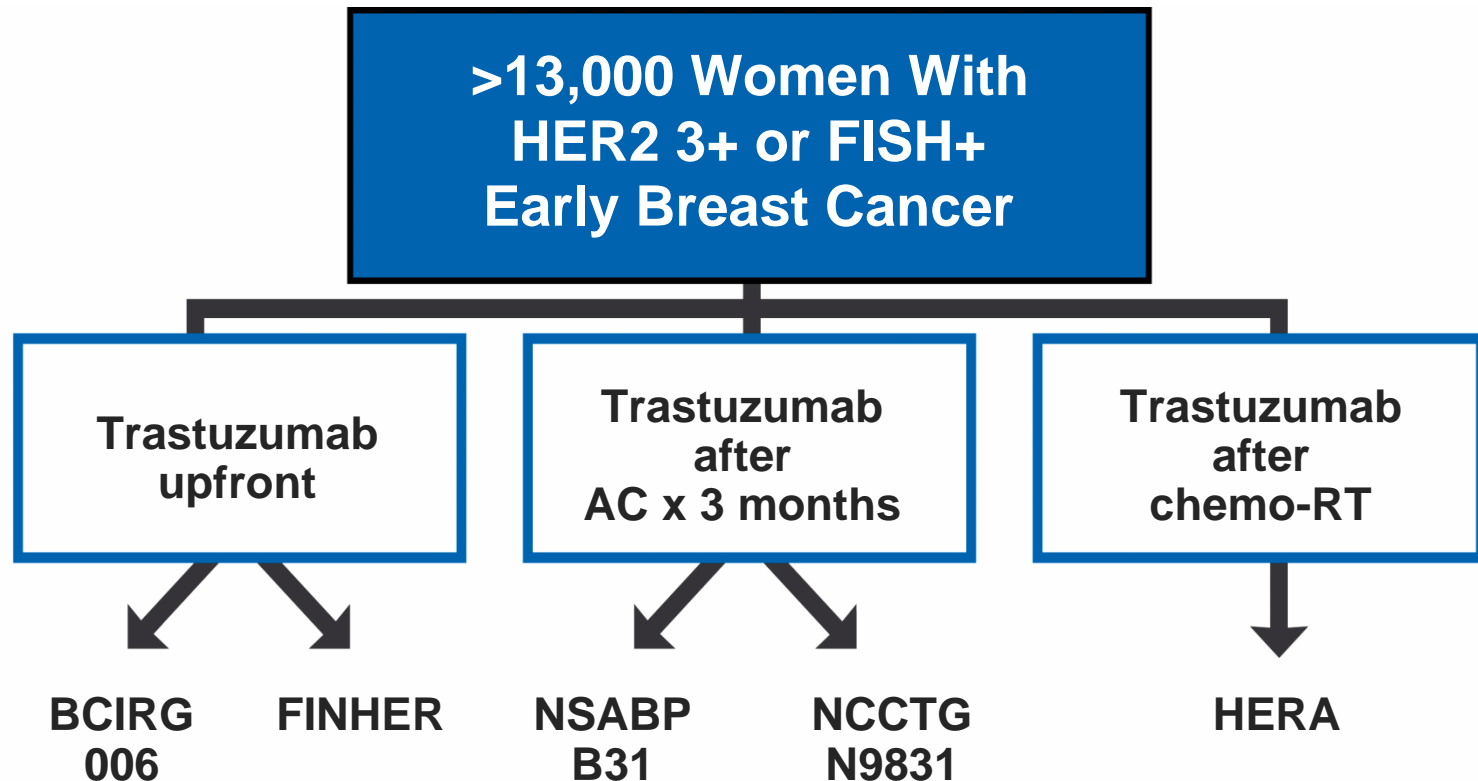
Institut Curie

Paris, France

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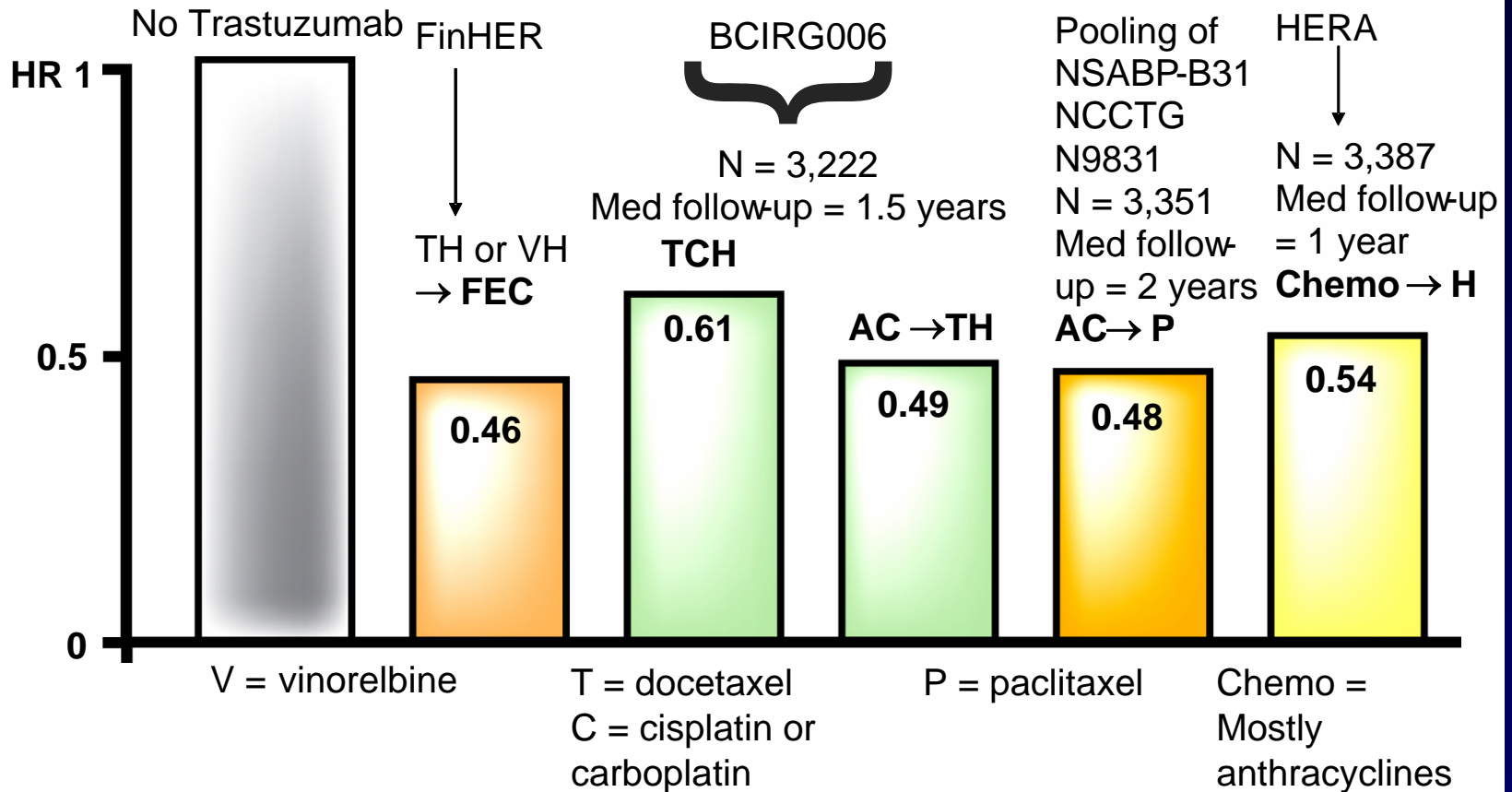
- **Introduction**
- **Resistance to trastuzumab**
- **Current alternative for HER2+ BC:
Lapatinib - Capecitabine**
- **Brain metastasis**
- **Comorbidity / cardiac toxicity**
- **New anti-HER2 agents and combinations**

Adjuvant Trials of Trastuzumab

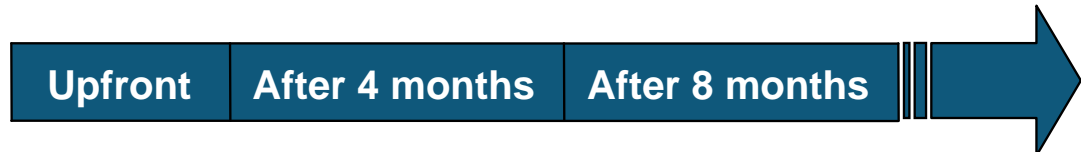


All trials strongly positive at median follow up times of 12-39 months

Efficacy Results From Adjuvant Trials of Trastuzumab



Timing of Trastuzumab (H) Initiation



Trastuzumab Represents the Foundation of Treatment for HER2+ Breast Cancer

- In advanced breast cancer, primary trastuzumab resistance is frequent
 - 60-70% with trastuzumab monotherapy
 - 30-50% with trastuzumab plus chemotherapy
- Eventually, all advanced breast cancer patients become resistant to Trastuzumab within months or years
- In early disease, primary trastuzumab resistance occurs in a significant proportion of patients

Main Features of Patients Relapsing after Adjuvant Trastuzumab

- **Adjuvant treatment**
 - Anthracycline / taxane
 - Sequential or concomittant tratuzumab
 - Duration of treatment
- **Time to recurrence**
 - Most relapses occur after termination of trastuzumab administered for one year
- **Site of recurrence**
 - CNS 12-24%
- **Comorbidity conditions**

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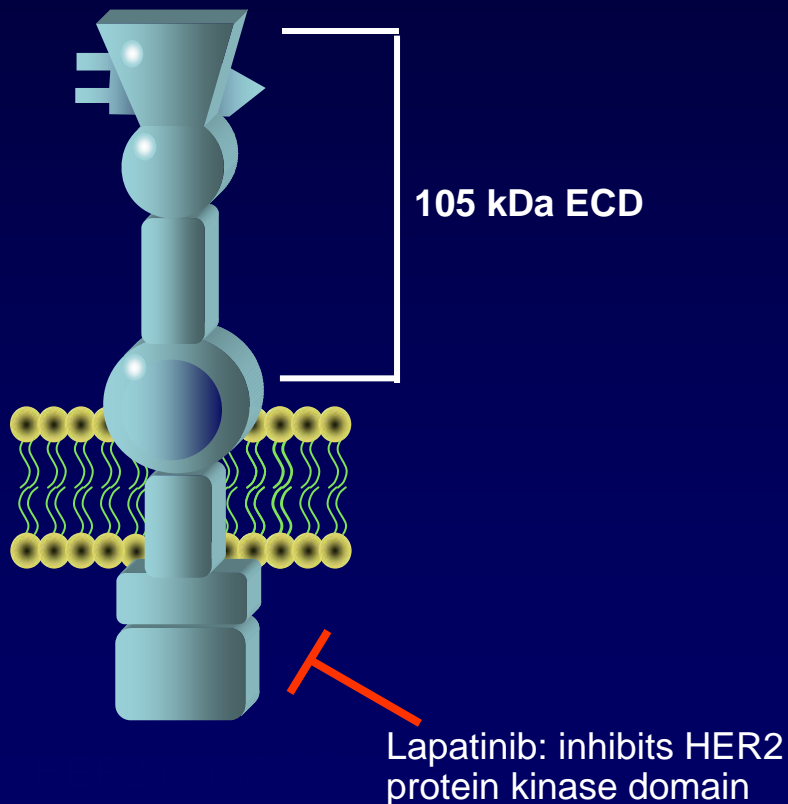
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Mechanisms of Resistance

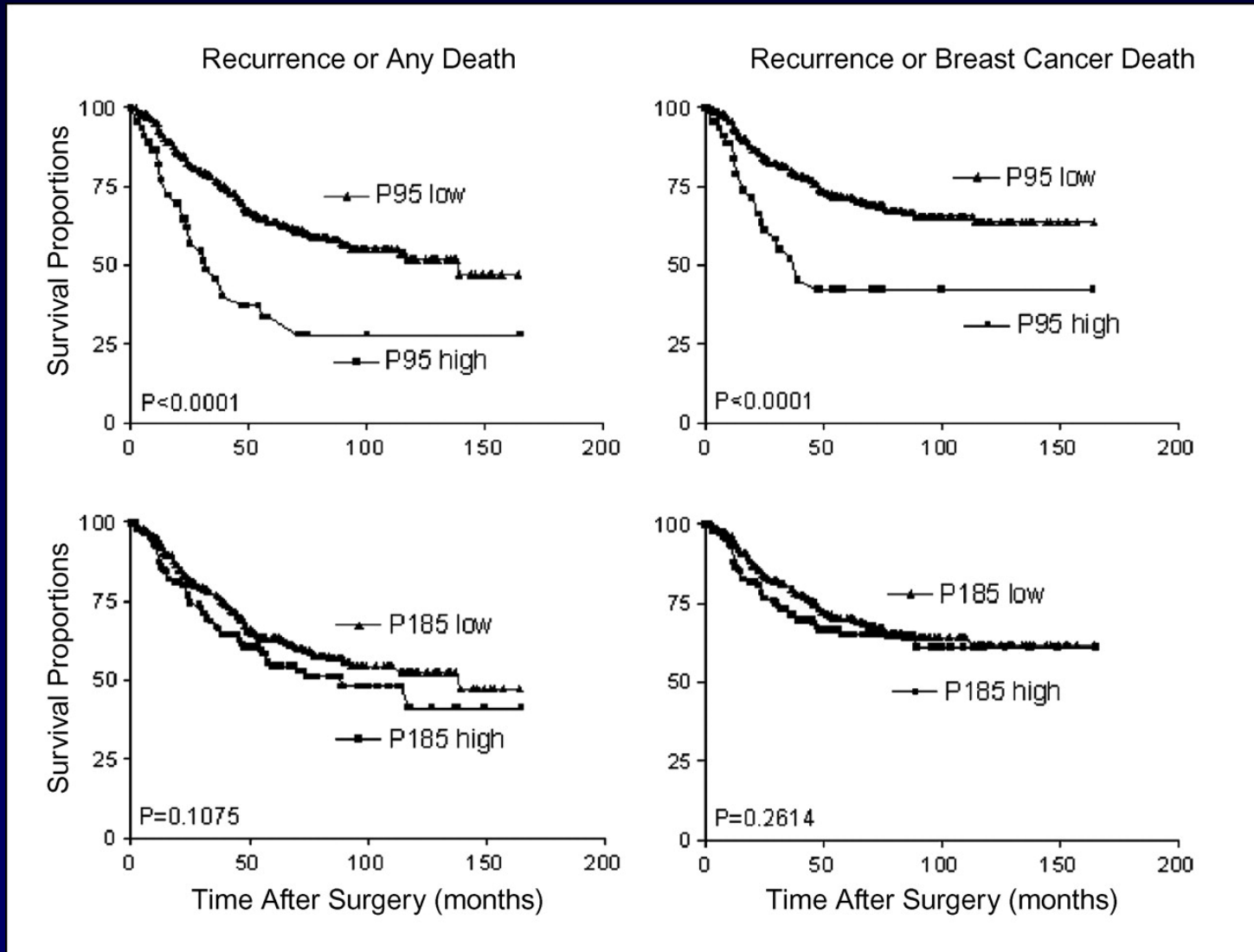
- **Receptor alteration**
 - Autophosphorylation / truncated receptor p95
- **Overexpression of sialomucine MUC4 complex**
- **Alteration of signal transduction**
 - PTEN deletion, PI3K mutations
 - Autophosphorylation MAPkinase AKT
 - low level p27^{kip1}
- **Collateral pathways activation: IGF1-IR**
- **Immunity dysfunction**

Truncated Receptors in 25% of HER2 Breast Cancer

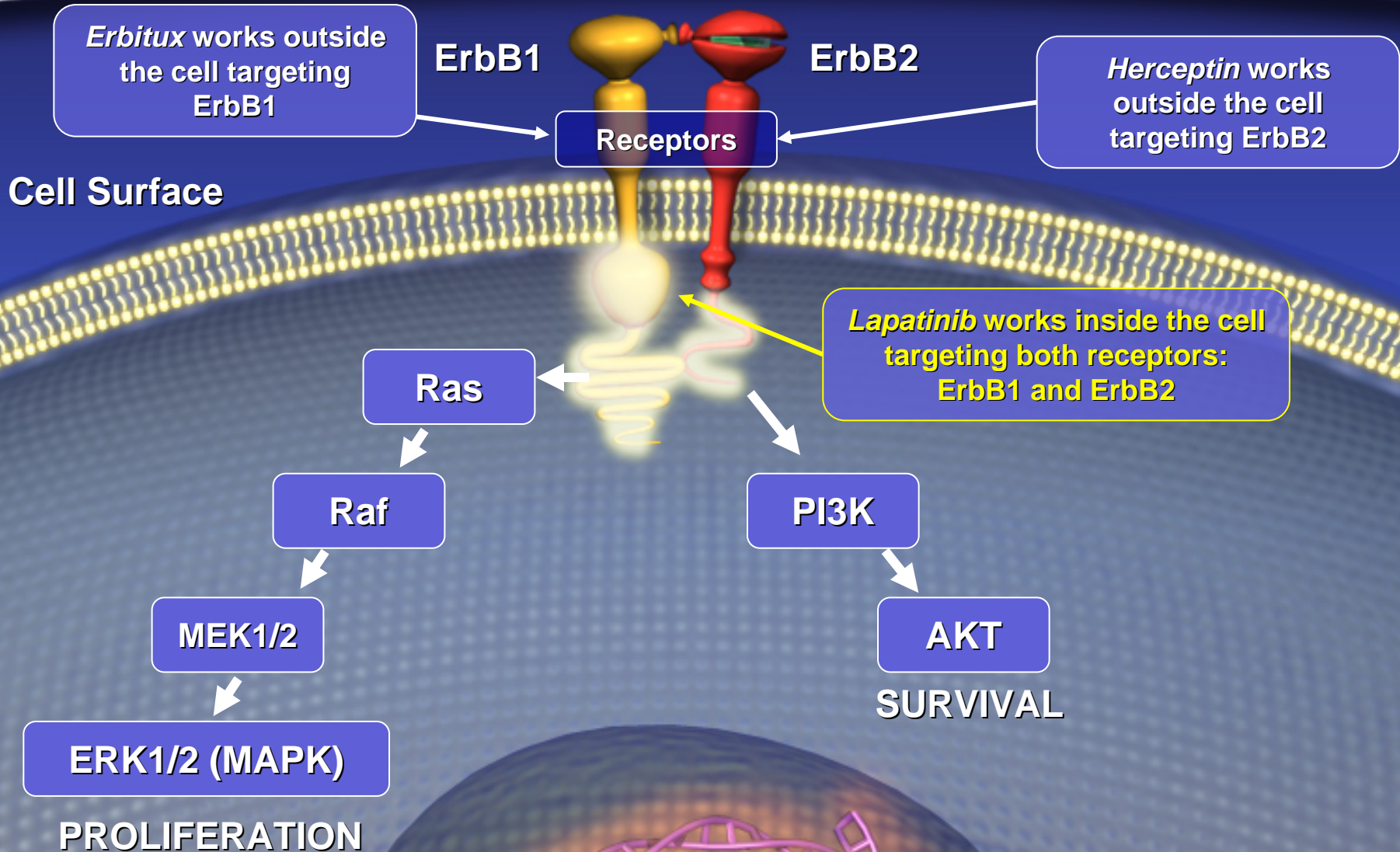
- **HER2 receptor proteolytic processing produces soluble 105 kDa ECD and a retained 95 kDa fragment**
 - Presence of 95 kDa fragment has increased transforming potential and linked to poor prognosis and metastasis
 - Increased serum levels of 105 kDa ECD potentially linked to chemotherapy resistance
 - Increased circulating 105-kDa HER2 ECD, found in many patients with HER2-positive breast cancer, correlates with worse prognosis



High Levels of p95Her2 are Correlated with Reduced Overall and Disease-free Survival in Patients with HER-2+ Breast Cancer Treated with Trastuzumab (n=483)



Lapatinib Mechanism of Action



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Study Design EGF 100151

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Stratification:

- Disease sites
- Stage of disease

R
A
N
D
O
M
I
Z
E

N=528

Lapatinib 1250 mg po qd continuously +
Capecitabine 2000 mg/m²/d po days 1-14 q 3 wk

Capecitabine 2500 mg/m²/d po days 1-14 q 3 wk

Patients on treatment until progression or unacceptable toxicity, then followed for survival

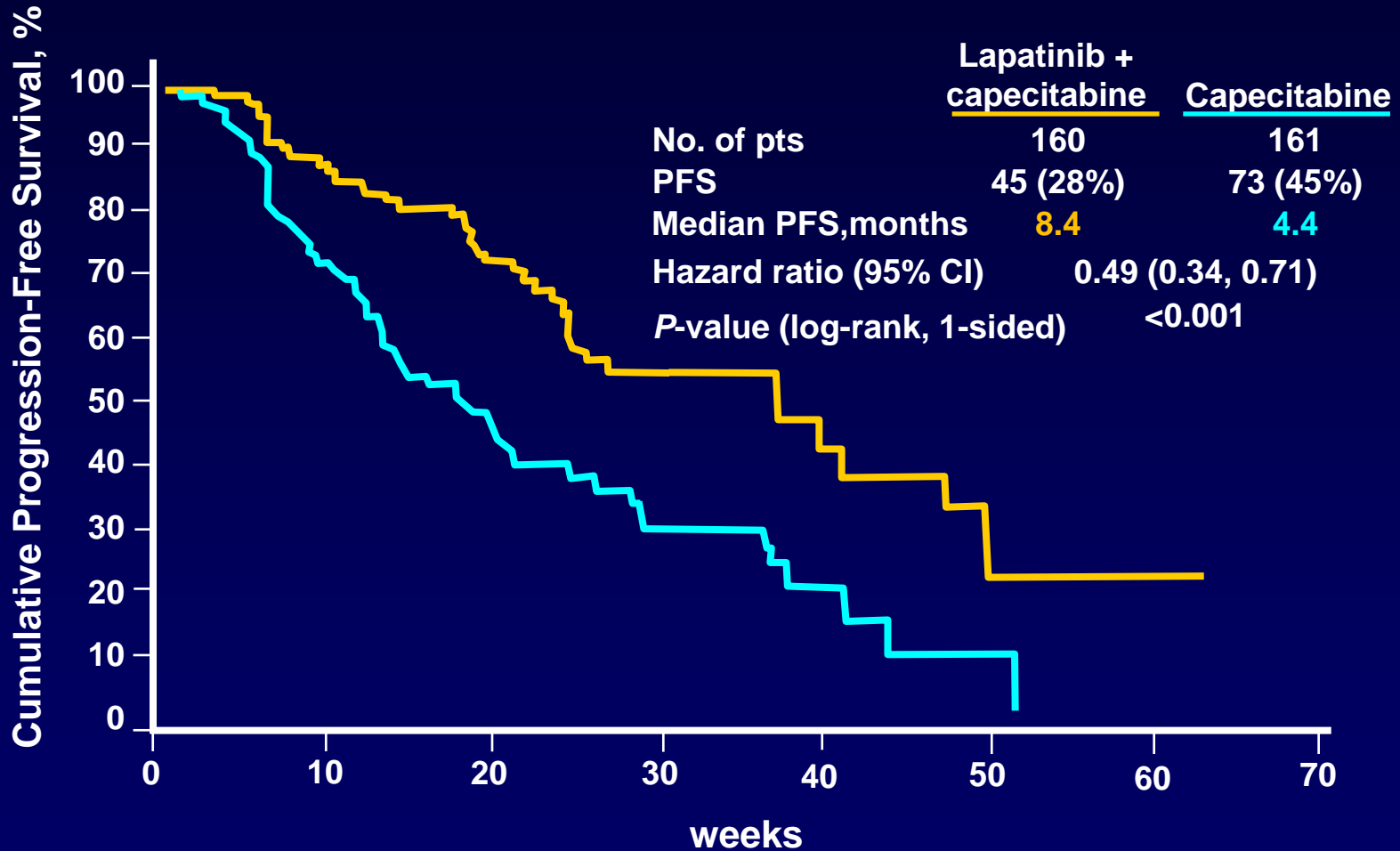
*Trastuzumab must have been administered for metastatic disease

Response Rate - ITT Population

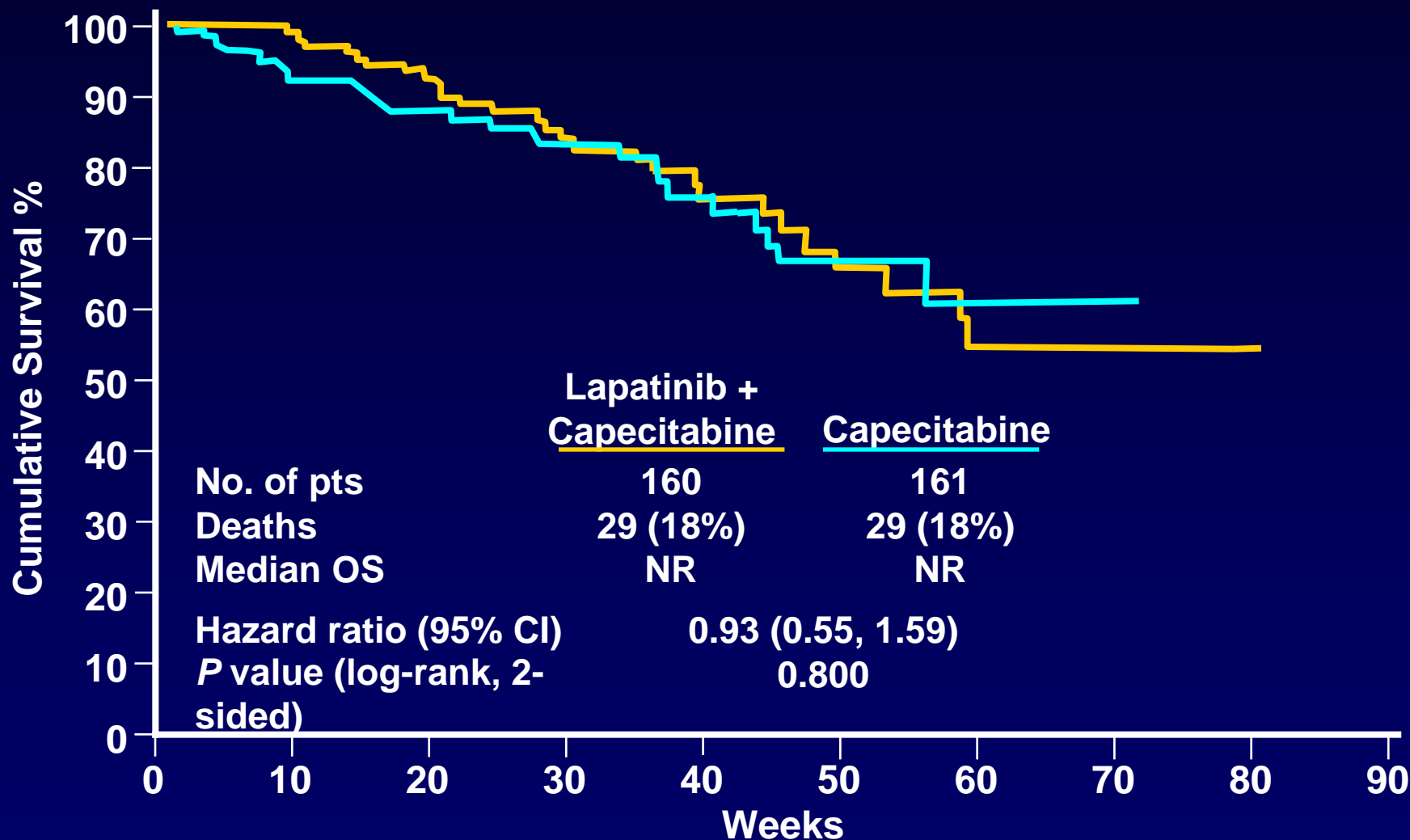
	Lapatinib + Capecitabine (n=160)	Capecitabine (n=161)
Complete response	1 (< 1%)	0 (0%)
Partial response	35 (22%)	23 (14%)
Overall response rate* (95% CI)	22.5% (16.3 - 29.8)	14.3% (9.3 - 20.7)

*P-value (Fisher's exact, 2-sided) = 0.113

Progression Free Survival



Overall Survival



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Brain Metastasis

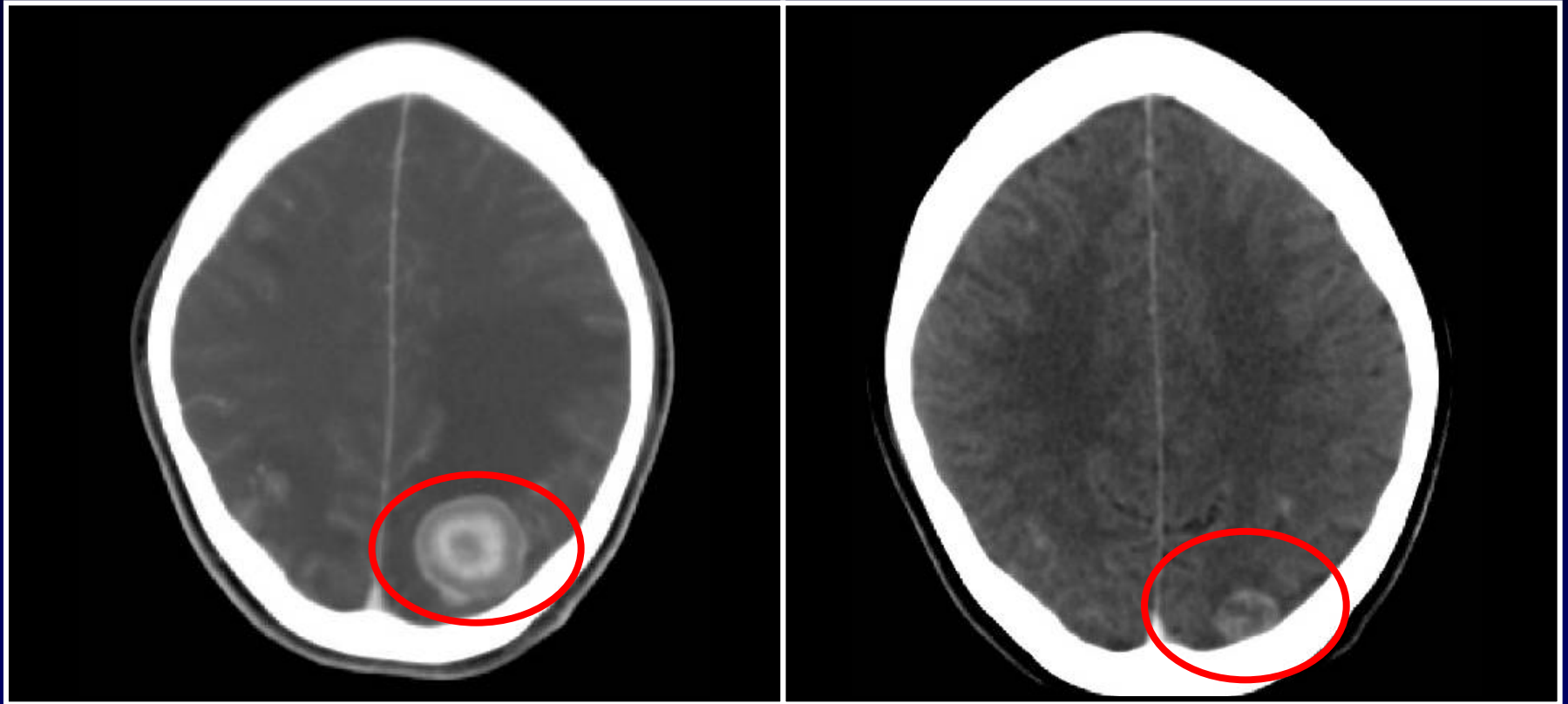
- High incidence of brain metastasis in HER2+ BC:
 - Inability of trastuzumab to cross the blood brain barrier
 - Prediction of HER2 BC to brain metastasis
- Incidence after trastuzumab
 - 25 - 43 % in metastatic setting
 - 12% - 24% of first site of relapse after adjuvant trastuzumab
- Lapatinib can reduce the risk of developing CNS mets and is active on established CNS mets

Brain Metastases as Site of Progression

	Lapatinib + Capecitabine (n=160)	Capecitabine (n=161)
Patients with CNS metastases at baseline	2	2
Patients with CNS relapse*	4	11
Patients with CNS as only site of relapse	3	10

*P-value (Fisher's exact, 2-sided) = 0.110

Lapatinib in First Line Treatment



Baseline

12 weeks

Brain Scan

Brain Metastasis (EGF105084)

HER2+ BC
Progressive brain metastasis
Prior trastuzumab and cranial RT
N = 242

Stratification:
PS and number of
prior trastuzumab-
containing
regimens

**Lapatinib
Monotherapy
750 mg BID**

PD

**Extension
arms**

Volumetric Reduction in CNS Lesions (Lapatinib Monotherapy)

	n - % Median (range), cm ³
≥ 50% CNS volumetric tumor reduction Absolute tumor volumetric reduction	19/241 - 7% 3.1 (0.17-29.7)
≥ 20%* CNS volumetric tumor reduction Absolute tumor volumetric reduction	46/241 - 19% 1.9 (0.08-29.7)

*Exploratory analysis

EGF105084 Lapatinib + Capecitabine Extension: Volumetric Reduction in Brain Metastases

	n (%) Median (range) cm ³
≥ 50% Volumetric CNS tumor reduction Absolute tumor volumetric reduction	8/40 – 20% 6.2 (3.2 - 12.9)
≥ 20% Volumetric CNS tumor reduction Absolute tumor volumetric reduction	16/40 – 40% 3.9 (0.6 - 12.9)

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Lapatinib Cardiac Tolerance: 3689 patients

Prior therapy	LVEF decrease	Asymptomatic LVEF decrease	Symptomatic LVEF decrease
Anthracyclines n = 552	12 (2,2%)	9 (1,6%)	3 (0,5%)
Trastuzumab (+ CT or after A) n = 826	14 (1,7%)	13 (1,6%)	1 (0,1%)
No A no T n = 2311	34 (1,5%)	31 (1,3%)	3 (0,1%)
TOTAL n = 3689	60 (1,6%)	53 (1,4%)	7 (0,2%)

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Targeting HER2+ Breast Cancer

- **New antibodies**
 - Pertuzumab (Omnitarg®)
 - TDM1
- **Tyrosine kinase inhibitors**
 - Lapatinib (Tyverb®)
 - HKI 272 (Neratinib)
- **Inhibitors of signal transduction**
 - mTOR inhibitors (everolimus, temsirolimus)
 - PI3K inhibitors
- **Vaccinations**
- **Associations (angiogenesis)**
 - Trastuzumab + bevacizumab
 - Lapatinib + pazopanib
- **Targeting others pathways : IGFR-IR**
- **HSP90 inhibitors**

Algorithm for the Treatment of HER2+ Breast Cancer After Adjuvant Trastuzumab

Adjuvant
trastuzumab

```
graph TD; A[Adjuvant trastuzumab] --> B[Trastuzumab rechallenge]; A --> C[Lapatinib + capecitabine]; A --> D[New anti-HER2 agents];
```

Trastuzumab
rechallenge

Lapatinib +
capecitabine

New anti-HER2
agents

None of these options has been tested in clinical trials!