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Targeted Therapies in Breast Cancer: Optimal Use of m-TOR Inhibitors

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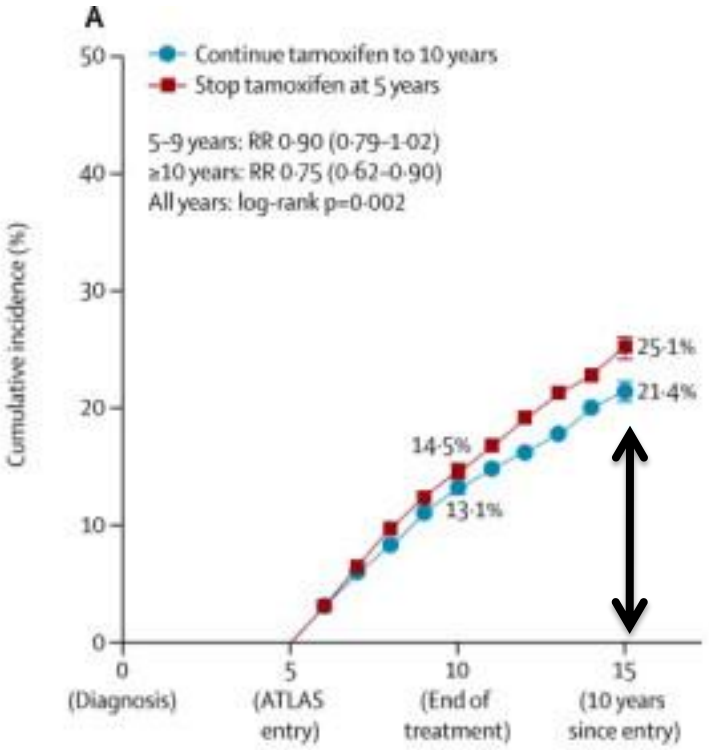
4th International Congress of Breast Disease Centers 2014
February 7th, 2014

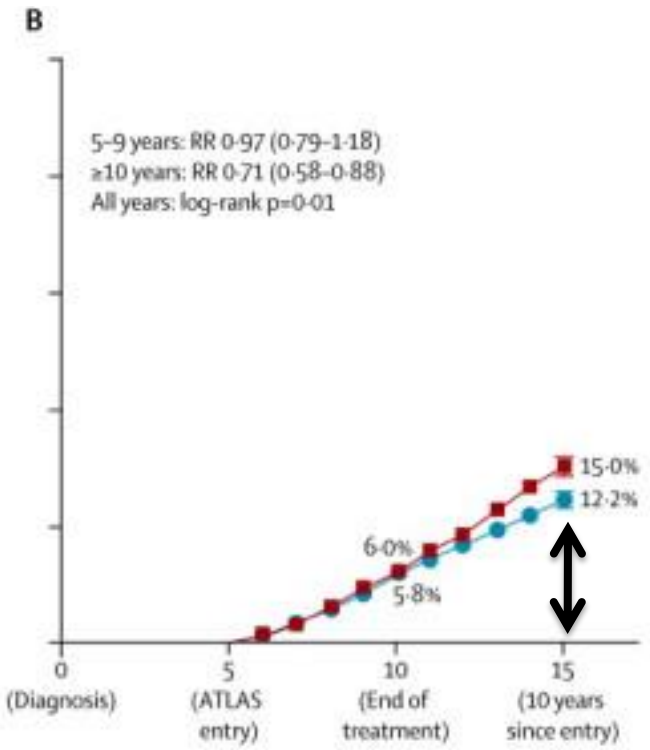
ER positive / HER-2 negative Breast Cancer

ATLAS: 5 versus 10 years of Tamoxifen

Recurrence

BC Mortality



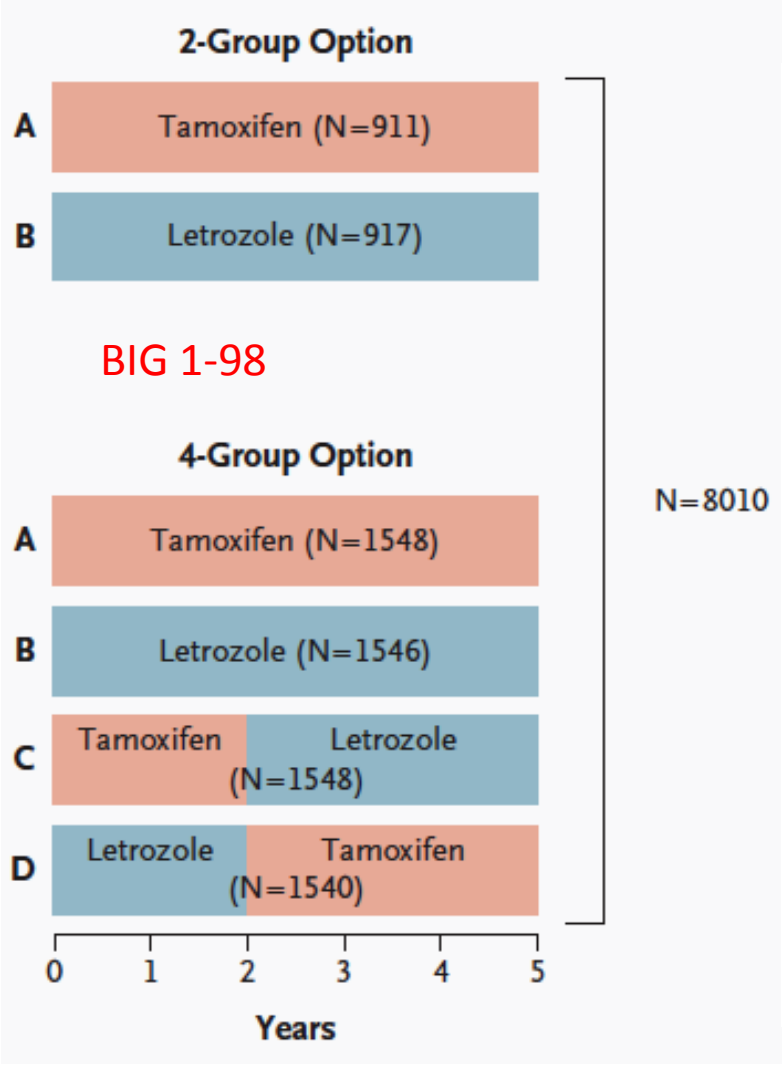


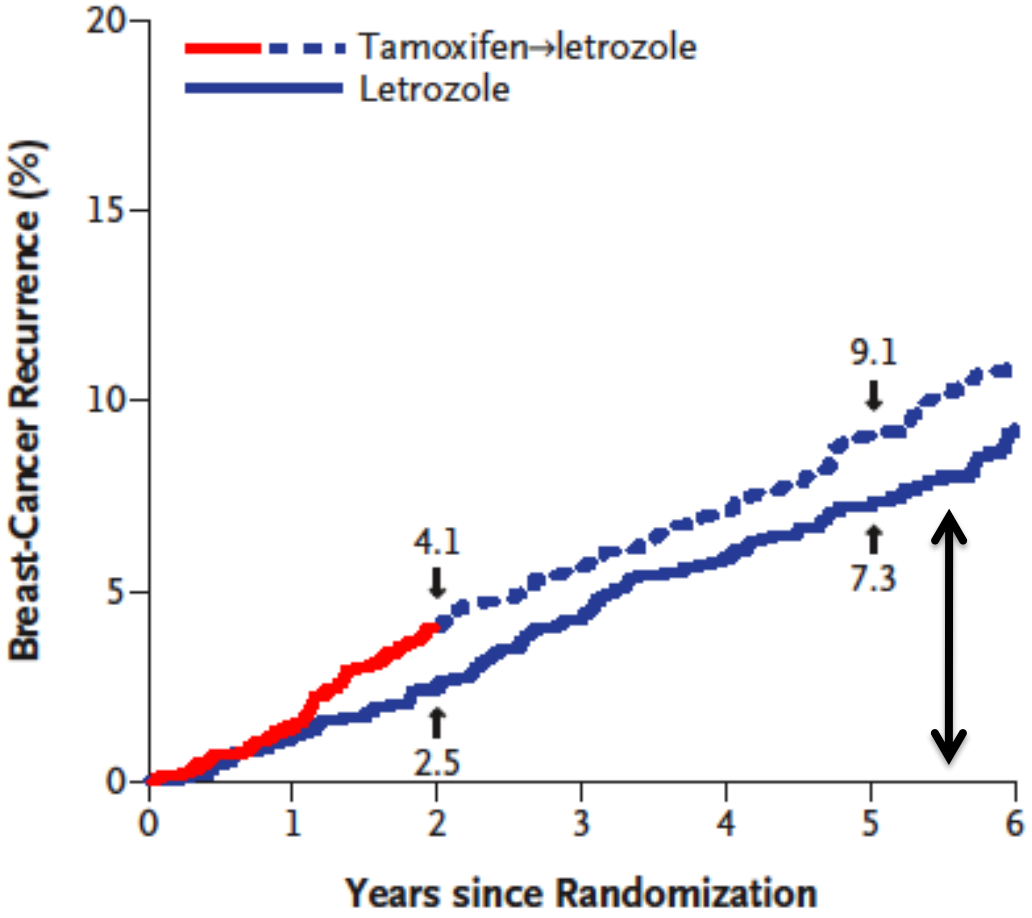
	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5

	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−3·2/94·0	−27·2/77·5	−2·5/10·6

Davies C et al. Lancet 2013

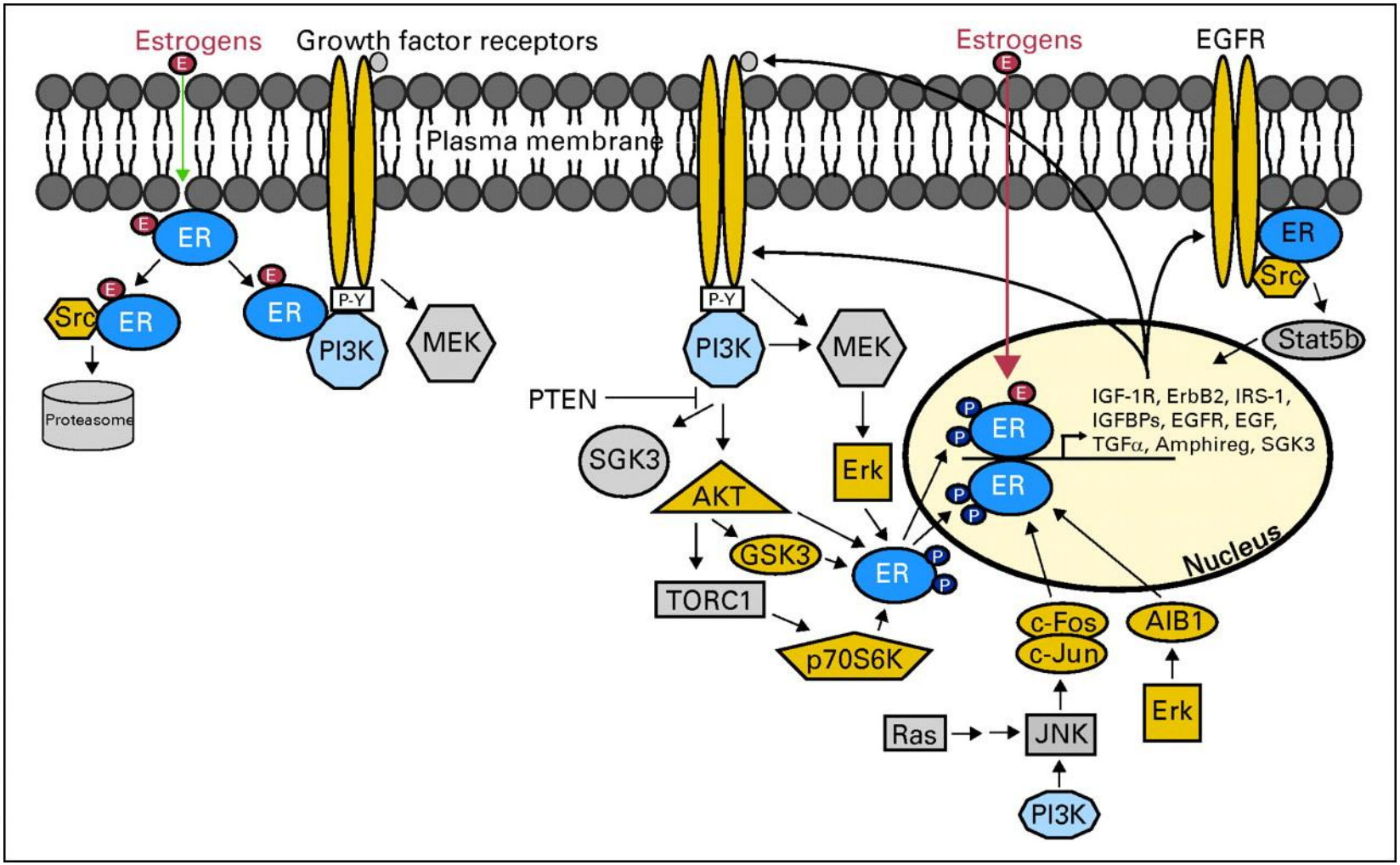
Aromatase Inhibitors: Upfront or Sequential





Mouridsen H et al. NEJM 2009

Reciprocal crosstalk between estrogen receptor (ER) α and growth factor receptor signaling pathways.



Miller T W et al. JCO 2011;29:4452-4461

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Proof of Concept Phase I Trial: Everolimus add-on after Progression on Letrozole

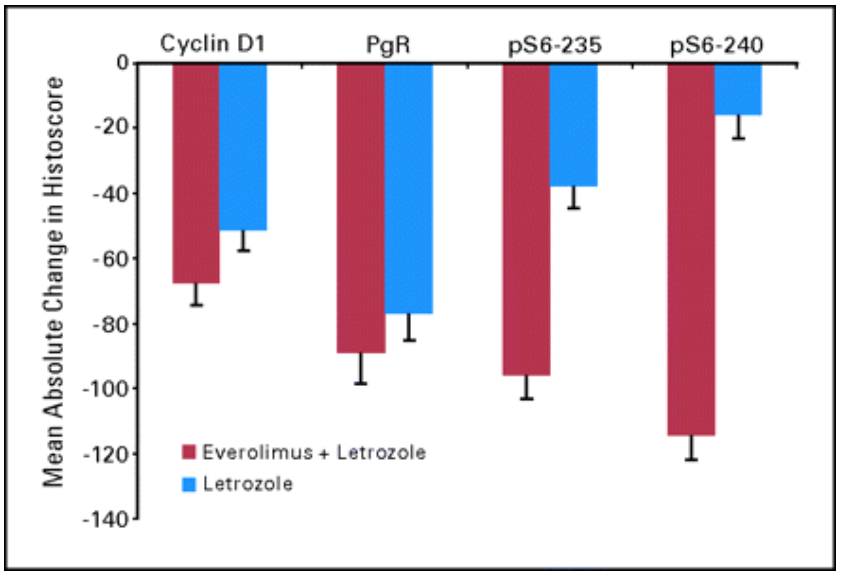
	All patients ($n = 18$)	RAD001 5 mg/day ($n = 6$)	RAD001 10 mg/day ($n = 12$)
Disease status on letrozole alone			
Duration of letrozole alone median (range) (mo)[a]	15.0 (1.7–49.2)	12.4 (2.3–27.7)	26.0 (1.7–49.2)
Best response on letrozole alone (n)			
Stable disease	15	5	10
Progressive disease	1	0	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)

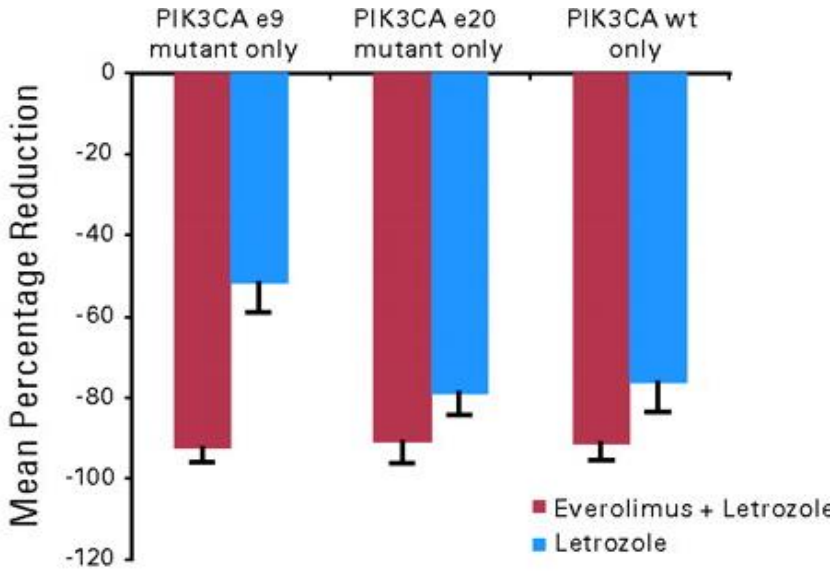
Awada et al. Eur J Cancer 2008.

Randomized Neoadjuvant Phase II Trial: Letrozole + Everolimus/ Placebo

Response by evaluation type	Letrozole + Everolimus N = 138	Letrozole + Placebo N = 132	
Clinical Palpation	68%	59%	**p = 0.06***
Ultrasound	58%	47%	**p = 0.04***
Mammography	36%	39%	**p = 0.7**

* Significant



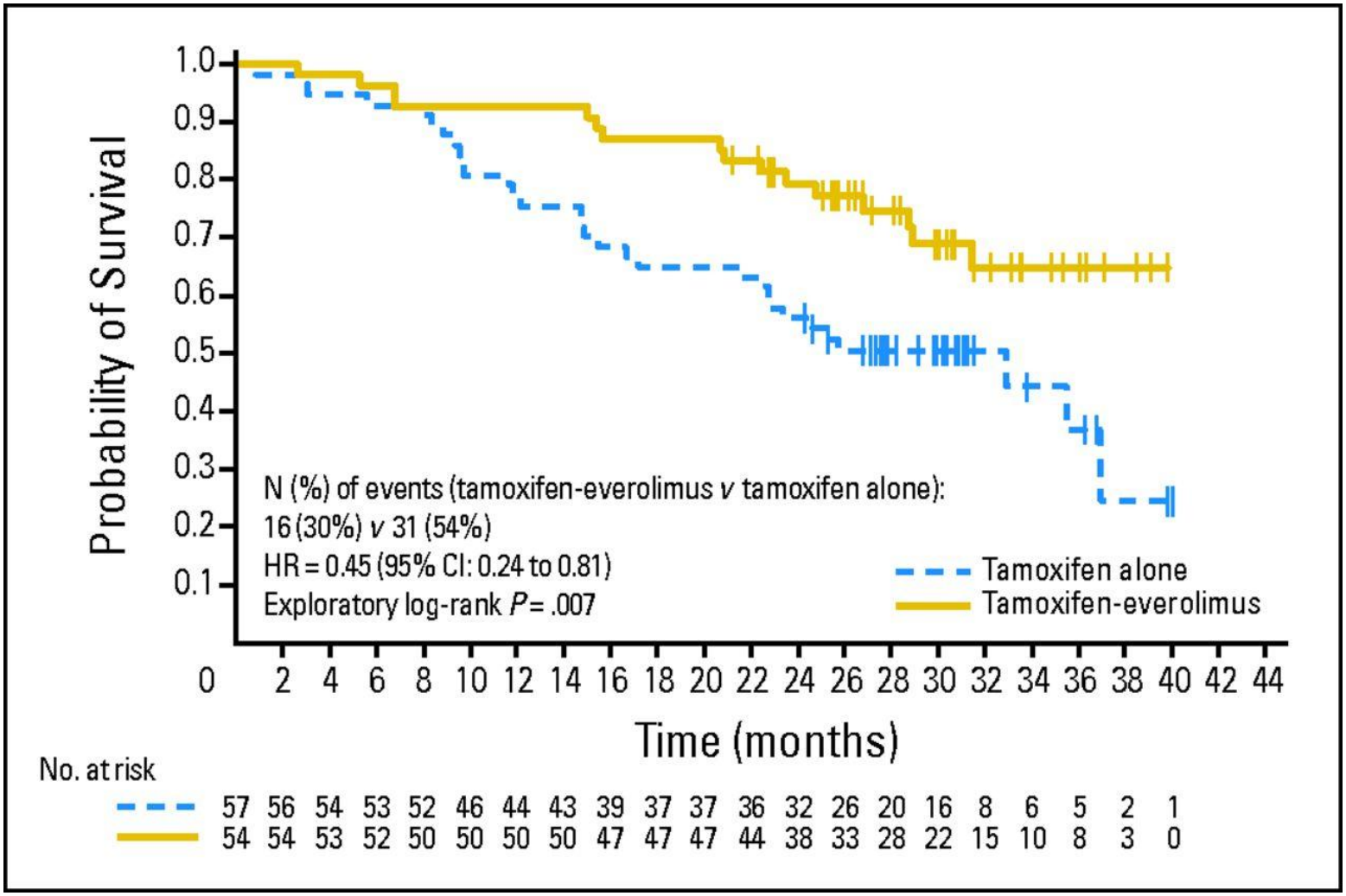


Baselga J et al. J Clin Oncol 2009

Randomized Trials: AI-refractory/ resistant

Treatment	setting	Pre treatment	phase	n	Effect on primary endpoint
Tamoxifen +/- everolimus *(Bachelot, J Clin Oncol, 2012)*	metastatic	Resistant to AI	Phase II randomized	111	Clinical benefit rate: 61% (47-74) vs 42% (29-56)
Exemestane +/- everolimus (BOLERO II) *(Baselga, NEJM, 2012)*	metastatic	Resistant to NSAI	Phase III registration	724	Primary endpoint: PFS HR: 0.43 (0.35-0.54) Median PFS: 6.9 vs 2.8 p<0.001

Overall survival in the intention-to-treat population for the overall patient population.



Bachelot T et al. JCO 2012;30:2718-2724

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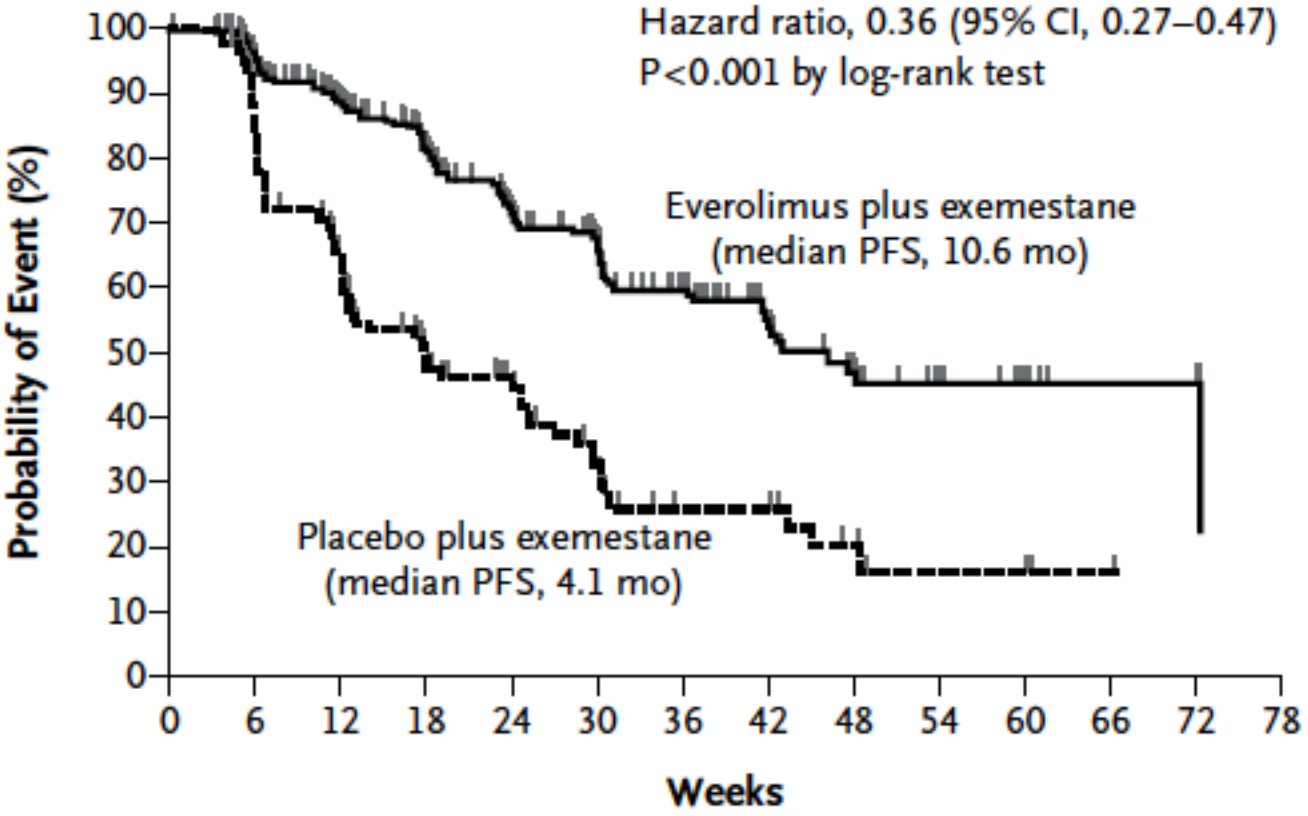
BOLERO-2: Phase III Trial

PFS by Central Assessment



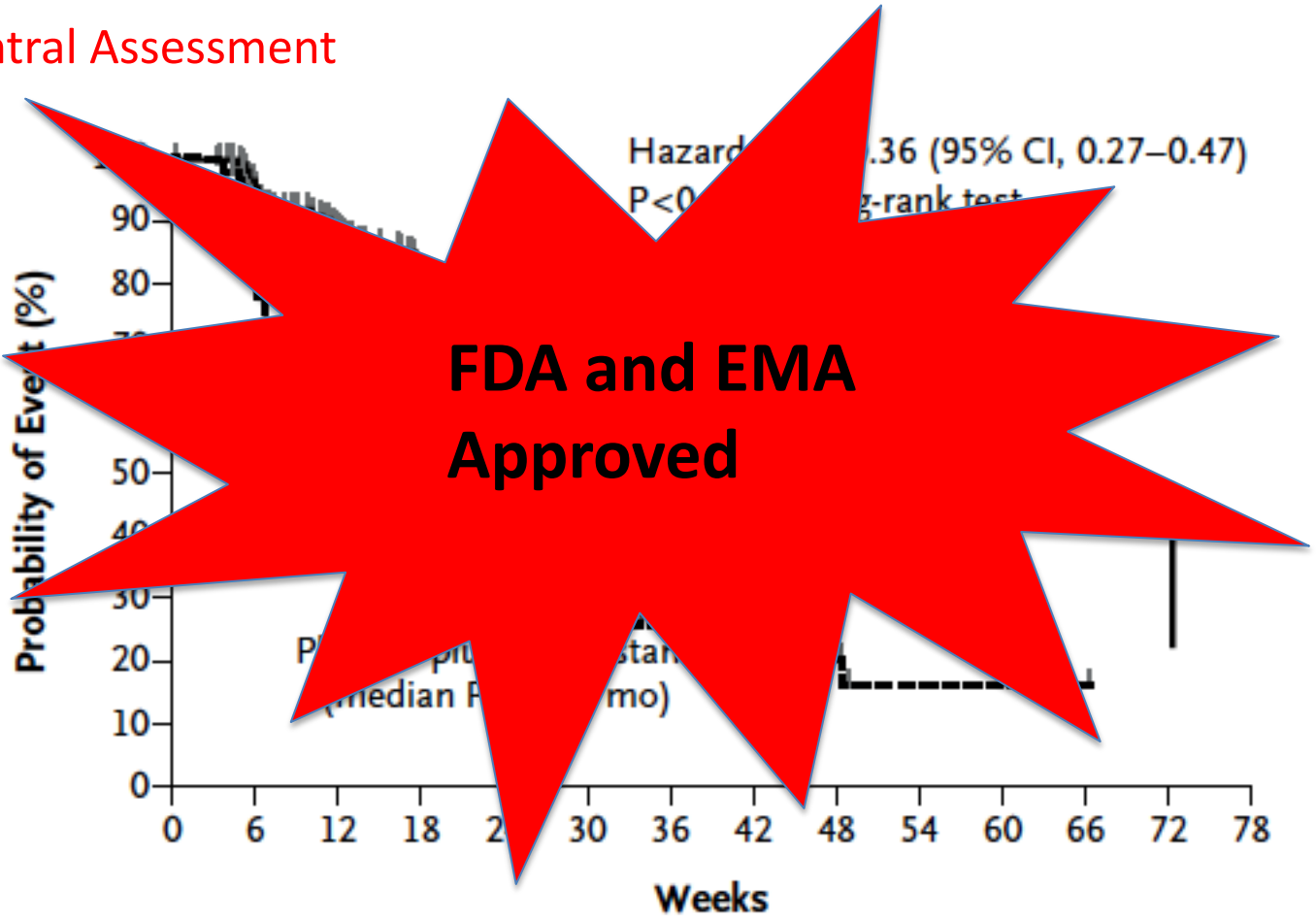
No. at Risk

Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Baselga J et al. NEJM 2012

BOLERO-2: Phase III Trial

PFS by Central Assessment



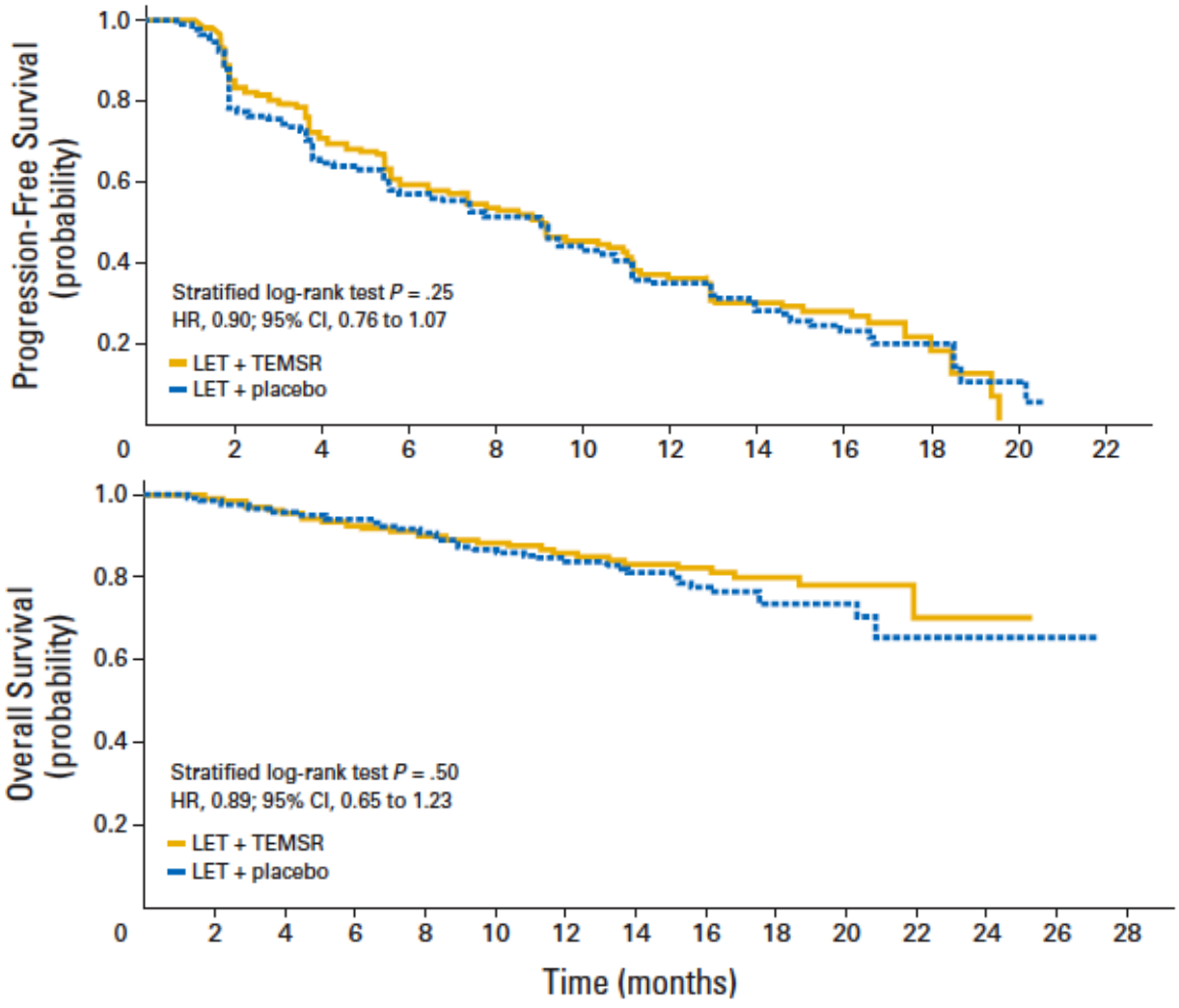
No. at Risk													
Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Baselga J et al. NEJM 2012

Unanswered Questions

- First-line setting?
- More toxic than chemotherapy?
- Role of exemestane?
- PI3K-AKT-mTOR pathway beyond progression?
- Biomarkers? (last part of the presentation)

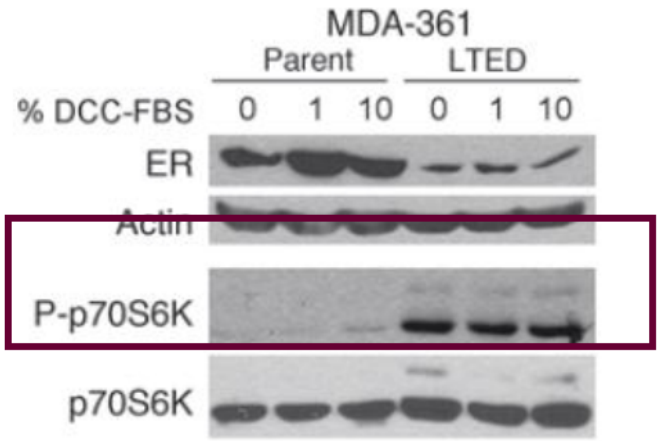
Phase III Trial in the 1st Line Setting: Letrozole + Temsirolimus / Placebo



Wolff A et al. J Clin Oncol 2013

mTOR activation can be acquired during disease progression and/or treatment exposure

Long term estrogen deprivation induces mTOR activation



Miller, JCI, 2010

Discrepancies primary versus metastases

		Metastasis negative	Metastasis positive
pAkt	Primary negative	0	6
	Primary positive	5	12
p4E-BP1	Primary negative	2	4
	Primary positive	4	13

Akcakanat, Cancer,2012

Courtesy A. Awada

Everolimus Toxicity in RCTs

	Tam	Tam + Eve
Fatigue	53%	72%
Stomatitis	7%	56%
Anorexia	18%	43%
Infection	19%	35%
Rash	7%	44%
Diarrhea	11%	21%
Pneumonitis	4%	17%
Lymphopenia	21%	48%
Neutropenia	19%	48%

Tamrad

	Exe + Pbo	Exe + Eve
Fatigue	26%	33%
Stomatitis	11%	56%
Anorexia	10%	29%
Infection	6%	14%
Rash	6%	36%
Diarrhea	16%	30%
Pneumonitis	0%	12%
Thrombocytopenia	<1%	12%
Hyperglycemia	2%	13%

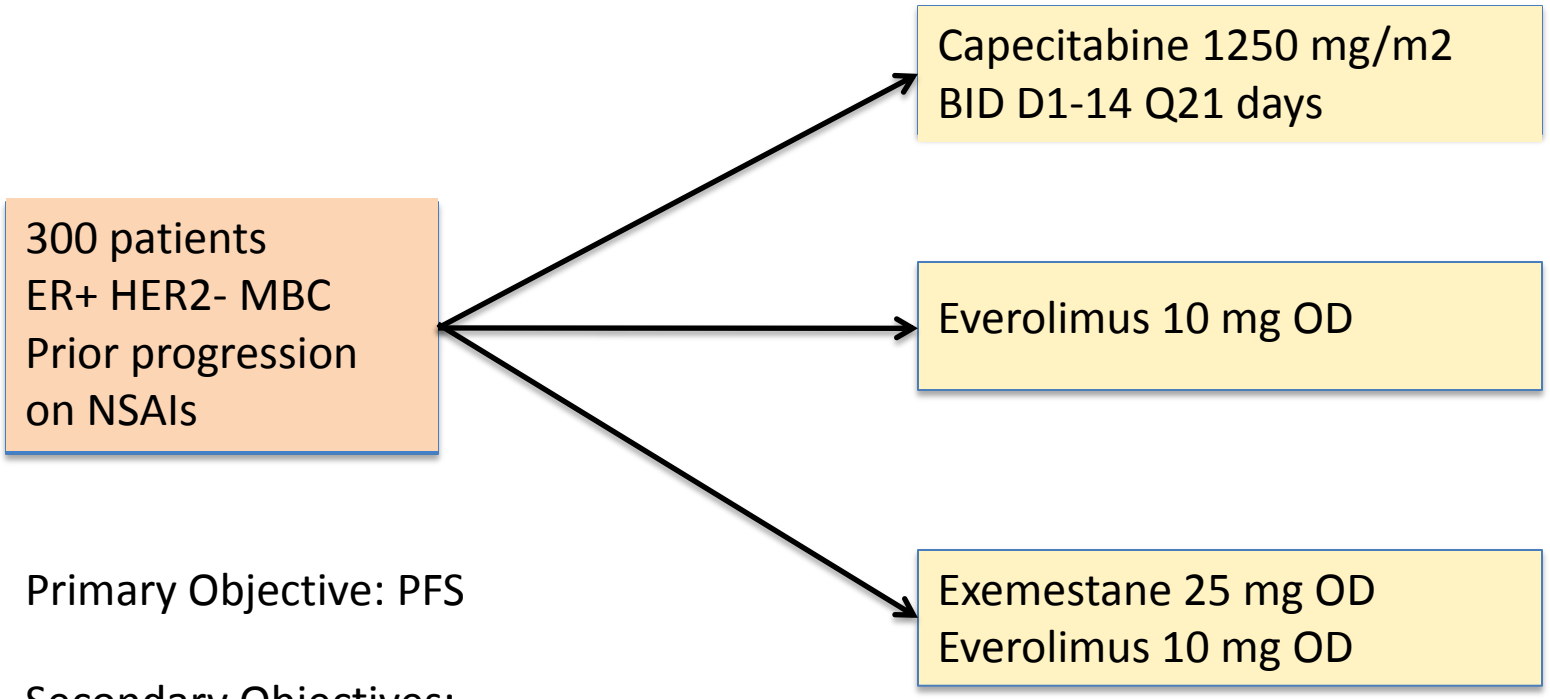
BOLERO-2

BOLERO-2 Trial: Quality of Life Assessment

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- HRQOL was assessed at baseline and every 6 weeks thereafter until disease progression and/or treatment discontinuation
- Baseline global health status scores were found to be similar between treatment groups
- Time to definitive deterioration: 8.3 months with EVE + EXE versus 5.8 months with PBO + EXE (hazard ratio, 0.74; P = .0084)

Burris HA 3rd et al. Cancer 2013

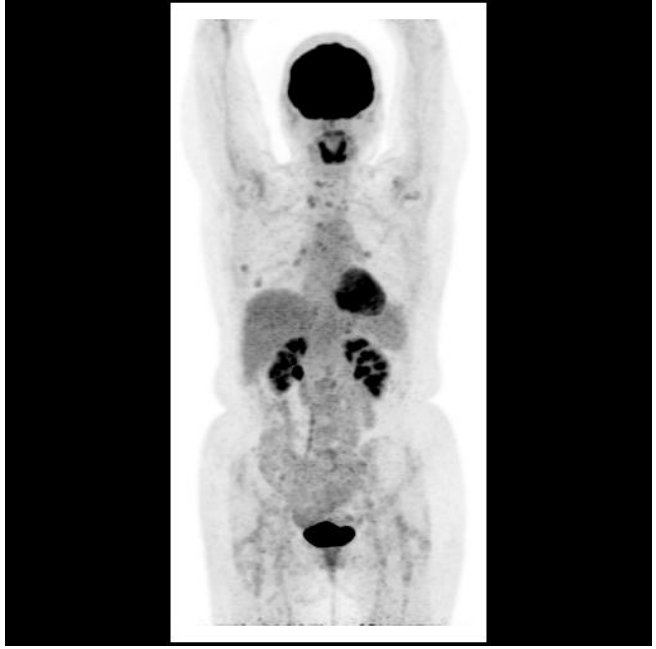
BOLERO-6: FDA "Imposed" Trial



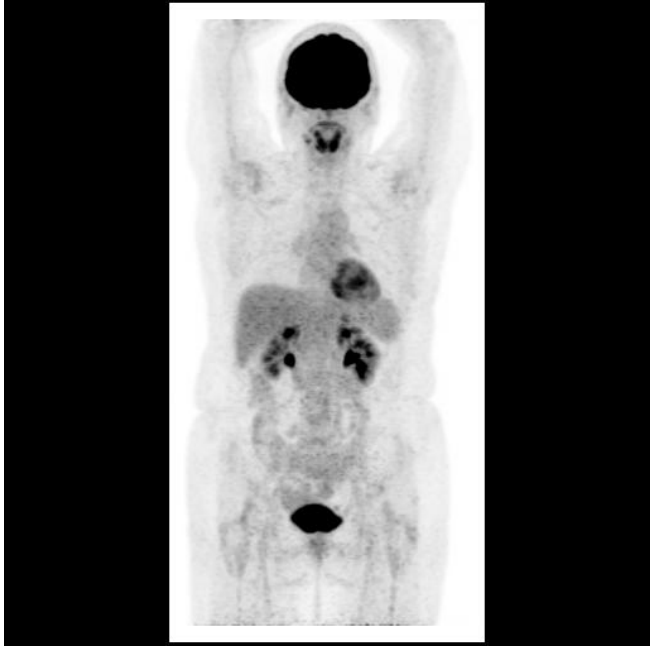
Primary Objective: PFS

Secondary Objectives:
- OS
- ORR
- CBR
- **QoL**
- **Safety**
- **Change in ECOG**

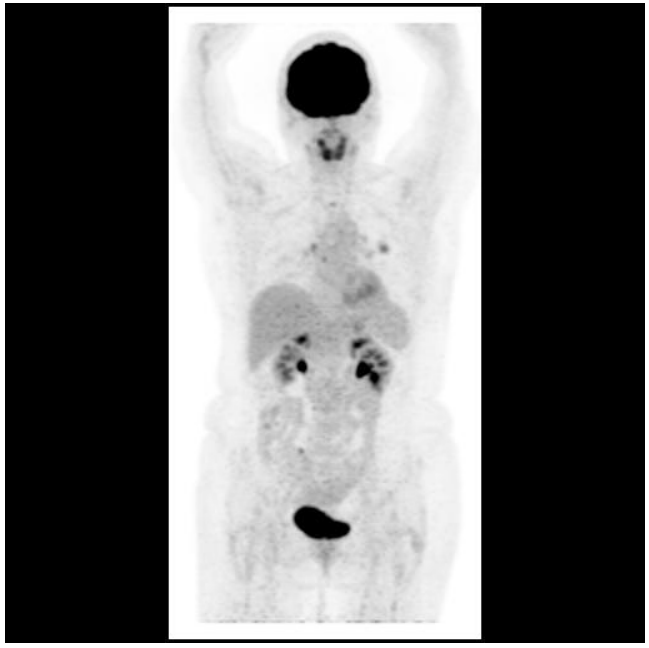
ClinicalTrials.gov Identifier:NCT01783444



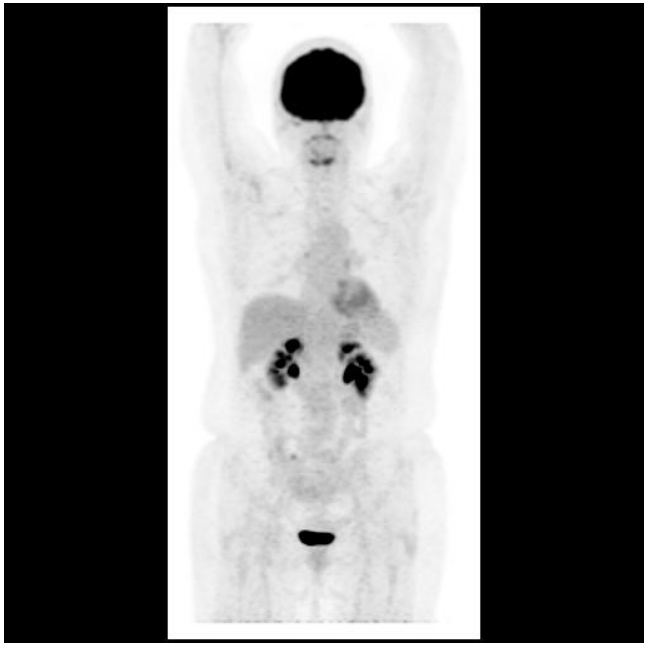
PD: start exemestane



CR on exemestane



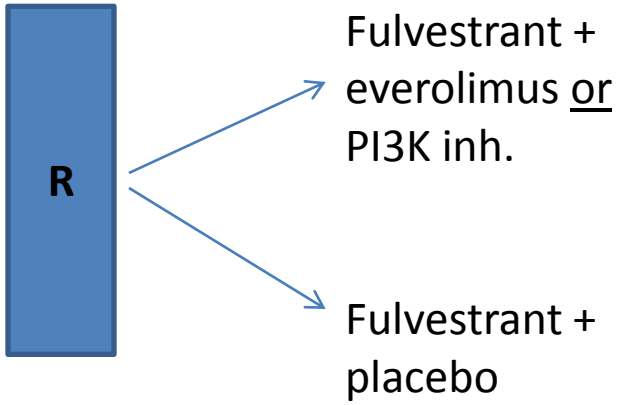
PD: add everolimus



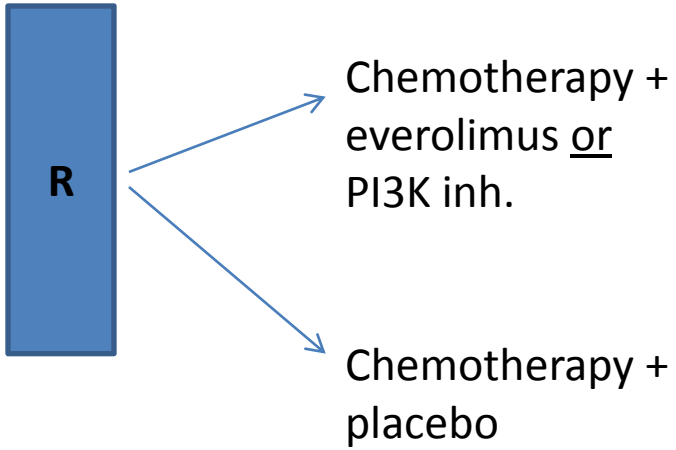
PR on exe + eve

Exemestane + Everolimus Progressing Patients : Is There Any Rationale to Keep « the Pressure » on the PI3K/mTOR Pathways ?!

- **Pts progression on Exemestane + Everolimus**
- **Pts candidates for endocrine agents**



- **Pts progression on Exemestane + everolimus**
- **Pts candidates for chemotherapy**



Courtesy A. Awada

Future Strategies

Other Combinations?

- mTOR inhibitors + IGF1-R inhibitors
- mTOR inhibitors + PI3K inhibitors
- mTOR inhibitors + CDK 4/6 inhibitors
- ……

More Specific Inhibition?

- Pan-PI3K inh: BKM120,…
- PI3K-alpha inh: GDC-0032, BYL719,…

Name	Target
BKM120 (Buparlisib)	Pan-PI3K
XL-147	Pan-PI3K
GDC-0941	Pan-PI3K
BYL-719	p110-α
GDC-0032	p110-α
INK-1117	p110-α

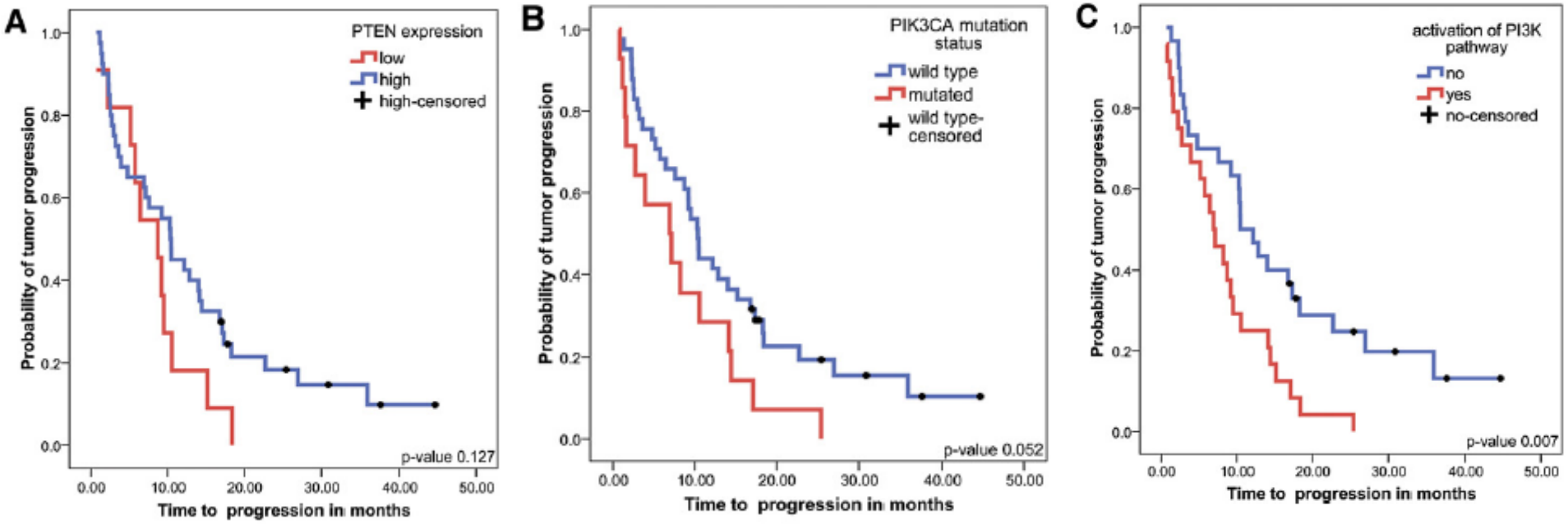
PI3K inh in Clinical Trials

Ongoing Adjuvant Trials of Everolimus in ER+ BC

Phase	Setting	Trial Population	Treatment Schema	Objective	Trial Identification
3	Adjuvant	At least 4+ LNs after surgery or at least 1+ LN if neoadjuvant chemotherapy	Everolimus 10 mg/day or placebo add-on to endocrine treatment after 3 years of start to complete 5 years	Primary: DFS	NCT01805271
3		High risk early breast cancer	Everolimus 10 mg/day or placebo for 1 year add-on to adjuvant endocrine treatment	Primary: DFS	NCT01674140

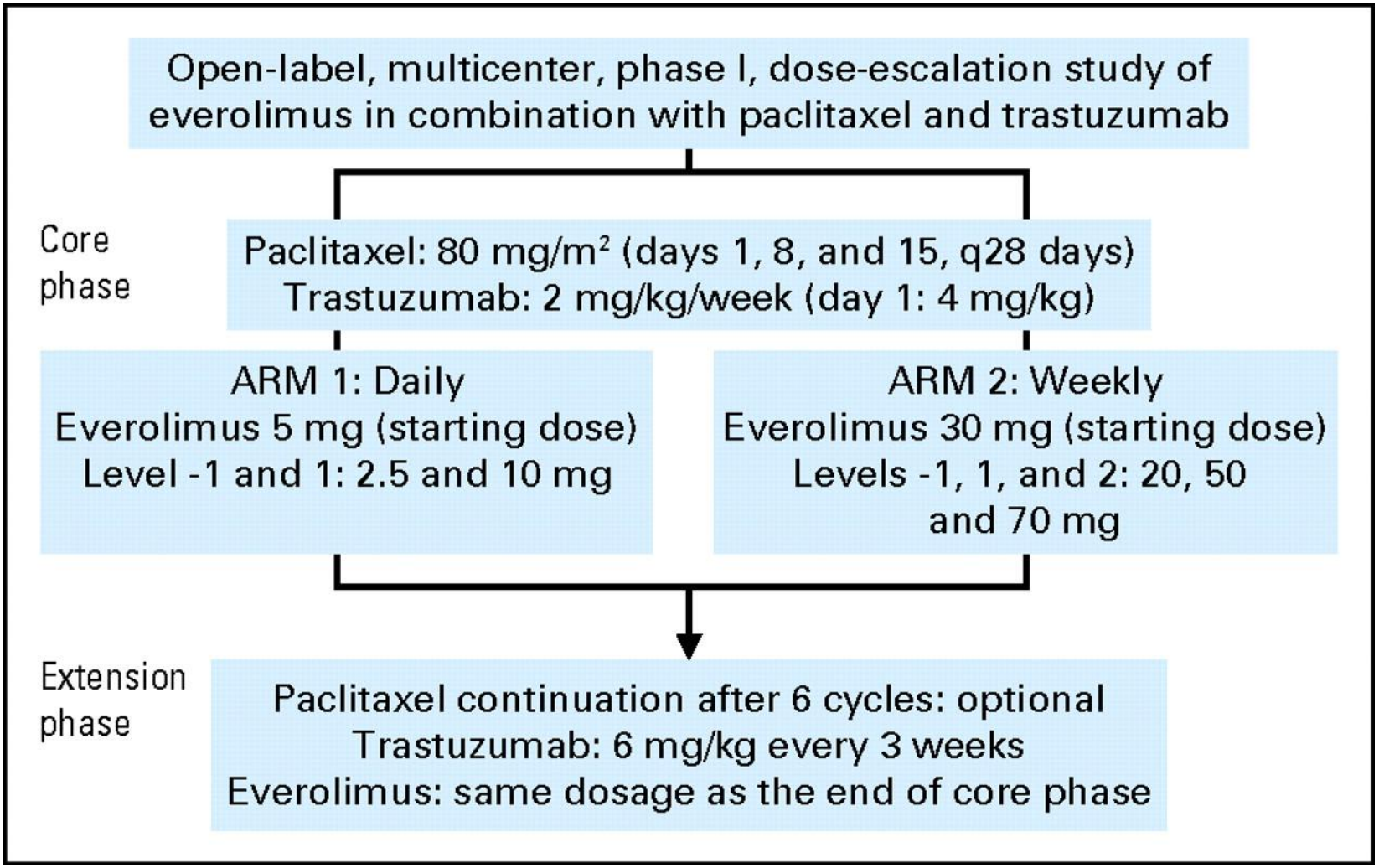
HER-2 positive Breast Cancer

PI3K-AKT-mTOR and Trastuzumab Resistance



Berns K et al. Cancer Cell 2007

Phase I trial: Study design. q28 days, every 28 days.



Andre F et al. JCO 2010;28:5110-5115

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Everolimus + Trastuzumab-chemo Combo after Progression on Trastuzumab-chemo

Table 1. Baseline Patient Demographic and Clinical Characteristics

	Everolimus Cohort							
	5 mg Daily (n = 6)		10 mg Daily (n = 17)		30 mg Each Week (n = 10)		All (N = 33)	
Characteristic	No.	%	No.	%	No.	%	No.	%
Resistant to trastuzumab‡	6	100	17	100	9	90	32	97
Pretreated with taxanes	6	100	16	94	9	90	31	94
Resistant to taxanes‡	5	83	6	35	2	20	13	39

Best Response	5 mg Daily (n = 5)	10 mg Daily (n = 13)	30 mg Each Week (n = 9)	All (N = 27)	
				No.	%
CR	1	1	0	2	7
PR	4	3	3	10	37
SD	0	8	5	13	48
PD	0	1	1	2	7
Clinical benefit rate, CR + PR + (SD ≥ 24 weeks)	5	8	7	20	74

Andre F et al.
J Clin Oncol 2010

Ongoing Phase III Trials with Everolimus + Chemo + Trastuzumab

	Patient population	N	Design	Treatment Arms	Stratification factors	Endpoints	Results
BOLERO-1	HER2+ ABC. First-line.	719	Randomization 2:1	Everolimus or placebo 10 mg/d + Paclitaxel 80 mg/m2 days 1-8-15 + Trastuzumab 2 mg/Kg weekly: 28-day cycle	- Prior adjuvant or neo-adjuvant trastuzumab - Visceral metastases	- Primary: PFS - Secondary: ORR, OS, safety, PK, biomarkers	Not yet reported.
BOLERO-3	HER2+ ABC. Prior taxane therapy and resistance to trastuzumab	569	Randomization 1:1	Everolimus or placebo 5 mg/d + Vinorelbine 25 mg/m2 days 1-8-15 + Trastuzumab 2 mg/Kg days 1-8-15: 21-day cycle	Prior lapatinib Number of prior chemotherapy regimens for advanced disease (1 versus 2-3)	Primary: PFS Secondary: OS, ORR, safety, PROs, lab measures	PFS: 7 months versus 5.78 months in favor of everolimus *

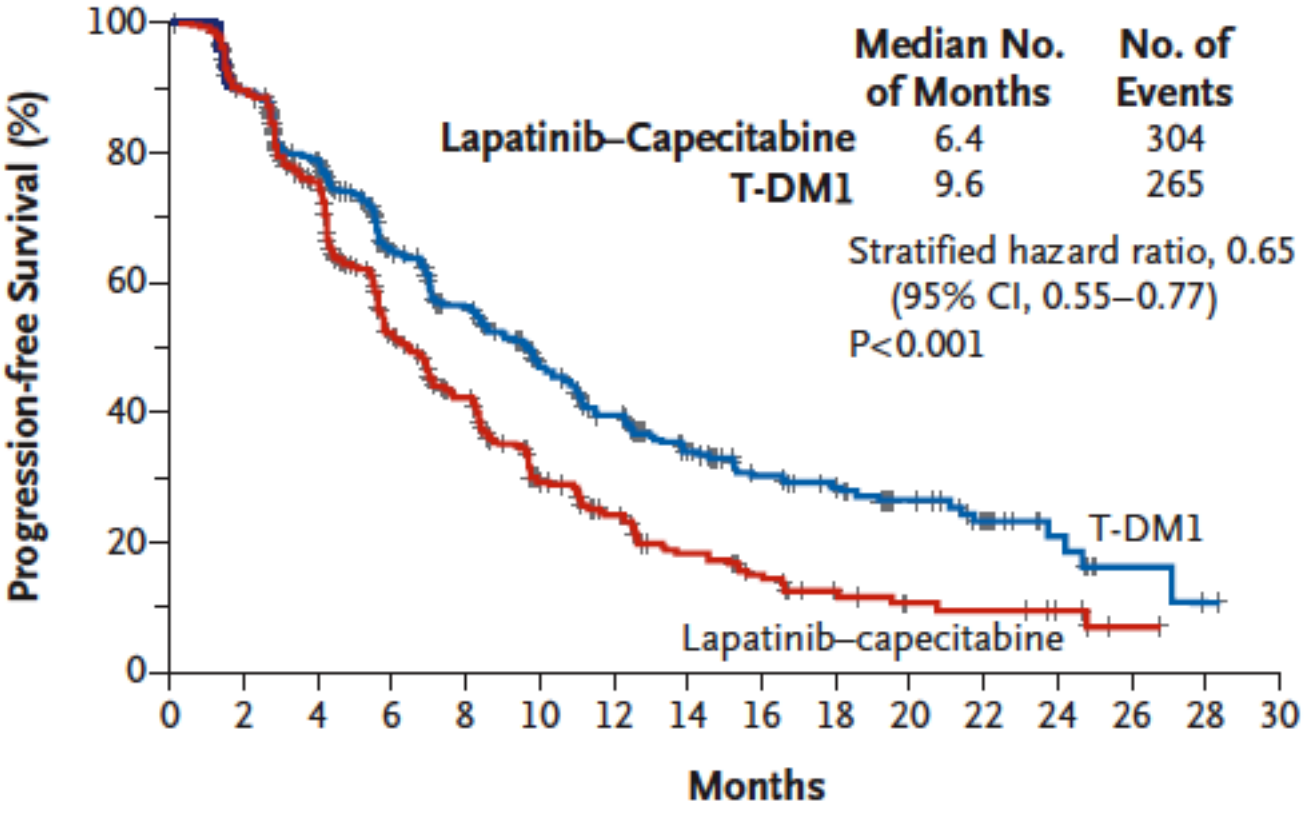
BOLERO-1: ClinicalTrials.gov Identifier: NCT00876395

BOLERO-3: J Clin Oncol 31, 2013 (suppl; abstr 505)

Trials with Anti-HER2 Agents and mTOR Inhibitors

Phase	Setting	Trial population	mTOR inhibitor	Anti-HER-2 agent	Chemotherapy	Endocrine agent
1b/2	Metastatic	HER-2+, trastuzumab refractory	Temsirolimus	Neratinib	None	None
2	Metastatic	HER-2+, trastuzumab refractory	Ridaforolimus	Trastuzumab	None	None
2	Metastatic	HER-2+, CNS metastases allowed	Everolimus	Lapatinib	None	None
2	Metastatic	HER-2+ with brain metastases	Everolimus	Trastuzumab	Vinorelbine	None
1b/2	Metastatic	HER-2+ with brain metastases	Everolimus	Lapatinib	Capecitabine	None
2	Metastatic	ER+, HER-2 + or - after progression on lapatinib and letrozole	Everolimus	Lapatinib	None	Letrozole

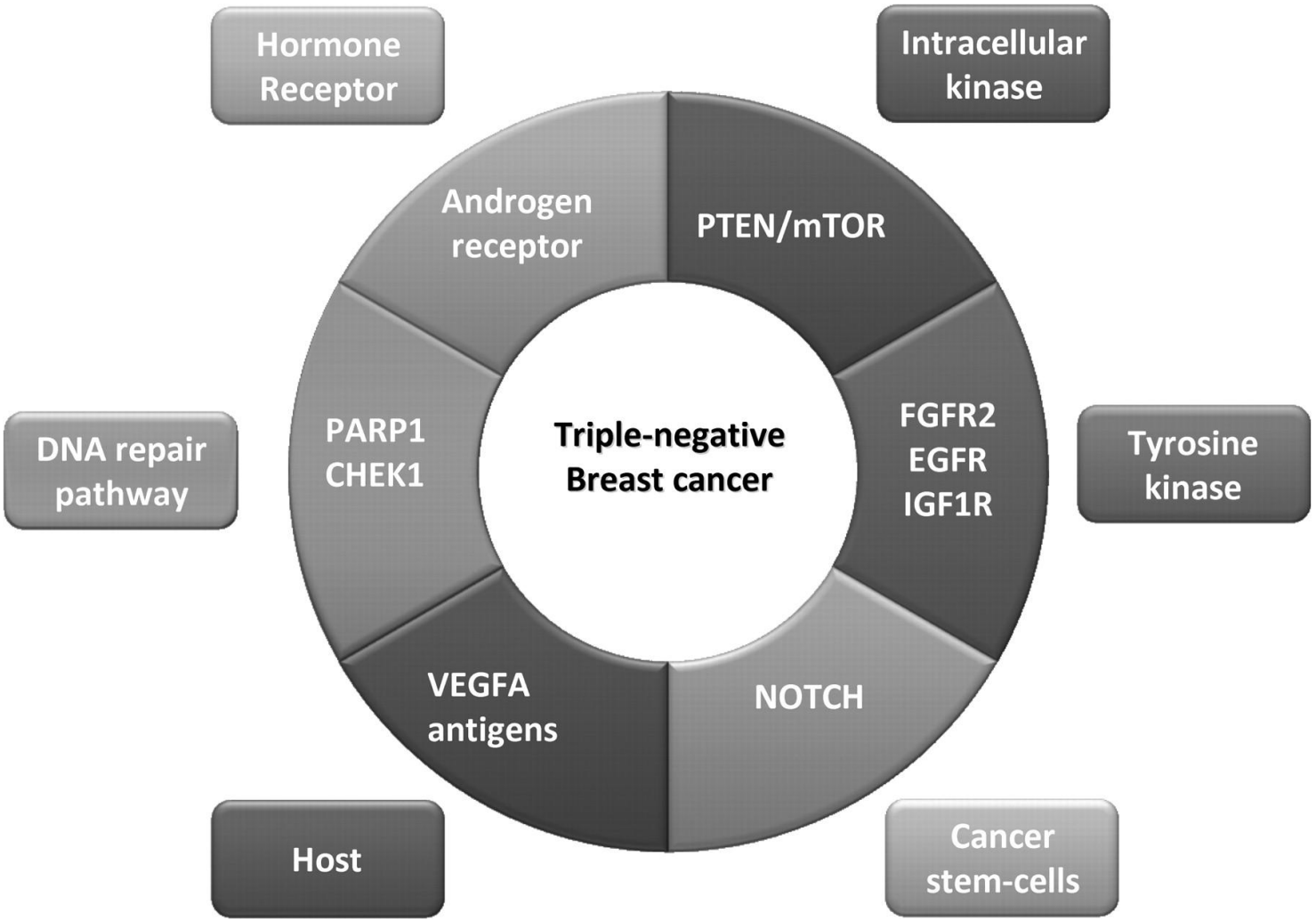
What role for mTOR inhibitors in HER-2+ BC in the era of T-DM1?



Verma S et al. NEJM 2012

Triple Negative Breast Cancer

Candidate targets and pathways in triple-negative breast cancer.



Berrada N et al. Ann Oncol 2010;21:vii30-vii35

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Annals of Oncology

TCGA Breast Cancer

"PI(3)K pathway activity, whether from gene, protein, or high PI(3)K/AKT pathway activities, was highest in basal-like cancers: loss of PTEN and INPP4B and/or amplification of PIK3CA"

Nature 2012

Subtype	Basal-like
$ER^+/HER2^-$ (%)	10
$HER2^+$ (%)	2
TNBCs (%)	80
TP53 pathway	*TP53* mut (84%); gain of *MDM2* (14%)
PIK3CA/PTEN pathway	PIK3CA mut (7%); PTEN mut/loss (35%); INPP4B loss (30%)
RB1 pathway	*RB1* mut/loss (20%); cyclin E1 amp (9%); high expression of *CDKN2A*; low expression of *RB1*
mRNA expression	Basal signature; high proliferation
Copy number	Most aneuploid; high genomic instability; 1q, 10p gain; 8p, 5q loss; *MYC* focal gain (40%)
DNA mutations	*TP53* (84%); *PIK3CA* (7%)
DNA methylation	Hypomethylated
Protein expression	High expression of DNA repair proteins, PTEN and INPP4B loss signature (pAKT)

Clinical trials testing everolimus in TNBC

Trial	Treatment	Setting	Class	Phase	n	pCR	Other endpoints
MDACC (Gonzalez-Angulo, ASCO 2012)	Paclitaxel +/- Everolimus Followed by FEC	neoadjuvant	TNBC	II R	50	30% vs 26%	Clinical response: T+R: 48% T: 30% P=0.075
Vanderbilt (PI: I. Mayer)	CISPLATIN + Paclitaxel +/- everolimus	Neoadjuvant	TNBC	II R	130	Ongoing (recruitment finished)	

Trend for efficacy in combination with paclitaxel
Combination with cisplatin: results available soon

A randomized phase II neoadjuvant study of cisplatin, paclitaxel with or without everolimus in patients with stage II/III TNBC

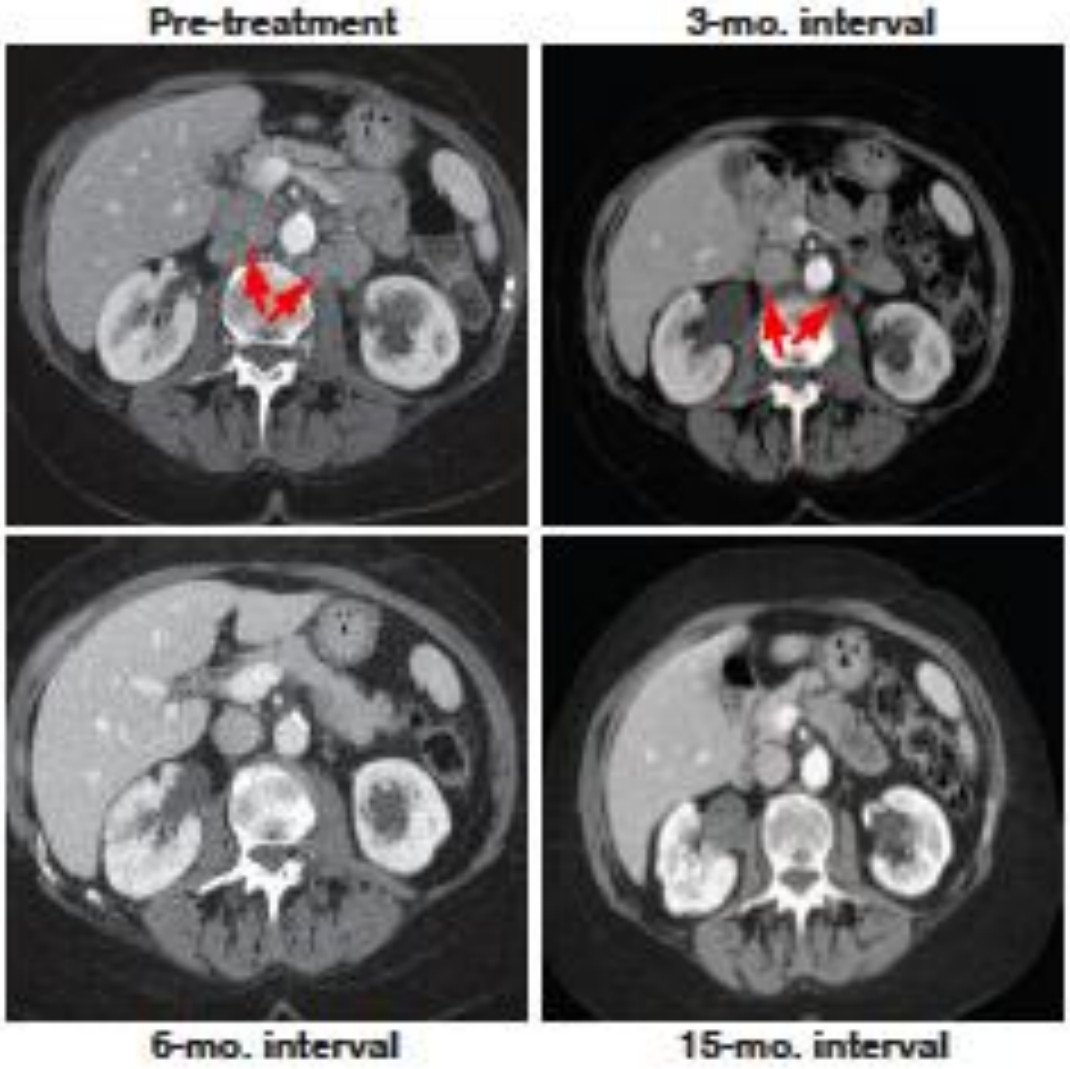
	Everolimus	Placebo
Evaluable Patients	82	38
pCR	35%	42%

Primary Objective: pCR

Mayer IA et al. San Antonio Breast Cancer Symposium 2013 PD 1-6

Biomarkers?

Everolimus in Bladder Cancer: a failed PFS goal



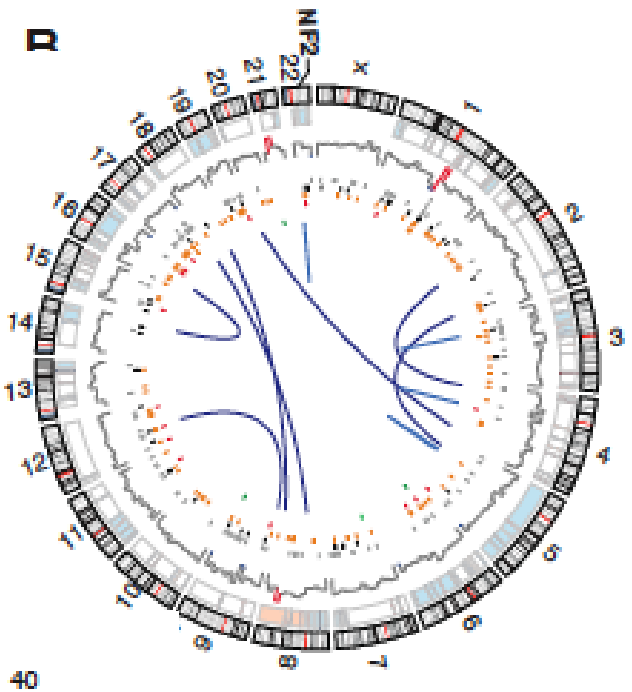
A bladder cancer patient achieving a durable (>2 years) and ongoing complete response to everolimus.

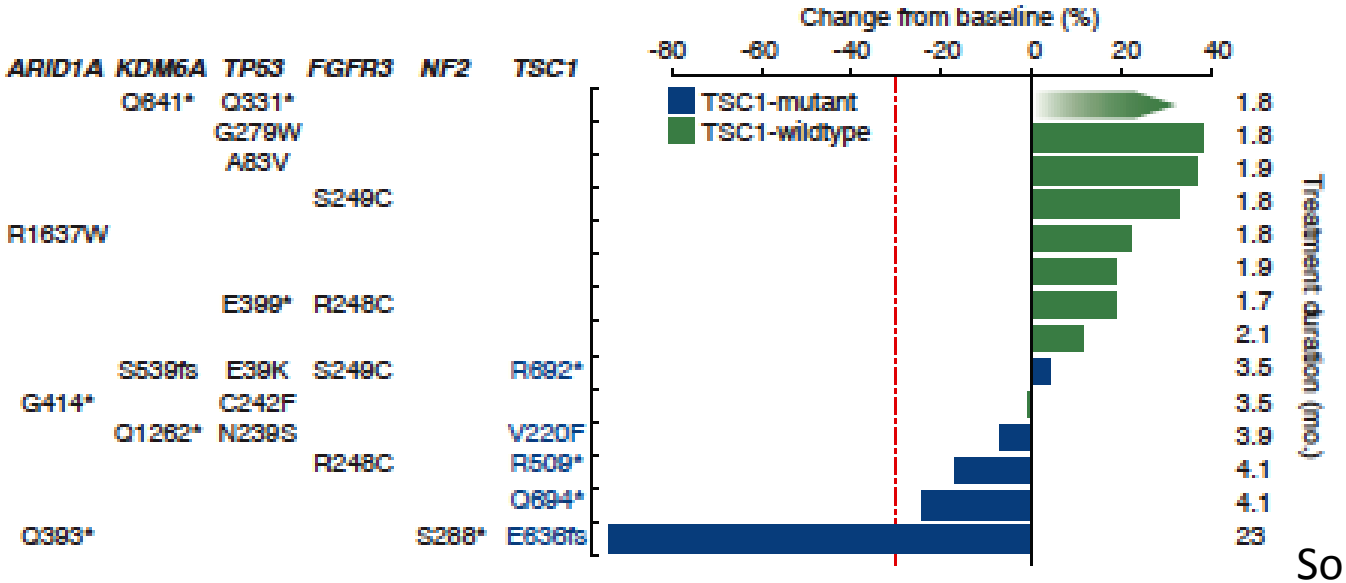
Solit D et al. Science 2012.

Genome Sequencing and Everolimus Sensitivity

1- A 2-base-pair deletion in the TSC1 gene resulting in a frameshift truncation (c1907_1908del, p.Glu836fs)

2- A nonsense mutation in the NF2 gene, creating a premature stop codon (c.836C>G, p.Ser288*)





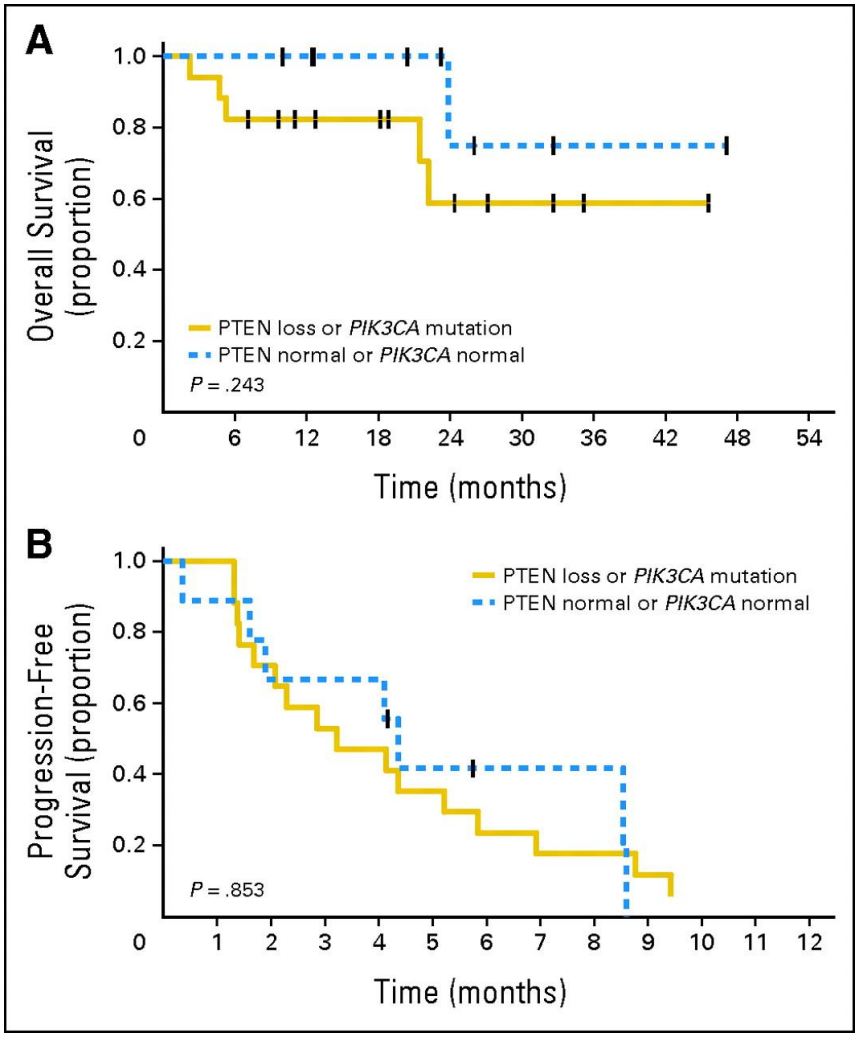
Solit D et al. Science 2012.

Next-Generation Sequencing from BOLERO-2

- Exon sequence and gene copy number variations were analyzed for 182 cancer-related genes by NGS (>250x coverage)
- Archival tumor specimens (mostly primary tumors) from 227 patients (157 in everolimus arm)
- Patients with no or only 1 genetic alteration in PI3K or FGFR pathways, or CCND1, had a greater treatment effect from everolimus (HR = 0.27, 95% CI 0.18-0.41, adjusted by covariates, in 76% of the NGS population)
- PI3K mutations not predictive!

Hortobagyi GN et al. J Clin Oncol 31, 2013 (suppl; abstr LBA509).

Effect of the presence of phosphatase and tensin homolog (PTEN) loss or PIK3CA mutation (A) on overall survival and (B) progression-free survival.



Morrow P K et al. JCO 2011;29:3126-3132

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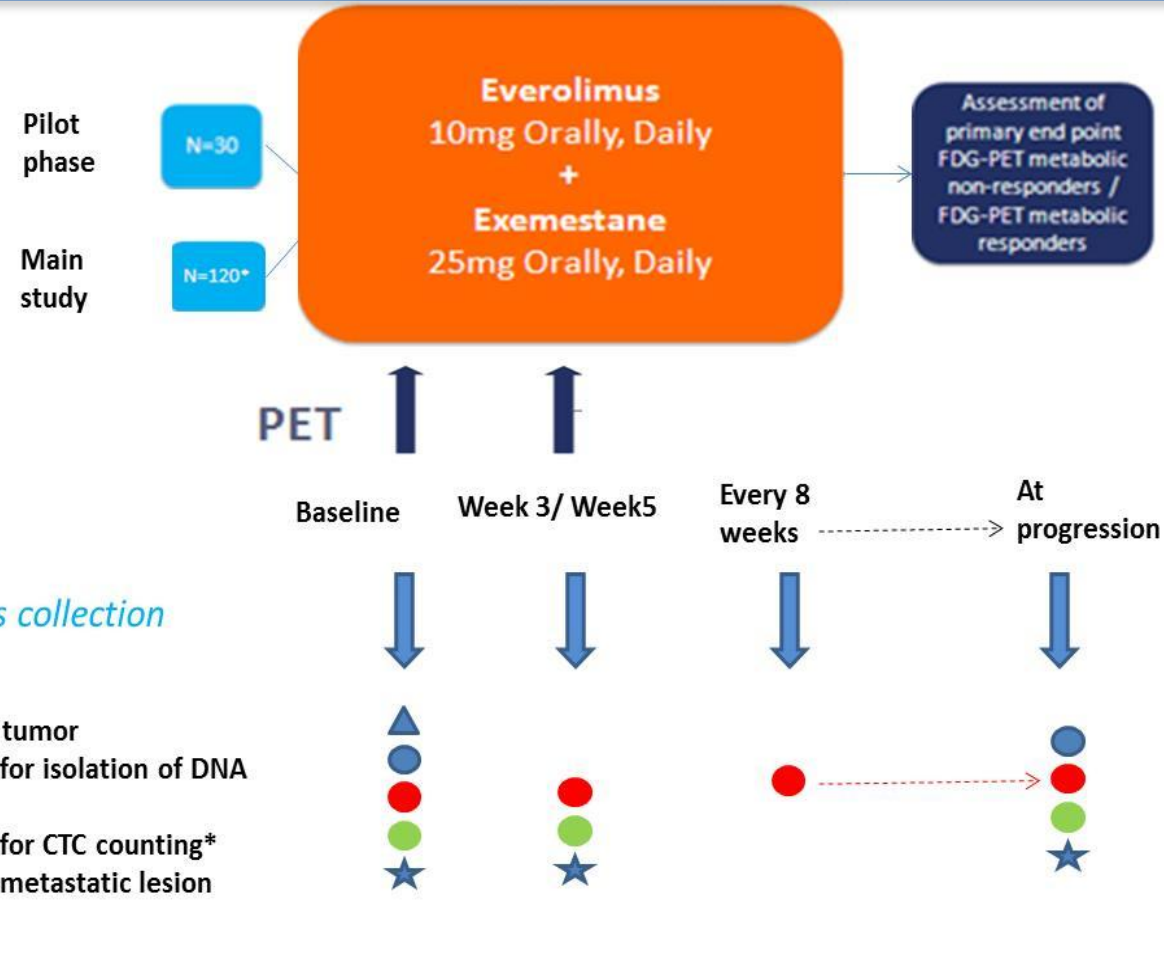
Nuclear Imaging: PEARL trial



PI: A. Gombos

- Biopsy of metastases is mandatory for patients with accessible lesions
- The second biopsy (at progression) will be taken from accessible non-metabolic responding sites
- Biopsy at FDG-PET/CT will be done only in patients with subcutaneus metastases

BIG 14-01

Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer

The AURORA PROGRAM

30 European centers
1300 patients
400 genes
ctDNA
RNAseq

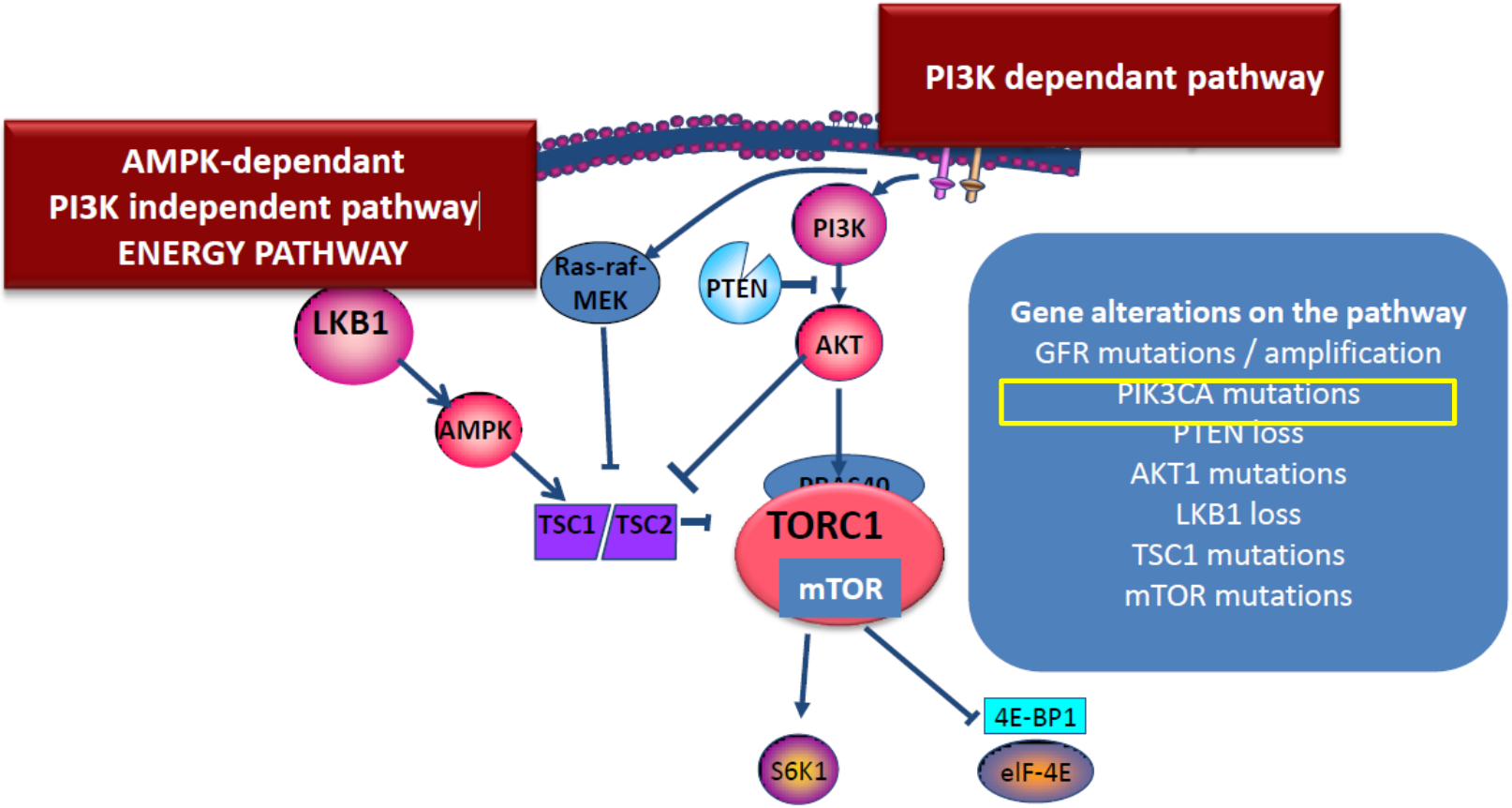
Questions?

philippe.aftimos@bordet.be

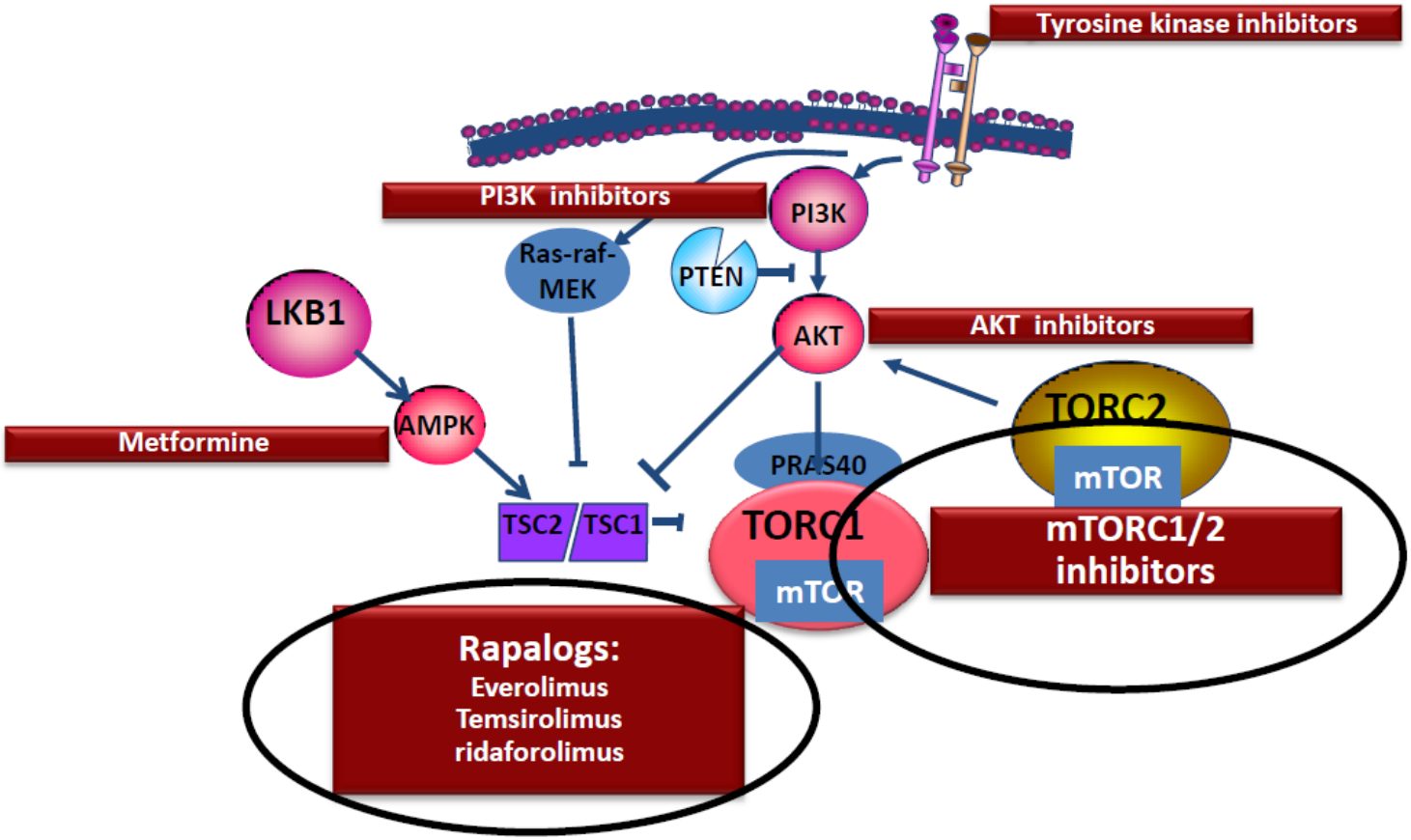
Twitter: @aftimosp

Backup slides

Mechanisms of TORC1 activation in cancer cells



Drugs targeting mTOR pathway



Rapalogs + Her2 inhibitors: Phase I/II Data

Study/Patient population	Treatments	N	Outcome
Disease progression on/after trastuzumab (Morrow, J Clin Oncol, 2012)	**Everolimus, trastuzumab** (without chemotherapy)	**47**	**Clinical benefit:34% ORR: 15%**
PD on/after trastuzumab (Andre, J Clin Oncol, 2010)	**Everolimus, trastuzumab, paclitaxel**	**33**	**ORR: 44%**
PD on/after trastuzumab (Jerusalem, BCRT, 2011)	**Everolimus, trastuzumab, vinorelbine**	**50**	**ORR: 19%**
Refractory to trastuzumab AND taxanes (Dalenc, ASCO, 2011)	**Everolimus, trastuzumab, paclitaxel**	**55**	**Clinical benefit:40% ORR: 20%**
PD after trastu (Gajria, ASCO, 2011)	**Temsirolimus / neratinib**	**6**	**4 PR / 6**

mTOR inhibitors overcome resistance to trastuzumab in phase I/II trials
Is it medically useful ?