

METASTASI VISCERALI: ALTRE OPZIONI OLTRE LA CHEMIOTERAPIA

EVEROLIMUS ED EXAMESTANE

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il disegno dello studio

BOLERO-2: Everolimus + Exemestane in HR⁺ Advanced Breast Cancer Progressing During/After NSAI Therapy

N = 724

- Postmenopausal ER⁺
- Unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

R
2:1

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

Placebo
+
EXE 25 mg daily (n = 239)

Stratification

1. Sensitivity to prior hormonal therapy

2. Presence of visceral disease

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; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.

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

pazienti arruolate

KEY INCLUSION CRITERIA

- Disease refractory to nonsteroidal aromatase inhibitors (NSAIs) was defined as recurrence during or within 12 months of end of adjuvant treatment or progression during or within 1 month of end of treatment for advanced disease

KEY EXCLUSION CRITERIA

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

**RESISTENZA A NSAIs IN
QUALSIASI LINEA DI
TRATTAMENTO**

**IMP
COINVOLGIM
VISCERALE**

**EMENDATO
FEB 2010**

BOLERO-2: Baseline Characteristics

Characteristic	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Median age, years (range)	62 (34 - 93)	61 (28 - 90)
Race		
Caucasian	74	78
Asian	20	19
Performance status 0	60	59
Metastatic site		
Liver	33	30
Lung	29	33
Bone	76	77
Visceral disease	56	56
Measurable disease ^a	70	68

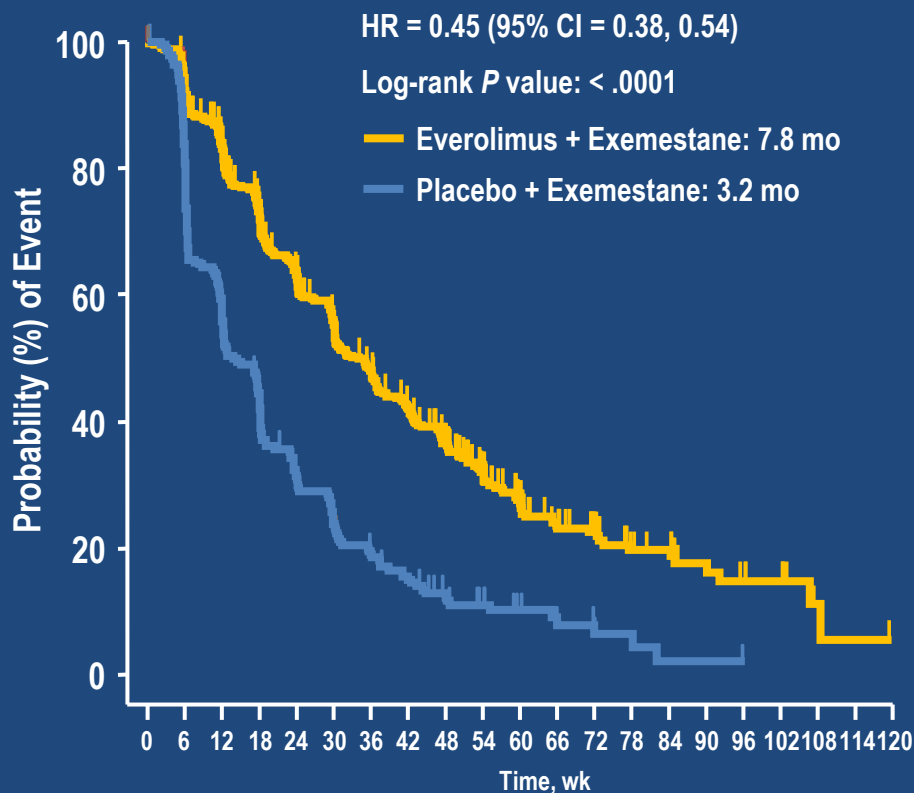
^a All other patients had ≥ 1 bone lesion.

BOLERO-2: Prior Therapy



	EVE + EXE	PBO + EXE
Therapy (%)	N = 485 (%)	N = 239 (%)
Sensitivity to previous hormonal therapy	84	84
Last treatment: LET/ANA	74	75
Last treatment		
Adjuvant	21	16
Metastatic	79	84
Previous tamoxifen	47	49
Previous fulvestrant	17	16
Previous chemotherapy for metastatic BC	26	24
Number of previous therapies: ≥ 3	54	53

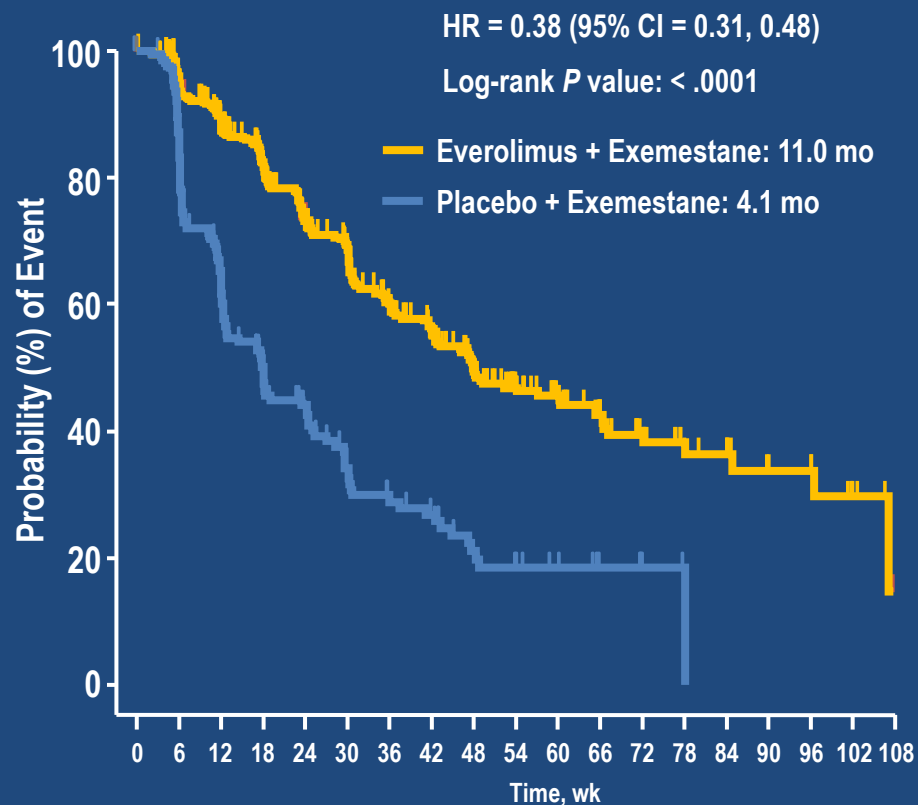
BOLERO-2: PFS at 18 Months' Median Follow-up



Number of patients still at risk

EVE+EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO+EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

Local Assessment

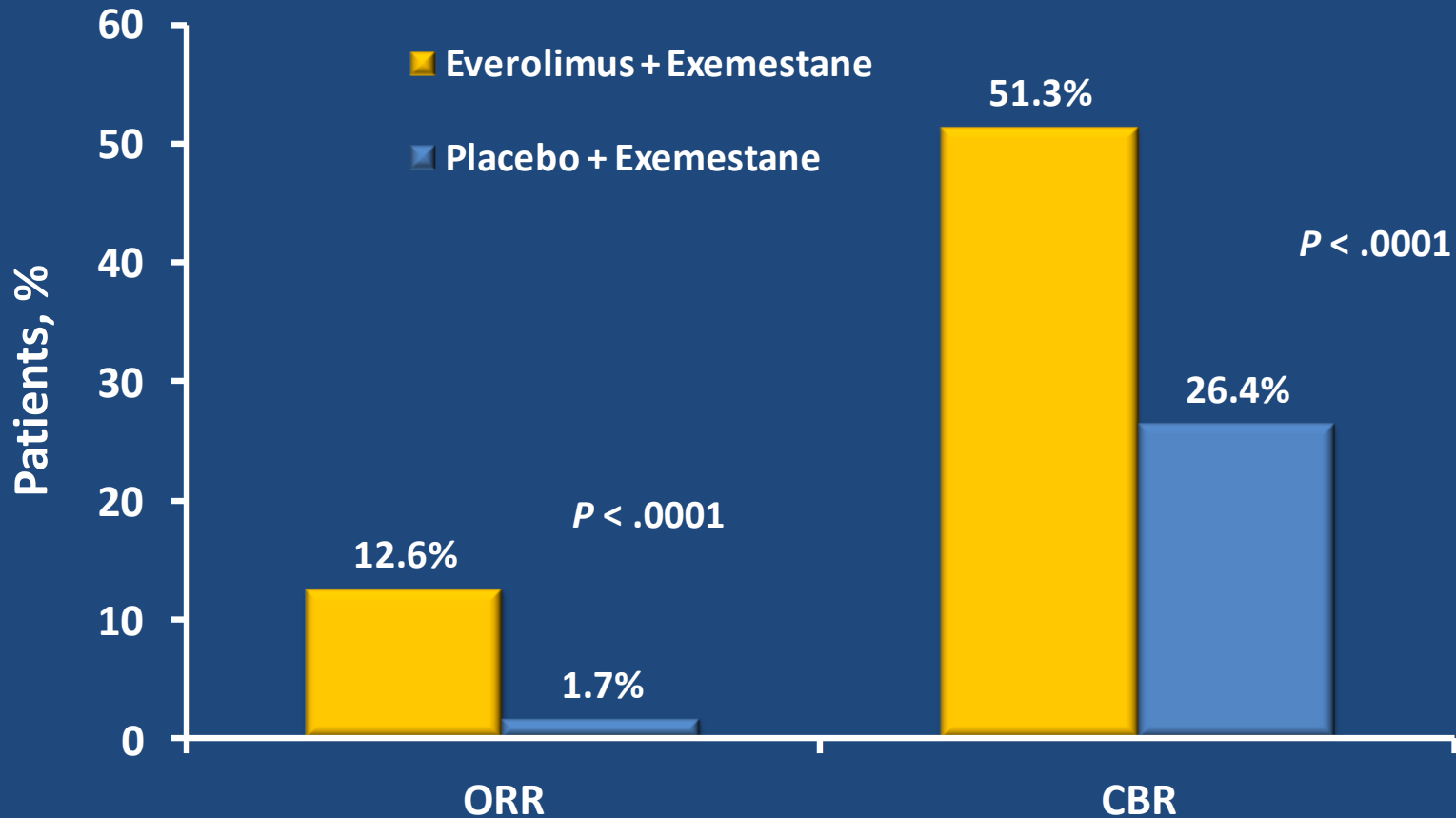


Number of patients still at risk

EVE+EXE	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
PBO+EXE	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

Central Assessment

BOLERO-2: Overall Response Rate and Clinical Benefit Rate (Local Assessment at 18 Months' Median Follow-up)



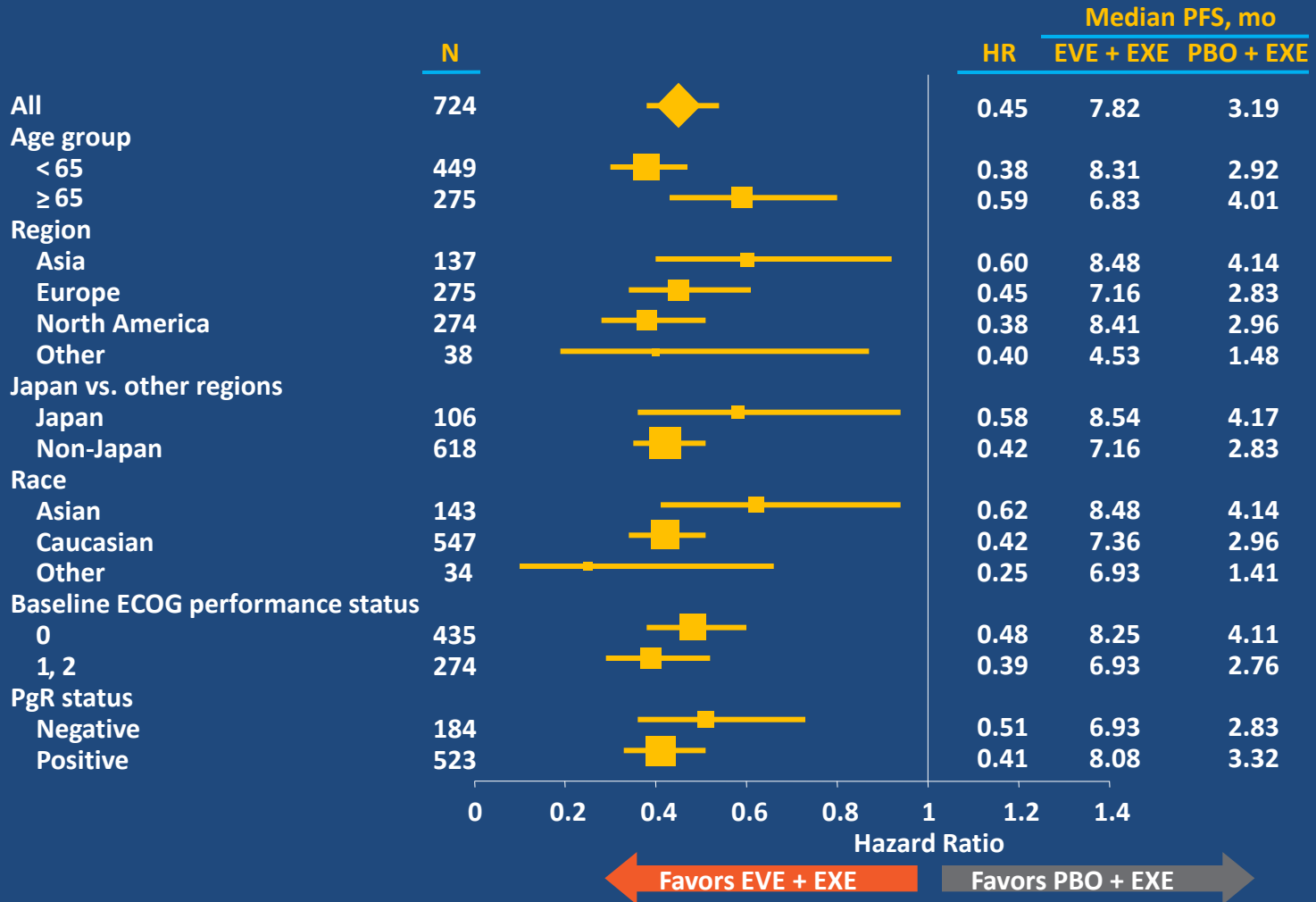
Abbreviations: CBR, clinical benefit rate; ORR, overall response rate.

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

BOLERO-2:

PFS in Prespecified Subgroups

(18 Months' Median Follow-up)



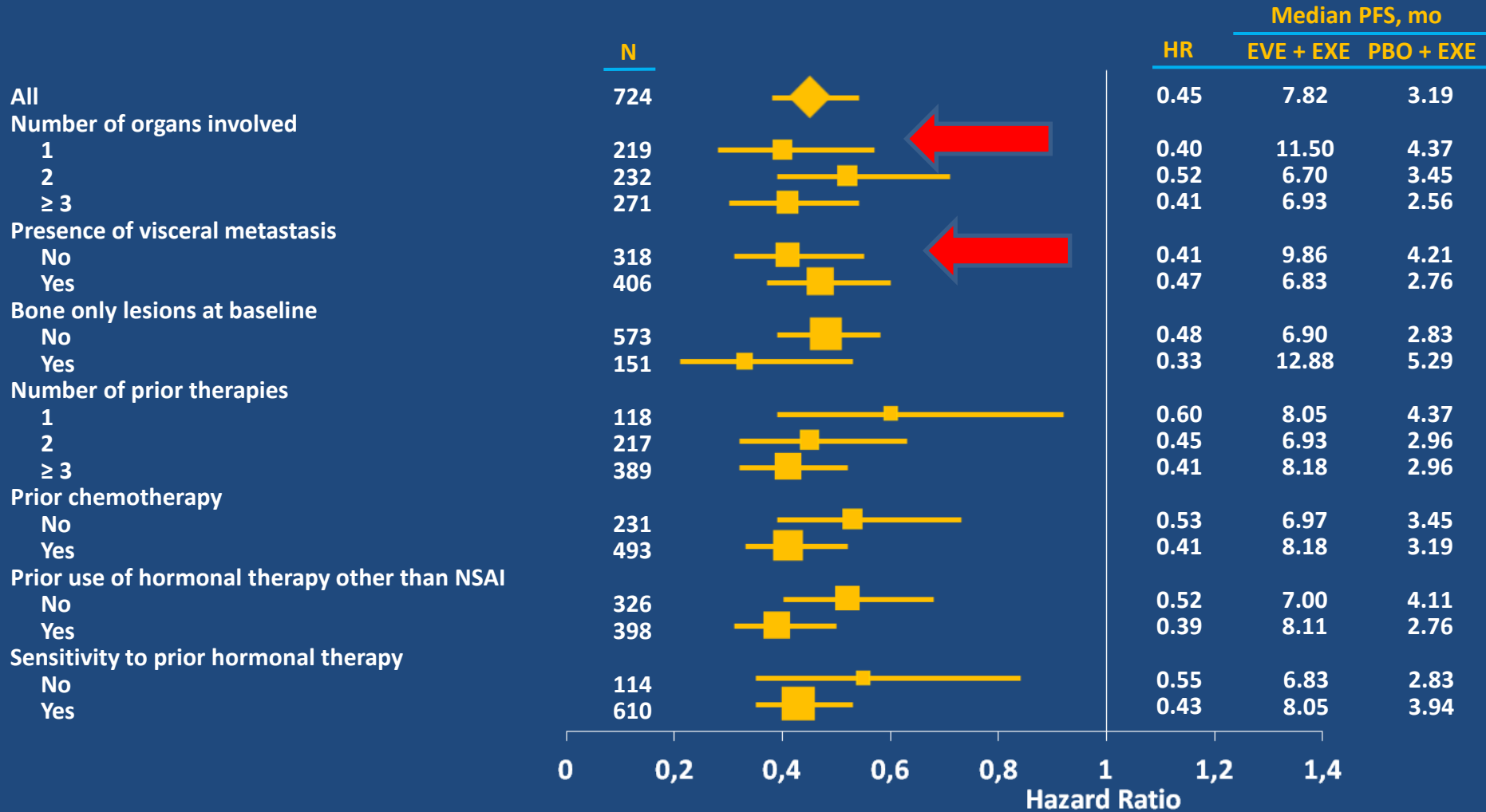
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; PgR, progesterone receptor.

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

BOLERO-2:

PFS in Prespecified Subgroups

(18 Months' Median Follow-up)



← Favours EVE + EXE Favours PBO + EXE →

Abbreviations: EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

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

VISCERAL METASTASIS - 18-mo FU of BOLERO-2

81% of pts had 2+ sites of visceral metastases, 50% had 3+

Patient Subgroup (n)	EVE+EXE (n=485) Median PFS	PBO+EXE (n=239) Median PFS	HR (95% CI)
With visceral mets (406)	6.8 mo	2.8 mo	0.47 (0.37-0.6)
Without visceral mets (318)	9.9 mo	4.2 mo	0.41 (0.31-0.55)
Bone-only disease (151)	12.9 mo	5.3 mo	0.33 (0.21-0.53)

ABC, Advanced Breast Cancer; CI, Confidence Interval; EVE, Everolimus; EXE, Exemestane; HR+ HER2-, Hormone receptor positive HER2 negative; HR, Hazard Ratio; mets, metastases; NSAI, Nonsteroidal aromatase inhibitor; PBO, Placebo; PFS, Progression free survival; PMW, postmenopausal women.

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

“Saper leggere” uno studio clinico per migliorare la pratica clinica

ALCUNE CONSIDERAZIONI SULLE PAZIENTI CON METASTASI VISCERALI...

- QUANDO la combinazione EVE+EXE ?
- Diversa TOLLERABILITA' ?

QUANDO la combinazione EVE+EXE ?

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)

↓ ↓

solo 20% pazienti in I
metastatica!

QUANDO la combinazione EVE+EXE ?

identikit delle pazienti arruolate nel BOLERO-2



Nonsteroidal
AI



FULVESTRANT



HT CHT



TAMOXIFEN



Nonsteroidal
AI



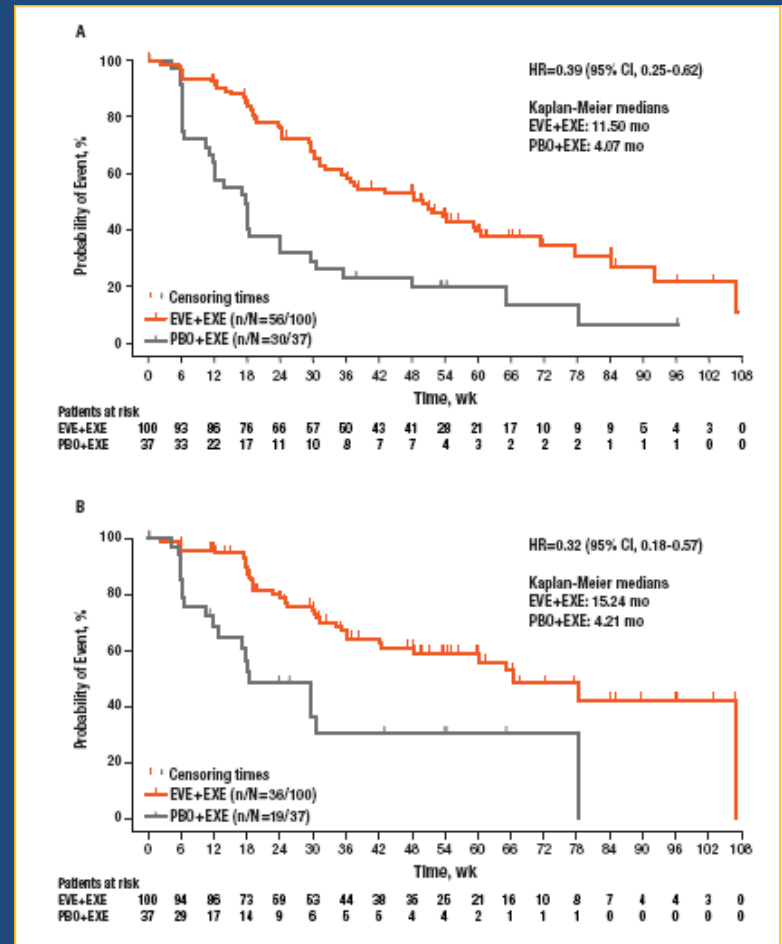
QUANDO la combinazione EVE+EXE ?

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BOLERO-2: Efficacy and Safety of First-Line Everolimus Plus Exemestane in Advanced Breast Cancer

Mario Campone,¹ Michael Gnant,² Patrick Neven,³ Barbara Pistilli,⁴ Hope S. Rugo,⁵ José Baselga,⁶ Hounayda Bauliy,⁷ Tetiana Taran,⁸ Tarek Sahnoud,⁸ Gabriel N. Hortobagyi⁹

- n=100 pts EVE+EXE; n=37 pts PBO+EXE recurrence during/after adjuvant therapy
- 74% EVE+EXE; 76% PBO+EXE previous adj CHT and ET
- PFS 11.5 vs 4.1, HR 0.39 (local assessment)
- PFS 15.2 vs 4.2, HR 0.32 (central assessment)



tollerabilita' del trattamento...

BOLERO-2: Most Common Adverse Events

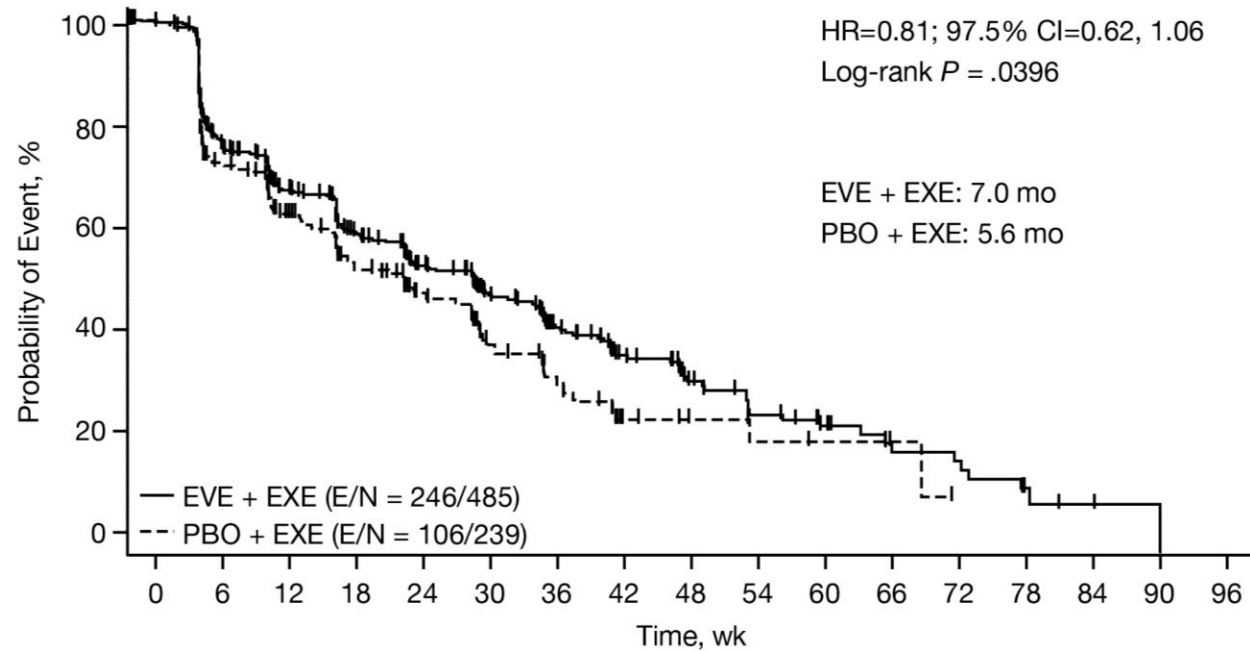
	Everolimus + Exemestane (n = 482), %			Placebo + Exemestane (n = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	59	8	0	12	< 1	0
Rash	39	1	0	7	0	0
Fatigue	37	4	< 1	27	1	0
Diarrhea	34	2	< 1	19	< 1	0
Appetite decreased	31	1	0	13	1	0
Nausea	31	< 1	< 1	29	1	0
Weight decreased	28	1	0	7	0	0
Noninfectious pneumonitis ^a	16	3	0	0	0	0
Hyperglycemia ^a	14	5	< 1	2	< 1	0

^a Adverse events of special interest. Abbreviations: EVE, everolimus; EXE, exemestane; PBO, placebo.

tollerabilita' del trattamento...

- Rates of AEs were similar (both overall and AEs of grade 3 or higher)
- The increase in frequency of AEs was due into difference in C...

Global health status EORTC-QLQC30 and B23



No. at risk

everolimus	485	425	299	239	187	149	109	75	56	33	25	14	11	8	2	1	0
placebo	239	200	115	82	60	44	27	17	9	7	4	4	1	0	0	0	0

Thaddeus, ASCO 2012