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Targeting the PI3K/AKT/ mTOR pathway in cancer

Sitges, Barcelona **28 February - 1 March 2014**

Efficacy of mTOR inhibition

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DISCLOSURE

- Roche : Board and reserach funding
- Novartis : Board and reserach funding, speaker fees
- Servier : Board

Efficacy of mTOR inhibition in the clinical setting

Early clinical trials

- Pharmacodynamic
- Phase I, Ib, II

Randomized clinical trials

- Neoadjuvant
- Fist line
- Second line

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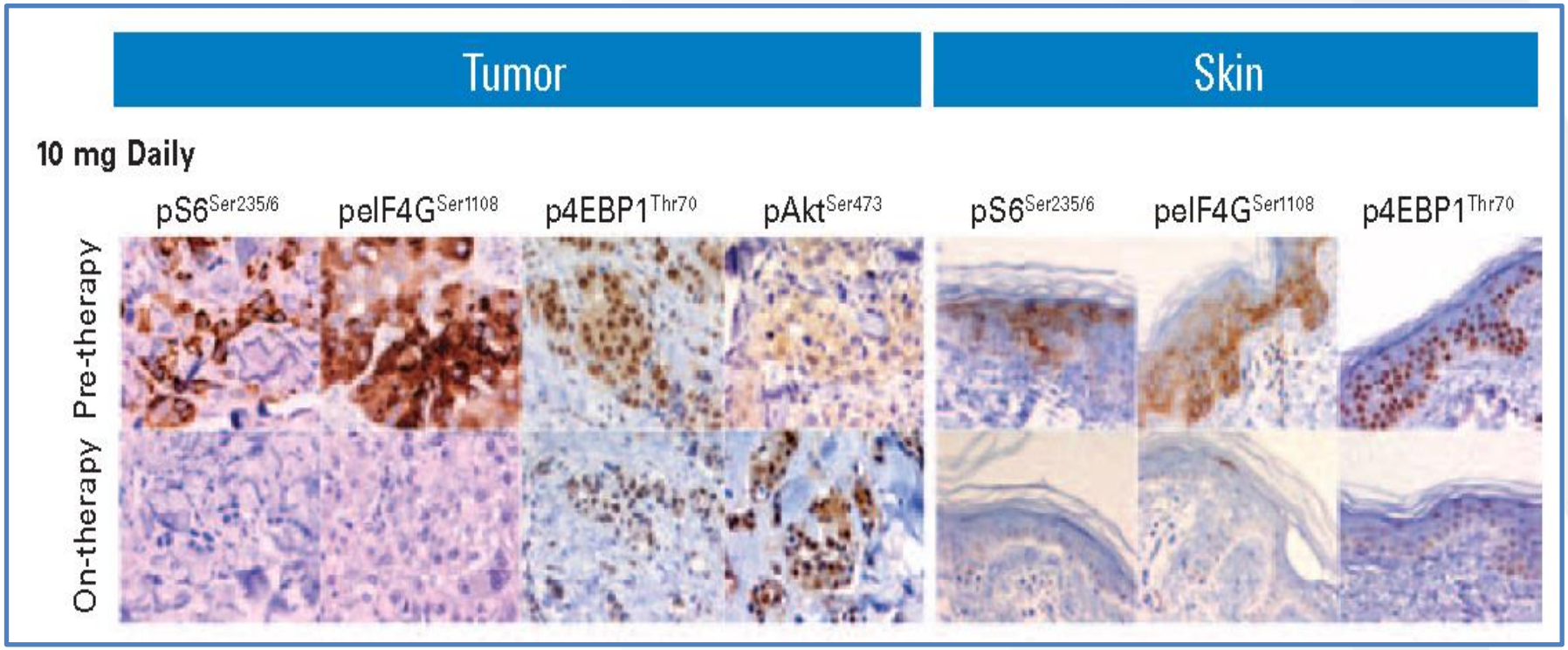
Early Clinical trials with mTOR inhibitor in Metastatic Breast Cancer (MBC)

	Trial	Pts/treatment	Results
Everolimus (advanced solid tumors)	Phase I Pharmacodynamic	55 p: 5mg/d 10 mg/d 20 mg/w 50 mg/w 75 mg/w	Dose dependent inhibition of mTOR pathways
Everolimus (Pretreated MBC)	Randomized Phase II	33 p: 10 mg/d 16 p: 70 mg/w	OR: 4 pts 0 pt
Everolimus + Letrozol (AI Pretreated MBC)	Phase Ib	6 p: LET+EVE 5 mg/d 12 p: LET+EVE 10 mg /d	CB: 2 pts 5 pts (1CR)

Tabernero et al. J Clin Oncol (2008) 26:1603-10.
Ellard et al. J Clin Oncol (2009) 27: 4536-41
Awada et al. Eur J Cancer (2008) 44:84-91

Phamacodynamic data: objective inhibition of mTOR late effectors and activation of pAkt



Tabernero et al. J Clin Oncol (2008) 26:1603-10.

Everolimus monotherapy for MBC (49 patients)
Clinical Benefice rate : 18%

- **Daily schedule (10mg/day) : 7/33 = 21%**
- **Weekly schedule (70mg/w) : 2/16 = 12%**

Table 4. Response

Response Category	No. of Patients		
	Daily Schedule (n = 33)	Weekly Schedule (n = 16)	All Patients (N = 49)
Complete response	1	0	1
Partial response	3	0	3
Stable disease ≥ 6 months	3	2	5
Stable disease < 6 months	12	2	14
Progressive disease	11	11	22
Inevaluable	3	1	4

Ellard et al. J Clin Oncol (2009) 27: 4536-41

Everolimus monotherapy for MBC (49 patients)

Almost all clinical benefice in ER+ HER2- patients (CBR 7/20, 35%)

Table 5. Response by Staining (daily schedule only)

Staining Status	No. of Patients				
	CR	PR	SD ≥ 6 Months	SD < 6 Months	PD
PTEN					
None	0	0	0	2	0
Positive	1	3	2	9	10
Unknown	0	0	1	1	1
pAKT					
Positive	0	1	1	7	7
Negative	1	2	1	4	3
Unknown	0	0	1	1	1
CA9					
Positive	0	0	0	1	1
Negative	1	3	2	10	9
Unknown	0	0	1	1	1
ER positive/HER2 positive	0	0	0	1	1
ER positive/HER2 negative	1	2	3	6	7
ER positive/HER2 unknown	0	1	0	0	0
ER negative/HER2 positive	0	0	0	2	1
ER negative/HER2 negative	0	0	0	3	2

Ellard et al. J Clin Oncol (2009) 27: 4536-41

Addition of everolimus to letrozole in patients with disease stabilization/progression on letrozole alone (18 patients)

CBR: 7/18 = 39%

	All patients (n = 18)	RAD001 5 mg/day (n = 6)	RAD001 10 mg/day (n = 12)
Disease status on letrozole alone			
Duration of letrozole alone median (range) (mo)[a]	15.0 (1.7–49.2)	12.4 (2.3–27.7)	26.0 (1.7–49.2)
Best response on letrozole alone (n)			
Stable disease	15	5	10
Progressive disease	1	0	1
Unknown	1	0	1
Not applicable	1	1	0
Best response to combined treatment			
Overall response (CR or PR) (%)	1 (5.6)	0	1 (8.3)
Complete response (%)	1 (5.6)	0	1 (8.3)
Duration (mo)[b]			22.3
Partial response (%)	0	0	0
Stable disease (%)	9 (50.0)	4 (66.7)	5 (41.7)[c]
Stable disease >6 mo (%)	6 (33.3)	2 (33.3)	4 (33.3)
Duration (mo)[d]		14, 21	8, 13, 17, 23
Progressive disease (%)	5 (27.8)	2 (33.3)	3 (25.0)
Unknown (%)	3 (16.7)[e]	0	3 (25.0)

Awada et al. Eur J Cancer (2008) 44:84-91

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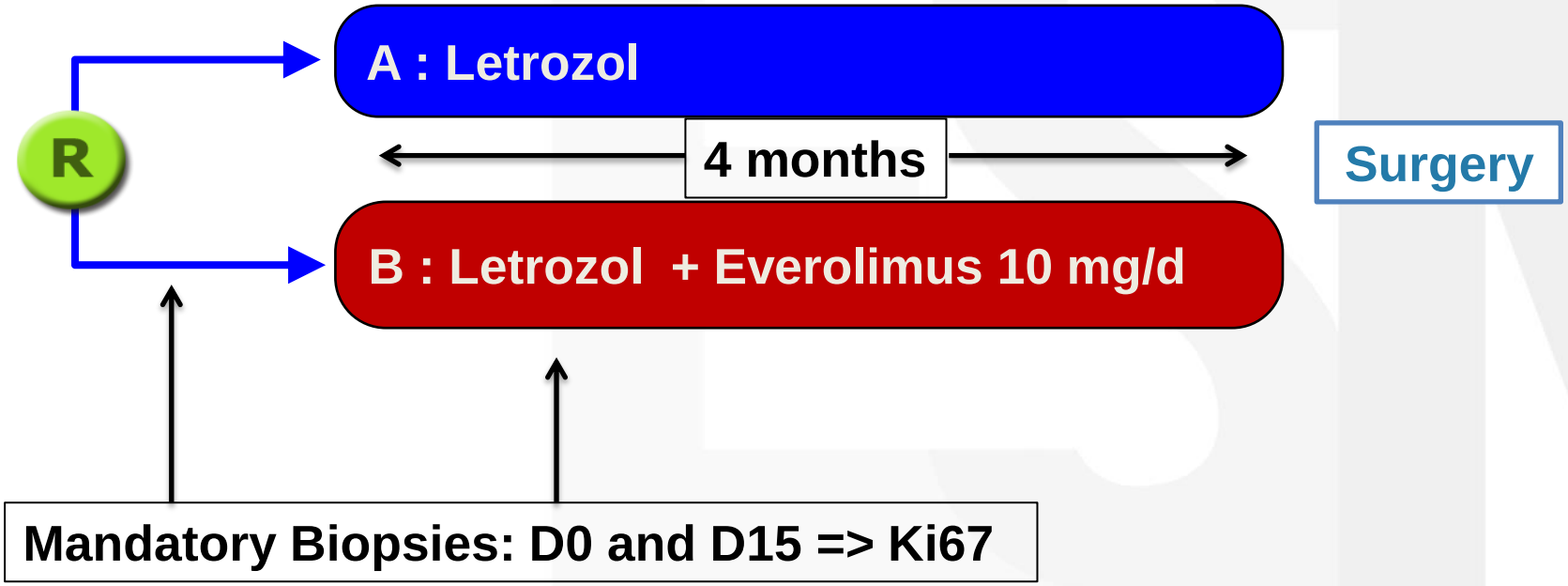
Neoadjuvant Letrozol Alone or With Everolimus in Early Breast Cancer : Randomized Phase II

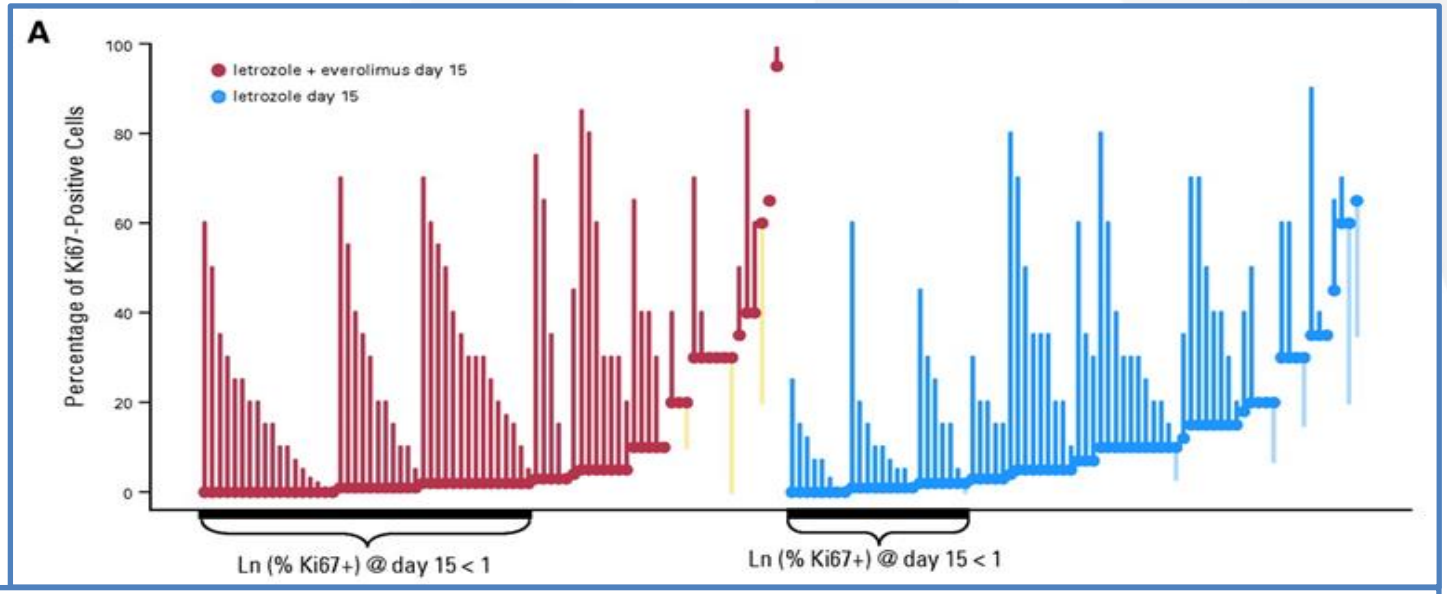
- Randomized Phase II, double blind
- Localized BC, ER+, T> 2cm, N = 170
- Primary end point : Clinical response at 4 months



Baselga J et al. JCO 2009;27:2630-2637

Neoadjuvant Letrozol Alone or With Everolimus in Early Breast Cancer : Randomized Phase II

Arme	Pts	Clinical Objective RR
Letrozole+everolimus	132	68% (LET+EVE)
Letrozole	138	59% (LET) *(p=0.062)*



« Antiproliferative response » : Let + Eve = 57% Let = 30%

Baselga J et al. JCO 2009;27:2630-2637

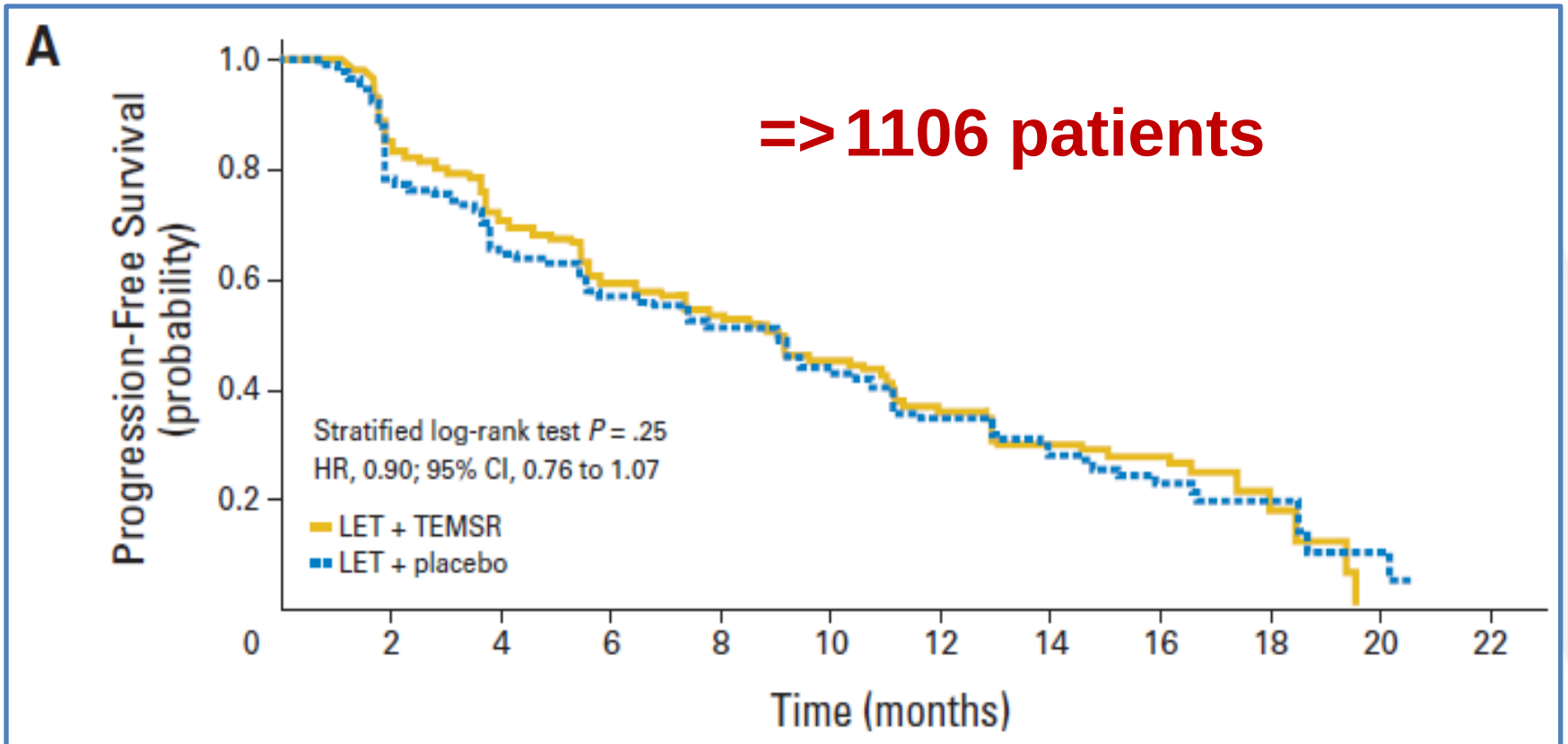
Temsirolimus for first line ER+ MBC: Randomized, double blinde Phase III

- ER+, Locally advanced or MBC, N = 1106
- No prior AI, or have stopped adjuvant treatment > 1year
- Most patients had received Tam in the adjuvant setting

- Primary end point : Progression free survival

Wolff et al. JCO 2012; 31:195-202

Temsirolimus for first line ER+ MBC: Randomized, double blinde Phase III



No. at risk/events												
LET + TEMSR	553	387/79	278/63	193/43	149/19	102/21	61/19	40/10	22/2	5/4	0/3	0/0
LET + placebo	553	365/110	276/58	211/35	154/18	110/21	65/21	37/9	18/6	6/2	2/0	0/0

Wolff et al. JCO 2012; 31:195-202

Temsirolimus for first line ER+ MBC: Randomized, double blinde Phase III

- Drug/drug schedule ?
- Patient population ?

=> Selection of AI pretreated mBC patients may enrich the study population with patients whose tumors are driven by activation of the PI3K/AKT/mTOR pathway.

Wolff et al. JCO 2012; 31:195-202

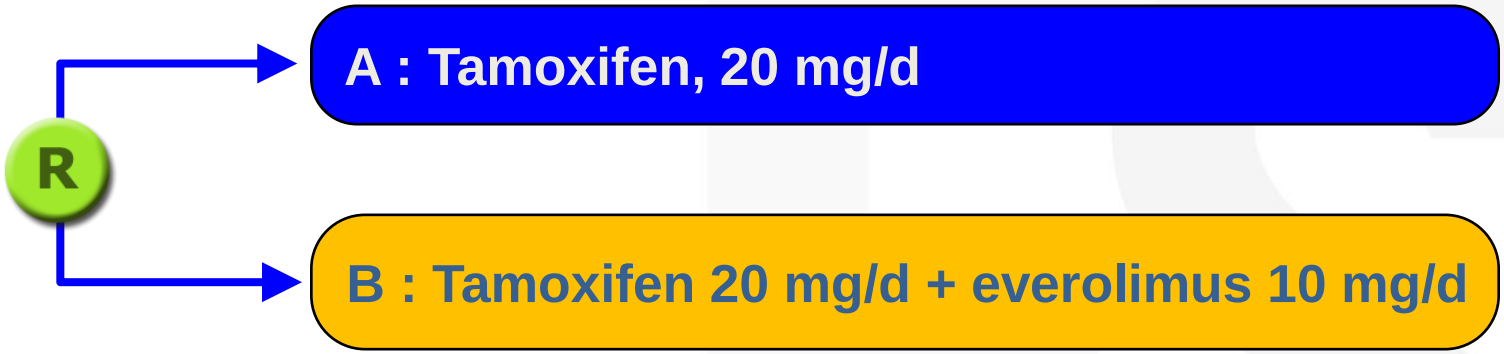
Randomized study of everolimus in ER+/HER2- metastatic breast cancer after AI failure:

TAMRAD and BOLERO-2

Bachelot T et al. J Clin Oncol 2012, 30:2718-24; Baselga J et al. NEJM 2012, 366:520-9.

TAMRAD PROTOCOL

- Randomized non-comparative Phase II
- Metastatic patients with prior exposure to AI, N = 111



- Stratification: Primary or secondary hormone resistance
- Endpoints:
  - Primary: CBR
  - Secondary: TTP, OS, transfer
- No crossover planned

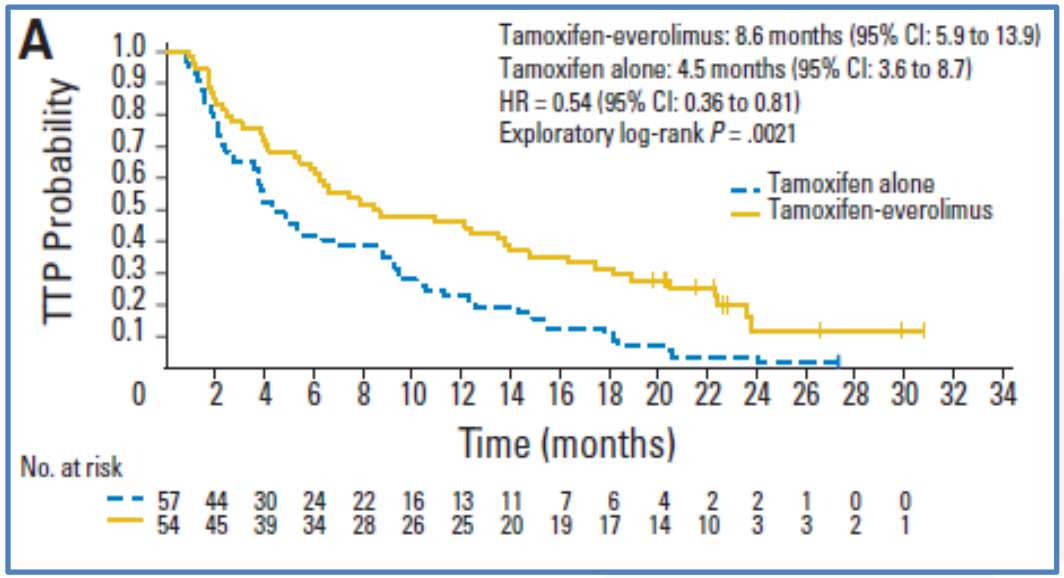
Bachelot T, et al. J Clin Oncol 2012

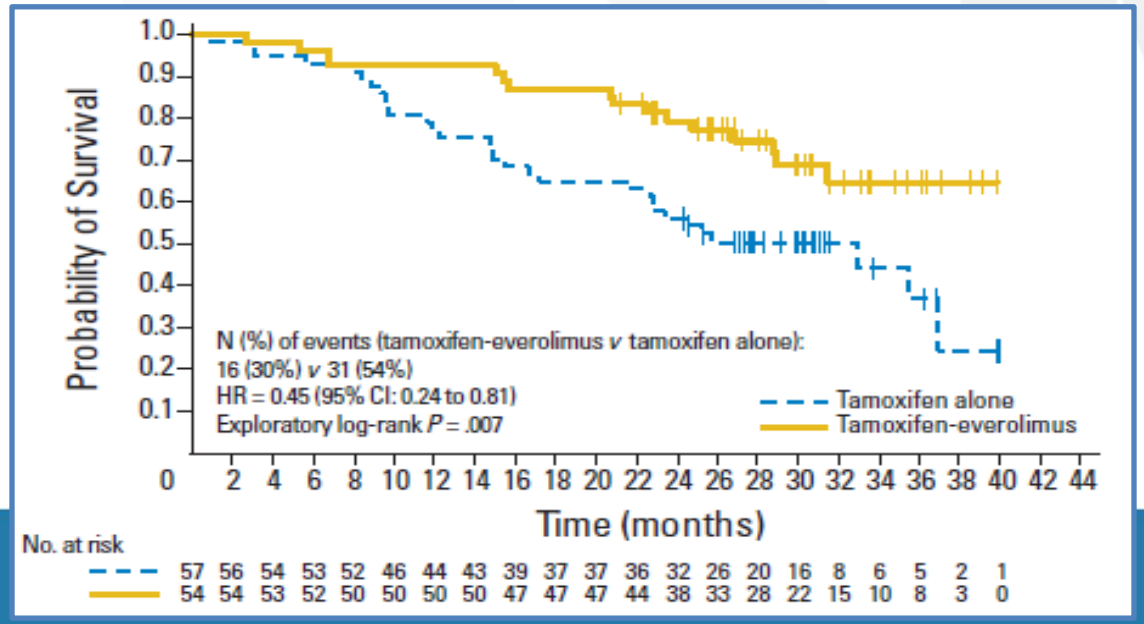
Patient Characteristics

	TAM n = 57	TAM + EVE n = 54
Median age, years (range)	66 (42-86)	62.5 (41-81)
Median duration of metastatic disease (months)	14.4 (0-102)	13.2 (1.2-94.8)
Disease stage, n (%)		
Bone	45 (78.9)	41 (75.9)
Bone only	13 (22.8)	16 (29.6)
Visceral	30 (52.6)	31 (57.4)
3 or more	16 (28.1)	14 (25.9)
Previous anti-aromatase treatment, n (%)		
Adjuvant only	19 (33.3)	15 (27.8)
Metastatic only	33 (57.9)	34 (63.0)
Adjuvant + metastatic	5 (8.8)	5 (9.2)
Previous adjuvant TAM treatment, n (%)	23 (40.4)	17 (31.5)
Previous chemotherapy, n (%)		
Adjuvant	32 (56.1)	25 (46.3)
Metastatic	15 (26.3)	13 (24.1)

Bachelot T, et al. J Clin Oncol 2012

TAMRAD : TTP and survival





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

BOLERO-2: Study Design

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: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- **Primary:** PFS *(Hypothesis : HR = 0.74, 528 events, 90% power)*
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

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Baselga J, et al. New Eng J Med 2012

BOLERO-2: Baseline Characteristics

Characteristic	Everolimus + Exemestane (N=485), %	Placebo + Exemestane (N=239), %
Median age (range), years	62 (34, 93)	61 (28, 90)
Race		
Caucasian	74	78
Asian	20	19
Performance status 0	60	59
Liver involvement	33	31
Lung involvement	29	33
Measurable disease[a]	70	68

[a] All other patients had ≥ 1 bone lesion.

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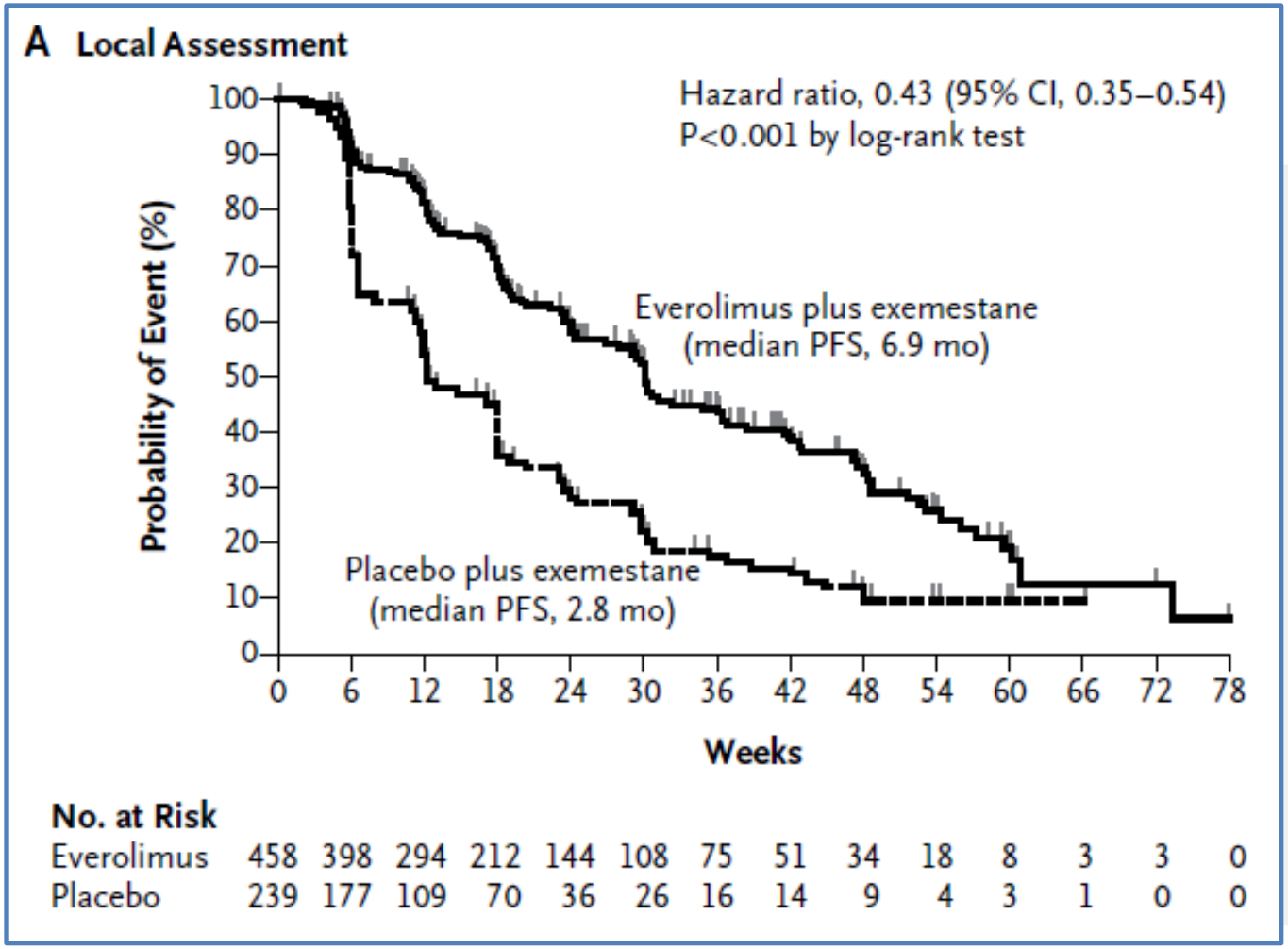
Baselga J, et al. New Eng J Med 2012

BOLERO-2: Prior Therapy

Therapy	Everolimus + Exemestane (N=485), %	Placebo + Exemestane (N=239), %
Sensitivity to prior hormonal therapy	84	84
Last treatment: LET/ ANA	74	75
Last treatment		
Adjuvant	21	15
Metastatic	79	85
Prior tamoxifen	47	50
Prior fulvestrant	17	16
Prior chemotherapy for metastatic BC	26	26
Number of prior therapies: ≥3	54	53

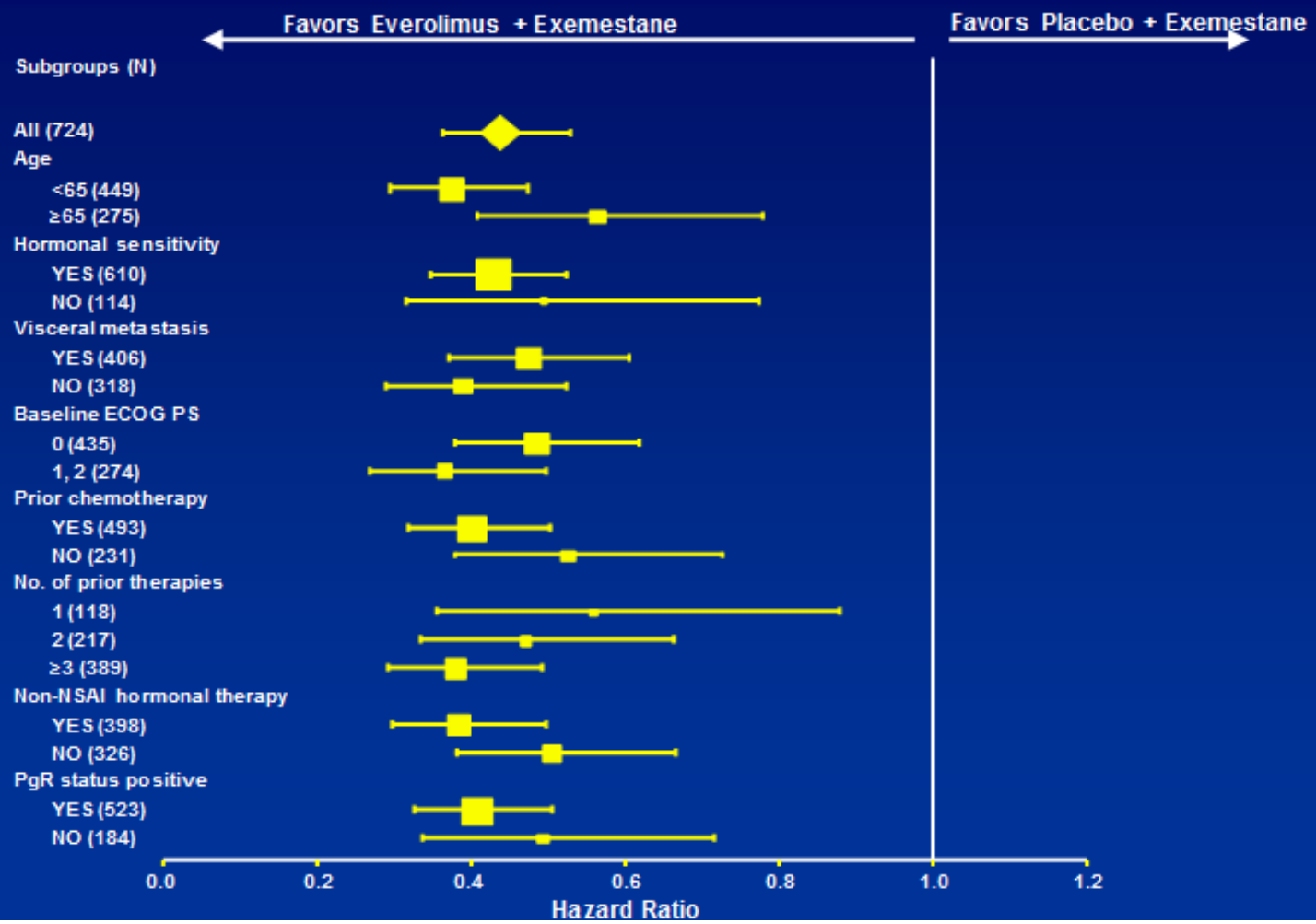
Baselga J, New Eng J Med 2012

BOLERO-2 : PFS



Baselga J, et al. New Eng J Med 2012

BOLERO-2 (12 mo f/up): PFS in Subgroups



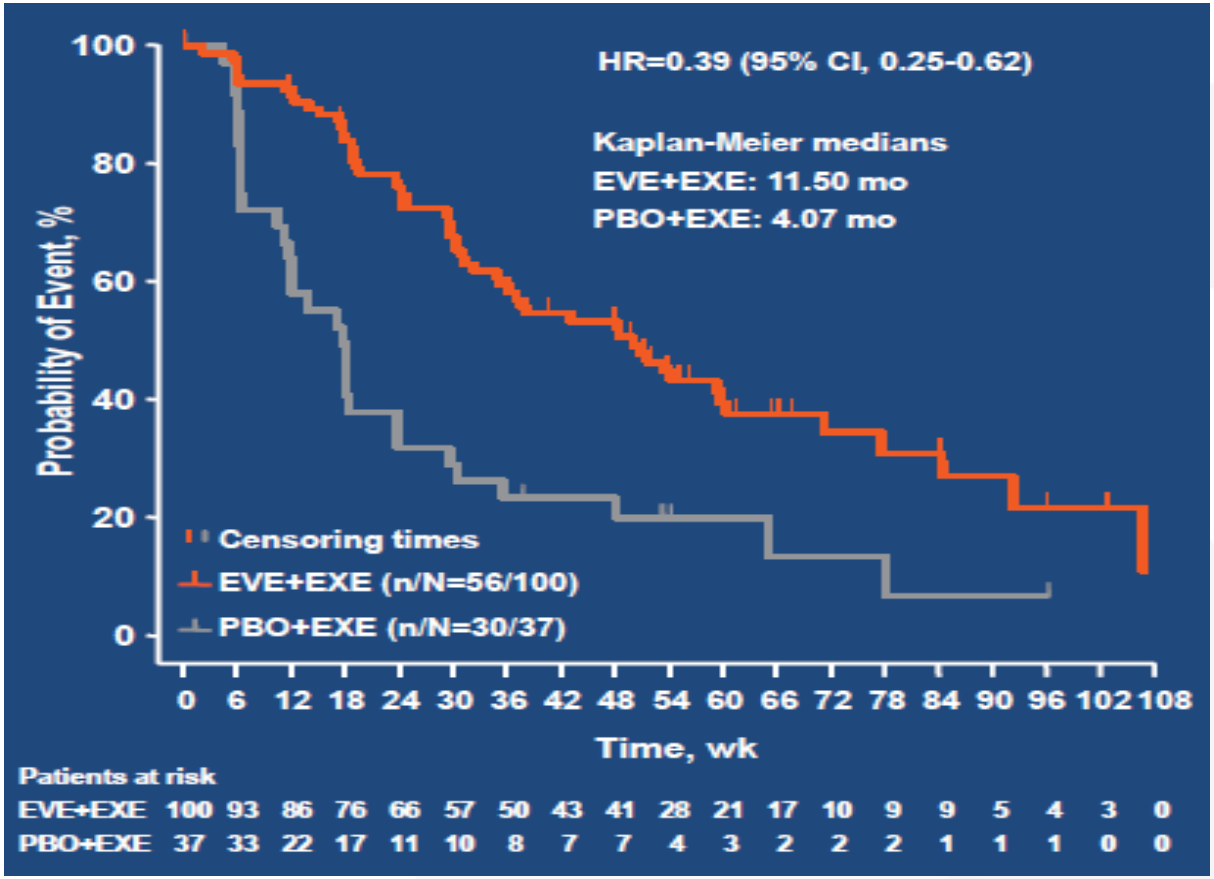
Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)

Efficacy on Visceral metastasis

61 years old, adjuvant anastrozol: 2005-2010. Liver mets: May 2012; letrozol May2012-Feb 2013
Start Everolimus and exemestane : Feb 2013

Campone M et al. Eur J Cancer. 2013;49:2621-32.

Efficacy on patients progressive while on or within one year of adjuvant AI



Piccart M. et al, SABCS 2012 (Abstract # P6-04-02)

Conclusion

- mTOR inhibition is feasible in the clinic with current drugs
- Consistent efficacy of everolimus and exemestan combination was shown for post menopausal patients with ER+/HER2- MBC, having progressed on NSAI.
- This efficacy seems to be equivalent across all clinically defined subgroups

Unanswered question :

- Efficacy in monotherapy ?
- Efficacy in first line MBC ?
- Efficacy for premenoposal patients ?
- Efficacy in the adjuvant setting ?
- Description of predictive biological biomarkeurs