Challenges and Success: Treatment of Metastatic Breast Cancer 2012

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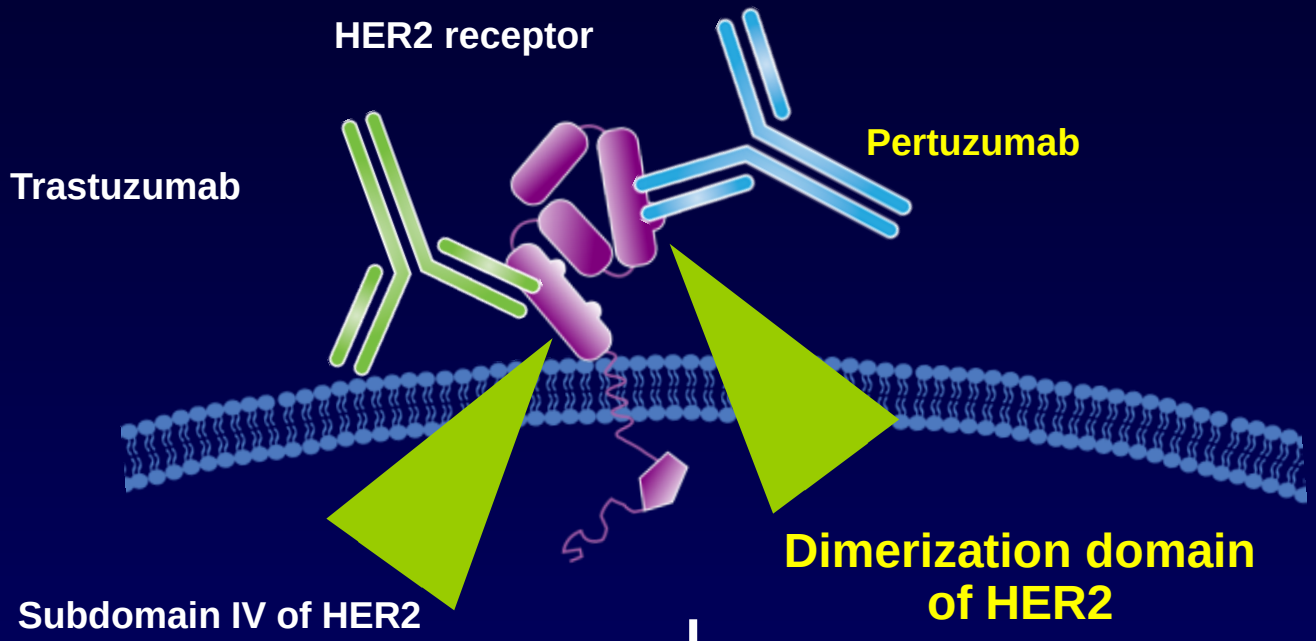
2012: What's New?

- HER2+ disease
  - A wealth of riches
- Reversing hormone resistance
- New treatments for triple negative disease
- The future
  - Moving forward from intrinsic subtypes
  - Consensus building

HER2 Positive MBC

- The problem
  - Despite high response rates, almost all patients eventually develop progressive disease in viscera or brain
- Can we improve up-front therapy?
  - Combined signal blockade
- Current standards
  - Continue HER2 directed therapy through progression
    - Capecitabine + lapatinib > capecitabine (Geyer et al)
    - Capecitabine + trastuzumab > capecitabine (von Minckwitz et al)
    - Lapatinib + trastuzumab > lapatinib (Blackwell et al)

Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



- Trastuzumab continually suppresses HER2 activity
- Flags cells for destruction by the immune system
  - Activates ADCC

- Pertuzumab inhibits HER2 forming dimer pairs
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
  - Activates ADCC

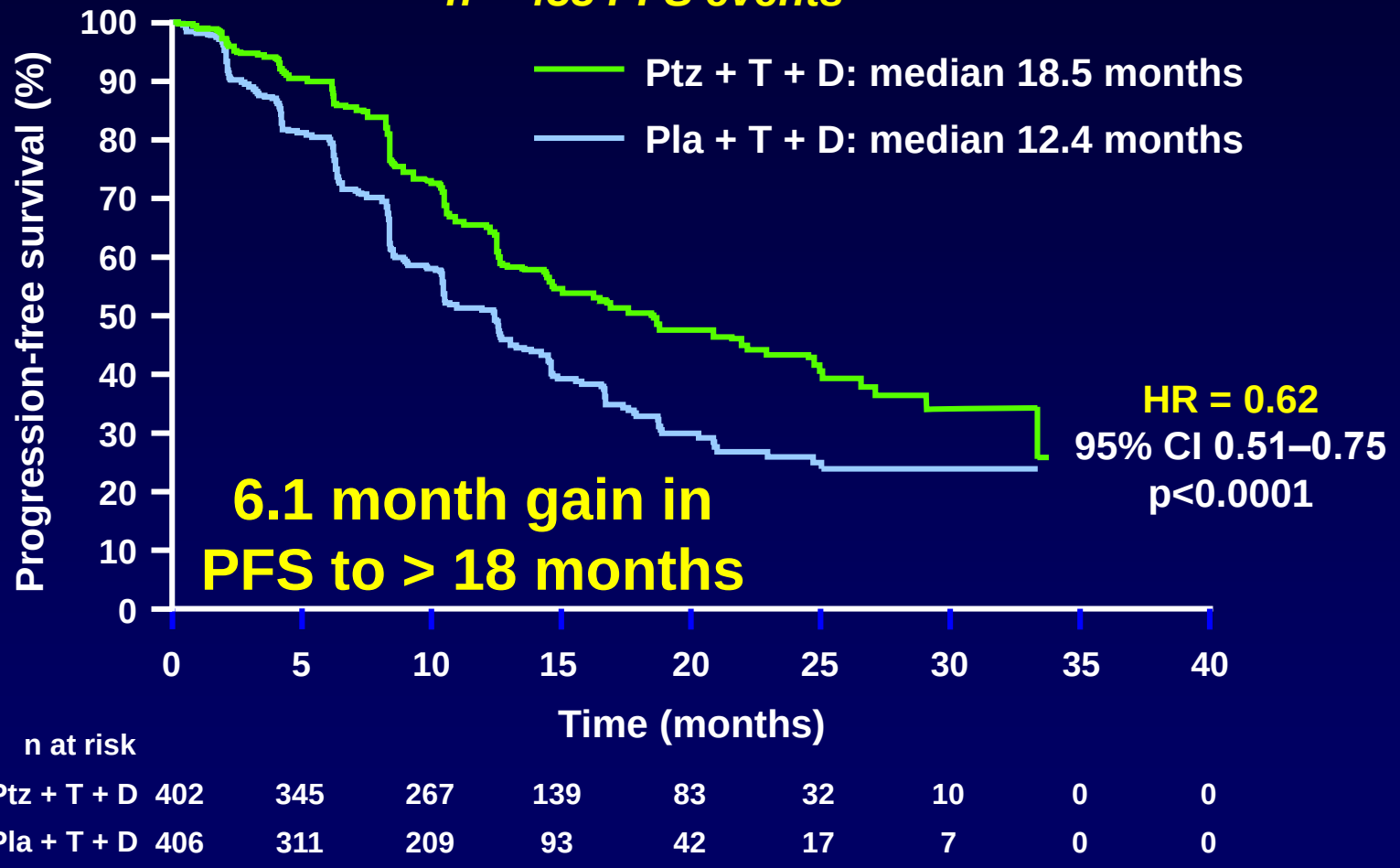
Cleopatra: Study Design and Patients

- Double-blind, placebo controlled phase III trial
  - Docetaxel 75 mg/m^2 escalated to 100 as tolerated, about 6 cycles
  - Trastuzumab and pertuzumab/placebo q 3 weeks
- Primary endpoint
  - Independently assessed PFS
- 808 patients with treatment naïve centrally confirmed HER2+ MBC
  - Adjuvant therapy
    - 53% no prior chemo
    - 10% prior trastuzumab
    - 49% ER+, 24% received endocrine therapy

Baselga et al, SABCS 2011 and NEJM, 2011

Primary Endpoint: Independently Assessed PFS

n = 433 PFS events



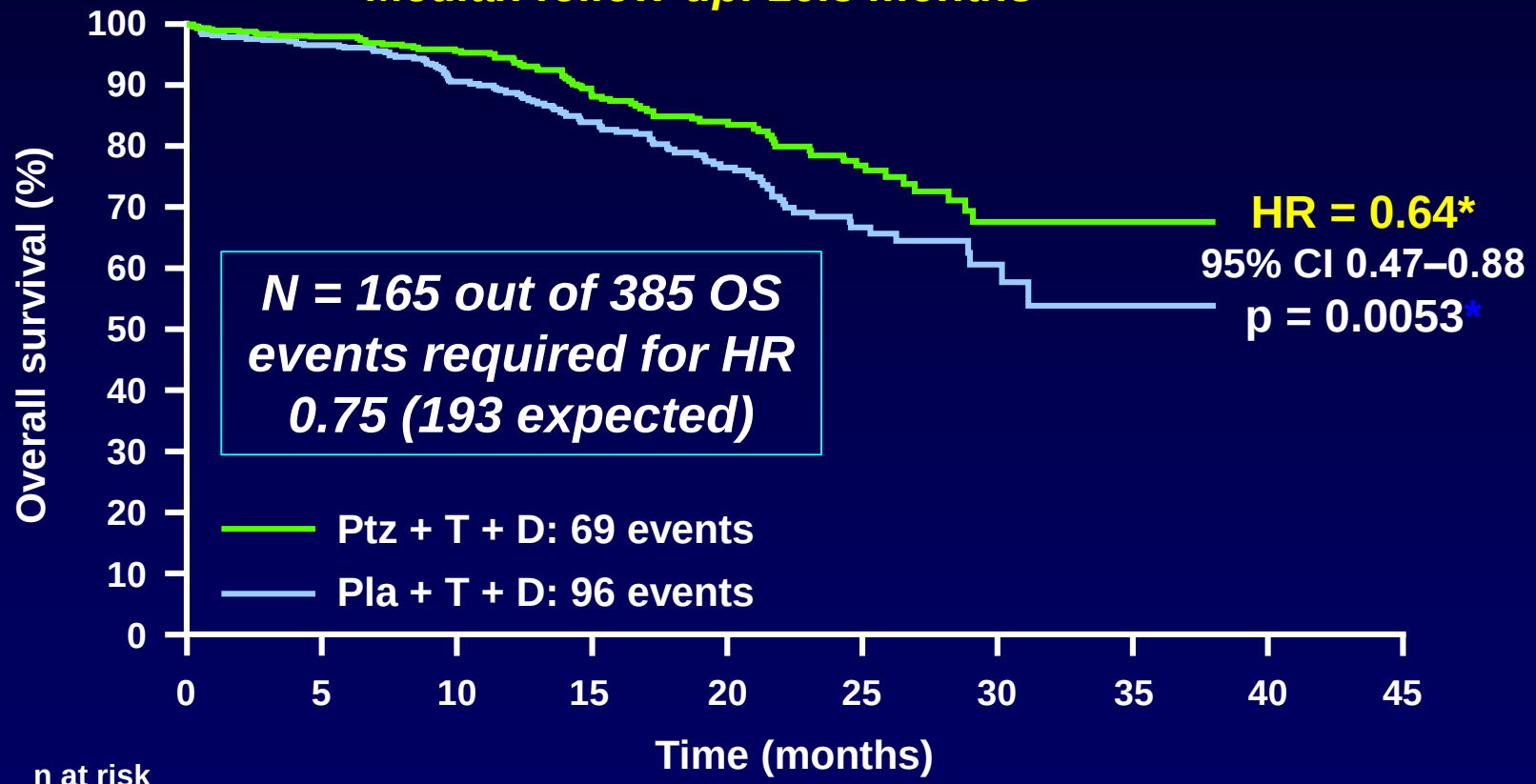
Stratified by prior treatment status and region

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga et al, SABCS 2011 and NEJM, 2011

Overall Survival: Predefined Interim Analysis

Median follow-up: 19.3 months



n at risk										
Pertuzumab + T + D	402	387	367	251	161	87	31	4	0	0
Placebo + T + D	406	383	347	228	143	67	24	2	0	0

*** The interim OS analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤0.603; p ≤0.0012)**

D, docetaxel; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga et al, SABCS 2011 and NEJM, 2011

Additional Data/Conclusions

- PFS benefit seen in essentially all predefined subsets
- Complete responses rare at 4 to 5.5% (partial response 65 to 75%) suggests presence of alternate resistance pathways
- Minimal additional toxicity with pertuzumab
- Survival impact is practice changing
  - Approved 6/2012 in the US

Historical Timeline: First-Line Treatment of HER2+ Disease –

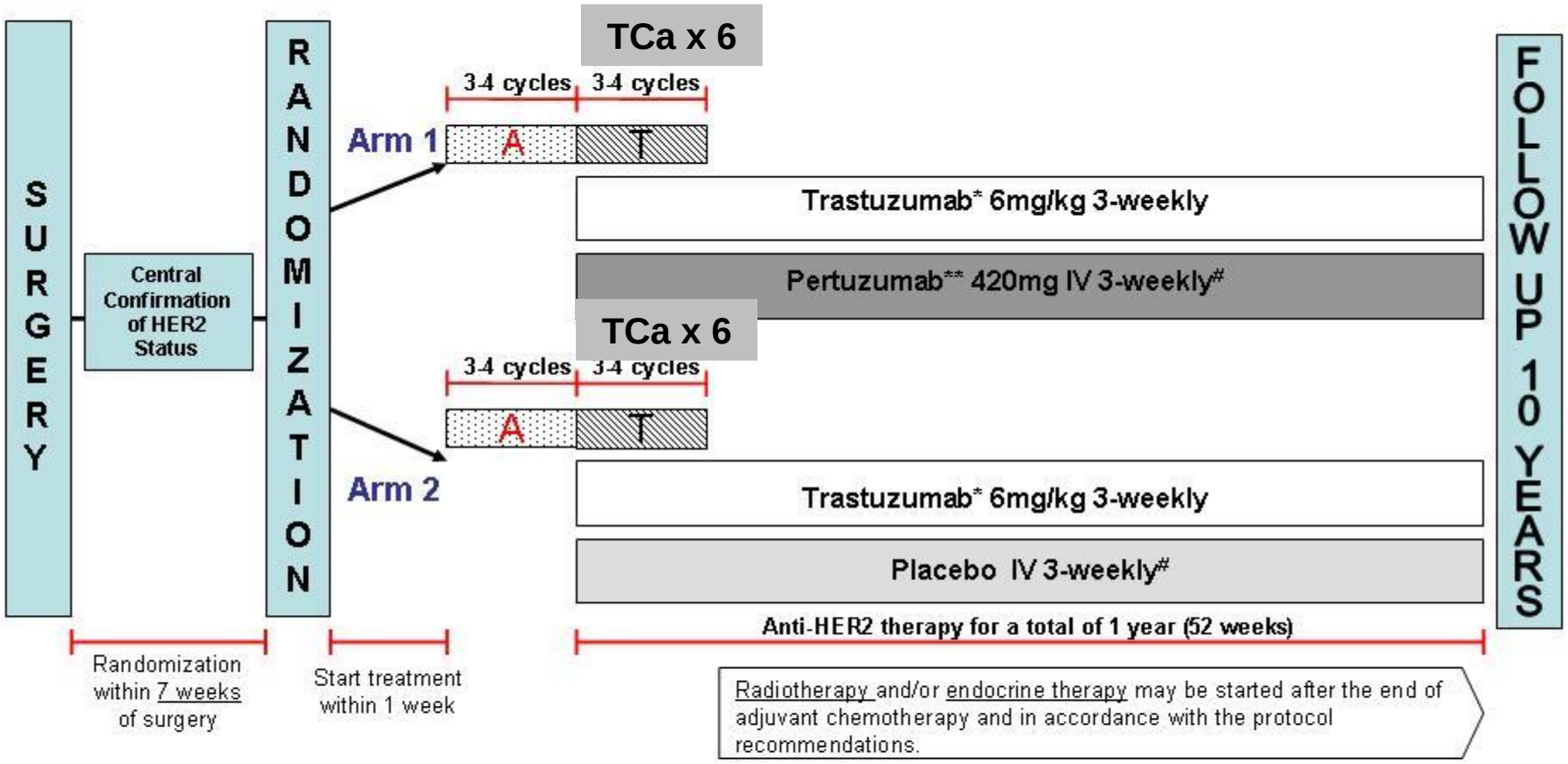
	Slamon[1] N=469*		Marty[2] N=186		Cleopatra[3] N=808		Averel[4] N=424	
	-Tr	+Tr	-Tr	+Tr	-P	+P	-B	+B
PFS/TTP (mo)	4.6	7.3	6.1	11.7	12.4	18.5	13.7	16.5
OS (mo)	20	26	23	31	NR @ med FU 19.3 mo		38.3	38.5

Slamon: q 3 wk paclitaxel or AC, all others q 3 week docetaxel

* FISH + subset

1. Slamon et al, NEJM 2001 and Mass et al, Clin Breast CA 2005. 2. Marty et al, JCO 2005. 3. Baselga et al, NEJM, 2011. 4. Gianni, SABCS 2011

APHINITY ADJUVANT TRIAL
N=3806



KEY

- A — 3-4 cycles of anthracycline containing chemotherapy
- T — 3-4 cycles of taxane containing chemotherapy
- Trastuzumab
- Placebo
- Pertuzumab

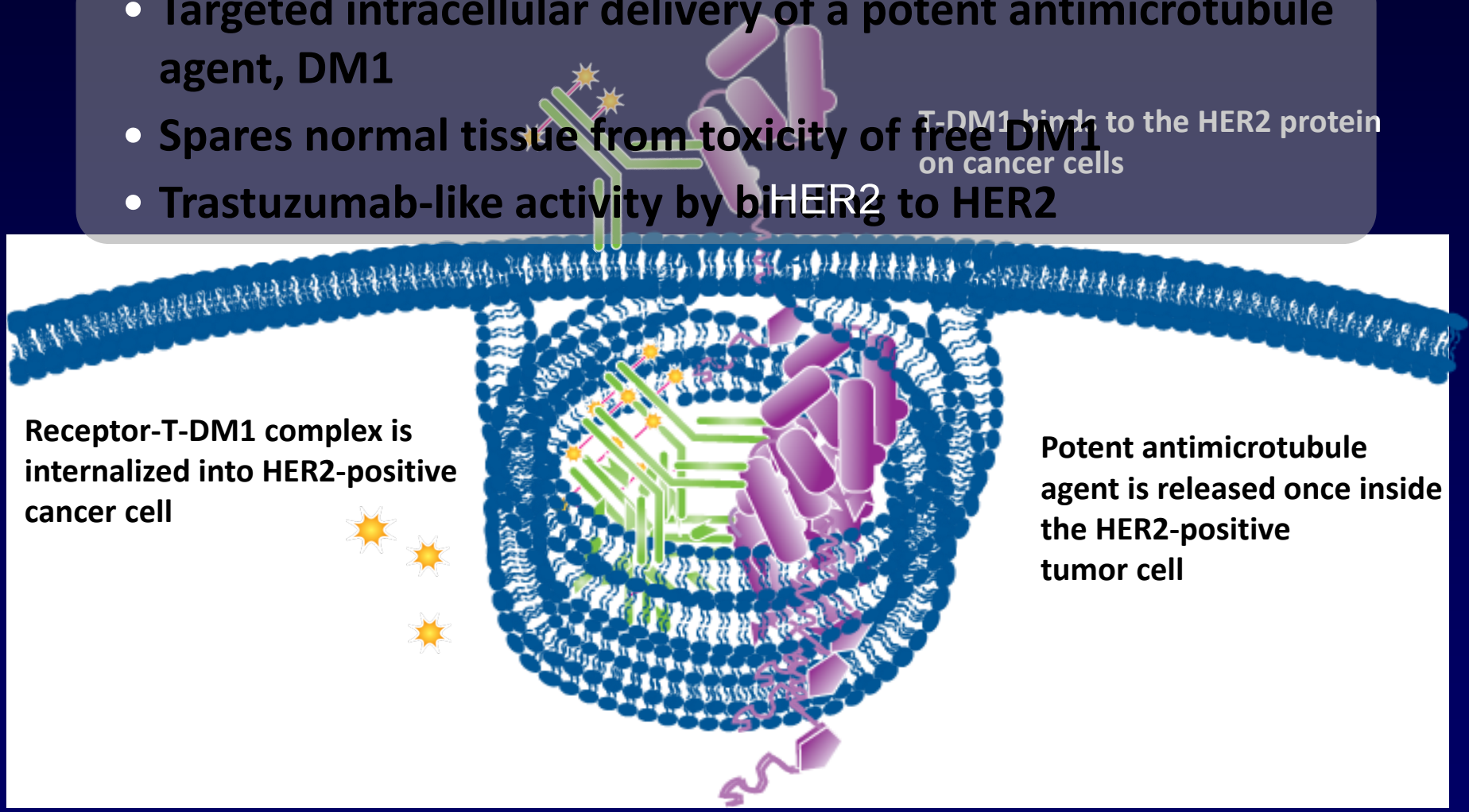
* Trastuzumab must be given at a 8mg/kg loading dose at the first trastuzumab cycle.
** Pertuzumab must be given at a 840mg/kg loading dose at the first pertuzumab cycle.

TCa = 6 cycles of docetaxel and carboplatin

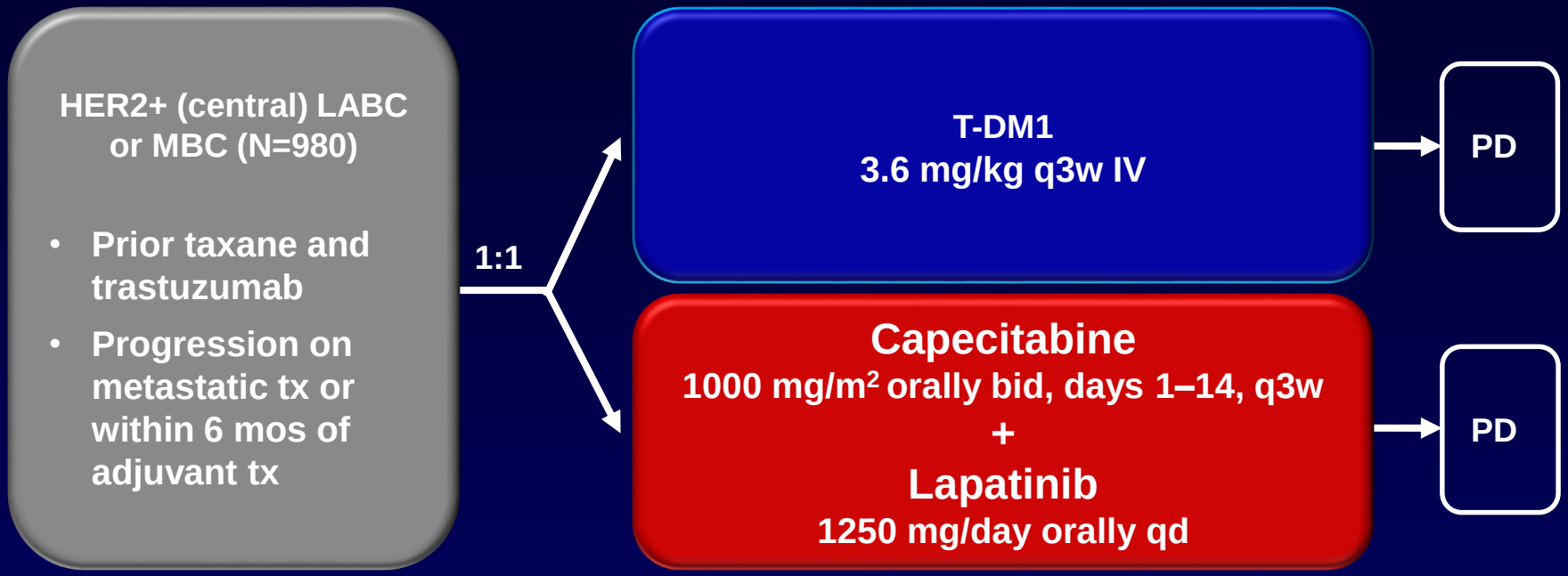
#All site, study and sponsor personnel will be blinded as to treatment assignment

T-DM1 selectively delivers DM1 to HER2-positive tumor cells

- **Targeted intracellular delivery of a potent antimicrotubule agent, DM1**
- **Spares normal tissue from toxicity of free DM1**
- **Trastuzumab-like activity by binding to HER2**



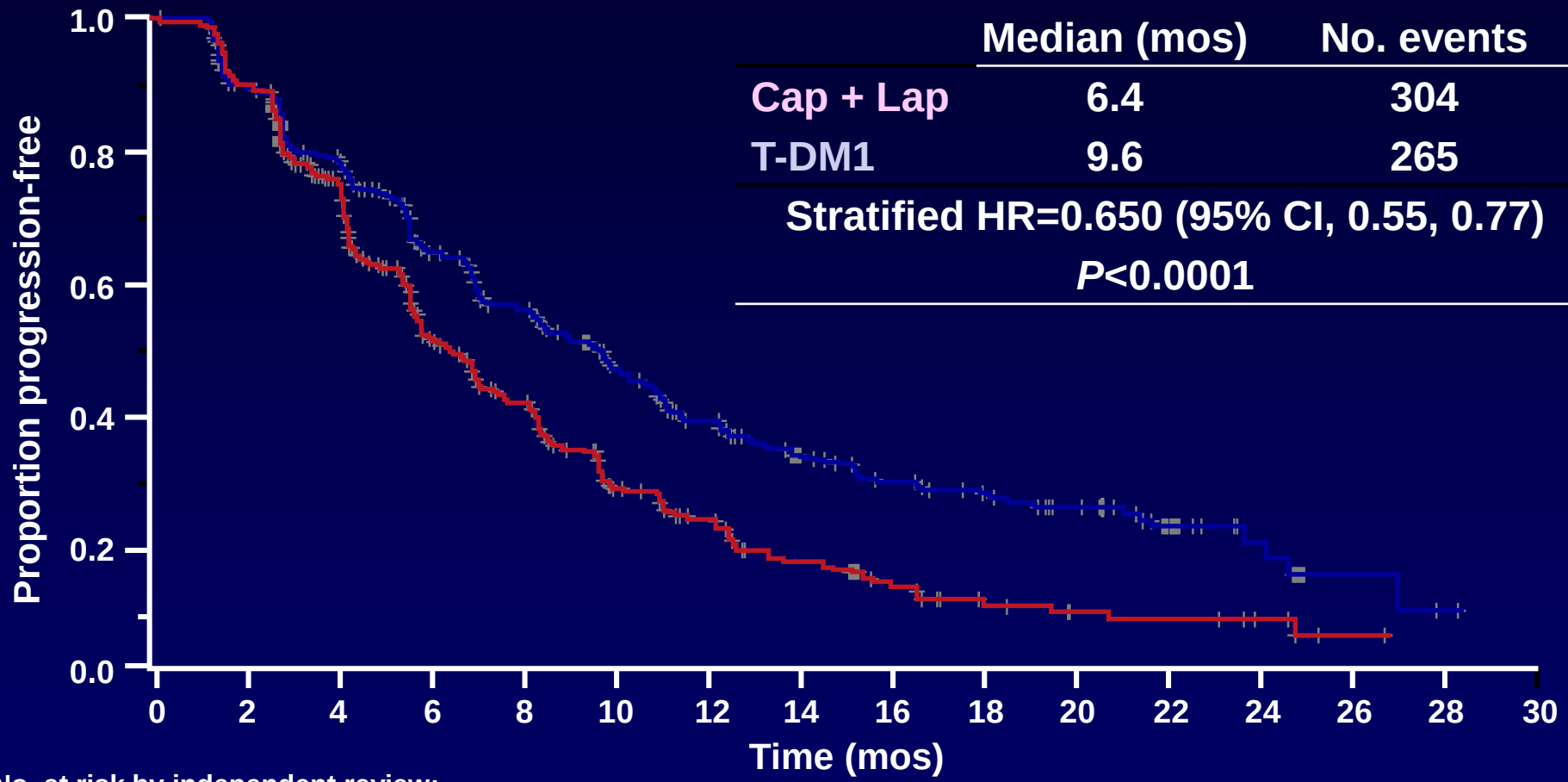
EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression
- **Statistical considerations:** Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary end points

Verma et al, NEJM 2012

Progression-Free Survival by Independent Review



	Median (mos)	No. events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)

P<0.0001

No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Unstratified HR=0.66 (*P*<0.0001).

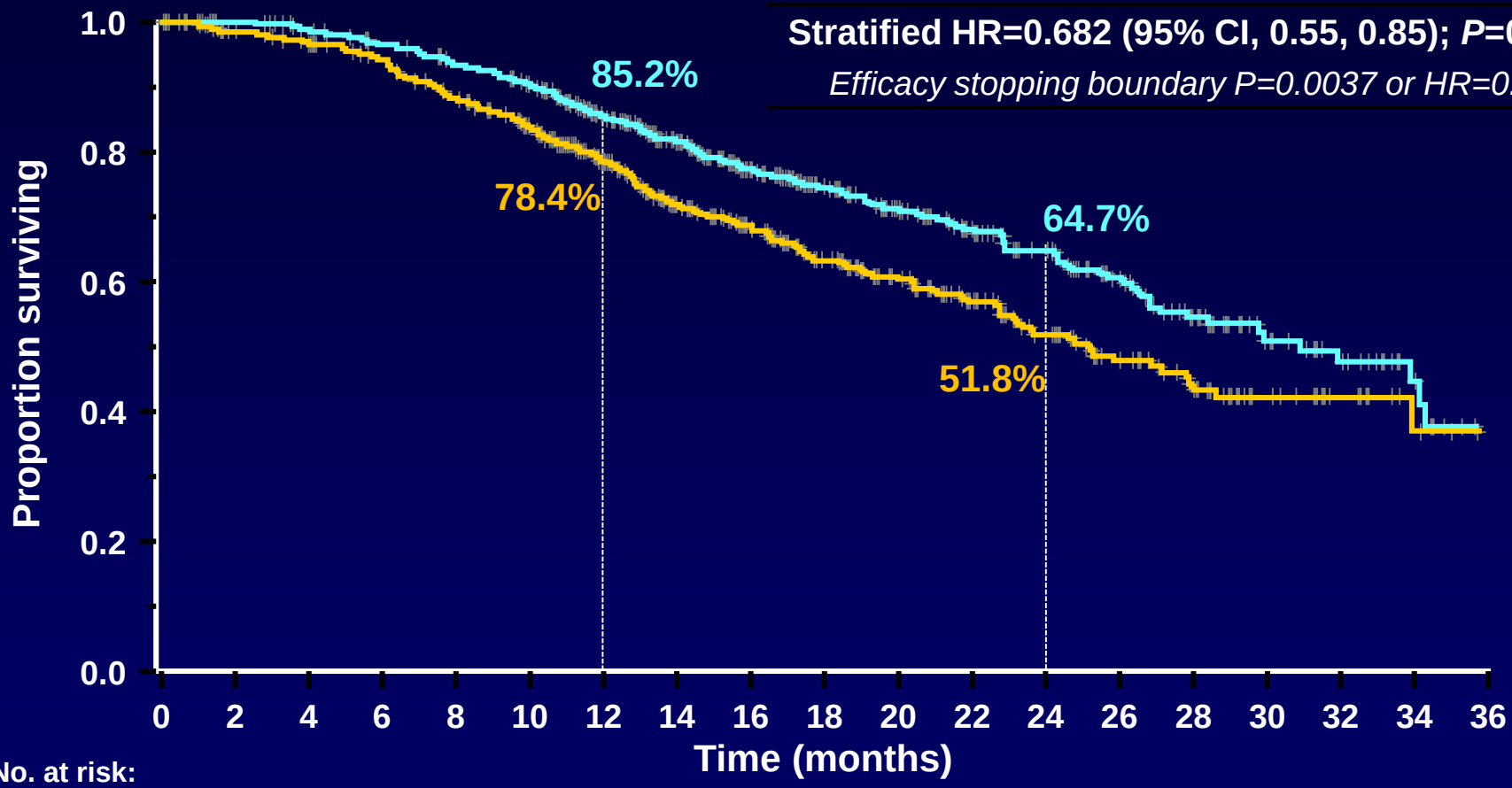
Median follow-up, mos (range): Cap + Lap, 12.4 (0–35); T-DM1, 12.9 (0–34)

Overall Survival: Confirmatory Analysis

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



No. at risk:																			
Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

Overview of Adverse Events

	Cap + Lap (n=488)	T-DM1 (n=490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death on treatment, n (%)[a]	5 (1.0)	1 (0.2)
LVEF <50% and ≥15-point decrease from baseline, %[b]	7 (1.6)	8 (1.7)

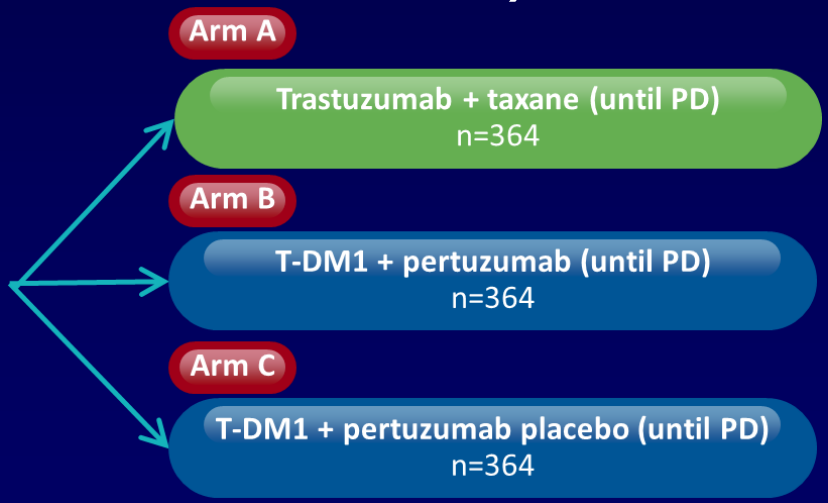
[a]Cap + Lap: CAD, multiorgan failure, coma, hydrocephalus, ARDS;
[a]T-DM1: metabolic encephalopathy.
[b]Evaluable pts: 445 (Cap + Lap); 481 (T-DM1).

- **Cap and Lap: More grade 3 diarrhea (21 vs 1.6%), hand foot syndrome (16 vs 0%)**
- **TDM1: More transaminiitis (4 vs 1%), grade 3/4 thrombocytopenia (13 vs 0%)**

Emilia and Ongoing Trials

- T-DM1 superior to cap/lap
  - PFS, OS, response, safety
  - Will clearly be a new standard in this setting
  - Approval expected towards the end of 2012/early 2013

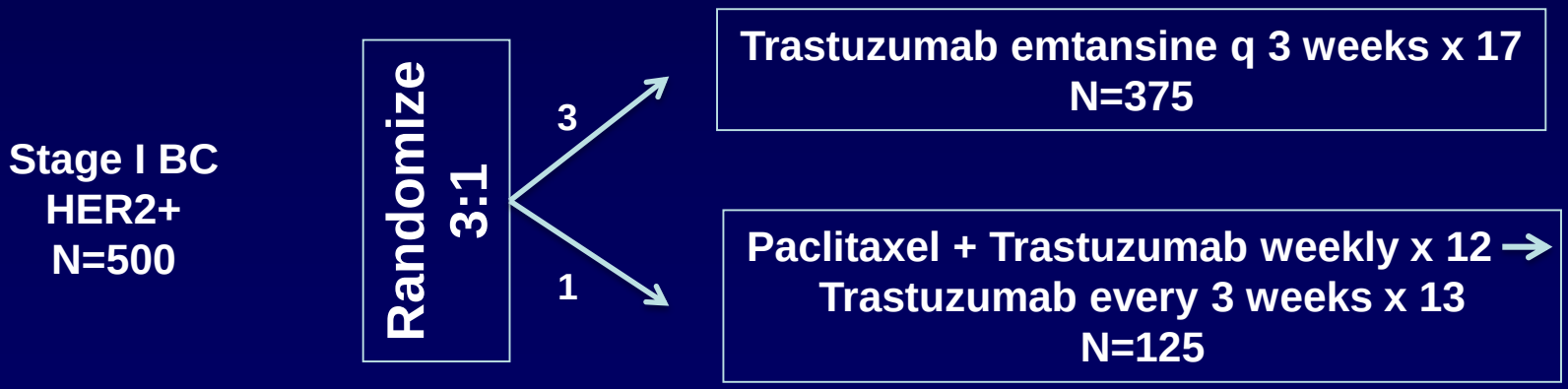
- Marianne (n=1092, untreated HER2+ MBC)
  - Three arms
    - Trastuzumab + taxane
    - TDM1 + pertuzumab
    - TDM1 plus placebo



- Th3RESA (n=795)
  - Prior trastuzumab/lapatinib/anthra/taxane/cape
  - 2:1 randomization to TDM1 v TPC

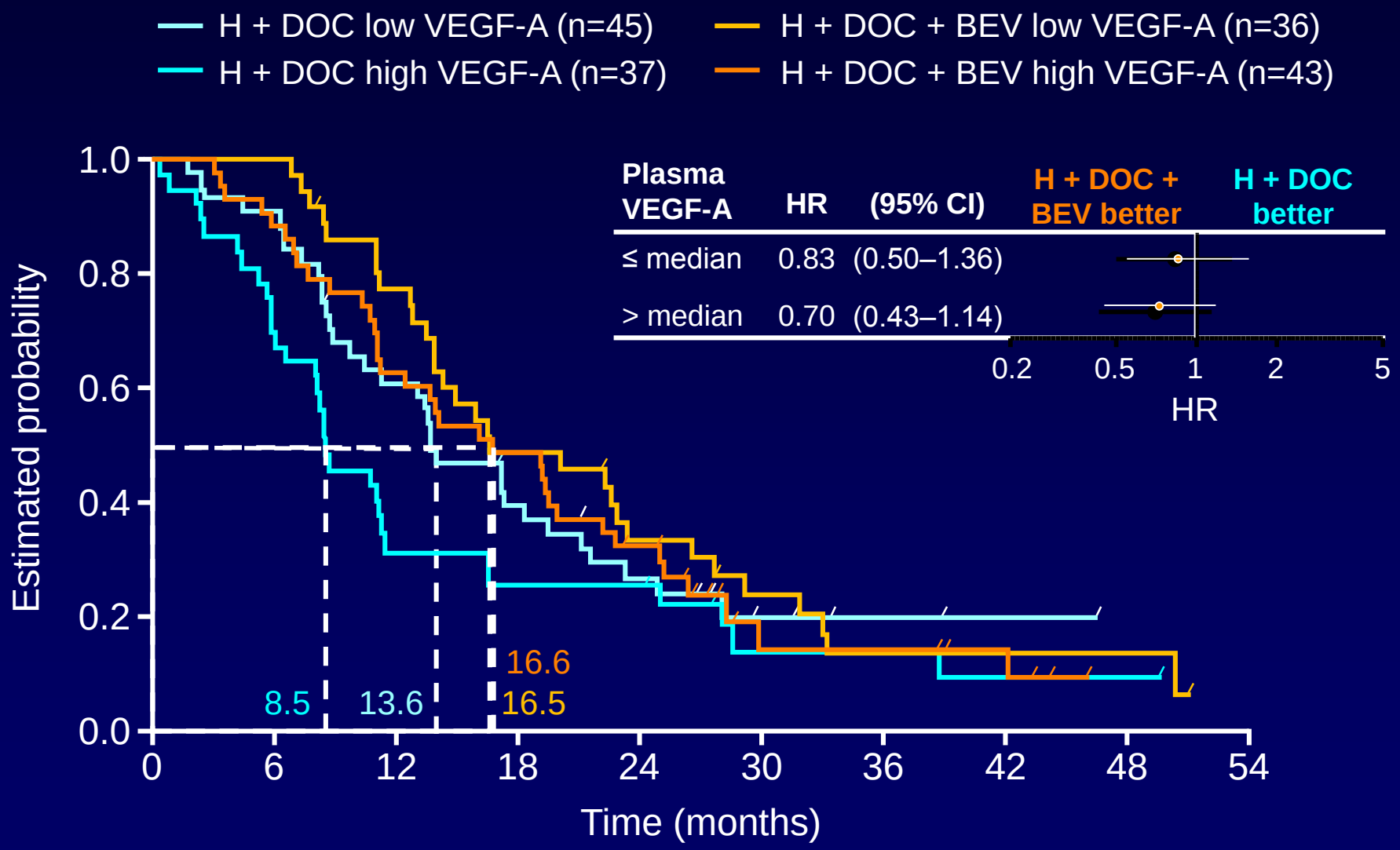
Trials in Early Stage Disease

- Post-neoadjuvant cooperative group
- Neoadjuvant company sponsored
- Adjuvant small tumors: **ATTEMPT** Trial
  - Tolaney PI (DFCI)

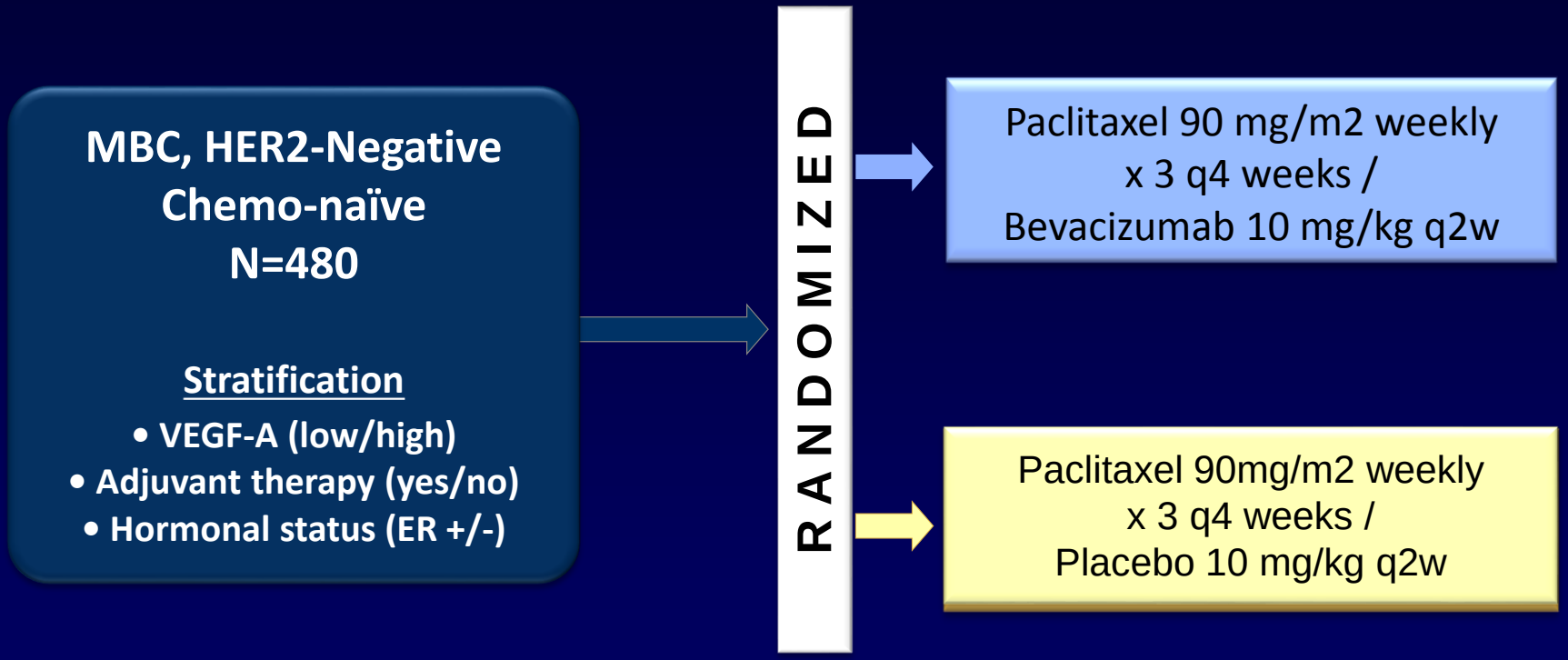


What About Bevacizumab (Avastin)?

AVEREL Investigator-Assessed PFS According to Baseline Plasma VEGF-A



Confirmatory Study Schema: MERiDiAN



Co-Primary Endpoints: PFS (All Patients) , PFS (VEGF high subset)

Secondary Endpoints: OS; ORR; Symptoms/QoL; Safety

The Problem in ER+ Tumors is Endocrine Therapy Resistance

- About 50% of hormone receptor-positive breast cancers are de novo resistant to endocrine therapy
- Almost all patients with advanced disease will develop acquired resistance to endocrine therapies
- The mechanisms of de novo and acquired resistance are likely similar, but are not completely understood
- Changing patterns of adjuvant therapy have decreased efficacy and reduced time to progession in the metastatic setting
- Is there a way to reverse hormone resistance in HER2 normal disease?

A Phase III Randomized Trial of Anastrozole versus Anastrozole and Fulvestrant as First-Line Therapy for MBC. SWOG S0226: Efficacy (Intent-to-Treat)

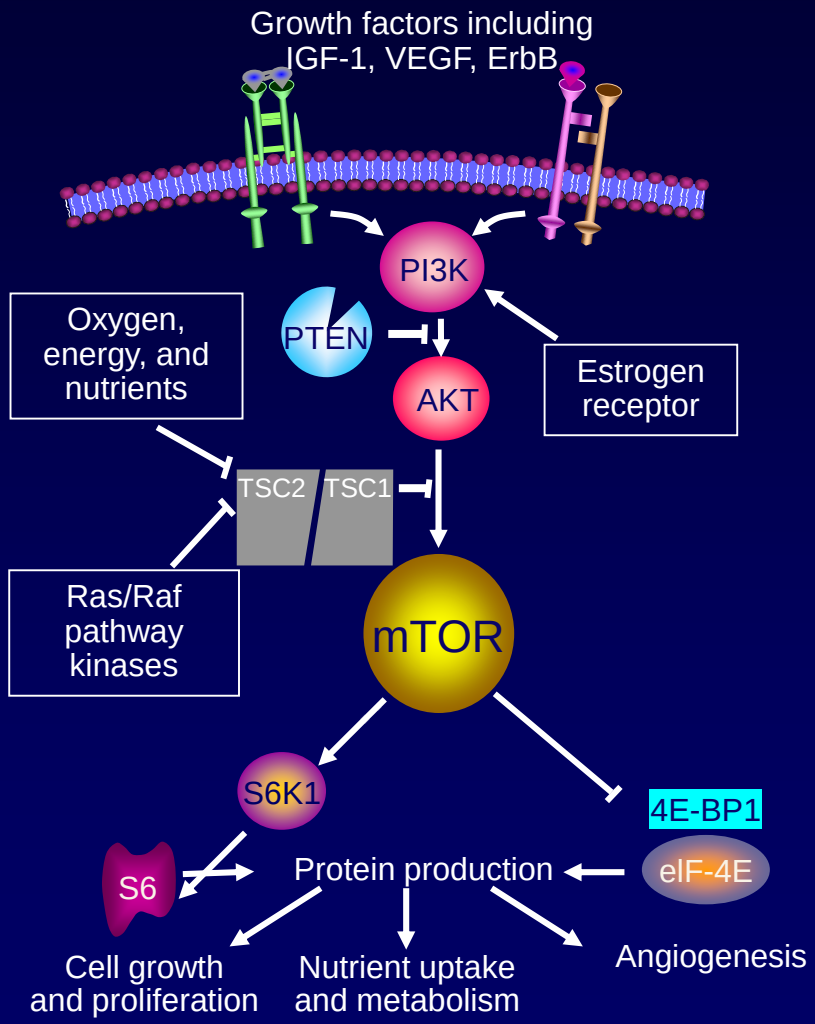
	Anastrozole (n = 345)	Anastrozole + fulvestrant (n = 349)	Hazard ratio	*p*-value
Median PFS	13.5 mos	15.0 mos	0.8	0.007
Median OS	41.3 mos	47.7 mos	0.81	0.049
Grade ≥3 AE	12.7%	14.5%*	—	NS

No prior adjuvant tamoxifen (n = 414)

	(n = 208)	(n = 206)		
Median PFS	12.6 mos	17 mos	0.74	0.0055
Median OS	39.7 mos	47.7 mos	0.74	0.0362

Mehta RS et al. San Antonio Breast Cancer Symposium 2011;Abstract S1-1.

The PI3K/AKT/mTOR Pathway

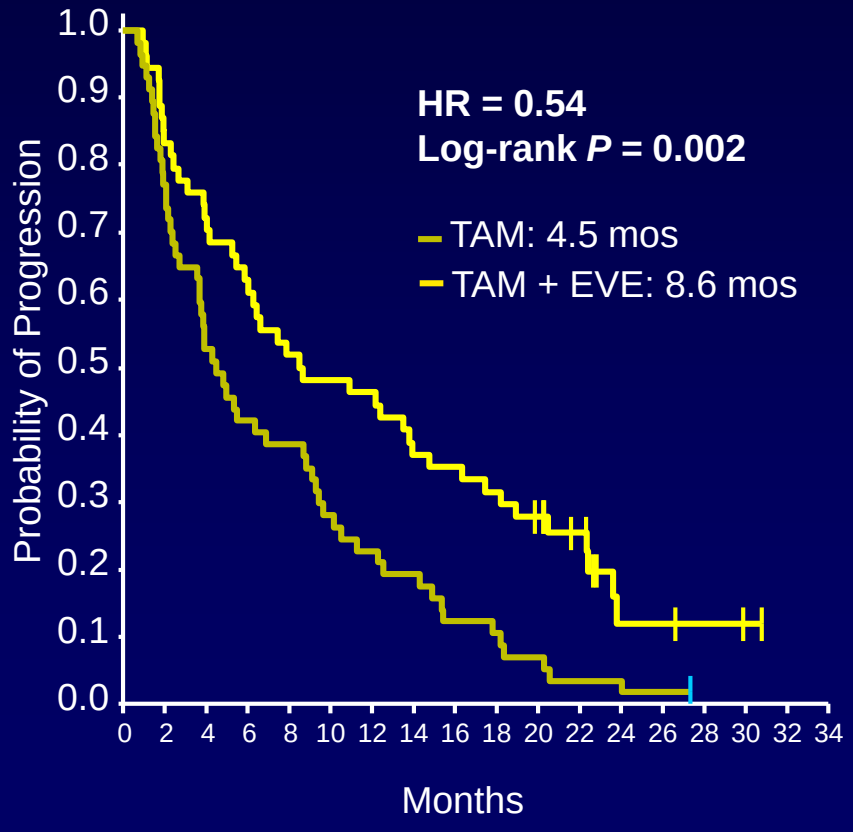


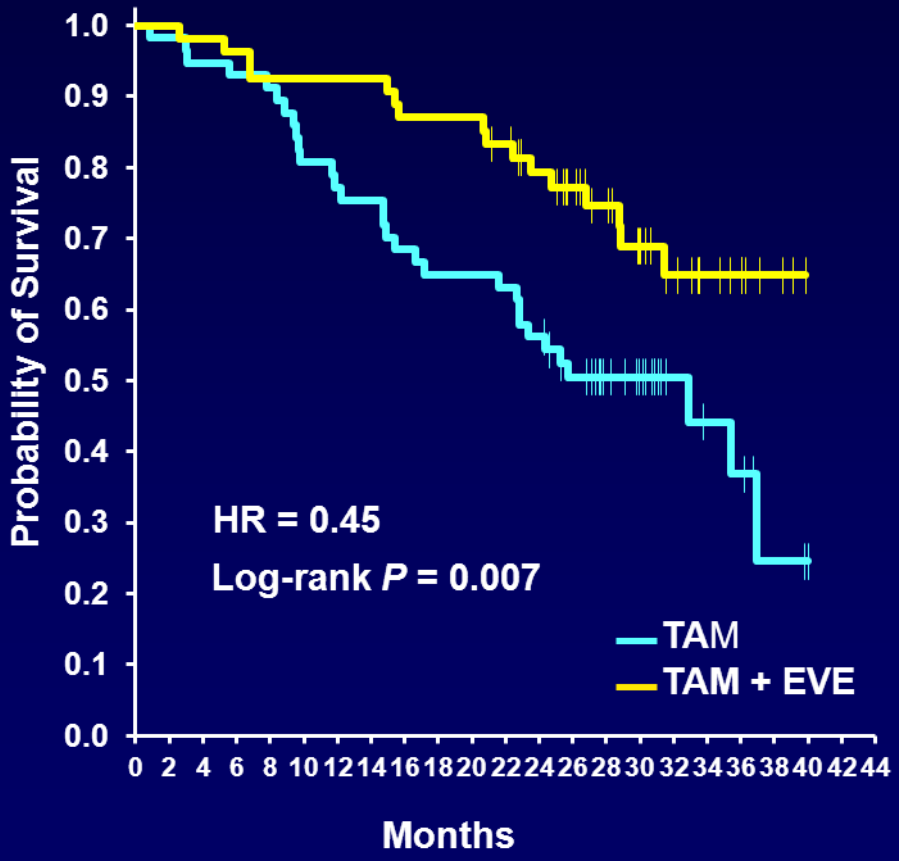
- mTOR (mammalian target of rapamycin) signaling plays a key role in
  - Cell growth
  - Cell proliferation
  - Regulation of
    - Apoptosis
    - Angiogenesis
    - Lymphocytes
    - Homeostasis

1. Bjornsti MA, et al. *Nat Rev Cancer*. 2004;34(5):335-348; 2. Crespo JL, et al. *Microbiol Mol Biol Rev*. 2002;66(4):579-591;
3. Huang S, et al. *Cancer Biol Ther*. 2003;2(3):222-232; 4. Mita MM, et al. *Clin Breast Cancer.* 2003;4(2):126-137;
5. Wullschleger S, et al. *Cell.* 2006;124(3):471-484; 6. Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889S-899S.

TAMRAD (Phase II): Tamoxifen ± Everolimus in Advanced BC

- **111 postmenopausal women with ER+ advanced BC previously treated with an AI were randomized in a phase II trial**



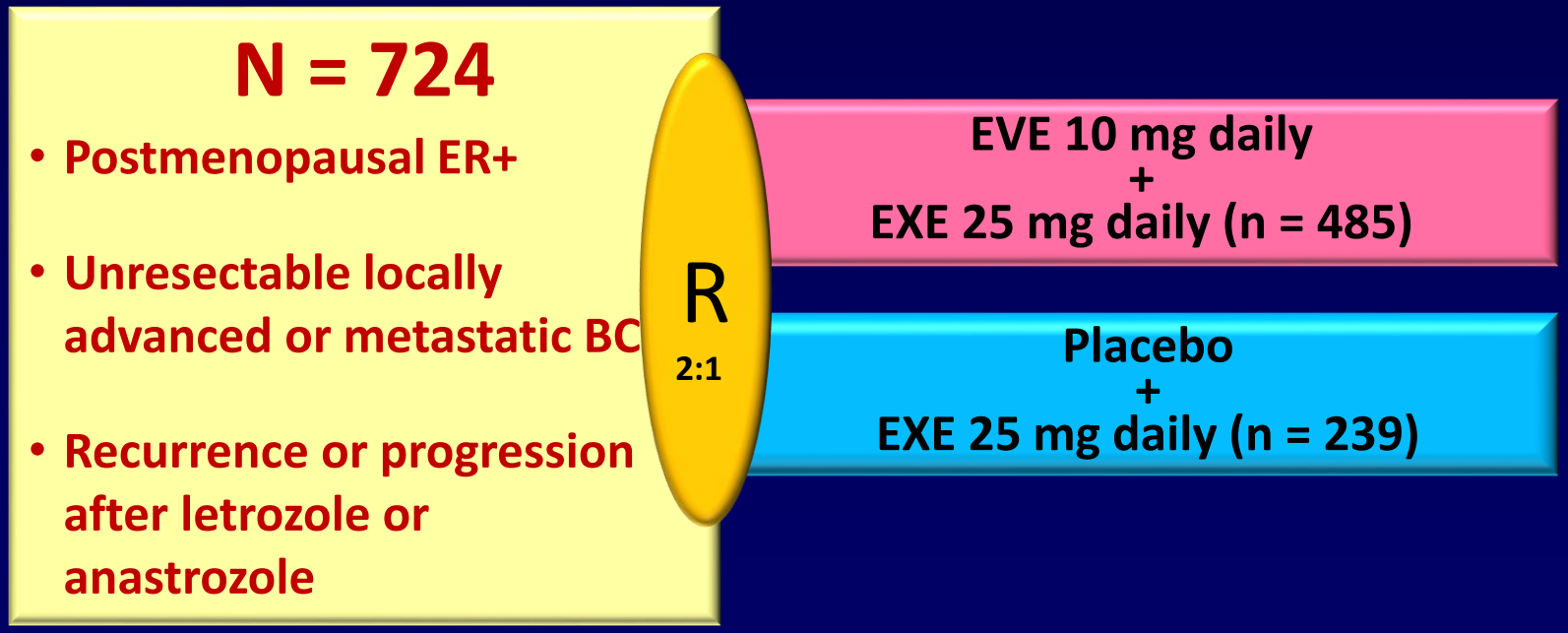


AI = aromatase inhibitor; BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; TAM = tamoxifen.

Bourgier C et al. ECCO/ESMO 2011 (Abstract #5005)

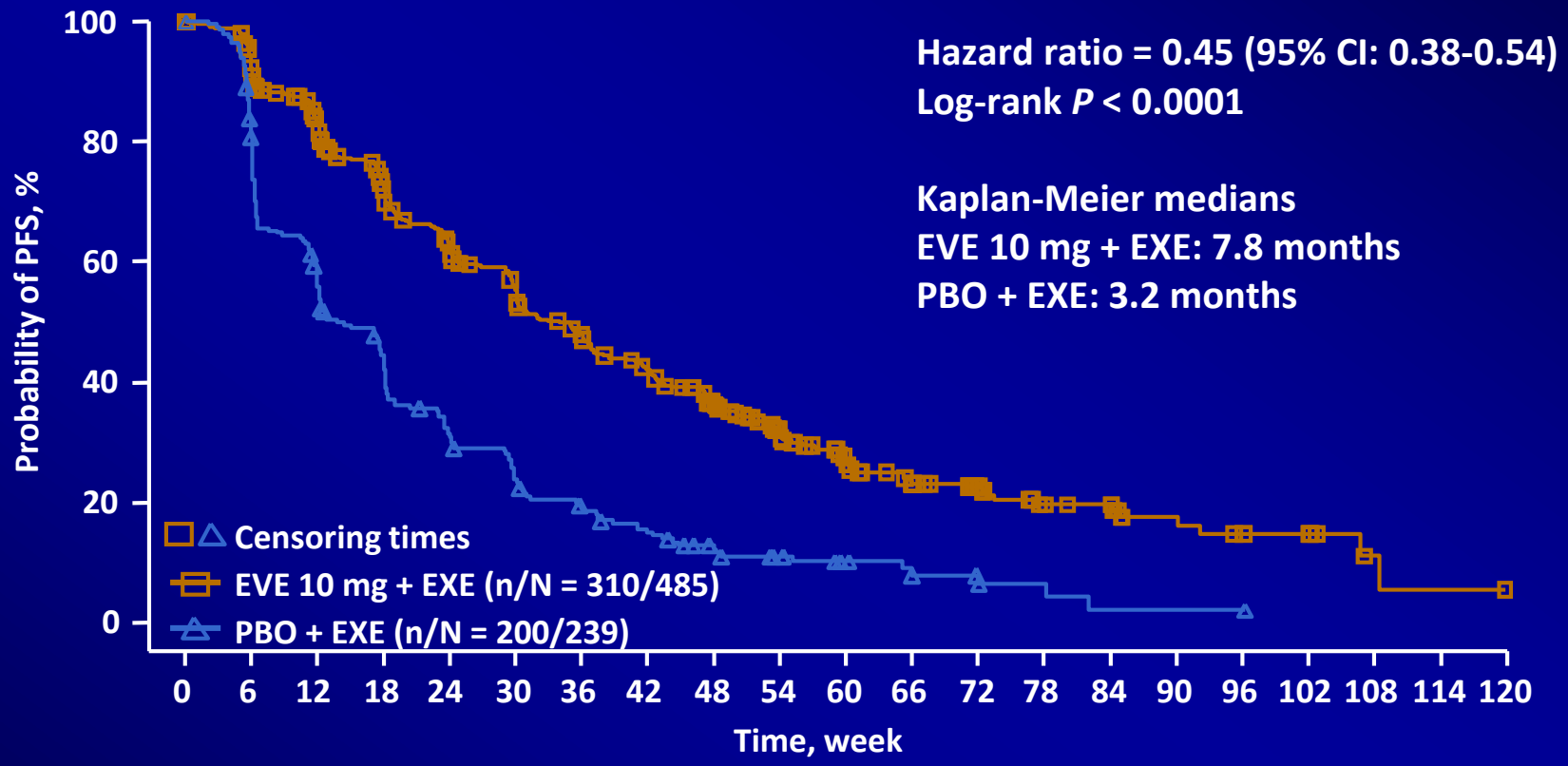
Bolero-2: Phase III Trial of Exemestane +/- Everolimus

- 724 PM women with ER+ MBC
  - Progression on letrozole or anastrozole
  - Up to two prior hormone agents
  - 84% sensitive to hormone therapy



Rugo et al, ASCO Breast Symposium, Baselga et al, NEJM 2011

PFS Based on Local Assessment at 18-month Follow-Up

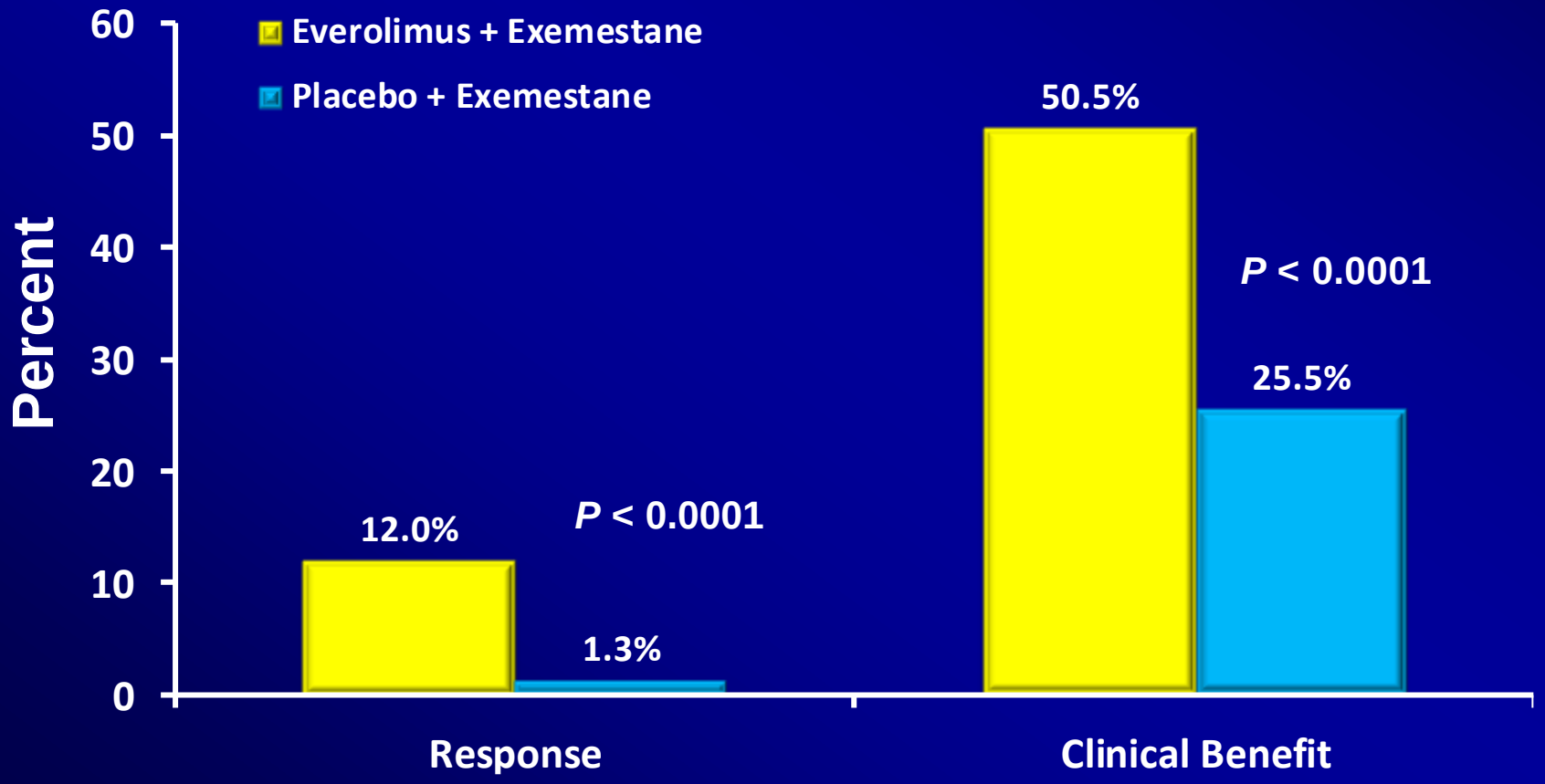


Number of Patients Still at Risk

EVE 10 mg + EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

Abbreviations: CI = confidence interval; EVE = everolimus; EXE = exemestane; PBO = placebo.

BOLERO-2 (18 mo f/up): Response & Clinical Benefit



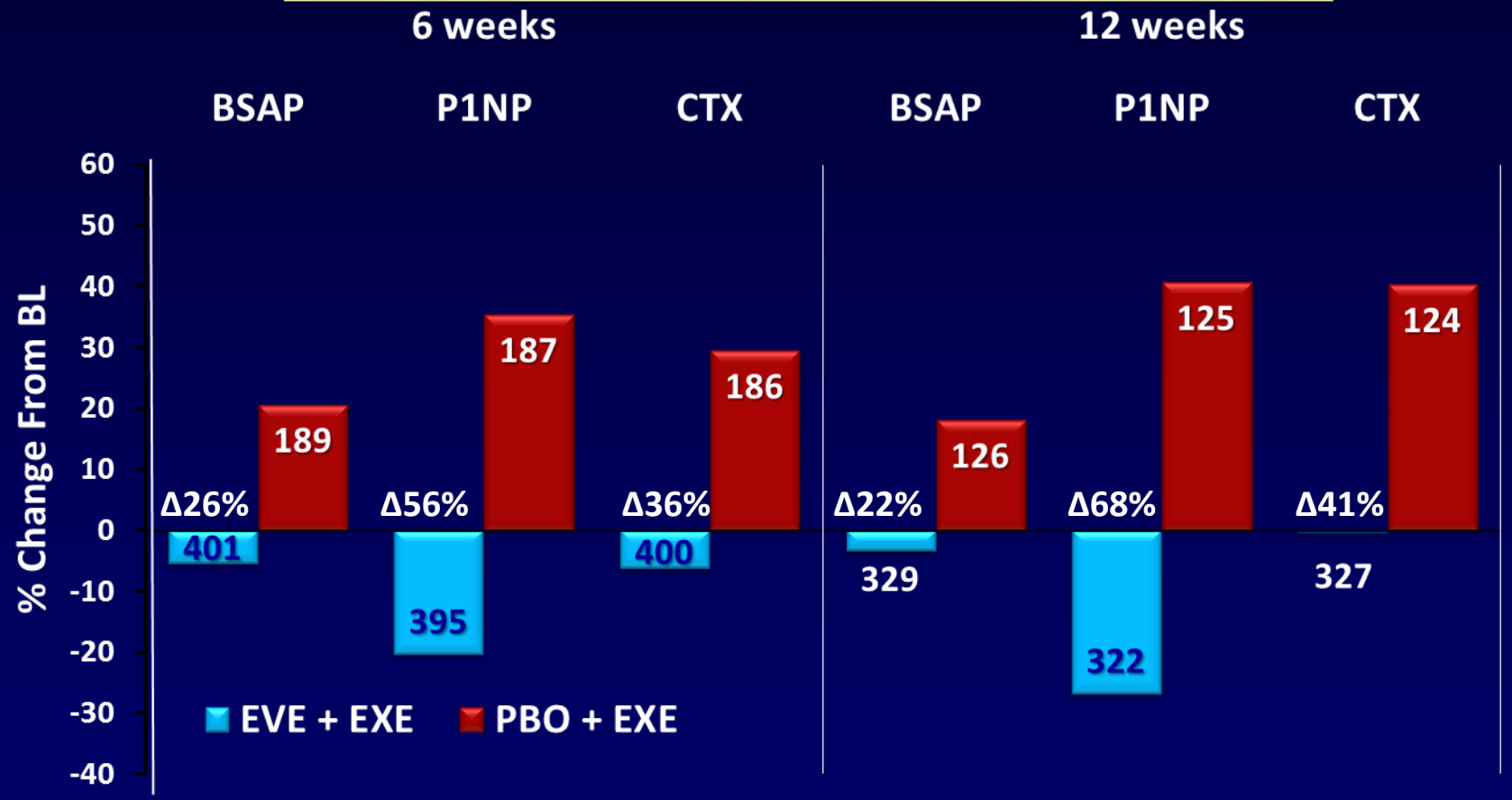
BOLERO-2 (18 mo f/up): Most Common Adverse Events

	Everolimus + Exemestane (n = 482), %			Placebo + Exemestane (n = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	59	8	0	11	<1	0
Rash	39	1	0	6	0	0
Fatigue	36	4	<1	27	1	0
Diarrhea	33	2	<1	19	<1	0
Appetite decreased	30	1	0	12	<1	0
Nausea	29	<1	<1	28	1	0
Weight decreased	25	1	0	6	0	0
Cough	25	<1	0	12	0	0

Hortobagyi G et al. SABCS 2011 (Abstract #S3-7), Baselga et al, 2011

EVE ⬇ Bone Turnover Marker Levels at 6 and 12 Weeks (Overall Population)

Bone metastases at BL[a]: 76% *versus* 77%
Bisphosphonate use at BL[a]: 44% *versus* 54%

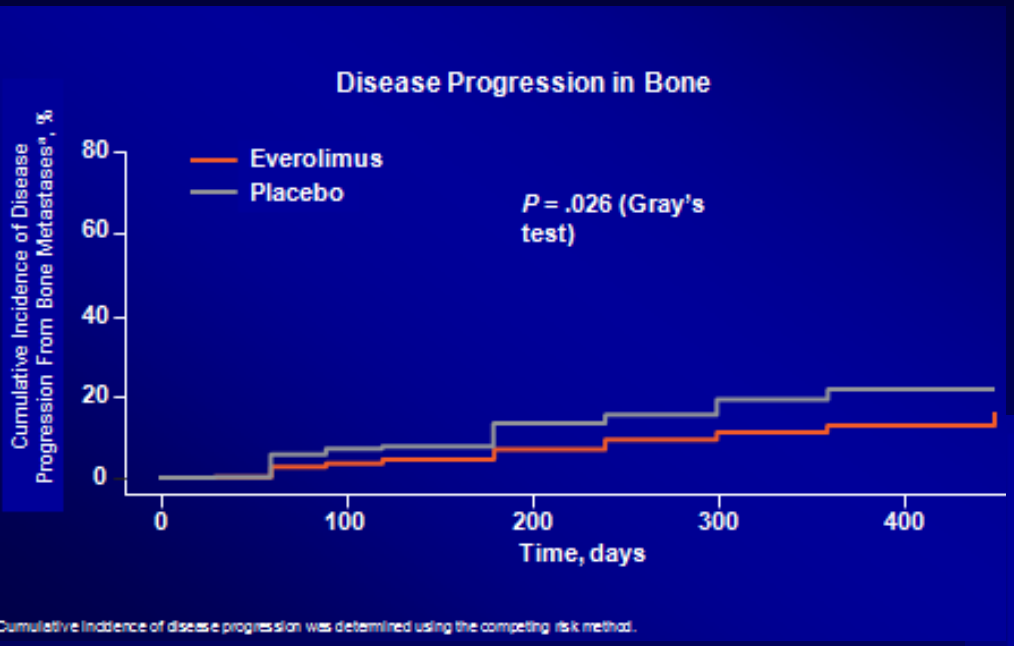


Abbreviations: BL, baseline; BSAP, bone-specific alkaline phosphatase; CTX, C-terminal cross-linking telopeptide of type I collagen; EVE, everolimus; EXE, exemestane; PBO, placebo; P1NP, amino-terminal propeptide of type I collagen.
Data from full analysis set.

[a] Proportions of patients with bone metastases or bisphosphonate use reflect the status at study entry among patients with baseline bone marker assessments.

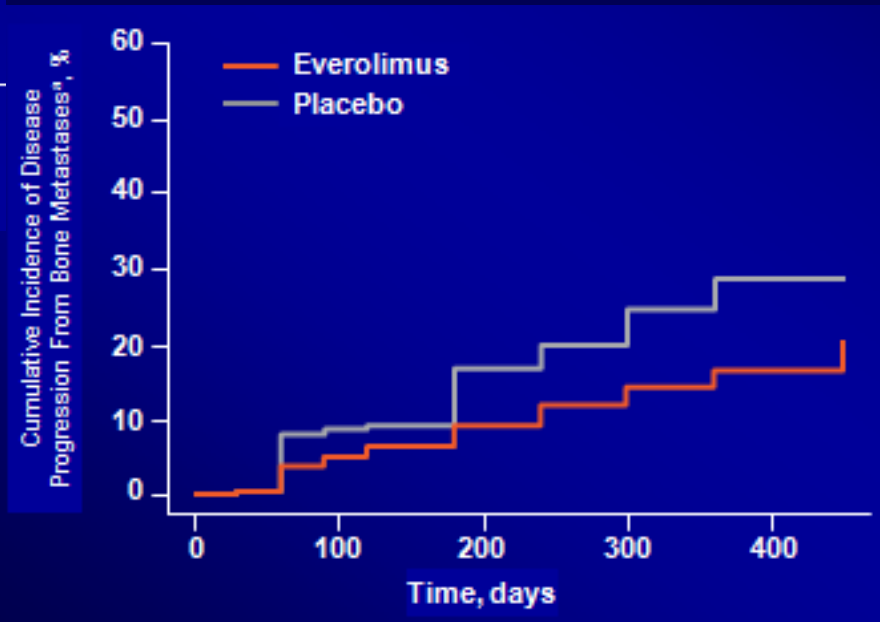
Everolimus Decreases Disease Progression in Bone

Overall Population (N=724)



Cumulative incidence of disease progression was determined using the competing risk method.

Patients with Bone Metastases at Baseline (N=554)

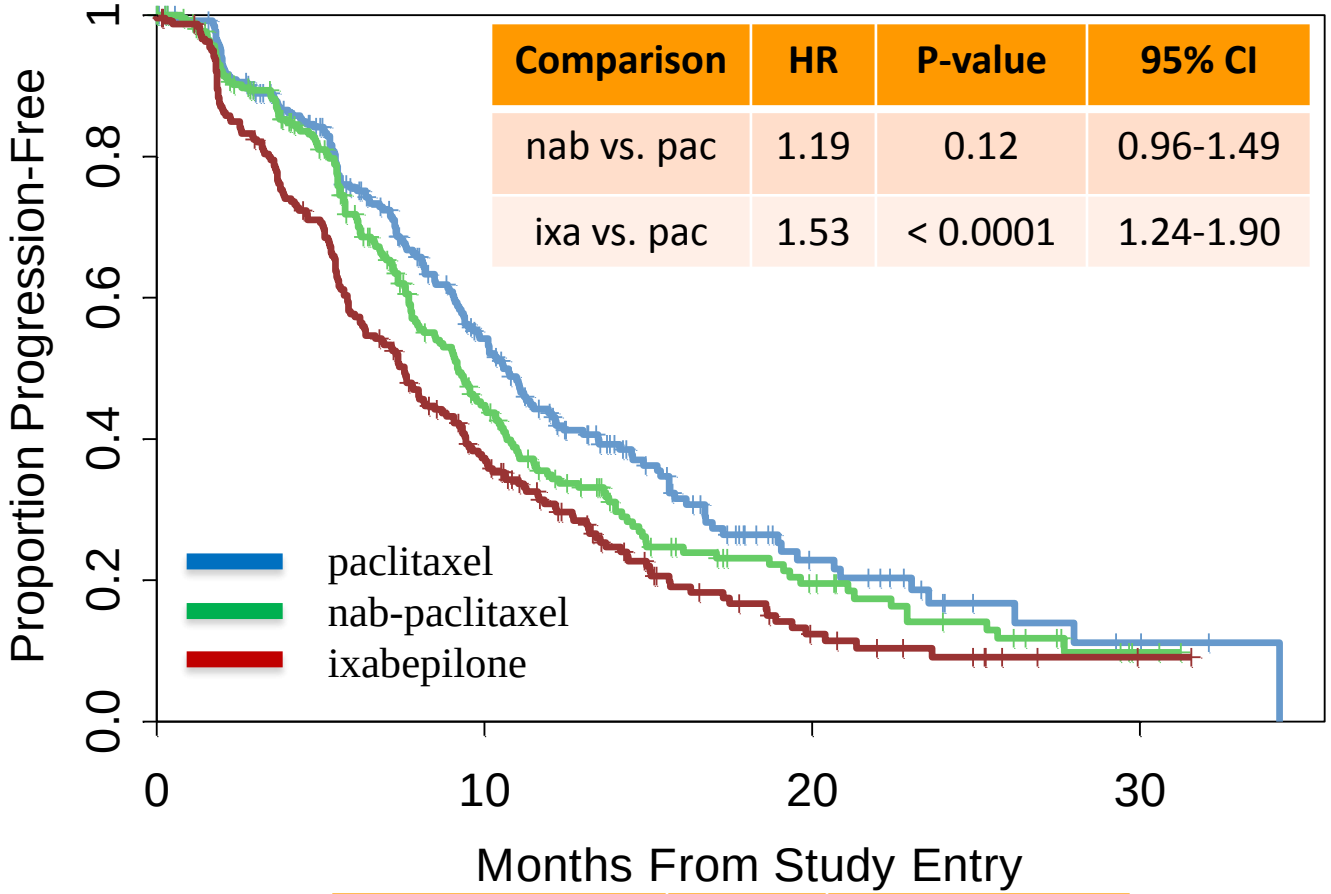


ive incidence of disease progression was determined using the competing risk method.

New Chemotherapy

- Eribulin approved for later during the course of advanced cancer
- CALGB 40502
  - Compared Taxol (paclitaxel) to Ixabepilone to Abraxane (nab-paclitaxel as treatment for metastatic disease.
  - More toxicity and less or similar efficacy compared to arms 2 and 3

CALGB 40502
Progression-Free Survival By Treatment Arm



Comparison	HR	P-value	95% CI
nab vs. pac	1.19	0.12	0.96-1.49
ixa vs. pac	1.53	< 0.0001	1.24-1.90

Agent	N	Median PFS
paclitaxel	283	10.6
nab-Paclitaxel	271	9.2
ixabepilone	245	7.6

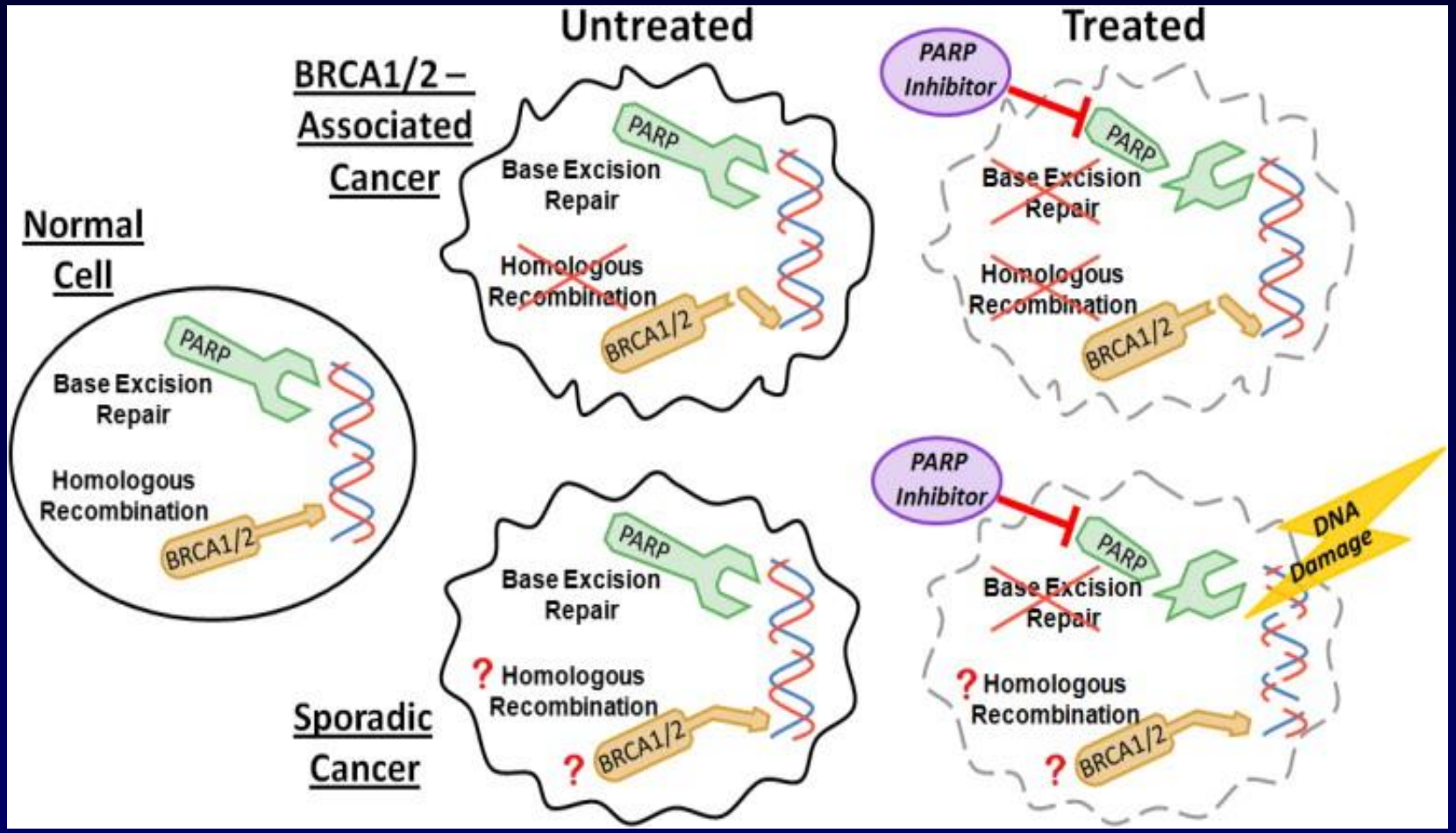
Summary and New Directions

- HER2 positive disease
  - Pertuzumab a new standard of care for advanced HER2+ breast cancer
  - TDM1 superior to lapatinib and capecitabine
  - Other combinations (MTOR, PIK3CA, etc)
- ER+
  - MTOR inhibition in the second-line setting
    - A new standard – FDA approved 7.2012
    - Move to earlier stage setting for higher risk disease
  - Explosion of new agents targeting this pathway in clinical trials
    - Combined inhibitors
- Critical to find markers that predict response to specific treatments

What Does the Future Hold?

- Genomic testing
  - Looking at the DNA of a tumor (or in normal cells) for mutations or deletions
- Gene expression testing
  - Looks at RNA for specific genes
- Recent data
  - Analysis of breast cancer through the Cancer Genome Atlas Network
    - Identified 4 main breast cancer classes
    - Identified some of the most common mutations
- What does this mean today?
  - Studies such as these help to identify potential targets for individualized cancer therapy
  - Given complexity of tumor alterations, combinations of therapies are likely to be most effective approach

PARP Inhibition



- Novel mechanism – inhibition of DNA damage repair
- Efficacy in BRCA-associated cancer

Ellisen LW. *Cancer Cell.* 2011;19(2):165-167.

PARP Inhibitors in Development

Agent	Company	Route	Current Trials
Rucaparib	Clovis	IV/Oral	BRCA+, post-neoadjuvant TNBC +cisplatin
Olaparib	AstraZeneca	Oral	BRCA+
Veliparib	Abbott	Oral	BRCA+, TNBC + paclit/carbo
Iniparib BSI-201	BiPar/Sanofi-Aventis	IV	Dose escalation
LT673 (2011	Biomarin	Oral	-
INO-1001	Inotek	IV	-
MK4827	Merck	Oral	-
CEP-9722	Cephalon	Oral	-
E7016	Eisai	Oral	-

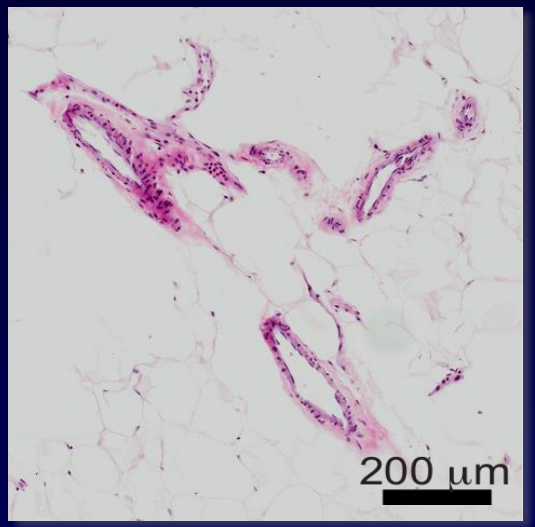
Plummer R *BCR* 2011 vol. 13 (4) pp. 218. with edits

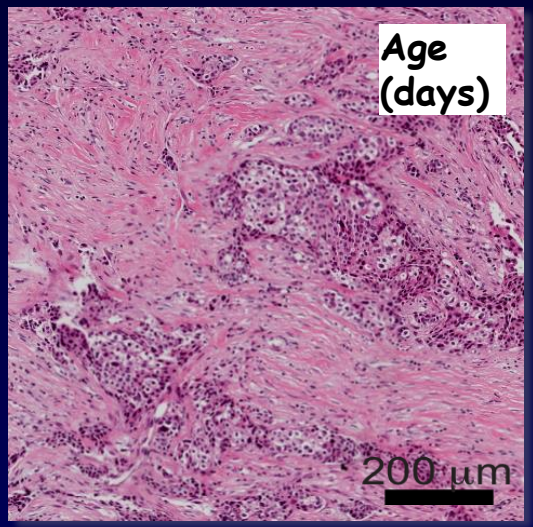
Leukocytes in Breast Cancer: Targets for Therapy ?

Distal normal

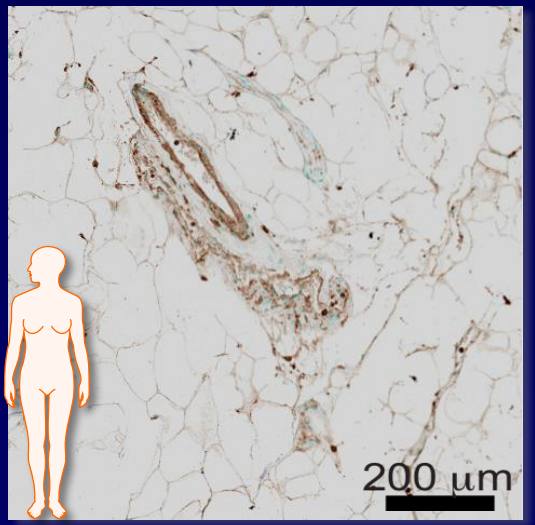
Inv. Ductal Carcinoma
CTX naive

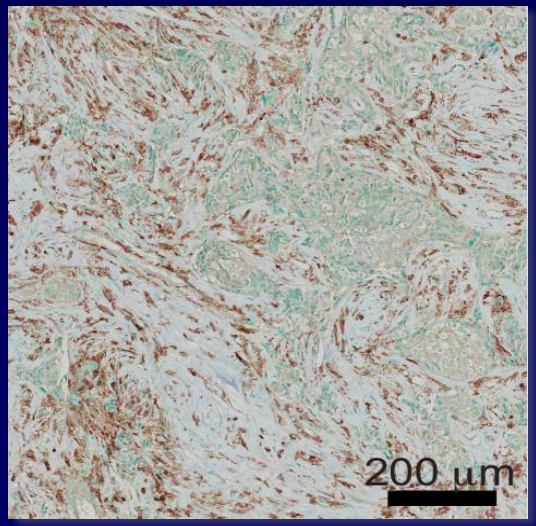
H&E





CD45

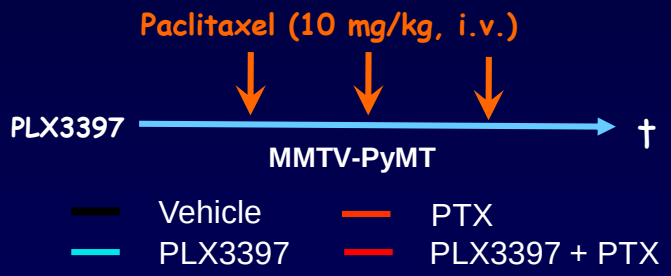


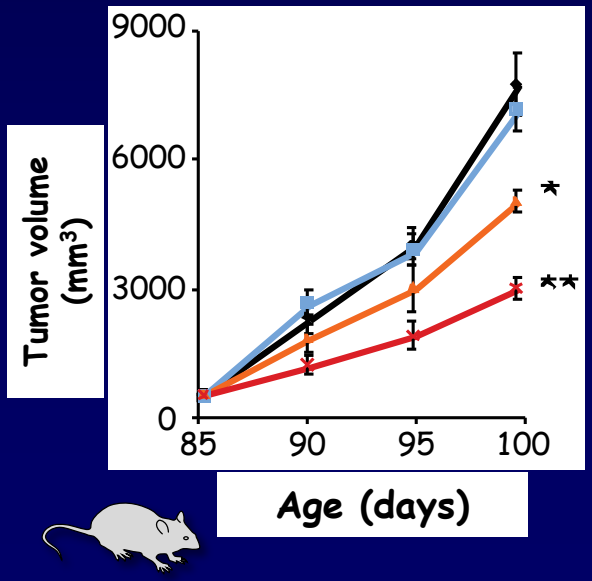


CD45: leukocyte common antigen

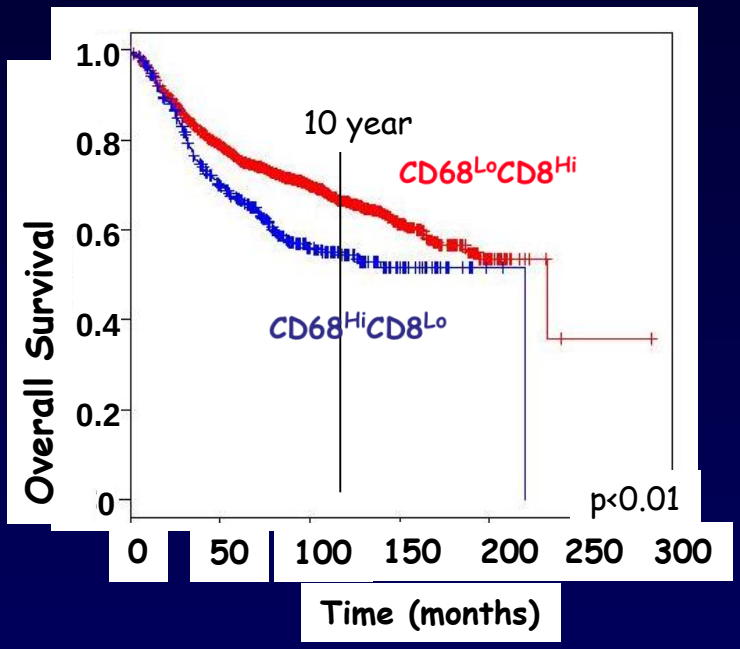
Ruffell et al., PNAS (2011)

Increased macrophage presence correlates with increased vessel density & decreased survival (Tsutsui et al., 2005; Bingle et al., 2002, Campbell et al, 2010)

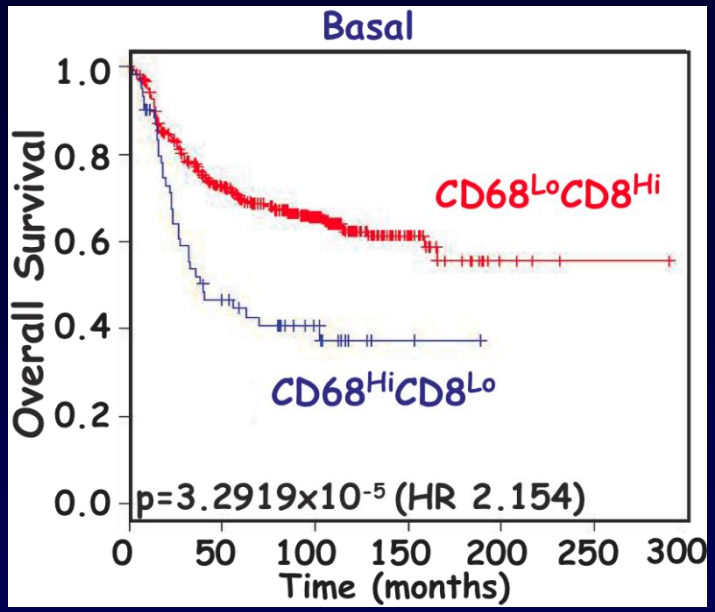


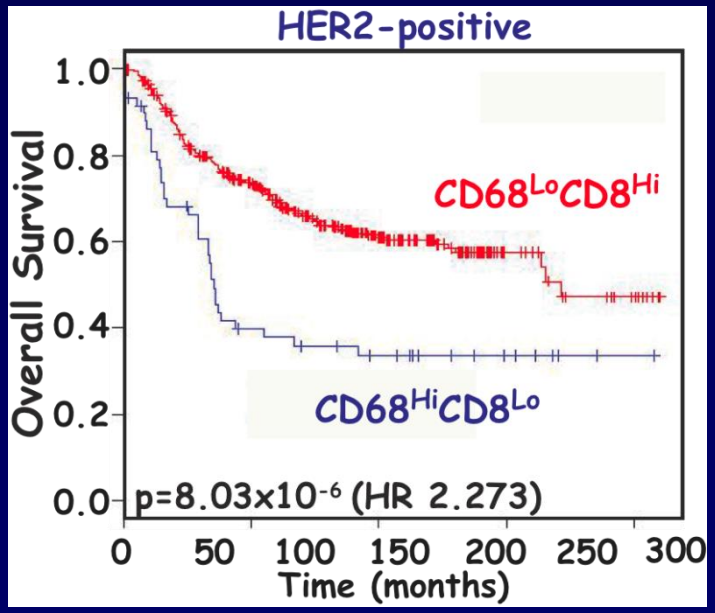


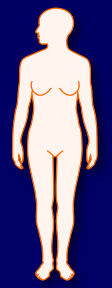
CD68/CD8 mRNA Ratio Correlates with OS



Gene expression from
22 data sets >4000 Patients







DeNardo et al., Cancer Discovery *(2011)*

US Patent #61/420,718

Phase 1b Study: all BC

PLX3397 oral daily dosing
Eribulin: 1.4 mg/m^2 iv, day 1 and 8
Each cycle of treatment lasts 21 days

First Cohort = 600 mg/day
3-6 patients

Second Cohort = 800 mg/day
3-6 patients

Third Cohort = 1000 mg/day
3-6 patients

Phase II Primary Endpoint: PFS at 12 weeks

Phase II Study: Metastatic TNBC

Lead in period of 5-7d with PLX3397 at MTD oral daily dosing (day -7/5 to day 0)

Biopsy for immune profiling

Starting Day 1
Add Eribulin 1.4 mg/m^2 iv day 1 and 8
Each cycle of treatment lasts 21 days

Komen Promise Grant: Coussens, Rugo, Hwang, Samson
Collaborators: Blackwell (Duke), Mayer (Vanderbilt)

PI: Hope Rugo M.D., UCSF

Clinical Trials!

Consensus Building: ABC1

- 30 International breast cancer experts 11.2011 organized by Fatima Cardoso
- Q2: From onset of diagnosis of MetaBC, patients should be offered personalised appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care
  - 100% vote yes
  - More next year!