V Sessione.Problematiche legate all'impiego di terapia sistemica

Farmaci a bersaglio molecolare nella malattia metastatica ormonoresponsiva

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HR+/HER2-
metastatic breast cancer

SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

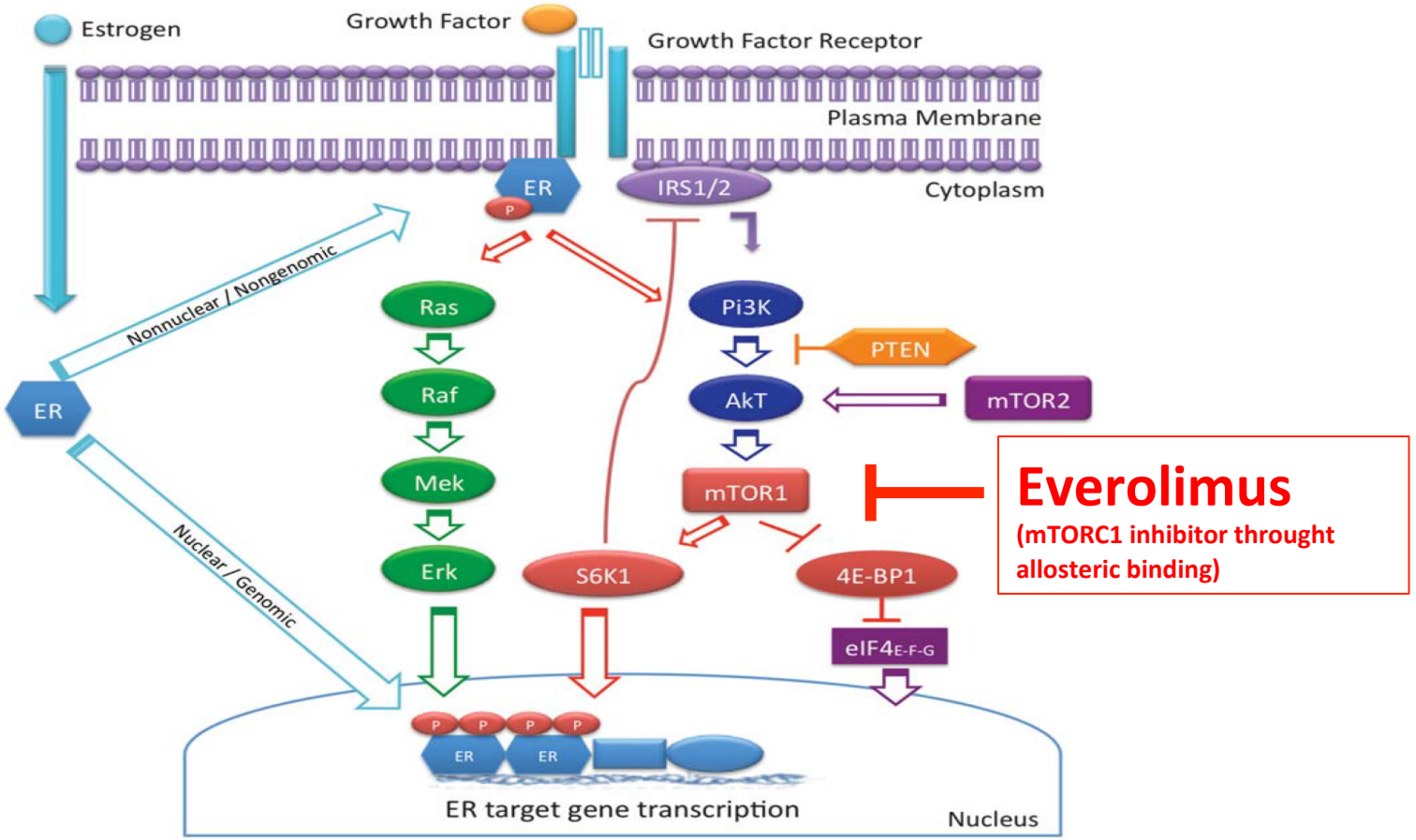
Postmenopausal Patients

- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)**
- **Steroidal aromatase inactivator (exemestane)**[1]
- **Fulvestrant**
- **Tamoxifen or Toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

[1] A single study (BOLERO-2) in women with hormone receptor-positive, HER-2 negative metastatic breast cancer and prior therapy with a nonsteroidal aromatase inhibitor demonstrated improvement in progression-free survival with the addition of everolimus (an mTOR inhibitor) to exemestane (HR 0.43; 95% CI, 0.35-0.54; log-rank $P < 0.001$) and with an increase in toxicity. No survival analysis is available. Consider the addition of everolimus to exemestane in women who fulfill the eligibility criteria of BOLERO-2.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PI3K/Akt/mTOR and endocrine pathways



One of the mechanisms of endocrine resistance is aberrant signaling of PI3KCA-Akt-mTOR pathway. There is a close interaction between mTOR pathway and ER. The kinase S6, a substrate of mTOR, phosphoyilates the activation function domain 1 of ER, which is responsable for ligand-independent receptor activation. Everolimus in combination with letrozole in neoadjuvant setting was more active than letrozole alone (Baselga J et al, JCO 2009). Inhibition of mTOR might overcome endocrine resistance.

Modified from Villareal-Garza et al, Ann Oncol 2012

BOLERO-2 (Ph III): Everolimus in Advanced BC

24 Countries, 196 sites

N = 724

- **Postmenopausal ER+,HER2-**
- **Advanced BC** (unresectable LABC or MBC)
- **NSAI refractory disease**:

recurrence during or within 12 mo after the end of adjuvant treatment

or

progression during or within 1 mo after the end of treatment for advanced disease

R
2:1

EVE 10 mg daily
+
EXE 25 mg daily (n = 485)

Placebo
+
EXE 25 mg daily (n = 239)

Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

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Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety

Key baseline characteristics

Median age	62 years
Race Caucasian Asian	 75% 20%
Visceral involvement	56%
Bone metastases	77%

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everol PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

Preplanned interim analysis after 359 PFS events

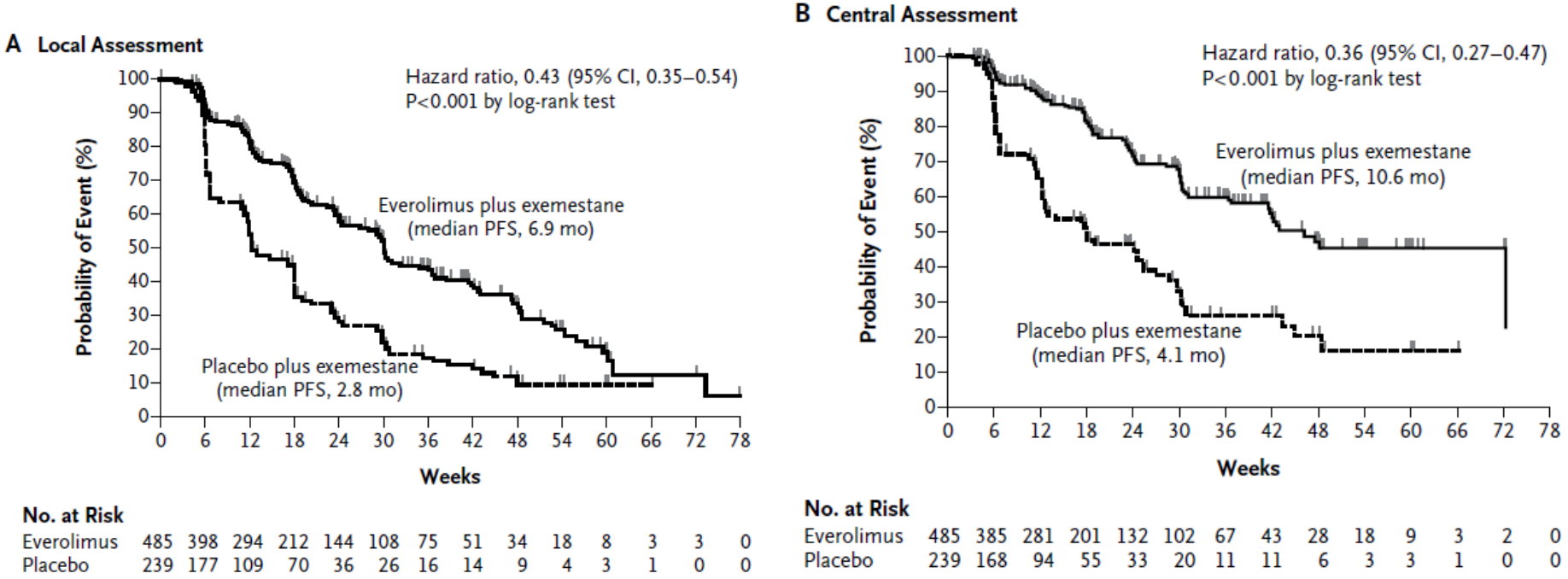
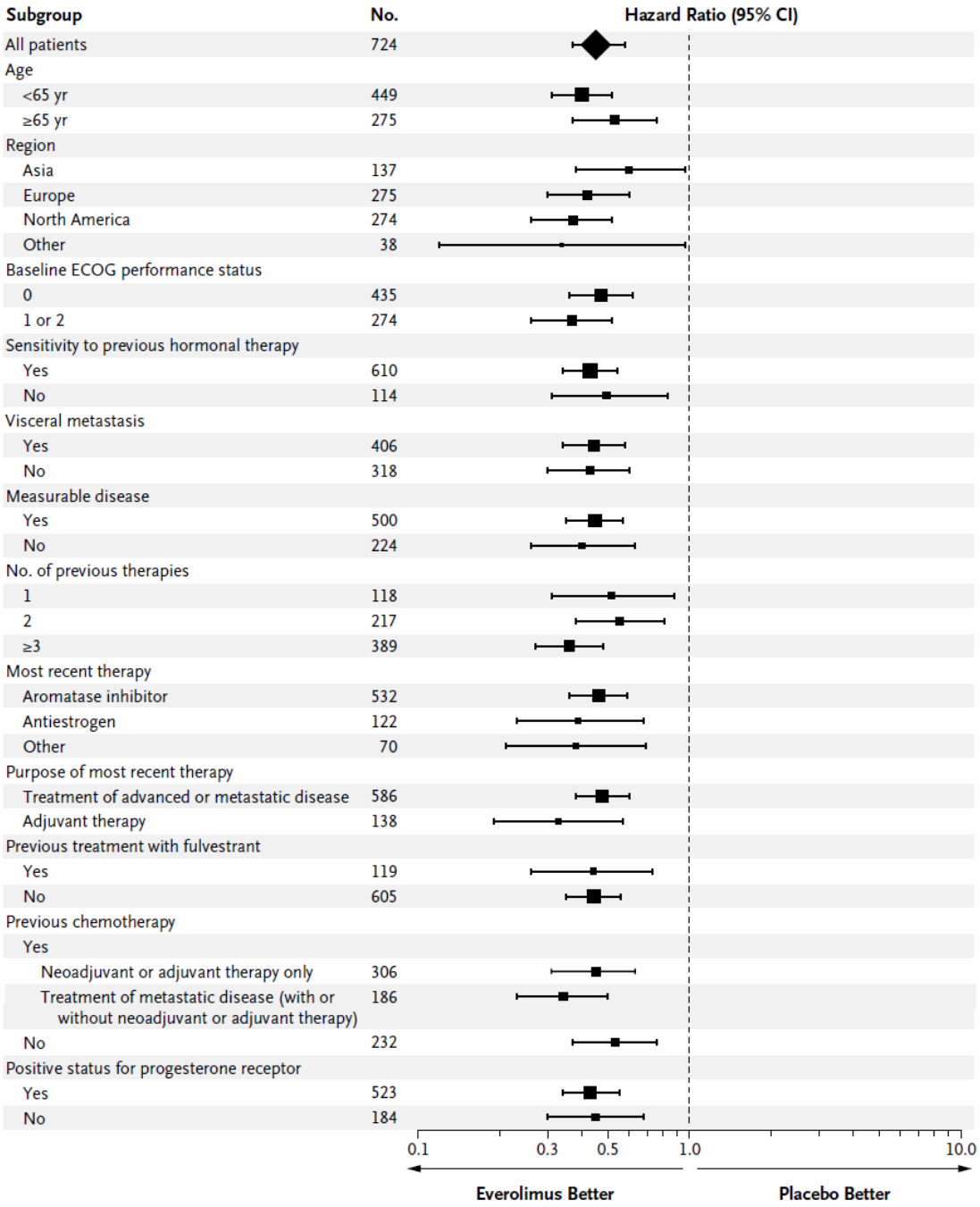


Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Panel A shows progression-free survival on the basis of local assessment of radiographic studies, and Panel B shows central assessment. PFS denotes progression-free survival.

Both analyses crossed the prespecified thresholds for significance

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529



PFS benefits were consistent in all subgroups

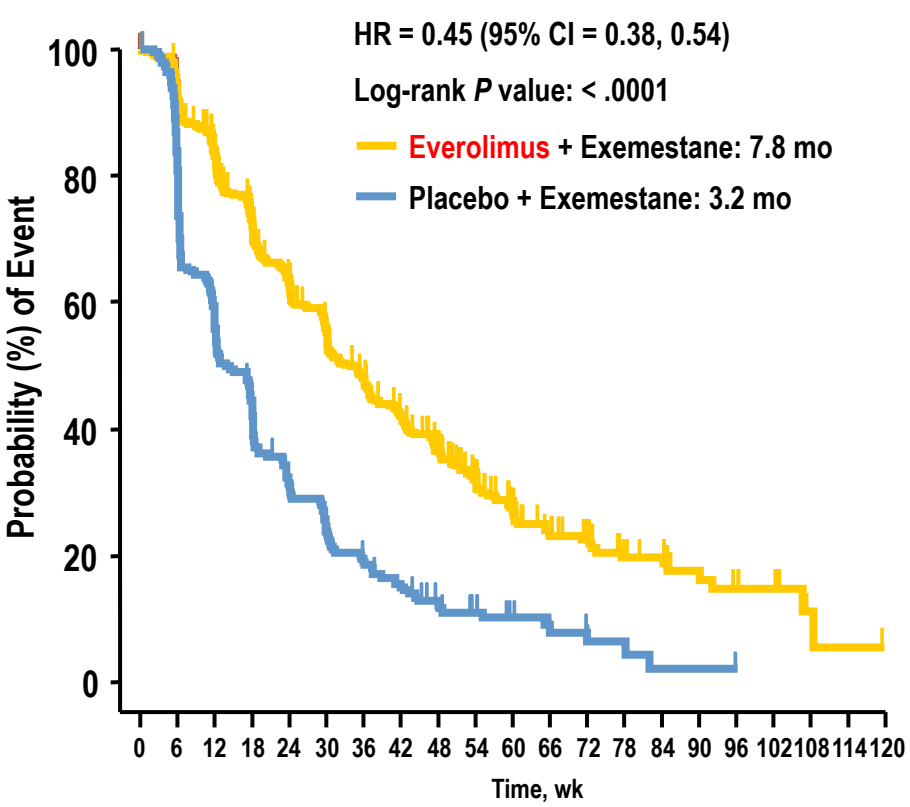
Baselga J et al. NEJM 2012;366:520-9

Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

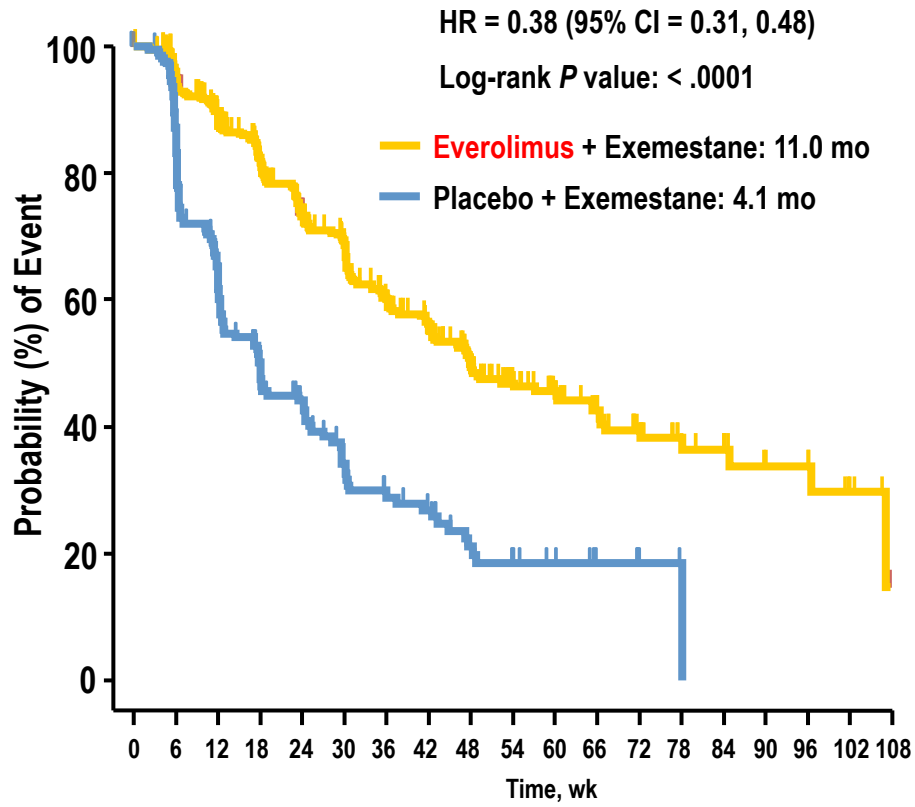
Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
Aspartate aminotransferase level increased	13	3	<1	6	1	0
Alanine aminotransferase level increased	11	3	<1	3	2	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Anemia	16	5	1	4	<1	<1

BOLERO-2 efficacy:

PFS at a median follow-up of 18 months



Local Assessment



Central Assessment

Addition of Everolimus to Exemestane more than doubled median PFS

Piccart M, et al. ASCO 2012, abstract #559.

BOLERO-2 (18 mo f/up): Overall Survival Was Numerically Better With Everolimus

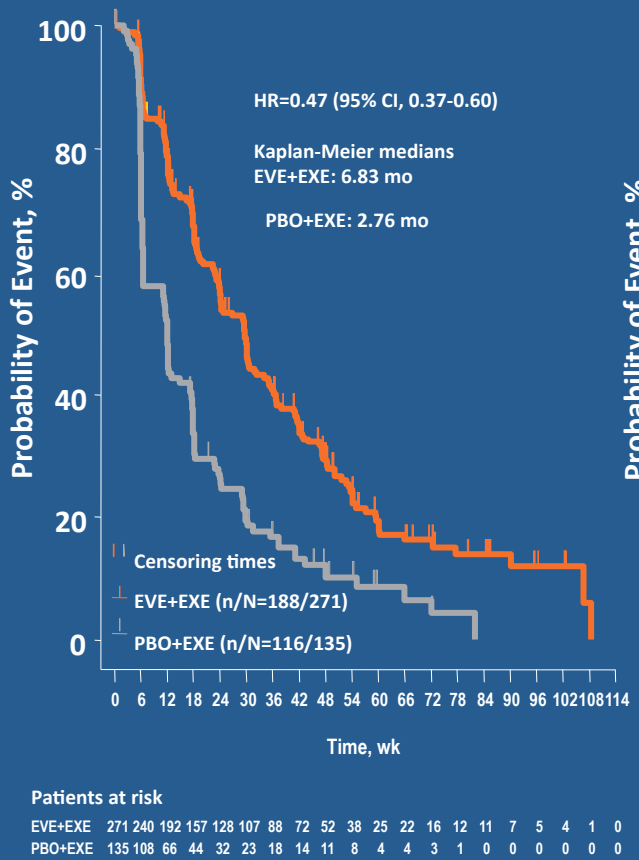
	PFS Interim[1] (7 mo follow-up)	PFS Update[2] (12 mo follow-up)	PFS Final[3] (18 mo update)
Cut-off Date	11-Feb-2011	8-Jul-2011	15-Dec-2011
OS events (EVE vs PBO%)	83 (10.6 vs 13.0%)	137 (17.3 vs 22.7%)	200 (25.4 vs 32.2%)
Δ OS events	**2.4%**	**5.4%**	**6.8%**

Abbreviations: EVE, everolimus; mo, month; OS, overall survival; PBO, placebo; PFS, progression-free survival; vs, versus.

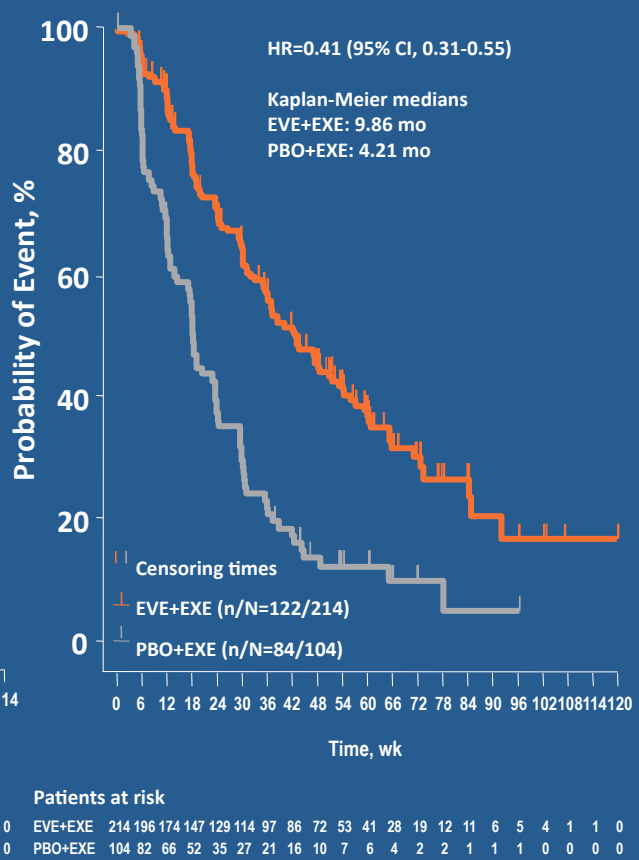
1. Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.
2. Hortobagyi G, et al. SABCS 2011; abstract S3-7 (oral).
3. Piccart M, et al. ASCO 2012; abstract 559 (poster).

BOLERO-2 (18-mo f/up): PFS Benefits Were Comparable In Patients With (A) Visceral Metastases, (B) Without Visceral Metastases, and (C) With Bone-Only Metastases

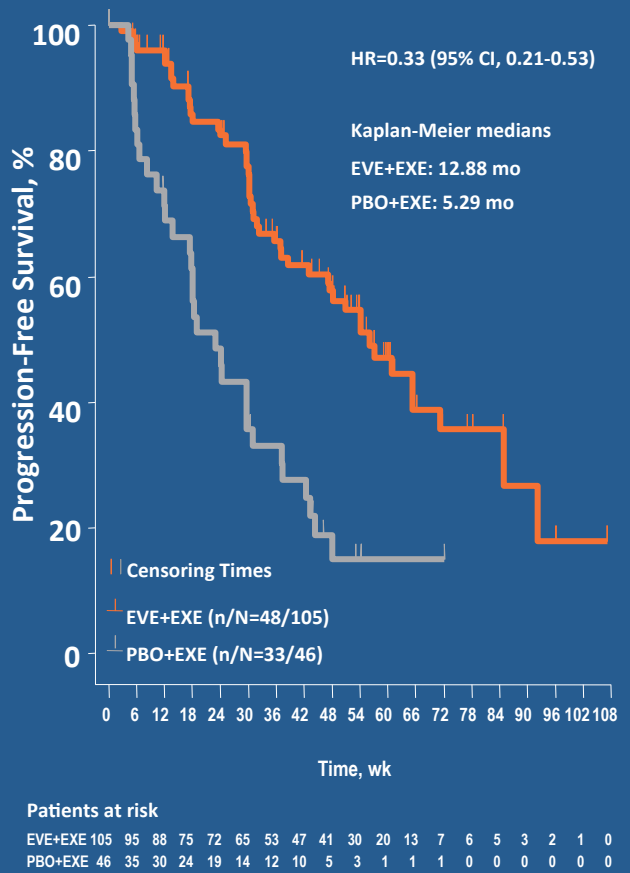
Mets: Polmonari, epatiche, pleura, riversamento pleurico,peritoneali, ascite



Mets: osso, linfonodi, derma



Mets ossee



Patients at risk

EVE+EXE	271	240	192	157	128	107	88	72	52	38	25	22	16	12	11	7	5	4	1	0
PBO+EXE	135	108	66	44	32	23	18	14	11	8	4	4	3	1	0	0	0	0	0	0

Patients at risk

EVE+EXE	214	196	174	147	129	114	97	86	72	53	41	28	19	12	11	6	5	4	1	1	0
PBO+EXE	104	82	66	52	35	27	21	16	10	7	6	4	2	2	1	1	1	0	0	0	0

Patients at risk

EVE+EXE	105	95	88	75	72	65	53	47	41	30	20	13	7	6	5	3	2	1	0			
PBO+EXE	46	35	30	24	19	14	12	10	5	3	1	1	1	0	0	0	0	0	0			

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Piccart M, et al. SABCS 2012; poster P6-04-02; Campone M, et al. ESMO 2012; abstract 324PD (poster discussion)

Pts with visceral metastases

KEY EXCLUSION CRITERIA

Patients with brain metastases, bilateral diffuse lymphangitic carcinomatosis , pts with massive lung (>50%) or liver (>1/3) involvement (i.e. disease burden that may constitute a visceral crisis)

Protocol amendament in FEB 2010 removed this exclusion criteria and appreciation of massive visceral involvment in the lung or liver was left to investigator discretion

56% (N=406) VISCERAL DISEASE (271 EVE+EXE; 135 PBO+EXE):

- 45% LUNG
- 51% LIVER
- 13% BOTH
- 84% 2+ SITES OF VISCERAL METASTASES

Campone M, et al. ESMO 2012, abstract 324PD., Campone et al. EJC 2013

BOLERO-2: Prior Therapy

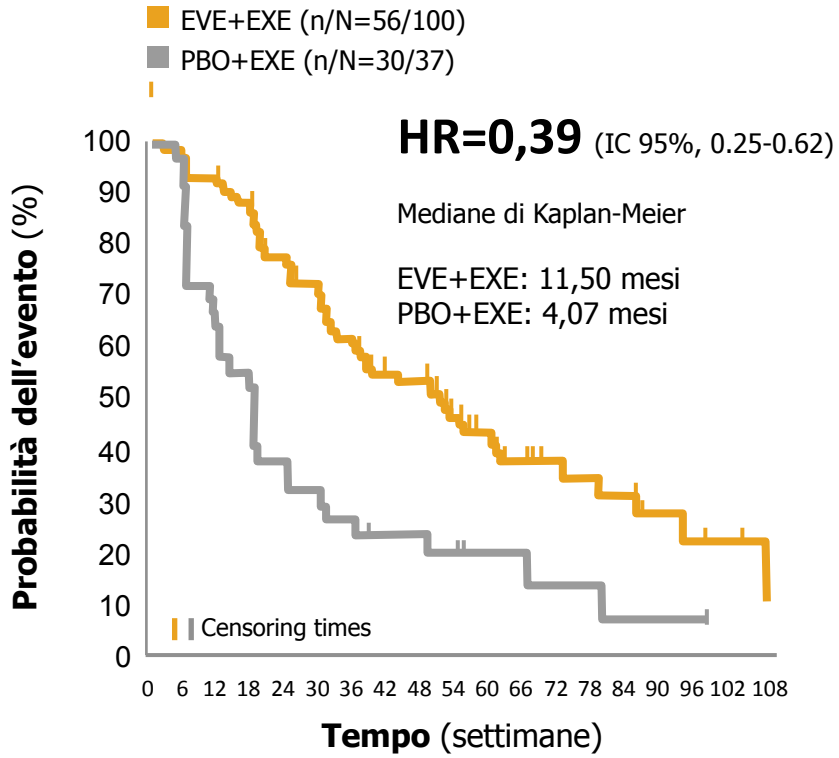
	Everolimus plus exemestane N=485 n (%)		Placebo plus exemestane N=239 n (%)		All patients N=724 n (%)	
Number of prior therapies in metastatic setting						
None	100	(20.6)	37	(15.5)	137	(18.9)
1	192	(39.6)	112	(46.9)	304	(42.0)
2	128	(26.4)	66	(27.6)	194	(26.8)

18.9% : first line therapy

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001038/WC500130788.pdf

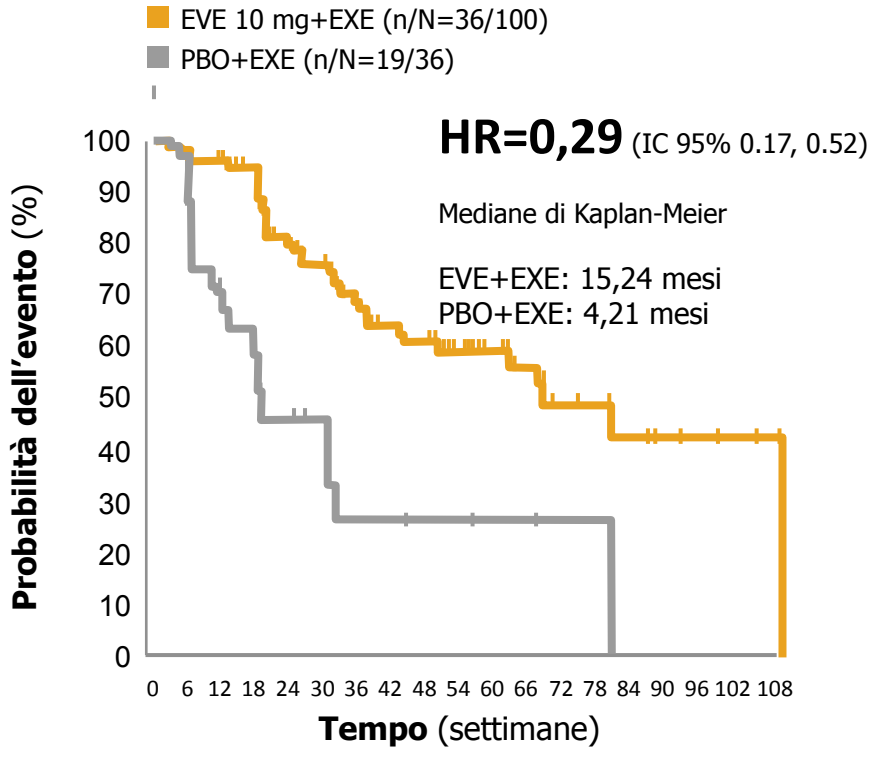
Efficacia in prima linea dell'associazione everolimus+exemestane (dati a 18 mesi)

Valutazione locale



Numero di pazienti ancora a rischio, n																		
EVE+EXE	100	93	86	76	66	57	50	43	41	28	21	17	10	9	9	5	4	3	0
PBO+EXE	37	33	22	17	11	10	8	7	7	4	3	2	2	2	1	1	1	0	0

Valutazione centrale



Numero di pazienti ancora a rischio, n																		
EVE 10 mg +EXE	100	94	86	73	59	53	44	38	35	25	21	16	10	8	7	4	4	3	0
PBO+EXE	36	28	16	13	8	5	4	4	3	3	2	1	1	1	0	0	0	0	0

Campone et al, Abstract 1.912_Presented at 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, Amsterdam, 27 September–1 October 2013

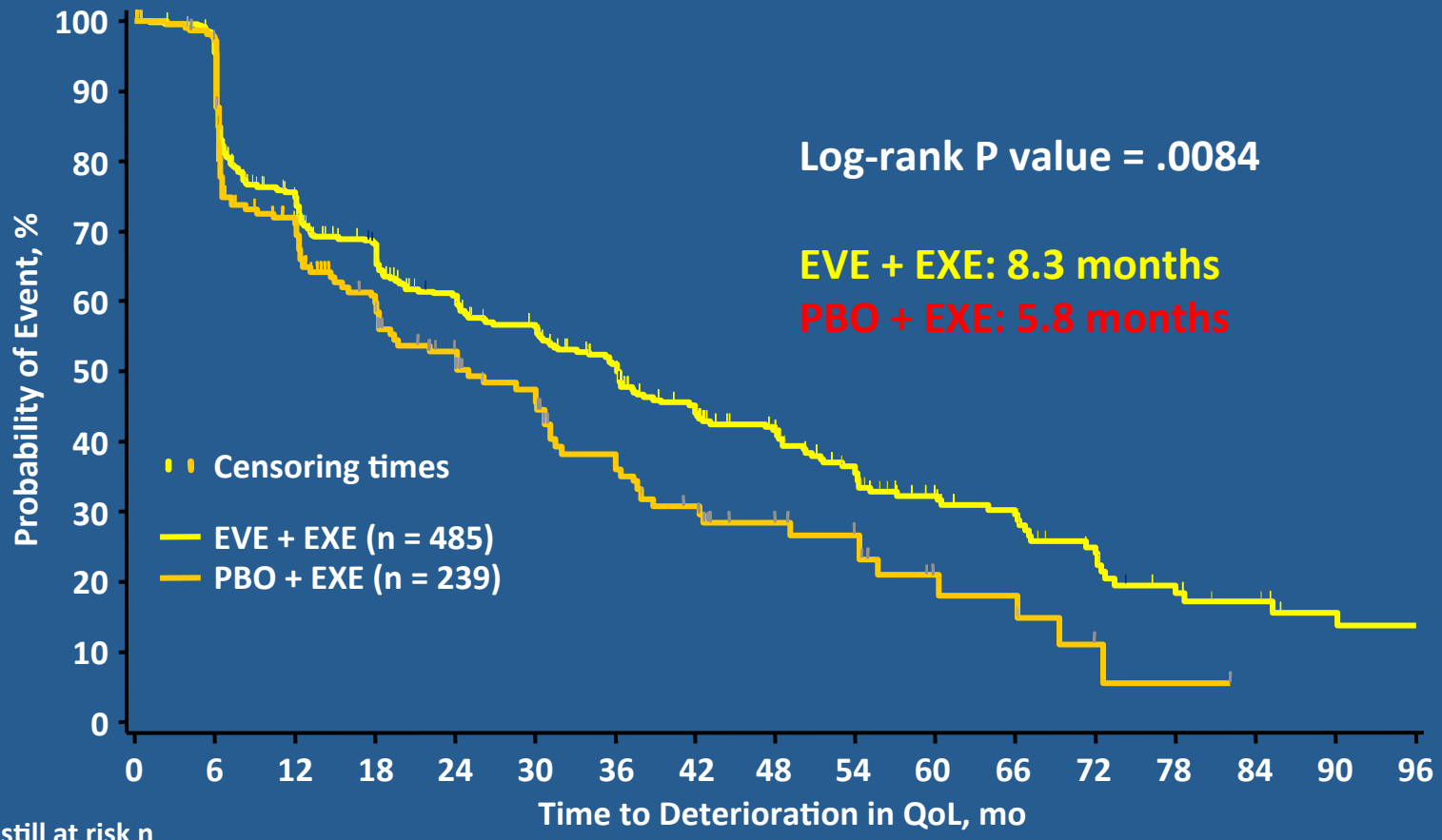
Trattamento in 1° linea metastatica: Profilo di sicurezza sovrapponibile a quello riscontrato nella popolazione totale dello studio

- A higher percentage of patients discontinued EVE+EXE because of AEs versus PBO+EXE (10% vs 8%, respectively)
  - Higher discontinuation rates may be attributable to the longer treatment duration of EVE versus PBO (31.1 weeks vs 15.6 weeks, respectively)
  - Pneumonitis was observed only in the EVE+EXE arm; most events were low grade and manageable using established strategies

Table 2. Most Common Adverse Events (Reported in ≥ 25% of Patients Receiving EVE+EXE) in Patients Who Recurred During/After Adjuvant[a] Therapy

	EVE+EXE (n = 100), %					PBO+EXE (n = 37), %				
	Grade					Grade				
Preferred Term	All	1	2	3	4	All	1	2	3	4
Stomatitis	68	38	26	4	0	22	16	5	0	0
Diarrhea	40	31	5	3	1	22	11	11	0	0
Rash	37	24	13	0	0	8	5	3	0	0
Fatigue	32	17	12	3	0	16	8	5	3	0
Weight decrease	30	13	16	1	0	11	3	8	0	0
Decreased appetite	28	23	5	0	0	11	8	3	0	0
Nausea	28	19	8	0	1	30	22	5	3	0
Cough	26	22	4	0	0	8	3	5	0	0
Pneumonitis[b]	22	11	10	1	0	0	0	0	0	0
Hyperglycemia[b]	17	5	4	7	1	3	0	0	3	0

BOLERO-2 (18 mo f/up): Adding Everolimus to Exemestane Maintained QOL*



Patients still at risk n

EVE + EXE	485	427	305	245	198	176	145	119	99	71	52	43	29	18	13	9	8
PBO + EXE	239	201	116	83	62	49	36	27	19	16	7	6	3	1	0	0	0

Abbreviations: EORTC, QLQ-C30 European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire; MID, minimal important difference; QOL, quality of life.

* QOL evaluated using the EORTC-QLQ-30 Global Health Scale with MID = 5%.

Beck JT, et al. ASCO 2012; abstract 539 (poster).

BOLERO-2 (18 mo f/up): Summary

- Addition of everolimus to exemestane prolongs PFS in patients with ER^+ $HER2^-$ breast cancer refractory to initial nonsteroidal aromatase inhibitors[1]
  - Local Assessment: Median 7.8 vs 3.2 months (HR = 0.45, P < .0001)
  - Central Assessment: Median 11.0 vs 4.1 months (HR = 0.38, *P* < .0001)
  - Benefit is observed in all subgroups
- Adverse events were consistent with previous experience with everolimus[1]

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- Adverse events were consistent with previous experience with everolimus[1]

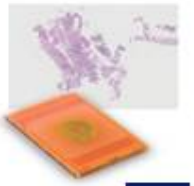
Genetic Alterations and Everolimus Efficacy in Hormone Receptor–positive, HER-2–negative Advanced Breast Cancer: Preliminary Correlative Results From BOLERO-2

Gabriel Hortobagyi, Martine Piccart, Hope Rugo, Howard Burris III, Mario Campone, Shinzaburo Noguchi, Alejandra Perez, Ines Deleu, Mikhail Shtivelband, Louise Provencher, Norikazu Masuda, Shaker Dakhil, Ian Anderson, David Chen, Amy Damask, Alan Huang, Douglas Robinson, Rob McDonald, Adnan Derti, Tetiana Taran, Tarek Sahmoud, David Lebwohl and José Baselga

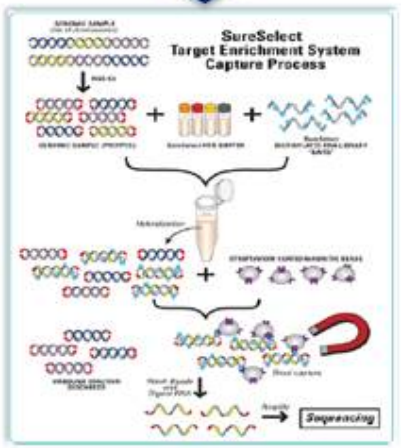
ASCO Annual '13 Meeting

Presented By Gabriel N. Hortobagyi, MD, FACP at 2013 ASCO Annual Meeting

Sample Analysis, Data Workflow, and Results



Fixed sample slides



DNA extraction,
Library construction,
Hybrid capture
(Agilent SureSelect™)

Sequencing
(Illumina HiSeq™ 2000)

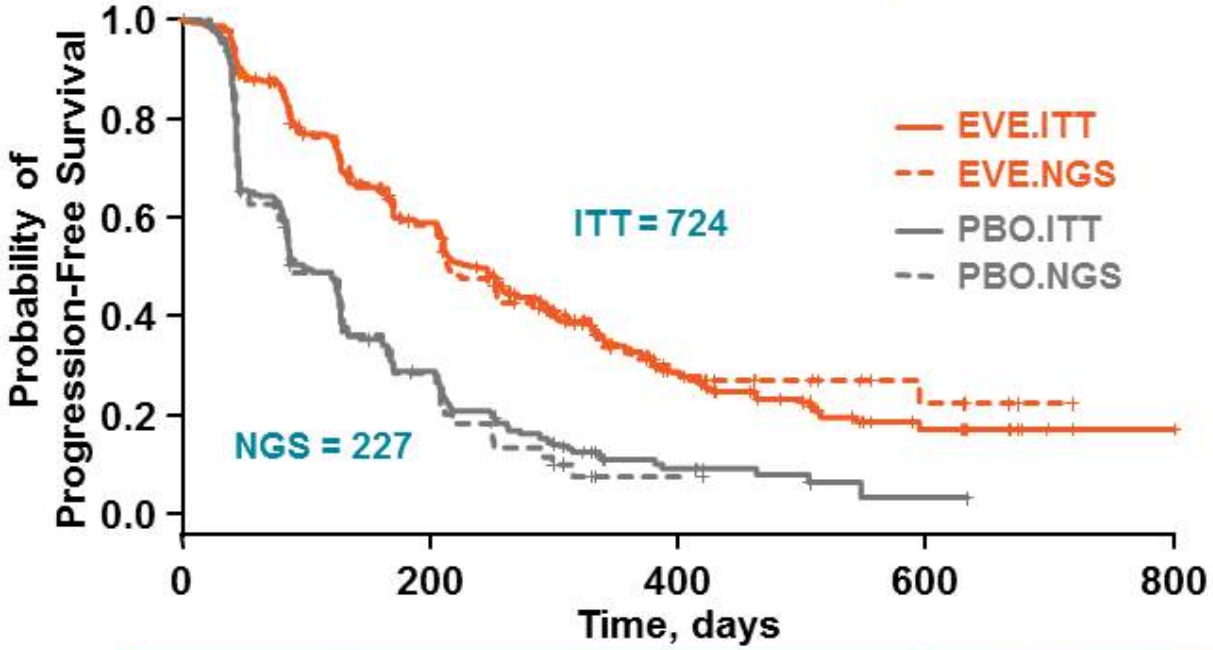
Analysis
- **Point Mutations**
- **Short Insertions/Deletions**
- **Copy Number Alterations**
- **Rearrangement**

Results
- 227 samples successfully analyzed ("NGS population")
- >250X unique coverage
  - Average coverage: 602 ± 202X
- Known somatic alterations: genetic alterations matched in COSMIC, but not in dbSNP
- Novel alterations: No match in both COSMIC and dbSNP

Abbreviations: COSMIC, Catalogue of Somatic Mutations in Cancer; dbSNP, Single Nucleotide Polymorphism Database.

182 oncogenes and tumor suppressor genes were analyzed using next generation *se*quenc*i*ng (NGS) on 227 samples ("NGS population").

NGS Population Is Representative of the Trial Population



- No major baseline clinical and demographic differences observed between ITT and NGS populations
- Clinical efficacies are comparable between the populations

Population	N (% ITT)	N Events (%)	PFS (months) Median (95%CI)	HR (95%CI)
ITT—EVE	485	293 (60.4%)	7.8 (6.9-8.5)	0.45 (0.38–0.54)
ITT—PBO	239	197 (82.4%)	3.2 (2.8-4.1)	
NGS—EVE	157 (32.4%)	94 (59.9%)	7.0 (6.2-9.6)	0.40 (0.28–0.55)
NGS—PBO	70 (29.3%)	59 (84.3%)	2.6 (1.7-4.2)	

Abbreviations: CI, confidence interval; EVE, everolimus; HR, hazard ratio; ITT, intent to treat; NGS, next generation sequencing ; PBO, placebo; PFS, progression-free survival.

Genetic Alterations in NGS Population

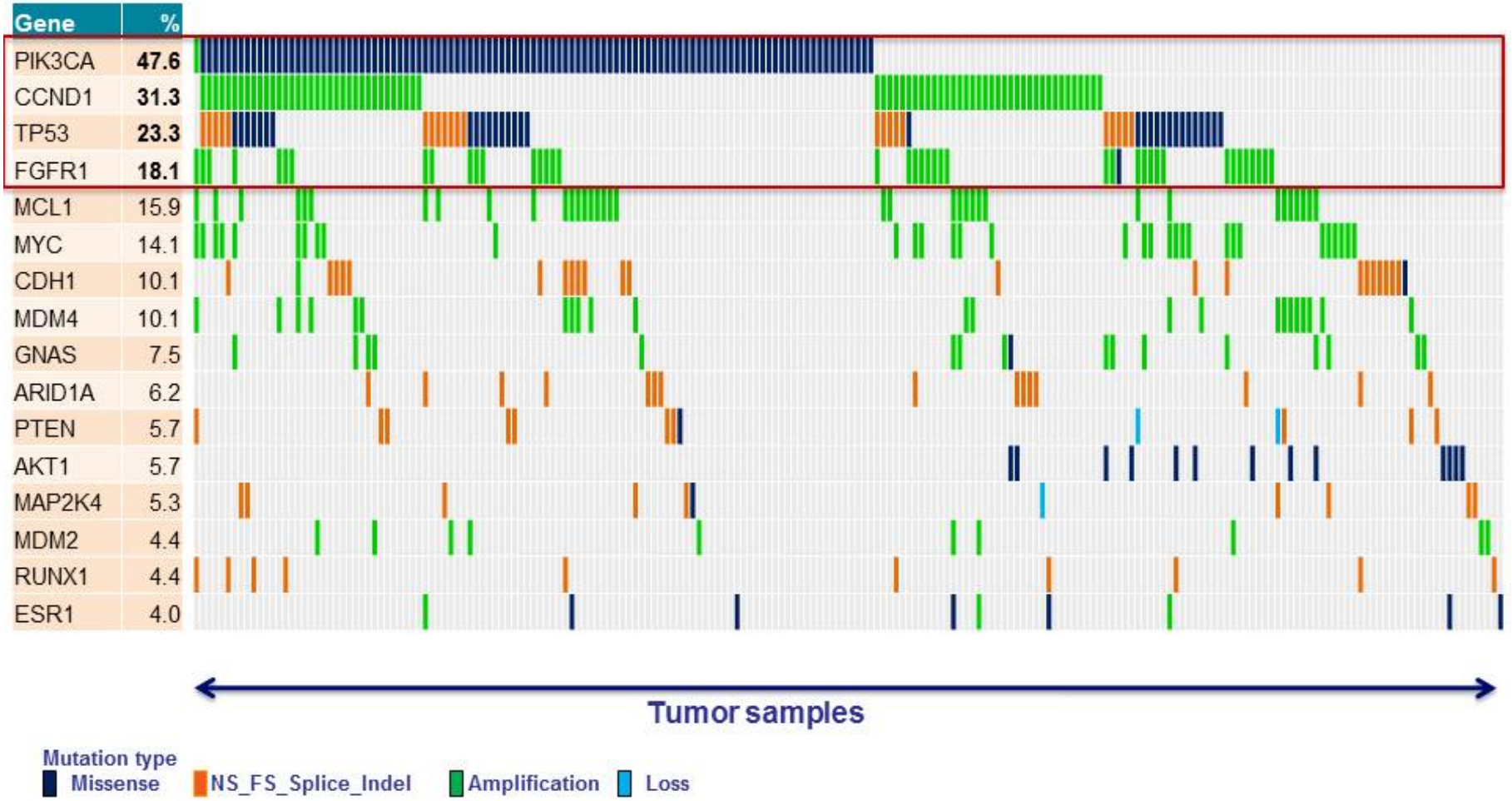
Alteration types	Sub-type	Number of alterations	Somatic alterations	Novel alterations
Sequence alteration	Missense	1,222	214	1,008
	Nonsense/Frameshift/ Splice variant/ Insertion/Deletion	254	128	126
Rearrangement		24	3	21
Copy number variations (CNV)	Amplification (≥6 copies)	522		
	Bi-allelic deletion	26		

Known somatic alterations are included in the correlative analysis.

Distribution of known genetic alterations	
Known somatic alteration/sample, mean (range)	4.1 (0-15)
Patients with at least one known somatic alteration, n	219
Genes with at least one known somatic alteration, n	104

Presented By Gabriel N. Hortobagyi, MD, FACP at 2013 ASCO Annual Meeting

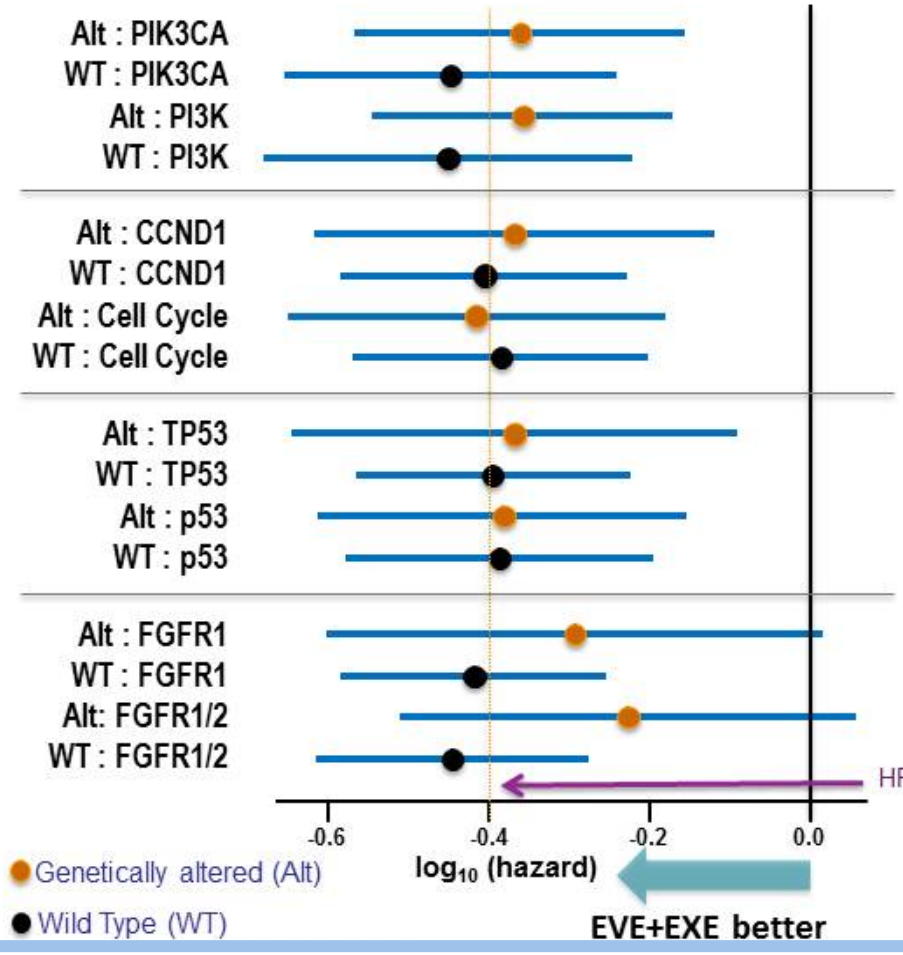
Frequency of Genetic Alterations in Key Pathways



Fibroblast growth factor receptor 1 (FGFR1)

Impact on Treatment by Genetic Status

The Most Frequently Altered Single Genes and Pathways



EVE benefit was present in the various subgroups based on altered single genes and pathways.

Pathway composition

- **PI3K:** PIK3CA, PTEN, AKT (**PIK3CA** Alt: 47.6%, total alteration: 55.5%)
- **Cell Cycle:** CCND1, CDK4, CDK6, CDKN2A, CDKN2B, (**CCND1** Alt: 31.3%, total alteration: 35.7%)
- **p53:** TP53, MDM2, MDM4 (**TP53** Alt: 23.3%, total alteration: 36.1%)
- **FGFR1/2:** FGFR1, FGFR2 (**FGFR1** Alt: 18.1%, total alteration: 21.1%)

No predictive marker of EVE efficacy was identified in subgroups defined by each of the 4 most frequently altered genes/pathways when assessed individually

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Patients With No or Single Genetic Alteration in PIK3CA/PTEN/CCND1 or FGFR1/2 Derive Greater PFS Benefit With EVE

Subgroup	N	Events (%)	Median PFS (d)	HR* (95%CI)
EVE: WT	43	19 (44%)	356	0.24 (0.11 - 0.54)
PBO: WT	18	14 (78%)	203	
EVE: Single	76	48 (63%)	214	0.26 (0.16 - 0.43)
PBO: Single	35	31 (89%)	77	
EVE: multiple	38	27 (71%)	138	0.78 (0.39 - 1.54)
PBO: multiple	17	14 (82%)	128	

*HR adjusted with imbalanced covariates

Subgroup	Definition		Size, %	
WT	No alteration in PIK3CA AND PTEN AND FGFR1/2 AND CCND1	Minimal	27%	76%
Single	Single alteration only in PIK3CA OR PTEN OR FGFR1/2 OR CCND1		49%	
Multiple	Two or more alterations in PIK3CA OR PTEN OR FGFR1/2 OR CCND1 genes	Multiple	24%	24%

A greater benefit from EVE derived in pts (76% of NGS population) with minimal genetic alterations in PI3KCA/PTEN/CCND1 or FGFR1-2 genes combined.

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HR+/HER2- ABC: **BOLERO 2**

- In post-menopausal HR+/HER2- ABC pts progressing during/after NSAIs, EVEROLIMUS + exemestane resulted on significant PFS benefit (BOLERO 2)[1].

- In retrospective biomarker analysis (BOLERO 2)[2]:

  - no predictive marker of EVE efficacy was identified in subgroups defined by each of the 4 most frequently altered genes/pathways when assessed individually;

  - a greater benefit from EVE derived in pts (76% of NGS population) with minimal genetic alterations in PI3KCA/PTEN/CCND1 or FGFR1-2 genes combined.

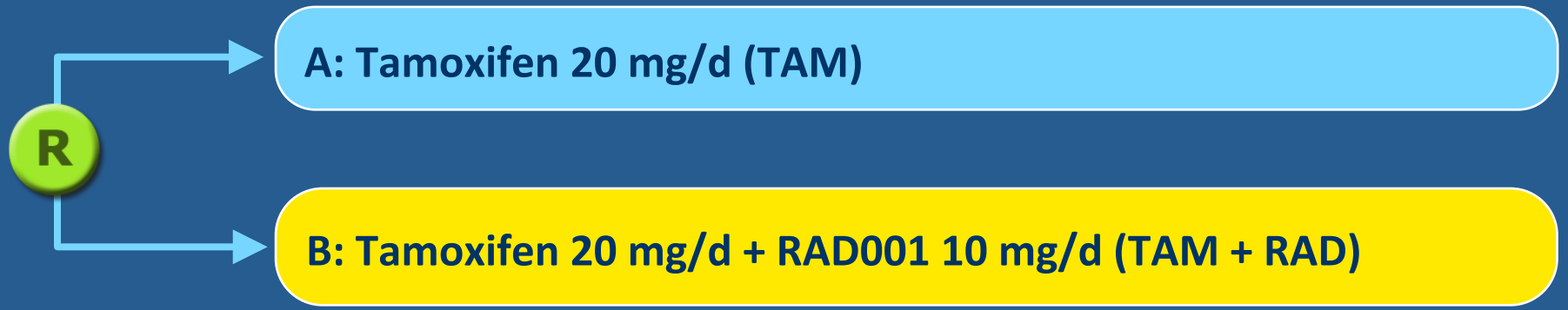
- **These results may only help to generate new hypotheses for combinations of novel targeted therapies for HR+/HER2- BC.**

1.Baselga J et al. NEJM 2012; 2.Hortobagyj G et al. ASCO 2013

TAMRAD Protocol

Randomized phase 2 trial

Metastatic patients with previous exposure to AIs



- **Stratification: primary or secondary hormone resistance**
  - **Primary: relapse during adjuvant AI treatment; progression within 6 months of starting AI treatment in metastatic setting**
  - **Secondary: late relapse (≥6 months) or previous response and subsequent progression to metastatic AI treatment**
- **No crossover planned**

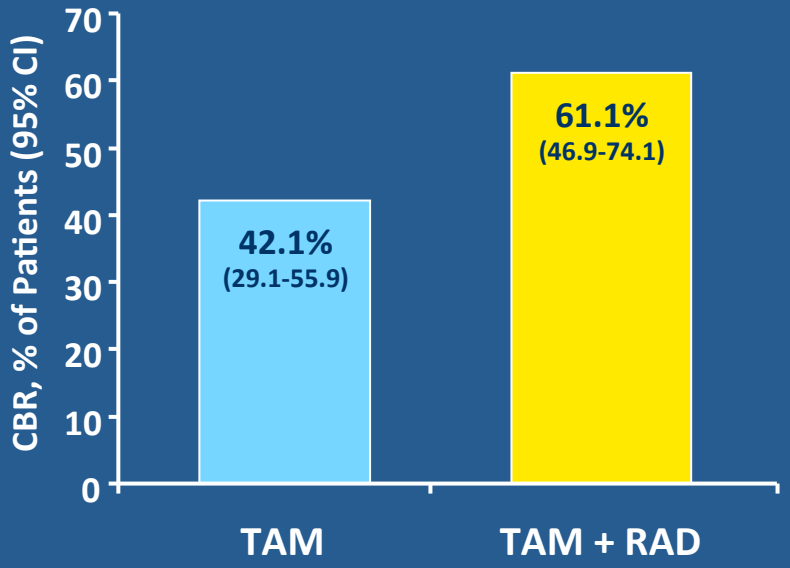
AI, aromatase inhibitor; RAD001, everolimus.

Bachelot T, et al. *J Clin Oncol. 2012;30:2718-24*

TAMRAD: Results

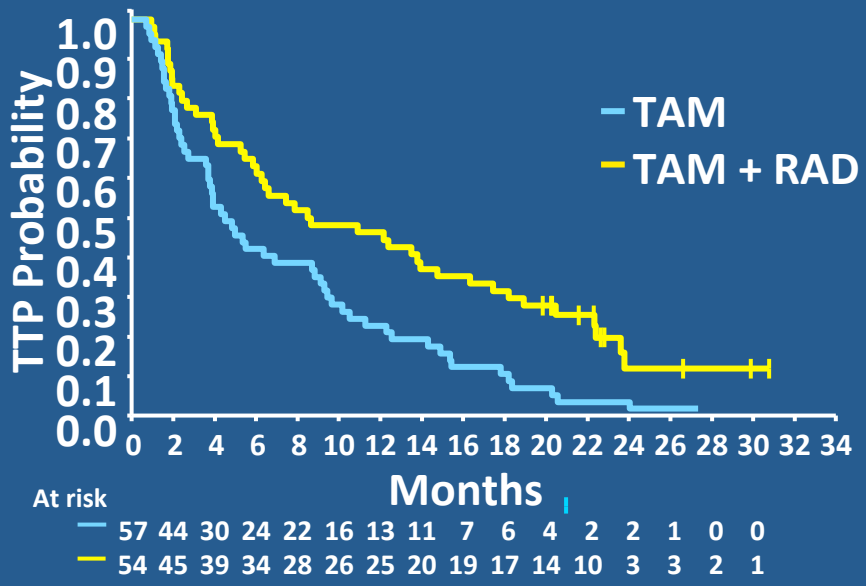
Primary endpoint: Clinical benefit rate

P = 0.045 (exploratory analysis)



Time to progression

- TAM: 4.5 months
- TAM + RAD: 8.6 months
- HR (95% CI) = 0.54 (0.36-0.81)
- *P* = 0.0021 (exploratory analysis)



CI, confidence interval; HR, hazard ratio; RAD, everolimus; TAM, tamoxifen.

Bachelot T, et al. *J Clin Oncol. 2012;30:2718-24*

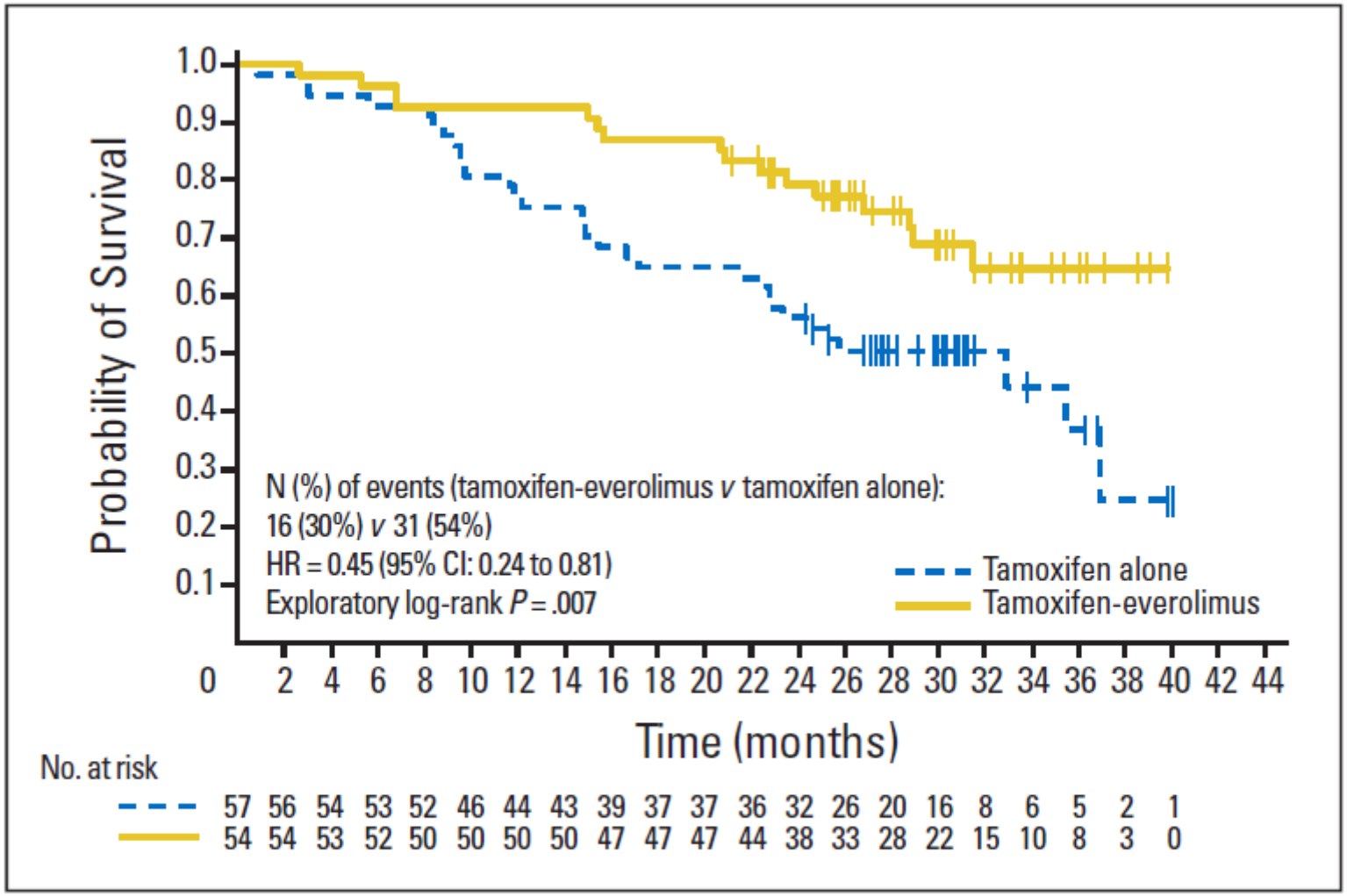
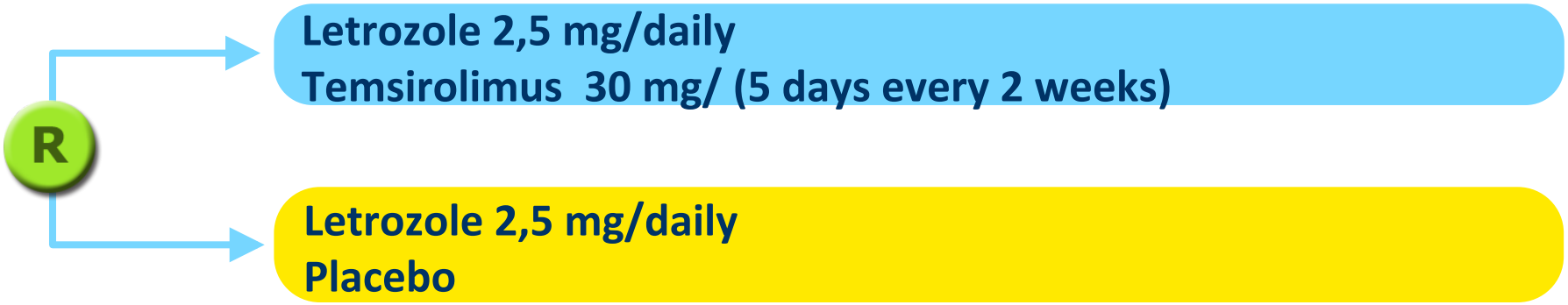


Fig 3. Overall survival in the intention-to-treat population for the overall patient population. HR, hazard ratio.

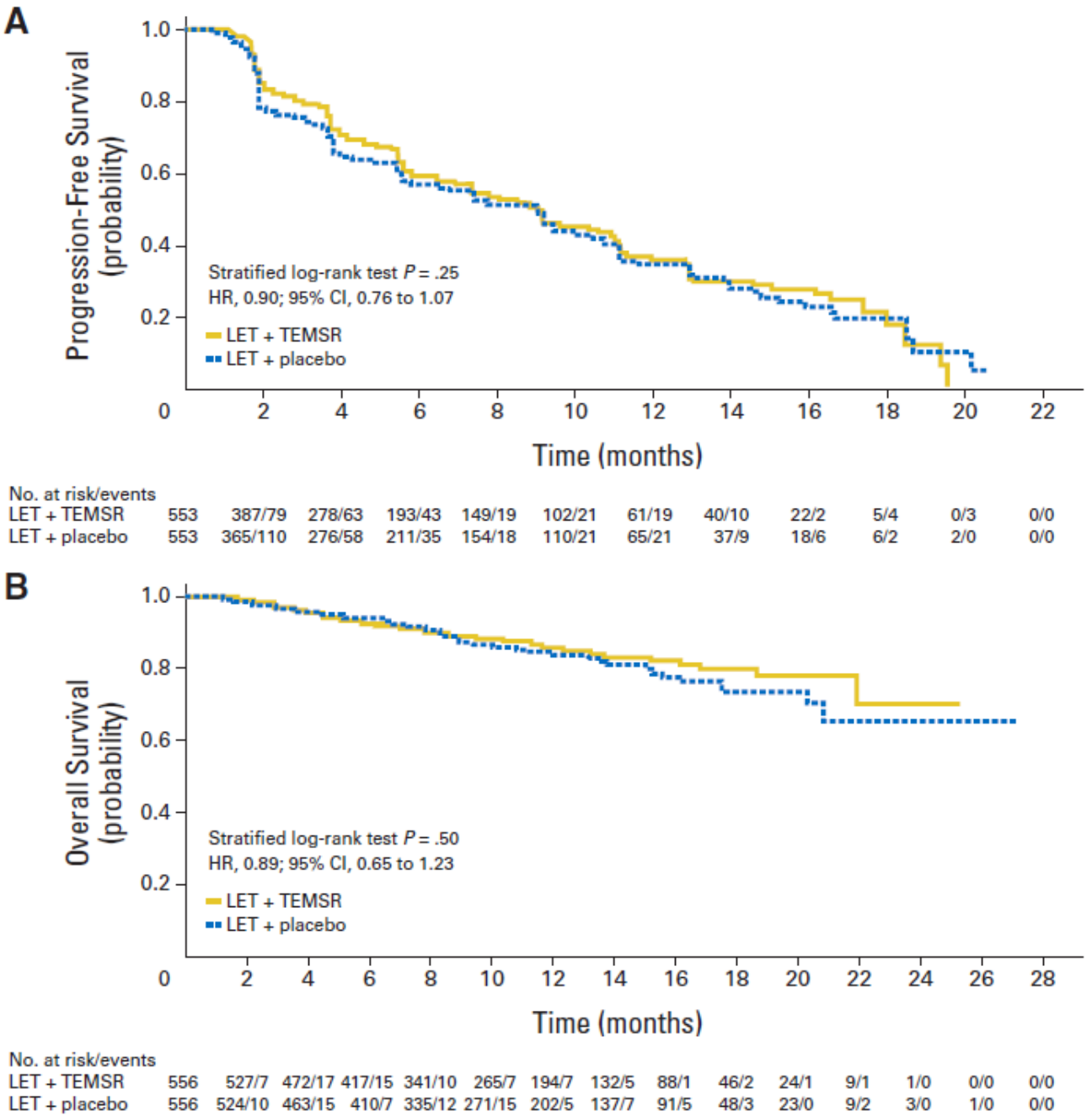
HORIZON Trial



1,112 pts wih AI-naive, HR+ ABC

An independent data monitoring committee recommended study termination for futility at the second preplanned interim analysis (382 PFS events).

Wolff AC, JCO 2013 31:195-202



Wolff AC, JCO 2013 31:195-202

In conclusion, despite single-agent activity when given IV in patients with advanced breast cancer, oral temsirolimus failed to improve PFS when added to letrozole in AI-naive postmenopausal patients as first-line therapy for advanced ER-positive breast cancer. This contrasts with the PFS benefit observed when everolimus was added to exemestane in patients with disease refractory/resistant to nonsteroidal AIs.[19] We speculate that prior exposure to AIs partly explains the different results observed in these two studies. Finally, we acknowledge the significant delay in the peer-review publication of the results of HORIZON (a study first reported in abstract/poster form in December 2006), which is a disservice to the scientific community, to all who support it, and ultimately to patients.[26,27]

LG AIOM Mammella
2013

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Opzioni terapeutiche in postmenopausa	
LG 2012	**LG 2013**
Tamoxifene AI Fulvestrant Progestinici	Tamoxifene AI Fulvestrant Progestinici Exemestane ed Everolimus

1. Studio BOLERO 2 Baselga J et al. N Engl J Med 2011;366: 520-529.

HR+/HER2+
metastatic breast cancer

Post-menopausal HR+/HER2+ MBC

Author	N. pts	Regimen	PFS	HR	P value
Kaufman JCO 2009	207	Trastuzumab+Anastrozole Anastrozole	4.8 mo 2.4 mo	0.53	0.0016
Johnston JCO 2009	219	Lapatinib+Letrozole Letrozole	8.2 mo 3.0 mo	0.71	0.019

THANK YOU !

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