Incontri
di aggiornamento
del Dipartimento
Oncologico

La via del segnale PI3K/AKT/mTOR

Inibitori di mTOR nel carcinoma mammario

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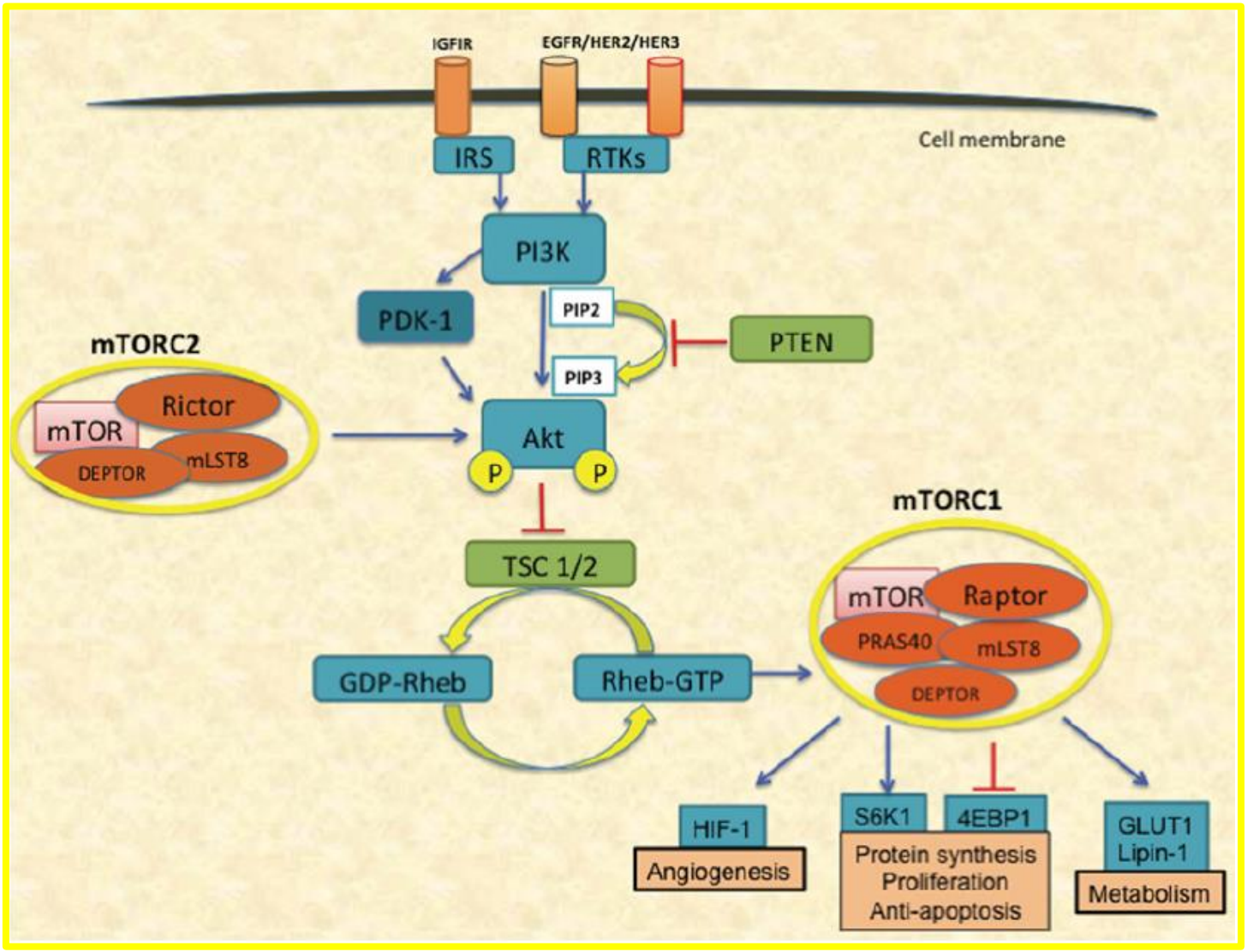
29 novembre 2016

The PI3K/AKT/mTOR pathway

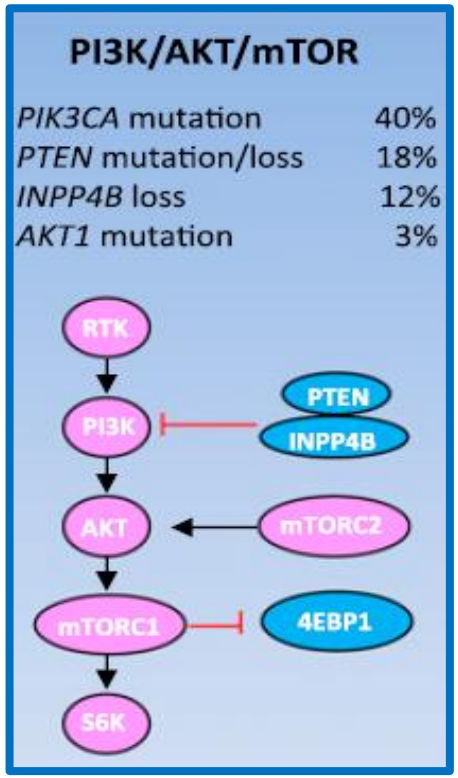


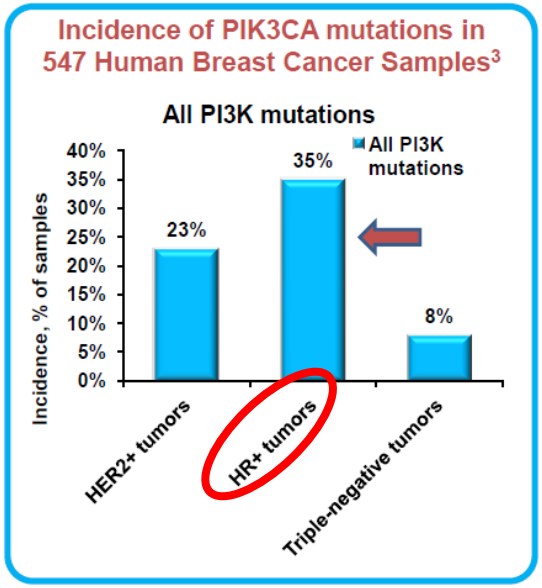
Bjornisti Ma et al., Nat Rev Cancer 2004. Wullshleger S et al., Cell 2006. Johnston SR et al., Clin Cancer Res 2005.

. . . in breast cancer

The PI3K/AKT/mTOR pathway is frequently activated in brest cancer due to:

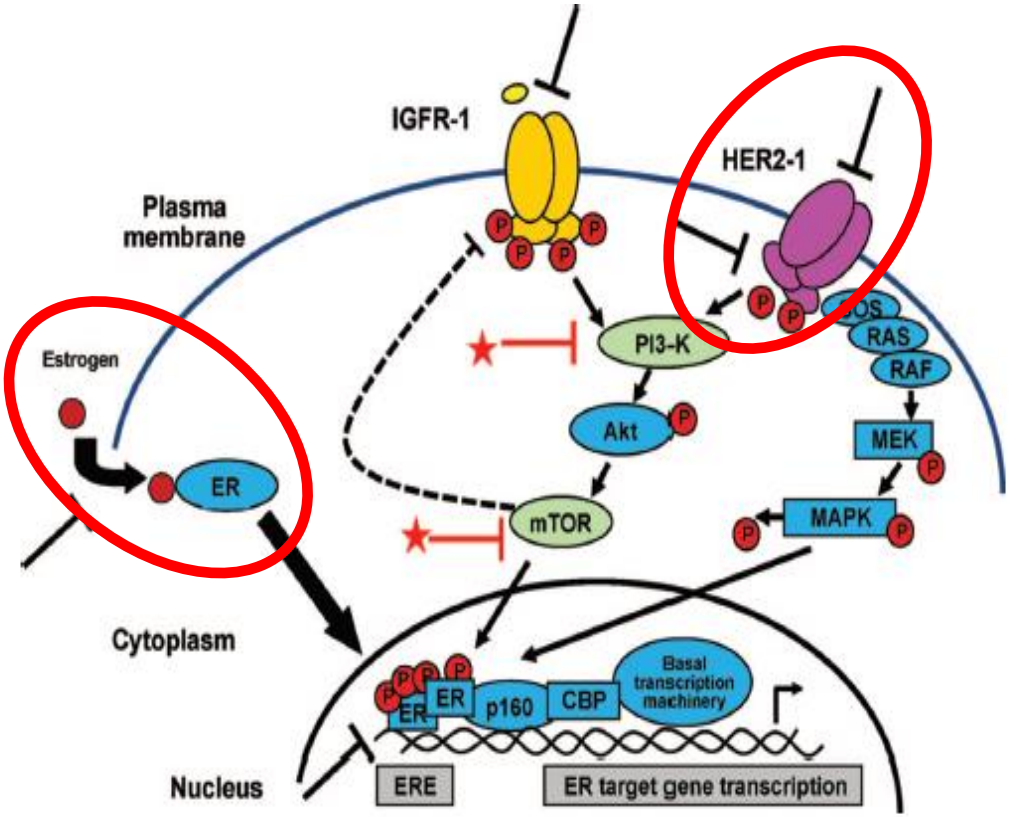
- *overexpression/mutation of RTK (ie, increased HER2-mediated signaling)*
- *mutational inactivation or loss of PTEN protein*
- *activating mutation or amplification of PIK3CA*
- *AKT activation*





Liu P et al., Nat Rev Drug Discover 2009.
Baselga J., Oncologist 2011.
Stemke-Hale K eta l., Cancer Res 2008.

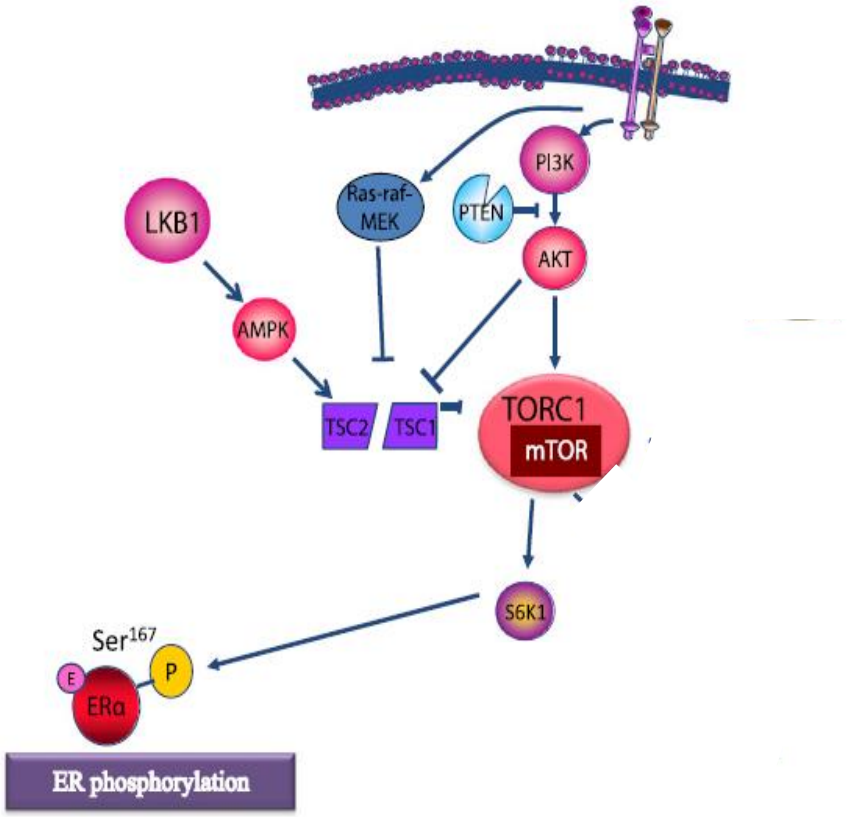
Crosstalk between mTOR signaling and signal transduction pathways



In breast cancer, the PI3K/AKT/mTOR pathway modulates responses to signals communicated through the ER and HER family of receptor (ie, HER2).

Kurokawa H et al., Cancer Res 2000.
Stoica GE et al., Mol Endocrinol 2003.

Crosstalk between ER and mTOR signaling (1)



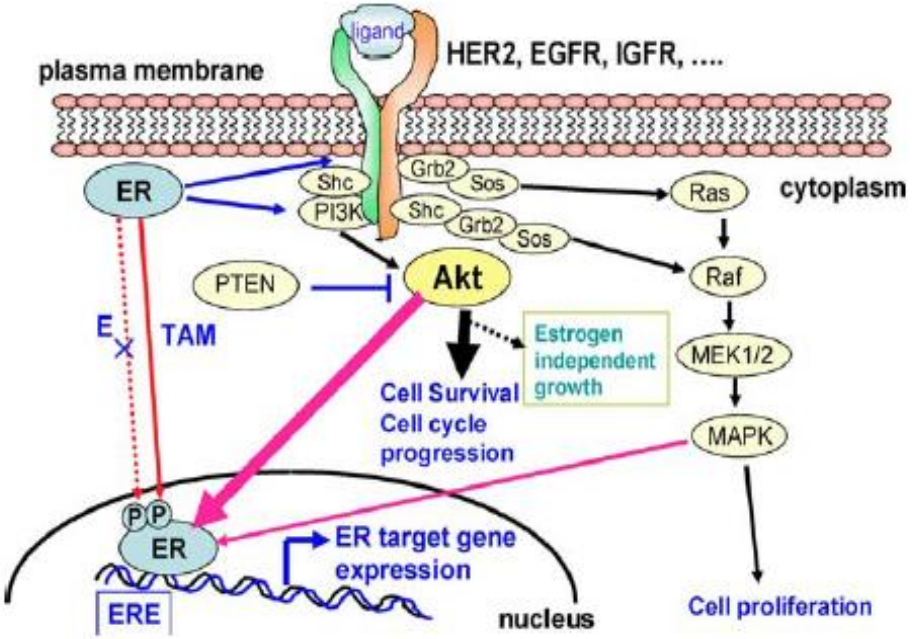
- *mTORC1 activates ER in a ligand-independent manner*.

A substrate of mTORC1, called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand-independent receptor activation.

- *Estradiol suppresses apoptosis induced by PI3K/mTOR blockage.*

Yamnik RL et al., J Biol Chem 2009.
Yamnik RL et al., FEBS Lett 2010.

Crosstalk between ER and mTOR signaling (2)

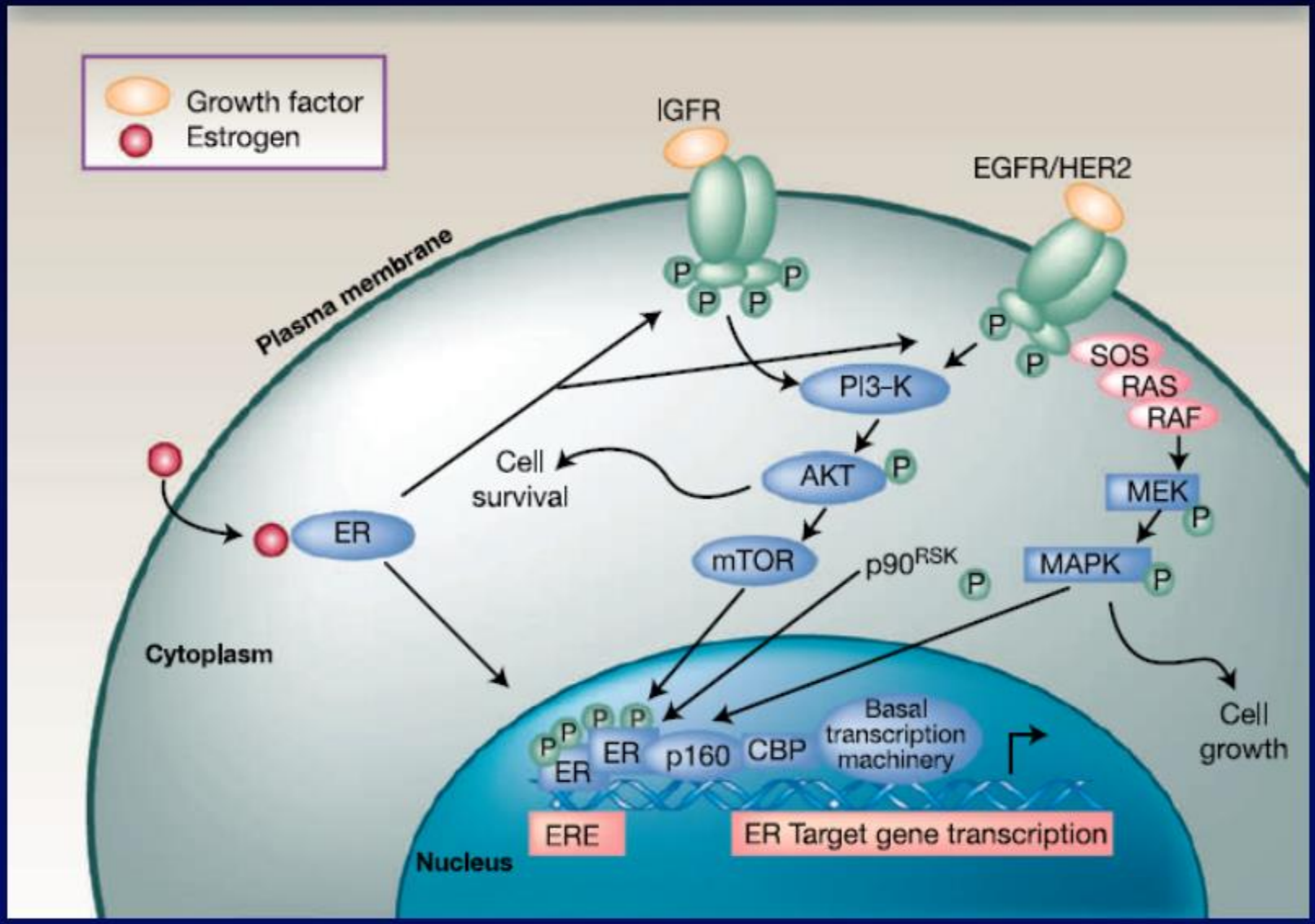


Possible mechanism for endocrine resistance in Akt-activated breast cancer cell.

- *The PI3K/AKT/mTOR pathway is important in the clinical sensitivity of breast cancer to endocrine therapy →* ***hyperactivation*** *of this signaling has been* ***associated with anti-estrogen resistance in ER+ breast cancer.***
- ***mTOR*** *is a rational* ***target to enhance the efficacy of hormonal therapy****.*

Perez-Tenorio G et al., Br J Cancer 2002.
Miller TW et al., J Clin Invest 2010.
Tokunaga E et al., Eur J Cancer 2006.

Overcoming Resistance: Inhibiting Crosstalk



Johnston SRD. *Clin Cancer Res.* 2010;16(7):1979-1987.

Preclinical data

Inhibition of mTOR Activity Restores Tamoxifen Response in Breast Cancer Cells with Aberrant Akt Activity

Linda A. deGraffenried,[1] William E. Friedrichs,[1]
Douglas H. Russell,[1] Elissa J. Donzis,[1]
Amanda K. Middleton,[1] Jessica M. Silva,[1]
Richard A. Roth,[2] and Manuel Hidalgo[3]

Clin Cancer Res 2004.

Akt-induced endocrine therapy resistance is reversed by inhibition of mTOR signaling

M. Beeram[1], Q.-T. N. Tan[2], R. R. Tekmal[3], D. Russell[1], A. Middleton[1] & L. A. deGraffenried[1*]

Ann Oncol 2007.

The mTOR pathway inhibitor RAD001 (everolimus) is highly efficacious in tamoxifen-sensitive and -resistant breast cancer xenografts

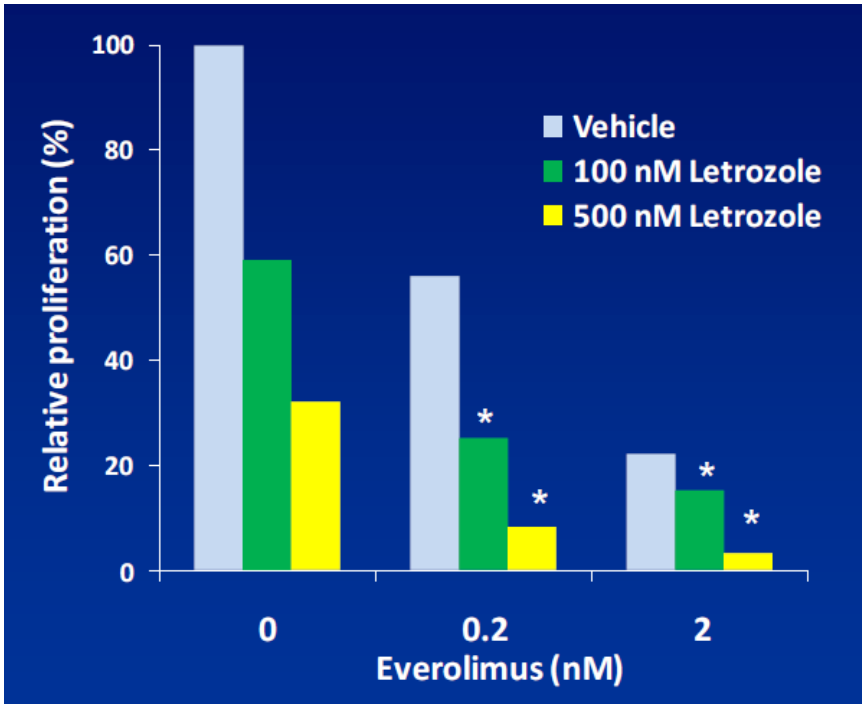
Diana Behrens · Anne E. Lykkesfeldt · Iduna Fichtner

Targeted Oncol 2007.

Breast cancer cells with upregulated AKT signaling are resistant to hormonal therapy, but *sensitivity may be restored* by treatment with everolimus or other mTOR inhibitor.

Dual Inhibition of mTOR and Estrogen Receptor Signaling *In vitro* Induces Cell Death in Models of Breast Cancer

Anne Boulay,[1] Joelle Rudloff,[1] Jingjing Ye,[2] Sabine Zumstein-Mecker,[1] Terence O'Reilly,[1] Dean B. Evans,[1] Shiuan Chen,[2] and Heidi A. Lane[1]



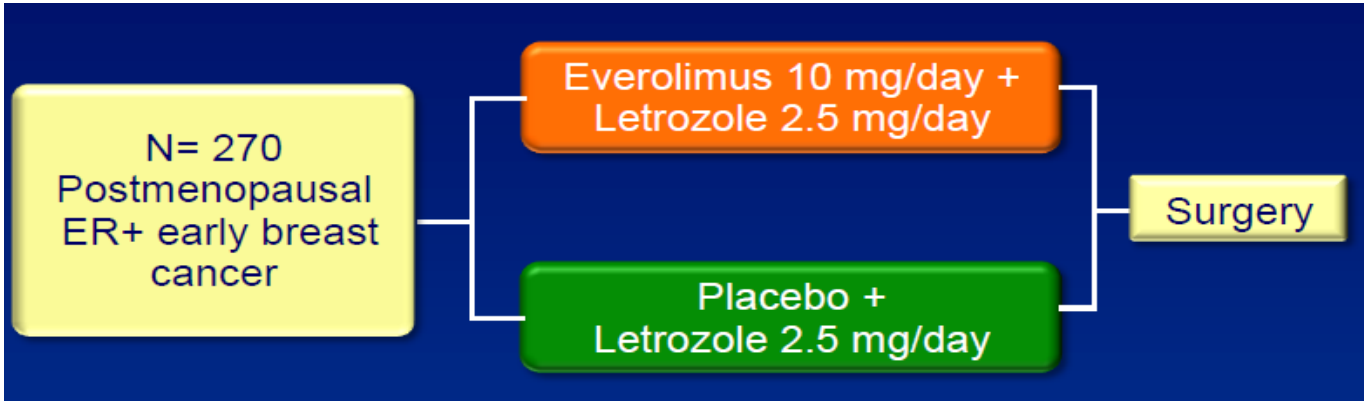
In preclinical models, the use of everolimus in combination with AI results in ***synergistic inhibition*** of the proliferation and induction of apoptosis.

Boulay A et al., Clin Cancer Res 2005.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Randomized Study of Neoadjuvant Everolimus Plus Letrozole Compared With Placebo Plus Letrozole in Patients With Estrogen Receptor–Positive Breast Cancer

José Baselga, Vladimir Semiglazov, Peter van Dam, Alexey Manikhas, Meritxell Bellet, José Mayordomo, Mario Campone, Ernst Kubista, Richard Greil, Giulia Bianchi, Jutta Steinseifer, Betty Molloy, Erika Tokaji, Humphrey Gardner, Penny Phillips, Michael Stumm, Heidi A. Lane, J. Michael Dixon, Walter Jonat, and Hope S. Rugo



Results:

- ✓ **Higher clinical response rate** (primary endpoint) (68% vs 59%; p=0.062)
- ✓ **Greater decrease in Ki67 proliferation index (**57% vs 30%; p<0.01)

Baselga J et al., JCO 2009.

mTOR inhibitors in metastatic breast cancer

Study name	Comparison arms	Study description	Key findings	References
Hormone receptor Positive, HER2 negative				
HORIZON study	Temsirolimus + letrozole *vs.* placebo + letrozole	Phase III study, ABC, First-line (*n*=11,112)	PFS: 8.9 *vs.* 9.0 months (*P*=0.25); subgroup analysis: in <65 months, 9.0 *vs.* 5.6 months (*P*=0.003)	41
BOLERO-2 study	Everolimus + exemestane *vs.* placebo + exemestane	Phase III study, ABC, relapsed or progressed on previous NSAI (*n*=724)	Central PFS: 10.6 *vs.* 4.1 months (*P*<0.0001); local PFS: 6.9 *vs.* 2.8 months (*P*<0.0001); OS: 31.0 *vs.* 26.6 months (*P*=0.14)	42,43
TAMRAD study	Everolimus + tamoxifen *vs.* tamoxifen	Phase II randomised study; ABC; relapsed or progressed on previous AI (*n*=111)	CBR: 61% *vs.* 42% (*P*=0.045); TTP: 8.6 *vs.* 4.5 months (*P*=0.002)	44
HER2 positive				
BOLERO-3	Everolimus + vinorelbine + trastuzumab *vs.* placebo + vinorelibine + trastuzumab	Phase III study, ABC, previous treatment with taxane, resistance to trastuzumab (*n*=569)	PFS: 7.0 *vs.* 5.8 months (*P*=0.0067); subgroup analysis: PFS improved in HR- cancers but not in HR+ cancers	45
BOLERO-1	Everolimus + paclitaxel + trastuzumab *vs.* placebo + paclitaxel + trastuzumab	Phase III study, ABC, first-line (*n*=719)	PFS: 14.9 *vs.* 14.5 months (*P*=0.1167); however, in HR negative subpopulation: 20.3 *vs.* 13.1 months (*P*=0.0049)	46

ABC, advanced breast cancer; PFS, progression-free survival; NSAI, non-steroidal aromatase inhibitor; AI, aromatase inhibitor; CBR, clinical benefit rate; TTP, time to progression; HR, hormone receptor.

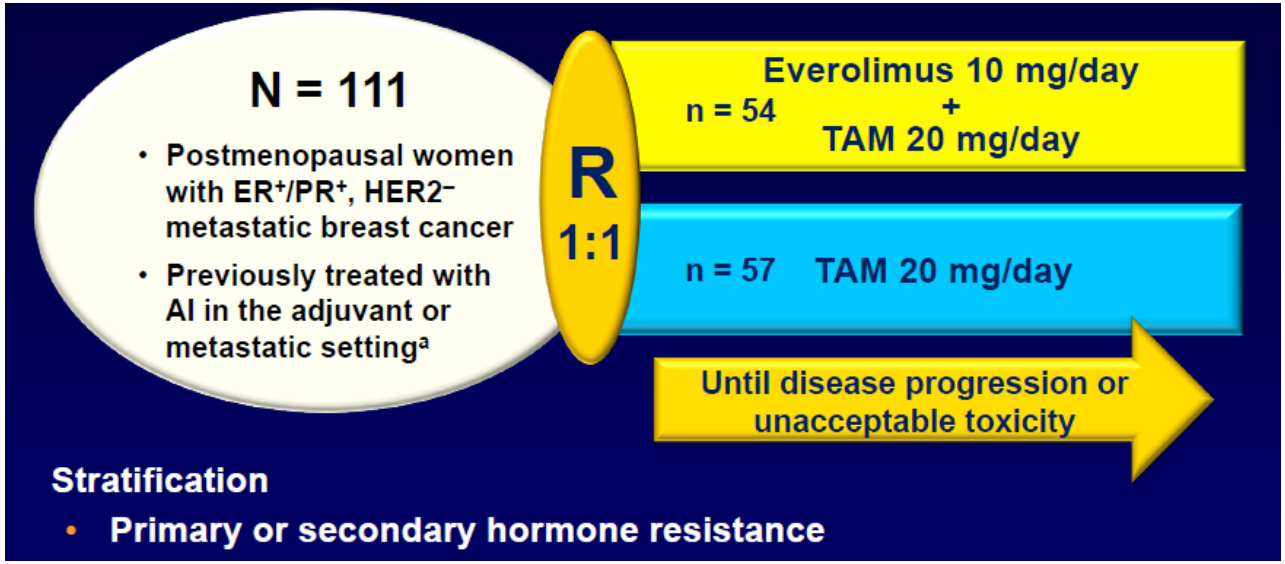
Lee et al., Cancer Biol Med 2015.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study

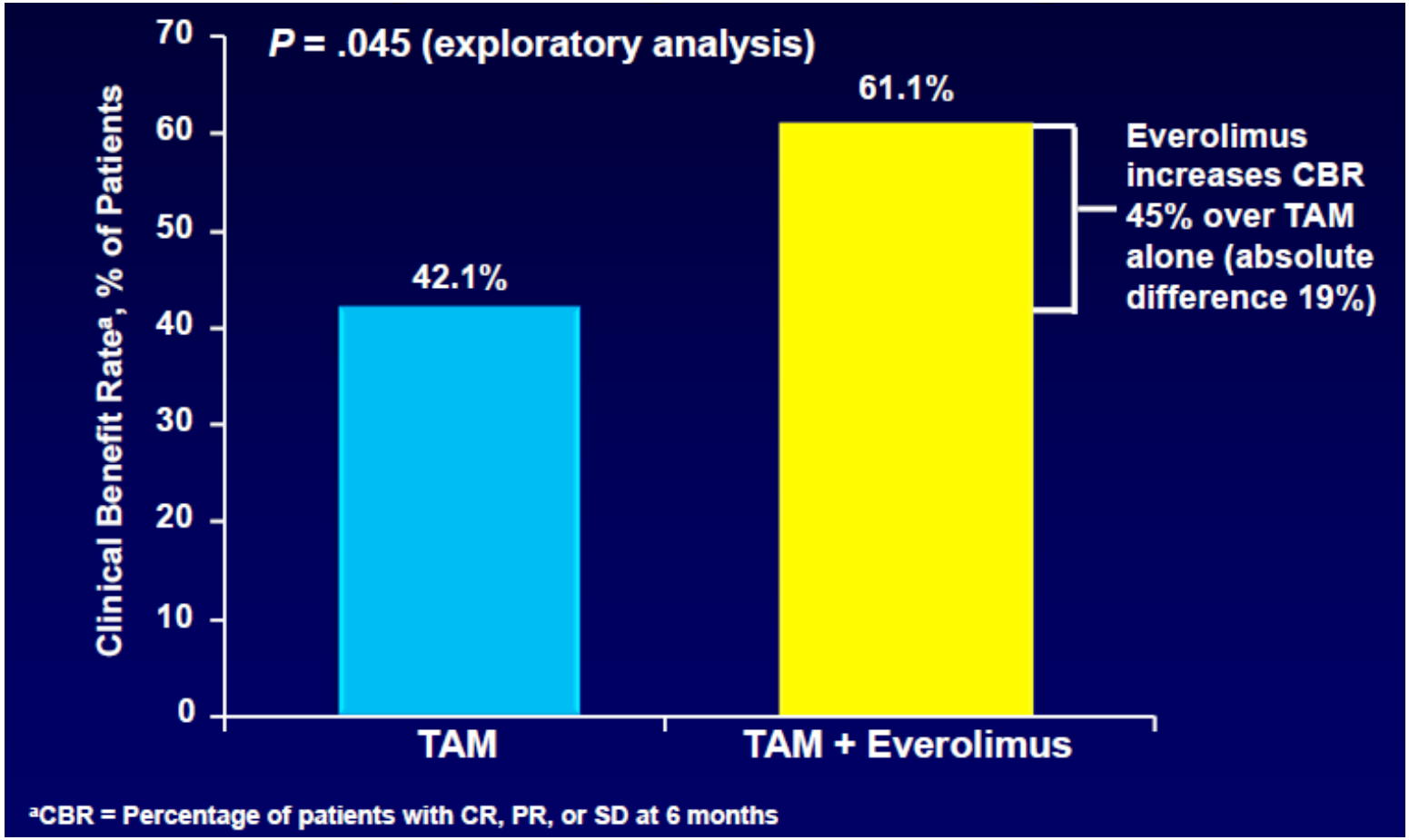
Thomas Bachelot, Céline Bourgier, Claire Cropet, Isabelle Ray-Coquard, Jean-Marc Ferrero, Gilles Freyer, Sophie Abadie-Lacourtoisie, Jean-Christophe Eymard, Marc Debled, Dominique Spaëth, Eric Legouffe, Djelila Allouache, Claude El Kouri, and Eric Pujade-Lauraine

TAMRAD



Bachelot T et al., JCO 2012.

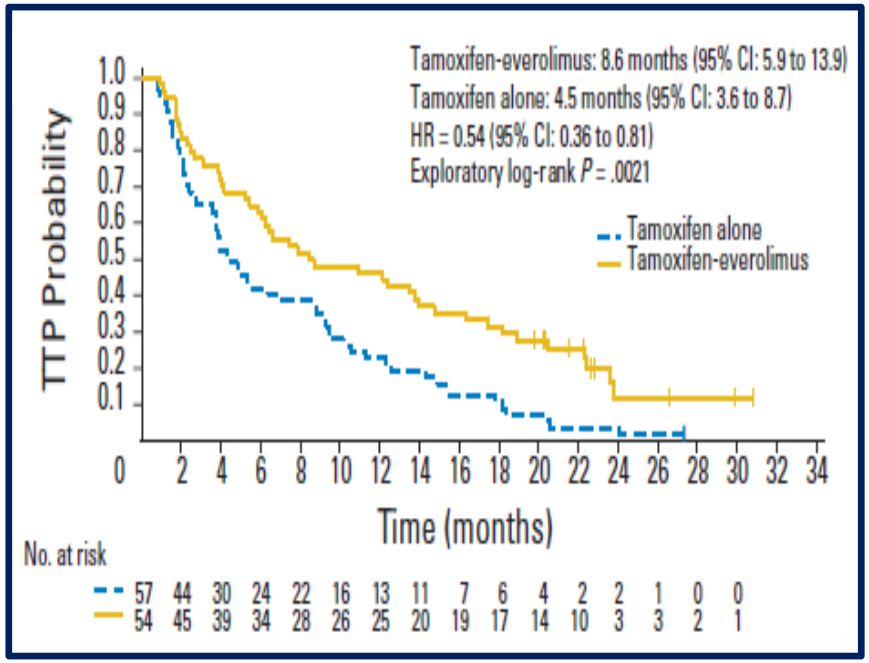
Clinical benefit rate (CBR): primary endpoint



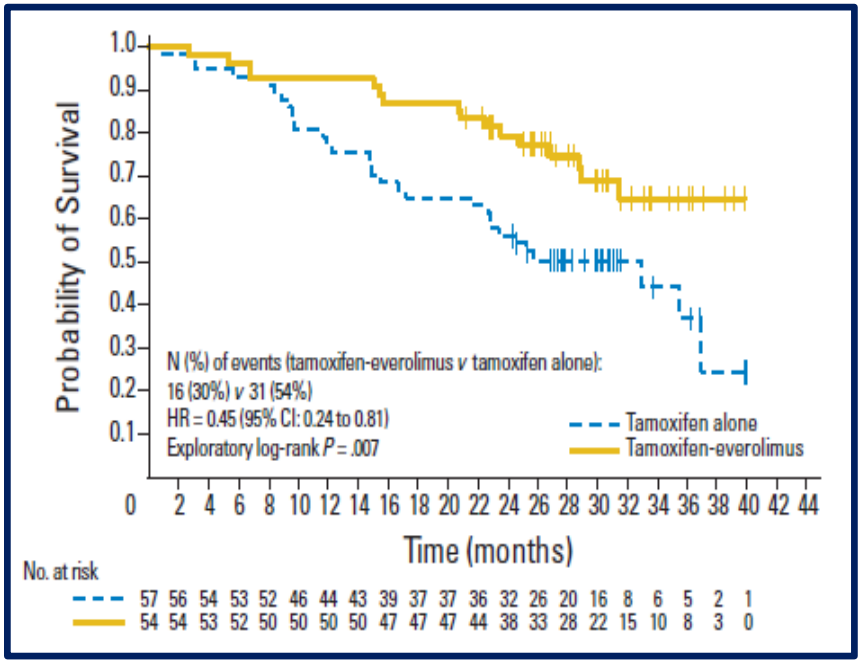
Bachelot T et al., JCO 2012.

Secondary endpoints

TTP

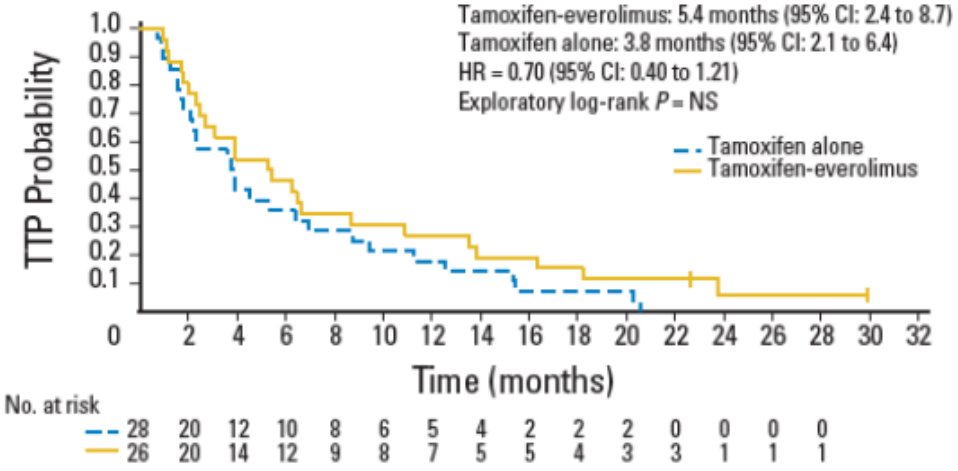


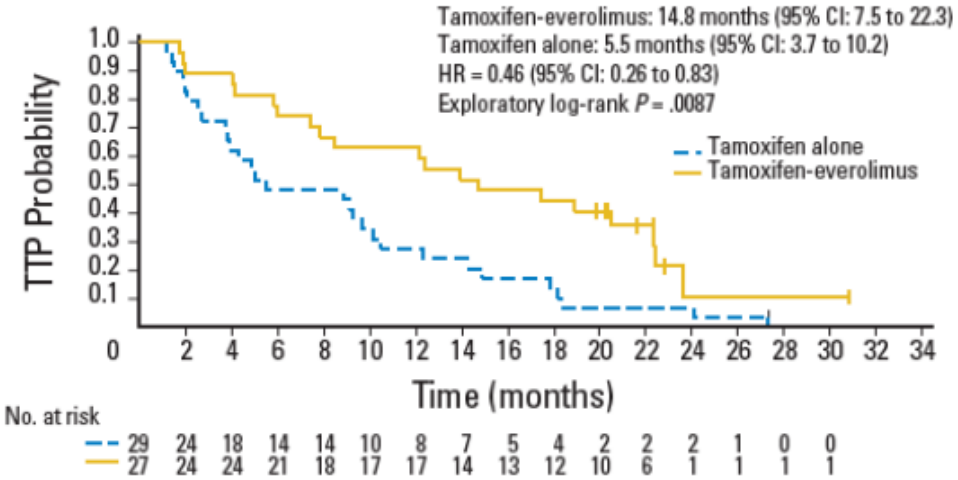
OS



Bachelot T et al., JCO 2012.

Who to select for everolimus?





Primary resistance

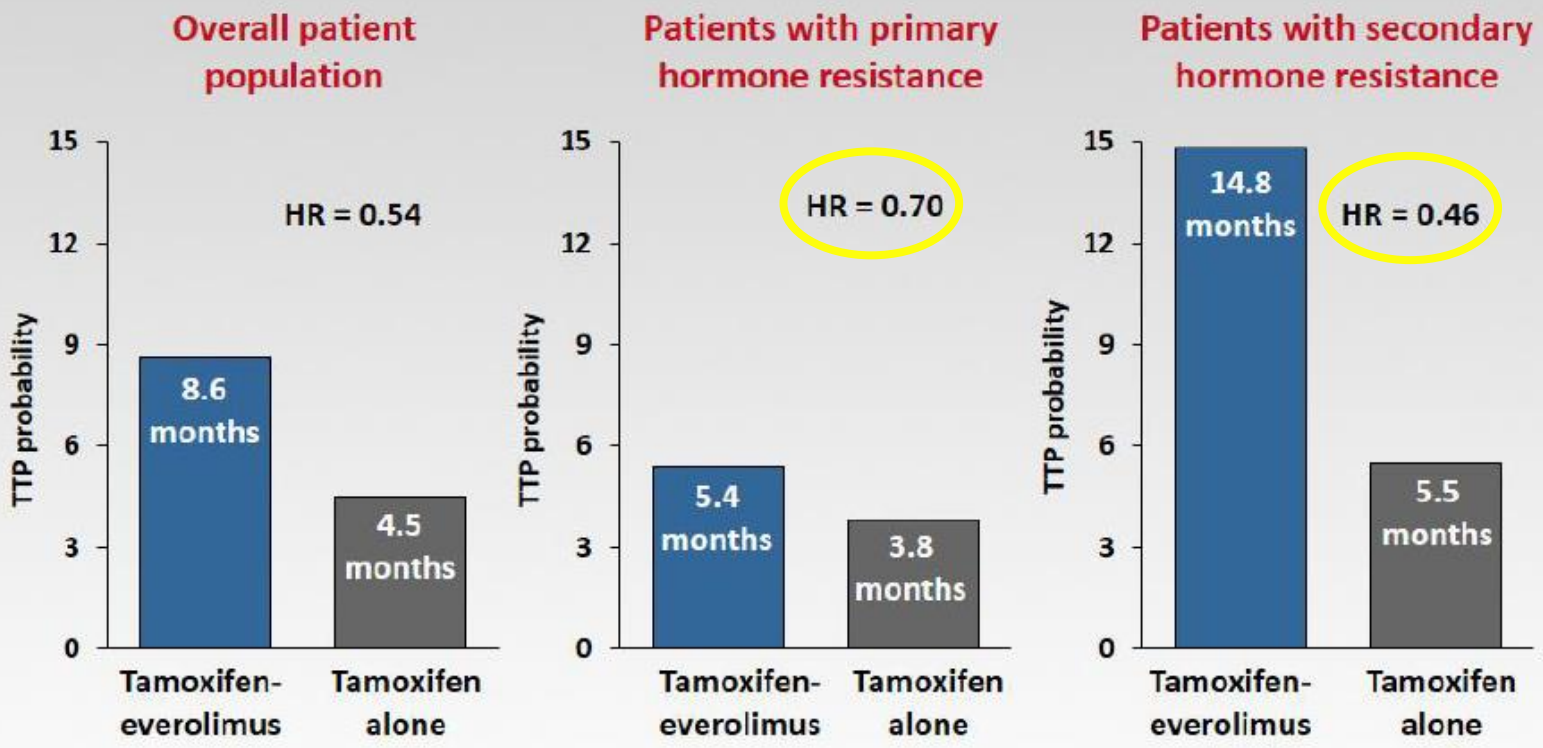
Relapsing on adjuvant AI
<6 months AI in advanced setting

Secondary resistance

Relapsing >6 months after adjuvant AI
>6 months AI in advanced setting

Bachelot T et al., JCO 2012.

Response to Therapy in Patients With Primary and Secondary Hormone Resistance

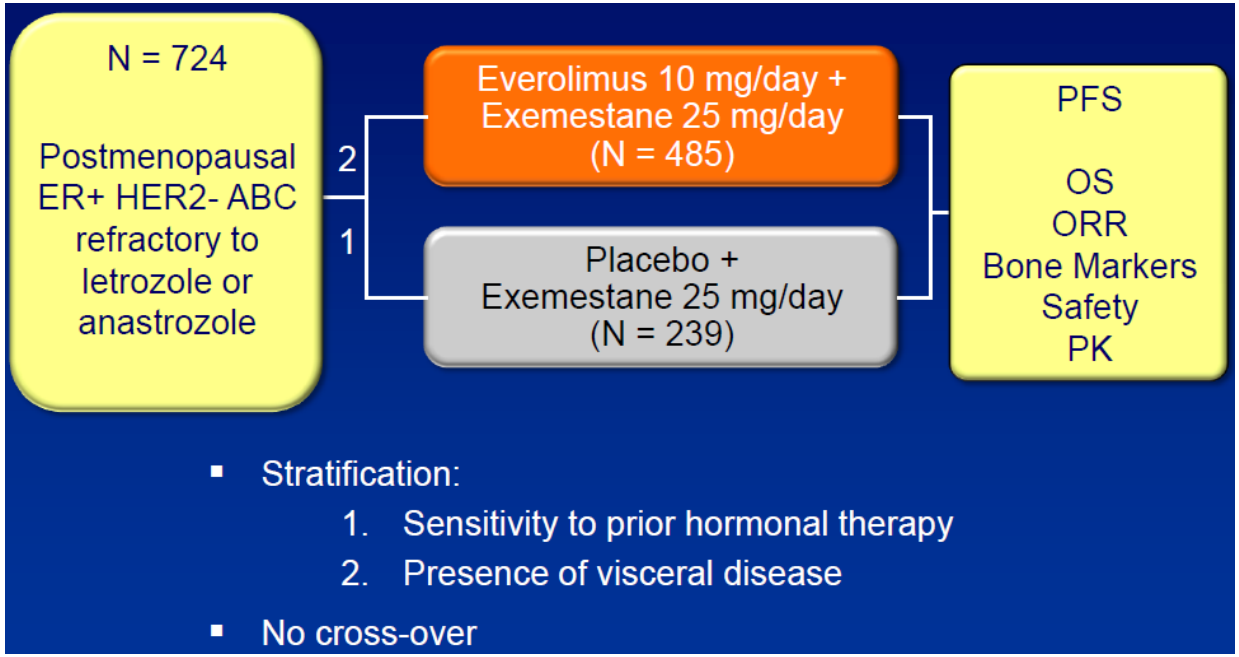


Bachelot T et al., JCO 2012.

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

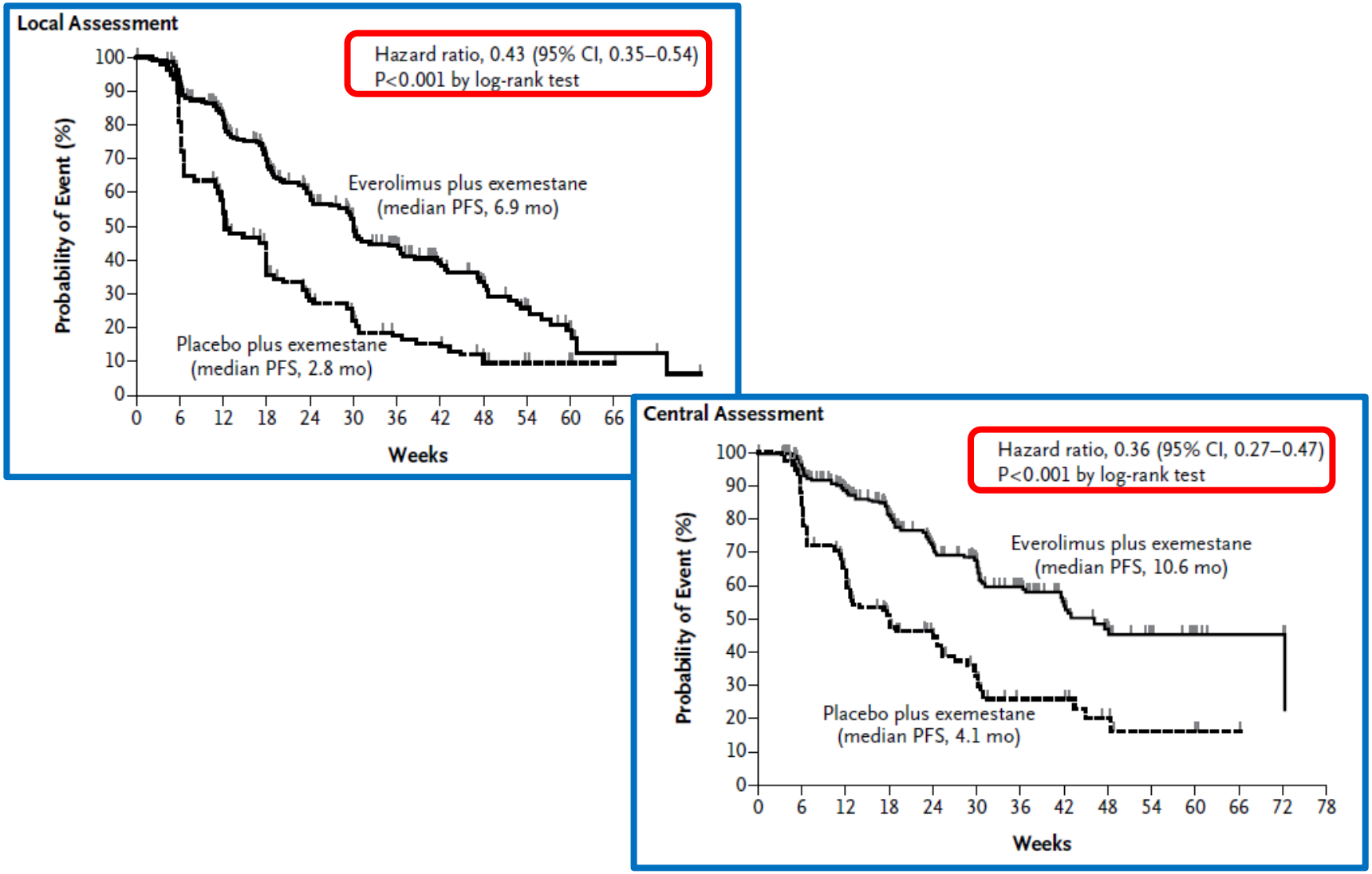
José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

BOLERO-2



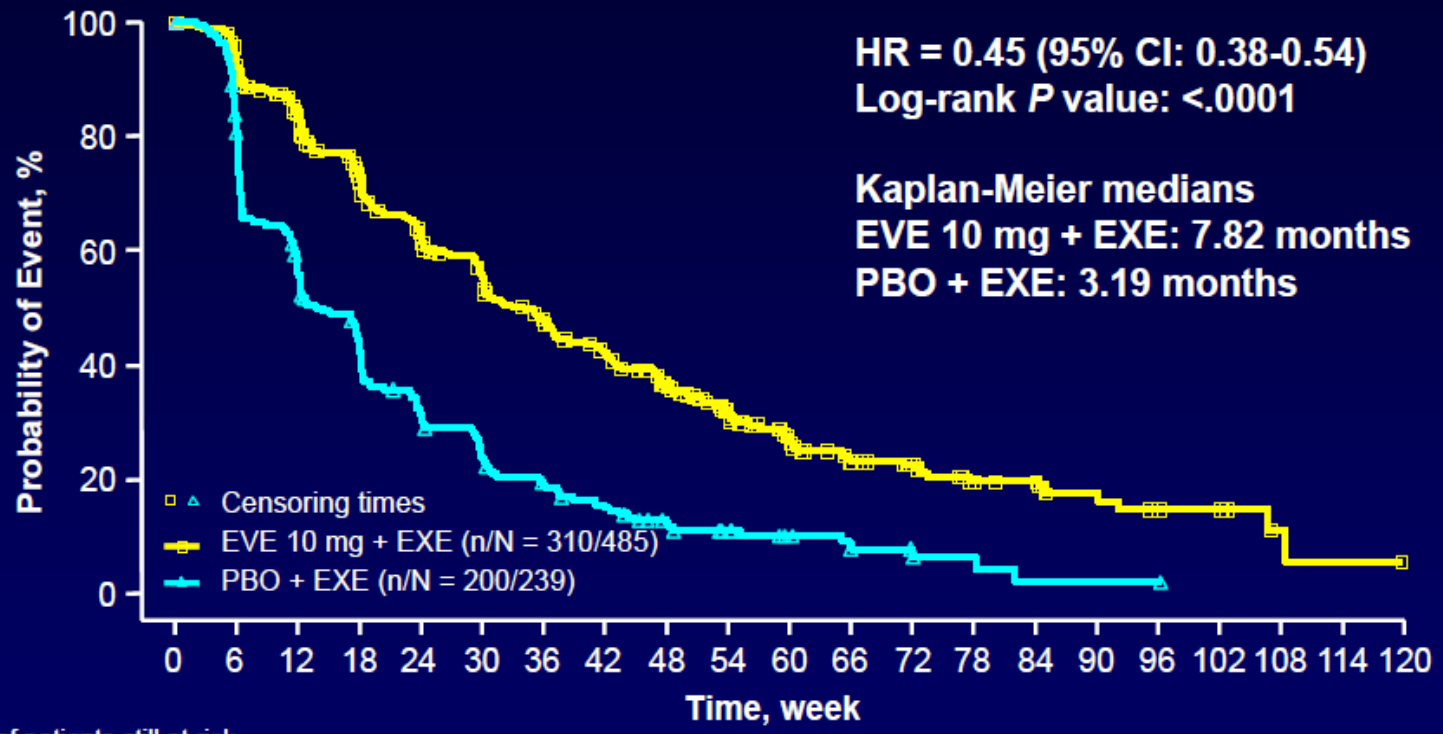
Baselga J T et al., NEJM 2012.

PFS: primary endpoint



Baselga J T et al., NEJM 2012.

BOLERO-2: PFS at 18-Month Follow-Up



HR = 0.45 (95% CI: 0.38-0.54)
Log-rank *P* value: <.0001

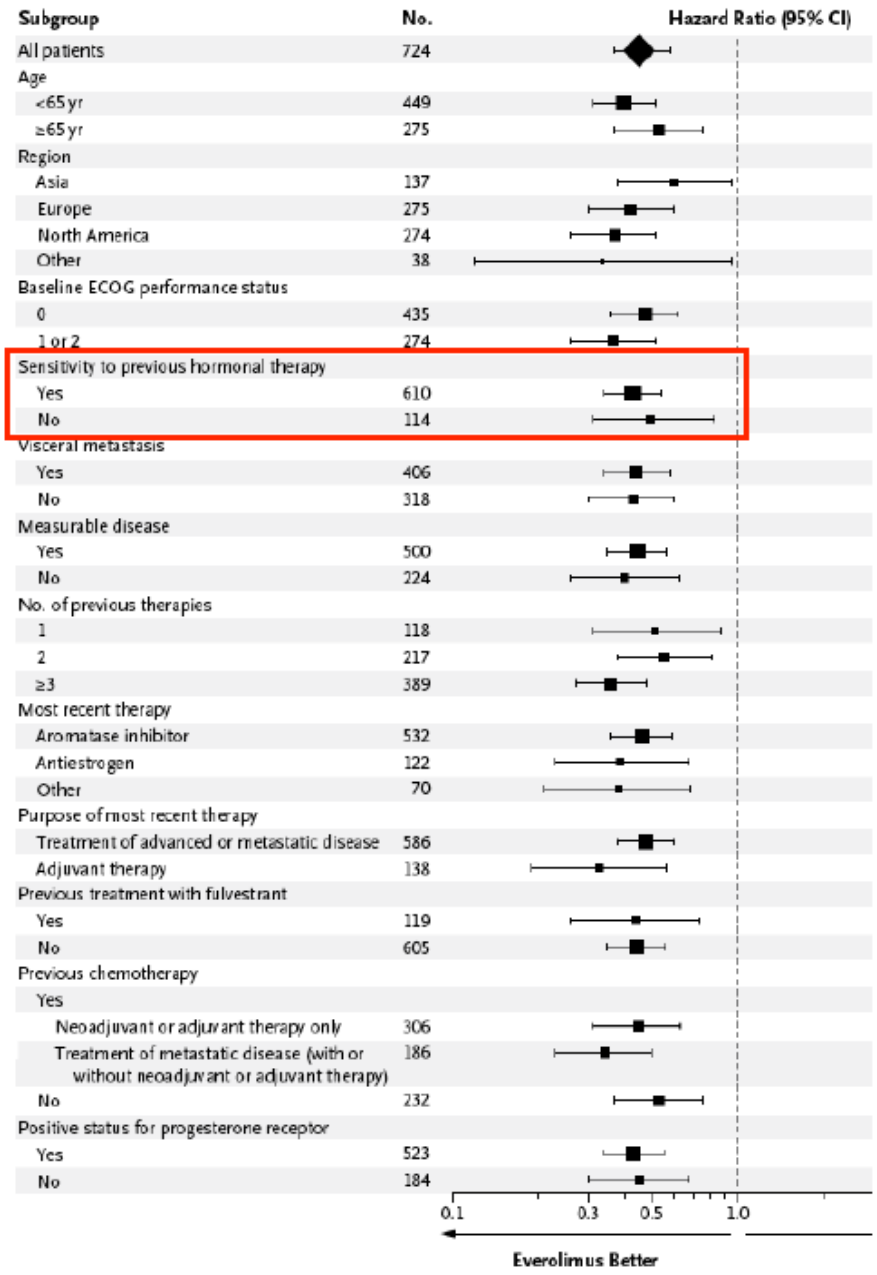
Kaplan-Meier medians
EVE 10 mg + EXE: 7.82 months
PBO + EXE: 3.19 months

Number of patients still at risk

EVE 10 mg + 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

EVE, everolimus; EXE, exemestane; PBO, placebo

Piccart MJ, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 559.

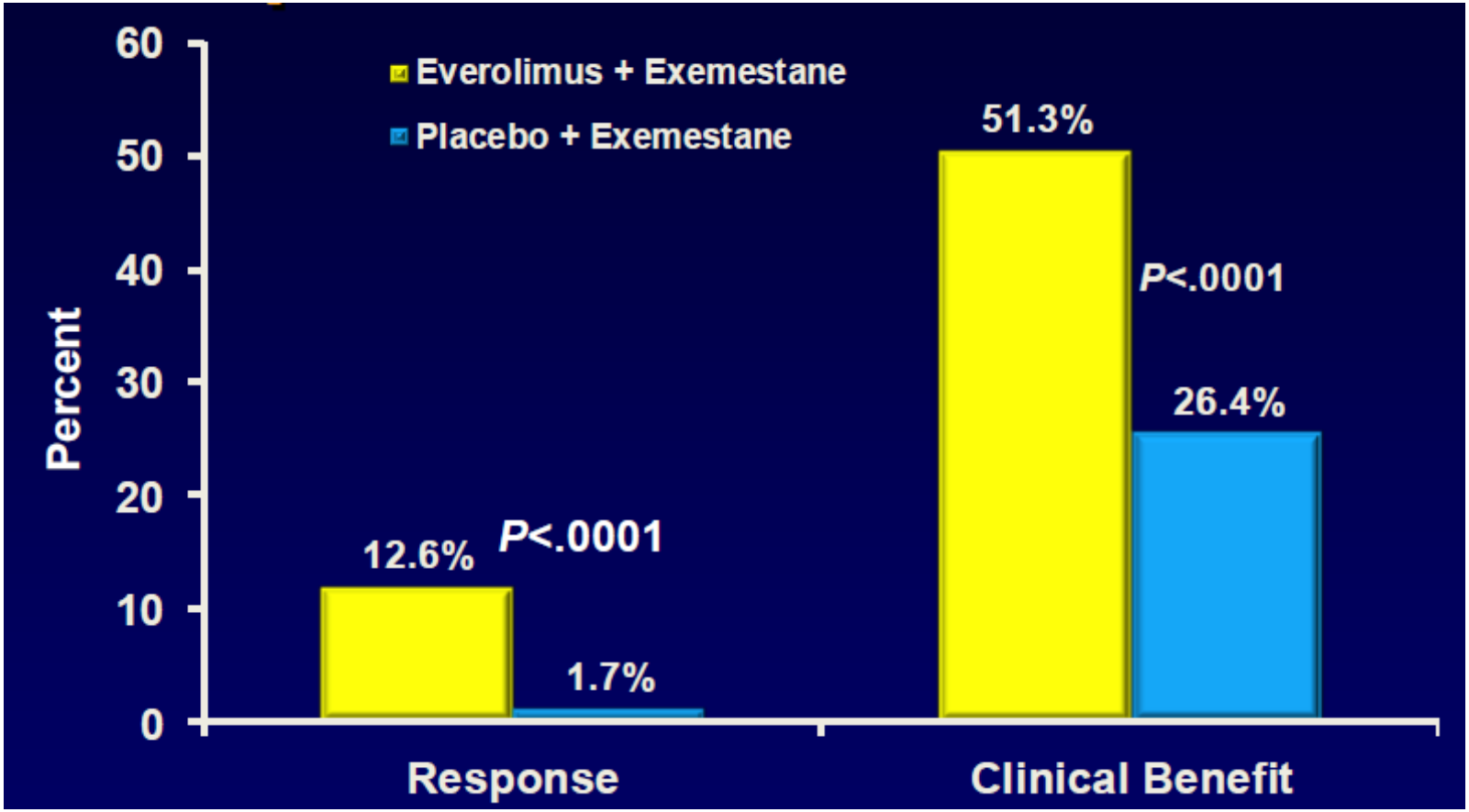


Subanalyses

No evidence of clinical subgroups that derive relatively more or less benefit.

Campone M et al., Eur J Cancer 2013.

Secondary endpoints

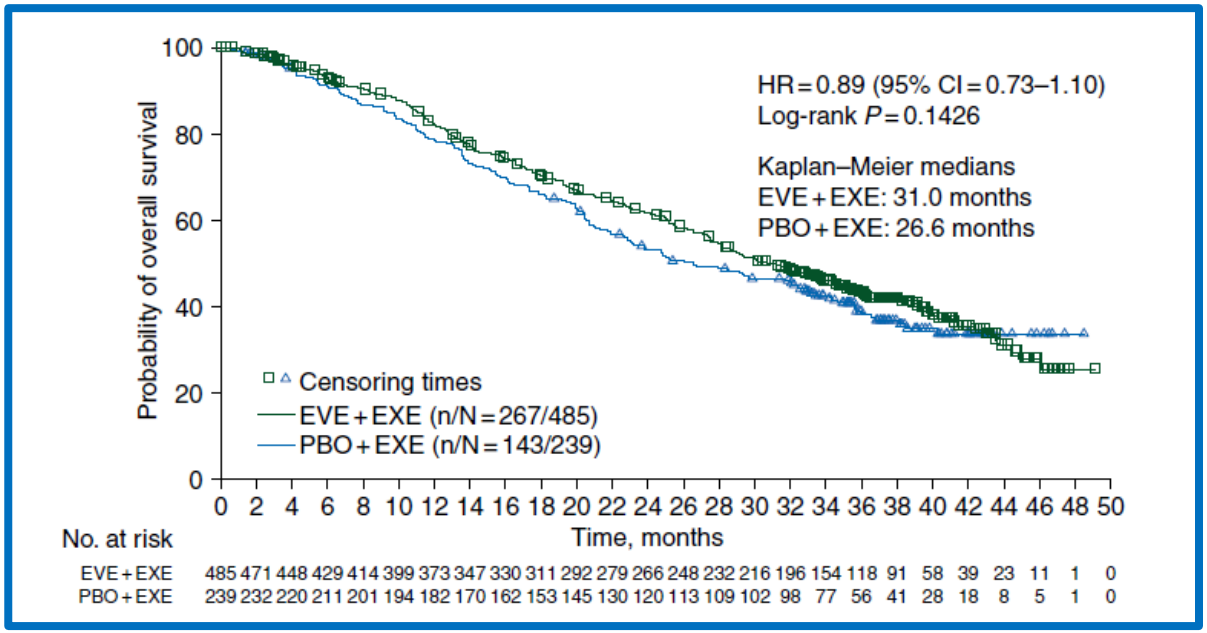


CBR is the proportion of patients with best overall CR, PR, or SD per RECIST at ≥6 months

Baselga J T et al., NEJM 2012.

Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†

M. Piccart[1*], G. N. Hortobagyi[2], M. Campone[3], K. I. Pritchard[4], F. Lebrun[1], Y. Ito[5], S. Noguchi[6], A. Perez[7], H. S. Rugo[8], I. Deleu[9], H. A. Burris III[10], L. Provencher[11], P. Neven[12], M. Gnant[13], M. Shtivelband[14], C. Wu[15], J. Fan[15], W. Feng[15], T. Taran[15] & J. Baselga[16]



Piccart M et al., Ann Oncol 2014.

Safety of everolimus plus exemestane in patients with hormone-receptor–positive, HER2–negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET)

G. Jerusalem[1*], G. Mariani[2], E. M. Ciruelos[3], M. Martin[4], V. C. G. Tjan-Heijnen[5], P. Neven[6], J. G. Gavila[7], A. Michelotti[8], F. Montemurro[9], D. Generali[10], E. Simoncini[11], I. Lang[12], J. Mardiak[13], B. Naume[14,15], M. Camozzi[16], K. Lorizzo[16], S. Bianchetti[16] & P. Conte[17,18]

- Higher incidence of adverse events with combination exemestane/everolimus
  - Predictable
  - Easily managed with dose reductions and interruptions

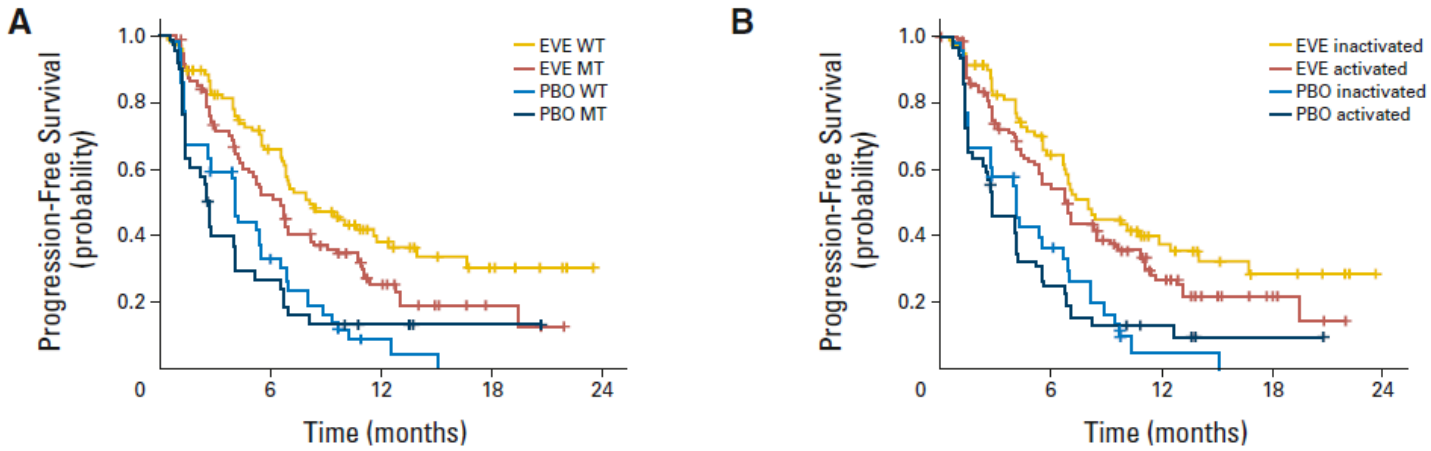
Adverse Event	Grade 3/4	Proportion Resolved	Median Time to Resolution (Weeks; 95% CI)
Stomatitis	8.1%	97%	3.1; 1.9 - 5.3
Fatigue	6.6%	72%	8.0; 2.7 - 18.7
Pneumonitis (noninfectious)	4.1%	80%	3.8; 1.3 - 7.1
Hyperglycemia and new diabetes	5.8%	46%	29.1; 10.1 - NA
Hyperlipidemia	0.8%	25%	NA; 19.3 - NA
Infections/infestations	6.6%	84%	3.0; 1.0 - 18.0

Jerusalem G M et al., Ann Oncol 2016.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From BOLERO-2

Gabriel N. Hortobagyi, David Chen, Martine Piccart, Hope S. Rugo, Howard A. Burris III, Kathleen I. Pritchard, Mario Campone, Shinzaburo Noguchi, Alejandra T. Perez, Ines Deleu, Mikhail Shtivelband, Norikazu Masuda, Shaker Dakhil, Ian Anderson, Douglas M. Robinson, Wei He, Abhishek Garg, E. Robert McDonald III, Hans Bitter, Alan Huang, Tetiana Taran, Thomas Bachelot, Fabienne Lebrun, David Lebwohl, and José Baselga



This exploratory analysis suggests that the **efficacy of everolimus was independent of the commonly altered genes or pathways**: PFS benefit was maintained regardless of alteration status of PIK3CA mutations (A) or PI3K pathway status (B).

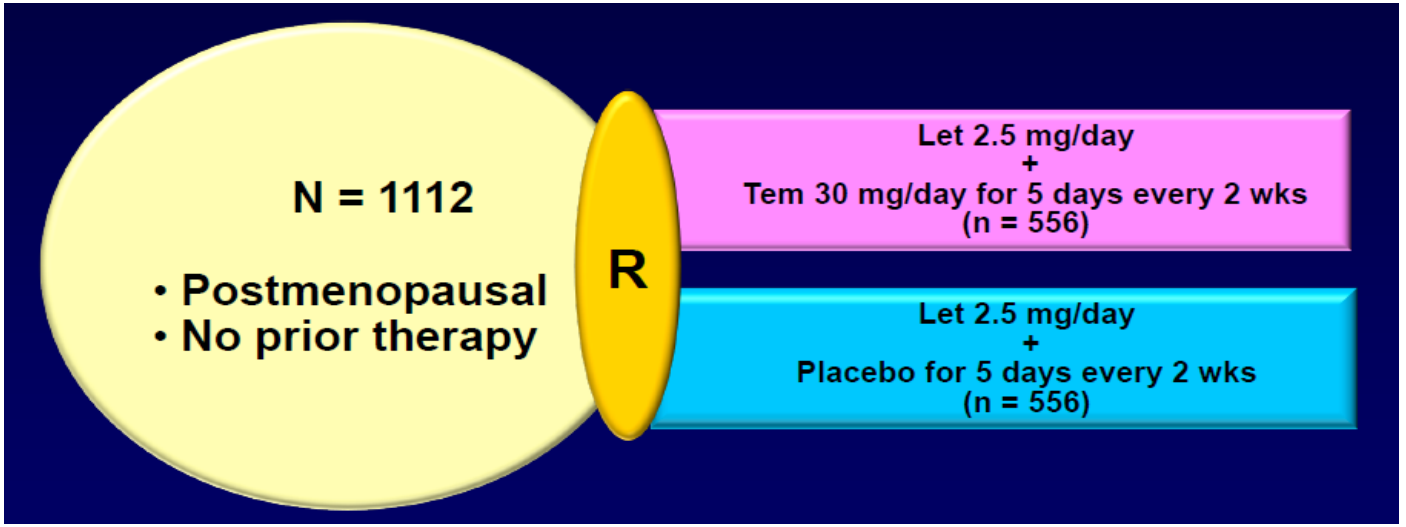
Hortobagyi G et al., JCO 2016.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

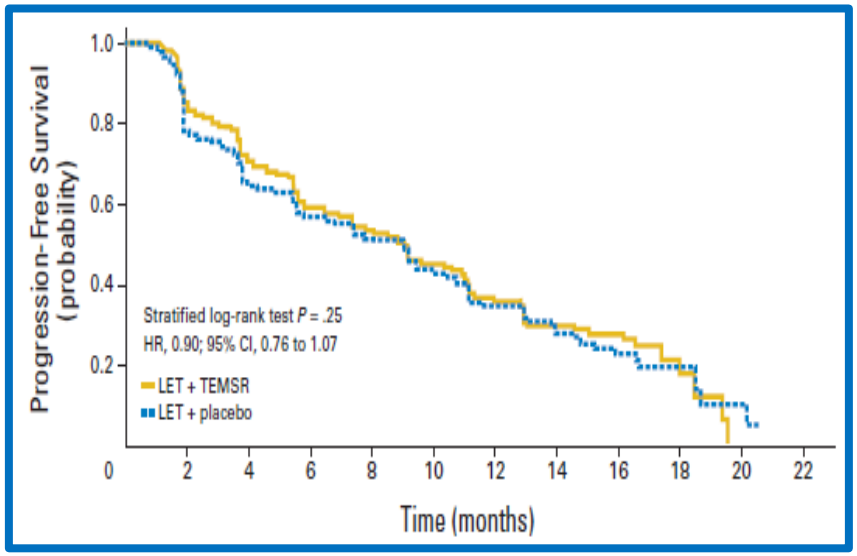
Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer

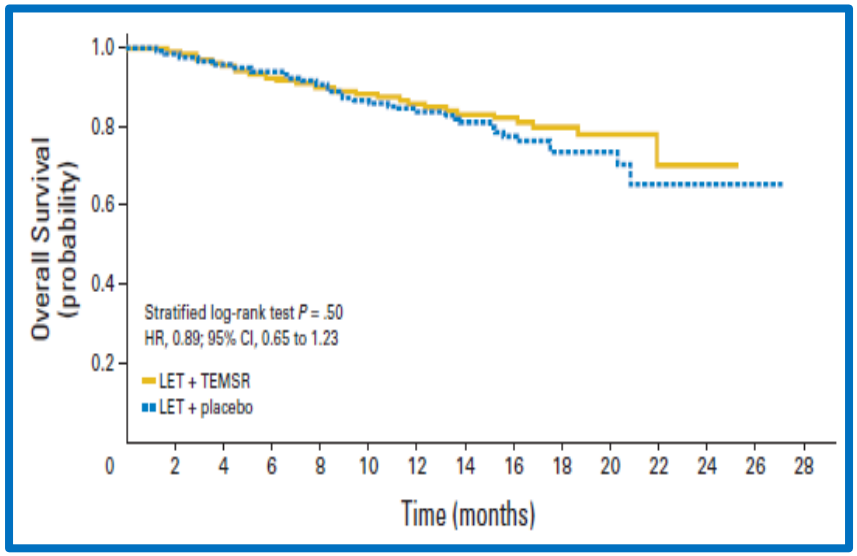
Antonio C. Wolff, Ann A. Lazar, Igor Bondarenko, August M. Garin, Stephen Brincat, Louis Chow, Yan Sun, Zora Neskovic-Konstantinovic, Rodrigo C. Guimaraes, Pierre Fumoleau, Arlene Chan, Soulef Hachemi, Andrew Strahs, Maria Cincotta, Anna Berkenblit, Mizue Krygowski, Lih Lisa Kang, Laurence Moore, and Daniel F. Hayes

HORIZON



Wolff AC et al., JCO 2013.



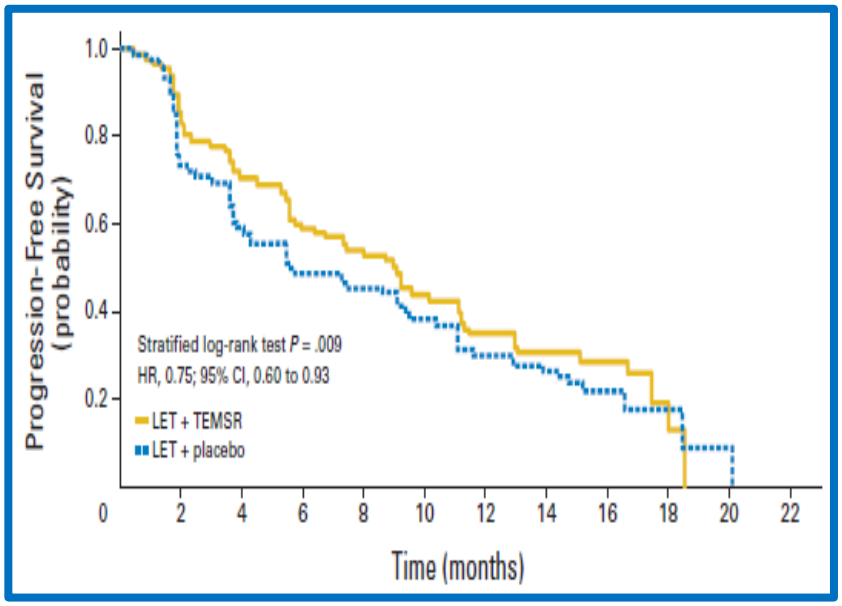


Trial was closed on the basis of data from a planned interim analysis that demonstrated a lack of benefit for the combination

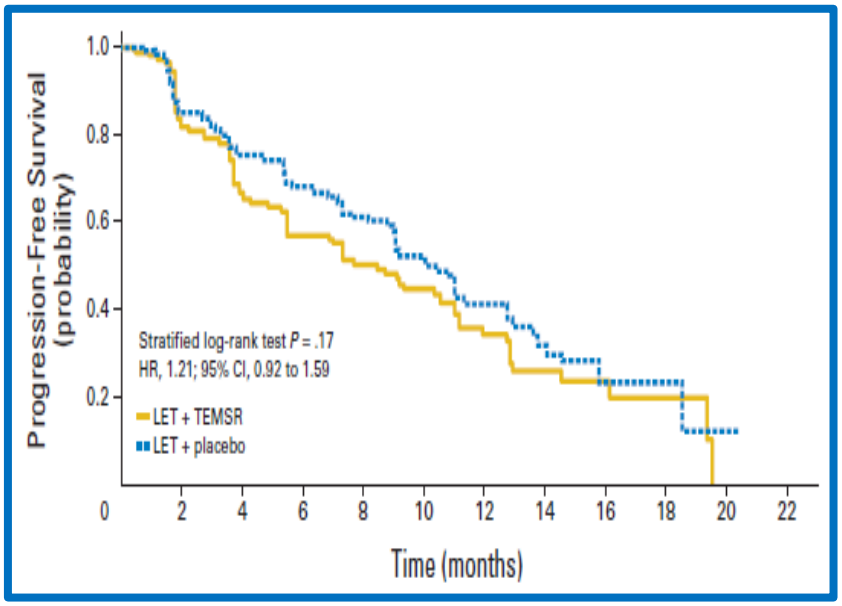
Characteristic	LET + TEM (n = 556)	LET Alone (n = 556)
Median PFS, months (95% CI)	8.9 months	9.0 months
	HR 0.90 (0.76-1.07); *P* =.25	
Median OS, months (95% CI)	NE	NE
	HR 0.89 (0.65-1.23); *P* = .50	
Objective response rate*	27%	27%

Wolff AC et al., JCO 2013.

An exploratory analysis: PFS by patient's age



≤ 65 years



> 65 years

Wolff AC et al., JCO 2013.

mTOR inhibitors in metastatic breast cancer

Study name	Comparison arms	Study description	Key findings	References
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TAMRAD study	Everolimus + tamoxifen *vs.* tamoxifen	Phase II randomised study; ABC; relapsed or progressed on previous AI (*n*=111)	CBR: 61% *vs.* 42% (*P*=0.045); TTP: 8.6 *vs.* 4.5 months (*P*=0.002)	44
HER2 positive				
BOLERO-3	Everolimus + vinorelbine + trastuzumab *vs.* placebo + vinorelibine + trastuzumab	Phase III study, ABC, previous treatment with taxane, resistance to trastuzumab (*n*=569)	PFS: 7.0 *vs.* 5.8 months (*P*=0.0067); subgroup analysis: PFS improved in HR- cancers but not in HR+ cancers	45
BOLERO-1	Everolimus + paclitaxel + trastuzumab *vs.* placebo + paclitaxel + trastuzumab	Phase III study, ABC, first-line (*n*=719)	PFS: 14.9 *vs.* 14.5 months (*P*=0.1167); however, in HR negative subpopulation: 20.3 *vs.* 13.1 months (*P*=0.0049)	46

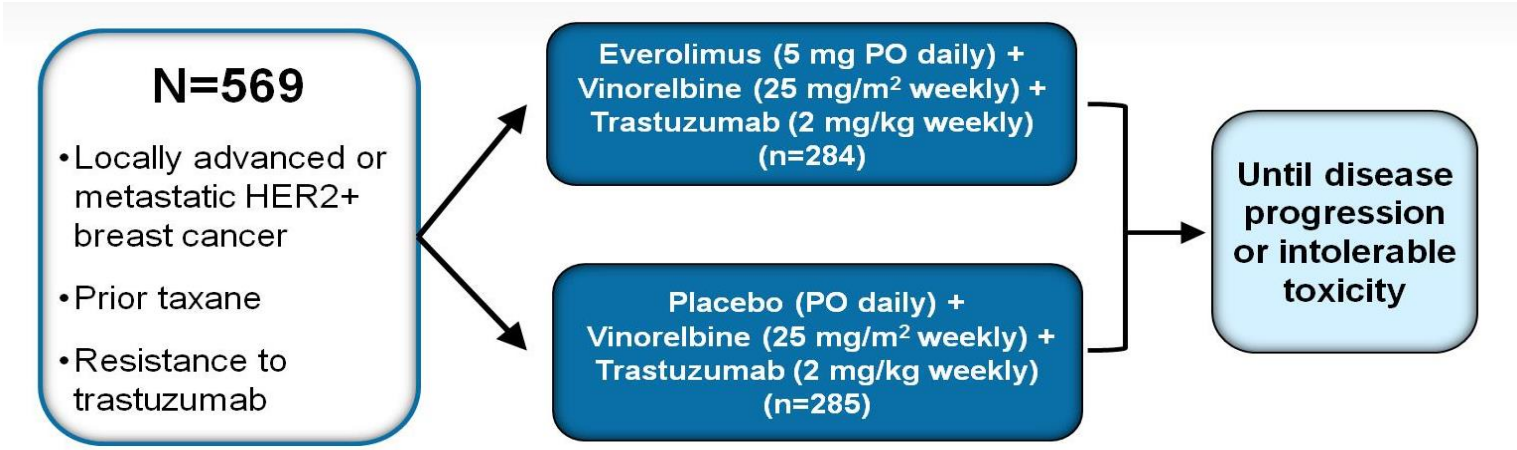
ABC, advanced breast cancer; PFS, progression-free survival; NSAI, non-steroidal aromatase inhibitor; AI, aromatase inhibitor; CBR, clinical benefit rate; TTP, time to progression; HR, hormone receptor.

Lee et al., Cancer Biol Med 2015.

Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial

Fabrice André, Ruth O'Regan, Mustafa Ozguroglu, Masakazu Toi, Binghe Xu, Guy Jerusalem, Norikazu Masuda, Sharon Wilks, Francis Arena, Claudine Isaacs, Yoon-Sim Yap, Zsuzsanna Papai, Istvan Lang, Anne Armstrong, Guillermo Lerzo, Michelle White, Kunwei Shen, Jennifer Litton, David Chen, Yufen Zhang, Shyanne Ali, Tetiana Taran, Luca Gianni

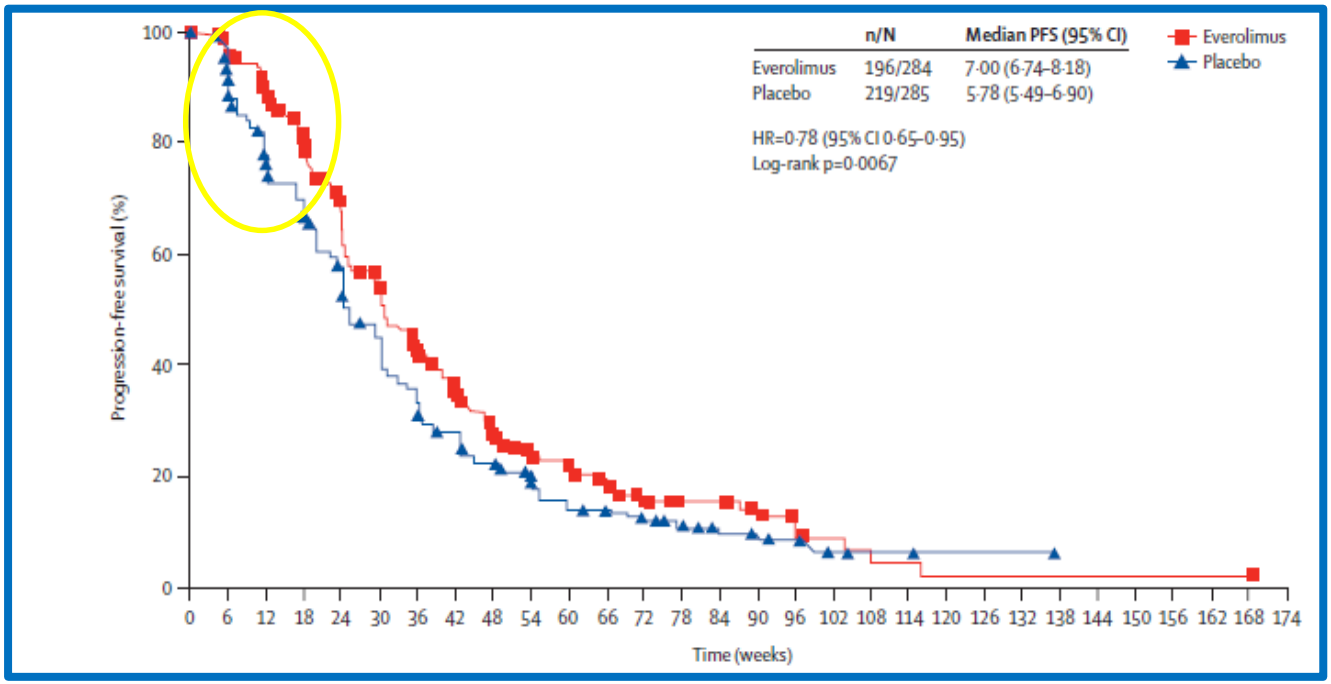
BOLERO-3



Andrè F et al., Lancet Oncol 2014.

In preclinical models, mTOR inhibitors synergize with trastuzumab and have shown to cause complete regression of mouse HER2+ mammary tumours (Lu et al, 2007)

PFS: primary endpoint

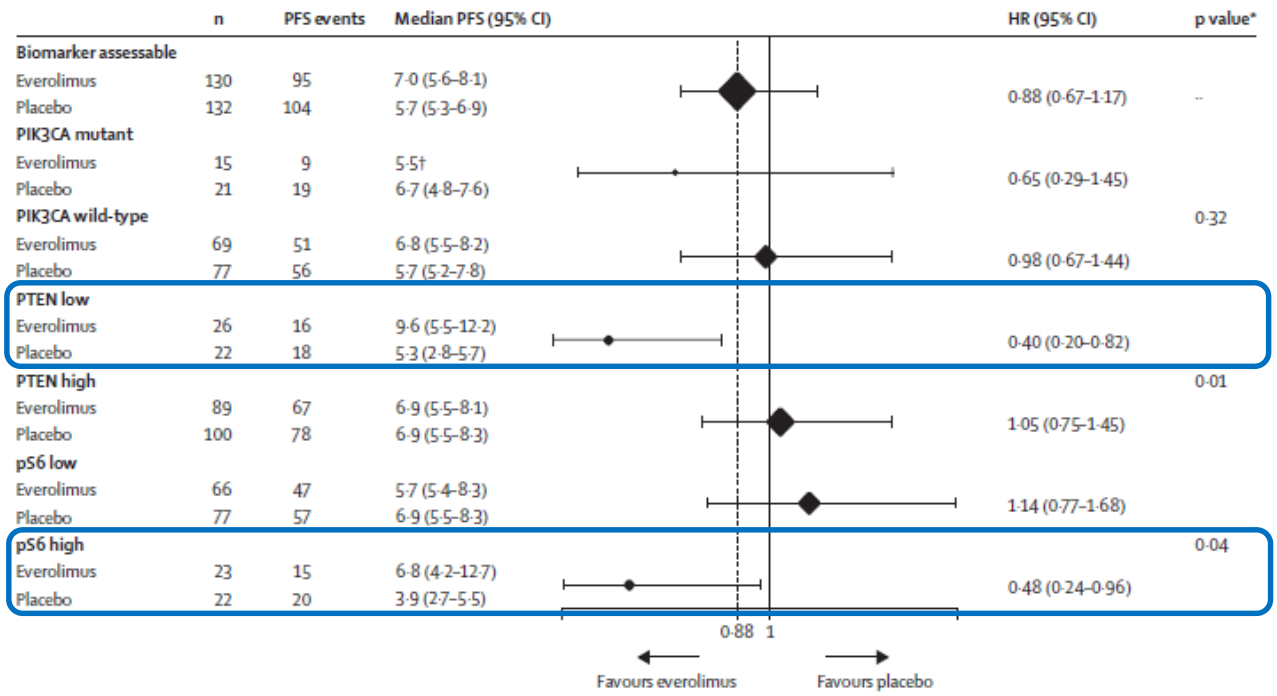


In BOLERO-3 clinical benefit appeared more pronounced in the HR⁻ subpopulation

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

Andrè F et al., Lancet Oncol 2014.

Exploratory analysis of PFS



The analysis suggest that the addition of everolimus may be most beneficial in patients with **low PTEN or high pS6 levels**.

Andrè F et al., Lancet Oncol 2014.

	Everolimus group (n=280)			Placebo group (n=282)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	24 (9%)	98 (35%)	106 (38%)	22 (8%)	90 (32%)	85 (30%)
Stomatitis	138 (49%)	37 (13%)	0	74 (26%)	4 (1%)	0
Anaemia	85 (30%)	47 (17%)	6 (2%)	66 (23%)	16 (6%)	1 (<1%)
Leucopenia	22 (8%)	85 (30%)	21 (8%)	23 (8%)	71 (25%)	11 (4%)
Fatique	87 (31%)	33 (12%)	1 (<1%)	107 (38%)	11 (4%)	0
Pyrexia	101 (36%)	7 (3%)	0	62 (22%)	3 (1%)	0
Diarrhoea	96 (34%)	11 (4%)	0	84 (30%)	2 (<1%)	0
Nausea	91 (33%)	7 (3%)	0	100 (35%)	3 (1%)	0
Decreased appetite	88 (31%)	4 (1%)	0	46 (16%)	3 (1%)	0
Constipation	82 (29%)	1 (<1%)	0	87 (31%)	1 (<1%)	0
Weight decreased	81 (29%)	2 (<1%)	0	43 (15%)	1 (<1%)	0
Cough	80 (29%)	1 (<1%)	0	53 (19%)	1 (<1%)	0
Asthenia	60 (21%)	14 (5%)	0	44 (16%)	10 (4%)	2 (<1%)
Headache	70 (25%)	2 (<1%)	0	56 (20%)	2 (<1%)	1 (<1%)
Rash	69 (25%)	0	0	49 (17%)	2 (<1%)	0
Epistaxis	60 (21%)	3 (1%)	0	38 (13%)	0	0
Vomiting	58 (21%)	2 (<1%)	0	57 (20%)	2 (<1%)	0
Dyspnoea	47 (17%)	4 (1%)	1 (<1%)	32 (11%)	9 (3%)	0
Arthralgia	46 (16%)	1 (<1%)	0	33 (12%)	2 (<1%)	0
Febrile neutropenia	3 (1%)	30 (11%)	14 (5%)	1 (<1%)	7 (2%)	3 (1%)
Abdominal pain	45 (16%)	0	0	48 (17%)	1 (<1%)	0

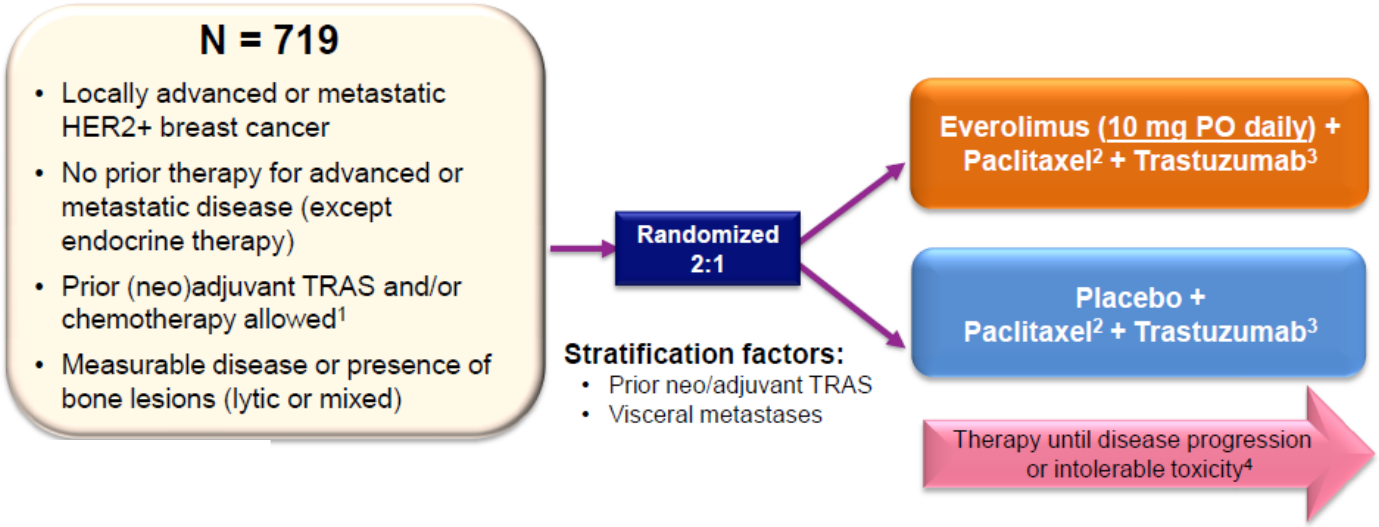
The clinical benefit should be considered in the context of **higher incidence of adverse events** (serious AEs were reported in 42% of patients in the everolimus versus 20% in the placebo group).

Andrè F et al., Lancet Oncol 2014.

Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial

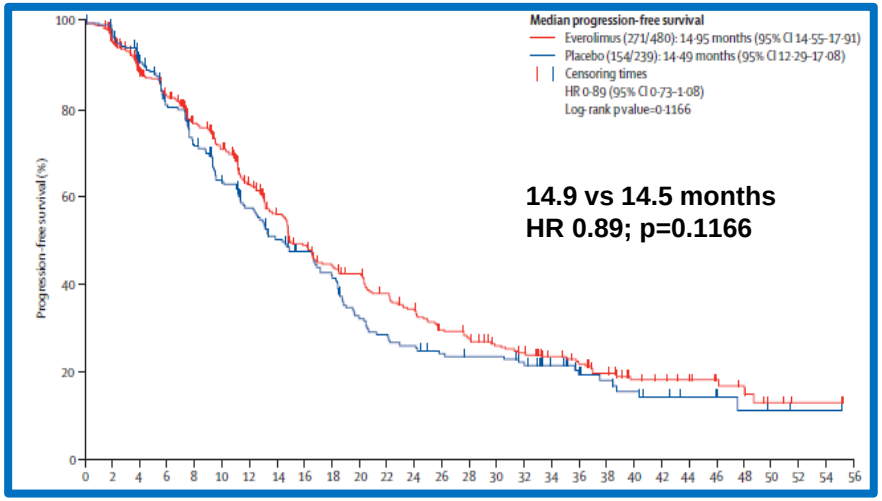
Sara A Hurvitz, Fabrice Andre, Zefei Jiang, Zhimin Shao, Max S Mano, Silvia P Neciosup, Ling-Min Tseng, Qingyuan Zhang, Kunwei Shen, Donggeng Liu, Lydia M Dreosti, Howard A Burris, Masakazu Toi, Marc E Buyse, David Cabaribere, Mary-Ann Lindsay, Shantha Rao, Lida Bubuteishvili Pacaud, Tetiana Taran, Dennis Slamon

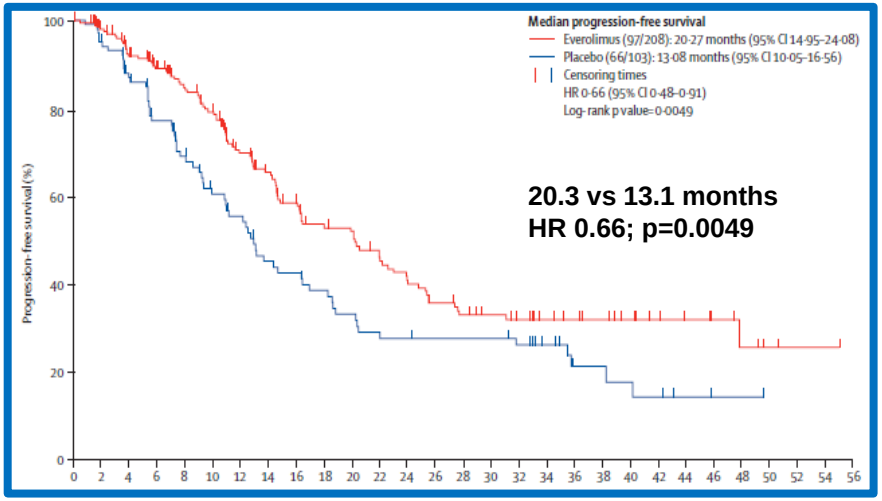
BOLERO-1/TRIO-019



Hurvitz SA et al., Lancet Oncol 2015.

PFS: primary endpoint





PFS (full analysis set)

PFS (HR-negative sub-population)

The addition of everolimus to trastuzumab plus paclitaxel in the first-line MBC setting did not improve outcomes but did **provide a "signal"** in particular in the hormone receptor–negative subset.

Hurvitz SA et al., Lancet Oncol 2015.

A Different Treatment Effect in the HR⁻ Subpopulation

- 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

- Substantial cross-talk exists between HER2 and ER pathways

- Inhibition of HER2 alone increases activation of ER transcription which may:
  - act as an escape mechanism from HER2-directed agents
  - provide alternative signals for the cells to survive

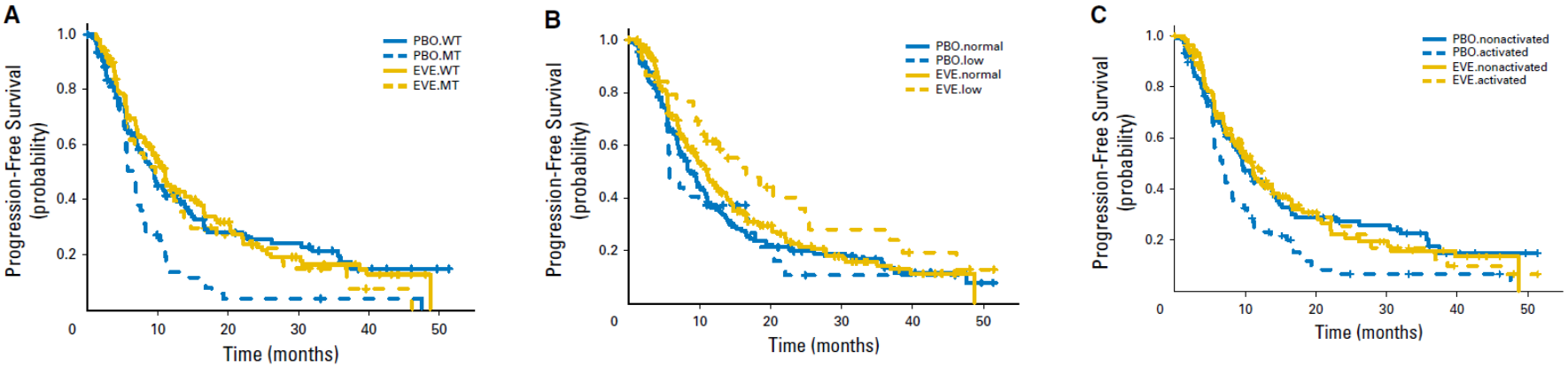
- The combination of everolimus and trastuzumab could be enhanced if the ER is inhibited concomitantly in HR+/HER2+ population

Blackwell KL, et al. *J Clin Oncol*. 2012;30(21):2585-2592.. Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791Nahta R, O'Regan RM. *Breast Cancer Res Treat* 2012; **135:** 39–48.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Molecular Alterations and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2–Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3

Fabrice André, Sara Hurvitz, Angelica Fasolo, Ling-Ming Tseng, Guy Jerusalem, Sharon Wilks, Ruth O'Regan, Claudine Isaacs, Masakazu Toi, Howard Burris, Wei He, Douglas Robinson, Markus Riester, Tetiana Taran, David Chen, and Dennis Slamon

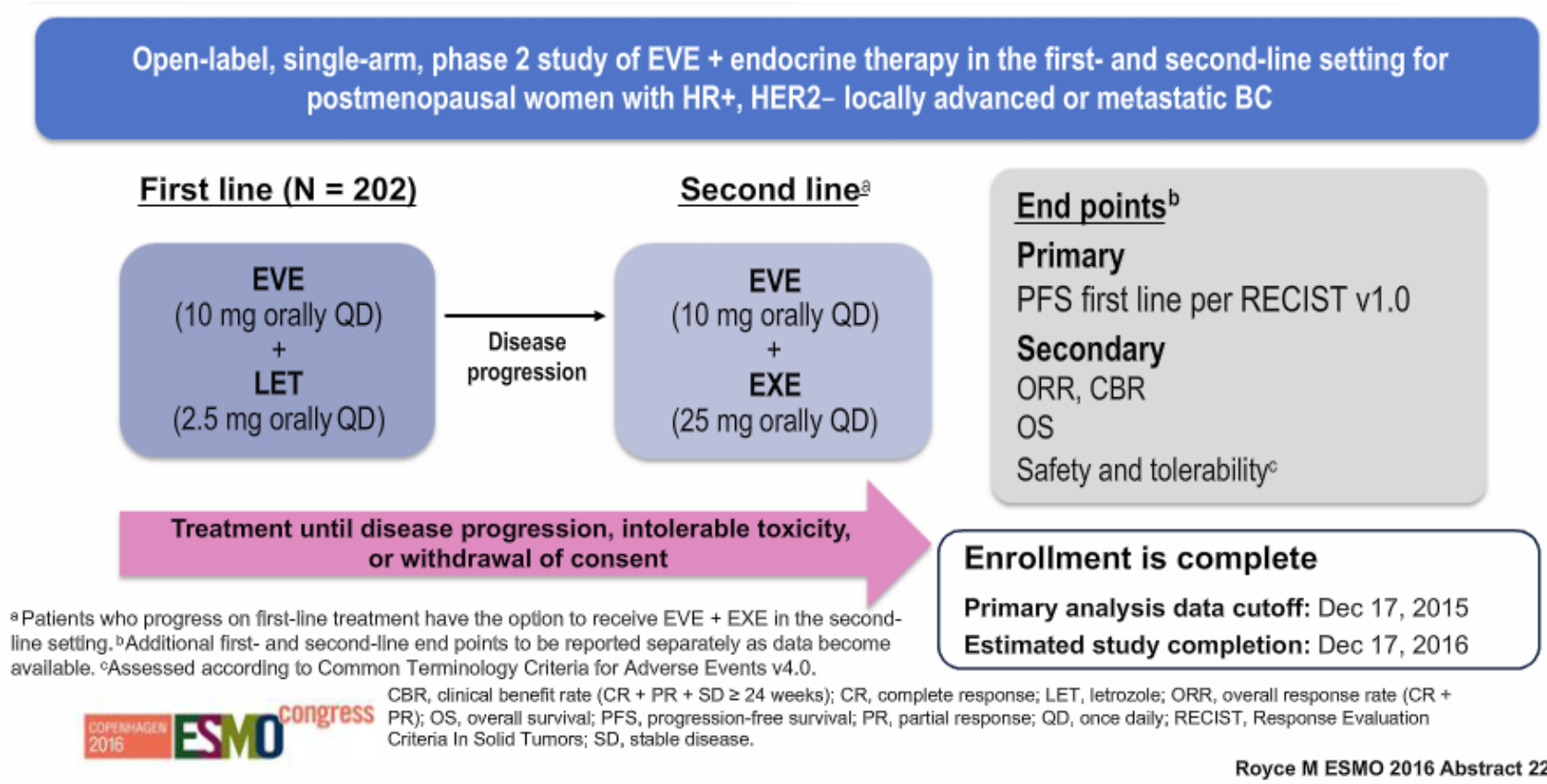


The combined exploratory analysis suggests that patients with HER2-positive advanced breast cancer having tumors with **PIK3CA mutations** (A), **PTEN loss** (B) **or hyperactive PI3K pathway** (C) could derive benefit from everolimus.

Andrè F et al., JCO 2016.

News from ESMO 2016…

BOLERO-4



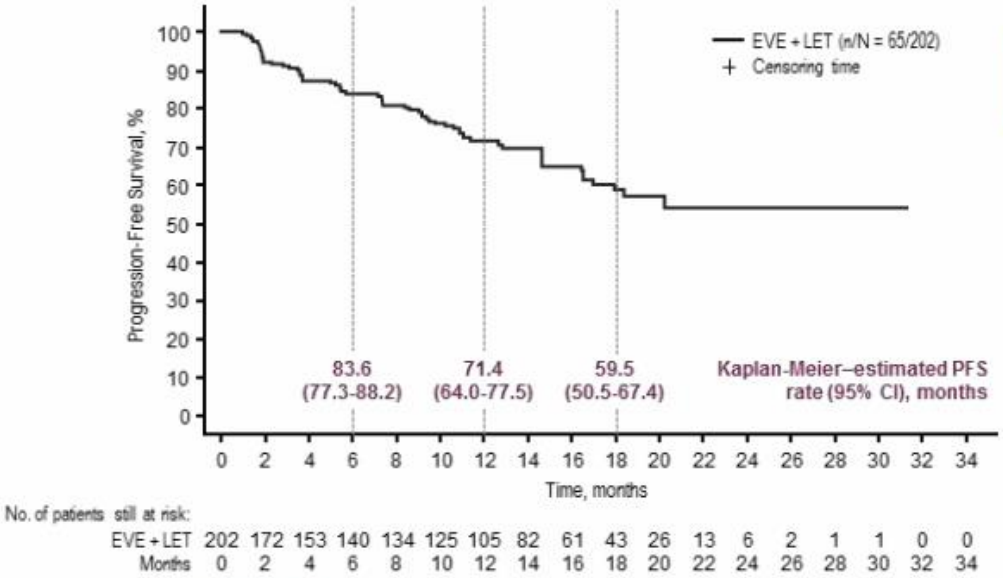
[a] Patients who progress on first-line treatment have the option to receive EVE + EXE in the second-line setting. [b] Additional first- and second-line end points to be reported separately as data become available. [c] Assessed according to Common Terminology Criteria for Adverse Events v4.0.

CBR, clinical benefit rate (CR + PR + SD ≥ 24 weeks); CR, complete response; LET, letrozole; ORR, overall response rate (CR + PR); OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Royce M ESMO 2016 Abstract 2220

PFS in the first line: primary endpoint

- **Locally assessed median PFS in the first line was not yet reached with a median follow-up of 17.5 months**



EVE + LET N = 202	
PFS events, n (%)	65 (32.2)
Progression, n (%)	62 (30.7)
Death, n (%)	3 (1.5)
Censored, n (%)	137 (67.8)
Percentile, months (95% CI)	
75th percentile	NE (NE-NE)
Median	NE (18.0-NE)
25th percentile	10.7 (7.4-14.7)

NE, not estimable.

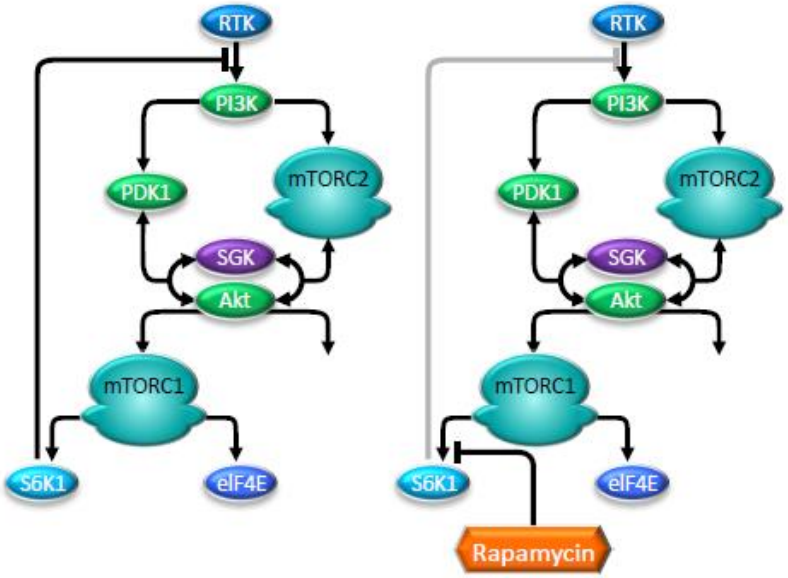
COPENHAGEN 2016 ESMO congress

Royce M ESMO 2016 Abstract 2220

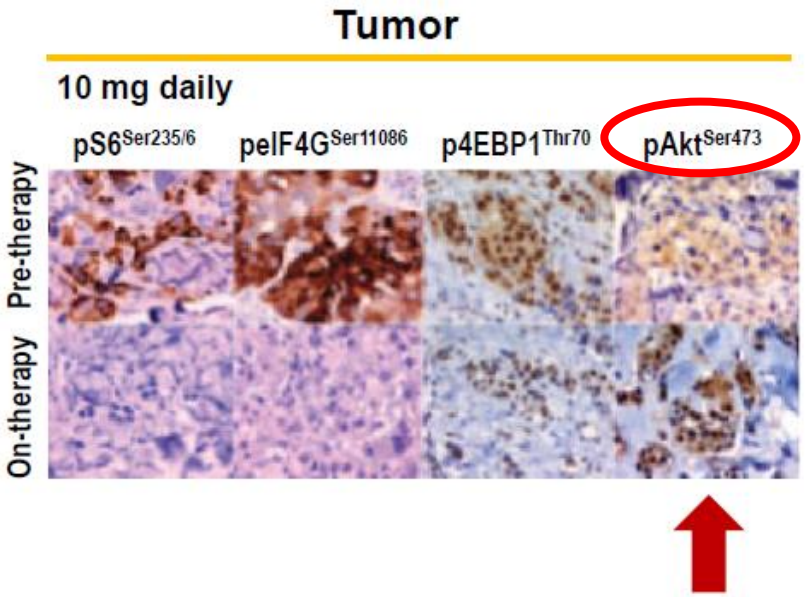
CONCLUSIONS:

- mTOR inhibition is **feasible in clinical** with current drug.
- Consistent efficacy of **everolimus and exemestane combination** → approved strategy **for post-menopausal patients with ER+/HER2- metastatic breast cancer having progressed on NSAI**.
- Identification and validation of **molecular predictive biomarkers** are needed to improve and predict the clinical efficacy of treatment in patients with breast cancer.
- The PI3K/AKT/mTOR pathway involves **a complex network of interactions with many parallel cascades,** so its inhibition releases negative feedback resulting in activation of compensatory signalling pathways, including PTEN loss.
- In addition, given the **heterogeneous genomic architecture of breast cancer**, there are often **multiple drivers in different pathways**, such that PI3K/AKT may not be the dominant regulator of mTOR in some cells.

mTORC1 Inhibition: Feedback Loop Activation of RTK/PI3K/AKT

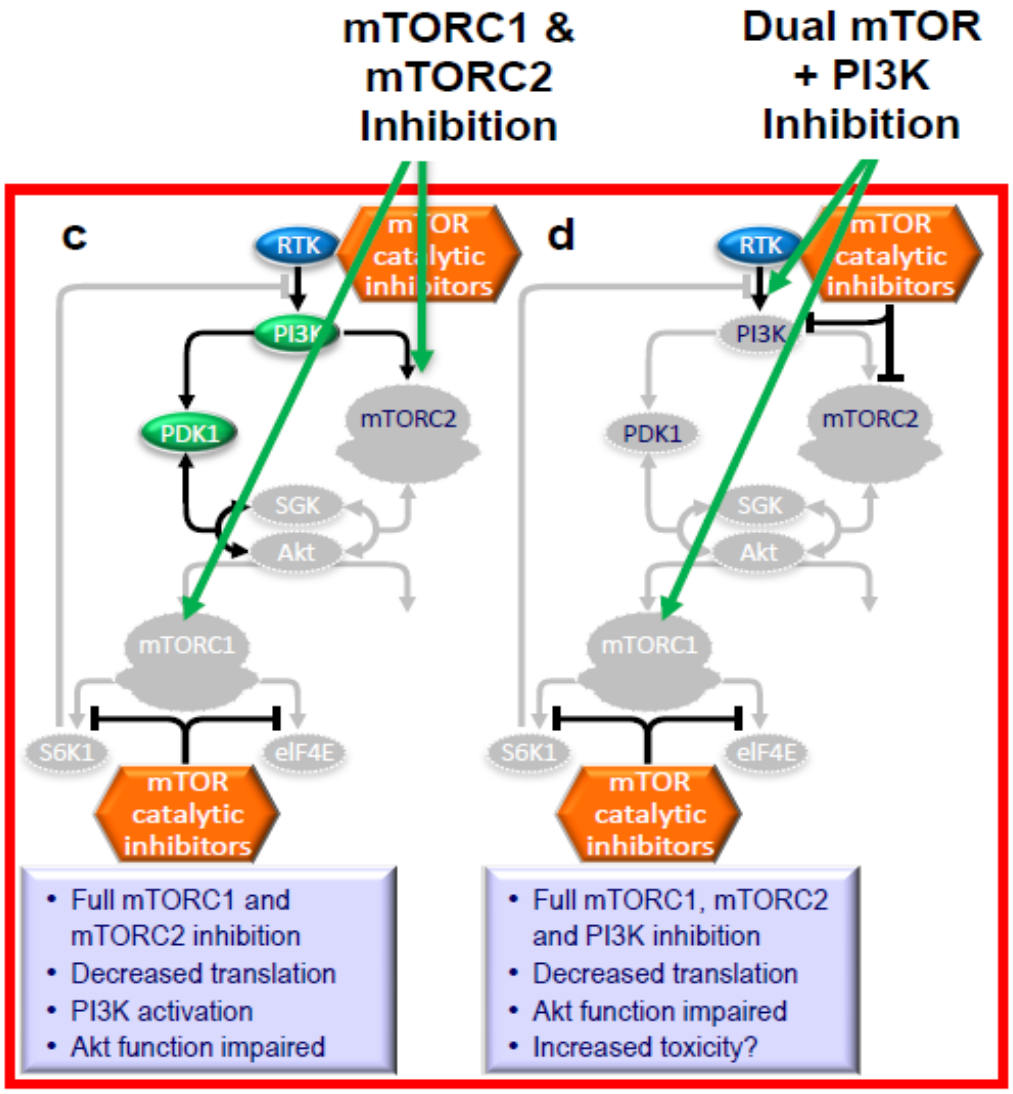


- Partial mTORC1 inhibition
- Decreased translation
- PI3K activation
- Increased survival

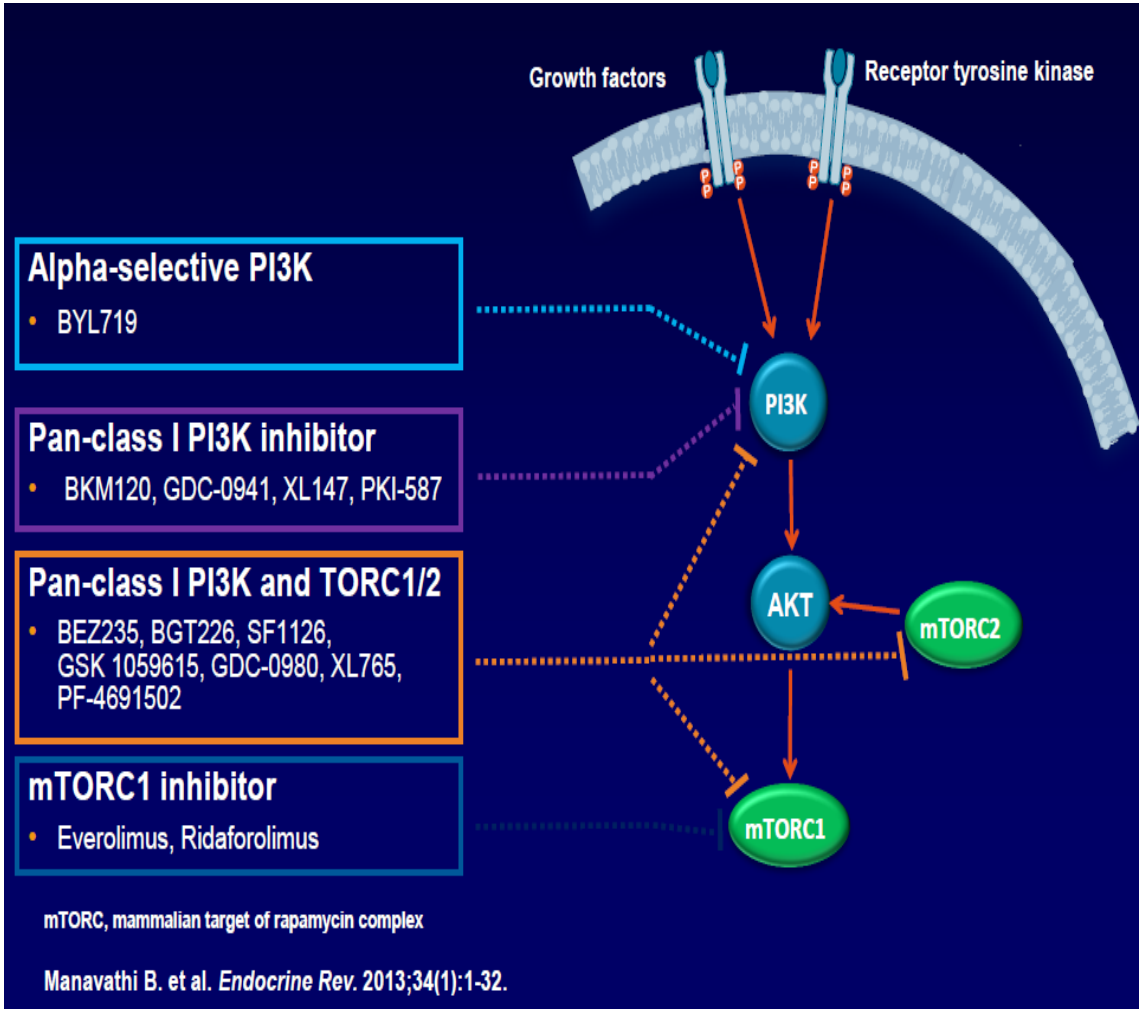


Zoncu R, et al. *Nat Rev Mol Cell Biol*. 2011;12(1):21-35.
Tabernero J, et al. *JCO*. 2008;26(10):1603-1610

Reversal of the Feedback Loop



IN THE FUTURE….



- PI3K inhibitors are currently in phase II/III clinical trials
- TORC1/TORC2 inhibitors are currently in clinical trials, but toxicity may become an issue
- Dual PI3K/mTOR inhibitors so far have been too toxic
- AKT inhibitors are currently in clinical trials, some have been quite toxic as well

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Numero per la Cura del Tumore

Grazie a tutti per l'attenzione

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