Inibitori di mTOR nel trattamento della malattia metastatica HER2-positiva: Lo studio BOLERO-1

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BOLERO-1:
First-Line Therapy in Women With HER2^{+} Advanced Breast Cancer

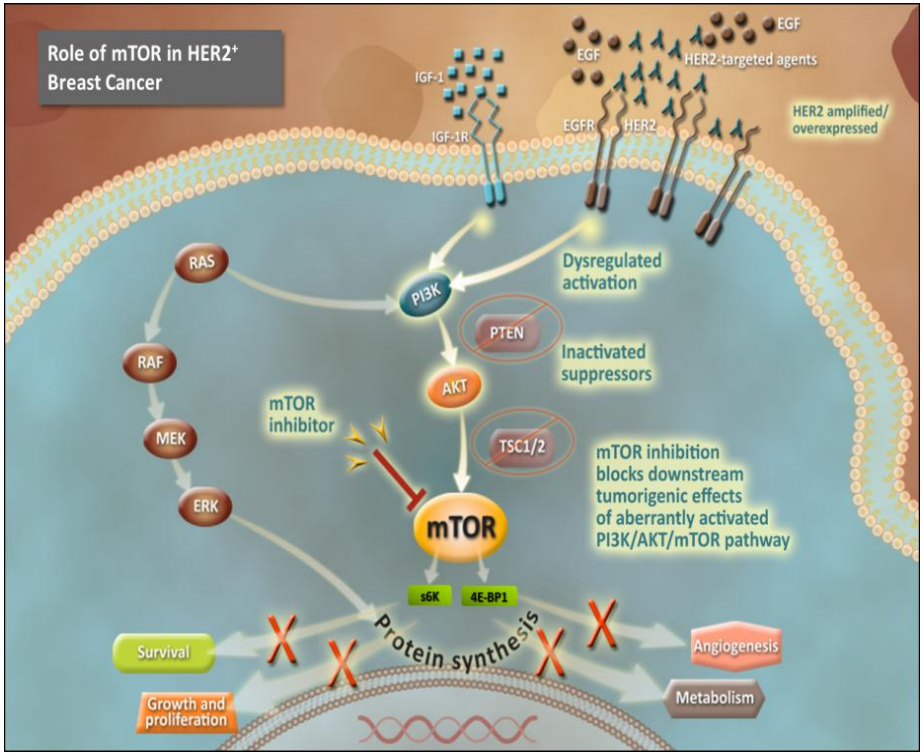
Targeting HER2$^+$ Advanced Breast Cancer

- HER2 overexpression occurs in ≈ 25% of all breast cancers and is associated with aggressive disease[1]
- HER2-targeted agents (TRAS and pertuzumab), in combination with chemotherapy (commonly taxanes), are recommended for first-line treatment of patients with HER2$^+$ advanced breast cancer[2-4]
- However, inherent resistance (lack of response) or acquired resistance (progression following a response) is common[5]
  - Of patients receiving first-line TRAS + paclitaxel, ≈ 38% did not achieve a response and half progressed within 14.5 months[6]
- Therefore, novel agents that can delay resistance are needed for patients with HER2$^+$ advanced breast cancer

Ferretti G, et al. *Curr Opin Obstet Gynecol*. 2007;19(1):56-62. 2. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V3.2014. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed December 8, 2014. 3. Cardoso F, et al. *Ann Oncol*. 2014;25(10):1871-1888. 4. Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099. 5. Hurvitz SA, et al. *Cancer Treat Rev*. 2013;39(3):219-229. 6. Baselga J, et al. *Ann Oncol*. 2014;25(3):592-598.

Aberrant PI3K/AKT/mTOR Pathway Activation May Lead to HER2–Targeted Therapy Resistance

- HER2 signaling relies heavily on the PI3K/AKT/mTOR pathway[1]
- Aberrant activation of the PI3K/AKT/mTOR pathway is associated with tumor growth and resistance to anticancer therapies[1]



Bender LM, Nahta R. *Front Biosci*. 2008;13:3906-3912; Houghton PJ. *Clin Cancer Res*. 2010;16(5):1368-1372; Pohlmann PR, et al. *Clin Cancer Res*. 2009;15(24):7479-7491; Cully M, et al. *Nat Rev Cancer*. 2006;6(3):184-192.

mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

1. LoRusso PM. *Oncology*. 2013;84(1):43-56.

Activity of the mTOR Inhibitor Everolimus in HER2$^+$ Breast Cancer

  - Combining EVE and TRAS resulted in greater inhibition of tumor growth than either agent alone in both TRAS-sensitive and -resistant breast cancer cell models[1-3]
  - EVE enhanced taxane-mediated growth inhibition of breast cancer stem cells and xenograft tumors[4]
- EVE + TRAS and the chemotherapy Paclitaxel demonstrated promising activity in patients with HER2$^+$ advanced breast cancer who progressed during prior trastuzumab and taxane therapy (N = 55)[5]
  - Overall response rate, 21.8%; clinical benefit rate, 36.4%
  - Median PFS, 5.5 months
  - Median OS, 18.1 months

- In BOLERO-3, the addition of EVE to TRAS + vinorelbine resulted in a significant 22% reduction in the risk of progression (7 vs 5.78 months; *P* = .0067)[6]

Clin Cancer Res. 2009;15(23):7266-7276. 4. Zhang X, et al. *Eur J Cancer*. 48(10):1581-1592.
5. Hurvitz SA, et al. *Breast Cancer Res Treat*. 2013;141(3):437-446. 6. Andre F, et al. *Lancet Oncol*. 2014;15(6):580-591.

A Different Treatment Effect Was Observed in the HR⁻ Subpopulation

- In BOLERO-3 (EVE + TRAS + vinorelbine in patients with TRAS-resistant and taxane-pretreated HER2⁺ advanced breast cancer), clinical benefit appeared more pronounced in the HR⁻ subpopulation[1]

	PFS Hazard Ratio (95% CI)
HR⁻ subpopulation	***0.65 (0.48-0.87)***
HR⁺ subpopulation	***0.93 (0.72-1.20)***

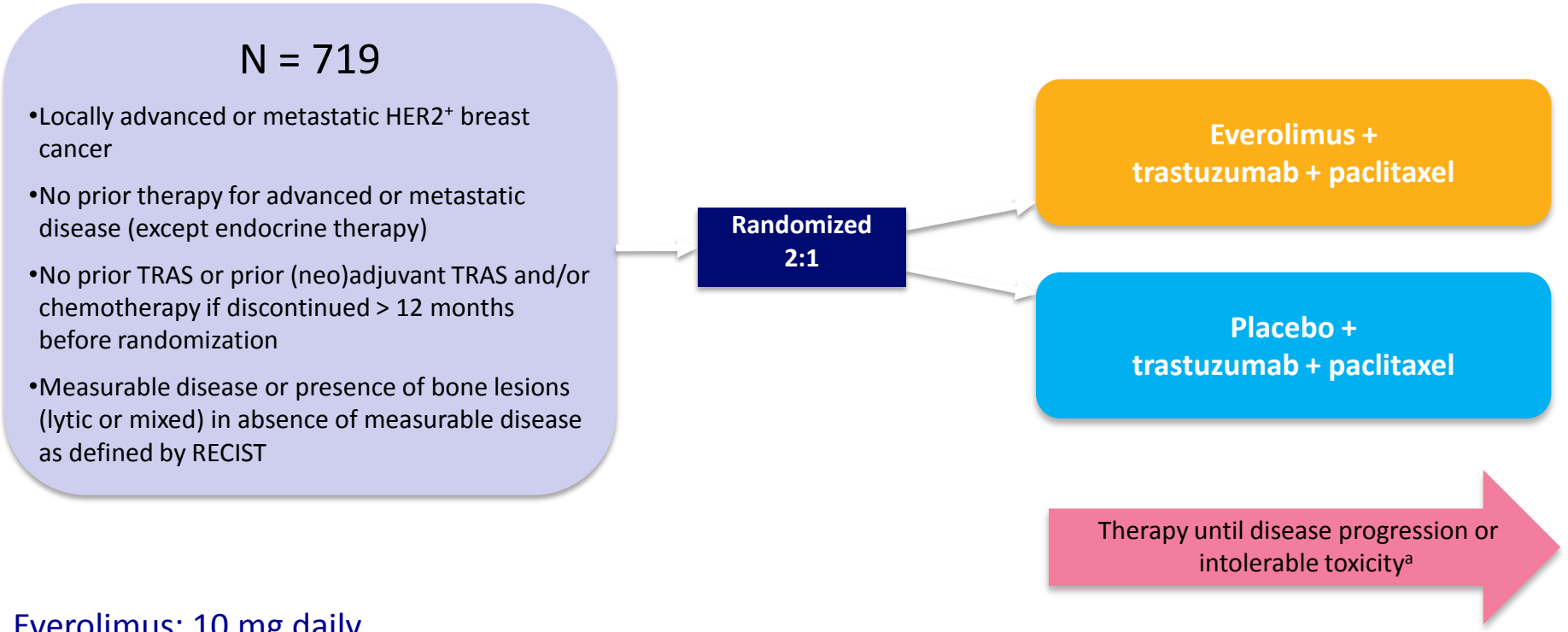
- Similar observations were described in recent phase 3 trials with other HER2-targeted agents, such as lapatinib, pertuzumab (CLEOPATRA), and T-DM1 (EMILIA), and in 7 trials in the neoadjuvant setting[2-5]
- In HER2⁺ breast cancer, patients with HR⁻ disease may derive greater PFS benefit from targeted therapies, since the absence of a functional hormone receptor may eliminate a potential escape mechanism for HER2-targeted therapies[1,3-5]

- **To prospectively validate this hypothesis, BOLERO-1 was amended to include PFS analysis in the HR⁻ subpopulation as a second primary endpoint[6]**

Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. 4. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.
5. Nahta R, O'Regan RM. *Breast Cancer Res Treat.* 2012;135(1):39-48. 6. Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

BOLERO-1 (TRIO 019): Study Design

- Phase 3 trial in first-line HER2$^+$ advanced breast cancer



Everolimus: 10 mg daily
Trastuzumab: 4-mg/kg loading dose on day 1 of cycle 1 followed by 2-mg/kg weekly doses
Paclitaxel: 80 mg/m^2 weekly

event; RECIST, Response Evaluation Criteria In Solid Tumors.

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Eligibility Criteria

Inclusion Criteria

- Women (age ≥ 18 years) with HER2-overexpressing, locally advanced or metastatic breast cancer
- Measurable disease or bone lesions (lytic or mixed) in the absence of measurable disease as defined by RECIST
- TRAS-naive or prior TRAS and/or chemotherapy (including taxanes) > 12 months before randomization
- ECOG performance status of 0 or 1

Key Exclusion Criteria

- Prior therapy with mTOR inhibitor
- Treatment for locally advanced or metastatic disease
- History of brain metastases
- Active cardiac disease or history of cardiac dysfunction

Eastern Cooperative Oncology Group.
Hurvitz SA, et al. SABCS 2014 [abstract S6-01].
Hurvitz SA, et al. ASCO 2012 [abstract TPS648].

Endpoints and Statistical Considerations

- The study had dual primary objectives—PFS by investigator assessment:
  - In the full study population
  - In the HR^- subpopulation
- The study was considered positive if either objective was met
- To conserve the type I error rate, ⟨ was split conservatively in favor of the full population
- Secondary endpoints included OS, ORR, CBR, time to response, duration of response, and safety

	⟨ Split	Rationale	Threshold
Full population	***80% (⟨ = 0.02)***	***Preserve maximum power***	***P = .0174***
HR^- subpopulation	***20% (⟨ = 0.005)***	***Provide statistical validity for the test independent of full population***	***P = .0044***

clinical benefit rate; ORR, overall response rate.

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Baseline Characteristics

	Full Population		HR^- Subpopulation	
	EVE + TRAS + PAC (n = 480)	PBO + TRAS + PAC (n = 239)	EVE + TRAS + PAC (n = 208)	PBO + TRAS + PAC (n = 103)
Race, %				
Caucasian	*45*	*41*	*46*	*38*
Asian	*41*	*44*	*41*	*46*
Black	*5*	*5*	*5*	*6*
Native American	*1*	*0*	*1*	*0*
Other	*8*	*11*	*7*	*11*
ECOG performance status, %				
0	*58*	*62*	*61*	*63*
1	*42*	*38*	*39*	*37*
Extent of disease at study entry, %				
Locally advanced	*7*	*7*	*8*	*8*
Metastatic	*93*	*93*	*92*	*92*
Hormone receptor status, %				
HR^+ (ER^+ and/or PgR^+)	*57*	*57*	*0*	*0*
HR^- (ER^- and PgR^-)	*43*	*43*	*100*	*100*
Visceral involvement, %	*70*	*71*	*65*	*70*
Lung	*45*	*43*	*43*	*41*
Liver	*37*	*46*	*33*	*49*
Lung and liver	*15*	*21*	*14*	*20*
Bone involvement, %	*44*	*49*	*33*	*45*

Prior Antineoplastic Therapy

	Full Population		HR⁻ Subpopulation	
	EVE + TRAS + PAC (n = 480), %	PBO + TRAS + PAC (n = 239), %	EVE + TRAS + PAC (n = 208), %	PBO + TRAS + PAC (n = 103), %
(Neo)adjuvant TRAS	*11*	*10*	*11*	*13*
(Neo)adjuvant chemotherapy	*45*	*52*	*39*	*52*
Any taxane	*24*	*27*	*25*	*25*
Anthracyclines	*39*	*47*	*34*	*50*
Other chemotherapy	*40*	*46*	*36*	*50*
Hormone therapy for HR⁺ disease	*25*	*23*	*N/A*	*N/A*
(Neo)adjuvant	*19*	*20*		
Metastatic only	*1*	*< 1*		
Both (neo)adjuvant and metastatic	*5*	*3*		
Radiotherapy	*36*	*41*	*26*	*39*
Surgery	*100*	*100*	*100*	*100*

N/A, not applicable.

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Patient Disposition

	Full Population		HR⁻ Subpopulation	
	EVE + TRAS + PAC (n = 480), %	PBO + TRAS + PAC (n = 239), %	EVE + TRAS + PAC (n = 208), %	PBO + TRAS + PAC (n = 103), %
Randomized	***100***	***100***	***100***	***100***
Treated	***98***	***100***	***99***	***100***
Protocol therapy ongoing	***10***	***11***	***14***	***13***
Study discontinued due to				
Disease progression	***51***	***65***	***43***	***65***
Consent withdrawal	***13***	***13***	***16***	***14***
Adverse event(s)	***12***	***4***	***14***	***4***
New cancer therapy	***5***	***3***	***5***	***3***
Administrative problems	***3***	***3***	***5***	***2***
Death	***3***	***0***	***1***	***0***
Protocol deviation	***1***	***1***	***1***	***0***
Lost to follow-up	***< 1***	***0***	***0***	***0***
Abnormal test results	***< 1***	***0***	***0***	***0***

- The median duration of study follow-up was 41.3 months

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

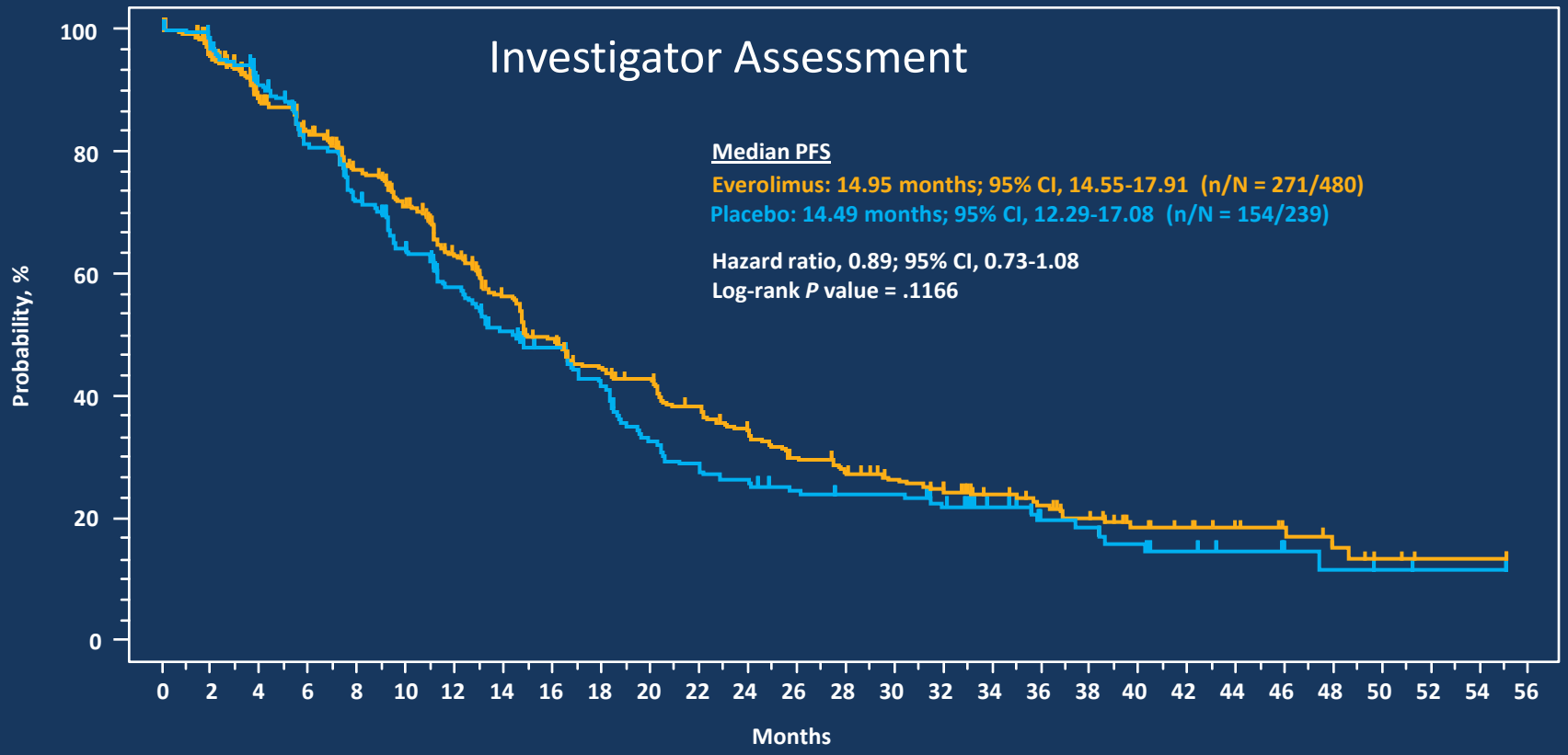
Treatment Exposure

	Full Population		HR⁻ Subpopulation	
	EVE + TRAS + PAC (n = 472)	PBO + TRAS + PAC (n = 238)	EVE + TRAS + PAC (n = 206)	PBO + TRAS + PAC (n = 103)
Median relative dose intensity				
Everolimus	***0.5***	***1***	***0.5***	***1***
Trastuzumab	***1***	***1***	***1***	***1***
Paclitaxel	***0.7***	***0.8***	***0.7***	***0.8***
Median duration of exposure, weeks				
Everolimus	***41***	***48***	***45***	***41***
Trastuzumab	***49***	***48***	***53***	***41***
Paclitaxel	***31***	***32***	***31***	***31***

- The median relative dose intensity of everolimus was 0.5
- Median exposure was longer for EVE than for PAC (41 vs 31 weeks)

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

PFS Full Population
Investigator Assessment



No. of patients still at risk

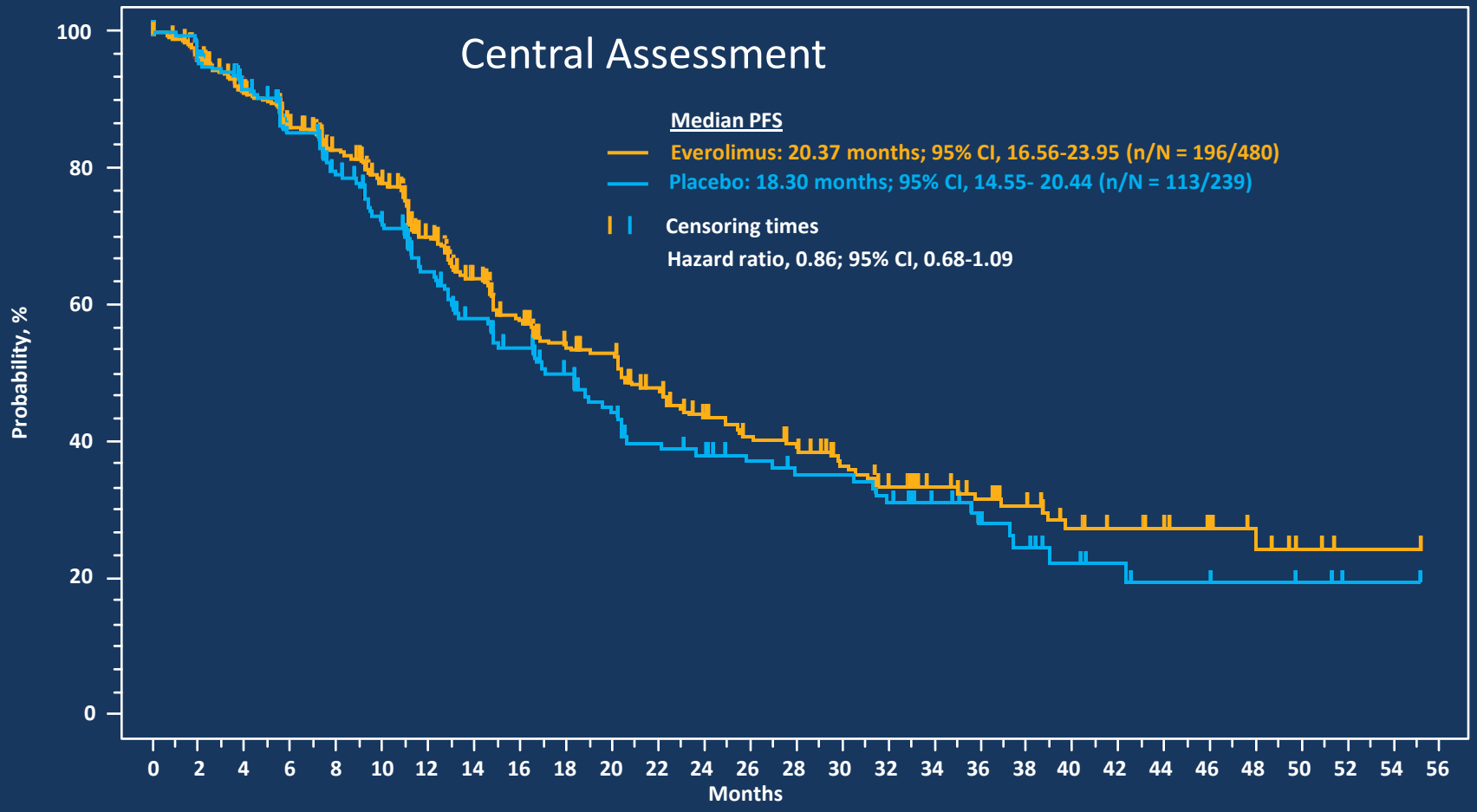
Everolimus	480	416	365	324	289	260	217	178	151	130	122	107	94	80	72	63	58	48	42	35	26	21	17	13	10	5	3	3	0
Placebo	239	221	199	166	144	123	106	91	80	69	53	47	43	38	36	36	31	24	17	15	12	9	7	6	4	3	1	1	0

- One-sided *P* value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and visceral metastasis (Y/N) from IWRS.

IWRS, interactive web response system; N, no; Y, yes.

Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. Figure reproduced with permission of Sara Hurvitz, MD.

PFS Full Population
Central Assessment

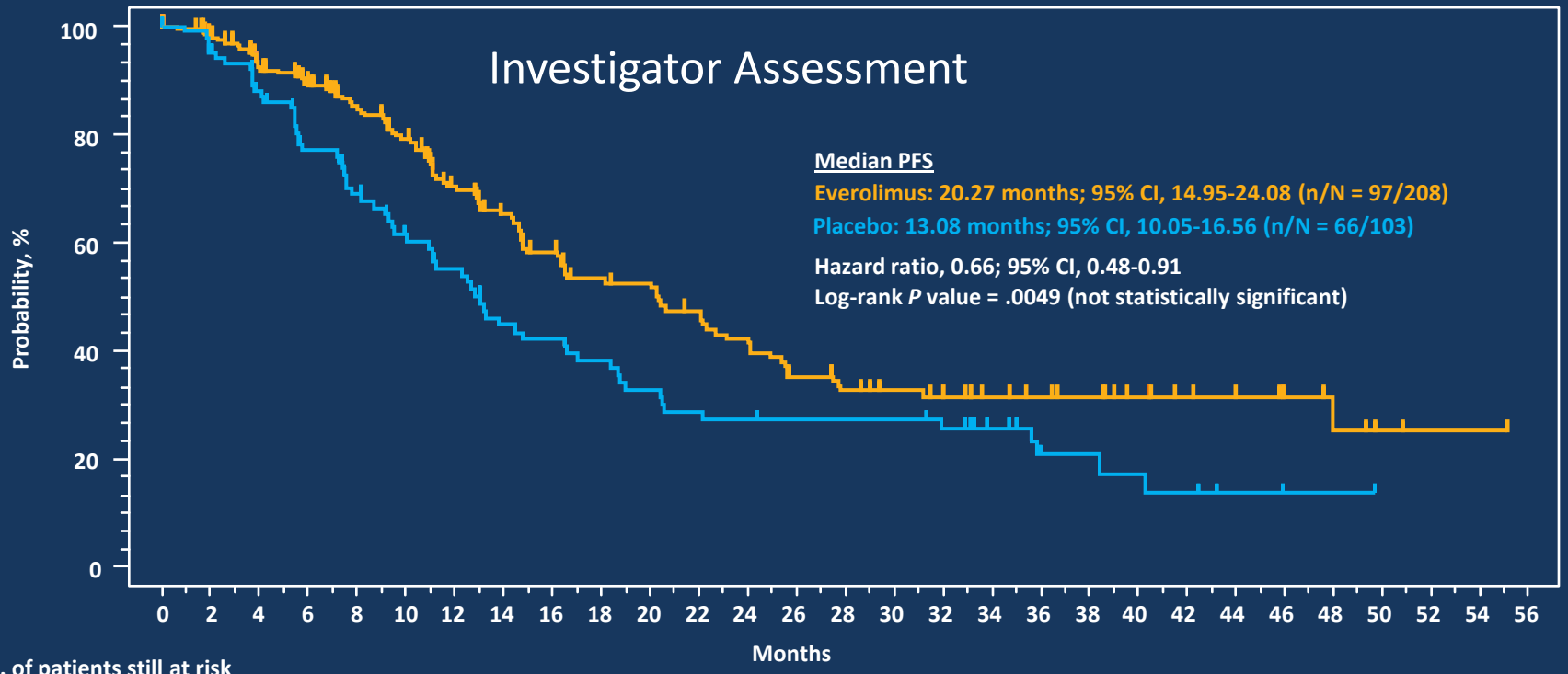


No. of patients still at risk

Everolimus	480	406	352	309	281	252	208	168	140	123	117	100	84	74	68	57	50	40	35	31	24	18	15	11	9	5	3	3	0
Placebo	239	212	189	158	138	120	97	82	73	63	53	46	43	38	35	35	29	23	17	14	10	8	6	6	5	4	1	1	0

Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. Figure reproduced with permission of Sara Hurvitz, MD.

PFS HR⁻ Subpopulation
Investigator Assessment



No. of patients still at risk

Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

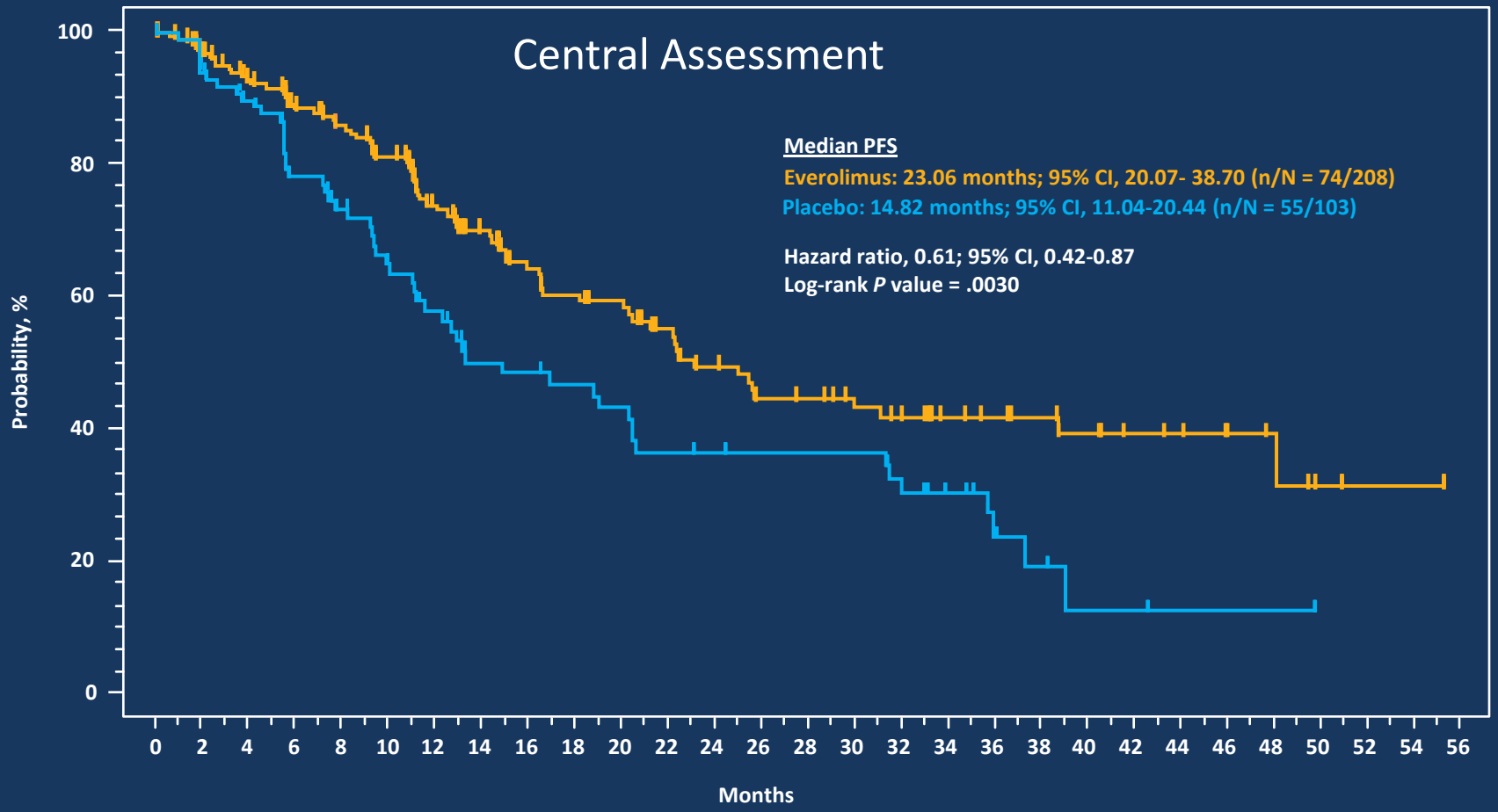
- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

Sensitivity analysis without censoring patients at the start of new antineoplastic therapy:

- Median PFS and 95% CIs
  - 20.27 months (14.82-24.08) for EVE (n = 102)
  - 12.88 months (10.94-16.56) for PBO (n = 68)
- Hazard ratio, 0.66 [0.48-0.9]; *P* = .0043

Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. Figure reproduced with permission of Sara Hurvitz, MD.

PFS HR⁻ Subpopulation
Central Assessment



No. of patients still at risk

Everolimus	208	174	156	139	131	118	96	78	65	60	57	49	42	36	34	30	28	22	20	18	15	10	9	6	5	2	1	1	0
Placebo	103	93	81	63	55	46	39	31	30	27	25	21	20	19	19	19	15	12	6	4	2	2	1	1	1	0	0	0	0

Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. Figure reproduced with permission of Sara Hurvitz, MD.

Response Rates

Response Rate, % (95% CI)	Full Population		HR^- Subpopulation	
	EVE + TRAS + PAC (n = 480)	PBO + TRAS + PAC (n = 239)	EVE + TRAS + PAC (n = 208)	PBO + TRAS + PAC (n = 103)
Overall response rate	***67.1 (62.7-71.3)***	***69.0 (62.8-74.8)***	***73.1 (66.5-79.0)***	***70.9 (61.1-79.4)***
	P = .7276		***P = .4085***	
Clinical benefit rate	***75.8 (71.7-79.6)***	***81.2 (75.6-85.9)***	***78.8 (72.7-84.2)***	***79.6 (70.5-86.9)***
	P = .9573		***P = .6382***	

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Overall Survival Results Are Immature

- As of the cutoff date (May 30, 2014), 263 deaths were recorded in the full population
  - 179 (37.3%) in the everolimus arm
  - 84 (35.1%) in the placebo arm
- The trial is ongoing and analyses of overall survival will be conducted following 438 deaths in the full population

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Most Frequent AEs

	EVE + TRAS + PAC (n = 472), %			PBO + TRAS + PAC (n = 238), %		
	Any Grade	*Grade 3*	*Grade 4*	*Any Grade*	*Grade 3*	*Grade 4*
Stomatitis	*67*	*13*	*0*	*32*	*1*	*0*
Diarrhea	*57*	*9*	*0*	*47*	*4*	*0*
Alopecia	*47*	*< 1*	*0*	*53*	*0*	*0*
Rash	*40*	*1*	*0*	*21*	*< 1*	*0*
Cough	*40*	*< 1*	*0*	*33*	*1*	*0*
Pyrexia	*39*	*2*	*0*	*27*	*1*	*0*
Fatigue	*35*	*5*	*0*	*36*	*3*	*0*
Epistaxis	*33*	*0*	*0*	*18*	*0*	*0*
Peripheral edema	*33*	*1*	*0*	*24*	*< 1*	*0*
Nausea	*33*	*1*	*0*	*35*	*1*	*0*
Peripheral neuropathy	*29*	*4*	*0*	*24*	*5*	*0*
Headache	*28*	*1*	*0*	*29*	*1*	*0*
Vomiting	*26*	*1*	*0*	*23*	*3*	*0*
Pneumonitis[a]	*16*	*4*	*1*	*4*	*< 1*	*0*
Hematologic						
Neutropenia	*38*	*21*	*4*	*25*	*11*	*4*
Anemia	*31*	*9*	*1*	*16*	*3*	*0*

Fatal Events

	Full Population		HR⁻ Subpopulation	
	EVE + TRAS + PAC (n = 472), %	PBO + TRAS + PAC (n = 238), %	EVE + TRAS + PAC (n = 206), %	PBO + TRAS + PAC (n = 103), %
All deaths	*37.7*	*35.3*	*35*	*43.7*
On-treatment deaths	*4.7*	*0.8*	*3.4*	*1.9*
Due to disease progression	*1.1*	*0.8*	*0.5*	*1.9*
Due to AE	*3.6*	*0*	*2.9*	*0*
Pneumonitis	*0.6*	*0*	*0.5*	*0*
Pulmonary embolism	*0.4*	*0*	*0*	*0*
Respiratory failure	*0.4*	*0*	*1*	*0*
Pulmonary edema	*0.2*	*0*	*0*	*0*
Pneumonia	*0.4*	*0*	*0.5*	*0*
Cardiorespiratory arrest	*0.2*	*0*	*0*	*0*
Sepsis	*0.6*	*0*	*0.5*	*0*
Fall	*0.2*	*0*	*0.5*	*0*
Diabetes	*0.2*	*0*	*0*	*0*
Cerebrovascular accident	*0.2*	*0*	*0*	*0*

Factors Influencing Deaths Due to AE

- All but 1 on-treatment deaths due to AEs occurred early in the study (during the first 15 months of study, which had a median duration of study follow-up of 41.3 months)
  - This may be associated with lack of experience in managing AEs of EVE when combined with chemotherapy
    - There appeared to be a higher rate of on-treatment deaths in regions with limited experience with EVE
  - In some cases, the protocol-defined AE management guidelines were not followed
  - Only 1 additional on-treatment death due to an AE was reported after the IDMC sent a communication to the investigators to reinforce the management of specific AEs
- Overall, this reinforces that proactive monitoring and early management of AEs are necessary in patients receiving EVE in combination with chemotherapy

independent data monitoring committee.

Safety in the HER2$^+$ Patient Population

- The safety profile of everolimus in patients with HER2$^+$ advanced breast cancer may be impacted by the chemotherapy regimen, everolimus dose, and patient population

HER2$^+$ Trial[1,2]	HER2$^+$ Disease Setting	EVE Dose	Chemotherapy
BOLERO-1	***First-line***	***10 mg***	***Paclitaxel***
BOLERO-3	***TRAS-resistant and taxane-pretreated***	***5 mg***	***Vinorelbine***

1. Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. 2. Andre F, et al. *Lancet Oncol*. 2014;15(6):580-591.

Everolimus Exhibits Distinct Safety Profiles in $HR^+/HER2^-$ vs $HER2^+$ Disease

- In everolimus trials, AEs were generally less common in patients with $HR^+/HER2^-$ vs $HER2^+$ advanced breast cancer, potentially reflective of the hormonal therapy vs chemotherapy combination agents, respectively[1-3]
- The safety profile of everolimus + exemestane in patients with $HR^+/HER2^-$ advanced breast cancer observed in BOLERO-2 has been confirmed in the large, ongoing, noninterventional study BRAWO and the expanded-access study BALLET[3-5]

Hurvitz SA, et al. SABCS 2014 [abstract S6-01]. 2. Andre F, et al. *Lancet Oncol*. 2014;15(6):580-591.
3. Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529. 4. Jackisch C, et al. SABCS 2014 [abstract P5-19-12].
5. Jerusalem G, et al. SABCS 2014 [abstract P5-19-02].

Summary

- **Primary objective was not met in the full study population**
- Median PFS was prolonged by 7.2 months in the HR^- subpopulation (20.27 months in the EVE arm vs 13.08 months in the PBO arm; hazard ratio, 0.66, *P* = .0049)
  - However, the protocol prespecified analysis did not cross the statistical significance threshold (*P* = .0044)
- Safety profile was consistent with results previously reported in BOLERO-3
- Higher rate of AE-related on-treatment deaths were reported for EVE vs PBO (3.6% vs 0%)
  - All but 1 AE-related on-treatment deaths occurred ≤ 15 months of study start
  - Proactive monitoring and early management of AEs in patients treated with everolimus and chemotherapy is critical
- OS follow-up is ongoing until 438 events reported

Hurvitz SA, et al. SABCS 2014 [abstract S6-01].

Spunti di riflessione

- La terapia endocrina avrebbe avuto un impatto nella popolazione HR+ (mancano dati sul tipo di trattamento endocrino precendente) ?

- Valutazioni statistiche (significatività vs impatto clinico)

STUDI IN CORSO:

- NCT 02153943 → Eve + Let + Trast
- NCT01791478 → PI3K inh + Let + Trast
- NSABP B52 → Let + CT + dual block anti HER2

…. Trast + Eve