

Case #4: Inflammatory Breast Cancer: Treatment Strategies



Alessandra Gennari, MD PhD

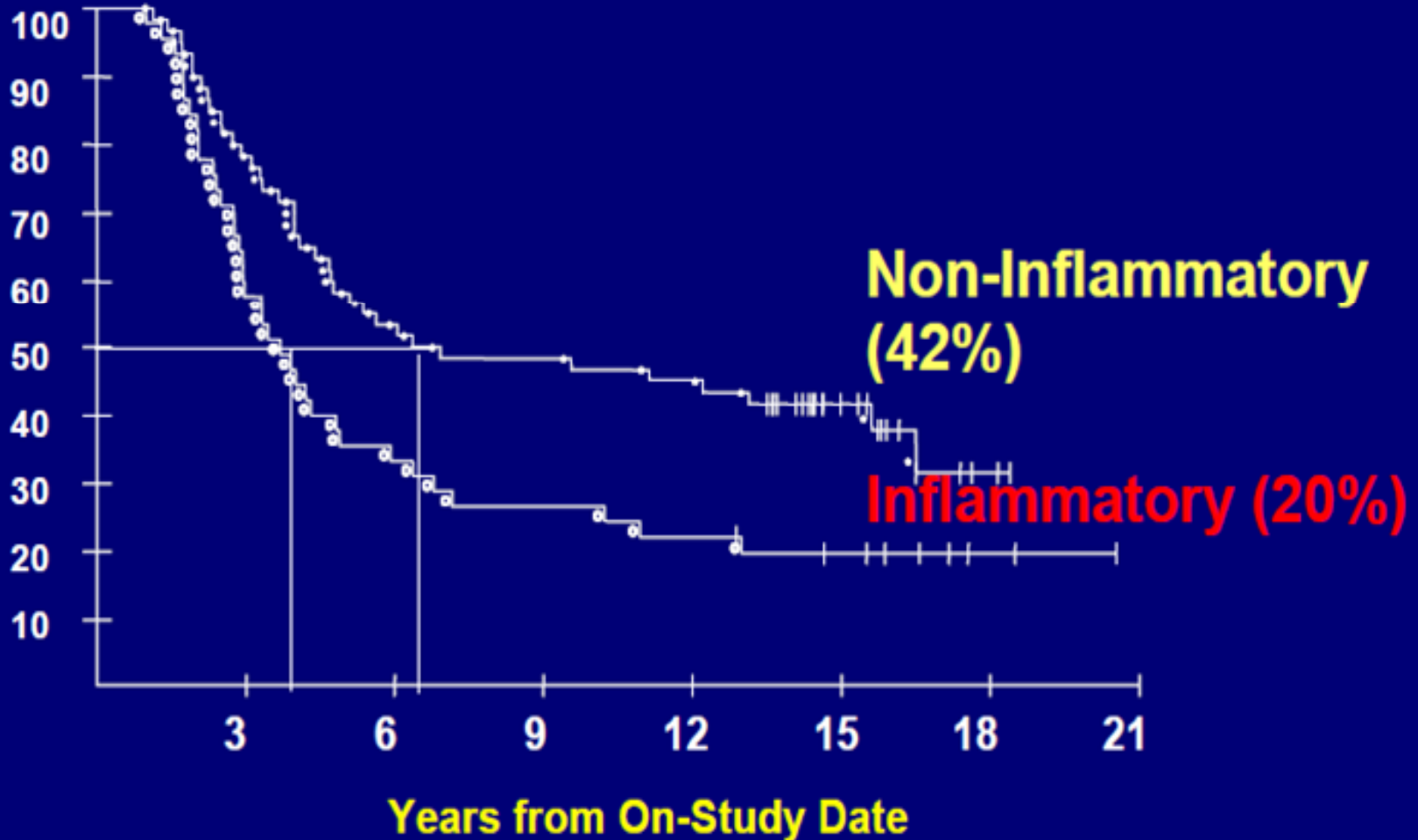
Division of Medical Oncology

Galliera Hospital

Genoa, Italy



IBC Survival: NCI MB 198



Patient and Disease Characteristics

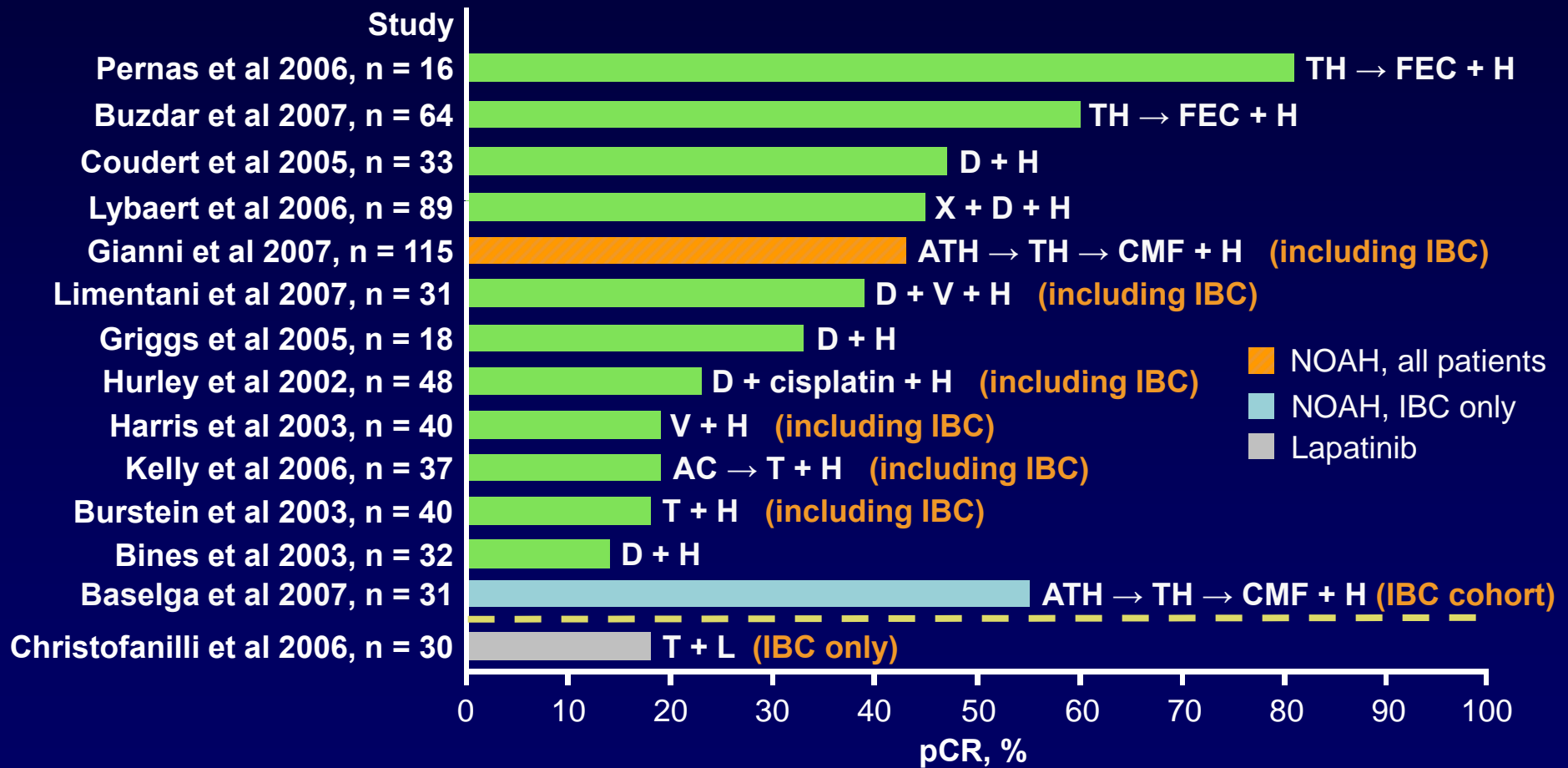
- 40-year-old, premenopausal
- IDC, inflammatory, G3, ER/PR negative, HER2 = IHC 3+
- No comorbidities, ECOG PS = 0
- LVEF + biochemistry = normal
- TREATMENT PLAN: Systemic therapy, surgery, radiotherapy

Multimodality therapy delivered with curative intent is the standard of care for patients with clinical stage IIIB disease. NCI, accessed april 13th 2010

1. Which Neoadjuvant Regimens?

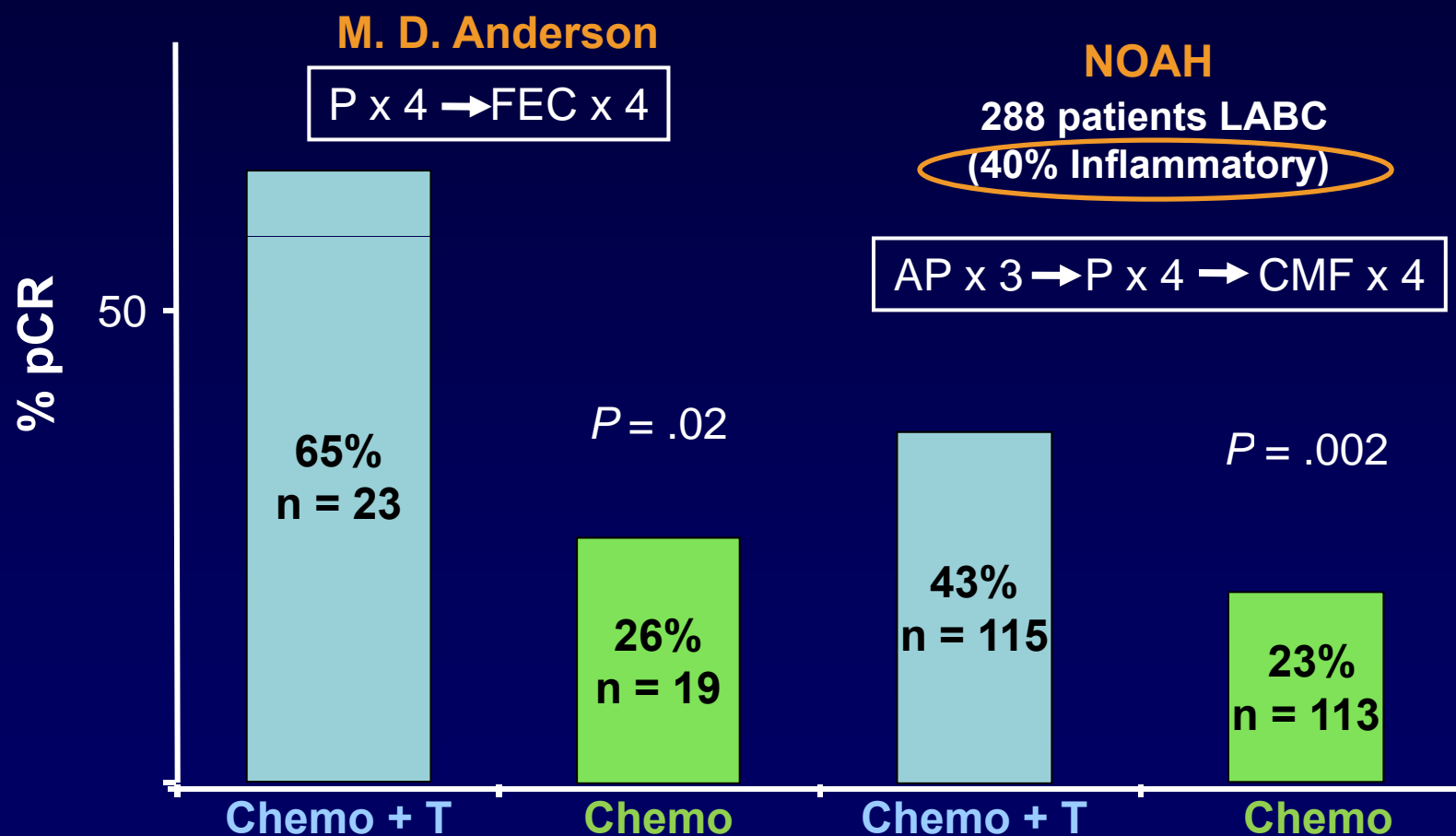
2. Trastuzumab: When?

Preoperative Therapy: pCR Rates in HER2-Positive Disease



L, lapatinib; V, vinorelbine; X, capecitabine; T/D, taxane; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab

Preoperative Chemo ± Trastuzumab Two Randomized Trials pCR Rates

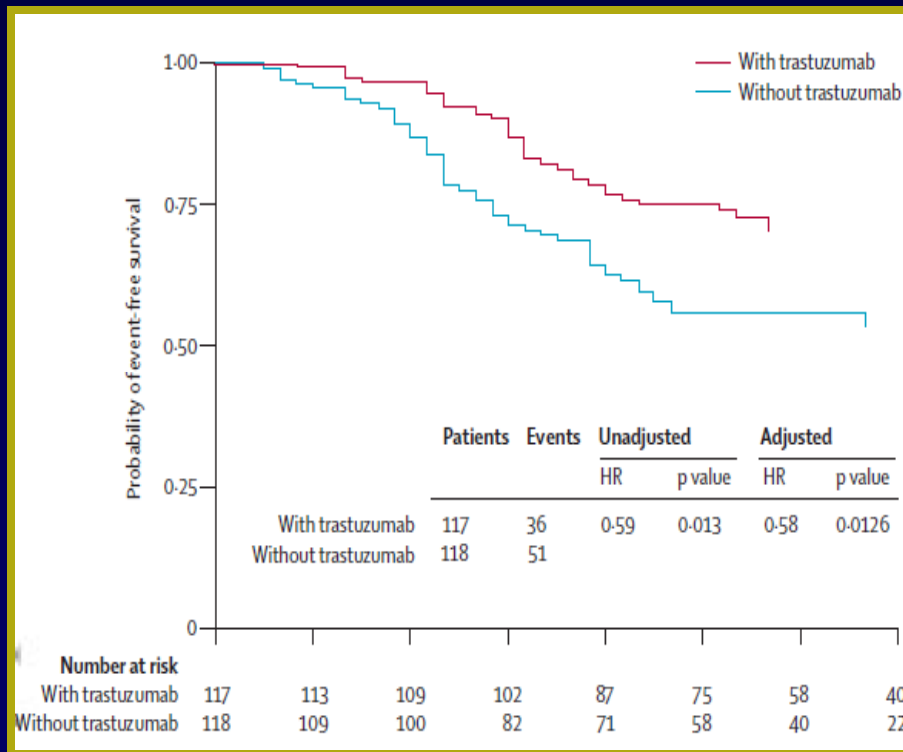


LABC- locally advanced breast cancer; T- trastuzumab

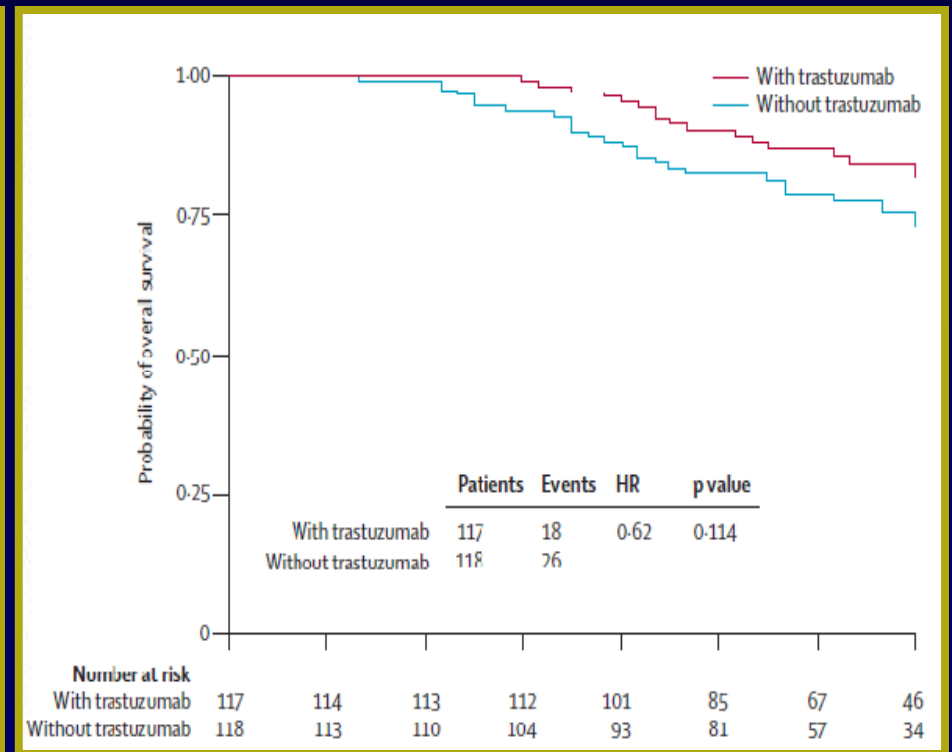
Buzdar A, et al. *Clin Cancer Res.* 2007;13(1):228-233. Gianni L, et al.; Gianni L, et al. *Cancer Res.* 2009;69(Suppl 1): Abstract 31.

NOAH: Event-Free Survival (EFS) and OS in HER2-Positive Population (ITT)

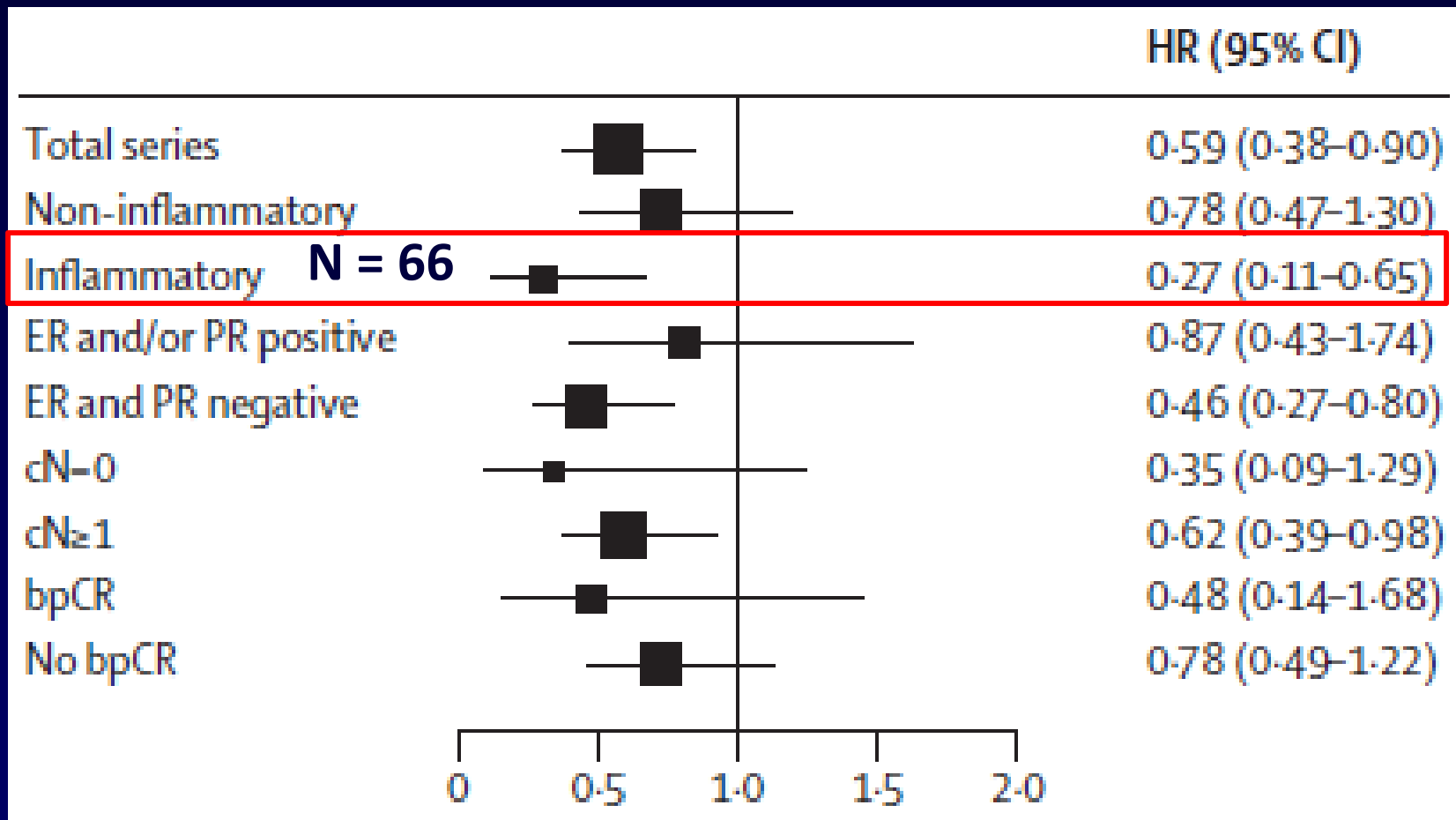
EFS



OS



NOAH: Analyses of EFS by Subgroup in Patients with HER2-Positive Disease



EGF102580: Lapatinib plus Paclitaxel as Neoadjuvant Therapy in Newly Diagnosed Inflammatory Breast Cancer

Cohort A: HER2 overexpressors

Cohort B: HER2 non-overexpressors

Lapatinib Monotherapy x 14 days

Pre-dose
Tumor Biopsy

Combination Therapy

12 weeks
IV Paclitaxel 80 mg/m²/week
+
Lapatinib 1500 mg PO once daily

Surgical Resection

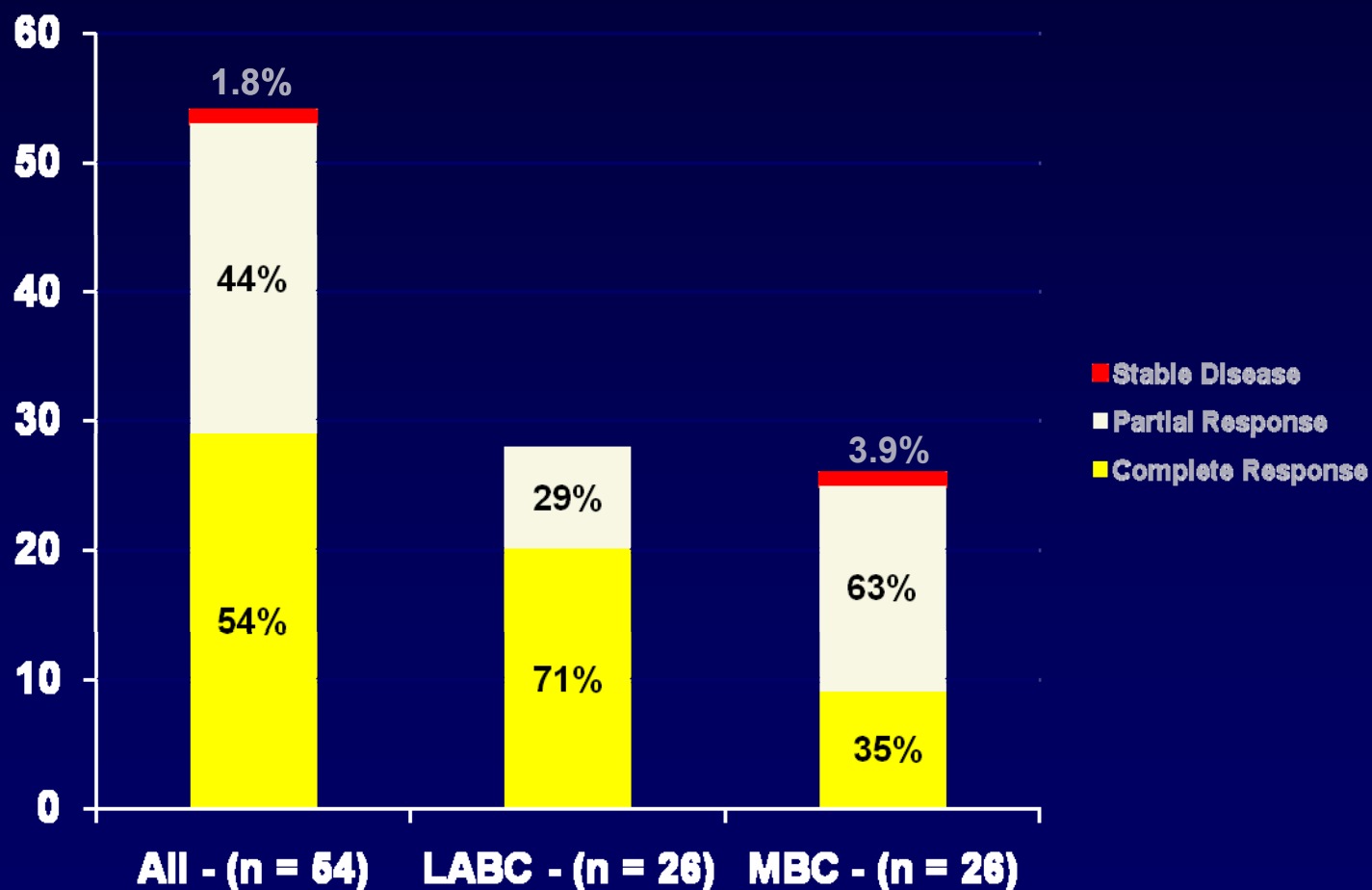
Tumor Tissue (250 mg)
at time of Surgical Resection
Assessment of pCR
Biomarker Analysis

Objective Response Rate

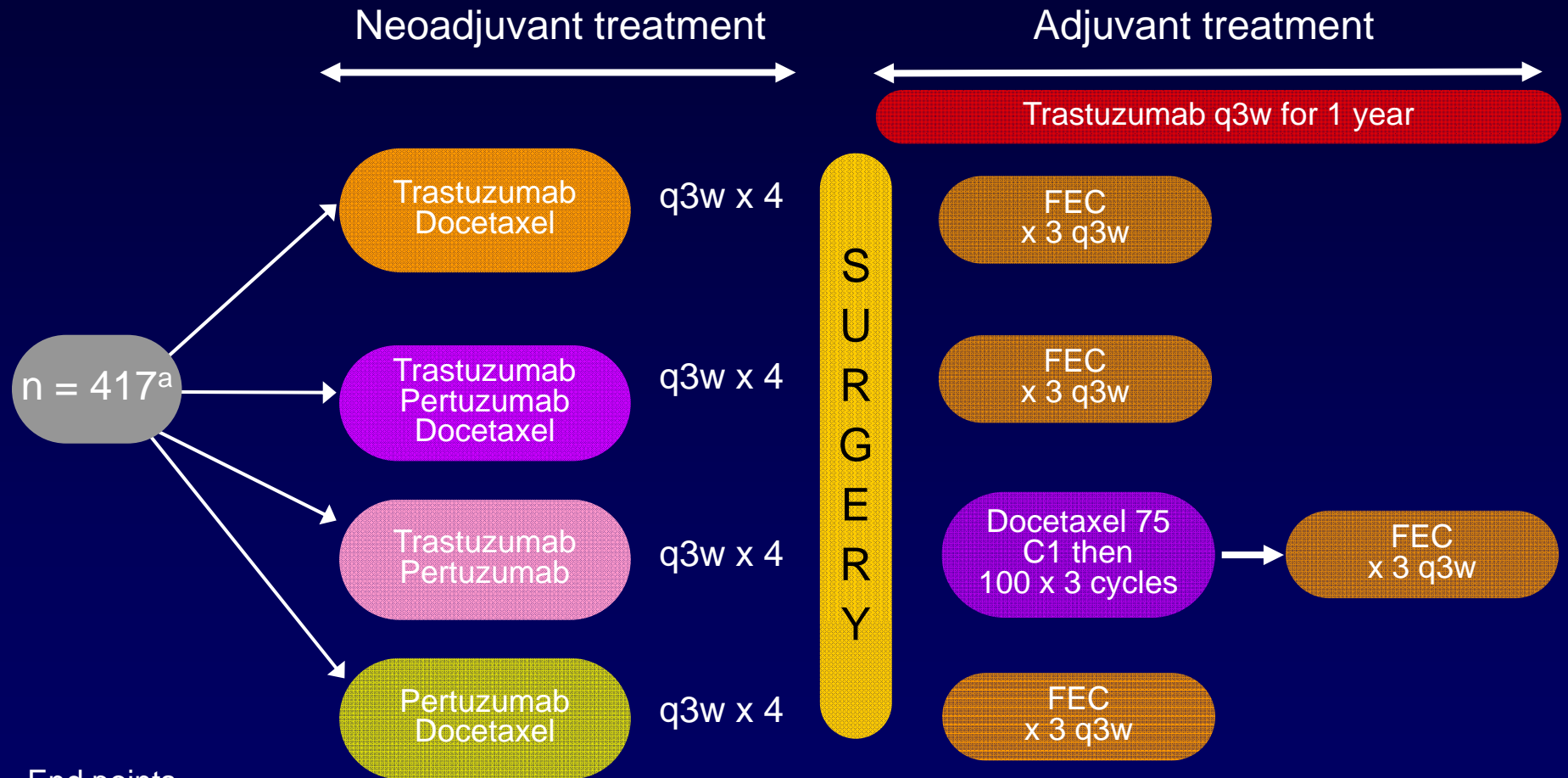
	Cohort A (HER2+) N=30	Cohort B (HER2-) N=5
Clinical Skin/Chest Wall Responses		
Complete Response (CR)	3 (10%)	0
Partial Response (PR)	20 (67%)	4 (80%)
Stable Disease (SD)	3 (10%)	0
Progressive Disease (PD)	0	1 (20%)
Unknown	4 (13%)	0
Response Rate (CR or PR)	77%	80%
Clinical response to lapatinib monotherapy (d14)	10 (30%)	0
Pathological Complete Responses*		
Pathological CR*	3/18 (17%)	0/3

- Defined as no evidence of residual invasive tumor, including no residual tumor in the axillary lymph nodes

Phase I-II Study of Liposomal Doxo, Trastuzumab, Paclitaxel



NEOSPHERE: A Phase II Study of Neoadjuvant Trastuzumab and Pertuzumab in Locally Advanced and Large Stage II HER2-Positive Breast Cancer



End points

- pathological CR at point of surgery
- biomarker analysis

^aRecruitment complete, data expected at ASCO 2010

q3w, every 3 weeks; FEC, 5-fluorouracil + epirubicin + cyclophosphamide

www.clinicaltrials.gov

Part I:
Which option would I choose for
neoadjuvant treatment of this
patient?

- **TAX + Trastuzumab → FEC**
- **Liposomal anthracycline + Taxane + Trastuzumab**

Postoperative Systemic Therapy

IBC

Standard Treatment

**Primary chemotherapy (CT)
+ trastuzumab for HER2-positive tumors**



Mastectomy + axillary dissection



RT



**No data of additional adjuvant CT benefit
Hormonal therapy if HR+
Continue trastuzumab up to 1 year in HER2-
positive tumors**

However.....

AFTER NEOADJUVANT TCH x 6:

1.5 cm focus of residual ER/PR-negative, HER2+
infiltrating ductal carcinoma. Node + (3/20)



RT to the breast and ipsilateral supraclavicular region
and 1 year trastuzumab



**Two months after completion of trastuzumab,
chest wall recurrence**

GBG-26: Study Design

MBC HER2-positive
Progression under trastuzumab-based first-line therapy (TFI <6 weeks)
with taxane (n = 114)
or monotherapy or nontaxane (n = 42)

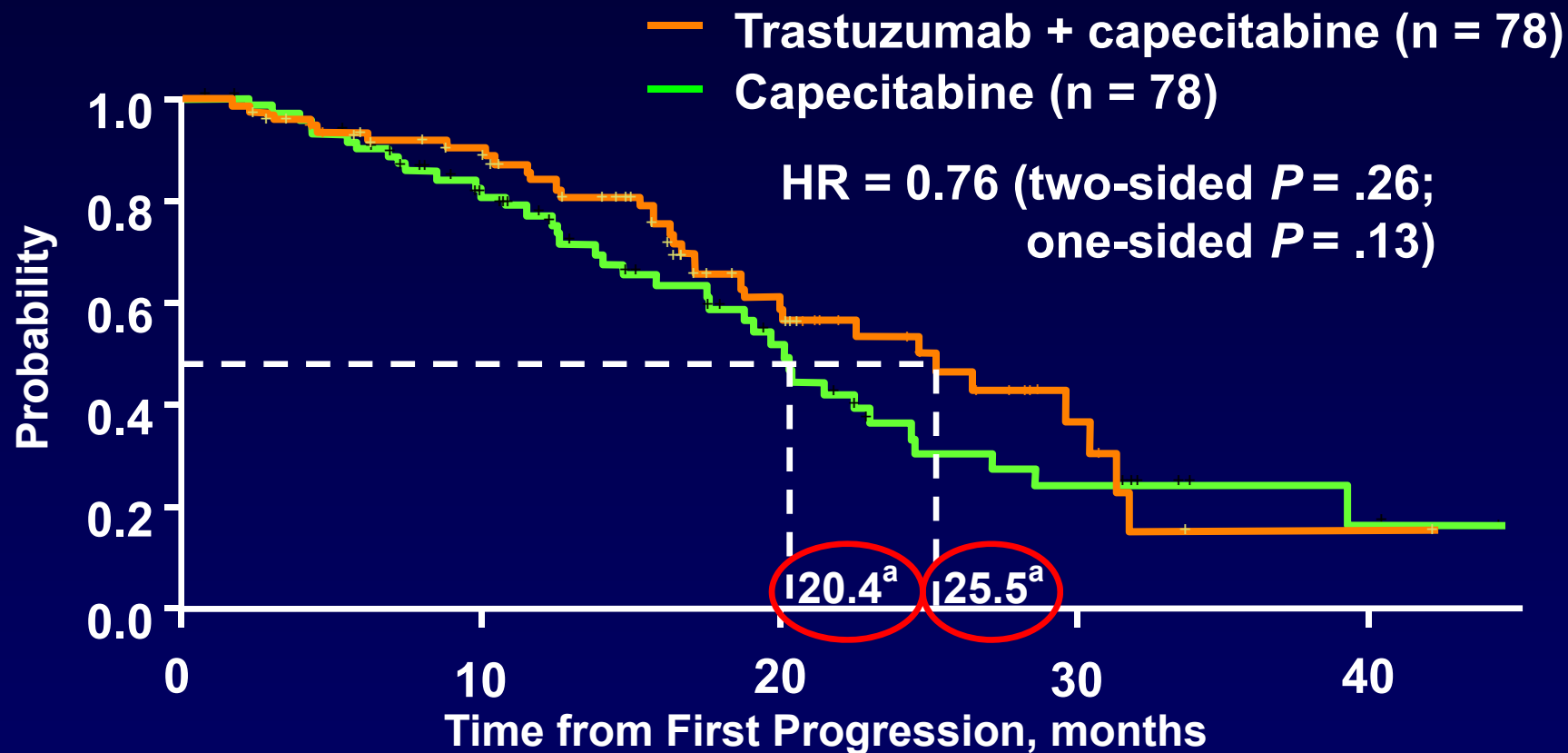
R

Capecitabine 2500 mg/m²
(1250 mg/m² bid) d1-14 q21 days
+
Continuation of
trastuzumab 6 mg/kg q3 weeks
(n = 78)

Capecitabine 2500 mg/m²
(1250 mg/m² bid) d1-14 q21
days
(n = 78)

R, randomization
TFI, treatment-free interval

Continuation of Trastuzumab + Capecitabine Suggests Improvement of Overall Survival



—	74	66	50	33	21	10	8	3	2
—	77	68	59	47	27	15	6	1	1

^aMedian survival in months OS, overall survival

EGF100151: Capecitabine + Lapatinib Versus Capecitabine in LABC or MBC

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

Stratification:

- Disease sites
- Stage of disease

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Lapatinib 1250 mg PO qd continuously +
capecitabine 2000 mg/m²/d
PO days 1-14 q3 weeks

Capecitabine 2500 mg/m²/d PO days
1-14 q 3 weeks

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

***Trastuzumab must have been administered for metastatic disease!!**

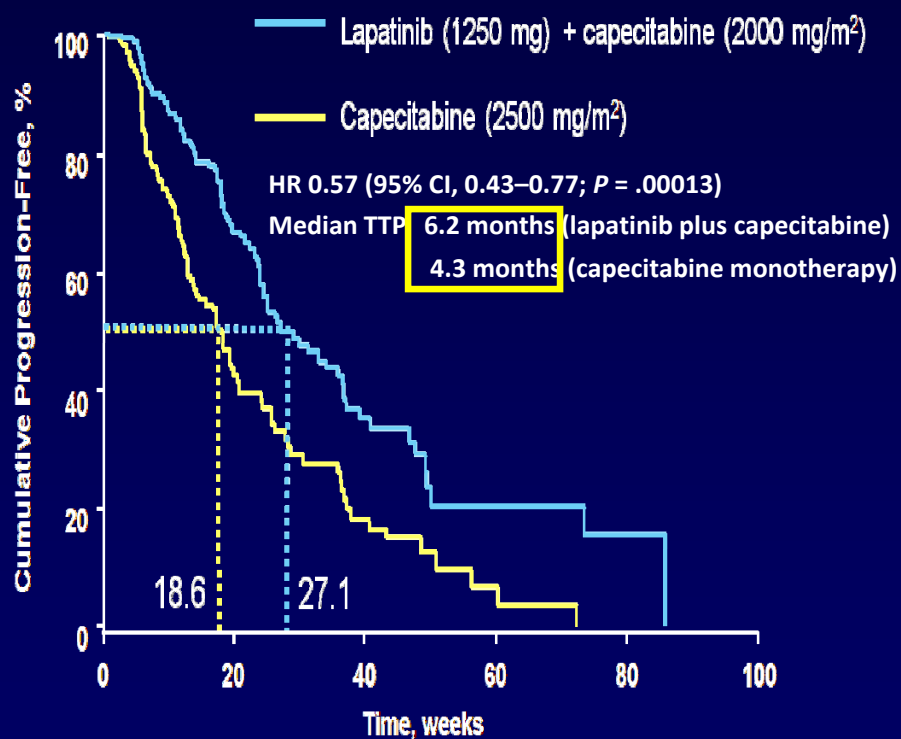
LABC, locally advanced breast cancer; MBC, metastatic breast cancer

Geyer C, et al. *N Engl J Med.* 2006;355(26):2733-2743.

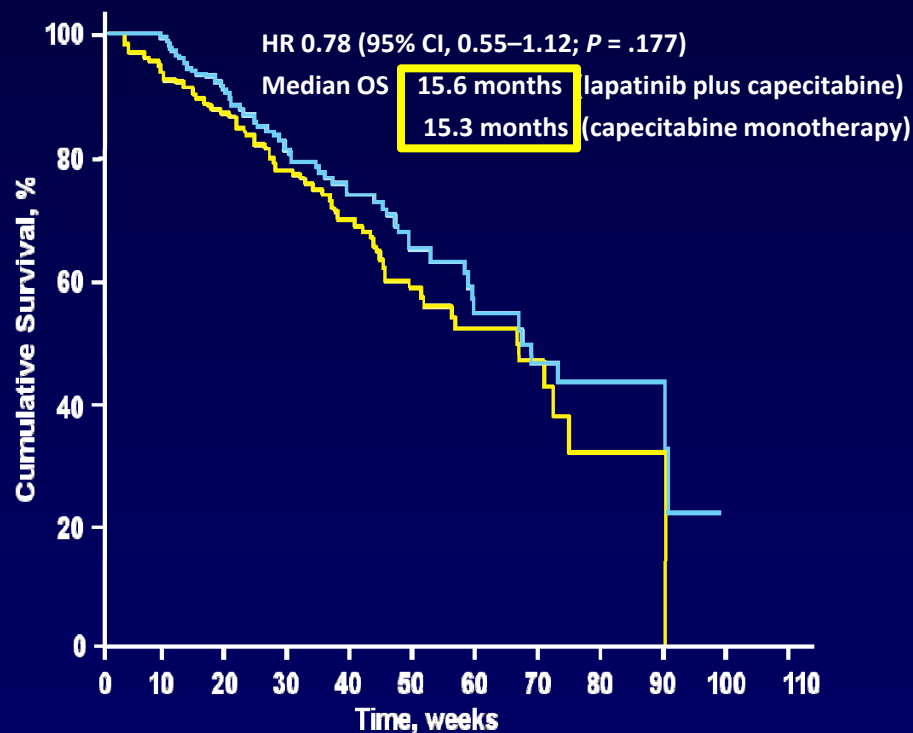
Cameron D, et al. *Breast Cancer Res Treat.* 2008;112(3):533-543.

EGF100151:Kaplan-Meier Estimates of Time to Progression and Overall Survival in ITT Population by Independent Review Committee

Median TTP



Overall Survival



Lapatinib Monotherapy in Relapsed/Refractory Pretreated Inflammatory Breast Cancer: Overall Best Response

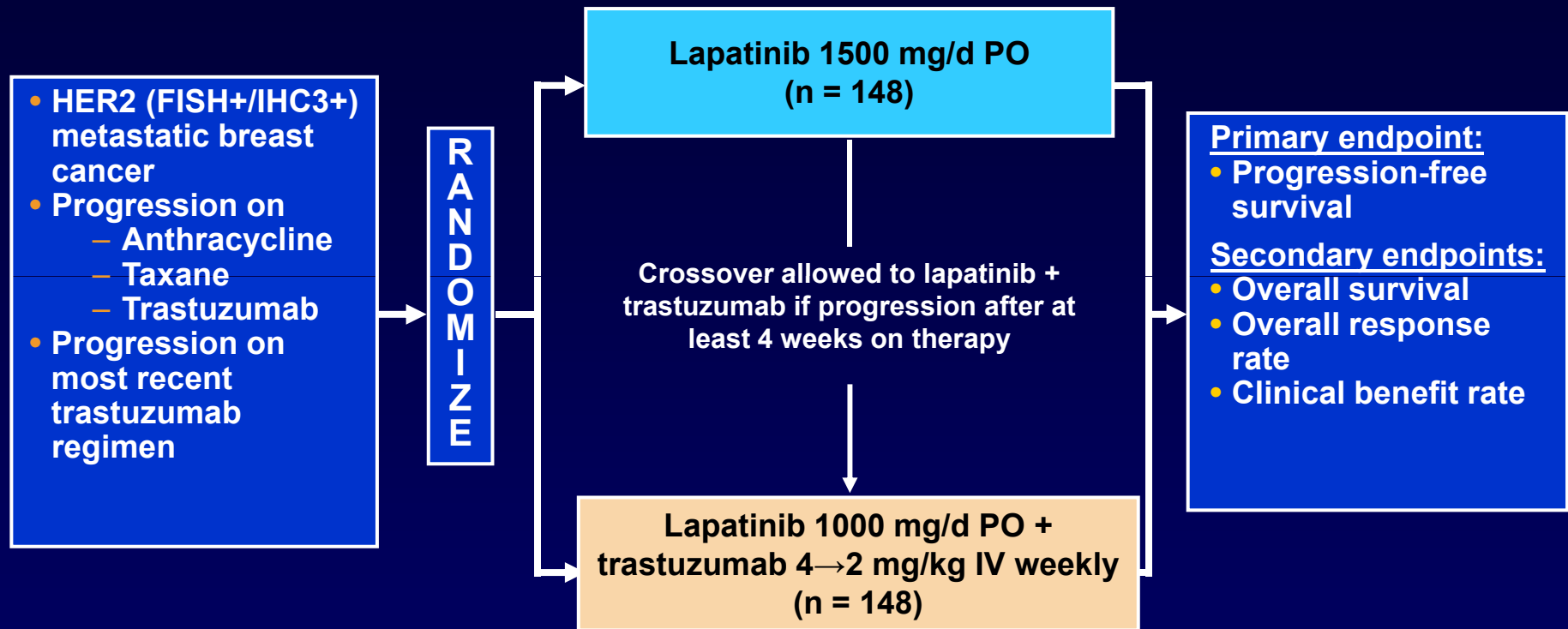
Cohort	No. of Pts	RECIST	Skin	Combined
A (HER2+)	126	15%	40%	39%
B (EGFR+, HER2-)	12	10%	8%	8%

HER2+ = IHC3+ or FISH+

New Approaches for HER2-Positive Trastuzumab-Pretreated MBC

- **Lapatinib/trastuzumab**
- **Pertuzumab**
- **Trastuzumab-DM1**
- **Neratinib**
- **Angiogenesis inhibitors**
- **Others (mTOR inhibitors, heat shock proteins)**

EGF104900: Phase III Study Evaluated Dual HER2 Blockade



- Staging occurred at 4, 8, 12, 16 weeks, and then every 8 weeks
- Steady state of single-agent lapatinib occurs at approximately 7 days

Blackwell KL, *J Clin Oncol* 2010;28(7):1124-1130.

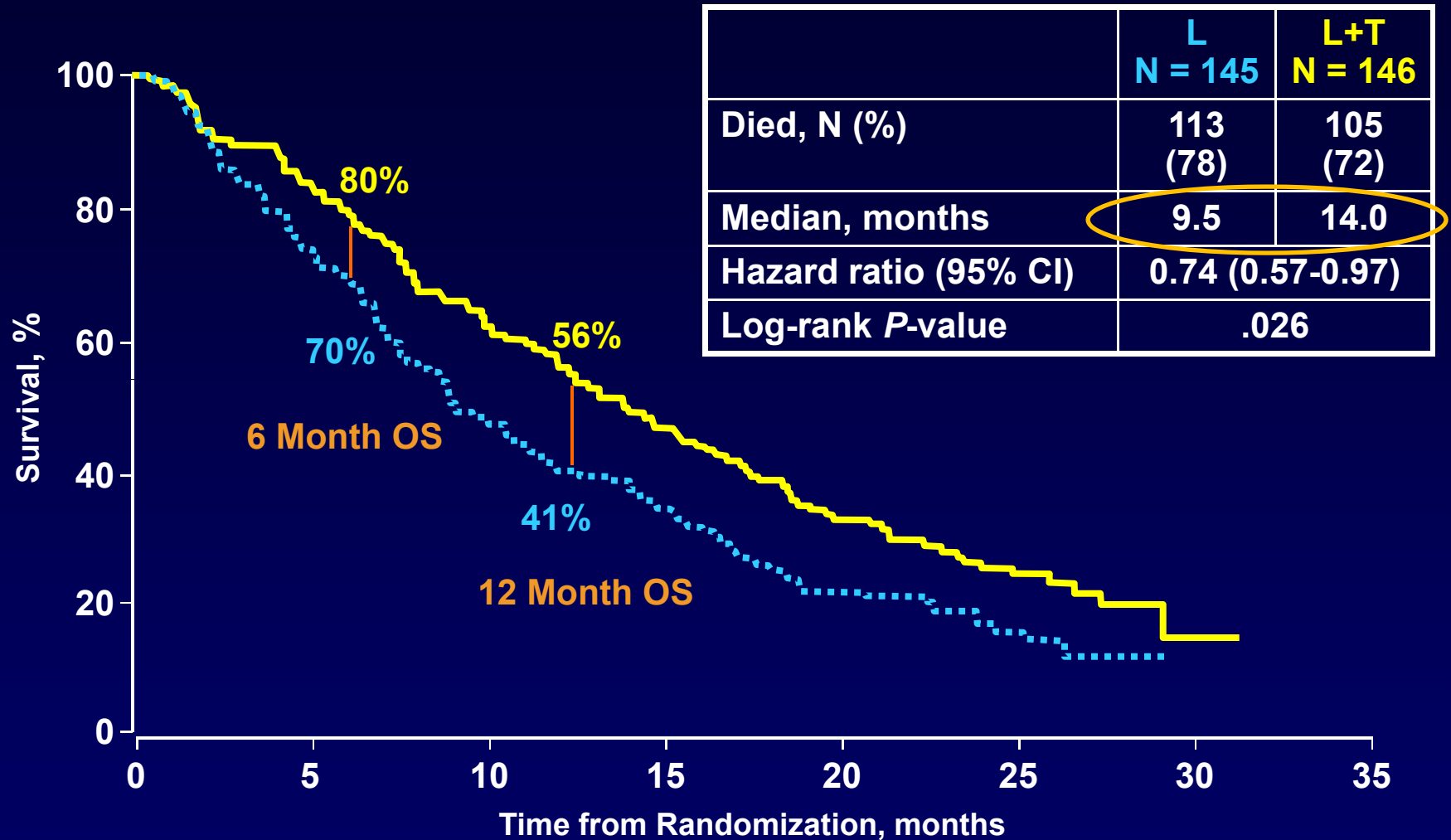
Blackwell KL, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 61.

Treatment Efficacy

	L N = 145	L + T N = 146
Response rate, %*	6.9	10.3
(95% CI)	(3.4, 12.3)	(5.9, 16.4)
Odds ratio (95% CI)		1.5 (0.6, 3.9) P = .46
Clinical benefit rate, %†	12.4	24.7
(95% CI)	(7.5, 18.9)	(17.9, 32.5)
Odds ratio (95% CI)		2.2 (1.2, 4.5) P = .01
Progression-free survival (median), weeks	8.1	12.0
Odds ratio (95% CI)		0.73 (0.57, 0.93) P = .008

*Confirmed CR+PR †CR+PR+SD ≥6 months

Updated Overall Survival (ITT)



Patients at risk:

Time (months)	0	5	10	15	20	25	30
L (dotted blue)	148	121	88	64	43	25	1
L+T (solid yellow)	148	102	65	47	28	13	

Blackwell KL, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 61.

HKI-272 (Neratinib), An Oral Irreversible Pan Erb Receptor Tyrosine Kinase Inhibitor: Tumor Response in Evaluable Population

	Prior Trastuzumab (n = 61)	No Prior Trastuzumab (n = 66)
Objective response rate, %	26	56
Partial response, %	26	56

Daily oral dose: 240 mg; dose reduction -1x: 24% of patients, 2x: 5%
16% of patients had dose reductions due to diarrhea

Phase III Randomized Open-Label Study of Neratinib vs Lapatinib + Capecitabine in HER2-Positive Locally Advanced or Metastatic Breast Cancer

Inclusion Criteria:

- Stage IIIB, IIIC, or IV HER2+ breast cancer
- Prior treatment with trastuzumab, and anthracycline, and a taxane
- Adequate renal and cardiac function

Exclusion Criteria:

- >2 trastuzumab regimens or prior treatment with capecitabine or lapatinib
- Bone or skin as only site of disease
- Active CNS metastases
- GI disorder with diarrhea

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Neratinib 240 mg PO qd

Lapatinib 1250 mg PO qd continuously + capecitabine 2000 mg/m²/d PO days 1-14 q3 weeks

- **Primary endpoint: PFS**
- **Secondary endpoint: Safety, quality of life**

Trastuzumab-DM1 *Molecular Structure*



- Trastuzumab-DM1 (T-DM1) contains the humanized anti-HER2 MoAb trastuzumab (T) to which a highly potent antimicrotubule drug (DM1), derived from maytansine, has been chemically linked
- The MCC linker employed in T-DM1 provides a stable bond between T and DM1 that is designed to prolong exposure and reduce the toxicity of T-DM1 while maintaining activity

A Phase II Study of Trastuzumab-DM1 (T-DM1) in Patients with HER2+ MBC who Were Previously Treated with an Anthracycline, a Taxane, Capecitabine, Lapatinib, and Trastuzumab

Tumor Response	IRF (N = 110)	Investigator (N = 110)
Objective response rate % (95% CI)	32.7 (24.1–42.1)	30.0 (22.0–39.4)
Clinical benefit rate, %) (95% CI)	44.5 (35.1–54.3)	40.0 (31.1–49.3)

IRF - Independent Review Facility

Objective Response - CR or PR determined by two consecutive tumor assessments at least 28 days apart.

Clinical Benefit - objective response or SD maintained for at least 6 months.

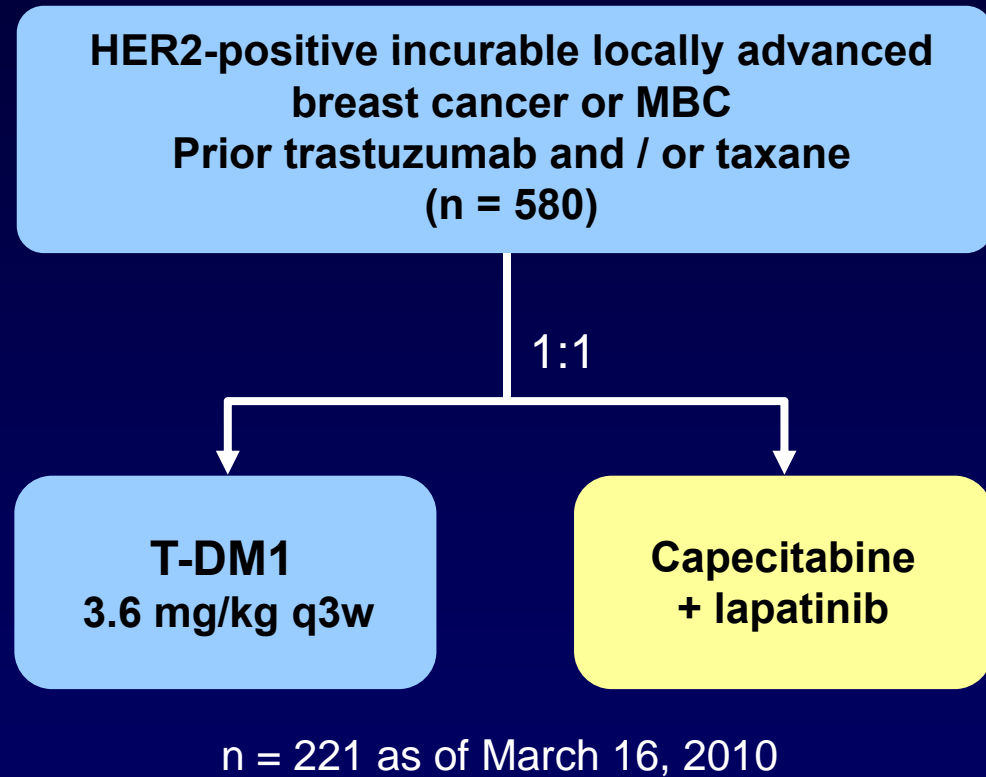
EMILIA: Ongoing Phase III Study of T-DM1 vs Capecitabine + Lapatinib in the Second-Line Setting

Primary endpoints

- PFS (independent assessment)
- Safety

Secondary endpoints

- OS
- PFS (investigator assessment)
- ORR
- CBR
- DoR
- Quality of life
- TTF



Rationale for Angiogenic Treatment in IBC

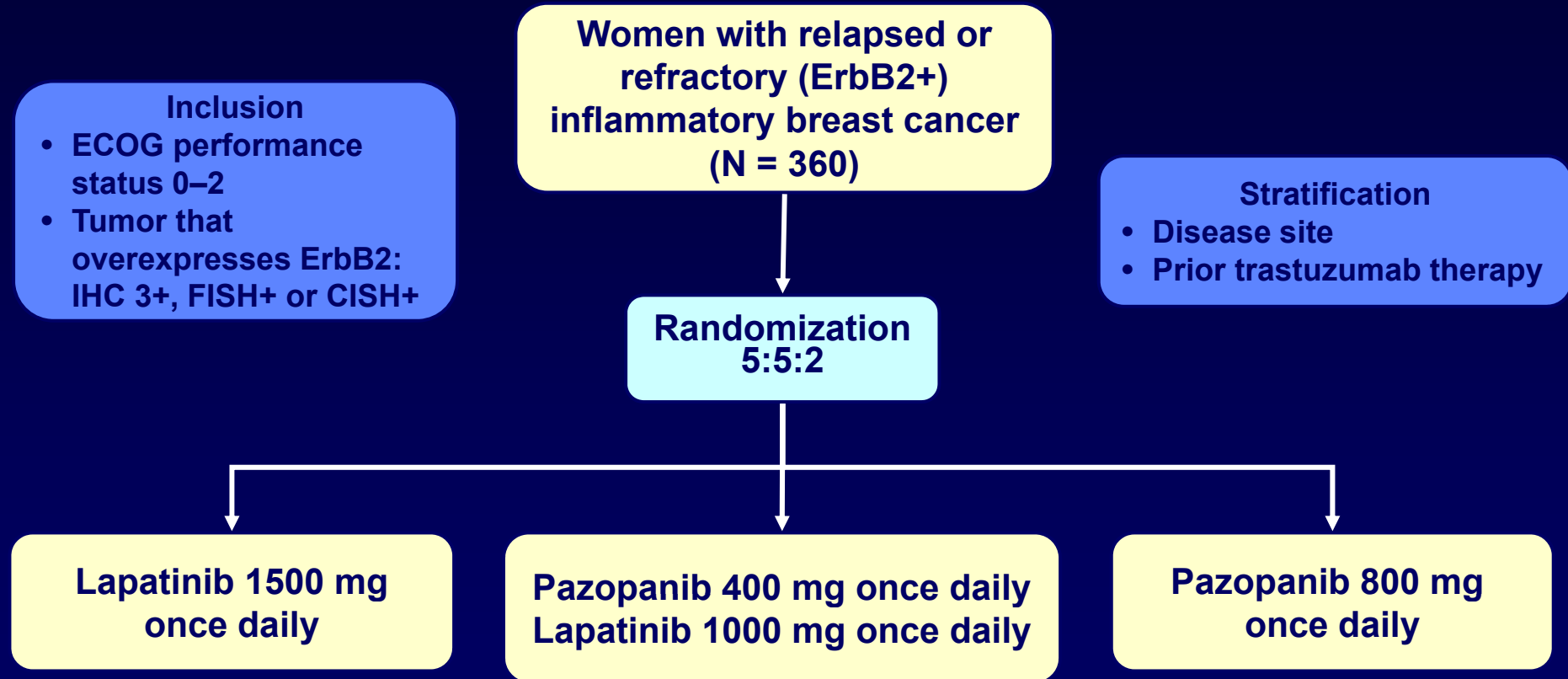
- Increase in angiogenic and lymphangiogenic(VEGFC and D) factors
- Increased microvessel density in inflammatory breast cancer*

	N	MVD (Range)	P Value
IBC	45	25.5 (0-110.0)	.009
Non-IBC	22	6.5 (0-92.5)	

*McCarthy NJ, et al. *Clin Cancer Res.* 2002;8(1):3857-3862.

- Increased expression of angiogenesis-related and lymphangiogenesis-related genes

Pazopanib Plus Lapatinib Compared to Lapatinib Alone in Patients with Inflammatory Breast Cancer



Key Messages: HER2-Positive IBC

- IBC is a rare disease with poor prognosis
- In addition to chemotherapy, trastuzumab should be given in neoadjuvant setting
- Lapatinib is effective in HER2-positive metastatic IBC
- Angiogenesis seems to be an important target in IBC

My Choice

- **Part I: Neoadjuvant Therapy:**
Upfront anthra:
Anthracycline/Taxane/trastuzumab
- **Part II:** lapatinib + capecitabine or
rechallenge with trastuzumab + CT

or
Clinical trial:
 - T-DM1
 - HER2 + angiogenesis targeting