The Georgia Society of Clinical Oncology's

SAN ANTONIO BREAST CANCER SYMPOSIUM REVIEW

Metastatic Disease Abstracts

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S1-4. Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg

Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Garnett S, Rukazenkov Y, Martin M. Hospital of Prato, Prato, Italy; Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium; First Faculty of Medicine of Charles University, Prague, Czech Republic; Instituto Nacional del Cáncer, Santiago, Chile; Dnipropetrovsk Municipal Clinical Hospital, Dnipropetrovsk, Ukraine; Republican Clinical Oncological Center, Kazan, Russian Federation; AZ Klina, Brasschaat, Belgium; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Medical Radiological Science Center, Obninsk, Russian Federation; Russian Cancer Research Centre, Moscow, Russian Federation; Kansas City Cancer Center, Kansas City; AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; Hospital Universitario Gregorio Maranon, Madrid, Spain.

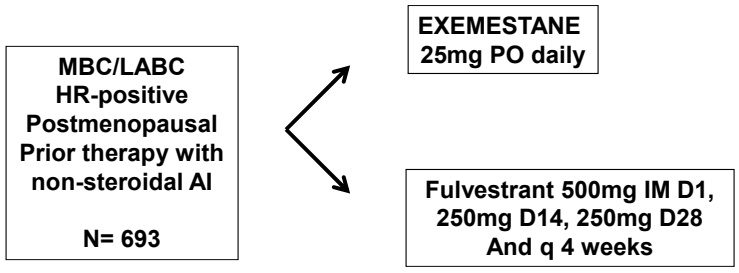
Second-line Fulvestrant vs Anastrozole

	Trial 0020*		Trial 0021**		Combined Analyses***	
	FUL	Anastrozole	FUL	Anastrozole	FUL	Anastrozole
	n=222	n=229	n=206	n=194	n=428	n=423
Median Time to Progression (TTP)	5.5 months	5.1 months	5.4 months	3.4 months	5.4 months	4.1 months
Clinical Benefit@	44.6%	45.0%	42.2%	36.1%	43.7%	41.1%
Median Duration of Response	14.3 months	14.0 months	19.3 months	10.5 months	16.7 months	13.6 months

Fulvestrant given 250 mg as once monthly injection

*Howell, A. et al. J Clin Oncol 2002
**Osborne, C.K. et al. J Clin Oncol 2002
***Howell, A. et al, Cancer 2005

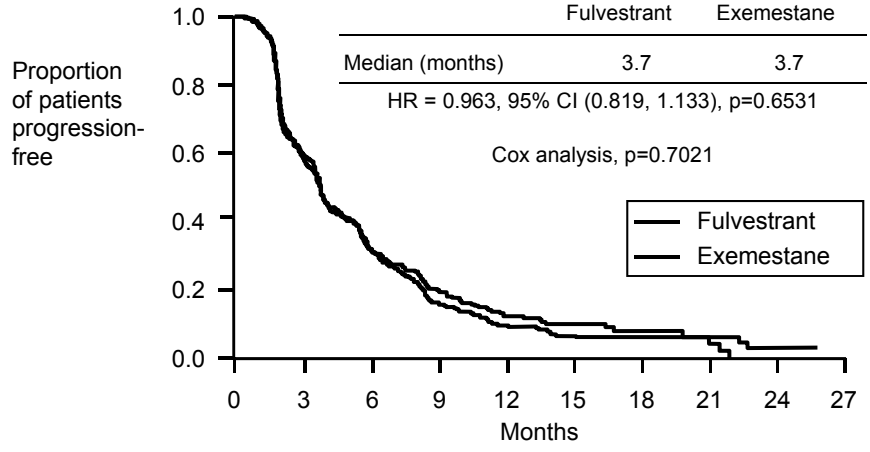
Evaluation of Fulvestrant and Exemestane Clinical Trial (EFECT)



Primary Endpoint: Time to progression

Chia, S. et al. J Clin Oncol 2007

Time to progression (ITT)



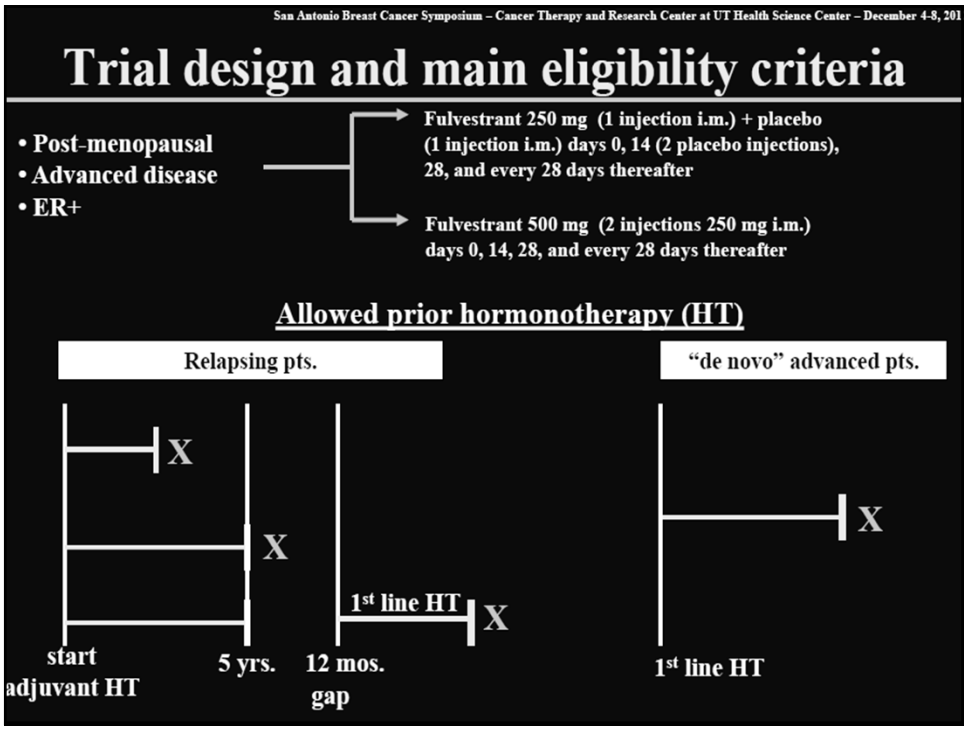
	Fulvestrant	Exemestane
Median (months)	3.7	3.7

HR = 0.963, 95% CI (0.819, 1.133), p=0.6531

Cox analysis, p=0.7021

At risk:										
Fulvestrant	351	195	96	50	25	12	4	2	0	0
Exemestane	342	190	98	41	21	12	8	6	1	0

Chia, S. et al. J Clin Oncol 2007



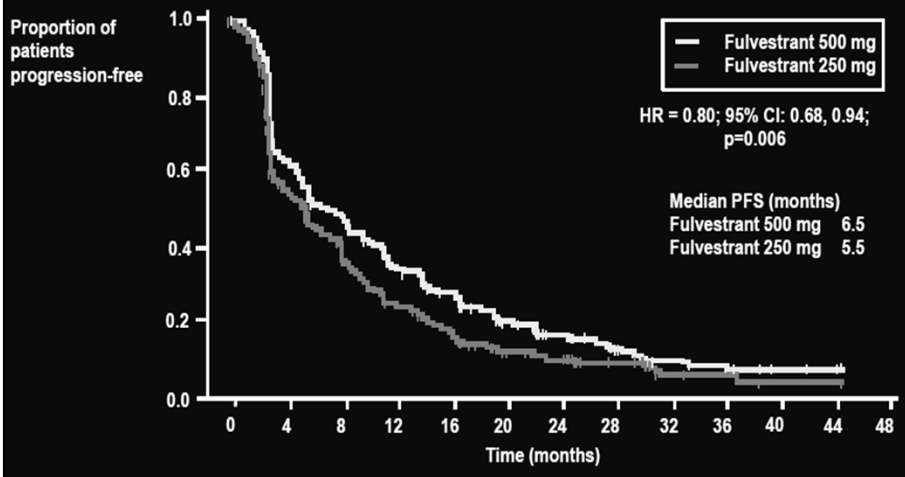
San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012

Main patient and tumor characteristics

	Fulvestrant 500 N=362	Fulvestrant 250 N=374
Age – median yrs.	61	61
% ER+	100	100
% PgR+/ - / unknown	67 / 25 / 8	71 / 26 / 3
% visceral involvement	57	53
% prior endocrine therapy		
- adjuvant setting	64	67
- advanced setting	48	49

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012

Primary endpoint: progression-free survival



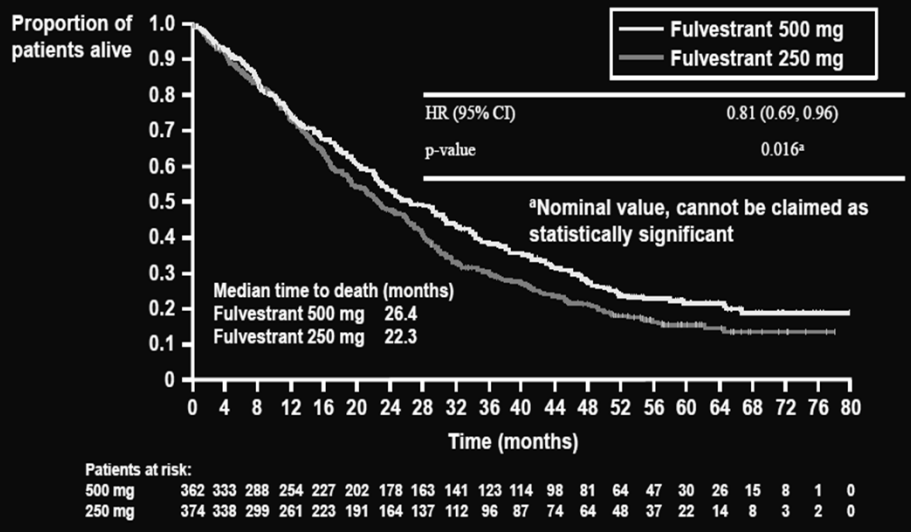
Patients at risk:

500 mg	362	216	163	113	90	54	37	19	12	7	3	2	0
250 mg	374	199	144	85	60	35	25	12	4	3	1	1	0

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Overall survival (final analysis at 75% maturity – full analysis set)



SAEs with outcome of death during the whole treatment period

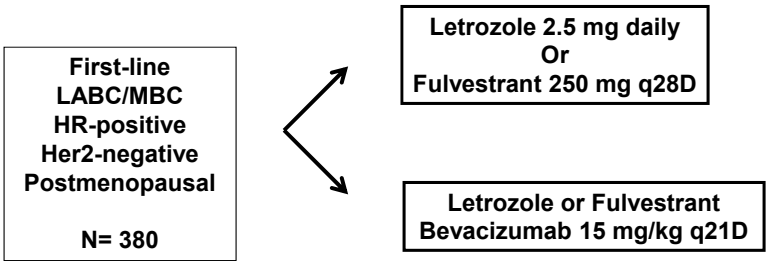
Preferred term	Number (%) of patients	
	Fulvestrant 500 mg N=361	Fulvestrant 250 mg N=374
Acute myocardial infarction	0	2 (0.5)
Acute renal failure	0	1 (0.3)
Aspiration	0	1 (0.3)
Cardiopulmonary failure	1 (0.3)	0
Suicide	0	1 (0.3)
Death (death cause unknown)	1 (0.3)	0
Dyspnea	2 (0.6)	0
Hypertension	0	1 (0.3)
Intestinal adenocarcinoma	1 (0.3)	0
Meningitis	0	1 (0.3)

All events occurring after first dose are summarized
Patient numbers are not mutually exclusive

S1-7. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer - First efficacy results from the LEA study

Martin M, Loibl S, von Minckwitz G, Morales S, Crespo C, Anton A, Guerrero A, Aktas B, Schoenegg W, Muñoz M, Garcia-Saenz JA, Gil M, Ramos M, Carrasco E, Liedtke C, Wachsmann G, Mehta K, De la Haba JR, On behalf of GEICAM (Spanish Breast Cancer Research Group), GBG (German Breast Group). Instituto de Investigacion Sanitaria Gregorio Marañon, Madrid, Spain; GBG (German Breast Group), Neu-Isenburg, Germany; University Women´s Hospital Essen, Germany; Medical Practice Berlin, Germany; University Women´s Hospital Muenster, Germany; Klinikum Boeblingen, Germany; H. Arnau Vilanova de Lerida, Spain; Hospital U. Ramon y Cajal, Spain; Hospital Universitario Miguel Servet, Spain; Instituto Valenciano de Oncologia, Spain; Hospital Clinic I Provincial, Spain; Hospital Clinico U. San Carlos, Spain; Instituto Catala d' Oncologia Hospitalet, Spain; GEICAM (Spanish Breast Cancer Research Group), Spain; Hospital U. Reina Sofia, Spain; Centro Oncologico de Galicia, Spain.

Study Design



Stratification
- Adjuvant AI
- Measurable disease
- Number of lesions
- Country (Spain/Germany)

Primary Endpoint: Progression-free Survival

90% received letrozole; 10% received fulvestrant

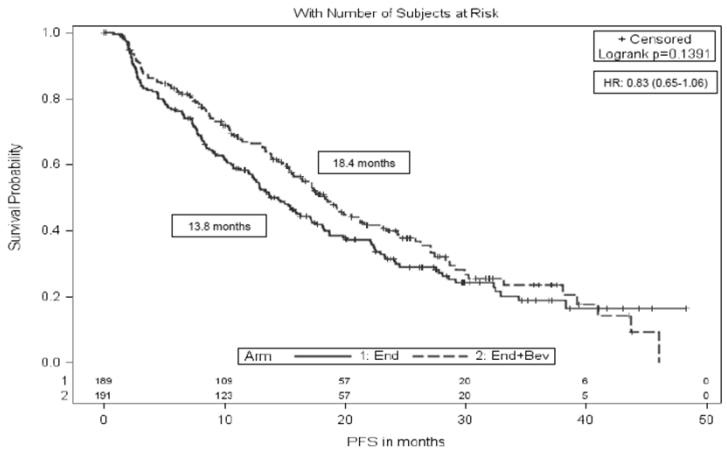
Baseline Characteristics

	ET n= 189	ET-B n= 191
Age in years,		
≤ 64	46%	52.8%
65-69	19%	17.8%
>70	34.9%	29.3%
Country		
Spain	71.4%	70.7%
Germany	28.6%	29.3%
ECOG PS		
0	71.4%	72.8%
1	28.6%	26.7%
Unknown	0	0.5%
Previous adjuvant chemotherapy		
Taxane, anthras or both	35.4%	34.5%
CMF	11.1%	9.4%
None	52.9%	55.5%
Previous adjuvant endocrine therapy		
Antiestrogens	31.2%	33.5%
Aromatase inhibitor	7.4%	4.2%
Both	12.7%	14.7%
None	48.7%	47.6%

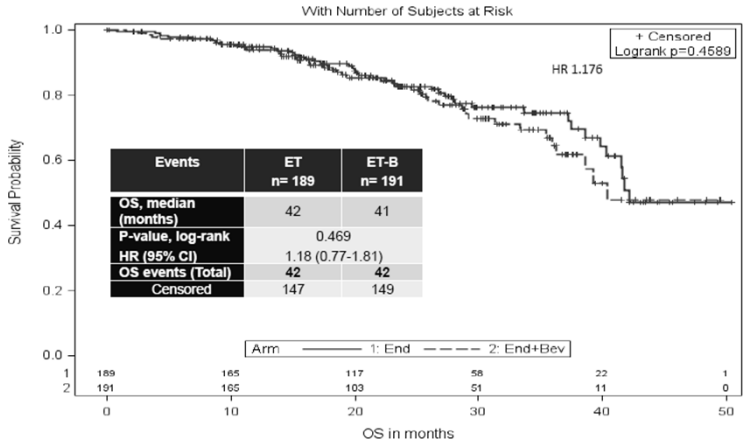
Baseline Characteristics

	ET n= 189	ET-B n= 191
Stage of disease at study entry		
Locally Advanced disease	3.2%	3.1%
Metastatic disease	82%	80.1%
Unknown	14.8%	16.8%
Number of metastatic sites		
Single	38%	42%
Multiple	62%	58%
Visceral disease		
Yes	48%	48%
No	52%	52%
Types of metastatic sites		
Lung	37%	32%
Liver	20%	21%
Bone	65%	65%
Other	61%	53%
Measurable disease		
Yes	79%	75%
No	21%	25%

Progression-Free Survival



Overall Survival



Events	ET n= 189	ET-B n= 191
OS, median (months)	42	41
P-value, log-rank	0.469	
HR (95% CI)	1.18 (0.77-1.81)	
OS events (Total)	42	42
Censored	147	149

Hematologic Toxicity

Toxicity NCI-CTCAE 3.0, (n %)	Grade	ET	ET-B	P-Value
Anemia	1-4	173 (98.9)	187 (100)	0.143
	3-4	1 (0.6)	2 (1.1)	N.S.
Neutropenia	1-4	10 (5.7)	21 (11.2)	0.061
	3-4	0	1 (0.5)	N.S.
Leucopenia	1-4	20 (11.4)	46 (24.6)	0.001
	3-4	0	4 (2.1)	N.S.
Thrombocytopenia	1-4	16 (9.1)	36 (19.3)	0.006
	3-4	4 (2.3)	3 (1.6)	N.S.

Non-hematologic Toxicity

Fatigue	1-4	51 (29.0)	95 (50.5)	<0.001
	3-4	1 (0.6)	4 (2.1)	0.373
Hypertension	1-4	28 (15.9)	111 (59.0)	<0.001
	3-4	0	6 (3.2)	0.030
Hemorrhage	1-4	3 (1.7)	35 (18.6)	<0.001
	3-4	0	0	N.A.
Liver enzyme elevation (ASAT)	1-4	49 (28.0)	87 (46.5)	<0.001
	3-4	0	3 (1.6)	0.249
Proteinuria	1-4	5 (2.8)	57 (30.3)	<0.001
	3-4	0	2 (1.1)	0.499
Thromboembolic events	1-4	1(0.6)	4(2.1)	0.373
	3-4	0 (0.0)	4 (2.1)	0.124

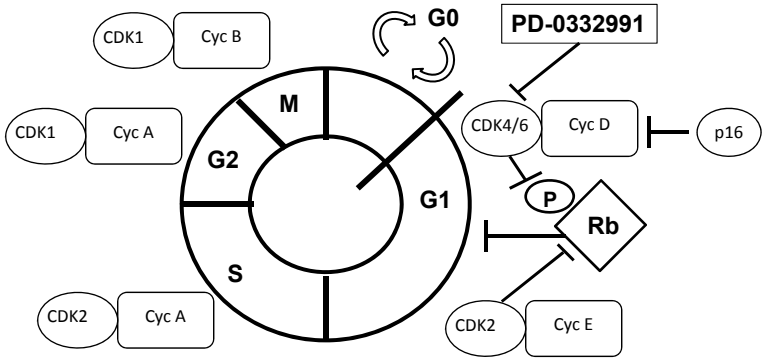
S1-6. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (cdk) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC)

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Breazna A, Kim ST, Randolph S, Slamon DJ. University of California, Los Angeles, CA; Irish Cooperative Oncology Research Group, Dublin, Ireland; Orszagos Onkologiai Intezet, Budapest, Hungary; Szent Margit Korhaz, Budapest, Hungary; Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Ukraine; Municipal Treatment-and-Prophylactic Institution "Donetsk City Oncological Dispensary", Ukraine; Technical University of Munich, Germany; Comprehensive Blood and Cancer Center, Bakersfield, CA; Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; University Hospital Mainz, Germany; Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; Comprehensive Cancer Centers of Nevada, Henderson, NV; Kyiv City Clinical Oncology Center, Ukraine; Pfizer Oncology, New York, NY; Pfizer Oncology, San Diego, CA.

Background

- Cyclin-dependent kinases (CDKs) play a key role in regulating cell cycle progression by interacting with specific cyclin proteins
- PD 0332991 is an oral, highly selective inhibitor of CDK 4/6 kinase activity blocking G1-S transition
- Targeting of CDK 4/6 requires intact Rb function
- Preclinical studies of ER-positive, luminal cell-lines showed that elevated cyclin D1 and Rb levels, lower p16 levels, were associated with increased sensitivity to PD 0332991
- Phase 1 portion of trial (N=12) recommended phase 2 dose of PD 0332991 125 mg po daily, 3 weeks on 1 week off in combination with letrozole 2.5 mg po daily

Mechanism of Action



Rentinoblastoma (Rb) protein

- Hyperphosphorylation of Rb is mediated by CDK4/6, leads to Rb inactivation
- Rb inactivation is required for progression in cell cycle
- Checkpoint aberrations associated with overexpression of cyclin D1, dysregulation of CDKs, loss of p16

Phase 2 Trial Design

Part 1

ER-positive Her2-negative MBC

N=66

PD 0332991 Letrozole

Letrozole

Part 2

ER-positive Her2-negative MBC with CCDN1 amp and/or loss of p16

N=99

PD 0332991 Letrozole

Letrozole

Primary Endpoint: PFS

Stratification

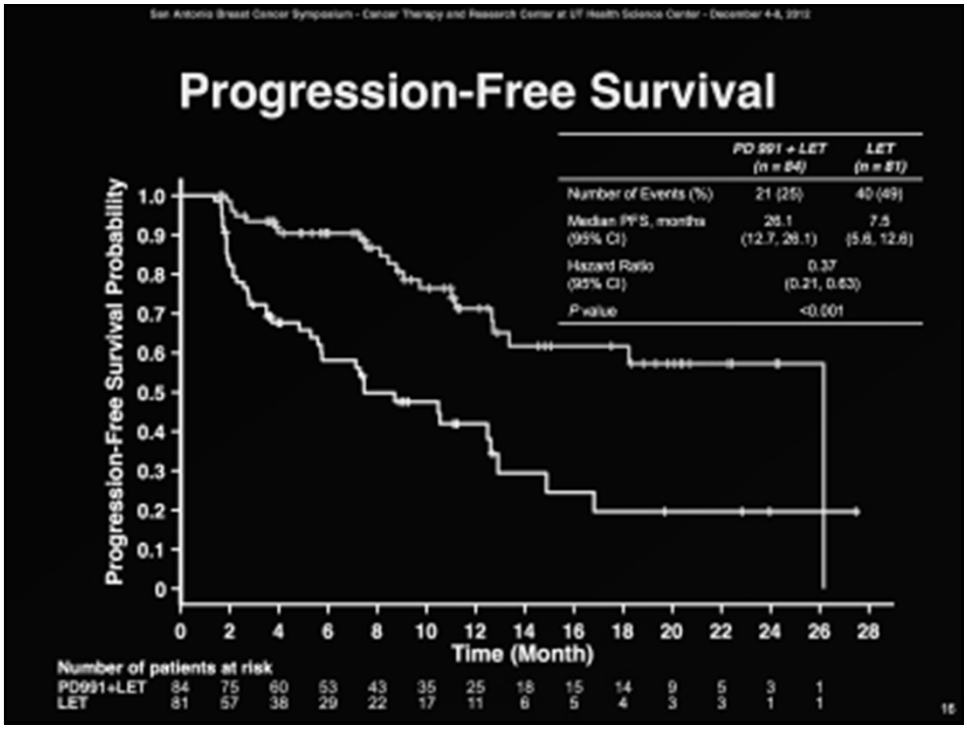
- Disease site (visceral vs bone-only vs other)
- Disease-free interval (> 12 mths vs ≤ 12 mths from adjuvant to recurrence or de novo advanced disease

Baseline Characteristics

Characteristic	PD + Letrozole N=84	Letrozole N=81
Median Age (range)	62 (41-89)	64 (38-84)
ECOG PS		
0	46 (55%)	45 (56%)
1	38 (45%)	36 (44%)
Disease Stage		
IIIB	3 (4%)	6 (7%)
IV	80 (95%)	75 (93%)
Other	1 (1%)	0 (0%)
Disease Site		
Visceral	37 (44%)	43 (53%)
Bone-only	18 (21%)	12 (13%)
Other	29 (34%)	26 (32%)
Disease-Free Interval		
> 12 months from adjuvant to recurrence	24 (29%)	30 (37%)
≤ 12 months or de novo	60 (71%)	51 (63%)
Prior Systemic Therapy		
None	44 (52%)	37 (46%)
Chemotherapy	34 (40%)	37 (46%)
Hormonal Therapy	26 (31%)	28 (35%)
Tamoxifen	23 (27%)	24 (30%)
Aromatase Inhibitor	14 (17%)	14 (17%)

Best Overall Response (ITT)

	PD + Letrozole N=84	Letrozole N=81
Objective Response Rate (95% CI)	34 (24, 46)	26 (17, 37)
Complete Response	0	1 (1)
Partial Response	29 (34%)	20 (25%)
Stable disease ≥ 24 weeks	30 (36%)	15 (18%)
Clinical Benefit Rate	59 (70%)	36 (44%)
Stable Disease < 24 weeks	14 (17%)	22 (27%)
Progressive Disease	3 (4%)	17 (21%)
Indeterminate	8 (10%)	6 (7%)



Most Common AEs

Adverse Event (n)	PD 0332991 Letrozole (n=83)			Letrozole (n=77)		
Grade	**1/2**	**3**	**4**	**1/2**	**3**	**4**
Neutropenia	19	46	5	3	1	0
Fatigue	29	2	2	21	1	0
Anemia	20	4	1	3	1	0
Nausea	19	2	0	10	1	0
Hot flashes	19	0	0	12	0	0
Alopecia	18	0	0	3	0	0
Arthralgias	18	0	0	14	1	0
Thrombocytopenia	11	1	0	0	0	0
Stomatitis	10	0	0	1	0	0

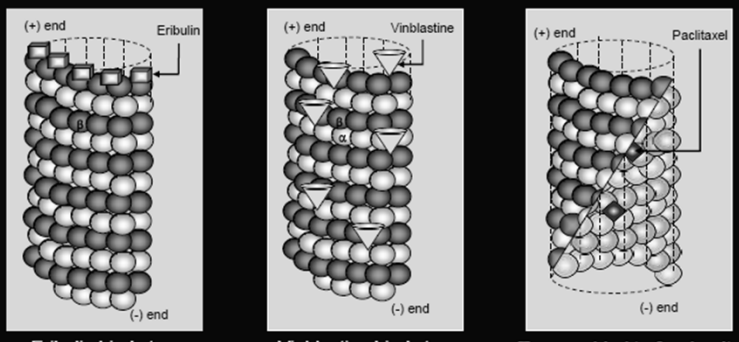
S6-6. A Phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes

Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Wanders J, Olivo MS, He Y, Dutcus CE, Cortes. Norris Cotton Cancer Center, Dartmouth- Hitchcock Medical Center, Lebanon, NH; Jules Bordet Institute, Brussels, Belgium; Leeds Institute of Molecular Medicine and St James's Institute of Oncology, Leeds, United Kingdom; University of Montreal, Montreal, Canada; Mayo Medical Clinic, Jacksonville, FL; Eisai Ltd., Hatfield, United Kingdom; Eisai Inc., Woodcliff Lake, NJ; Vall D'Hebron University Hospital, Barcelona, Spain.

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012

Eribulin Has A Novel Mechanism Of Action Distinct From Most Other Tubulin-Targeted Agents

- Eribulin is a structurally simplified, synthetic analog of halichondrin B, a marine sponge natural product, and a non-taxane microtubule dynamics inhibitor



Eribulin binds to (+) ends

Vinblastine binds to (+) ends and along sides

Taxanes bind to β subunits at inside surface

α subunits are light blue; β subunits are dark blue

Jordan et al. Mol Cancer Ther 2005;4:1086-95; Kuznetsov et al. Cancer Res 2004;64:5760-6; Smith et al. Biochemistry 2010;49:1331-7; Towle et al. Cancer Res 2001;61:1013-21

EMBRACE study design

- Global, randomized, open-label Phase III trial (Study 305)

Patients (N=762)
- Locally recurrent or MBC
- 2-5 prior chemotherapies
  - ≥2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤6 months of last chemotherapy
- Neuropathy ≤grade 2
- ECOG ≤2

Eribulin mesylate
1.4 mg/m², 2-5 min IV
Day 1, 8 q21 days

Randomization 2:1

Treatment of Physician's Choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological)* or supportive care only†

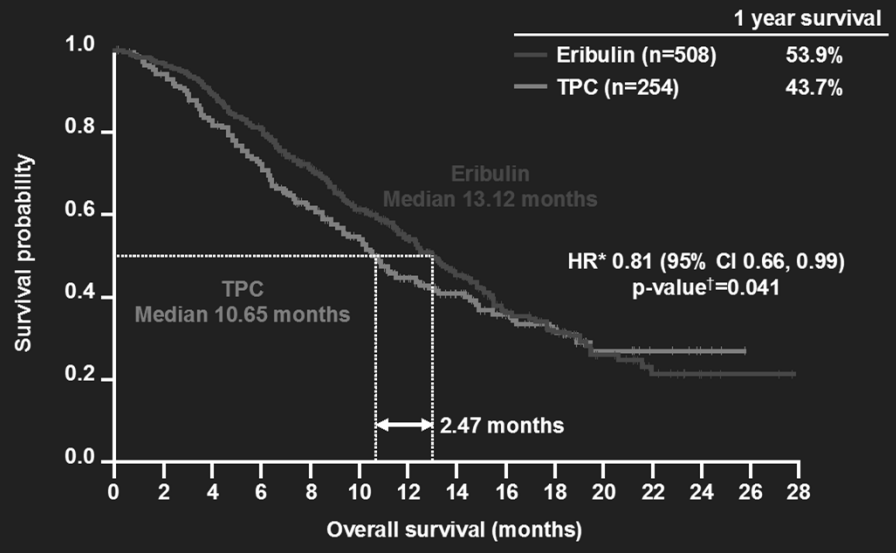
Primary endpoint
- Overall survival

Secondary endpoints
- PFS
- ORR
- Safety

- Stratification:
  - Geographical region, prior capecitabine, HER2/*neu* status

* Approved for treatment of cancer
†Or palliative treatment or radiotherapy administered according to local practice, if applicable
ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PFS, progression-free survival; HER2/*neu*, human epidermal growth factor receptor 2

Overall survival



ITT population; *HR Cox model including geographic region, HER2/*neu* status, and prior capecitabine therapy as strata
†p value from stratified log-rank test (pre-defined primary analysis); HR, hazard ratio; CI, confidence intervals

Study Design

- Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)

Locally advanced or MBC

- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m²† 2- to 5-min IV
Day 1 & 8 q21 days

Randomization 1:1

Capecitabine
1250 mg/m² BID orally
Days 1-14, q21 days

Co-primary endpoint

- OS and PFS

Secondary endpoints

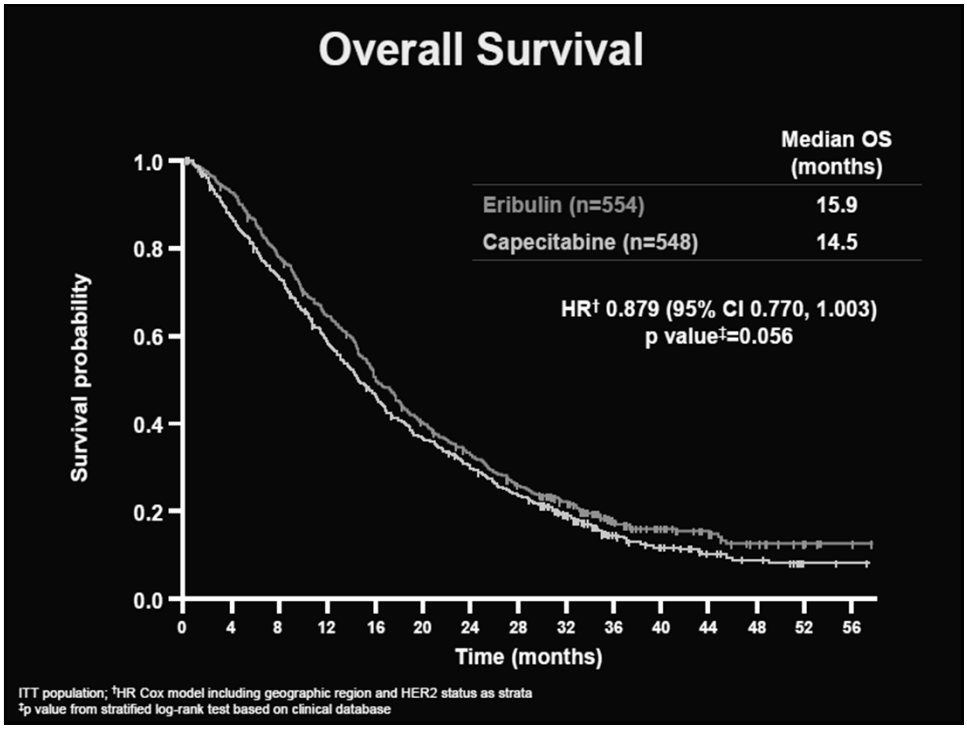
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

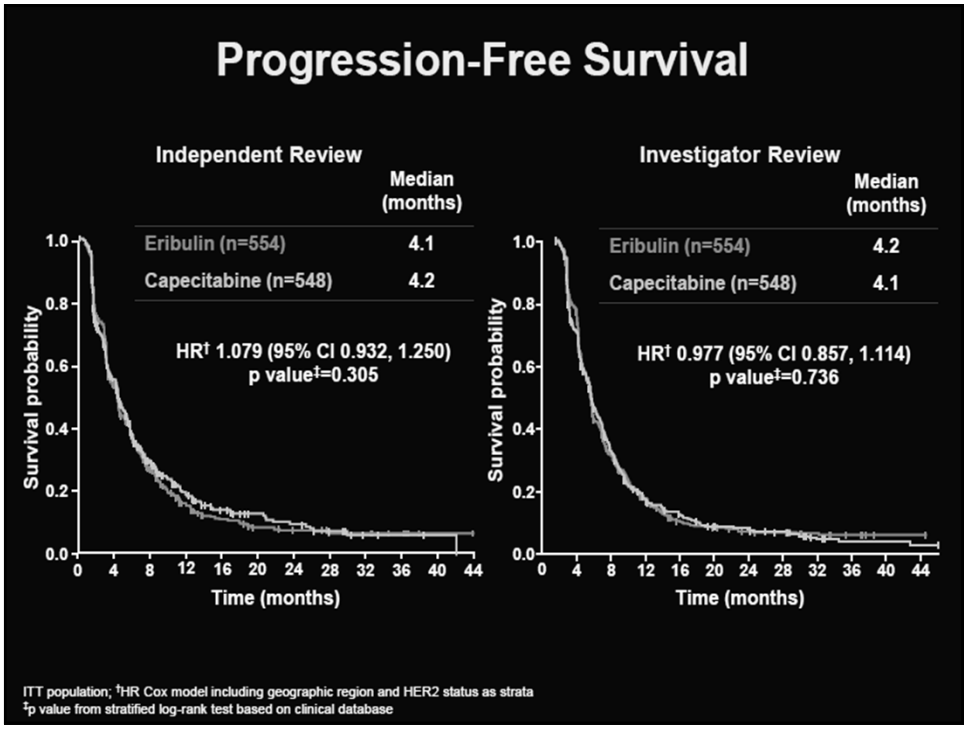
- Stratification:
  - Geographical region, HER2 status

Patient and Disease Characteristics

		Eribulin (n=554)	Capecitabine (n=548)
Median age (range)		54.0 (24-80)	53.0 (26-80)
ECOG performance, %	0	45	42
	1	53	55
	2+	2	3
Number of prior chemotherapy regimens for advanced disease, %	0	21	19
	1	50	53
	2	28	27
	>2	1	1
Sites of disease†, %	Visceral	84	88
	Non-visceral only	15	11
HER2 status‡, %	Positive	16	15
	Negative	68	69
ER status‡, %	Positive	47	51
	Negative	42	39
PR status‡, %	Positive	41	43
	Negative	47	45
Triple (ER/PR/HER2) negative, %		27	25

ITT population
†Determined by independent assessment; missing patients for sites of disease were 1% for eribulin and 1% for capecitabine
‡Assays carried out and defined locally
Unknown patients for eribulin and capecitabine were: HER2 status 17% and 16% ; ER status 11% and 10%; PR status 12% and 12%, respectively


Overall Survival
Median OS (months)
Eribulin (n=554) 15.9
Capecitabine (n=548) 14.5
HR† 0.879 (95% CI 0.770, 1.003)
p value‡=0.056
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56
Time (months)
ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database


Progression-Free Survival
Independent Review
Median (months)
Eribulin (n=554) 4.1
Capecitabine (n=548) 4.2
HR† 1.079 (95% CI 0.932, 1.250)
p value‡=0.305
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0 4 8 12 16 20 24 28 32 36 40 44
Time (months)
Investigator Review
Median (months)
Eribulin (n=554) 4.2
Capecitabine (n=548) 4.1
HR† 0.977 (95% CI 0.857, 1.114)
p value‡=0.736
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0 4 8 12 16 20 24 28 32 36 40 44
Time (months)
ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

Response Rates

	Independent Review		Investigator Review	
	Eribulin (n=554)	Capecitabine (n=548)	Eribulin (n=554)	Capecitabine (n=548)
Objective response rate (CR+PR), %	11	12	16	20
p value	0.849		0.100	
SD, %	57	55	60	51
PD, %	23	24	18	23
NE, %	2	1	6	6
Unknown, %	8	8	0	0
Unconfirmed CR/PR	-	-	4	3
Clinical benefit rate (CR + PR + SD ≥6 months),%	26	27	33	34

ITT population
Independent review,: eribulin arm 1 CR; Investigator review: eribulin arm 4 CR, capecitabine arm 10 CR
Unconfirmed PR/CR: confirmed per RECIST but bone scan missing at confirmation visit as required by protocol amendment

Hematologic Adverse Events†

	Eribulin (n=544)			Capecitabine (n=546)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Neutropenia	54	25	21	16	4	<1
Leukopenia	31	13	2	10	2	<1
Anemia	19	2	0	18	<1	<1
Thrombocytopenia	5	<1	0	6	<1	<1
Febrile neutropenia	2	2	<1	<1	<1	<1

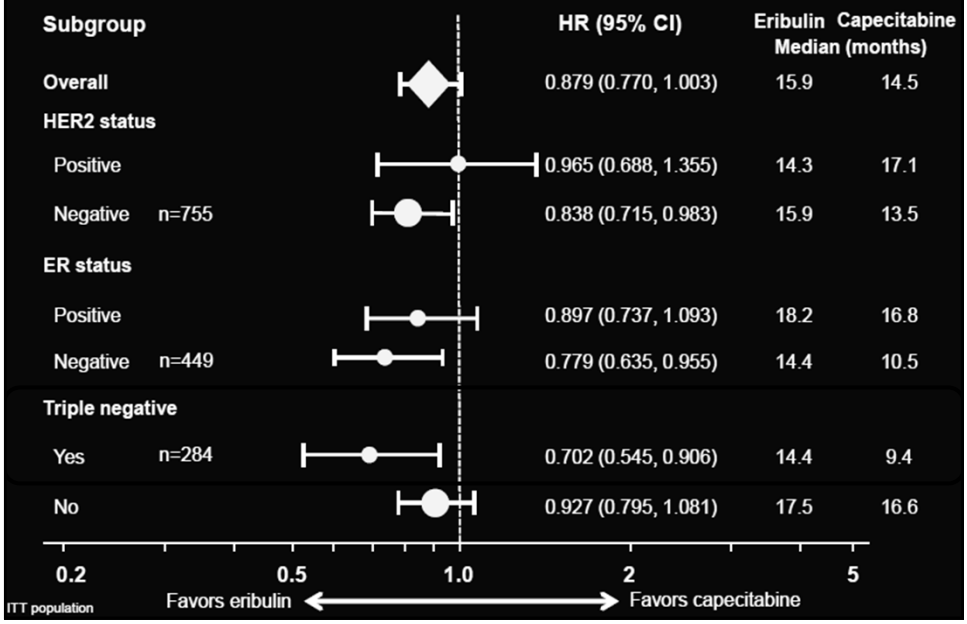
Safety population
†Incidence >10% (all grades) or 1% (Grade 3 or higher) in either arm
If a subject had two or more AEs in the same system organ class or with the same preferred term with different CTCAE grades, then the event with the highest grade was used for that subject

Non-Hematologic Adverse Events†

	Eribulin (n=544)			Capecitabine (n=546)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hand-foot syndrome	<1	0	0	45	14	0
Alopecia	35	-	-	4	-	-
Diarrhea	14	1	0	29	5	<1
Nausea	22	<1	0	24	2	0
Vomiting	12	<1	<1	17	2	0
Fatigue	17	2	0	15	2	<1
Asthenia	15	4	<1	15	4	0
Decreased appetite	13	<1	0	15	2	0
Peripheral sensory neuropathy	13	4	0	7	<1	0
Pyrexia	13	<1	0	6	<1	0
Headache	13	<1	0	10	<1	<1
Dyspnea	10	2	<1‡	11	3	<1‡
Back pain	10	2	0	8	<1	0

Safety population
†Incidence >10% (all grades) or 1% (Grade 3 or higher) in either arm; ‡Grade 5 events also occurred in 0.7% and 0.5% of patients, respectively
If a subject had two or more AEs in the same system organ class or with the same preferred term with different CTCAE grades, then the event with the highest grade was used for that subject

Overall Survival By Receptor Status

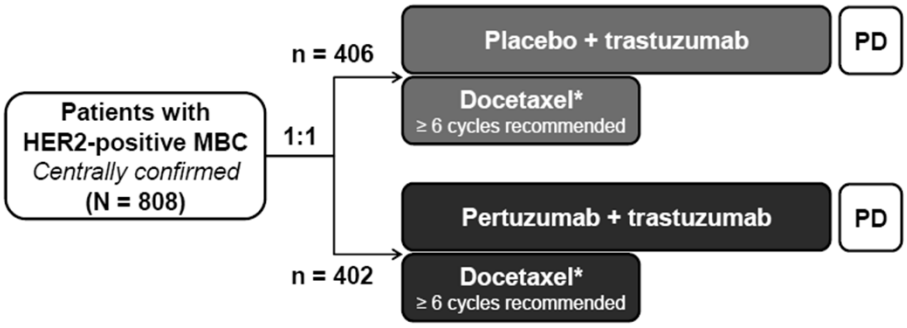


ITT population

S5-1. Biomarker analyses in CLEOPATRA: A phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC)

Baselga J, Cortés J, Im S-A, Clark E, Kiermaier A, Ross G, Swain SM. Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; Vall d'Hebron University Hospital, Barcelona, Spain; Seoul National University College of Medicine, Seoul, Korea; Roche Products Limited, Welwyn, United Kingdom; F. Hoffmann-La Roche Limited, Basel, Switzerland; MedStar Washington Hospital Center, Washington, DC.

CLEOPATRA: Study design[1,2]

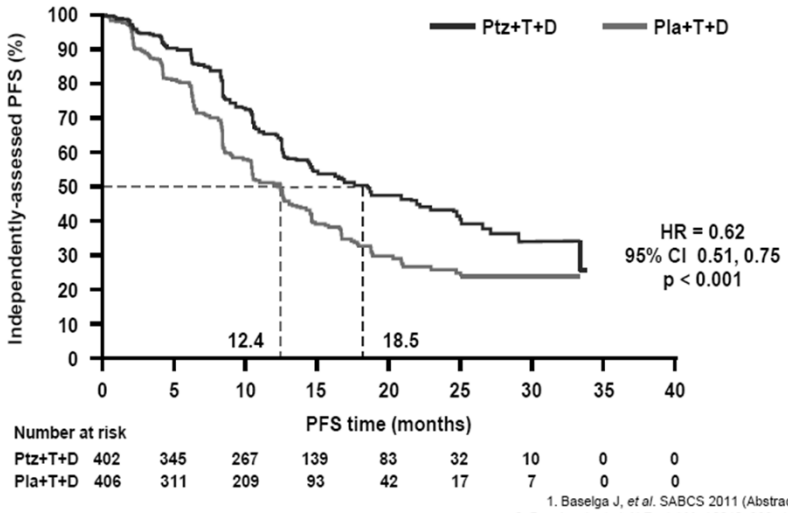


- Primary endpoint: Independently-assessed progression-free survival (PFS)
- Collection of tumor tissue (archival in >90%) and serum samples was mandatory
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion
HER2, human epidermal growth factor receptor 2; PD, progressive disease

1. Baselga J, *et al*. SABCS 2011 (Abstract S5-5);
2. Baselga J, *et al*. *N Engl J Med* 2012; 366: 109–119.

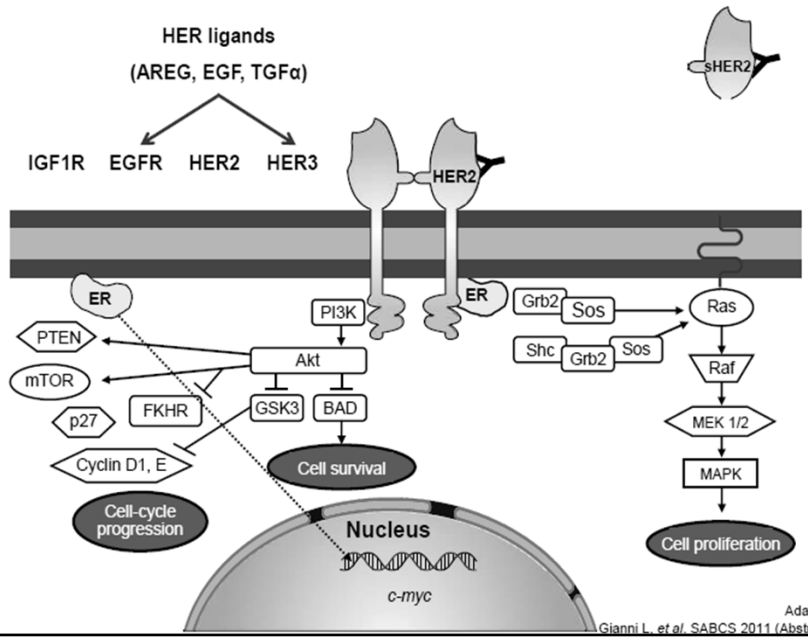
CLEOPATRA: Significant improvement in median PFS[1,2] (and OS)[3] with pertuzumab



D, docetaxel; Ptz, pertuzumab; T, trastuzumab

1. Baselga J, *et al*. SABCS 2011 (Abstract S5-5);
2. Baselga J, *et al*. *N Engl J Med* 2012; 366: 109–119;
3. Swain S, *et al*. SABCS 2012 (Poster P5-18-26).

The HER2 signalling pathway



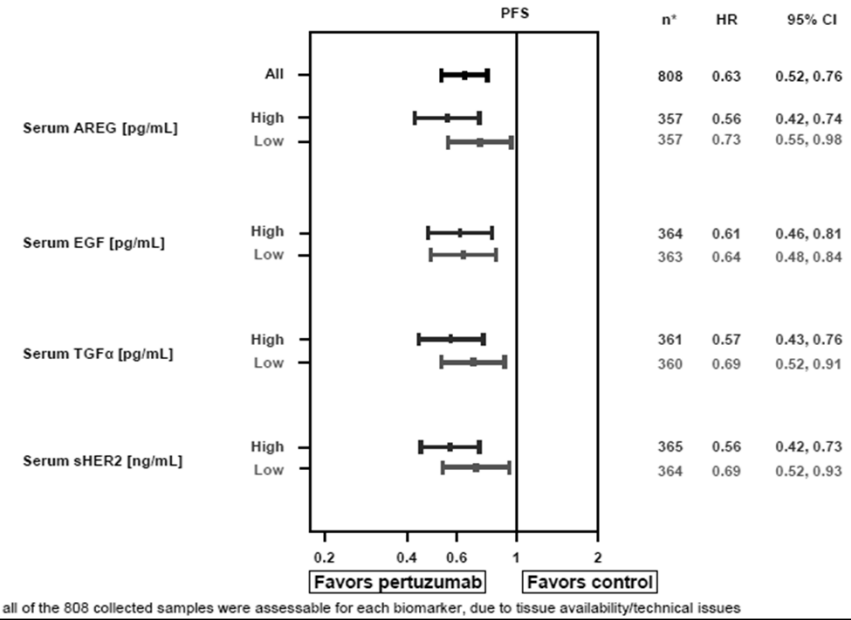
Adapted from:
Gianni L, *et al*. SABCS 2011 (Abstract S5-1).

Assay methods

Assay method	Marker	Successful analyses, n
IHC (by modified H-score)	HER2	806
	HER3	497
	IGF1R	486
	PTEN	497
	pAKT	465
qRT-PCR (by CR)	*EGFR*	720
	HER2	748
	HER3	740
	AREG	673
	Betacellulin	583
FISH	*c-myc*	591
Mutational analyses	*PIK3CA* (8 mutations, 4 hotspots)	684
ELISA (serum analyses)	sHER2	723
	AREG	714
	EGF	727
	TGFα	721

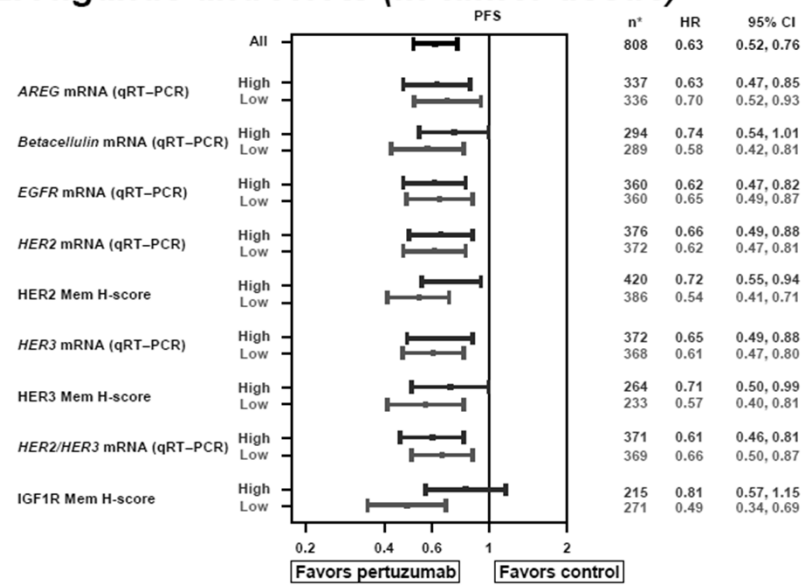
CR, concentration ratio

Predictive analysis of pertuzumab PFS benefit *Serum markers*



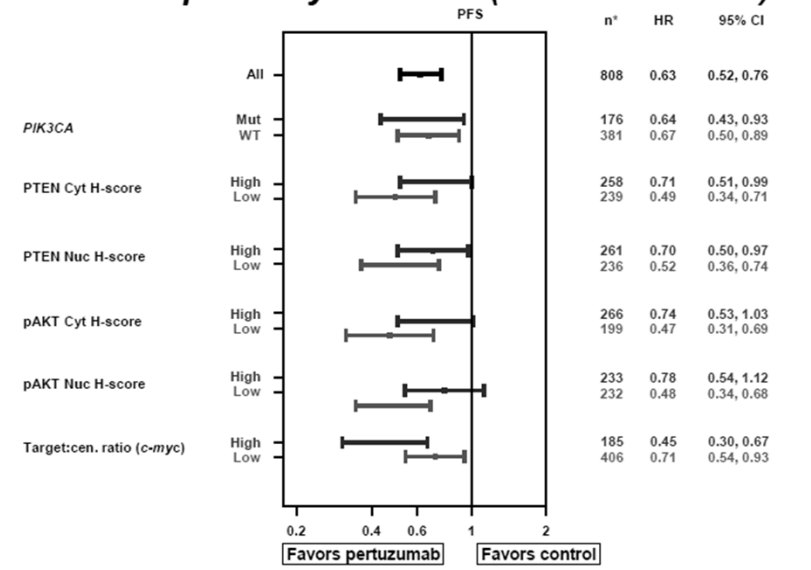
* Not all of the 808 collected samples were assessable for each biomarker, due to tissue availability/technical issues

Predictive analysis of pertuzumab PFS benefit *HER ligands and RTKs (in tumor tissue)*



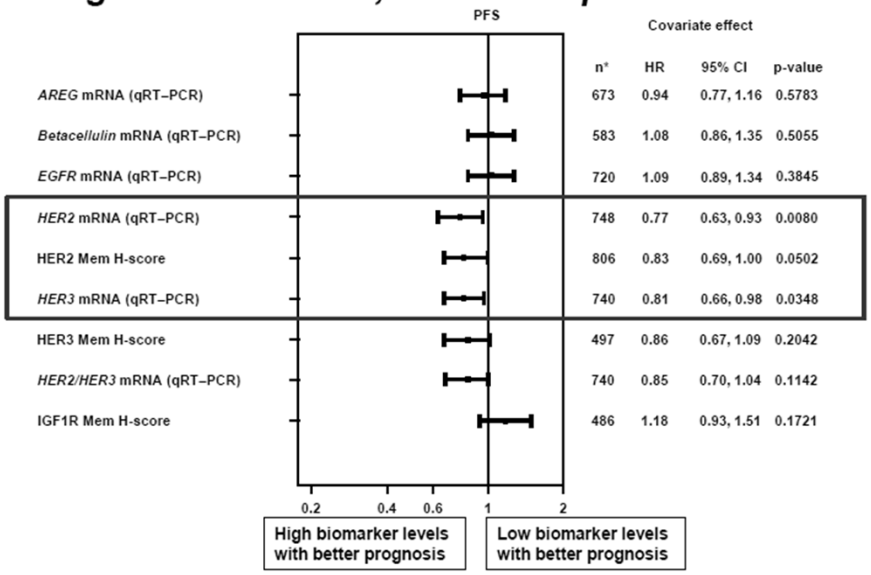
* Not all of the 808 collected samples were assessable for each biomarker, due to tissue availability/technical issues
Mem, membrane; RTK, receptor tyrosine kinase

Predictive analysis of pertuzumab PFS benefit *Intracellular pathway markers (in tumor tissue)*



* Not all of the 808 collected samples were assessable for each biomarker, due to tissue availability/technical issues
Cyt, cytoplasmic; Mut, mutated; Nuc, nuclear; WT, wild-type

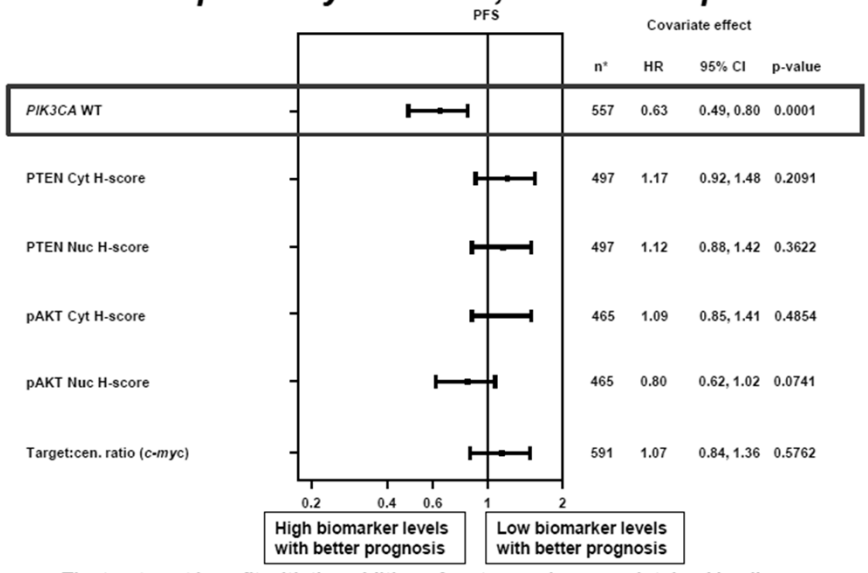
Prognostic effects independent of treatment arm
HER ligands and RTKs, both arms pooled



The treatment benefit with the addition of pertuzumab was maintained in all cases
HR < 1.00 in all cases (p = 0.0004 – < 0.0001)*

* Slide 10

Prognostic effects independent of treatment arm
Intracellular pathway markers, both arms pooled

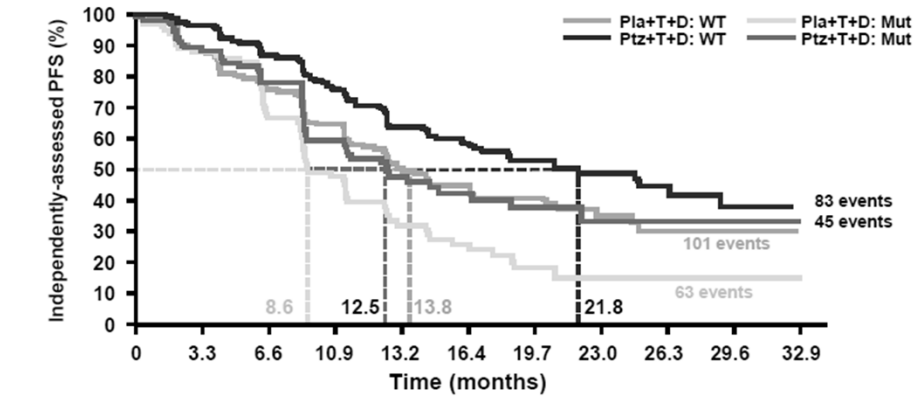


The treatment benefit with the addition of pertuzumab was maintained in all cases
HR < 1.00 in all cases (p = 0.0003 – < 0.0001)*

* Slide 11

San Antonio Breast Cancer Symposium – Henry B. Gonzalez Convention Center – December 4–8, 2012

PIK3CA mutation associated with poorer prognosis *Both arms*



Number at risk

Pla+T+D WT	191	164	136	114	66	46	23	17	9	3	1
Pla+T+D Mut	90	76	56	37	21	17	8	4	3	2	1
Ptz+T+D WT	190	179	159	137	90	71	46	26	16	5	3
Ptz+T+D Mut	86	71	61	44	29	25	12	6	2	1	1

Mut, mutated; WT, wild-type

Conclusions

- Fulvestrant 500 mg is better than 250 mg
- Bevacizumab did not lead to significant increase in PFS when added to first-line AI
- Await results from phase 3 trial of novel CDK inhibitor, PD 0332991
- Eribulin was well-tolerated with no difference in efficacy to capecitabine in anthracycline/taxane-pretreated patients
  - Triple negative subset may benefit from eribulin
- After exploring a broad panel of potential biomarkers, HER2 remains the only biomarker for selecting HER2-targeted therapy