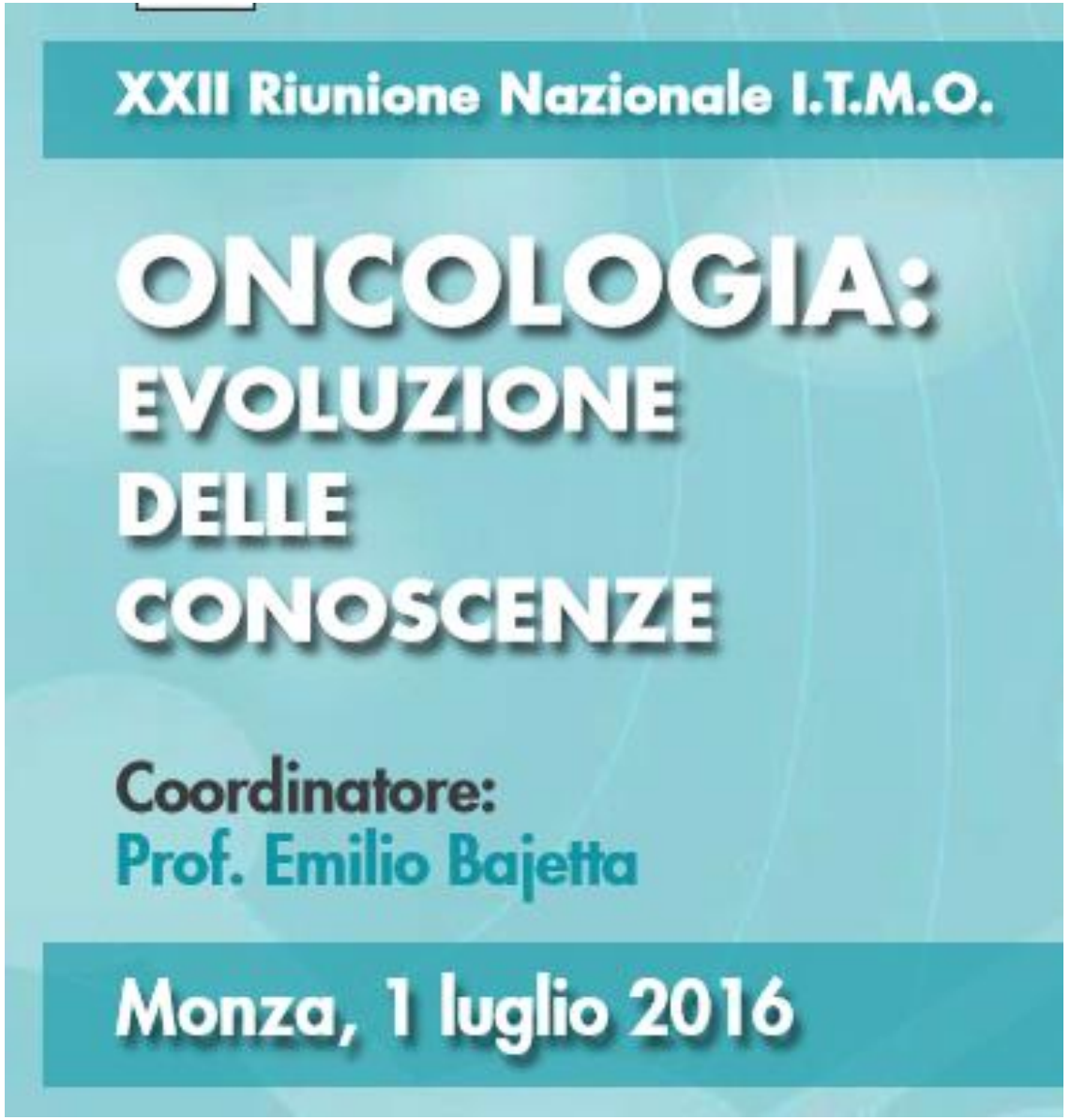
Carcinoma mammario:

Malattia metastatica

Dr.ssa Alessia Levaggi



HR+/Her2-

HOT TOPICS

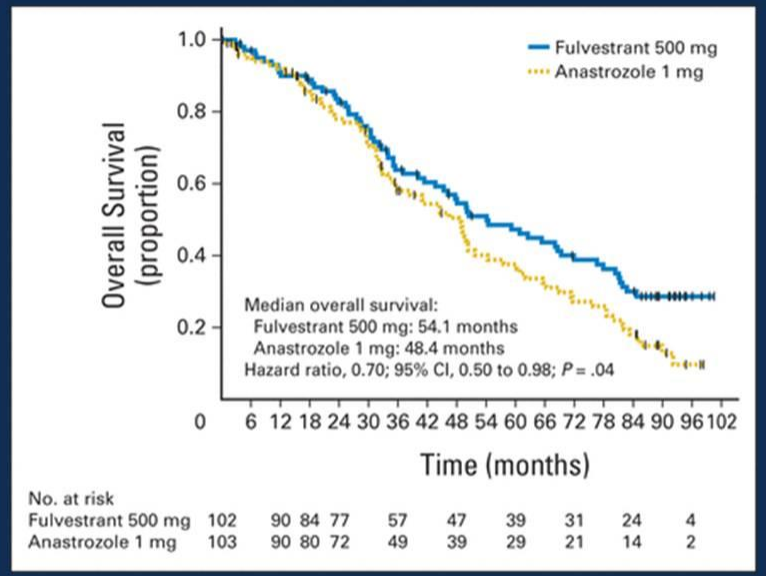
- Terapia ormonale
- Terapia ormonale + agenti target

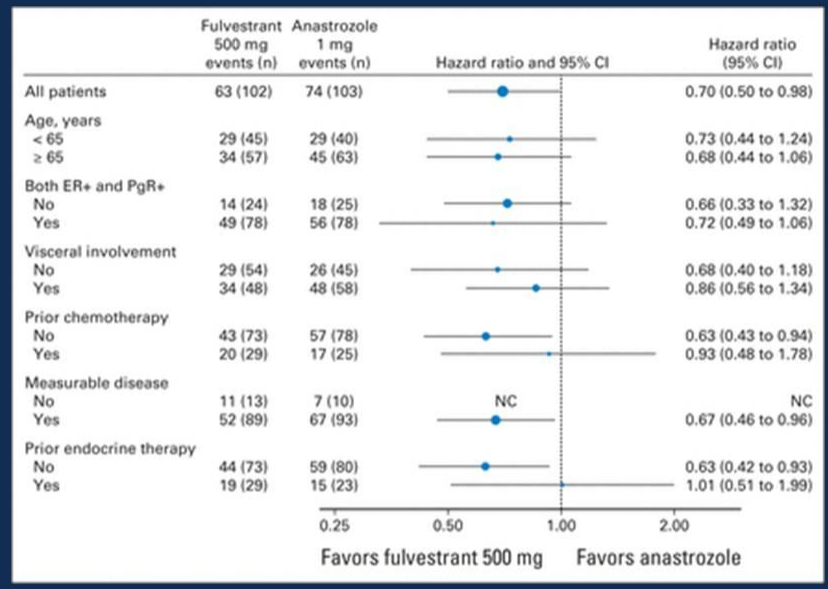
NEXT STEPS

- Biomarcatori predittivi
- Terapie future

HR+/Her2-: terapia ormonale

FIRST Trial: Overall Survival



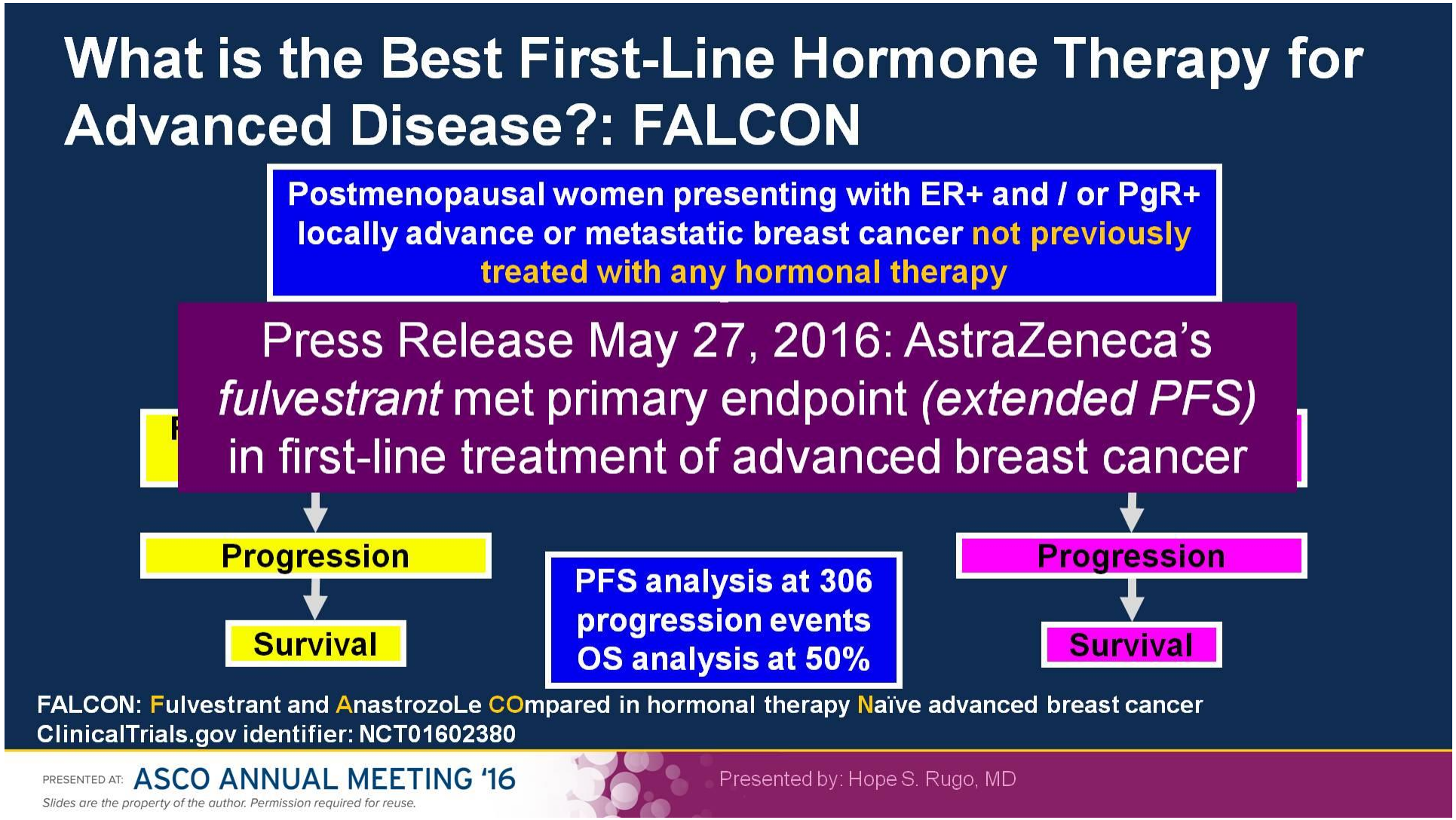


	Fulvestrant 500 mg events (n)	Anastrozole 1 mg events (n)	Hazard ratio and 95% CI	Hazard ratio (95% CI)
All patients	63 (102)	74 (103)		0.70 (0.50 to 0.98)
Age, years				
< 65	29 (45)	29 (40)		0.73 (0.44 to 1.24)
≥ 65	34 (57)	45 (63)		0.68 (0.44 to 1.06)
Both ER+ and PgR+				
No	14 (24)	18 (25)		0.66 (0.33 to 1.32)
Yes	49 (78)	56 (78)		0.72 (0.49 to 1.06)
Visceral involvement				
No	29 (54)	26 (45)		0.68 (0.40 to 1.18)
Yes	34 (48)	48 (58)		0.86 (0.56 to 1.34)
Prior chemotherapy				
No	43 (73)	57 (78)		0.63 (0.43 to 0.94)
Yes	20 (29)	17 (25)		0.93 (0.48 to 1.78)
Measurable disease				
No	11 (13)	7 (10)	NC	NC
Yes	52 (89)	67 (93)		0.67 (0.46 to 0.96)
Prior endocrine therapy				
No	44 (73)	59 (80)		0.63 (0.42 to 0.93)
Yes	19 (29)	15 (23)		1.01 (0.51 to 1.99)

- Data obtained as post hoc assessment
- Not all participated in OS FU
  - 16/102 for fulvestrant
  - 19/103 for anastrozole

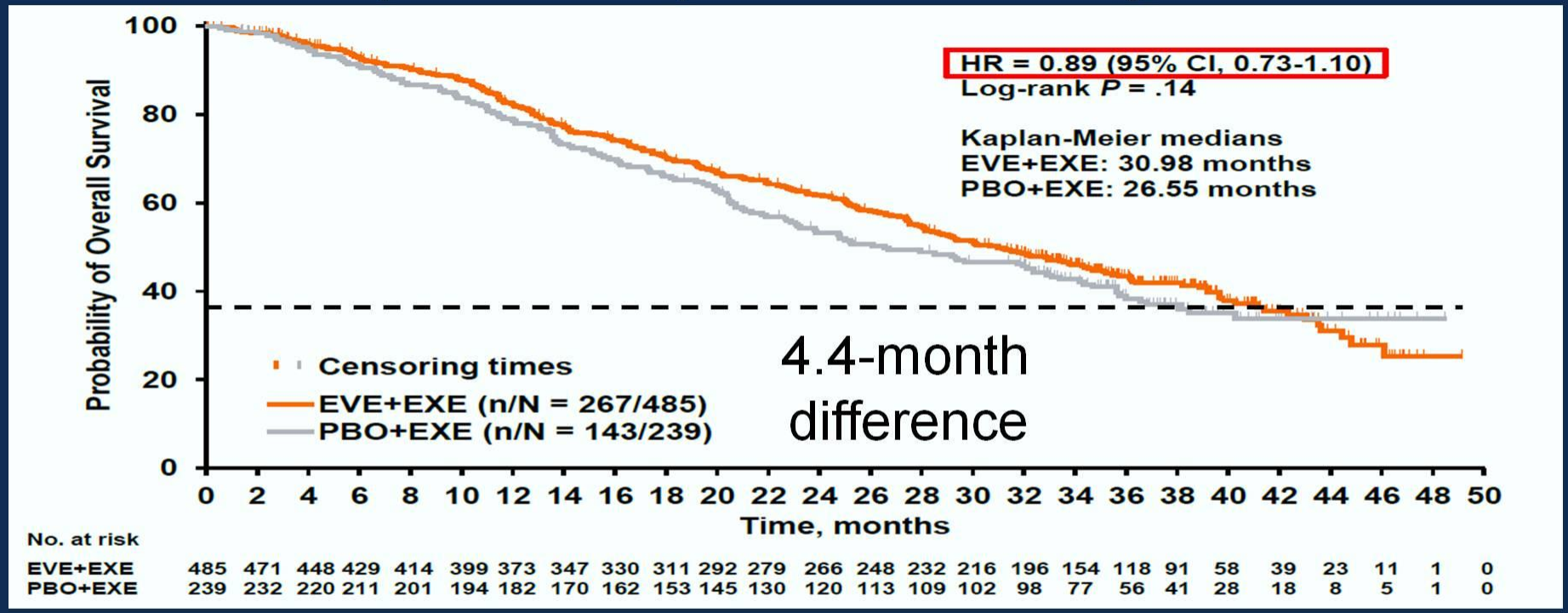
Ellis et al, JCO 2015

HR+/Her2-: terapia ormonale



HR+/Her2-: terapia ormonale + agenti target

BOLERO-2 (39-Month) Final OS Analysis



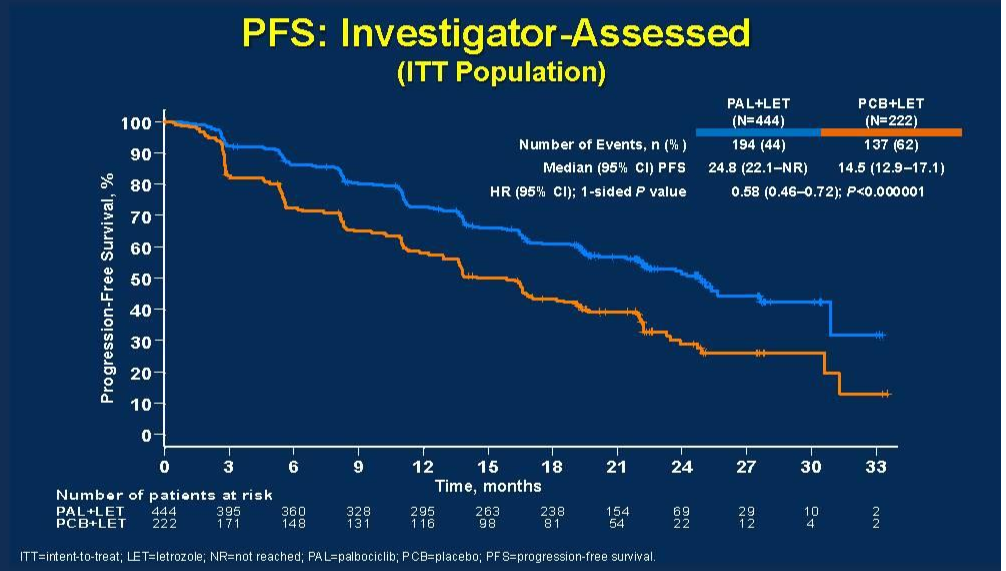
Toxicity management critical

Piccart M, et al. Ann Oncol 2014

HR+/Her2-: terapia ormonale + agenti target

Paloma 2

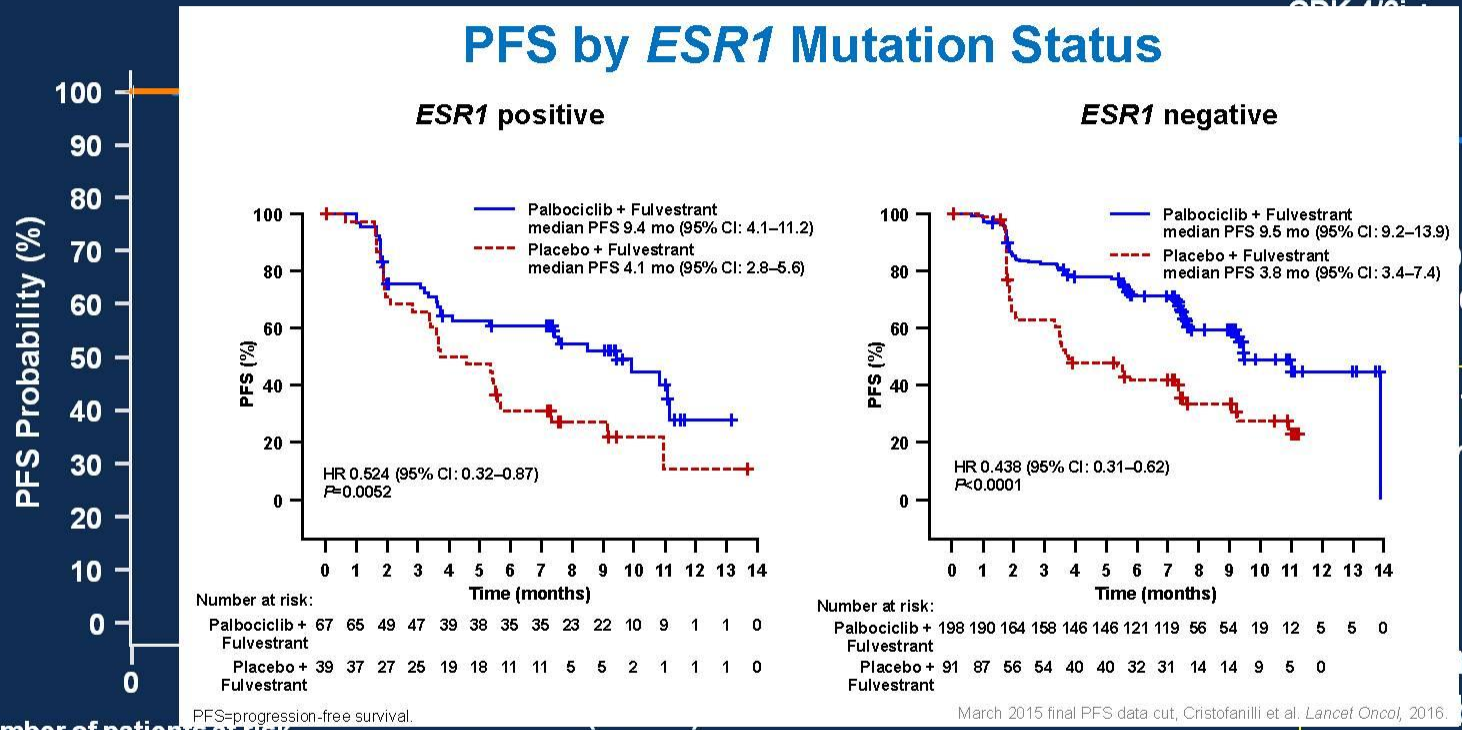
- Randomized 666 pts 2:1 to Let/palbo vs Let/placebo
- Median age 62 (28 to 89)
- 43% hormone naïve, 49% visceral disease
- PFS (inv)
  - 24.8 vs 14.5 months
  - p< 0.000001, HR 0.58
- Confirmed by central review



Finn et al, ASCO 2016

HR+/Her2-: terapia ormonale + agenti target

Paloma 3: PFS (ITT Population)



PFS=progression-free survival.

March 2015 final PFS data cut, Cristofanilli et al. *Lancet Oncol*, 2016.

Placebo + Fulvestrant n=174

3.8 (3.5, 5.5)

.318, 0.560)

000001

firmed on
ral blinded
audit of 211
pts

effect in all
ogroups

Number of patients at risk

PAL+FUL	347	279	132	59	16	6
PCB+FUL	174	109	42	16	6	1

Turner et al, LBA 502; NEJM 2015

TNBC

HOT TOPICS

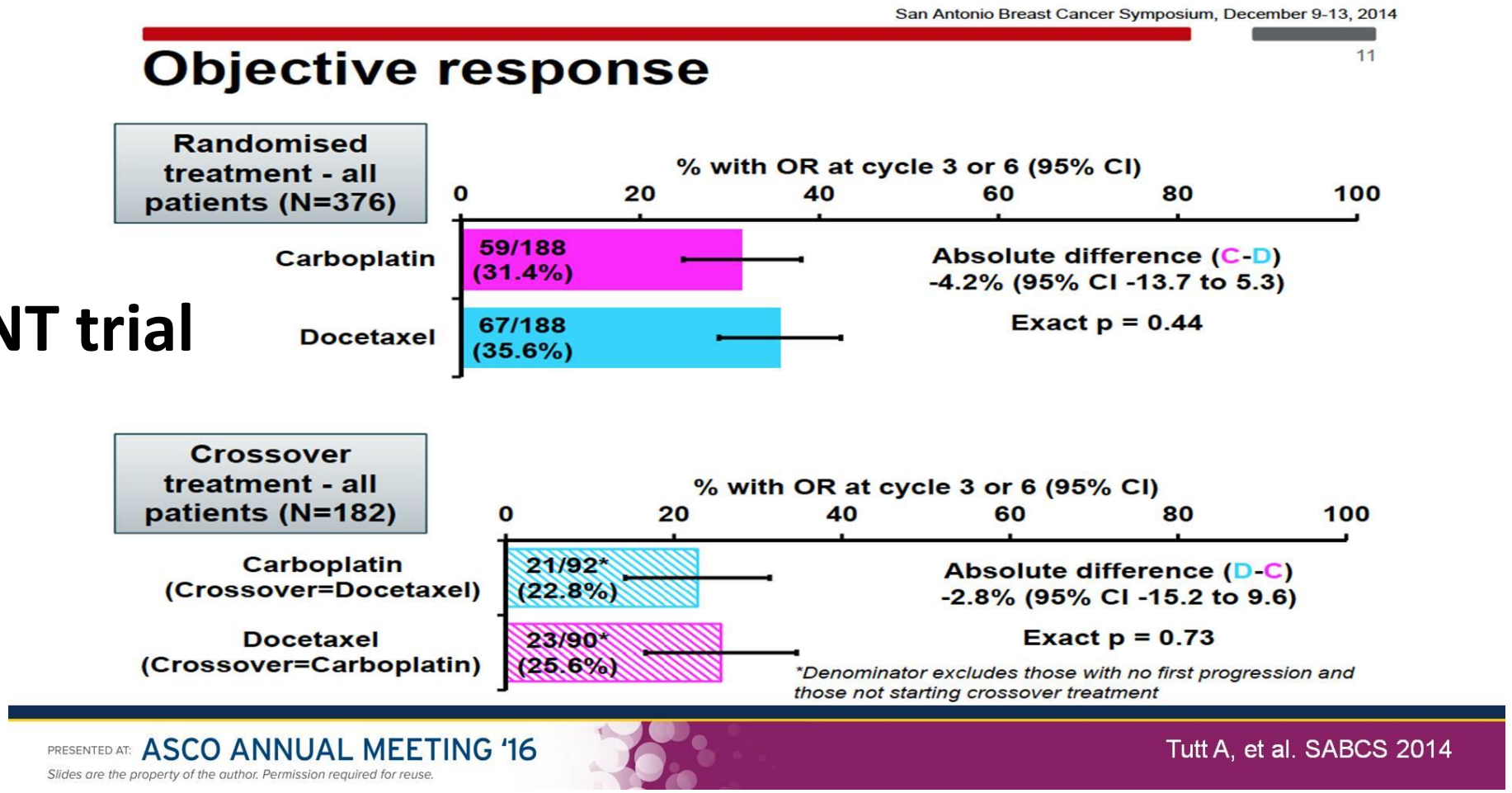
- Ruolo del platino

NEXT STEPS

- Immunoterapia
- Antiandrogeni

TNBC: ruolo del platino

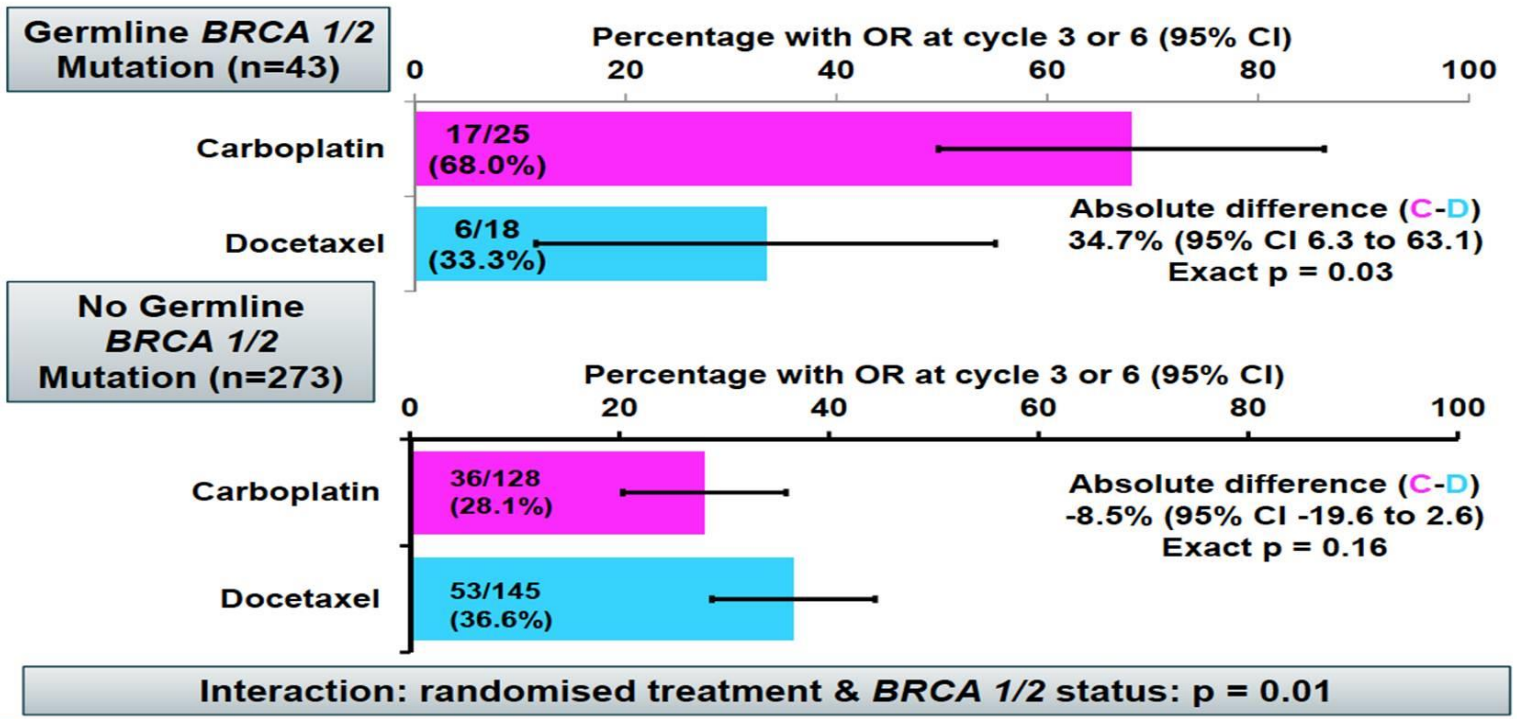
TNT trial



Presented By Rebecca Dent at 2016 ASCO Annual Meeting

TNBC: ruolo del platino

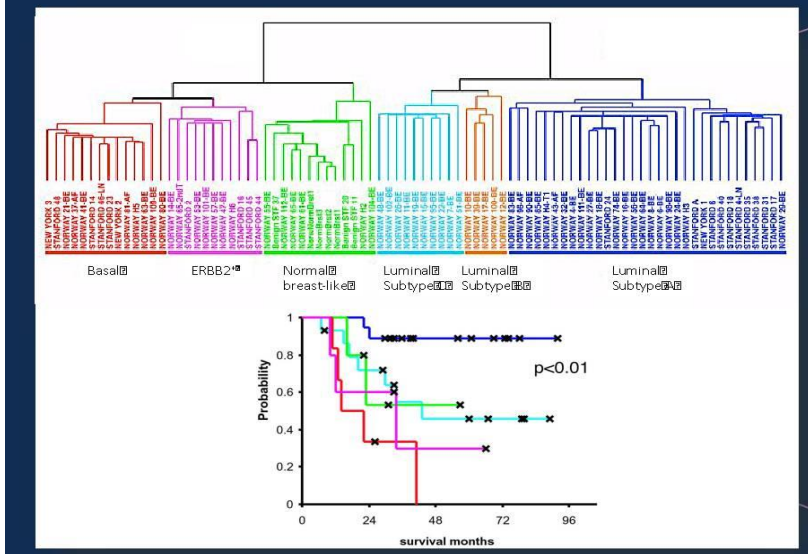
Objective response – *BRCA 1/2* status

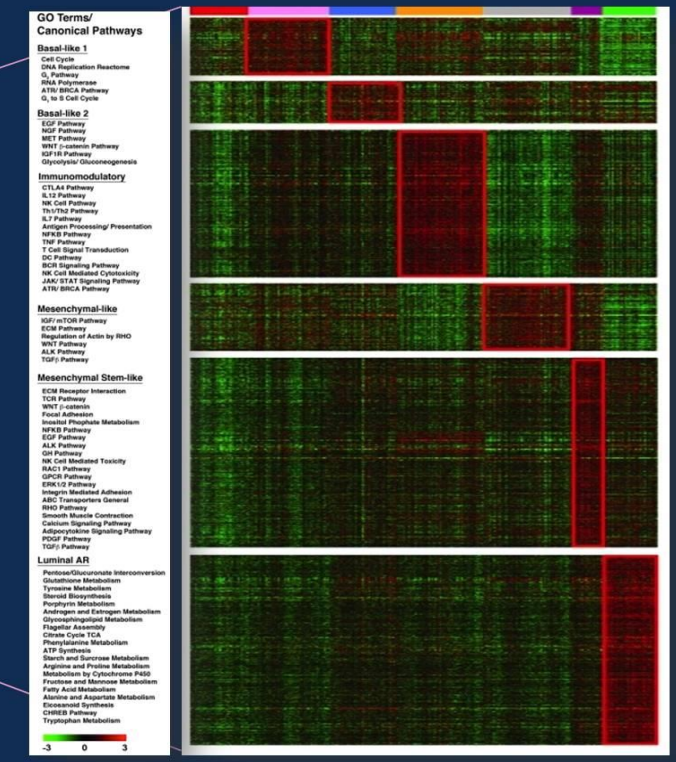


Presented By Rebecca Dent at 2016 ASCO Annual Meeting

TNBC: immunoterapia

Is there a subtype of TNBC to target with immunotherapy?





Immunomodulatory subtype: Associated with an immune modulatory gene signature characterized by elevated expression of genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing.

Lehmann et. al *JCI* 2011

TNBC: immunoterapia

Agente		N. pazienti	ORR (95% CI)	Autore
Atezolizumab	Anti PD-L1	21	19%	Emens LA AACR 2015
Avelumab	Anti PD-L1	58	8.6%	Dirix L. et al SABCS 2015
Pembrolizumab	Anti PD-1	27	18.5%	Nanda L. et al JCO 2015

TNBC: immunoterapia

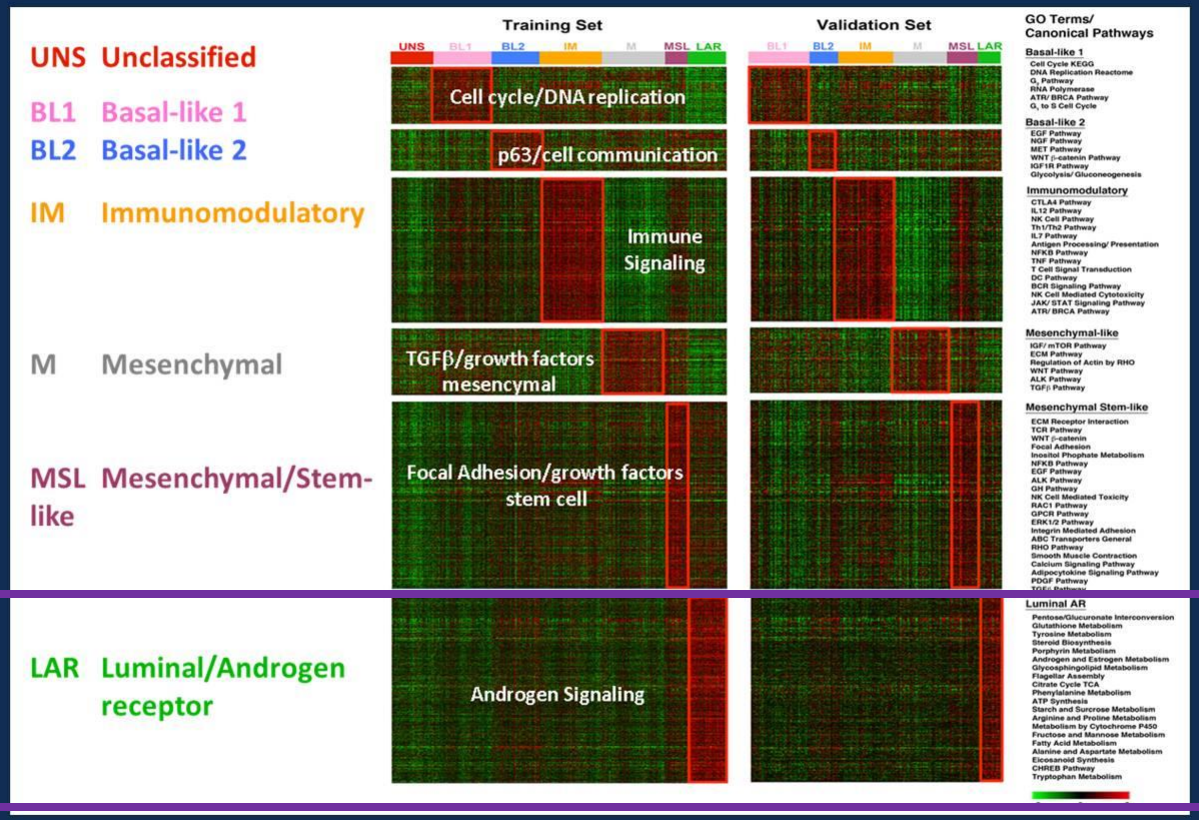
Phase Ib study of atezolizumab + nab-paclitaxel: efficacy

Best Overall Response	1st Line N=13	2nd Line N=9	3rd Line N=10
ORR	46%	22%	40%
CR	8%	0	0
PR	38%	22%	40%
SD	38%	67%	30%
PD	15%	0	30%

Adams et al ASCO 2016

TNBC: antiandrogeni

Dissecting the Biology of TNBC: Vanderbilt 7 subtypes

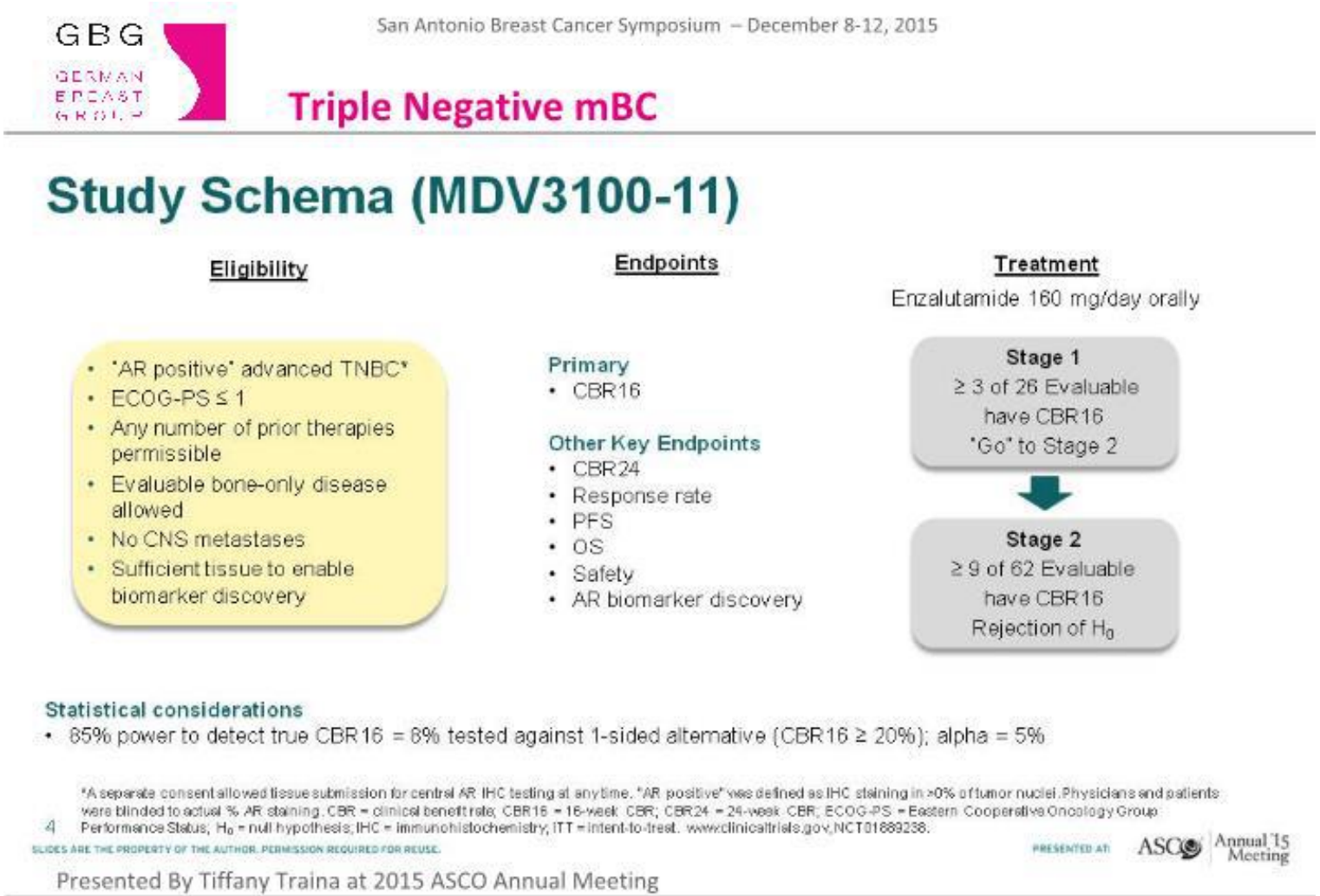


PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: *Lehmann/Pietenpol, JCI 2011*

Presented By Carey Anders at 2016 ASCO Annual Meeting

TNBC: antiandrogeni



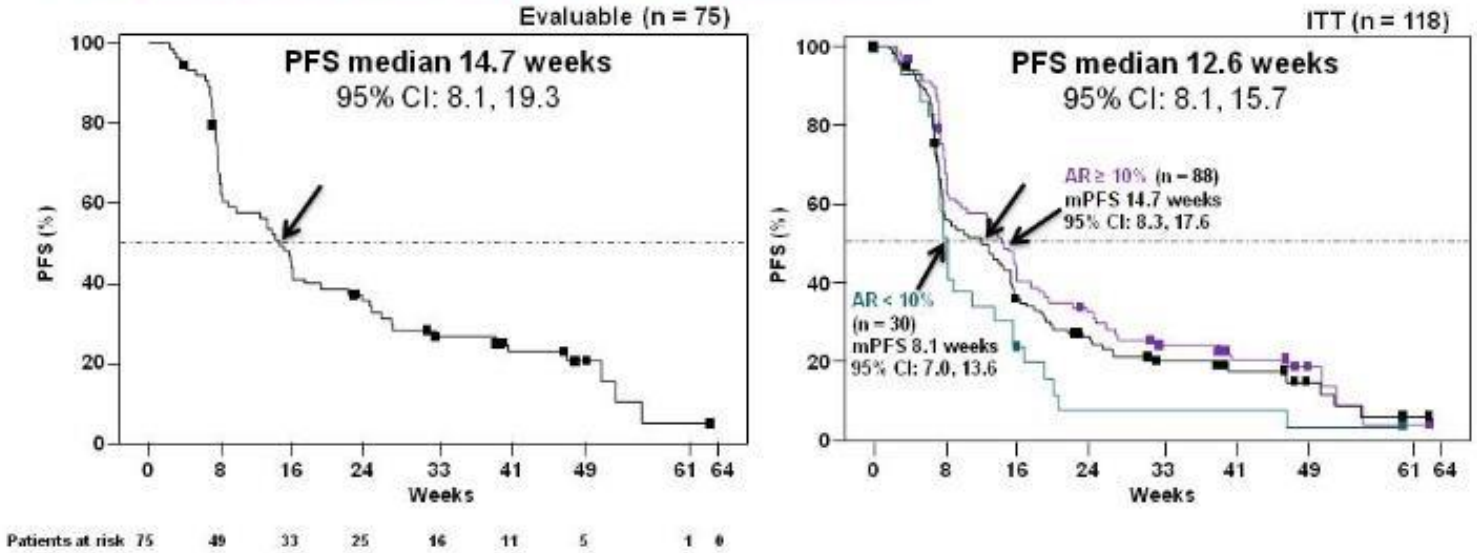
TNBC: antiandrogeni

GBG GERMAN BREAST GROUP

San Antonio Breast Cancer Symposium – December 8-12, 2015

Triple Negative mBC

PFS in Evaluable and ITT Populations



Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment;
ITT = AR IHC > 0% by central assessment and received ≥ 1 dose of enzalutamide.
Data cutoff 24 March 2015.

10

NCT01889238 PRESENTED AT: ASCO Annual '15 Meeting

Presented By Tiffany Traina at 2015 ASCO Annual Meeting

Her2+ BC

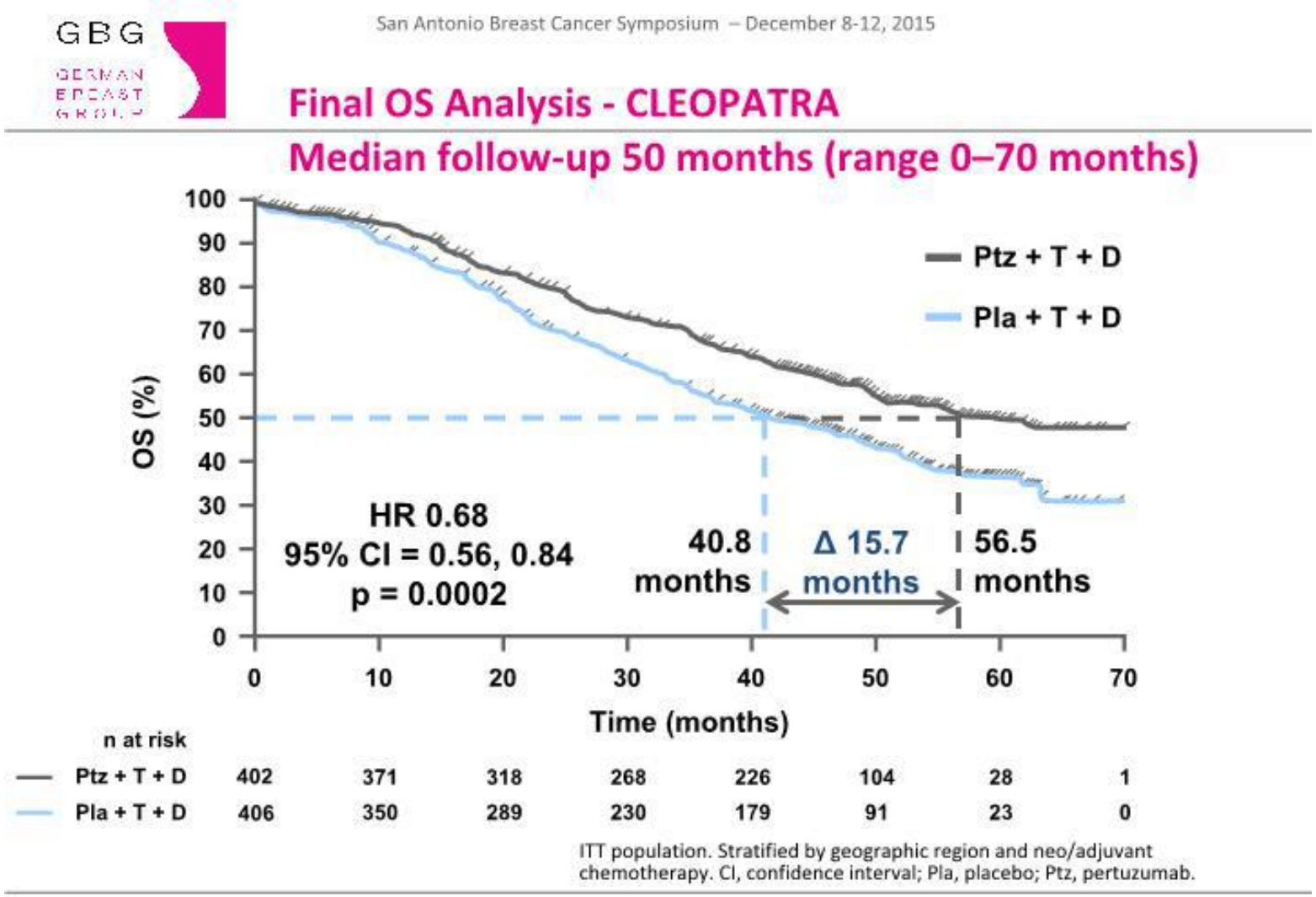
HOT TOPICS

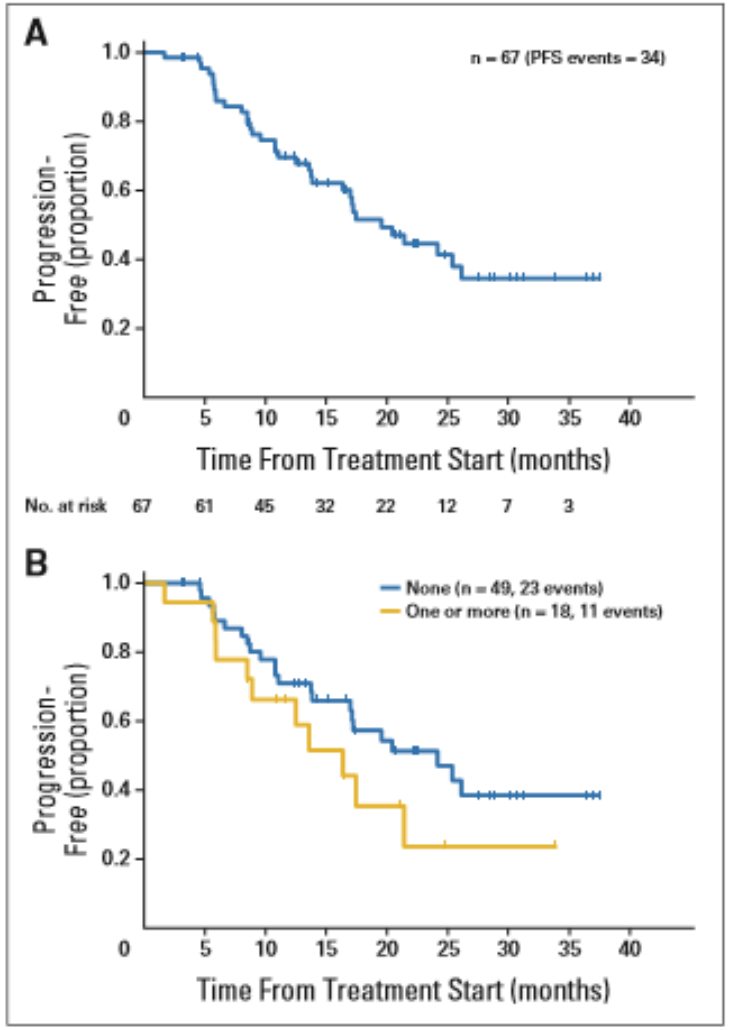
- Doppio blocco anti HER2
- TDM-1

NEXT STEPS

- Superamento della resistenza
- Nuovi farmaco

HER2+: la I linea, doppio blocco





Phase II Study of Paclitaxel Given Once per Week Along With Trastuzumab and Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

Chau Dang, Neil Iyengar, Farrah Datko, Gabriella D'Andrea,

Table 3. Adverse Events (safety population)

Adverse Event	Grade 1 to 2 No.	Grade 1 to 2 %	Grade 3 to 4 No.	Grade 3 to 4 %
Diarrhea	54	81	2	3
Fatigue	53	79	4	6
Peripheral neuropathy	53	79	2	3
Alopecia	48	72	0	
AST elevation	42	63	2	3
ALT elevation	37	55	2	3
Dry skin	35	52	1	1.5
Mucositis	37	55	0	
Acneiform rash	37	55	0	
Nausea	33	49	1	1.5
Arthralgia	36	54	0	
Hot flashes	33	49	0	
Dyspepsia	26	43	0	
Xerophthalmia	28	42	0	
Palmar-plantar erythrodysesthesia syndrome	25	37	2	3
Anorexia	23	34	0	
Cough	35	52	0	
Peripheral edema	26	39	0	
Epistaxis	25	37	0	
Epiphora	24	36	0	
Dyspnea	22	33	0	

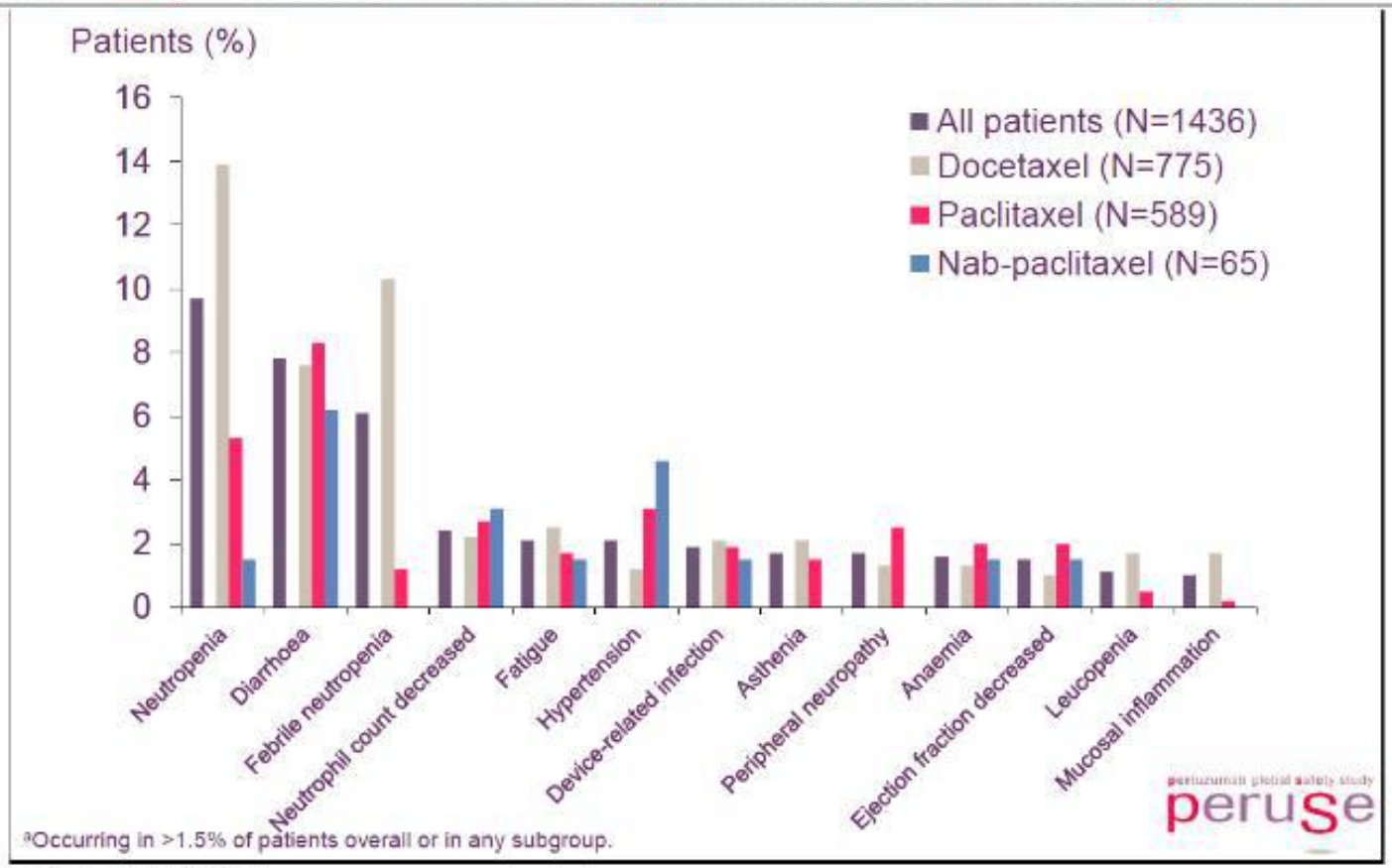
NOTE. Safety population includes all patients who received at least one dose of study drug. Adverse events of all grades shown have a frequency of 25% or higher.

HER2+: doppio blocco, quale partner?

GBG GERMAN BREAST GROUP

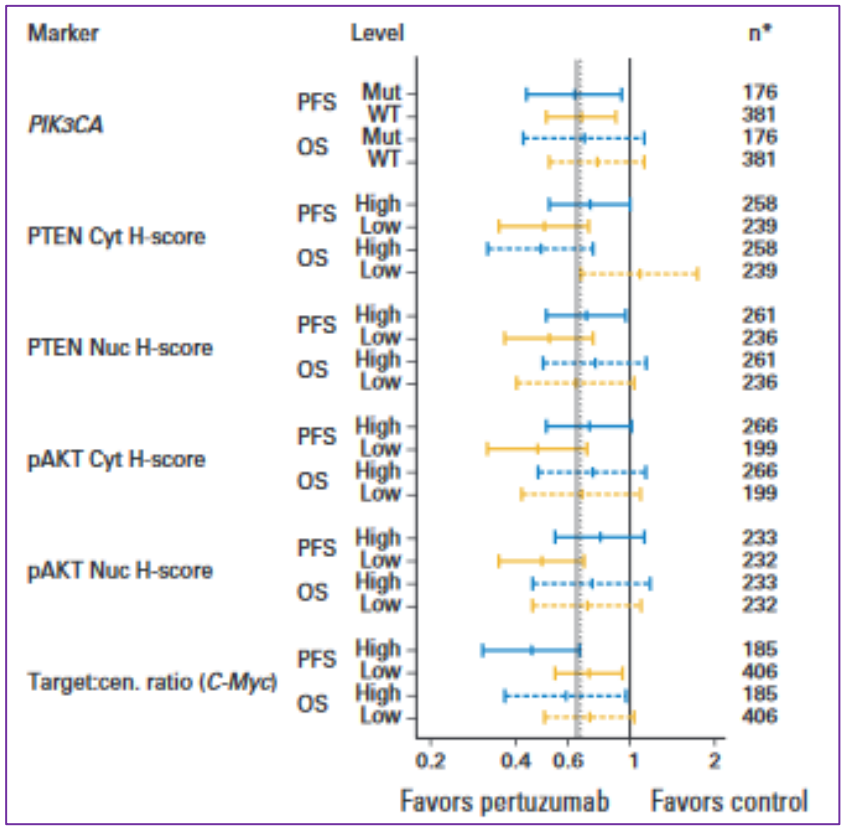
San Antonio Breast Cancer Symposium – December 8-12, 2015

PERUSE – most frequent adverse events ≥ grade 3



Miles D et al. ECC 2015

HER2+: doppio blocco, in tutte le pazienti?



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Treatment of HER2-Positive Metastatic Breast Cancer

TO THE EDITOR: Swain and colleagues (Feb. 19 issue)[1] report an important overall survival benefit of 15.7 months for the addition of pertuzumab to trastuzumab and docetaxel as first-line treatment of metastatic breast cancer that is positive for human epidermal growth factor receptor 2 (HER2). The study included a large proportion of patients who did not receive adjuvant or neoadjuvant trastuzumab, which is in contrast with current clinical practice in most countries. It will be informative to know the overall survival specifically in patients who received adjuvant or neoadjuvant trastuzumab and the absolute improvement by adding pertuzumab, because this result may well differ from the reported 15.7 months.

Mette S. van Ramshorst, M.D.
Gabe S. Sonke, M.D., Ph.D.

THE AUTHORS REPLY: In response to van Ramshorst and Sonke regarding outcomes in the subgroup of 88 patients with prior trastuzumab treatment for early breast cancer: the hazard ratio for death from any cause favored the pertuzumab group (in which patients received pertuzumab, trastuzumab, and docetaxel; hazard ratio, 0.80; 95% confidence interval, 0.44 to 1.47); owing to the small number of patients, the confidence intervals were wide. The median overall survival was 46.6 months among 41 patients in the control group (in which patients received placebo, trastuzumab, and docetaxel) and 53.8 months among 47 patients in the pertuzumab group.

Although the proportion of patients with prior trastuzumab treatment was lower in our study than in current clinical practice, historical context is important. Study recruitment began

Baselga, JCO 2014

HER2+: la II linea, TDM-1

EMILIA Phase III Study: T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC

Stratified by world region, number of previous chemotherapy regimens for MBC or unresectable locally advanced breast cancer, presence of visceral disease

Patients with HER2-positive locally advanced or MBC* (N = 980)

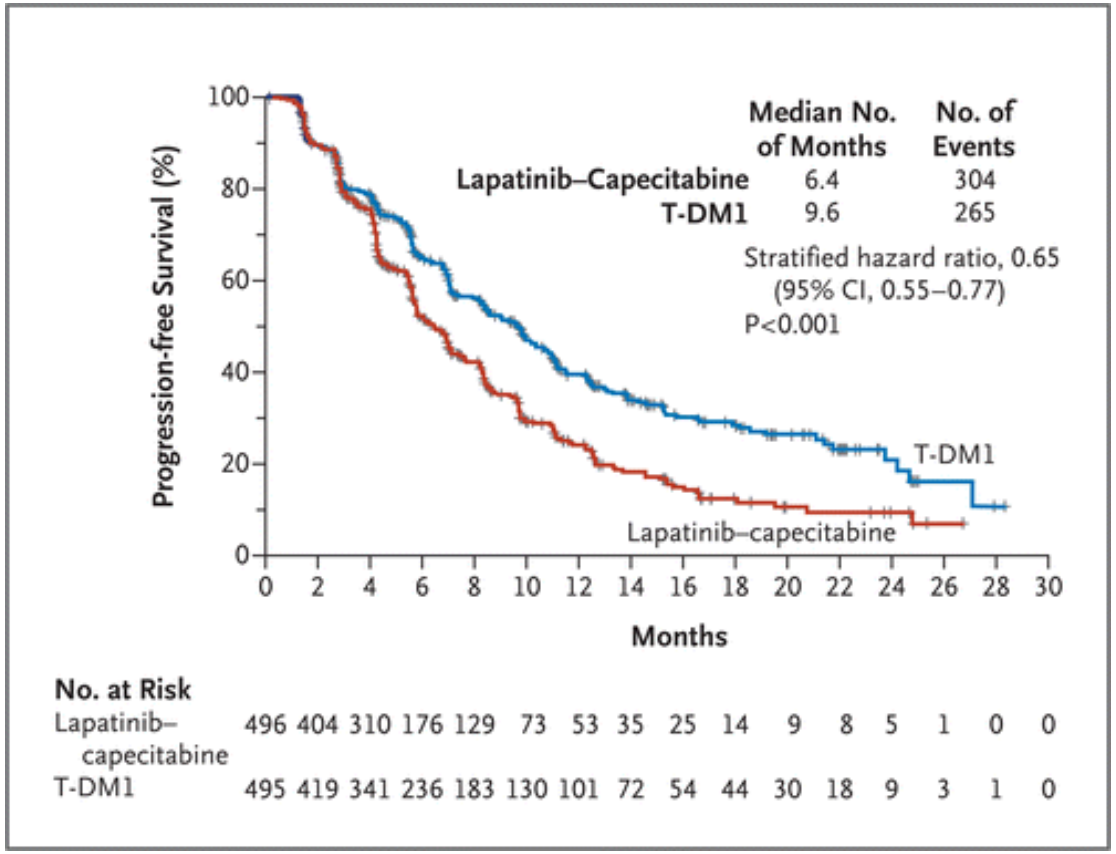
*All pts received previous taxane and trastuzumab

- T-DM1 3.6 mg/kg by IV every 3 wks (n = 495)
- Capecitabine 1000 mg/m^2 orally twice daily on Days 1-14, every 3 wks + Lapatinib 1250 mg/day orally continuously (n = 496)

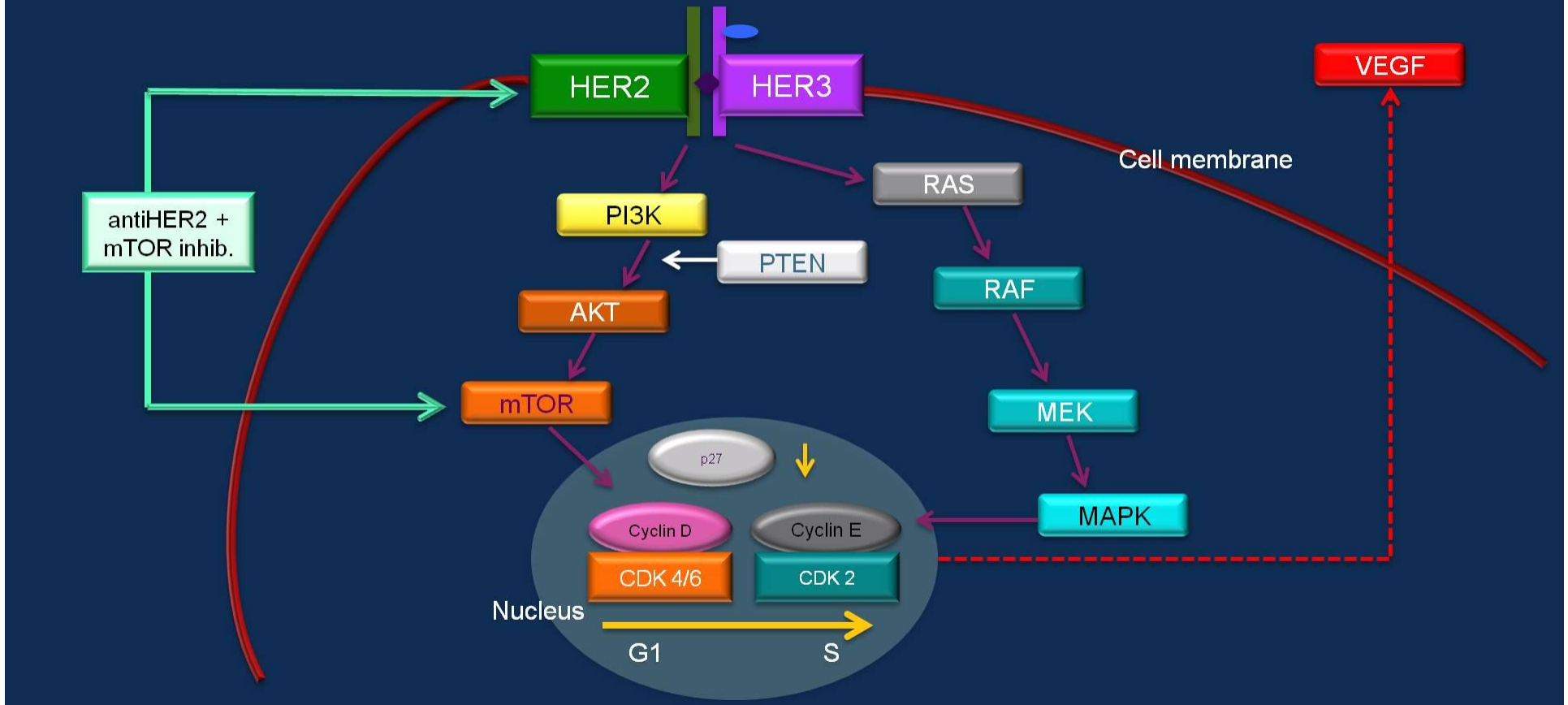
→ *PD*

- Primary endpoint: PFS by IRF, OS, safety
- Secondary endpoints: QoL (FACT B), DOR, PFS by investigator assessment

Verma S, et al. NEJM 2012;367:1783-91.



Simultaneous blockade of the HER2 pathway



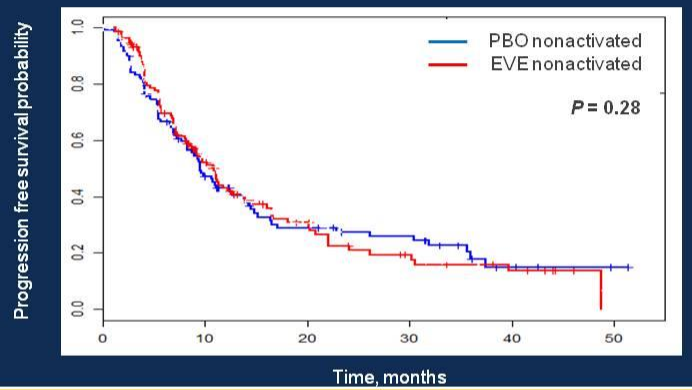
PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Miguel Martin

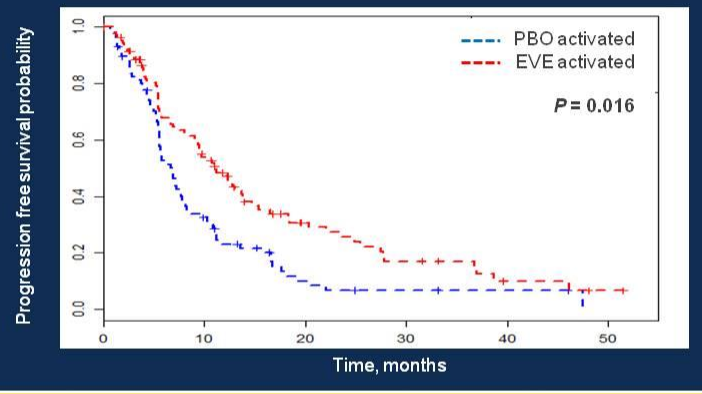
Presented By Miguel Martin at 2016 ASCO Annual Meeting

BOLERO-1 and BOLERO-3 Combined Analysis: PFS Benefit of EVE in Patients With Hyperactive PI3K Pathway

Pooled analysis: KM curve by treatment in the PI3K non-activated group



Pooled analysis: KM curve by treatment in the PI3K activated group



PI3K pathway normal (55.9% in combined population)

Population	Treatment	n	Events	Median PFS, mo	HR (95% CI)
BOL-1	PBO	41	26	17.08	1.18 (0.72 – 1.95)
	EVE	72	40	18.17	
BOL-3	PBO	70	50	6.97	1.19 (0.8 – 1.77)
	EVE	67	49	6.77	
BOL-1 + BOL-3	PBO	111	76		1.19 (0.87 – 1.62)
	EVE	139	89		

PI3K pathway hyperactive (44.1% in combined population)

Population	Treatment	n	Events	Median PFS, mo	HR (95% CI)
BOL-1	PBO	35	27	10.94	0.72 (0.44 – 1.17)
	EVE	66	44	13.90	
BOL-3	PBO	54	46	5.59	0.62 (0.39 – 0.98)
	EVE	42	31	8.05	
BOL-1 + BOL-3	PBO	89	73		0.67 (0.48 – 0.93)
	EVE	108	75		

Slamon D, et al. ASCO 2015. Abstract 512 [Oral].

Presented By Kimberly Blackwell at 2016 ASCO Annual Meeting