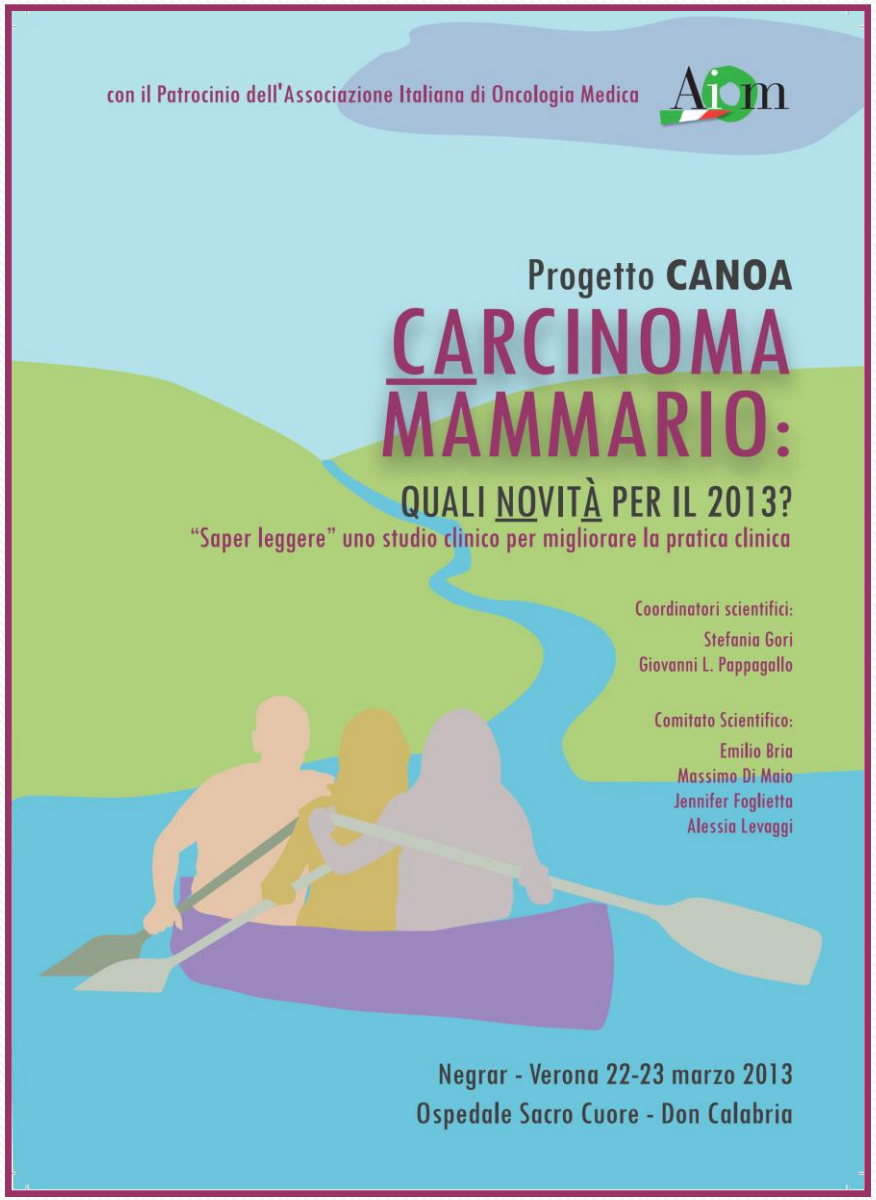


CLEOPATRA study in the 1st-line metastatic breast cancer patients

Ilaria Marech, MD

Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine and Clinical Oncology

University of Bari Medical School
Bari, Italy

Director: Angelo Vacca, MD, PhD

Milestones in the development of treatment of HER2-positive metastatic breast cancer

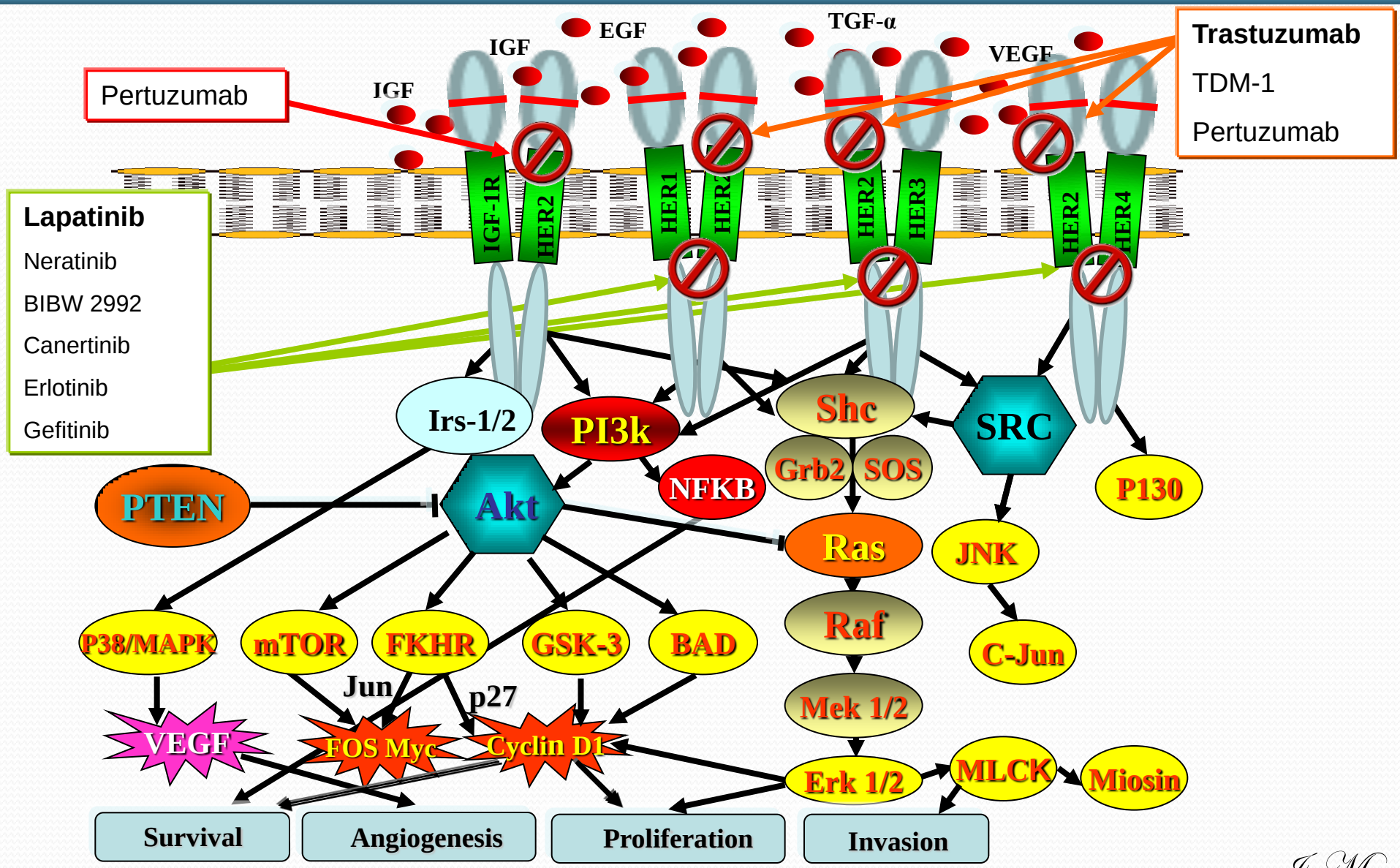
research → progress

- 1996: Trastuzumab first trial
- 2001: Trastuzumab pivotal trial
- 2006: Lapatinib Capecitabine
- 2009: Trastuzumab beyond progression; anti-HER2 plus endocrine therapy
- 2011: CLEOPATRA
- 2012: EMILIA

Try to identify markers of resistance, sensitivity and to elaborate strategy to improve the efficacy of HER2 targeting in the clinic of newer molecules/approaches

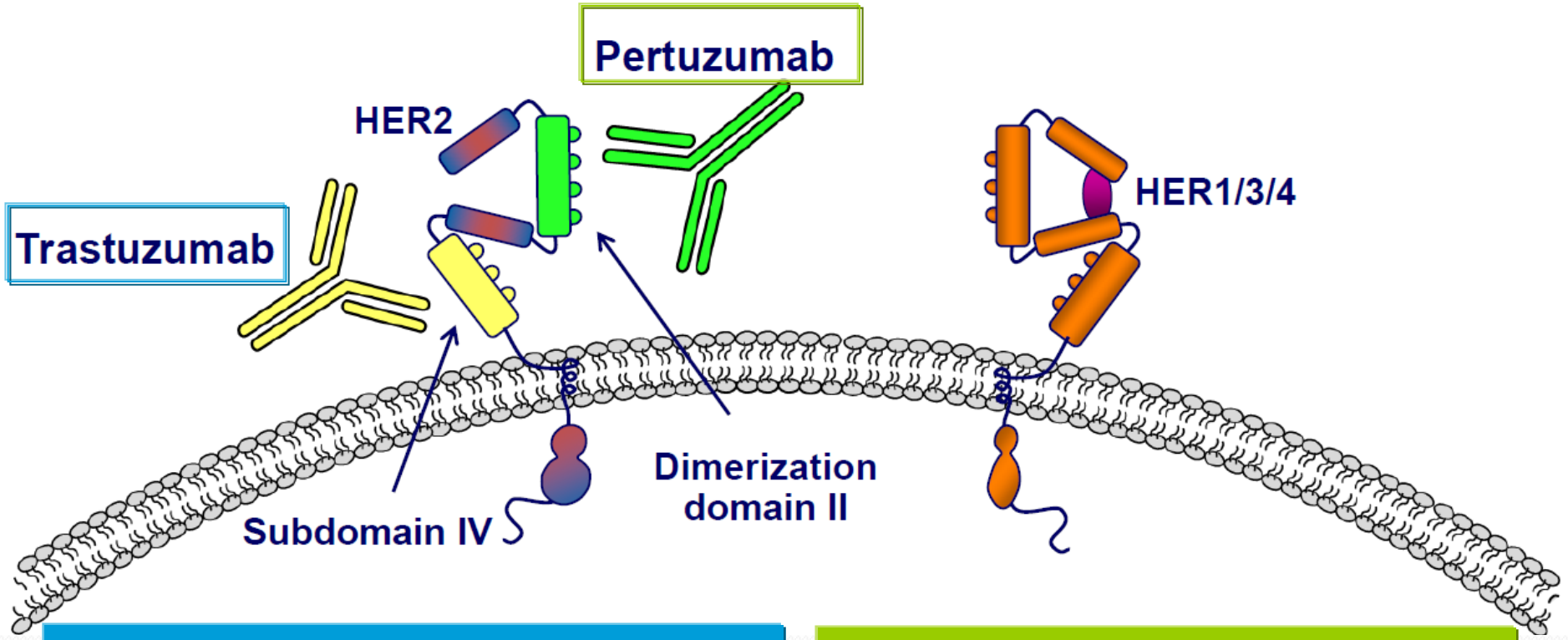
I M

Overcoming resistance to HER2 inhibitors



Adapted from Marech et al. J Cancer Ther 2012

Pertuzumab and trastuzumab: complementary mechanism of action



Trastuzumab

- inhibits ligand-independent HER2 signaling
- activates ADCC*

Pertuzumab

- inhibits ligand-dependent HER2 dimerization and signaling
- activates ADCC*

Adapted from Baselga et al. N Engl J Med 2012

*ADCC, Ab-Dependent Cell-Mediated Cytotoxicity

Multiple HER2 targeting in trastuzumab resistant patients

Phase II Trial

HER2-positive MBC* progressed on trastuzumab + chemotherapy

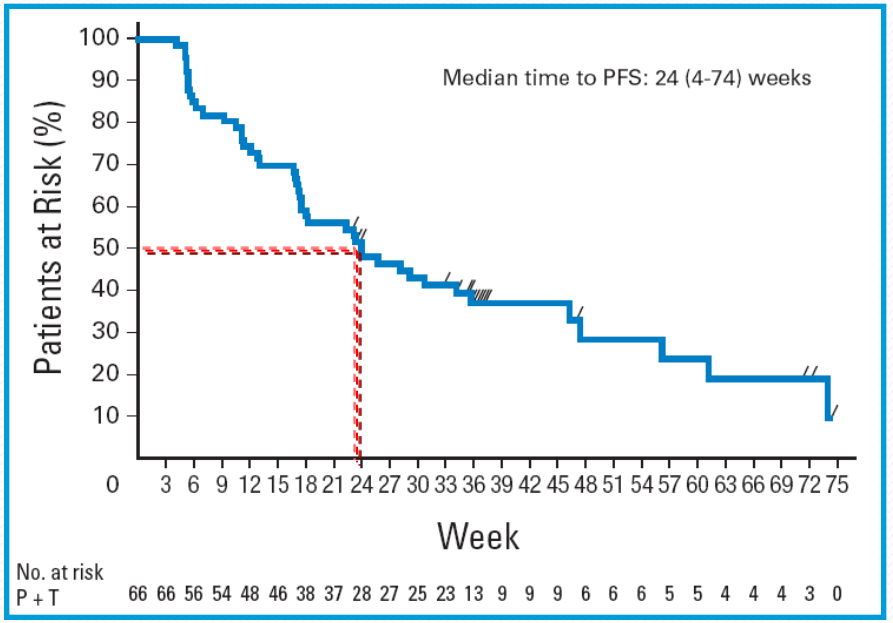
(n=66)

→ **Pertuzumab + Trastuzumab**

Best Overall Response	No. of Patients	%	80% CI (%)*
Complete response	5	7.6	3.7 to 13.6%
Partial response	11	16.7	10.9 to 24.1
Stable disease ≥ 6 months	17	25.8	18.8 to 33.9
Progressive disease	33	50	41.5 to 58.5
At cycle 2	11	16.7	
At cycles 4-6 (without prior response)	15	22.7	

*As a result of the limited sample size, a one-sided significance level of $P = .1$ was specified in the protocol to provide an estimation of the activity of the treatment combination, particularly with a focus on the lower bound for this activity. Therefore, two-sided 80% CIs are presented.

* MBC, Metastatic Breast Cancer



Baselga et al. J Clin Oncol 2010

CLEOPATRA study

The NEW ENGLAND JOURNAL of MEDICINE

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Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

Baselga et al. N Engl J Med 2012

CLEOPATRA study

A Phase III, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

J Baselga,[1] S-B Kim,[2] S-A Im,[3] R Hegg,[4] Y-H Im,[5] L Roman,[6] J L Pedrini,[7] J Cortés,[8] A Knott,[9] E Clark,[9] G Ross[9] and S M Swain[10]

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CLEOPATRA study: design

Patients with locally recurrent, unresectable, or MBC* HER2-positive (*centrally confirmed*) (N = 808)

1:1

n=406

- **Placebo + trastuzumab** → PD***
- **Docetaxel**** ≥ 6 cycles recommended

n=402

- **Pertuzumab + trastuzumab** → PD***
- **Docetaxel**** ≥ 6 cycles recommended

- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- 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

* MBC, Metastatic Breast Cancer
** < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion
*** PD, Progressive Disease

Baselga et al. N Engl J Med 2012

CLEOPATRA study: elegibility criteria

Inclusion criteria:

- centrally confirmed human epidermal growth factor receptor 2 (HER2)-positive immunohistochemistry 3+ and/or fluorescence in situ hybridization-positive) locally recurrent, unresectable, or metastatic breast cancer (MBC)
- measurable and/or non-measurable disease
- LVEF* ≥ 50% at baseline**
- ECOG (Eastern Cooperative Oncology Group) PS: 0-1
- no more than one hormonal regimen for MBC*** prior to randomization
- prior neo(adjuvant) therapy including trastuzumab**** was allowed
- desease-free interval ≥ 12 months

Exclusion criteria:

- central nervous system metastases
- prior exposure to a cumulative dose of doxorubicin > 360 mg/mq
- history of congestive heart failure or decline in LVEF to <50% during or following prior therapy with trastuzumab
- current uncontrolled medical conditions that could limit a patient's ability to undertake study therapy

* Left Ventricular Ejection Fraction
** determined by echocardiography or multiple-gated acquisition scanning
*** Metastatic Breast Cancer
**** with an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of MBC

Baselga et al. N Engl J Med 2012

CLEOPATRA study: patient characteristics

Characteristic	Placebo plus Trastuzumab plus Docetaxel (N=406)	Pertuzumab plus Trastuzumab plus Docetaxel (N=402)
Female sex — no. (%)	404 (99.5)	402 (100.0)
Age — yr		
Median	54.0	54.0
Range	27–89	22–82
Race or ethnic group — no. (%)†		
Asian	133 (32.8)	128 (31.8)
Black	20 (4.9)	10 (2.5)
White	235 (57.9)	245 (60.9)
Other	18 (4.4)	19 (4.7)
Region — no. (%)		
Asia	128 (31.5)	125 (31.1)
Europe	152 (37.4)	154 (38.3)
North America	68 (16.7)	67 (16.7)
South America	58 (14.3)	56 (13.9)
ECOG performance status — no. (%)‡		
0	248 (61.1)	274 (68.2)
1	157 (38.7)	125 (31.1)
≥2	1 (0.2)	3 (0.7)
Disease type at screening — no. (%)		
Nonvisceral	90 (22.2)	88 (21.9)
Visceral	316 (77.8)	314 (78.1)

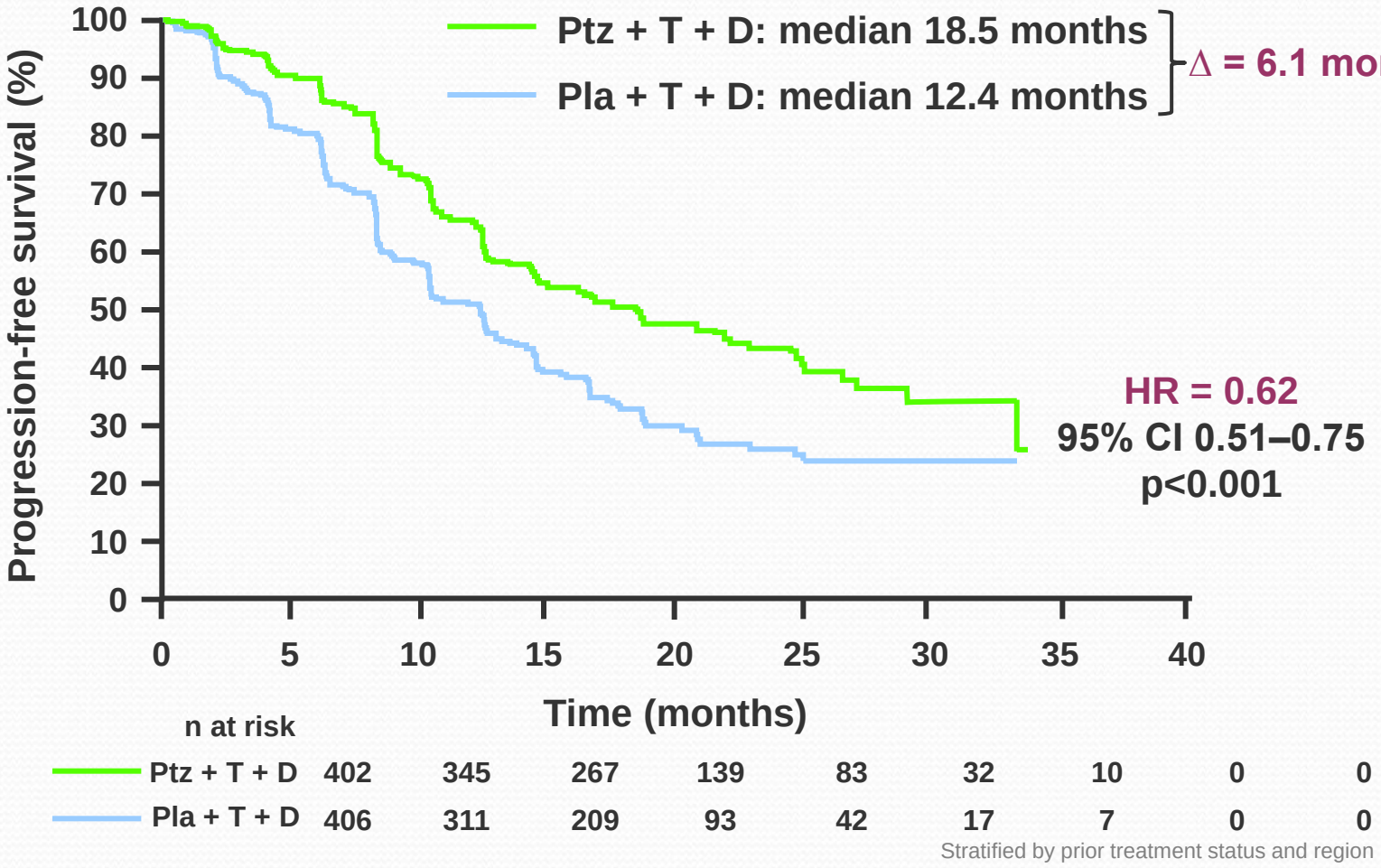
Characteristic	Placebo plus Trastuzumab plus Docetaxel (N=406)	Pertuzumab plus Trastuzumab plus Docetaxel (N=402)
Hormone-receptor status — no. (%)		
ER-positive, PgR-positive, or both	199 (49.0)	189 (47.0)
ER-negative and PgR-negative	196 (48.3)	212 (52.7)
Unknown	11 (2.7)	1 (0.2)
HER2 status, assessed by immunohistochemistry — no. (%)		
0 or 1+	2 (0.5)	4 (1.0)
2+	32 (7.9)	47 (11.7)
3+	371 (91.4)	350 (87.1)
Data not available	1 (0.2)	1 (0.2)
HER2 status, assessed by FISH — no. (%)		
Positive	383 (94.3)	384 (95.5)
Negative	4 (1.0)	1 (0.2)
Data not available	19 (4.7)	17 (4.2)
Prior adjuvant or neoadjuvant chemotherapy — no. (%)		
No	214 (52.7)	218 (54.2)
Yes§	192 (47.3)	184 (45.8)
Anthracycline	164 (40.4)	150 (37.3)
Hormone	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

Only about 20% of patients had received (neo)adjuvant trastuzumab

Baselga et al. N Engl J Med 2012

CLEOPATRA results: PFS, independently assessed (primary end point)

Independently assessed Progression-free Survival
n = 433 PFS events

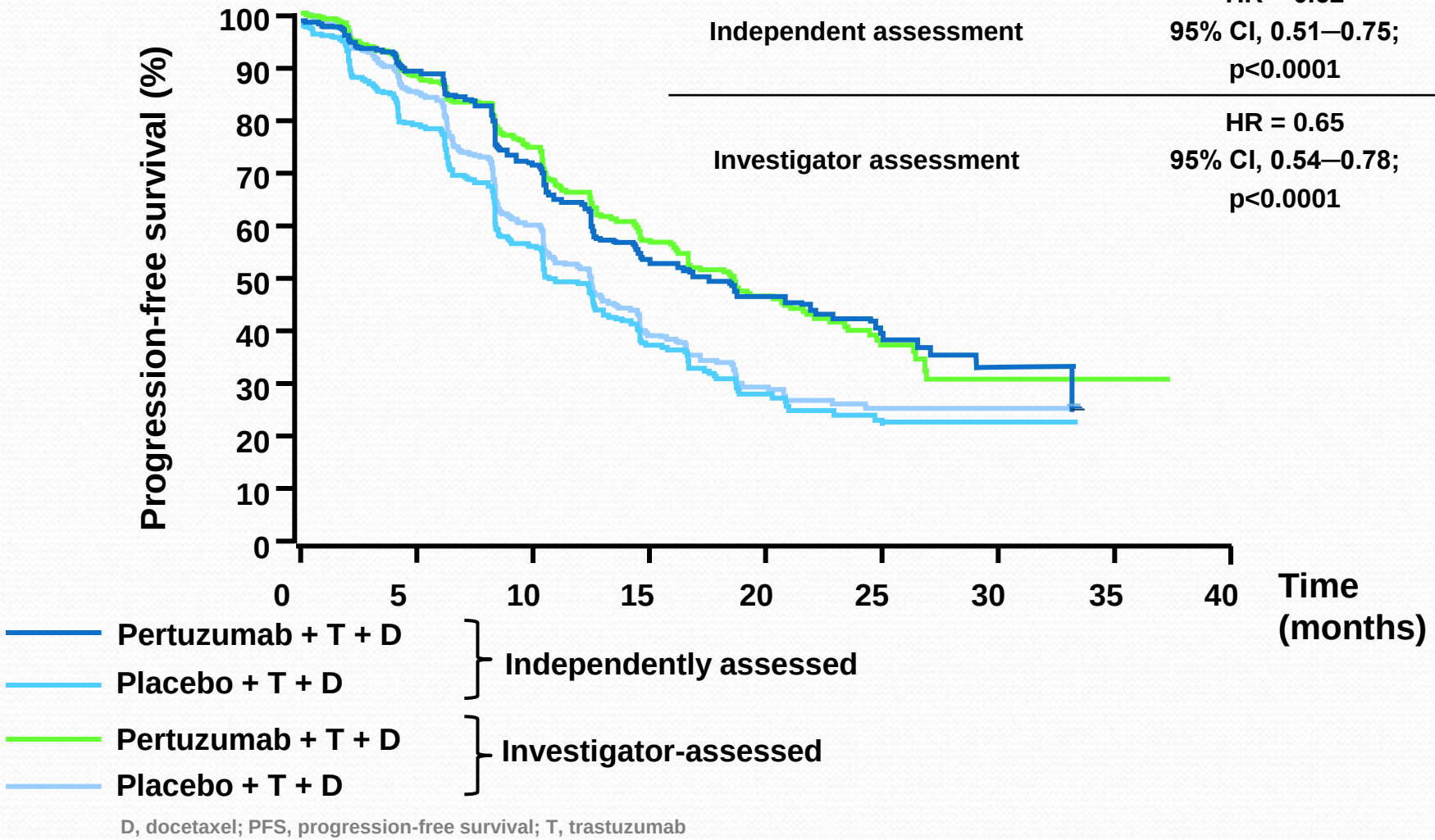


Stratified by prior treatment status and region

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

Baselga et al. N Engl J Med 2012

CLEOPATRA results: PFS, independently and investigator assessed (primary and secondary end point)



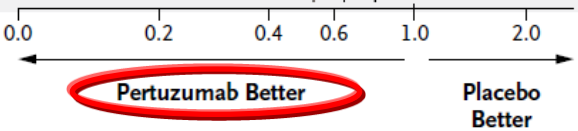
D, docetaxel; PFS, progression-free survival; T, trastuzumab

Adapted from Baselga et al. N Engl J Med 2012

Miles et al. J Clin Oncol 2012 (abstract ASCO 2012)

CLEOPATRA results: PFS in prespecified subgroups

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	808	0.63 (0.52–0.76)
Previous neoadjuvant or adjuvant chemotherapy		
No	432	0.63 (0.49–0.82)
Yes	376	0.61 (0.46–0.81)
Geographic region		
Europe	306	0.72 (0.53–0.97)
North America	135	0.51 (0.31–0.84)
South America	114	0.46 (0.27–0.78)
Asia	253	0.68 (0.48–0.95)
Age group		
<65 yr	681	0.65 (0.53–0.80)
≥65 yr	127	0.52 (0.31–0.86)
<75 yr	789	0.64 (0.53–0.78)
≥75 yr	19	0.55 (0.12–2.54)
Race or ethnic group		
White	480	0.62 (0.49–0.80)
Black	30	0.64 (0.23–1.79)
Asian	261	0.68 (0.49–0.95)
Other	37	0.39 (0.13–1.18)
Disease type		
Visceral disease	630	0.55 (0.45–0.68)
Nonvisceral disease	178	0.96 (0.61–1.52)
Hormone-receptor status		
ER-positive, PgR-positive, or both	388	0.72 (0.55–0.95)
ER-negative and PgR-negative	408	0.55 (0.42–0.72)
ER and PgR status unknown	12	—
HER2 status		
IHC 3+	721	0.60 (0.49–0.74)
FISH-positive	767	0.64 (0.53–0.78)



Baselga et al. N Engl J Med 2012

CLEOPATRA results: independently assessed PFS by prior trastuzumab therapy in patients with(neo)adjuvant treatment

	Placebo + trastuzumab + docetaxel Median PFS, months	Pertuzumab + trastuzimab + docetaxel Median PFS, months	Hazard ratio (CI)
Prior (neo)adjuvant trastuzumab treatment (n = 88)	10.4	16.9	0.62 (0.35-1.07)
No prior (neo)adjuvant trastuzumab treatment (n = 288)	12.6	21.6	0.60 (0.43-0.83)

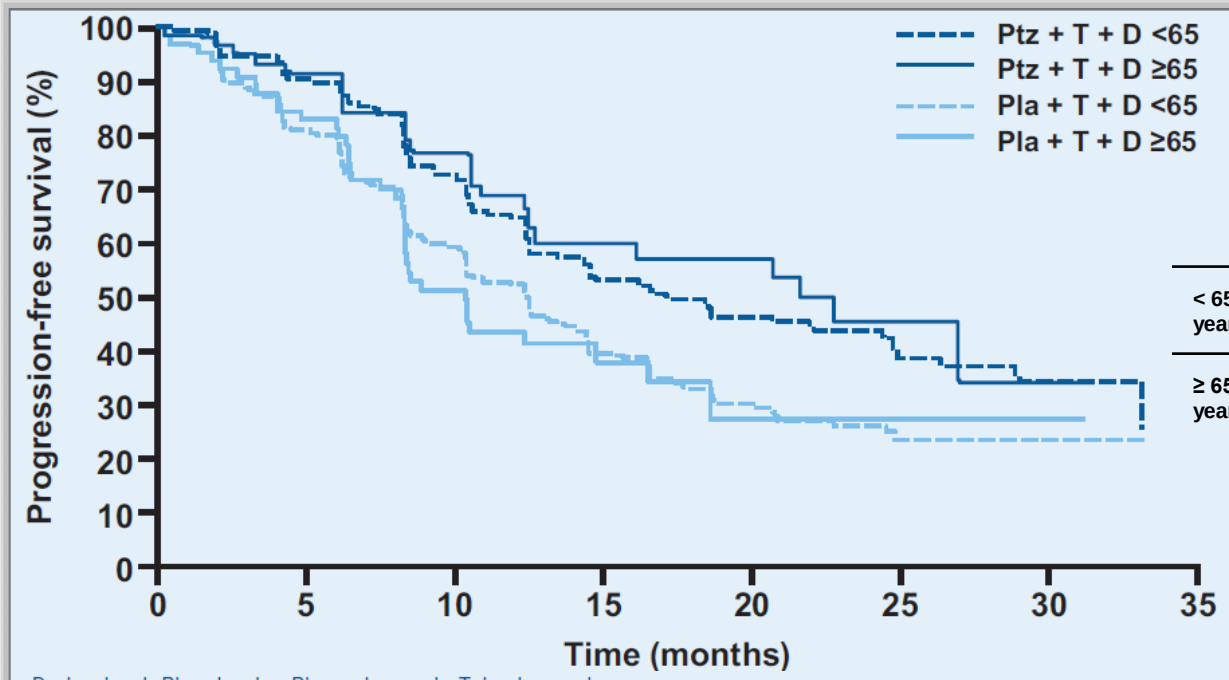
PFS, progression-free survival

Baselga et al. N Engl J Med 2012

CLEOPATRA results: PFS, independently assessed in elderly patients

n (%)	<65 years: Placebo + trastuzumab + docetaxel (n=339)	<65 years: Pertuzumab + trastuzumab + docetaxel (n=342)	≥65 years: Placebo + trastuzumab + docetaxel (n=67)	≥65 years: Pertuzumab + trastuzumab + docetaxel (n=60)
ECOG PS				
0	208 (61.4)	235 (68.7)	40 (59.7)	39 (65.0)
1	130 (38.3)	105 (30.7)	27 (40.3)	20 (33.3)
2*	0 (0.0)	2 (0.6)	0 (0.0)	1 (1.7)
3*	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Disease type				
Visceral disease	261 (77.0)	269 (78.7)	55 (82.1)	45 (75.0)
Non-visceral disease	78 (23.0)	73 (21.3)	12 (17.9)	15 (25.0)

ECOG PS, Eastern Cooperative Oncology Group performance status
* Protocol violation



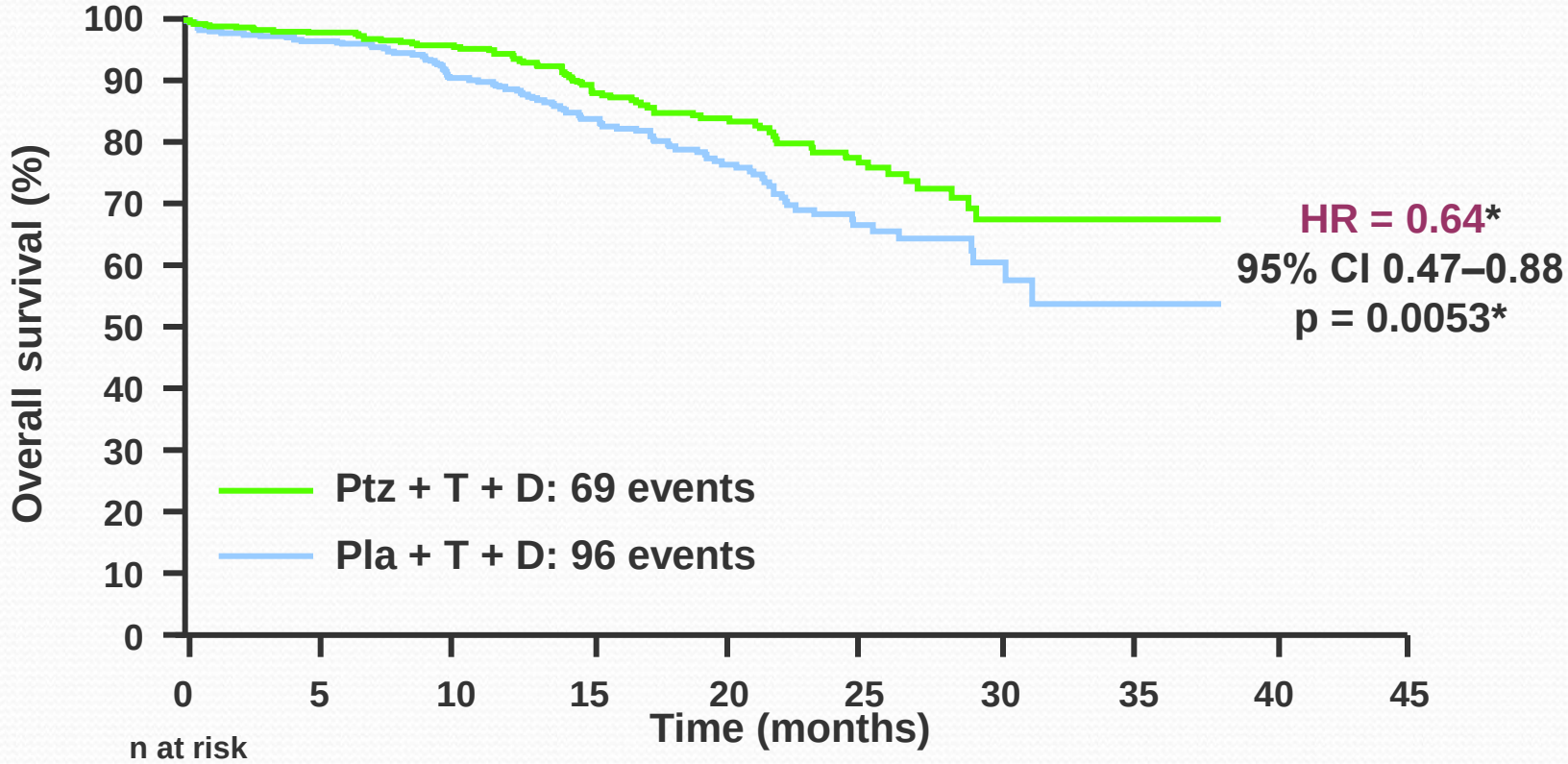
D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

	Pertuzumab arm median PFS, months	Placebo arm median PFS, months	HR (CI)
< 65 years	17.2	12.5	0.55 (0.53-0.80) p<0.0001
≥ 65 years	21.6	10.4	0.52 (0.31-0.86) p=0.0098

Miles et al. San Antonio Breast Cancer Symposium – December 4–8, 2012 (poster)

CLEOPATRA results: OS (secondary end point)

Interim analysis



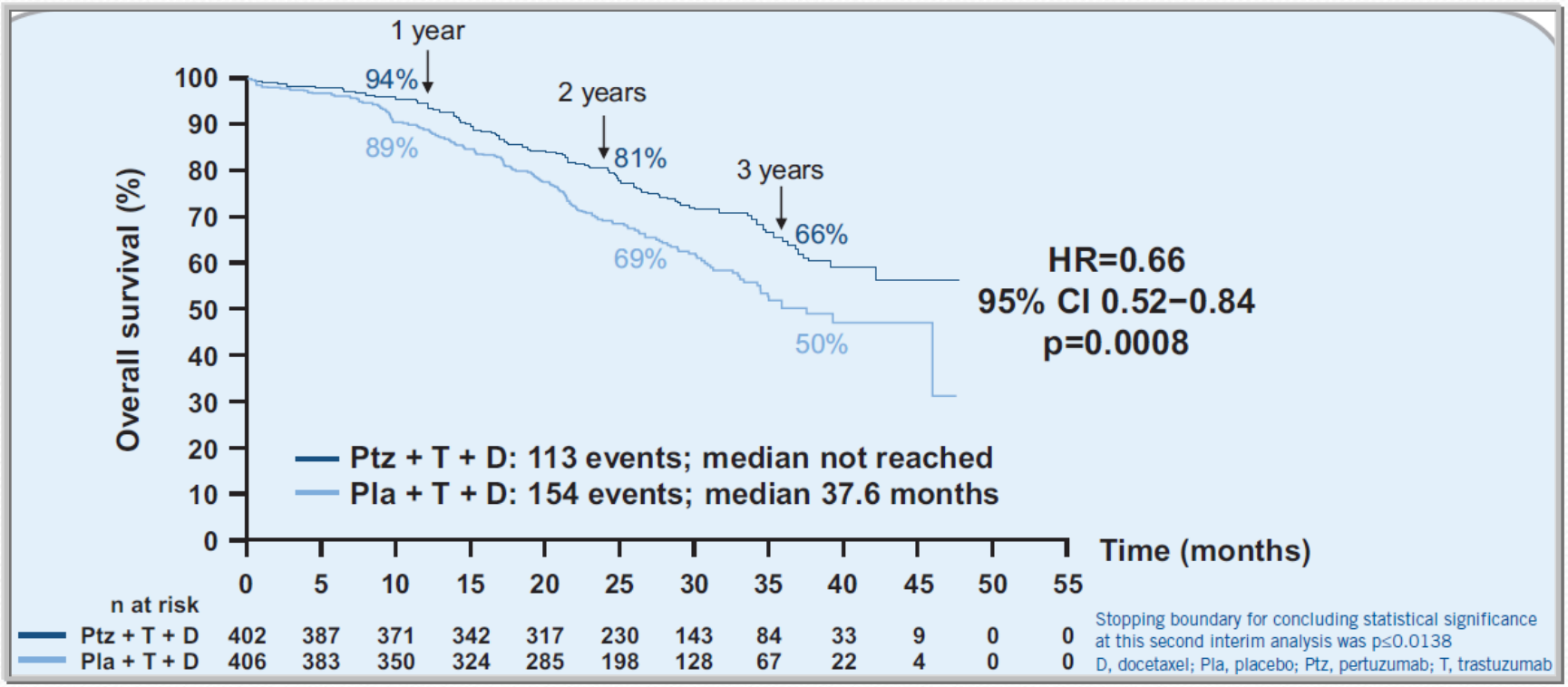
n at risk										
Pertuzumab + T + D	402	387	367	251	161	87	31	4	0	0
Placebo + T + D	406	383	347	228	143	67	24	2	0	0

* 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

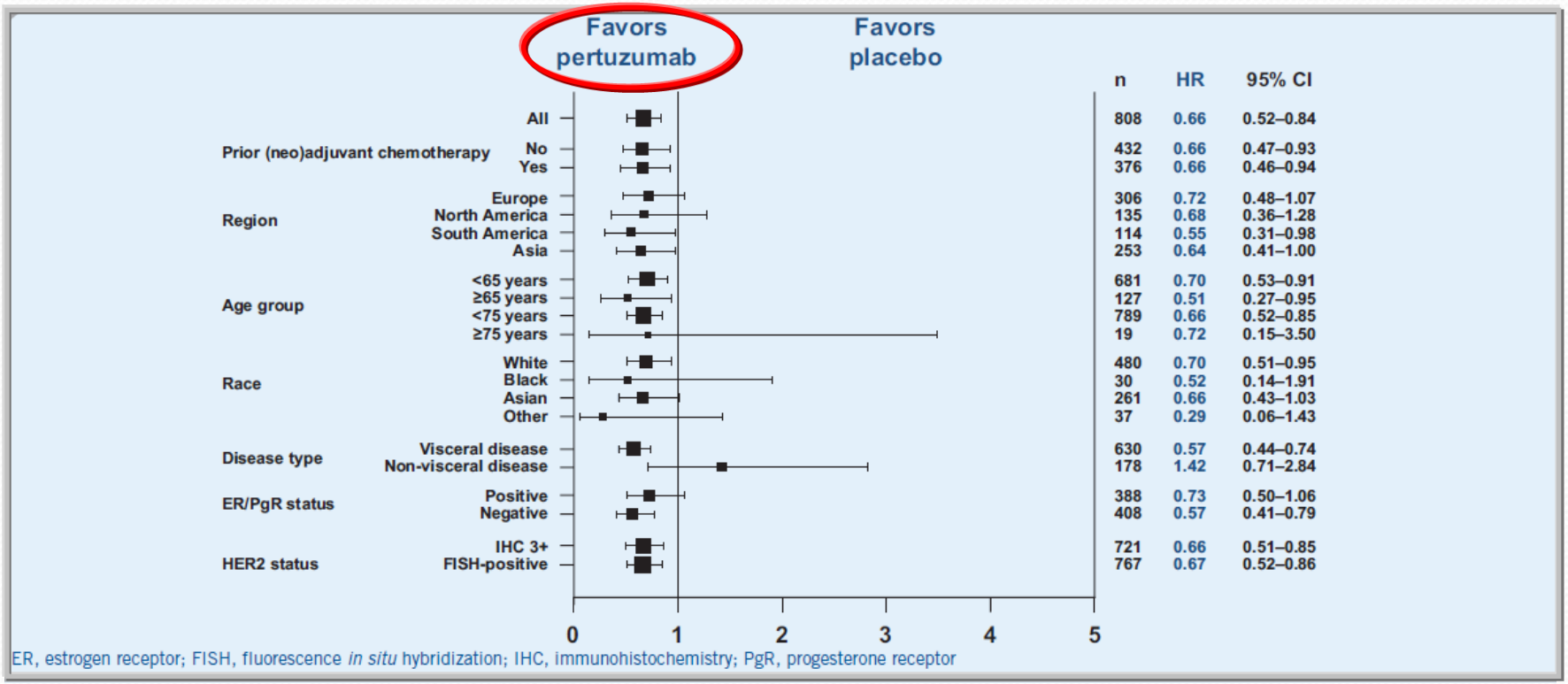
Baselga et al. N Engl J Med 2012

Confirmatory overall survival analysis of CLEOPATRA study



Swain et al. San Antonio Breast Cancer Symposium – December 4−8, 2012 (poster)

Confirmatory overall survival analysis in predefined subgroups of CLEOPATRA study



Swain et al. San Antonio Breast Cancer Symposium – December 4−8, 2012 (poster)

CLEOPATRA results: overall response (secondary end point)

Overall response, as assessed at an Independent Review Facility*

Response, number (%)	Placebo + trastuzumab + docetaxel (n = 336)	Pertuzumab + trastuzumab + docetaxel (n = 343)
Objective response	233 (69.3)	275 (80.2)
Complete response	14 (4.2)	19 (5.5)
Partial response	219 (65.2)	256 (74.6)
Stable response	70 (20.8)	50 (14.6)
Progressive disease	28 (8.3)	13 (3.8)
Not assessable	2 (0.6)	2 (0.6)
Not assessement performed	3 (0.9)	3 (0.9)

*Total numbers in the two groups represent the number of patients with measurable disease at baseline, as assessed at an independent review facility

Baselga et al. N Engl J Med 2012

CLEOPATRA results: safety (secondary end point)

Adverse event, n (%)	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Diarrhea	184 (46.3)	**272 (66.8)**
Alopecia	240 (60.5)	248 (60.9)
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	**137 (33.7)**
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	79 (19.9)	**113 (27.8)**
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	30 (7.6)	**56 (13.8)**
Dry skin	17 (4.3)	**43 (10.6)**

Baselga et al. N Engl J Med 2012

CLEOPATRA results: safety (secondary end point)

Toxicity grade ≥ 3

Adverse event, grade ≥ 3, n (%)	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Neutropenia	182 (45.8)	199 (48.9)
Febrile neutropenia	30 (7.6)	**56 (13.8)**
Diarrhea	20 (5.0)	32 (7.9)
Peripheral neuropathy	7 (1.8)	11 (2.7)
Anemia	14 (3.5)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Fatigue	13 (3.3)	9 (2.2)
LV systolic disfunction	**11 (2.8)**	**5 (1.2)**
Dyspnea	8 (2.0)	4 (1.0)

Adapted from Baselga et al. N Engl J Med 2012

CLEOPATRA results: safety (secondary end point)

n (%)	Placebo + trastuzumab + docetaxel		Pertuzumab + trastuzumab + docetaxel	
Data cutoff date	May 2011 (n=397)	May 2012 (n=396)	May 2011 (n=407)	May 2012 (n=408)
LVSD (all grades)	33 (8.3)	34 (8.6)	18 (4.4)	22 (5.4)
Symptomatic LVSD	7 (1.8)	7 (1.8)	4 (1.0)	5 (1.2)
LVEF decline to <50% and by ≥10% points from baseline*	25/379 (6.6)	28/378 (7.4)	15/393 (3.8)	18/394 (4.6)
LVEF recovery to ≥50%*	18/25 (72.0)	25/28 (89.3)	13/15 (86.7)	16/18 (88.9)

* In patients with post-baseline assessment
LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction

n/N (%)	Placebo + trastuzumab + docetaxel (n=396)	Pertuzumab + trastuzumab + docetaxel (n=408)
Total	**152 (38.4)**	**113 (27.7)**
Disease progression	136 (34.3)	100 (24.5)
Febrile neutropenia or infection	5 (1.3)	5 (1.2)
Other/unknown	13 (3.3)	11 (2.7)

he sum of causes of death is greater than the total number of deaths as primary and underlying (if reported) causes of death are shown

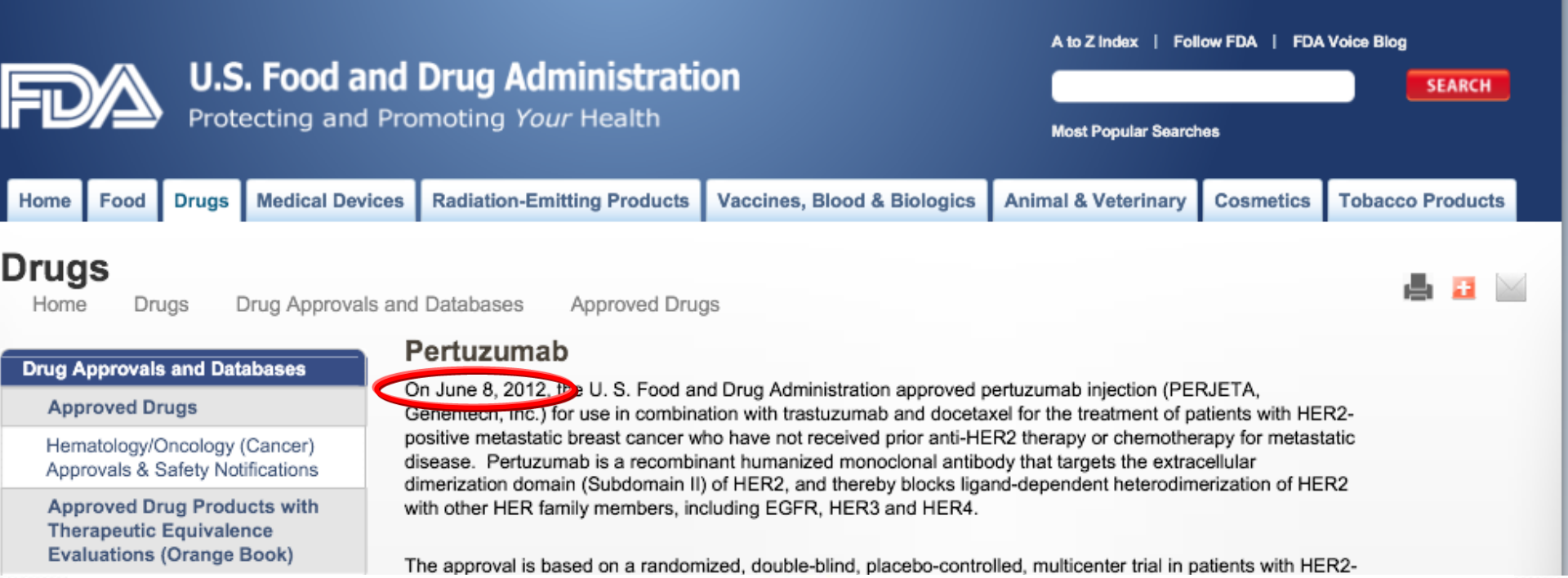
Swain et al. San Antonio Breast Cancer Symposium – December 4−8, 2012 (poster)

CLEOPATRA study: conclusions

- the combination of pertuzumab and trastuzumab with docetaxel as first-line therapy increased PFS and OS in patients with HER2-positive MBC* in predefined subgroups
- PFS benefit of the pertuzumab addition to trastuzumab plus docetaxel therapy in patients who had received prior (neo)adjuvant chemotherapy with trastuzumab was similar to the benefit observed in patients who had received prior (neo)adjuvant chemotherapy without trastuzumab
- although adverse events (any grade) were reported more frequently in the pertuzumab group than in the control group, the combination therapy with pertuzumab did not increase the rates of symptomatic or asymptomatic cardiac dysfunction
- these results show that combined HER2 blockade and chemotherapy using pertuzumab plus trastuzumab plus docetaxel can be considered a standard of care for patients with HER2-positive MBC* in the first-line setting.

*MBC, metastatic breast cancer

Baselga et al. N Engl J Med 2012
Swain et al. San Antonio Breast Cancer Symposium – December 4–8, 2012 (poster)
Miles et al. San Antonio Breast Cancer Symposium – December 4–8, 2012 (poster)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/803313/2012
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

On 13 December 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Perjeta, 420 mg, concentrate for solution for infusion intended for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. The applicant for this medicinal product is Roche Registration Ltd.They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

I M

Thank you !!

Schwartz JD, MD

If it was easy, they wouldn't have asked us to do it

anonymous c. 2009