GBCC 2015 & 4th IBCS

Together For A Cancer-Free Tomorrow

National Cancer Centre Singapore
SingHealth

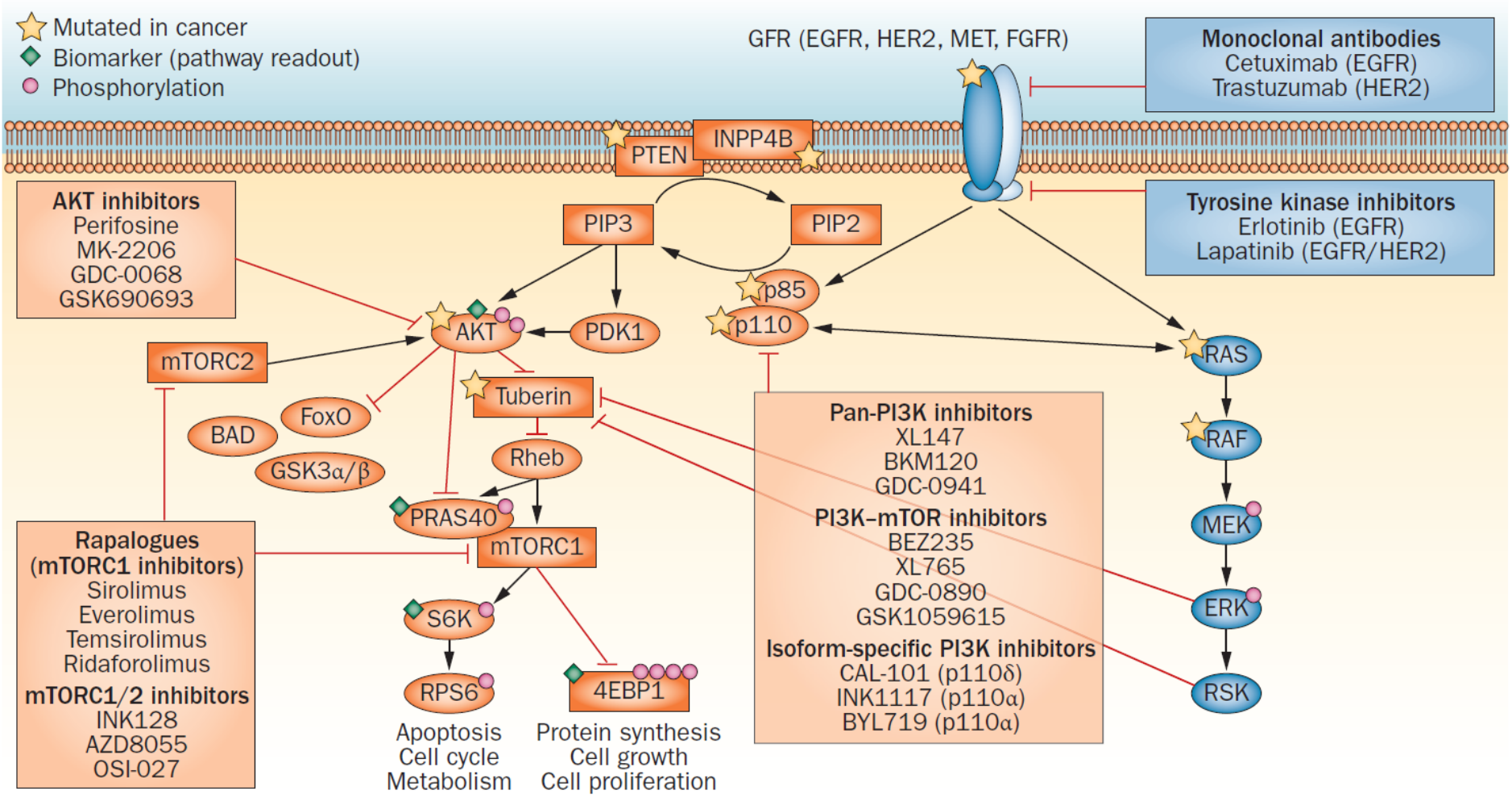
PI3K/AKT/mTOR Inhibitors in Breast Cancer

Dr Yoon-Sim YAP
Division of Medical Oncology,
National Cancer Centre Singapore
Global Breast Cancer Conference 2015

Outline

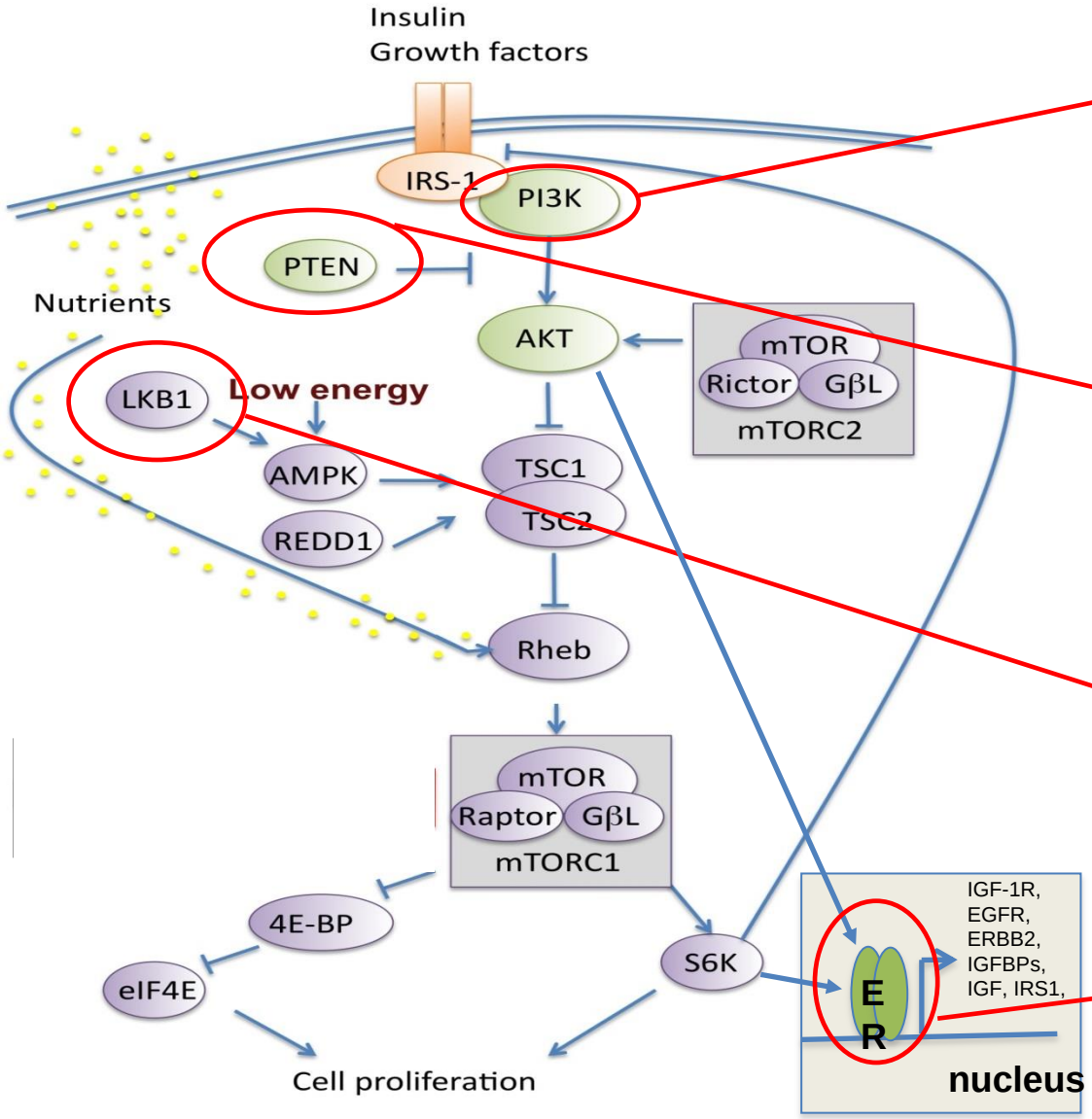
- Overview of PI3K/Akt/mTOR Pathway
- Rationale and Preclinical Data
- Clinical Trials and Predictive Biomarkers
  - Hormone receptor +, HER2 –
  - HER2 +
  - Triple Negative
- Toxicities
- Overcoming Resistance; Novel Combinations

PI3K/AKT/mTOR Pathway



Rodon et al, Nature Reviews Clin Onc 2013

In ER+ breast cancer



Activating mutations in the catalytic domain of PI3K (*PIK3CA*) have been identified in 30-40% of ER+ breast cancers

15-35% of breast cancer demonstrate reduced expression of PTEN, which has been associated with poor response to tamoxifen

Other factors (loss of LKB1) can activate mTOR independent of the upstream growth factor / PI3K / Akt axis

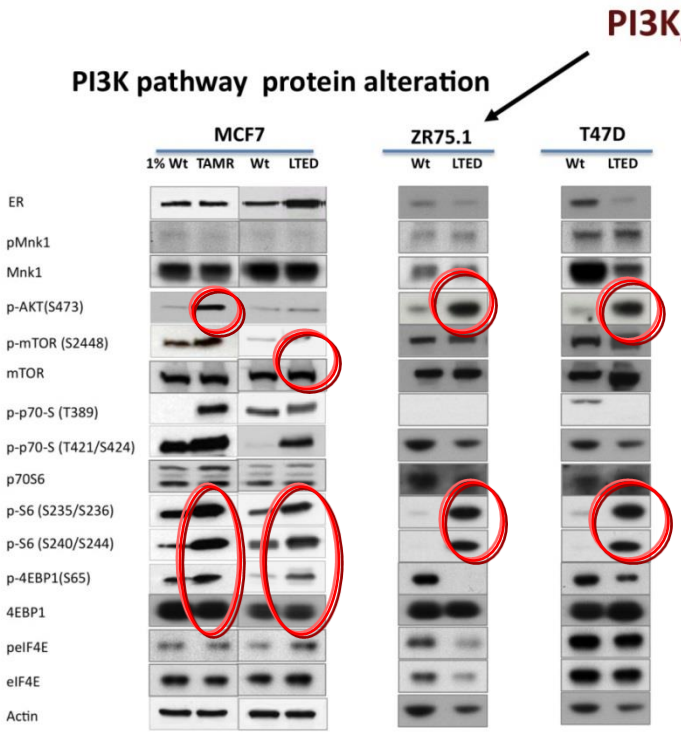
Akt and mTOR (via S6K) can phosphorylate ER independent of E2 ligand

Johnston, ASCO 2013

Role of PI3K/AKT/mTOR pathway in Endocrine Resistance

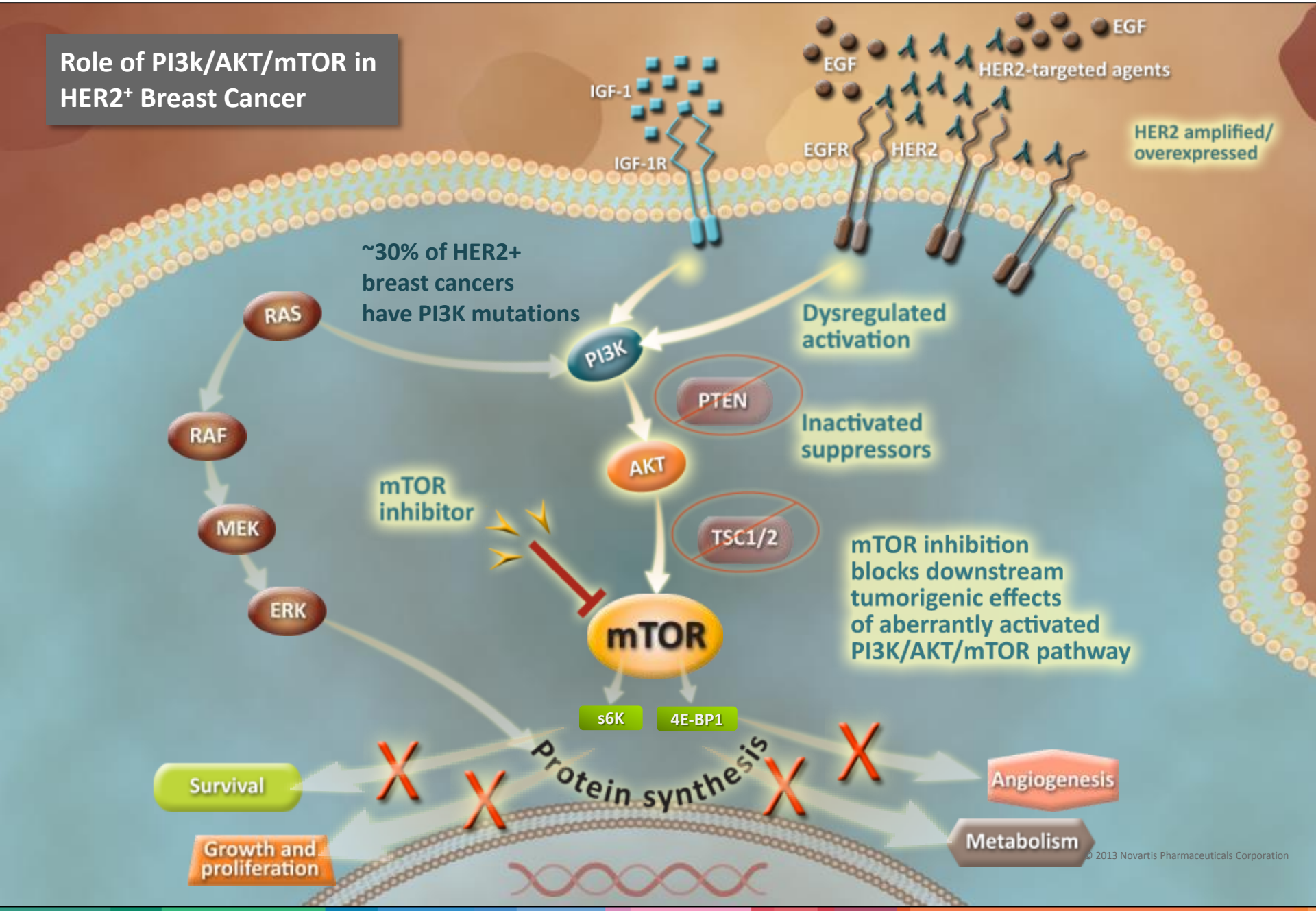
- Long term estrogen deprivation (LTED) & acquired endocrine resistance:
  - Studies have demonstrated persistence of an active ER pathway [1]
  - LTED can ⬆ ERα levels & ⬆ activation of the PI3K/mTOR pathway [2]
  - Hyper-activation of the PI3K/mTOR pathway is a key mediatior [3]

1. Martin LA, et al. J Biol Chem. 2003;278:30458-68;
2. Santen RJ, et al. Endo-Rel Cancer. 2005;12:S61-S73;
3. Miller TW, et al. J Clin Invest. 2010;120(7):2406-413



4. Weigel et al Breast Cancer Res. 2012 14(3):R78.

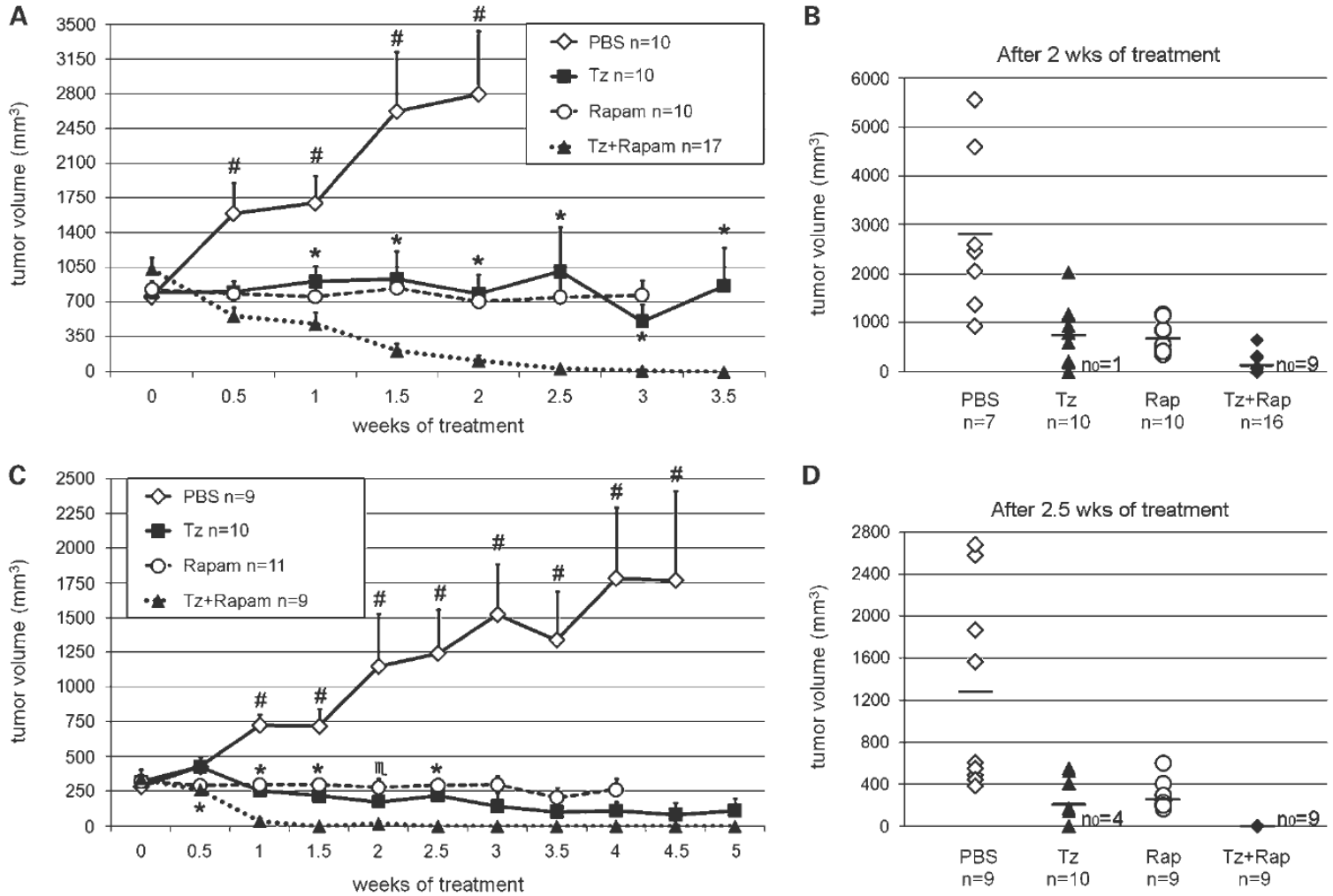
Pathway description	p.Value		
	MCF7	T47D	ZR75.1
PI3K/AKT signalling	0.045	0.027	5×10^{-3}
PTEN signalling	0.032	0.035	0.03
IGF1 signalling	3.19×10^{-2}	3.5×10^{-4}	4.69×10^{-2}
ERK5 signalling	6×10^{-2}	0.0125	0.0129


Role of PI3k/AKT/mTOR in HER2+ Breast Cancer
IGF-1
IGF-1R
EGF
EGF
HER2-targeted agents
EGFR
HER2
HER2 amplified/ overexpressed
~30% of HER2+ breast cancers have PI3K mutations
RAS
PI3K
Dysregulated activation
PTEN
Inactivated suppressors
RAF
AKT
mTOR inhibitor
MEK
TSC1/2
ERK
mTOR inhibition blocks downstream tumorigenic effects of aberrantly activated PI3K/AKT/mTOR pathway
mTOR
s6K
4E-BP1
Protein synthesis
Survival
Angiogenesis
Growth and proliferation
Metabolism
© 2013 Novartis Pharmaceuticals Corporation

Synergy of Rapamycin with Trastuzumab to induce complete tumour regression

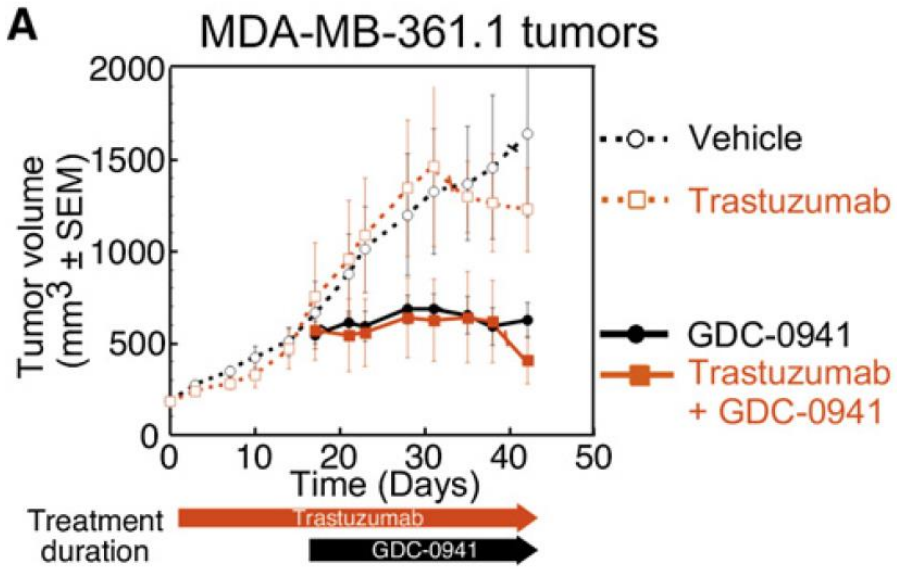
Together For A Cancer-Free Tomorrow

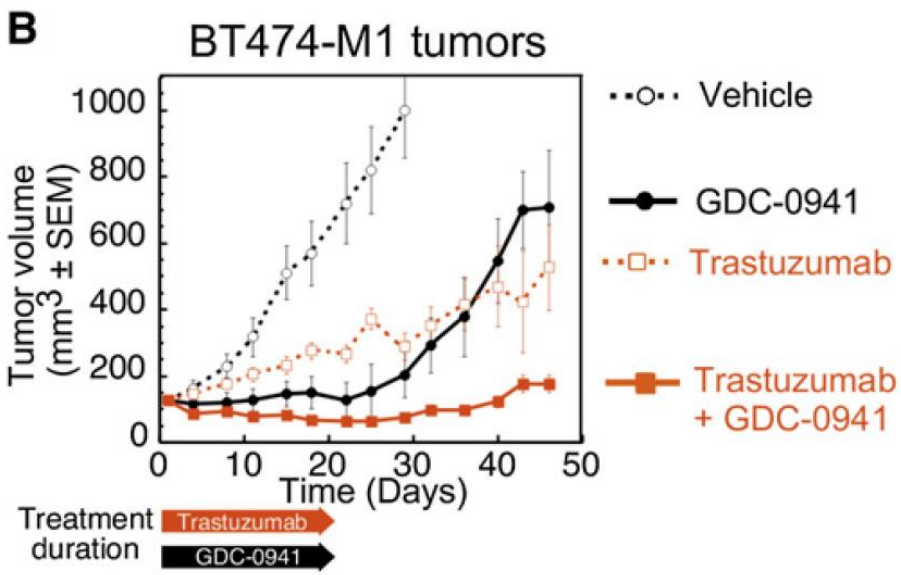
National Cancer Centre Singapore
SingHealth



Miller et al, CCR 2009

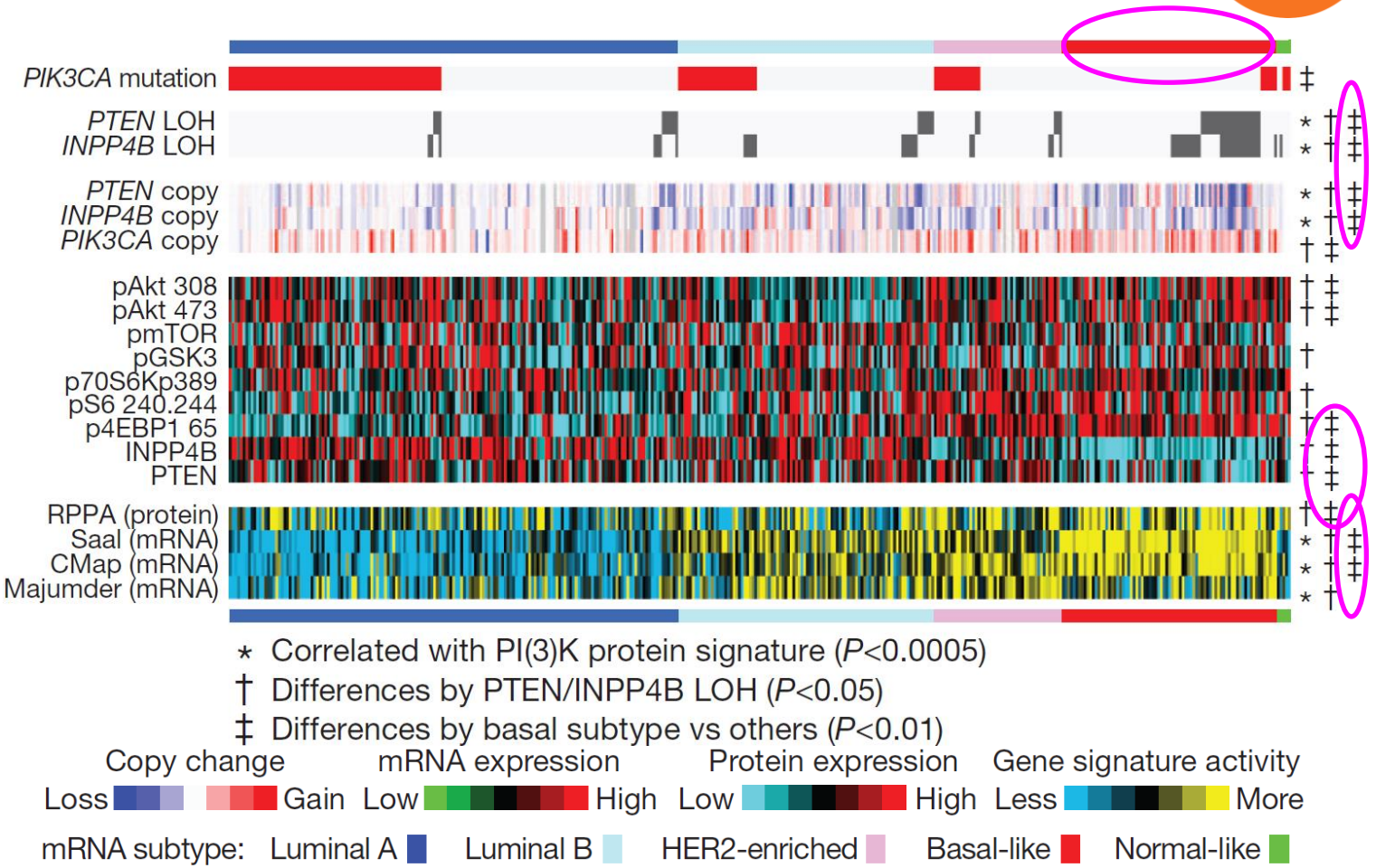
PI3K Inhibitor GDC-0941 : Efficacy in Treating Trastuzumab-Resistant and Trastuzumab-Sensitive Tumors In Vivo





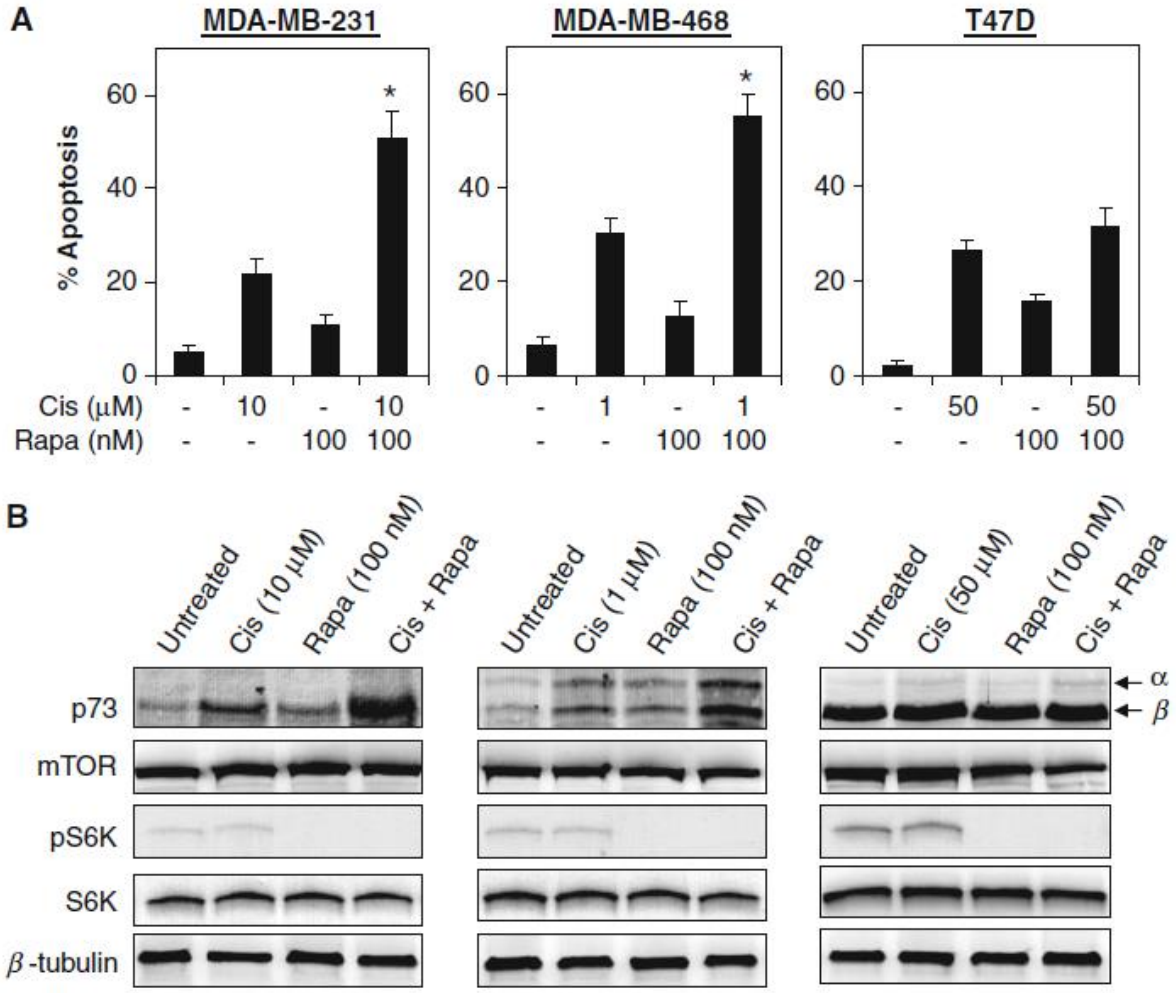
Junttila et al, Cancer 2009

Triple Negative Breast Cancer



Integrated analysis of the PI3K pathway (TCGA, Nature 2012) shows overexpression of pAkt, pS6, p4EBP1 on RPPA, and correlation with INPP4B and PTEN loss in basal-like subtypes. PI3K pathway protein and mRNA signatures were enriched in basal subtypes.

Rapamycin synergizes cisplatin sensitivity in triple negative breast cancer cells



Wong, BCRT 2011

Clinical Trials

Together For A Cancer-Free Tomorrow

National Cancer Centre Singapore
SingHealth

Clinical Trials

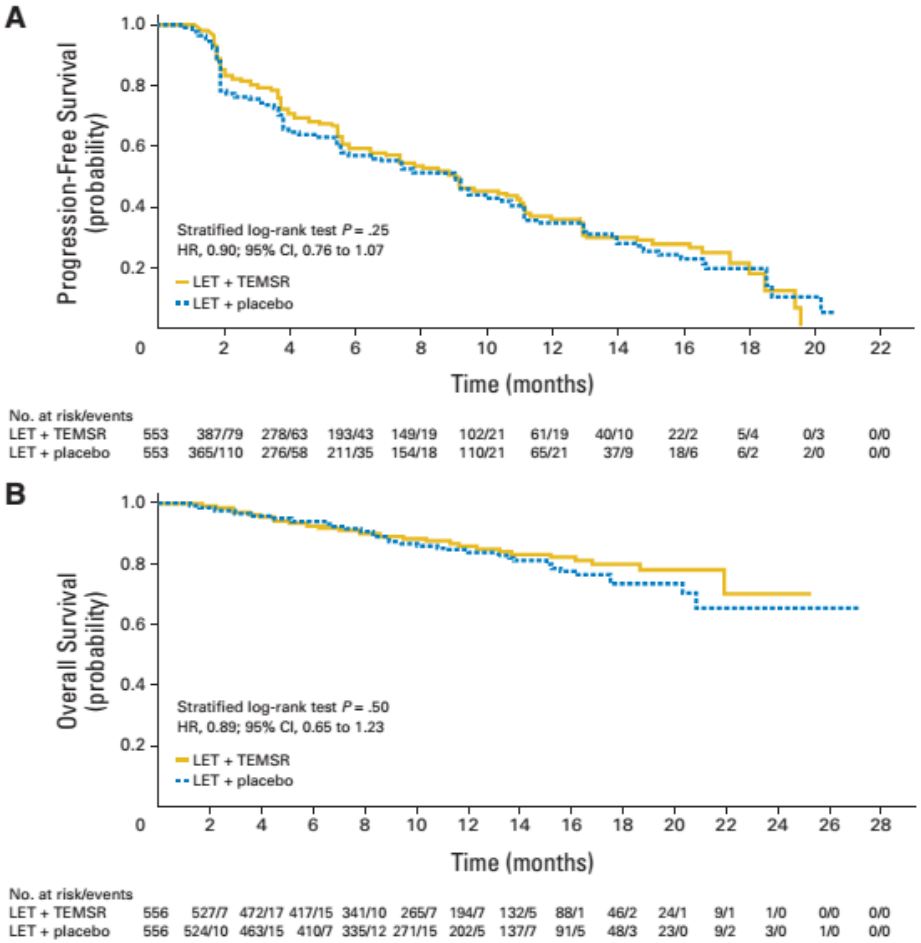
- **Focus on Randomised Studies**

- mTOR Inhibitors
  - Hormone receptor + (HORIZON, BOLERO-2, TAMRAD)
  - HER2 + (BOLERO-3, BOLERO-1)
  - Triple Negative

- PI3K Inhibitors

- AKT Inhibitors

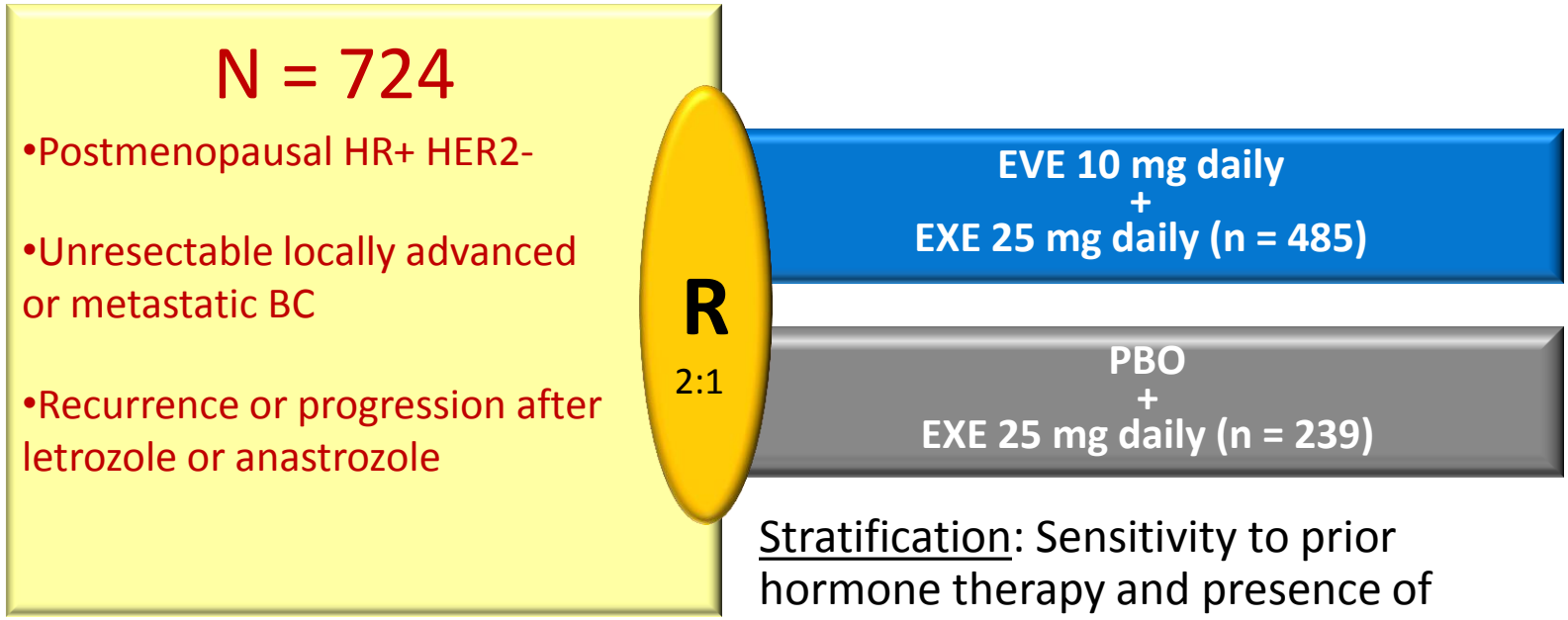
Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy (HORIZON)



Why?
Drug factor?
Dosing?
Setting?
Patient Selection?

Wolff et al, JCO 2012

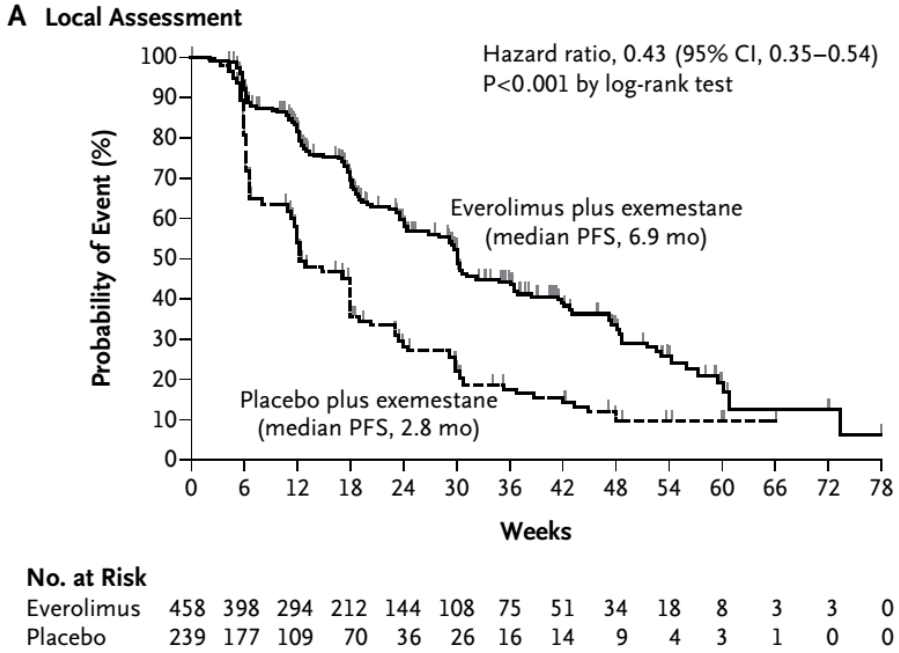
BOLERO-2 (Ph III): Everolimus in advanced BC

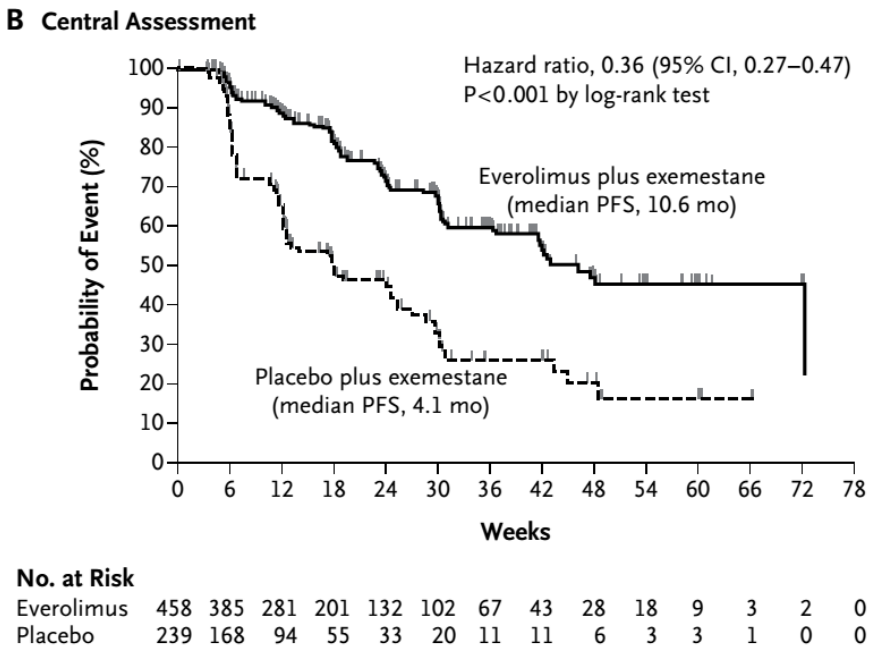


Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

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

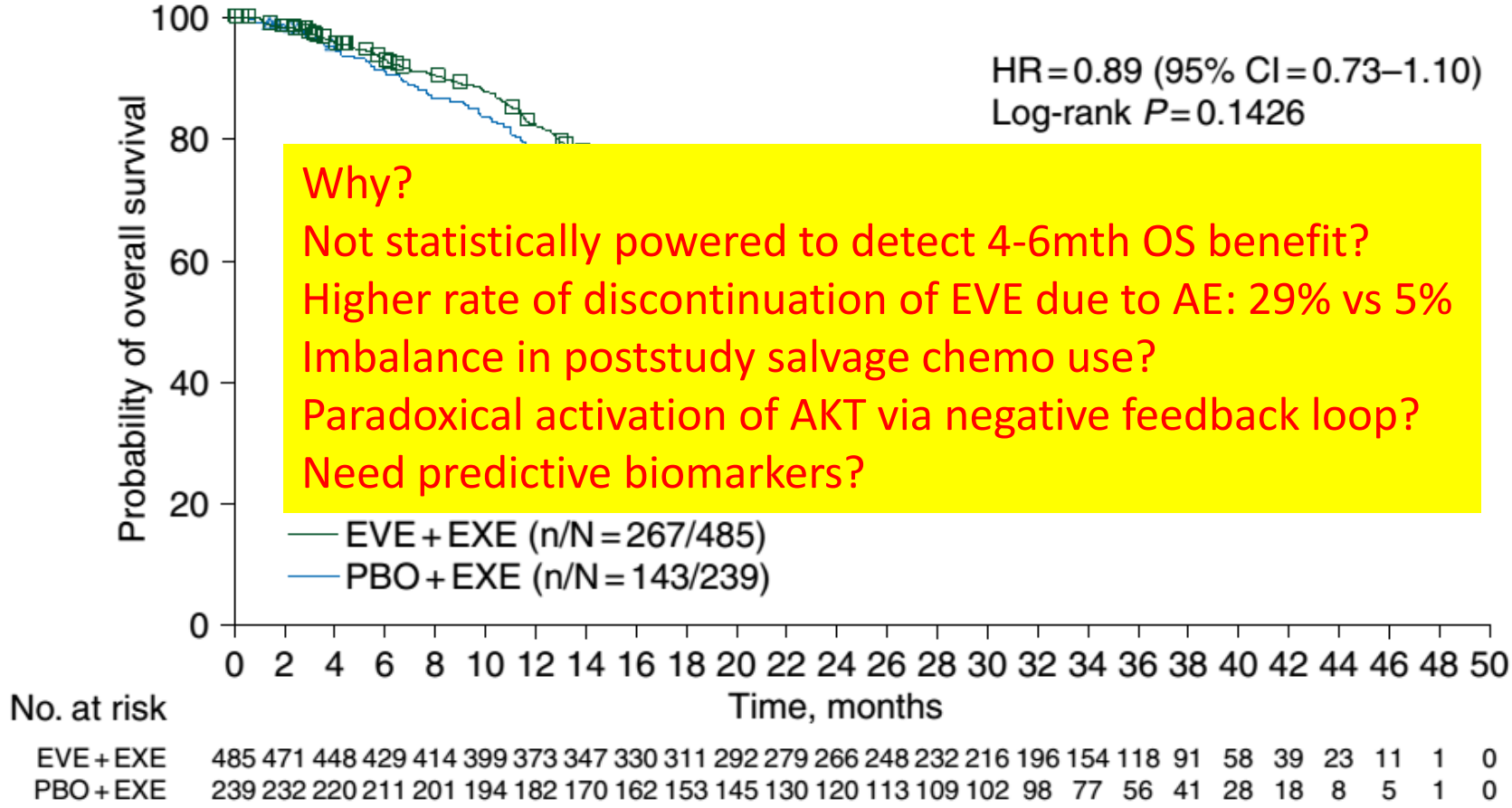
BOLERO-2: PFS Results





Baselga et al, NEJM 2011

BOLERO-2: Overall Survival Results

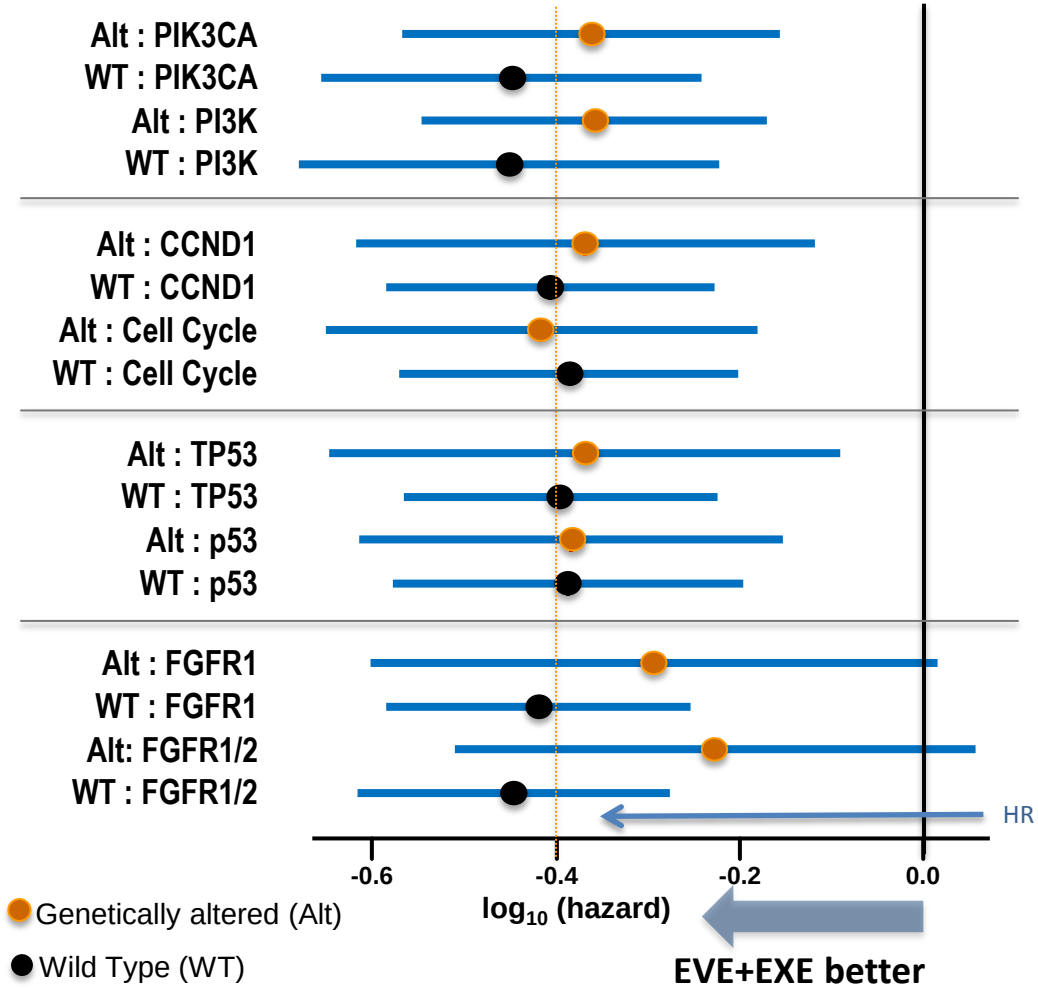


Why?
Not statistically powered to detect 4-6mth OS benefit?
Higher rate of discontinuation of EVE due to AE: 29% vs 5%
Imbalance in poststudy salvage chemo use?
Paradoxical activation of AKT via negative feedback loop?
Need predictive biomarkers?

Piccart et al, Ann Onc 2014

Impact on Treatment by Genetic Status

The Most Frequently Altered Single Genes and Pathways



Positive treatment effect in favor of everolimus across the various genetic marker subgroups

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%)

Hortobagyi et al, ASCO 2013

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

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	

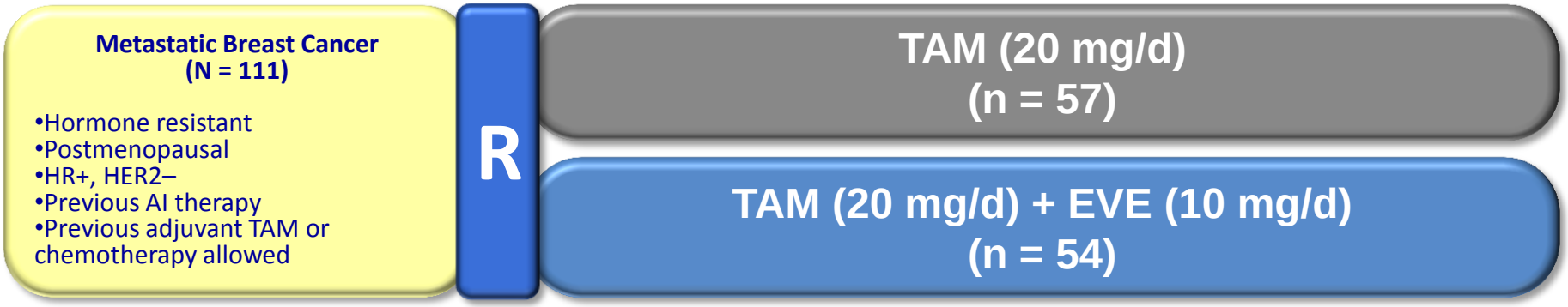
*HR adjusted with imbalanced covariates

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%

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

Hortobagyi et al, ASCO 2013

TAMRAD: Phase II in patients with metastatic breast cancer and prior exposure to AI

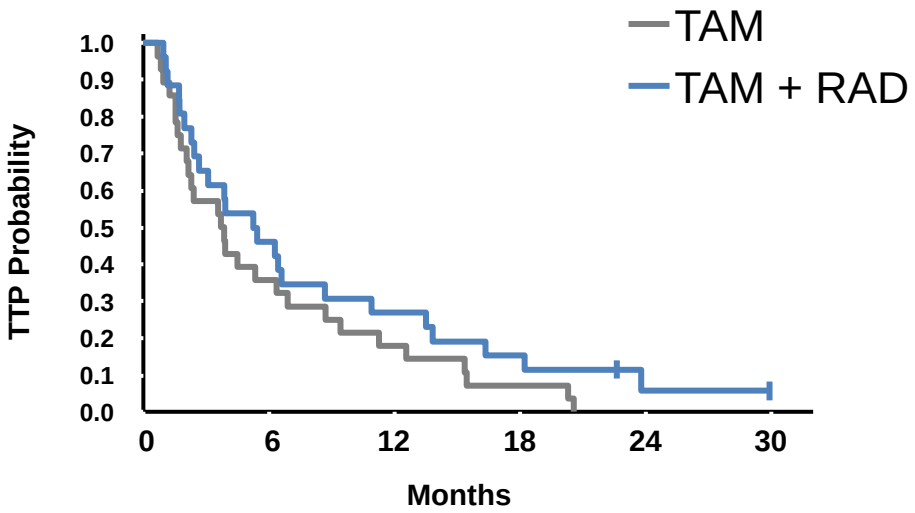


- **Stratification: Primary or secondary hormone resistance:**
  - **Primary:**
    Relapsing during or within 6 months of stopping adjuvant AI treatment or progressing within 6 months of starting AI treatment in the metastatic setting
  - **Secondary:**
    Relapsing 6 months after stopping adjuvant AIs or responding for 6 months to AIs in the metastatic setting

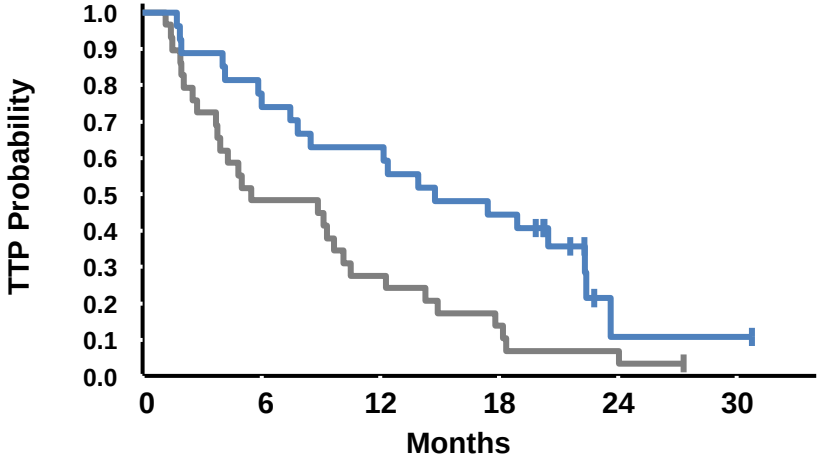
Bachelot et al, JCO 2012

TAMRAD: Time to Progression as a function of Intrinsic Hormone Resistance

- **Primary resistance**
  - TAM: 3.8 months
  - TAM + RAD: 5.4 months
  - HR = 0.70 (0.40-1.21)
  - *p* = NS (exploratory analysis)



- **Secondary resistance**
  - TAM: 5.5 months
  - TAM + RAD: 14.8 months
  - HR = 0.46 (0.26-0.83)
  - p = 0.0087 (exploratory analysis)



Bachelot T, et al. J Clin Oncol. 2012;22(30):2718-2724

Candidate Markers for Everolimus Efficacy

Canonical pathway

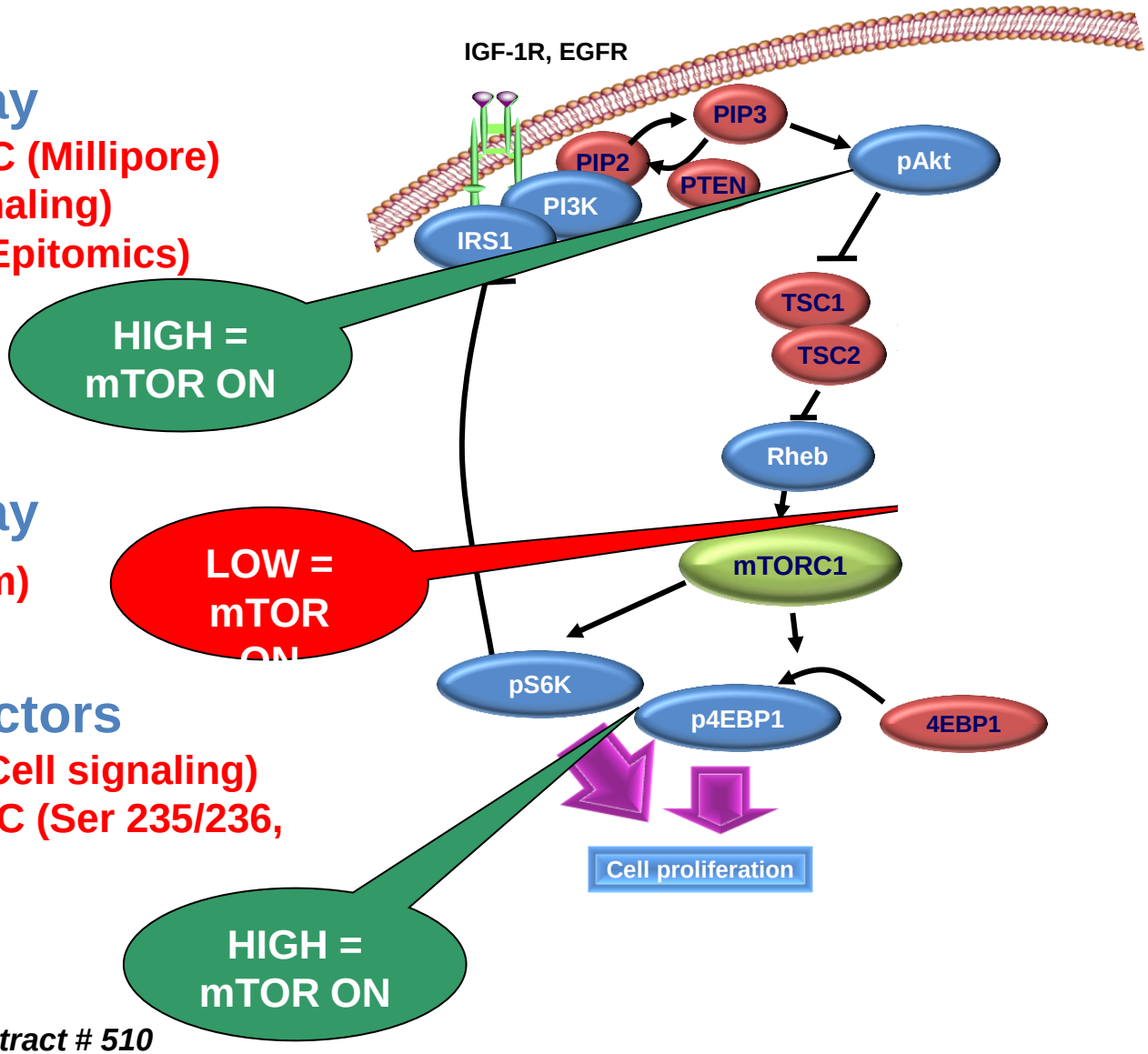
- PI3K: mutation & IHC (Millipore)
- PTEN: IHC (Cell signaling)
- pAkt: IHC (Ser 473, Epitomics)
- KRAS: mutation

Metabolic Pathway

LKB1: IHC (Abcam)

Downstream effectors

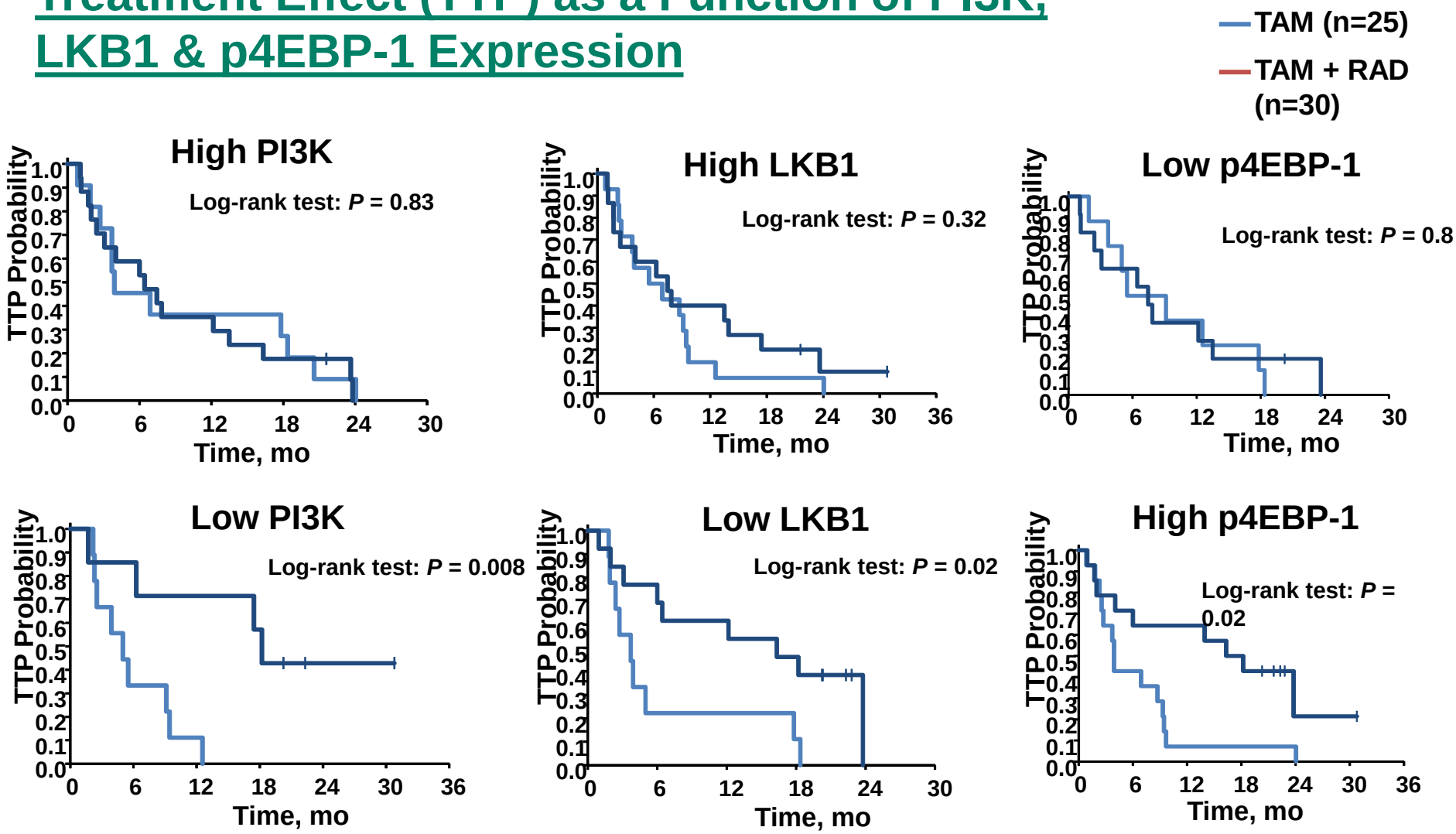
- pS6K: IHC (Ser 65, Cell signaling)
- 4EBP1 / p4EBP1: IHC (Ser 235/236, Cell signaling)



IHC= immunohistochemistry.

Arnedos M, et al. ASCO 2013 Abstract # 510

Treatment Effect (TTP) as a Function of PI3K, LKB1 & p4EBP-1 Expression



Arnedos M, et al. ASCO 2013 Abstract # 510; Treilleuz et al, Ann Onc 2015

HER2+ Breast Cancer
BOLERO-3: Study Design

Together For A Cancer-Free Tomorrow

National Cancer Centre Singapore
SingHealth

Phase 3 Study

N = 569

- Locally advanced or metastatic HER2$^+$ breast cancer
- Prior taxane required

R
1:1

Treatment Groups

Everolimus (5 mg PO daily) + Vinorelbine (25 mg/m^2 weekly) + Trastuzumab (2 mg/kg weekly†) (n = 284)

Placebo (PO daily) + Vinorelbine (25 mg/m^2 weekly) + Trastuzumab (2 mg/kg weekly†) (n = 285)

Therapy until PD or intolerable toxicity

- **Stratification by prior lapatinib use (yes/no)**

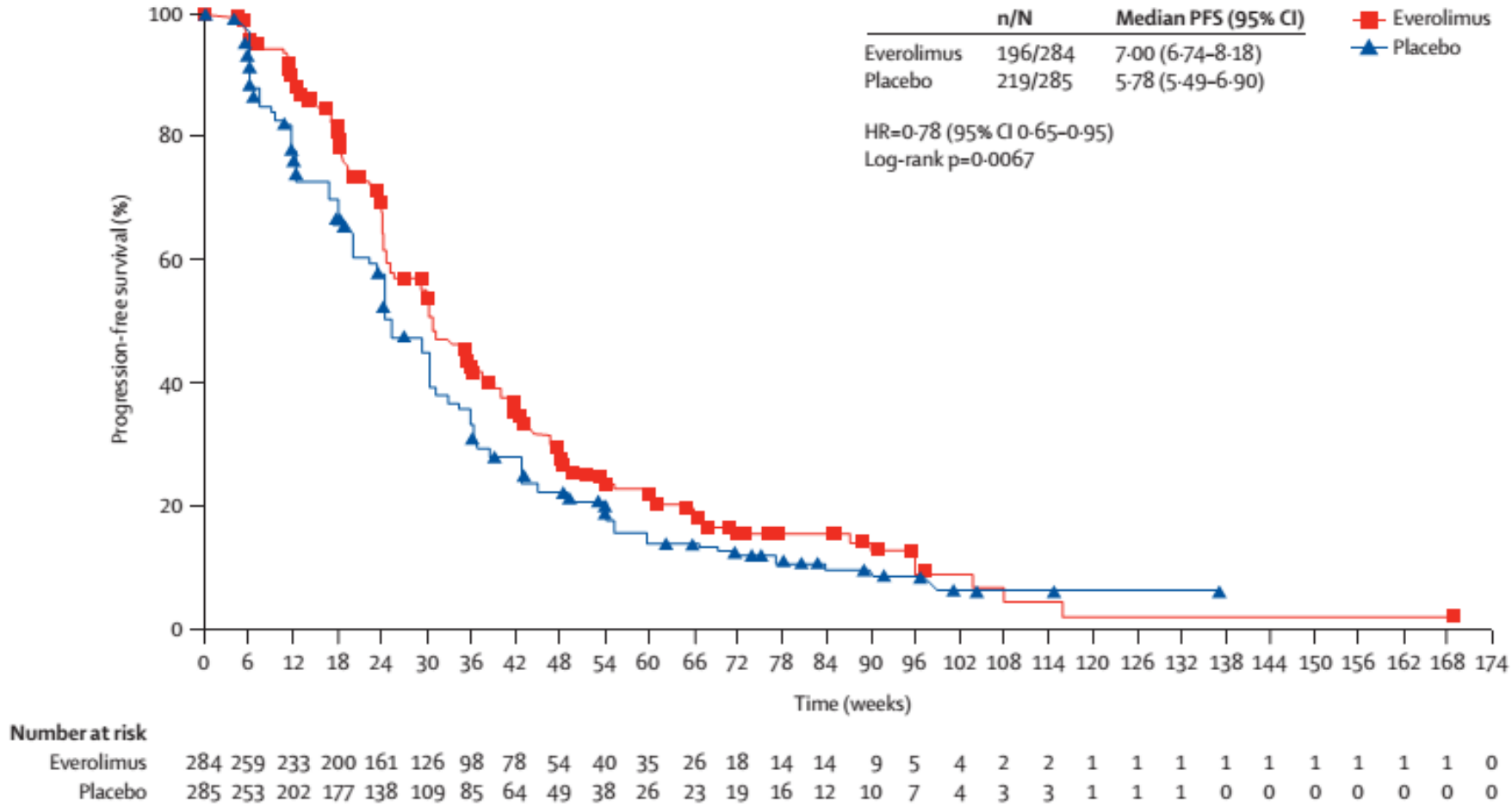
Follow-up/Survival

Key Endpoints:
- Primary: PFS
- Secondary: OS, ORR, time to deterioration of ECOG PS, safety, DoR, CBR, and QoL

*Resistance to prior trastuzumab required
†Following a 4-mg/kg loading dose on day 1, cycle 1 (1 cycle = every 21 days).
Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; EVE, everolimus; PD, progressive disease; PO, oral; PS, performance status; QoL, quality of life; TRAS, trastuzumab.
http://www.clinicaltrials.gov/ct2/show/NCT01007942?term=BOLERO3&rank=1

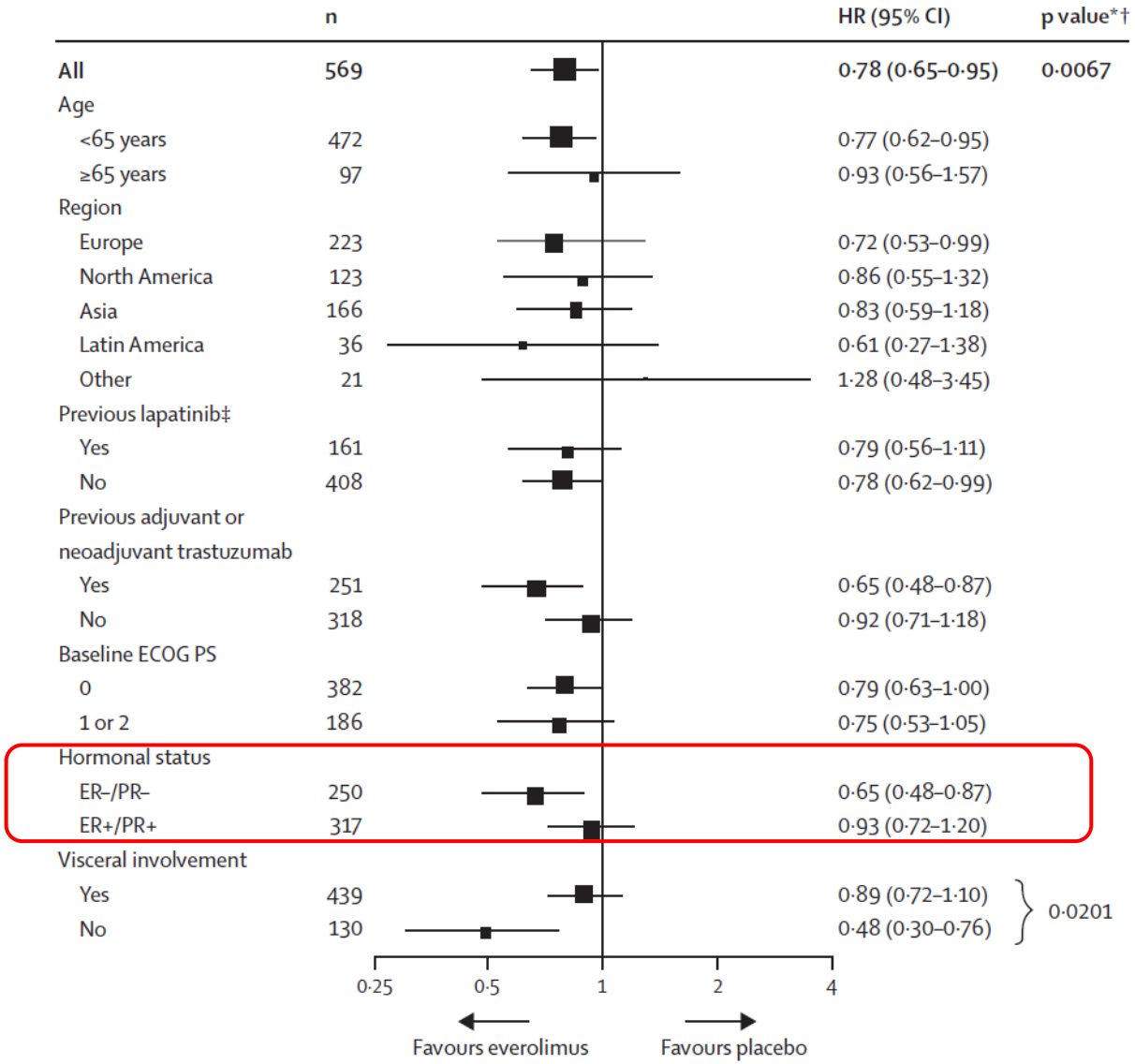
Presented by: Ruth M. O'Regan, ASCO 2013

BOLERO-3: PFS Results



Andre et al, Lancet Oncology 2014

BOLERO-3: Forest plot of PFS

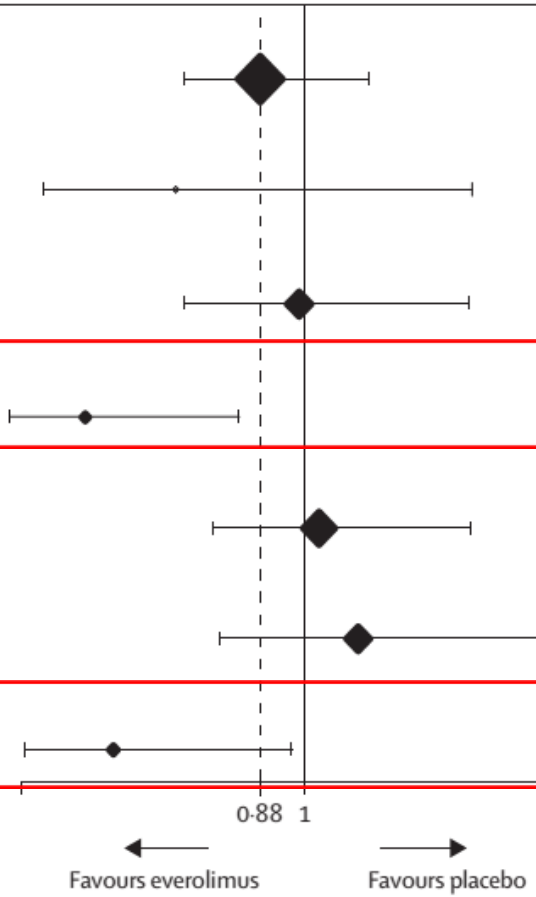


PFS according to pS6, PTEN, and PIK3CA status in patients with assessable biomarker data (BOLERO-3)

Together For A Cancer-Free Tomorrow

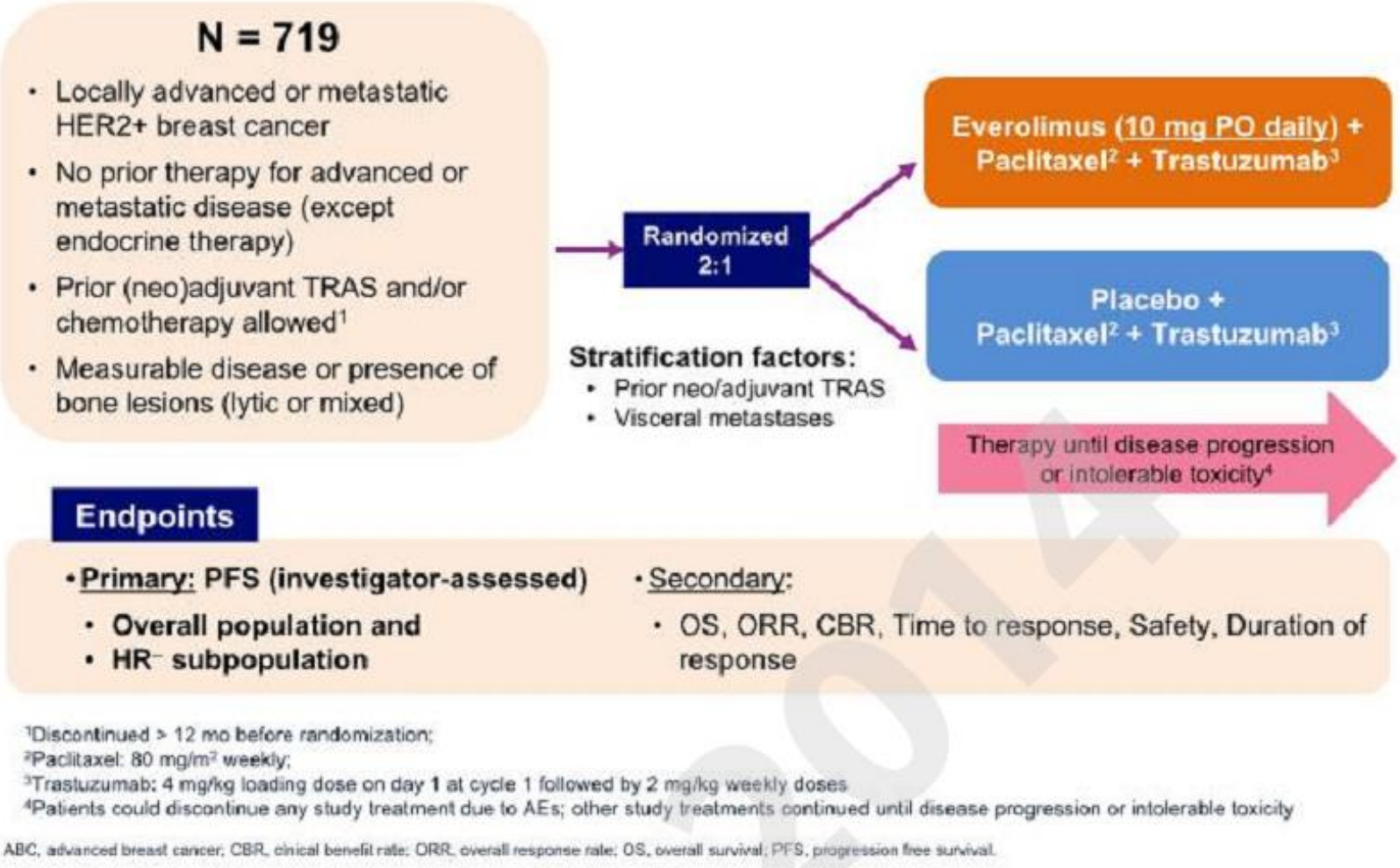
National Cancer Centre Singapore
SingHealth

	n	PFS events	Median PFS (95% CI)	HR (95% CI)	p value*
Biomarker assessable					
Everolimus	130	95	7·0 (5·6–8·1)	0·88 (0·67–1·17)	..
Placebo	132	104	5·7 (5·3–6·9)		
PIK3CA mutant					
Everolimus	15	9	5·5†	0·65 (0·29–1·45)	
Placebo	21	19	6·7 (4·8–7·6)		
PIK3CA wild-type					0·32
Everolimus	69	51	6·8 (5·5–8·2)	0·98 (0·67–1·44)	
Placebo	77	56	5·7 (5·2–7·8)		
PTEN low					
Everolimus	26	16	9·6 (5·5–12·2)	0·40 (0·20–0·82)	
Placebo	22	18	5·3 (2·8–5·7)		
PTEN high					0·01
Everolimus	89	67	6·9 (5·5–8·1)	1·05 (0·75–1·45)	
Placebo	100	78	6·9 (5·5–8·3)		
pS6 low					
Everolimus	66	47	5·7 (5·4–8·3)	1·14 (0·77–1·68)	
Placebo	77	57	6·9 (5·5–8·3)		
pS6 high					0·04
Everolimus	23	15	6·8 (4·2–12·7)	0·48 (0·24–0·96)	
Placebo	22	20	3·9 (2·7–5·5)		



Andre et al, Lancet Oncology 2014

BOLERO-1/TRIO 019

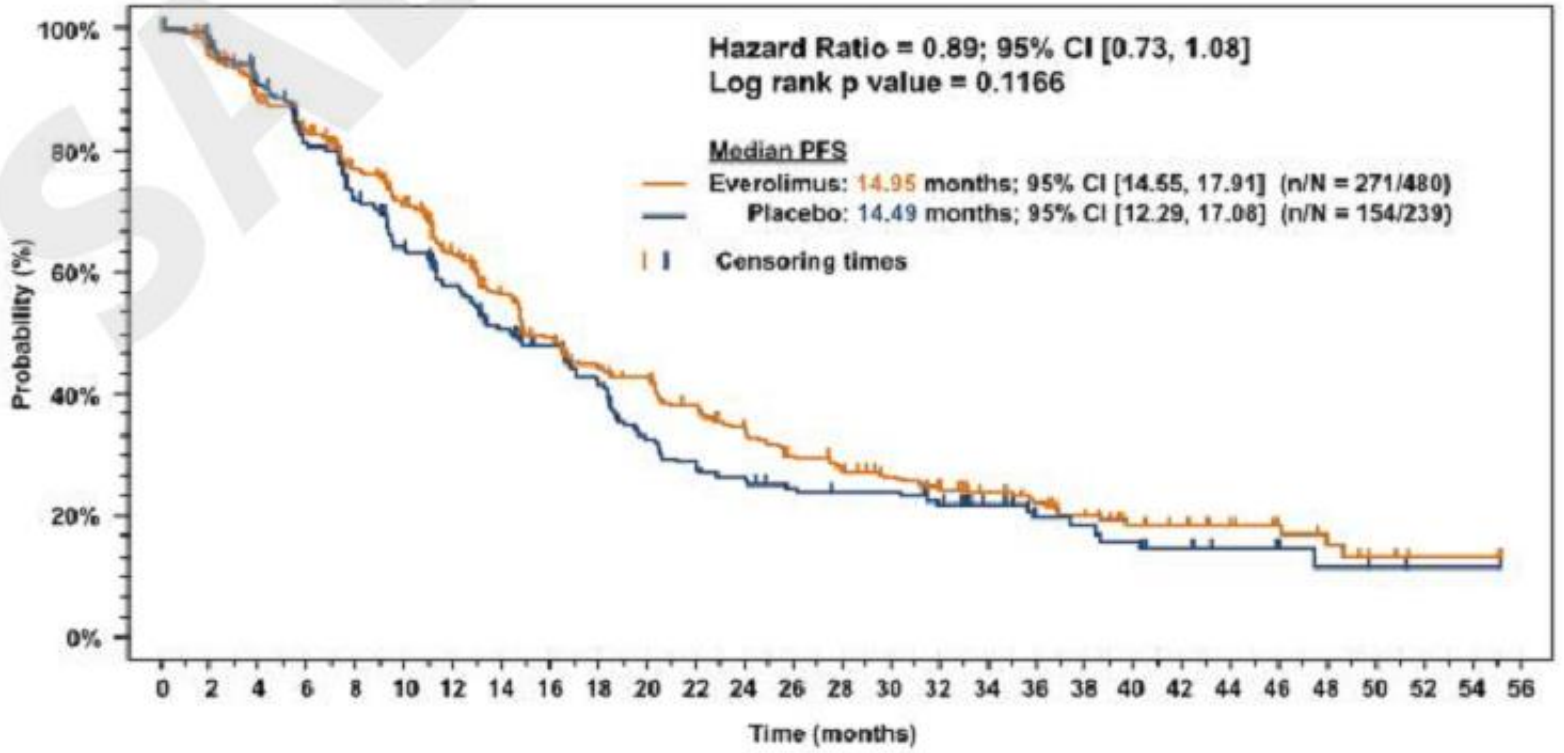


[1]Discontinued > 12 mo before randomization;
[2]Paclitaxel: 80 mg/m² weekly;
[3]Trastuzumab: 4 mg/kg loading dose on day 1 at cycle 1 followed by 2 mg/kg weekly doses
[4]Patients could discontinue any study treatment due to AEs; other study treatments continued until disease progression or intolerable toxicity

ABC, advanced breast cancer; CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Hurvitz et al, SABCS 2014

BOLERO-1/TRIO 019: PFS Full Population (Investigator-assessment)



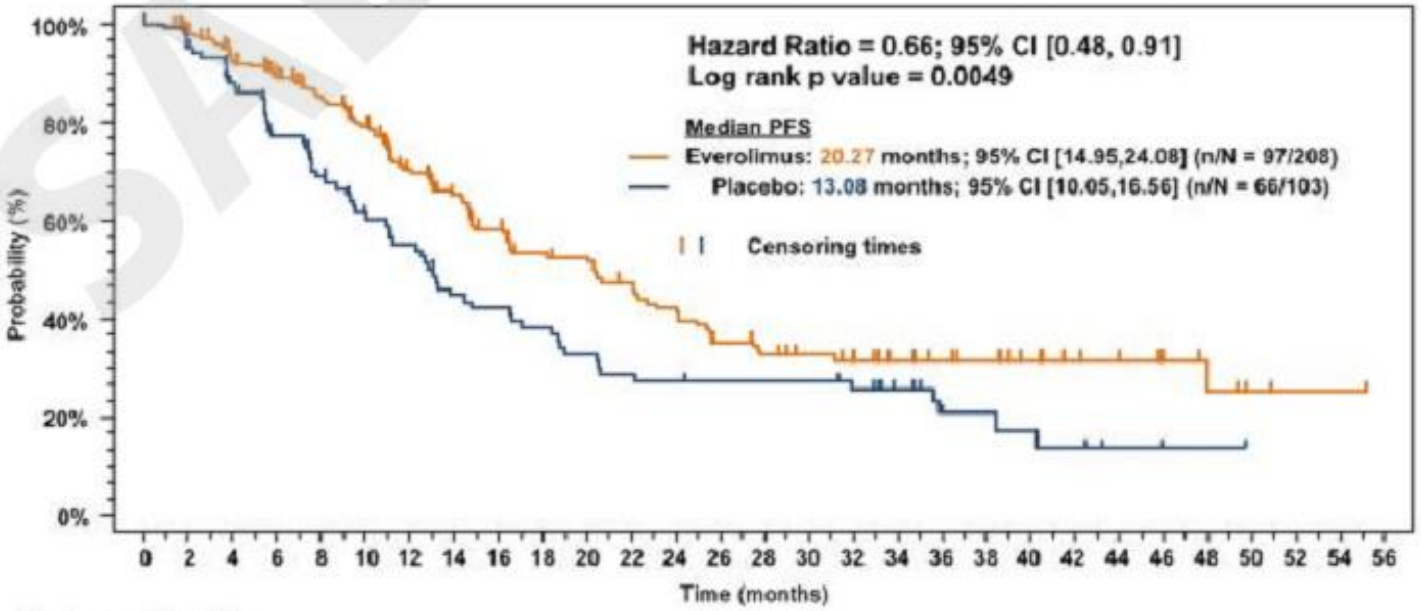
No. of patients still at risk

Everolimus	480	416	365	324	289	260	217	178	151	130	122	107	94	80	72	63	58	48	42	35	26	21	17	13	10	5	3	3	0
Placebo	239	221	199	166	144	123	106	91	80	69	53	47	43	38	36	36	31	24	17	15	12	9	7	6	4	3	1	1	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

Hurvitz et al, SABCS 2014

BOLERO-1/TRIO 019: PFS HR- Subpopulation (Investigator-assessment)



No. of patients still at risk

Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

- Sensitivity analysis without censoring patients at the start of new antineoplastic therapy:
  - Median PFS and 95% CIs
    - 20.27 mo (14.82, 24.08) for everolimus [n = 102]
    - 12.88 mo (10.94, 16.56) for placebo [n = 68]
  - HR=0.66 [0.48, 0.9], p = 0.0043

Hurvitz et al, SABCS 2014

BOLERO-1/TRIO 019:Treatment exposure

Therapy	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 472)	PBO + TRAS + PAC (N = 238)	EVE + TRAS + PAC (N = 206)	PBO + TRAS + PAC (N = 103)
Relative dose intensity (median)				
Everolimus	0.5	1	0.5	1
Trastuzumab	1	1	1	1
Paclitaxel	0.7	0.8	0.7	0.8
Duration of exposure (median, weeks)				
Everolimus	41	48	45	41
Trastuzumab	49	48	53	41
Paclitaxel	31	32	31	31

Safety profile was consistent with results previously reported: stomatitis, diarrhea, neutropaenia, anaemia etc.

Higher rate of AE-related on-treatment deaths with everolimus (3.6% vs 0%); mainly related to respiratory problems/pneumonitis.

Proactive monitoring and early management of AEs is critical.

Hurvitz et al, SABCS 2014

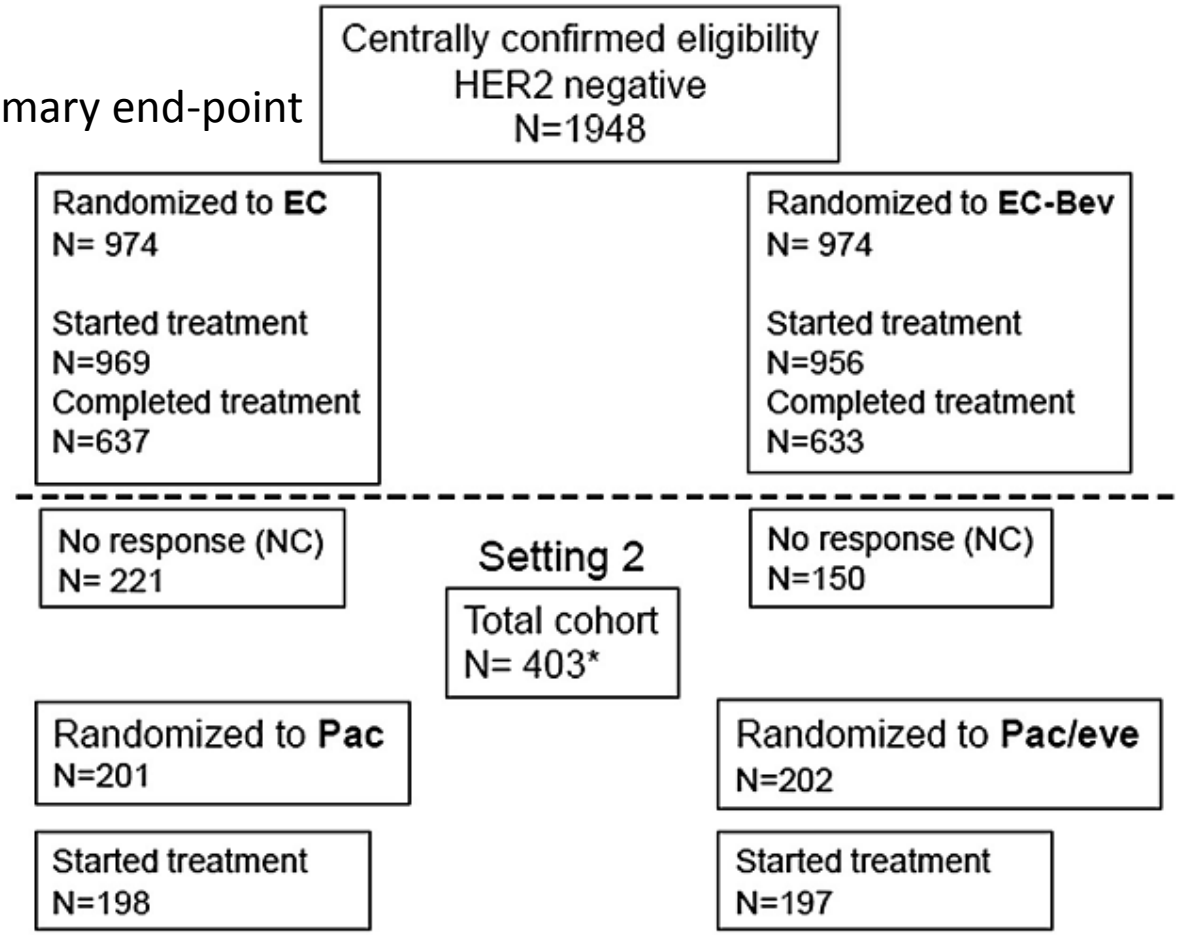
Open-label randomized clinical trial of neoadjuvant chemotherapy with paclitaxel followed by FEC versus the combination of paclitaxel and everolimus followed by FEC in triple negative breast cancer

Variables	Patients per treatment arm				*P*-value
	T-FEC ($n = 27$)		TR-FEC ($n = 23$)		
	No.	%	No.	%	
Response (12 weeks)					
Complete response	3	11.11	0	0	0.075
Partial response	5	18.82	11	47.83	
Stable disease	16	59.26	11	47.83	
Progressive disease	3	11.11	1	4.35	
Response (24 weeks)					
Complete response	4	14.81	2	8.7	0.274
Partial response	16	59.26	11	47.83	
Stable disease	7	25.93	7	30.43	
Progressive disease	0	0	3	13.04	
Pathologic complete response					
Yes	7	25.93	7	30.43	0.761
No	20	74.07	16	69.57	

Gonzalez-Angulo et al, Ann Onc 2014

Neoadjuvant chemotherapy with paclitaxel + everolimus for breast cancers not responding to EC ± bevacizumab (Geparquinto)

pCR(ypT0 ypN0):Primary end-point



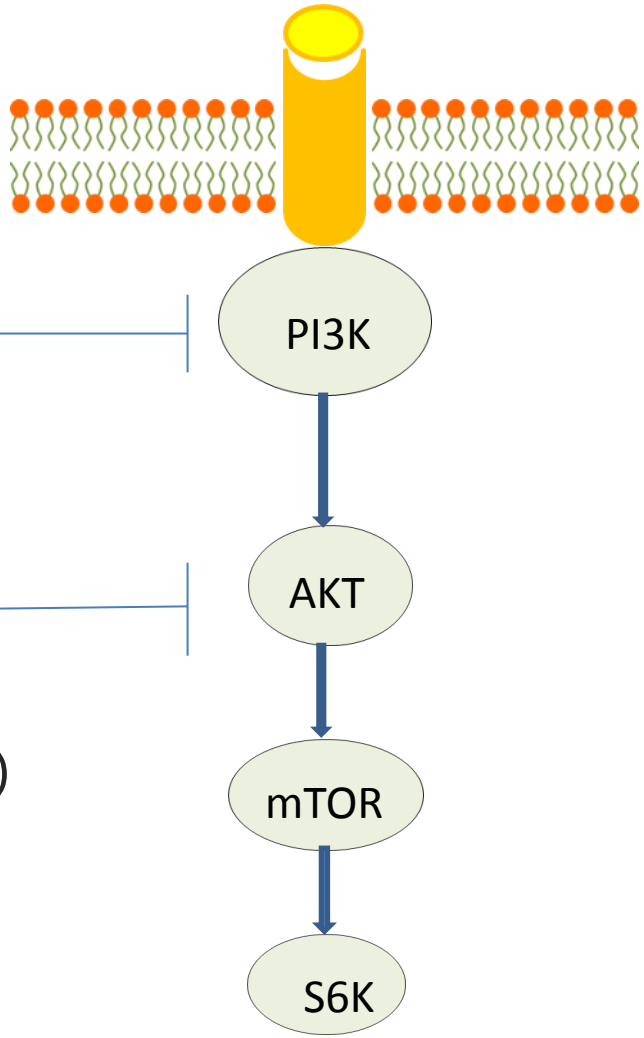
pCR: 5.6%

pCR 3.6%
P=0.476

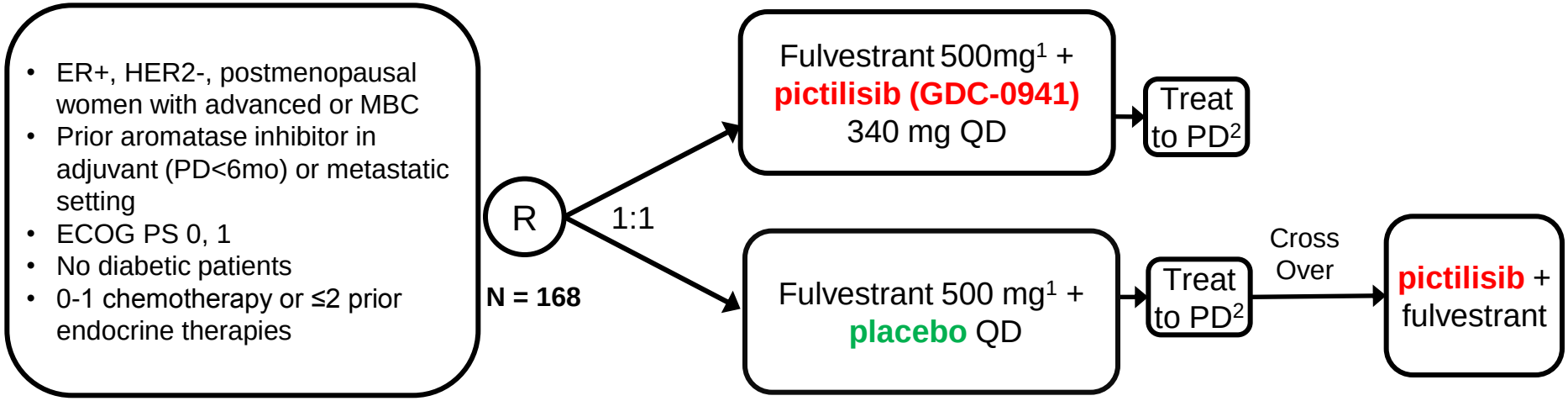
Huober et al, EJC 2013

How about targeting upstream?

- PI3K Inhibitors
- AKT Inhibitors
  (mainly Phase 1-2; no results from randomised trials currently)



FERGI Study Design – Part I



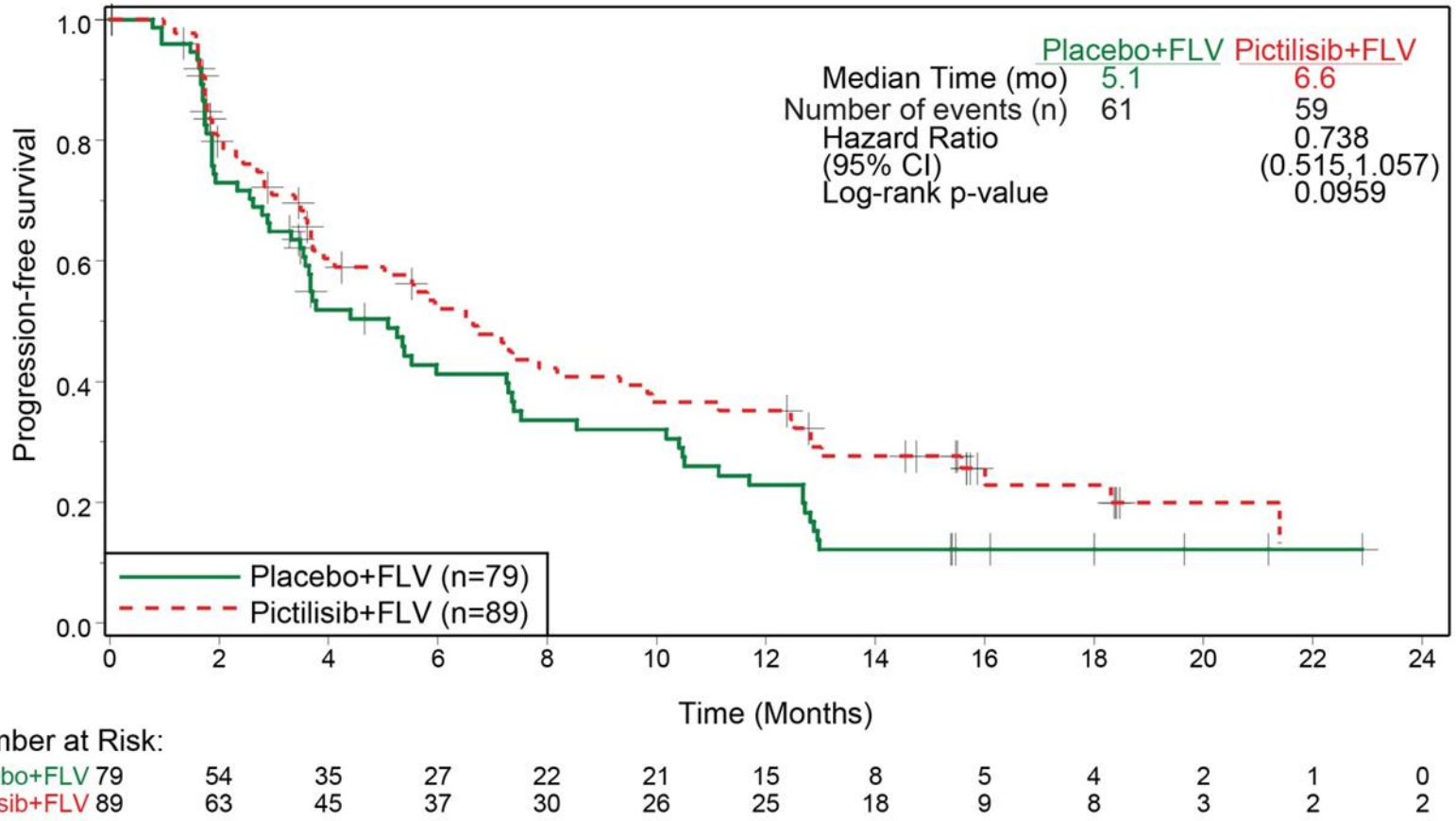
Stratification factors	1° objective	2° objectives
• *PIK3CA*-MT and *PTEN* loss[3] • Measurable disease • 1º vs. 2º resistance[4]	• PFS in the ITT • PFS in *PIK3CA*-MT pts • Safety	• Objective response rate • Duration of objective response • PK

[1] Administered on D1 of each 28 day cycle and C1D15; [2] Tumor assessments performed every 8 weeks; [3]Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 were detected by RT-PCR; [4] Disease relapse during or within 6 months of completing AI treatment in the adjuvant setting, or disease progression within 6 months of starting AI treatment in the metastatic setting. [5] Data presented is with an additional year of follow up per-protocol primary analysis

- Median duration of follow up 17.5 months

Courtesy of Dr. Ian Krop, SABCS 2014

Progression-Free Survival in the ITT Population



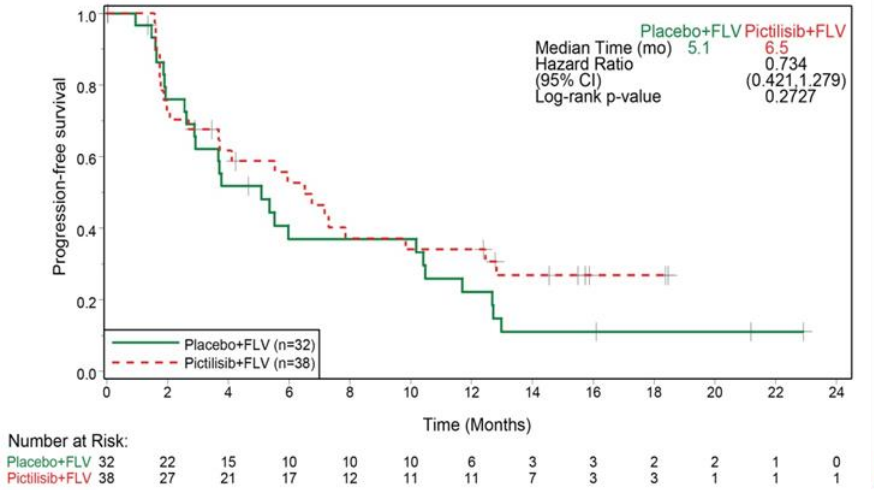
Number at Risk:

Placebo+FLV	79	54	35	27	22	21	15	8	5	4	2	1	0
Pictilisib+FLV	89	63	45	37	30	26	25	18	9	8	3	2	2

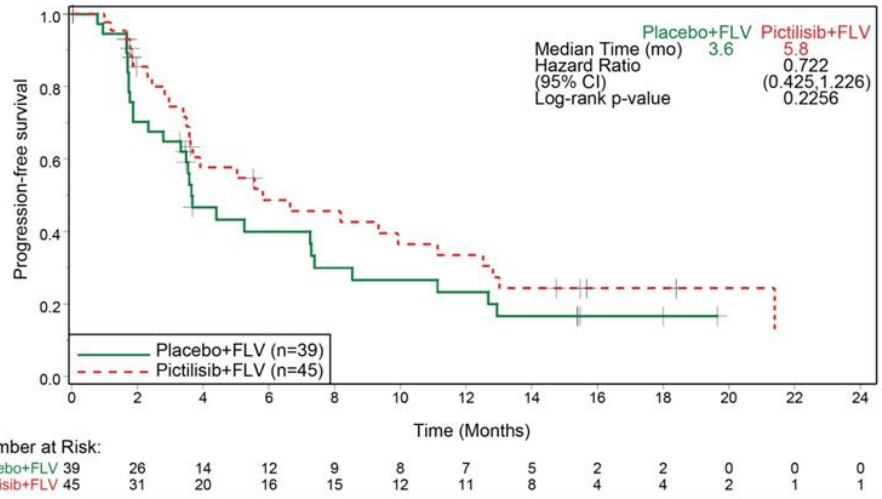
Courtesy of Dr. Ian Krop, SABCS 2014

Progression-Free Survival based on Tumor *PIK3CA* Mutation Status

PIK3CA-Mutant Population



PIK3CA "Wild-Type" Population

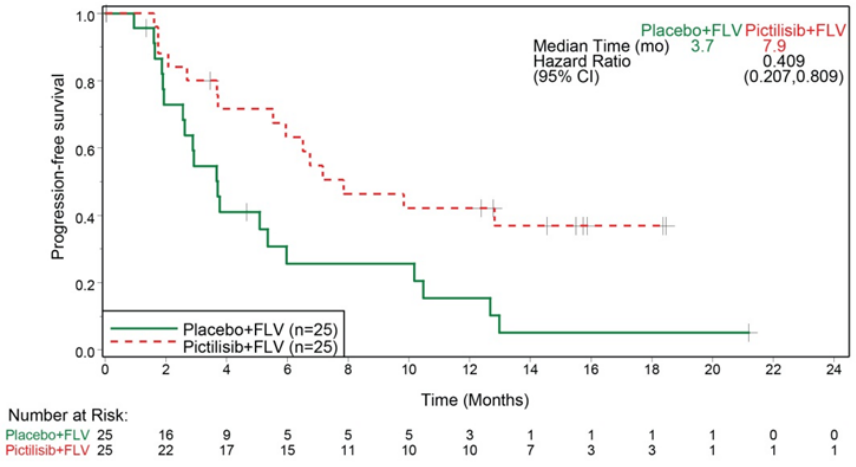


- PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant

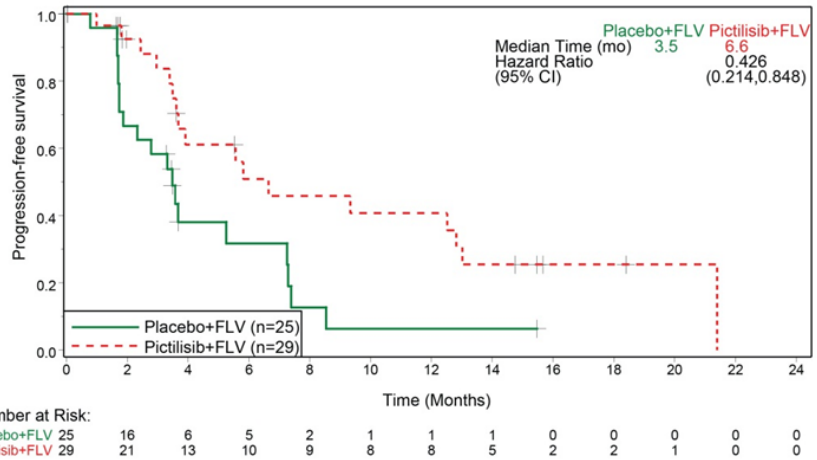
Courtesy of Dr. Ian Krop, SABCS 2014

Progression-Free Survival in Patients with ER and PR Positive Disease Based on Tumor *PIK3CA* Mutation Status

PR+ and *PIK3CA* mutation



PR+ and *PIK3CA* "Wild-Type"



Courtesy of Dr. Ian Krop, SABCS 2014

AEs Related to Any Study Drug

	Pictilisib (n=89)		Placebo (n=79)	
Adverse Event[1,2]	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Diarrhea	56 (63%)	5 (7%)	7 (9%)	-
Nausea	43 (48%)	3 (3.4%)	15 (19%)	-
Rash[3]	38 (43%)	15 (17%)	5 (6%)	-
Dysgeusia	31 (35%)	-	-	-
Fatigue	24 (27%)	5 (6%)	16 (20%)	-
Vomiting	18 (20%)	3 (3%)	3 (4%)	-
Decreased appetite	17 (19%)	1 (1%)	5 (6%)	-
Hyperglycemia	15 (17%)	4 (5%)	4 (5%)	-
Stomatitis	14 (16%)	2 (2%)	2 (2%)	-
Hot flush	10 (11%)	-	10 (13%)	-
AST increased	10 (11%)	3 (3%)	7 (8%)	2 (3%)
Dyspepsia	8 (9%)	-	2 (3%)	-
Mucosal inflammation	9 (10%)	-	2 (3%)	-
Pneumonitis	7 (8%)	1 (1%)	1 (1%)	-
Colitis	4 (5%)	3 (3%)	-	-

[1]Adverse events independent of attribution; based on CTCAE v.3
[2]Adverse events >10% except pneumonitis and colitis
[3]Includes all rash, generalized, maculo-papular, pruritic, erythematous and papular rash

- There were 28 (31%) SAEs in treatment arm vs 16 (20%) in placebo arm
- Safety is consistent with our single agent phase I experience
- No drug-drug interaction between pictilisib and fulvestrant
- There were no treatment related deaths reported

Courtesy of Dr. Ian Krop, SABCS 2014

Patient Disposition

	Pictilisib	Placebo
Randomized (ITT)	89	79
Treated (Safety evaluable)	89	79
Discontinued pictilisib/placebo[1]	80 (90%)	69 (87%)
Disease progression	50 (56%)	57 (72%)
Non-PD	30 (34%)	12 (15%)
Adverse Events	16 (18%)	2 (2.5%)
Protocol-violation	0	1 (1%)
Withdrawal by subject	5 (6%)	4 (5%)
Physician Decision	8 (9%)	5 (6%)
Other	1 (1%)	0
Discontinued fulvestrant for non-PD[1]	18 (20%)	15 (19%)
Dose reduction for an AE[2]	21 (24%)	1 (1%)

[1]From treatment discontinuation eCRFs
[2]From AE eCRFs

- High rate of discontinuation of pictilisib for non-PD events, most occurred in the early cycles

Courtesy of Dr. Ian Krop, SABCS 2014

PI3K Inhibitors in breast cancer

- PI3K mutation status not predictive of benefit?
  - Archived tissues? Not reflective of latest PI3K mutation status?
  - Other biomarkers?
    - PTEN, LKBP, pS6 etc?
  - Circulating markers?; tumour heterogeneity and evolution

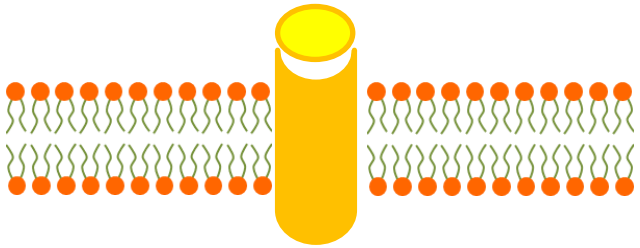
- Toxicity Issues
- Some similarities with mTOR inhibitors

- Are all PI3K inhibitors the same?

Phase I-III trials in Breast Cancer and/or Solid Tumours

Together For A Cancer-Free Tomorrow

National Cancer Centre Singapore
SingHealth



Pan PI3K	Isoform-selective(α/β)
BKM120	BYL719(α)
GDC0941	GDC0032(α)
BAY1082439	MLN1117 (α)
BAY80-6946	SAR260301(β)
ZSTK474	AZD8186(β)
PX-866	GSK2636771(β)
XL147	
CH5132799	
WX-037	
CUDC-907	

PI3K/mTOR	
BEZ235	PF-05212384
BGT226	PF-04691502
GDC-0980	GSK2126458
XL765	GSK1059615
LY3023414	DS7423
VS5584	SF1126

AKT1/2/3	
MK2206	Perifosine
GDC0068	BAY1125976
GSK2141795	ARQ 092
AZD5363	

mTORC1	mTORC1 and 2
Everolimus	AZD2014
Sirolimus	AZD8055
Temsirolimus	MLN0128
Ridaforolimus	OSI-027
	CC-223
	DS-3078a

AKT/p70S6 kinase
LY2780301

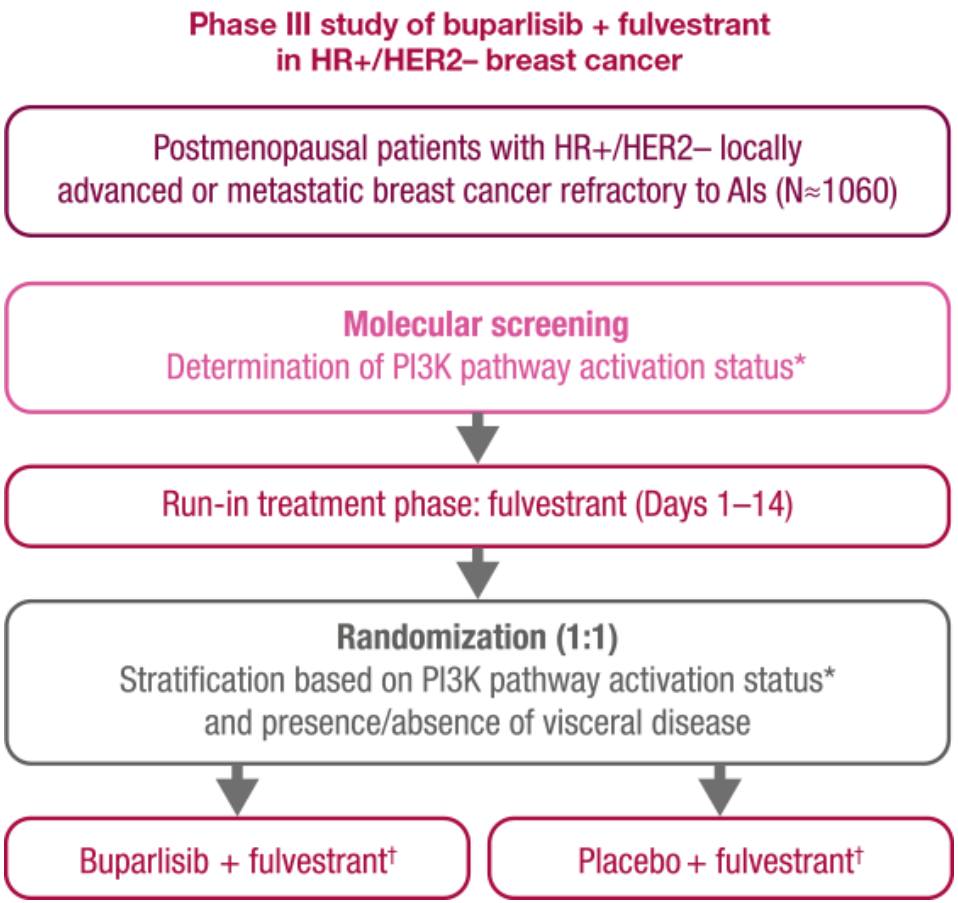
Not all PI3K/AKT/mTOR Inhibitors are the same!

https://www.clinicaltrials.gov/

Are all PI3K/AKT/mTOR Inhibitors the same?

- Different targets, different selectivity for various isoforms
- Different pharmacology
- Optimal dosing schedule?
- Any differences in toxicity profile?

BELLE-2 Study



Endpoints

Primary end point

- Progression-free survival‡

Key secondary end point

- Overall survival‡

Other Secondary endpoints

- Progression-free survival§
- Overall survival§
- Objective response rate‡,§
- Clinical benefit rate‡,§
- Time to ECOG PS deterioration‡,§
- Safety
- Pharmacokinetic profile
- Quality of life

Toxicities

Toxicity profile may vary with different agents.

- Metabolic: hyperglycaemia, hyperlipidaemia
- Dermatological: rash, photosensitivity
- Gastrointestinal: mucositis, nausea/vomiting, diarrhoea, transaminitis
- Respiratory: pneumonitis
- Haematological: cytopaenias, immunosuppression, infections
- Constitutional: fatigue, anorexia

Possible drug interactions.

Optimal management of adverse effects is crucial for safety and compliance.

Overcoming Resistance

Potential Combinations

- PI3K/AKT/mTOR Inhibitor and Endocrine therapy
- PI3K/AKT/mTOR Inhibitor and anti-HER2 therapy +/- endocrine therapy?
- PI3K/AKT/mTOR Inhibitor and Chemotherapy
- PI3K inhibitor and mTOR Inhibitor
- PI3K/AKT Inhibitor and MEK Inhibitor
- PI3K Inhibitor and PARP Inhibitor
- PI3K Inhibitor and CDK Inhibitor
- PI3K Inhibitor and immunotherapy?
- Etc

Conclusions

- PI3K/AKT/mTOR Inhibitors have activity in breast cancer; clinical efficacy data is mainly in the setting of hormone receptor+, HER2- subtype for now. In HER2+ disease, benefit is seen mainly in ER- subset (BOLERO-1 and 3).
- Several other clinical trials in progress.
- Biomarkers predictive of benefit are currently unclear.
- Combination therapy with other agents may be more efficacious, though clinical data is awaited.
- Toxicity can be an issue; need to monitor and manage appropriately.

Together For A Cancer-Free Tomorrow

National Cancer Centre Singapore
SingHealth

Thank you for your attention!