New Targeted Agents in Luminal Breast Cancer

Jose Baselga, MD, PhD
Associate Director, Massachusetts General Hospital Cancer Center
Chief, Division of Hematology/Oncology
Professor of Medicine, Harvard Medical School

HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

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Physician in Chief

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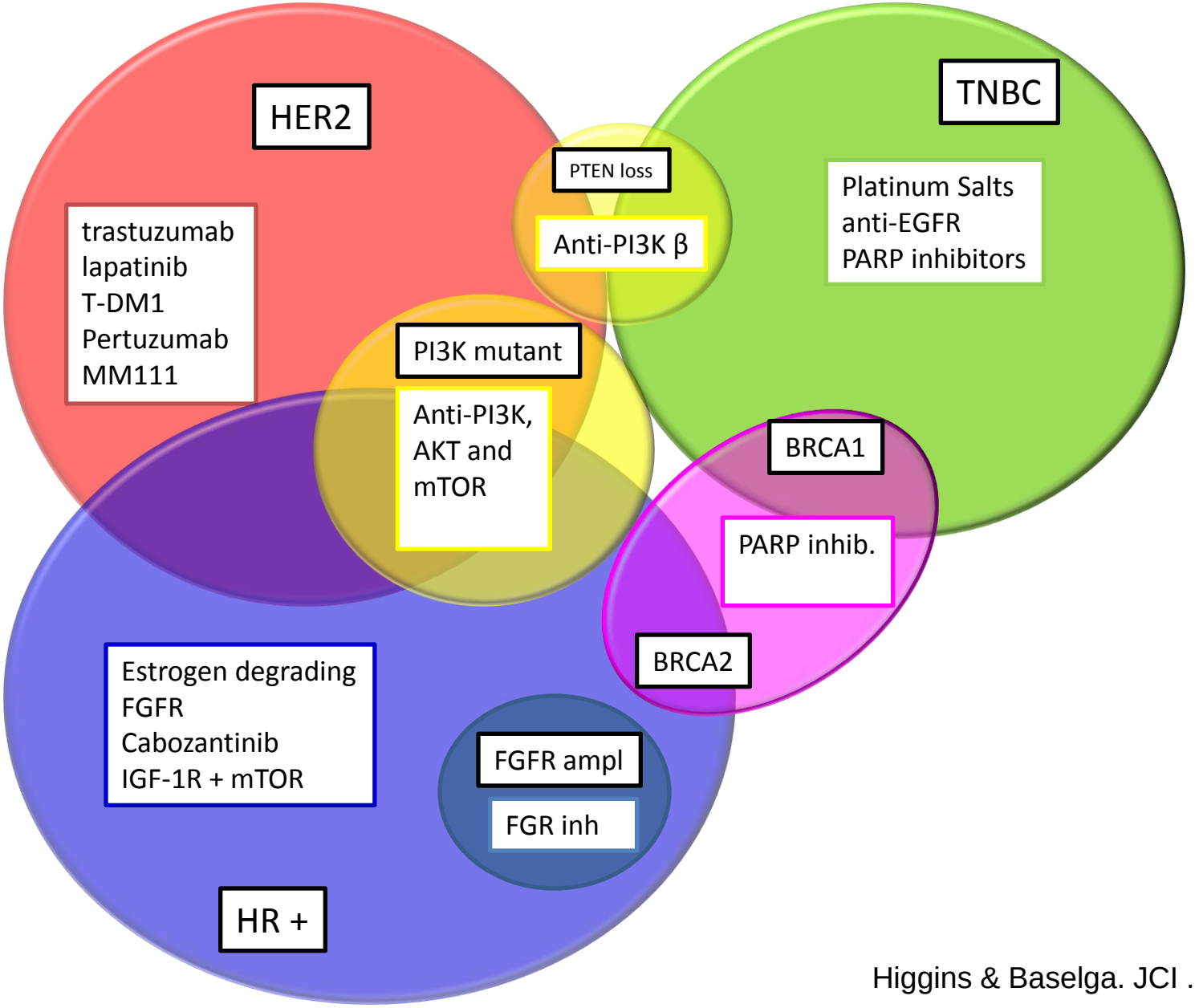
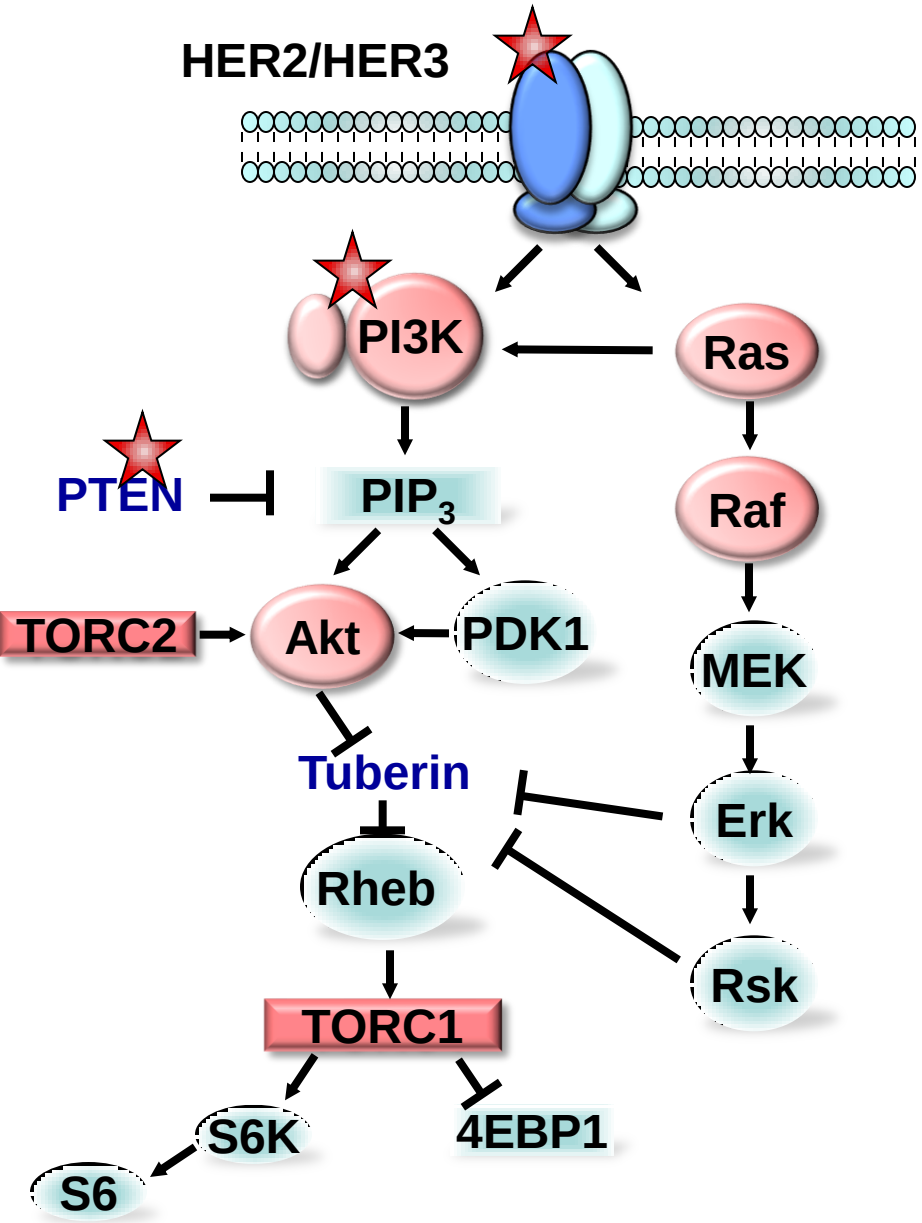
MEMORIAL SLOAN-KETTERING CANCER CENTER
ESTABLISHED 1884

Targeted therapies for breast cancer subtypes



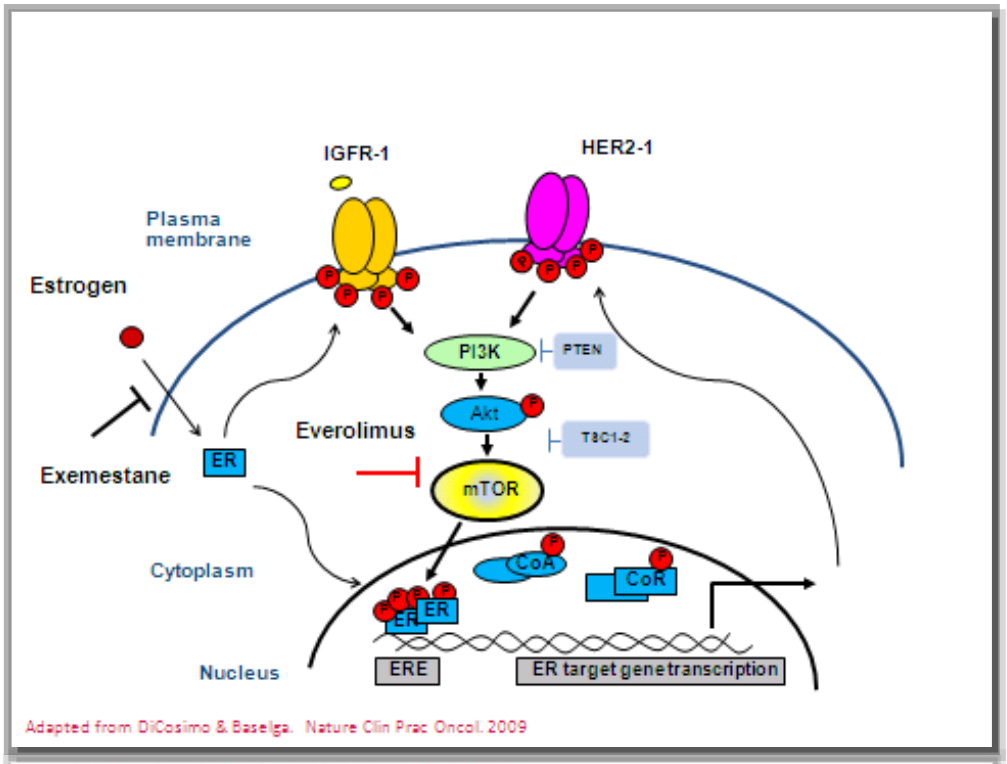
Higgins & Baselga. JCI . 2011

The PI3K/Akt/mTOR pathway and Breast Cancer



- Constitutive activation of the PI3K pathway is frequent.
- PI3K pathway activation conveys malignant transformation, cell growth and invasion, tumor neoangiogensis and resistance towards anti-cancer treatments.
- Known mechanisms of PI3K pathway activation include activating mutations of RTKs, gain-of-function mutation of the PIK3CA gene, and loss-of-function mutations of PTEN.

Crosstalk between ER and mTOR Signaling



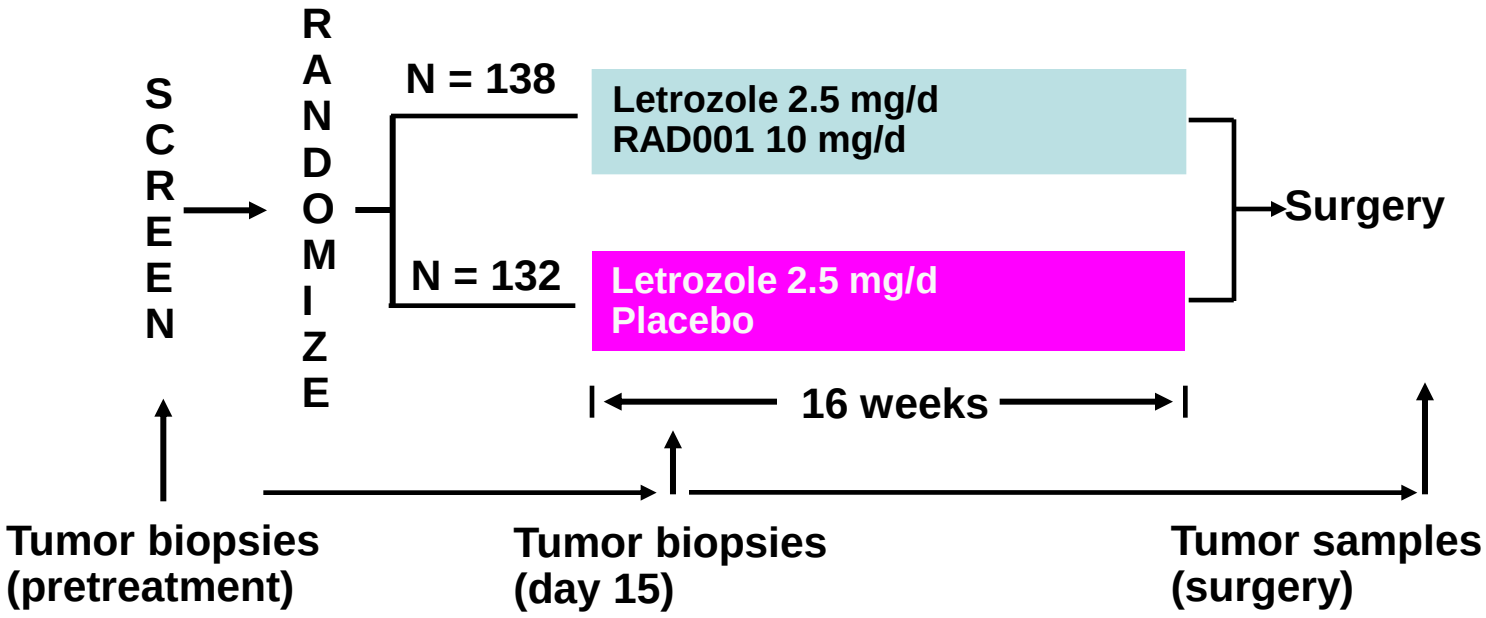
Adapted from DiCosimo & Baselga. Nature Clin Prac Oncol. 2009

- mTORC1 activates ER in a ligand-independent fashion[1]
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade[2]
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells[3]
- mTOR is a rational target to enhance the efficacy of hormonal therapy

1. Yamnik, RL. J Biol Chem 2009; 284(10):6361-6369.
2. Crowder, RJ. Cancer Res 2009;69:3955-62.
3. Miller, TW. J Clin Invest 2010; 120(7):2406-2413.

Phase II neoadjuvant everolimus (RAD001) breast cancer study

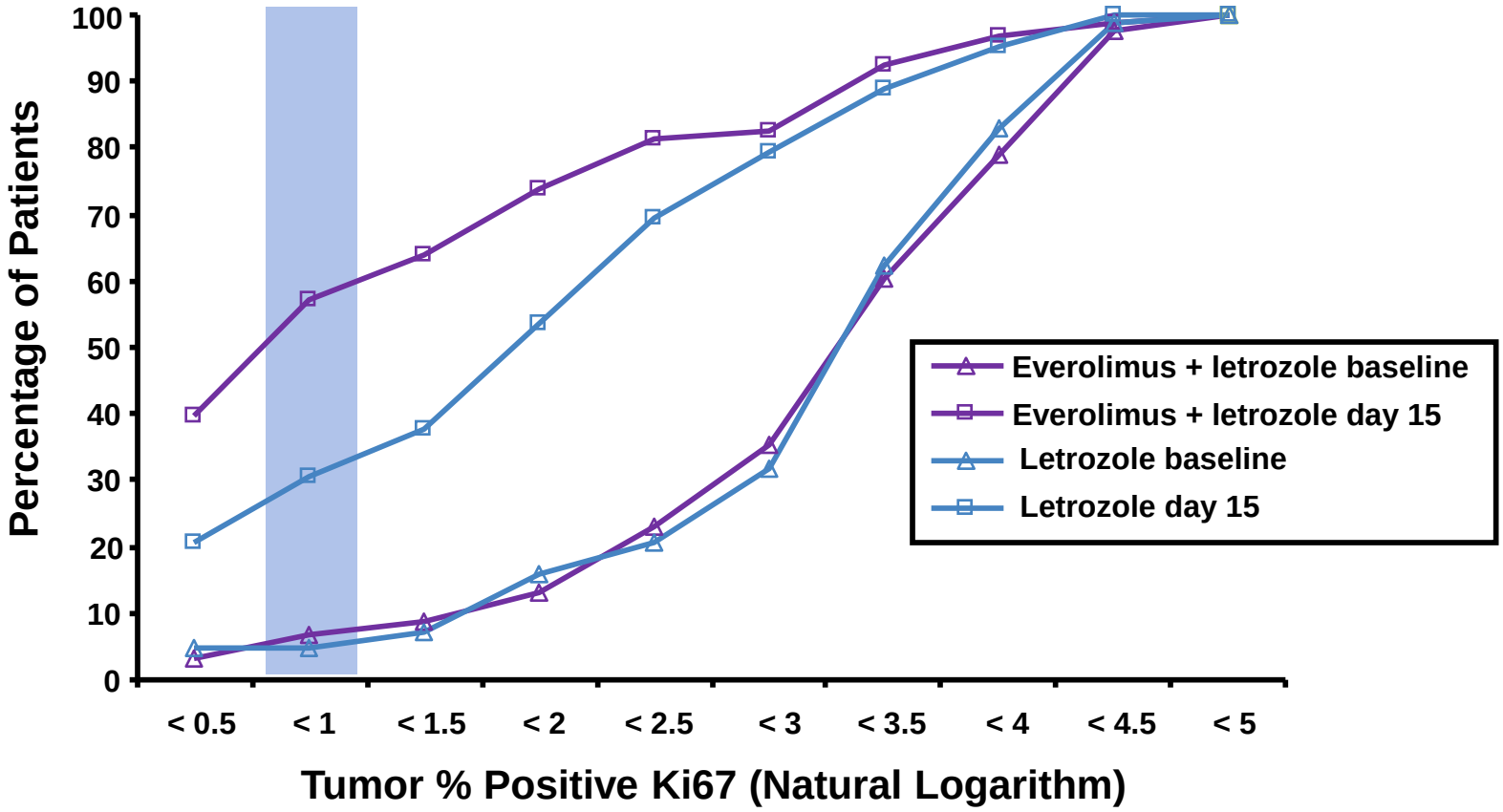
- Newly diagnosed, untreated patients with ER^+ localized breast cancer likely to benefit from hormonal therapy
- Palpable tumor: > 2 cm diameter



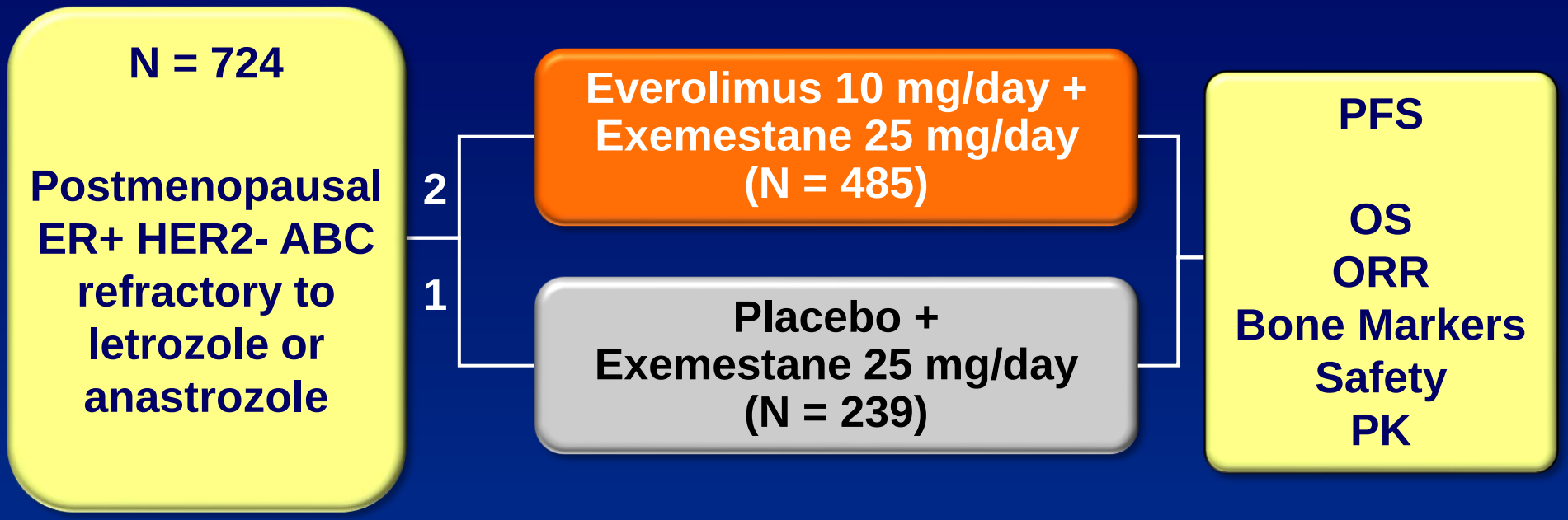
Baselga *et al*. J Clin Oncol. 2009

Phase II neoadjuvant everolimus (RAD001) breast cancer study – Change in Ki67

- At day 15, a large difference in Ki67 values is seen between the everolimus + letrozole and the placebo + letrozole arms, which was not seen at baseline



BOLERO-2: Trial Design

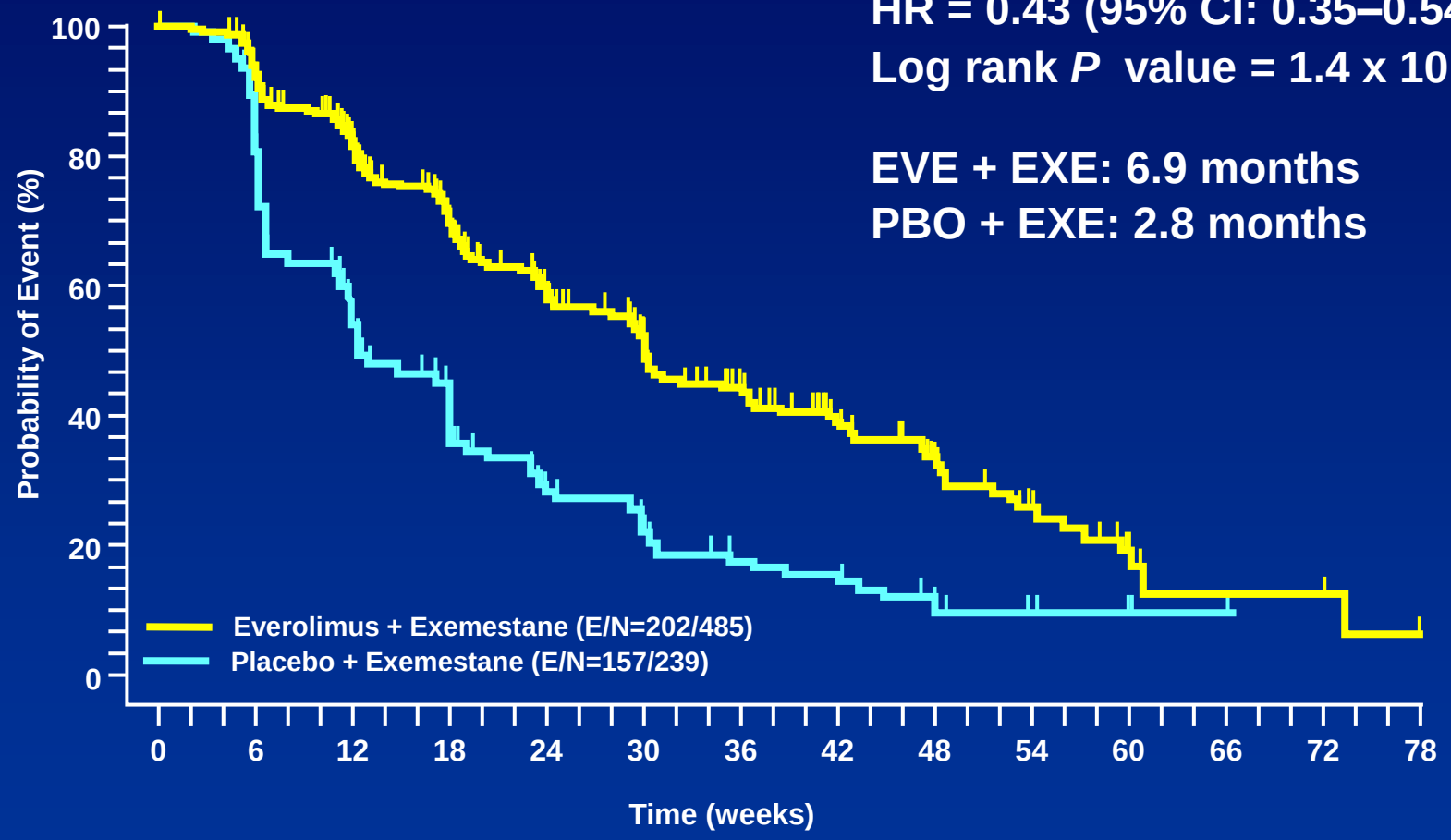


- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
- No cross-over

ABC: advanced breast cancer, NSAI: non steroidal aromatase inhibitors, HER2-: human epidermal growth factor receptor 2 – negative; PFS: progression-free survival; PK: pharmacokinetics

Baselga J *et al*. N Engl J Med. 2012

BOLERO-2 Primary Endpoint: PFS Local Assessment



No. of Patients Still at Risk:

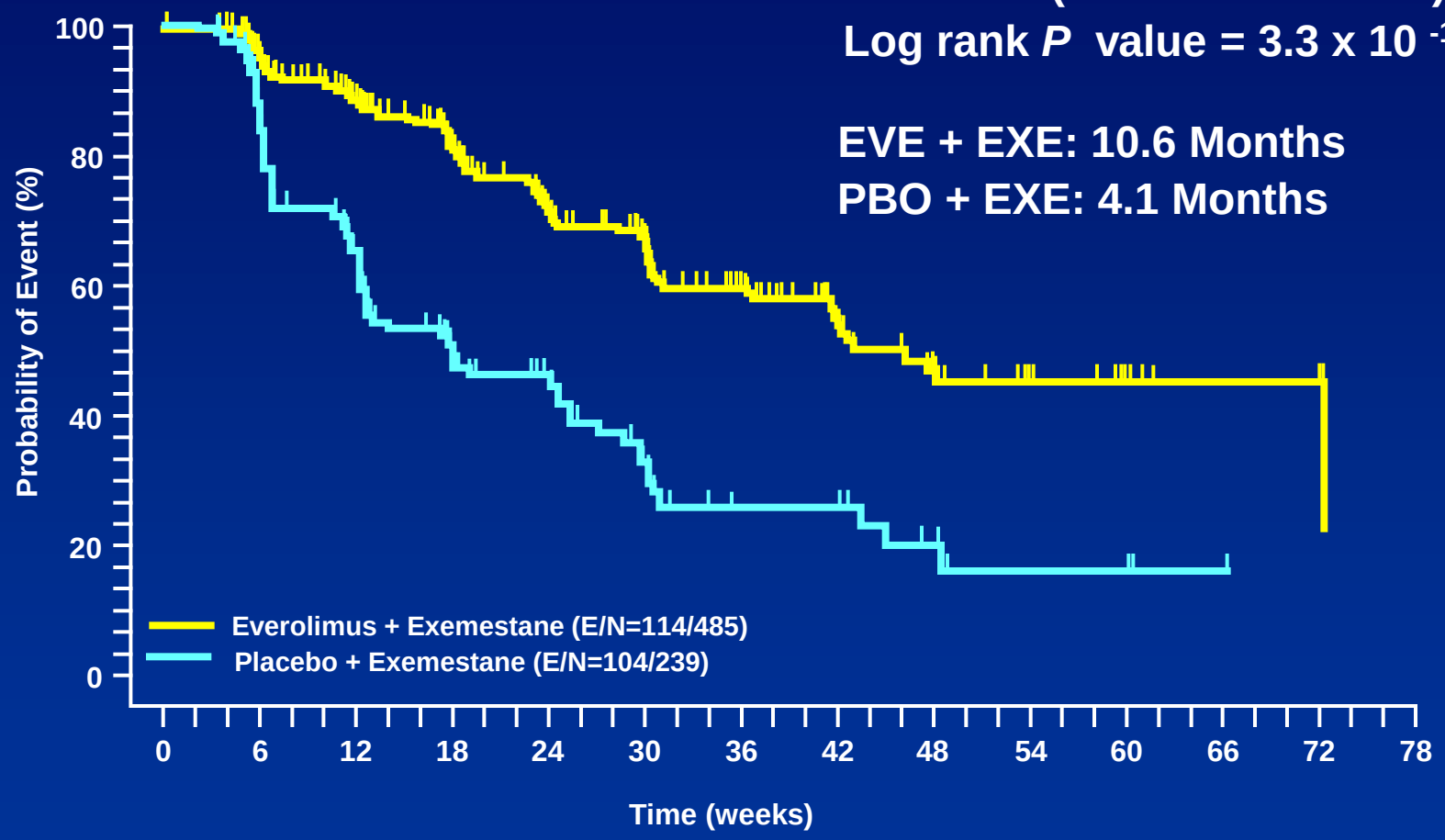
Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

Baselga J *et al*. N Engl J Med. 2012

BOLERO-2 Primary Endpoint: PFS Central Assessment

HR = 0.36 (95% CI: 0.27–0.47)
Log rank *P* value = 3.3 x 10^{-15}

EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

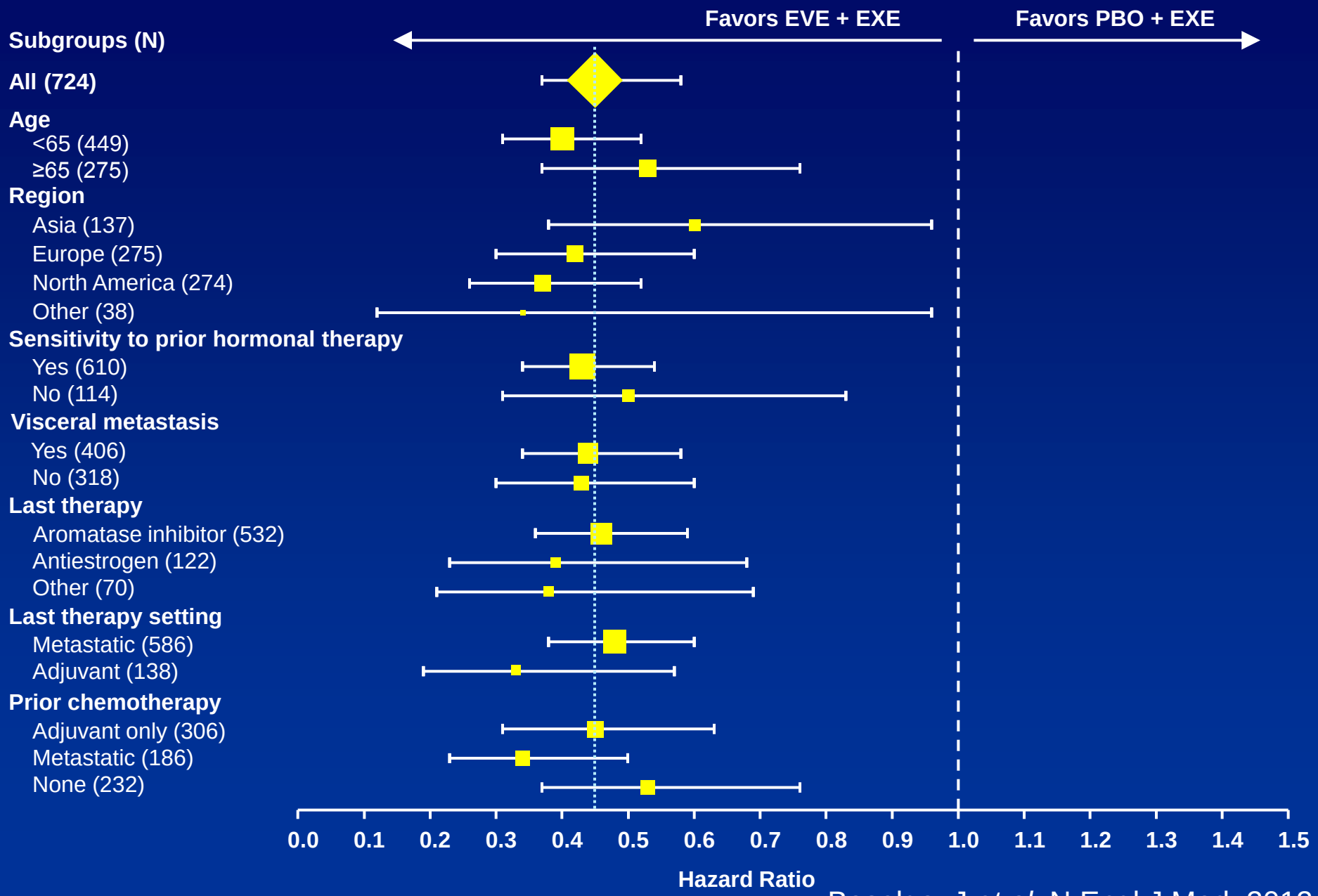


No. of Patients Still at Risk:

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

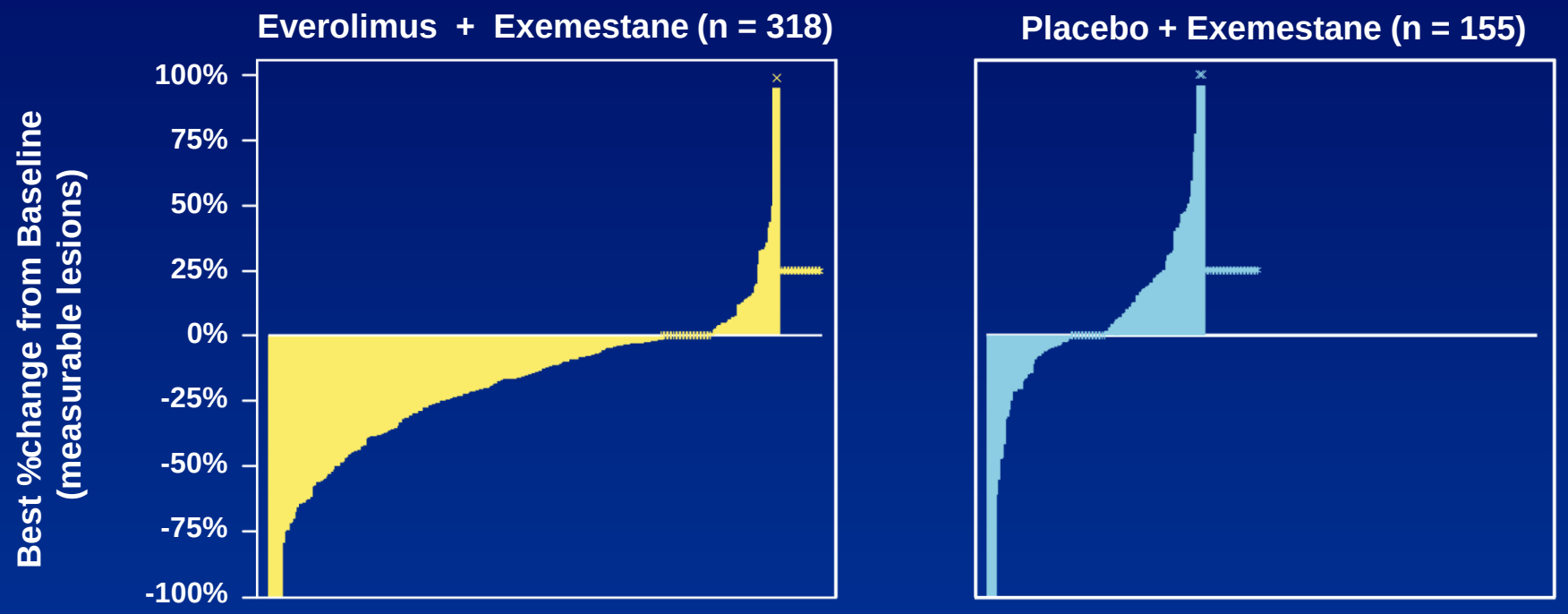
Baselga J *et al*. N Engl J Med. 2012

BOLERO 2: PFS Subgroup Analyses



Baselga J *et al*. N Engl J Med. 2012

BOLERO-2 (Longer Term Data): Reduction in Tumor Volume

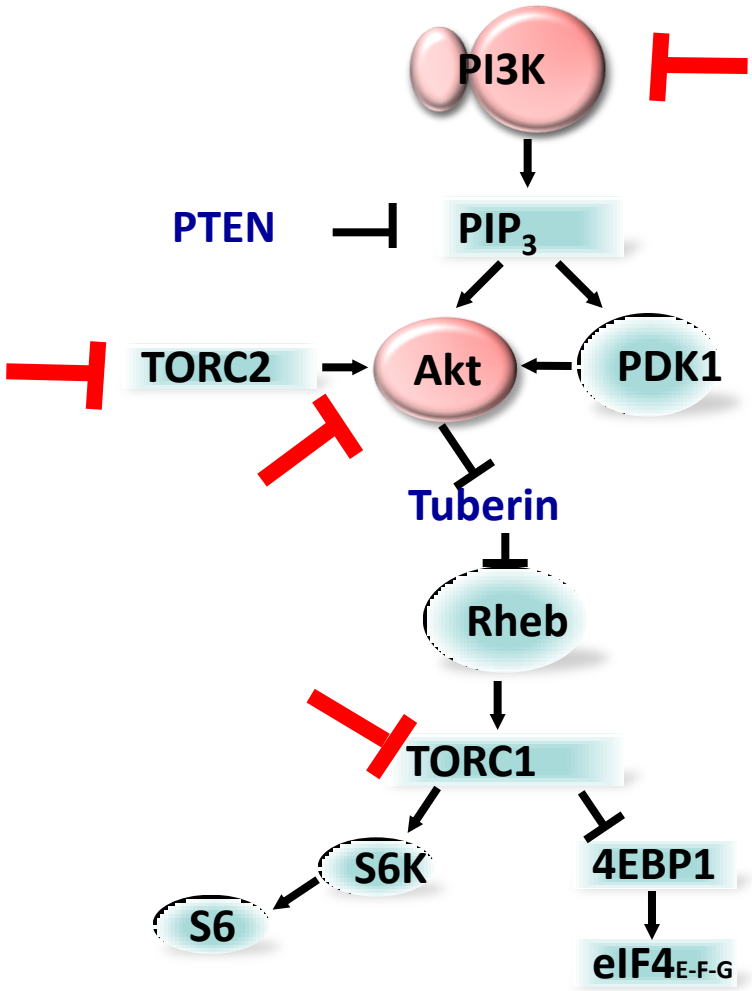


Decrease in best percentage change from baseline	70.75% (225)	29.68% (46)
Zero change in best percentage change from baseline	9.12% (29)	12.90% (20)
Increase in best percentage change from baseline	12.26% (39)	36.77% (57)
% change in target lesion available but contradicted by Overall lesion response = PD	7.86% (25)	20.65% (32)

X - Best % change from baseline > 100%.

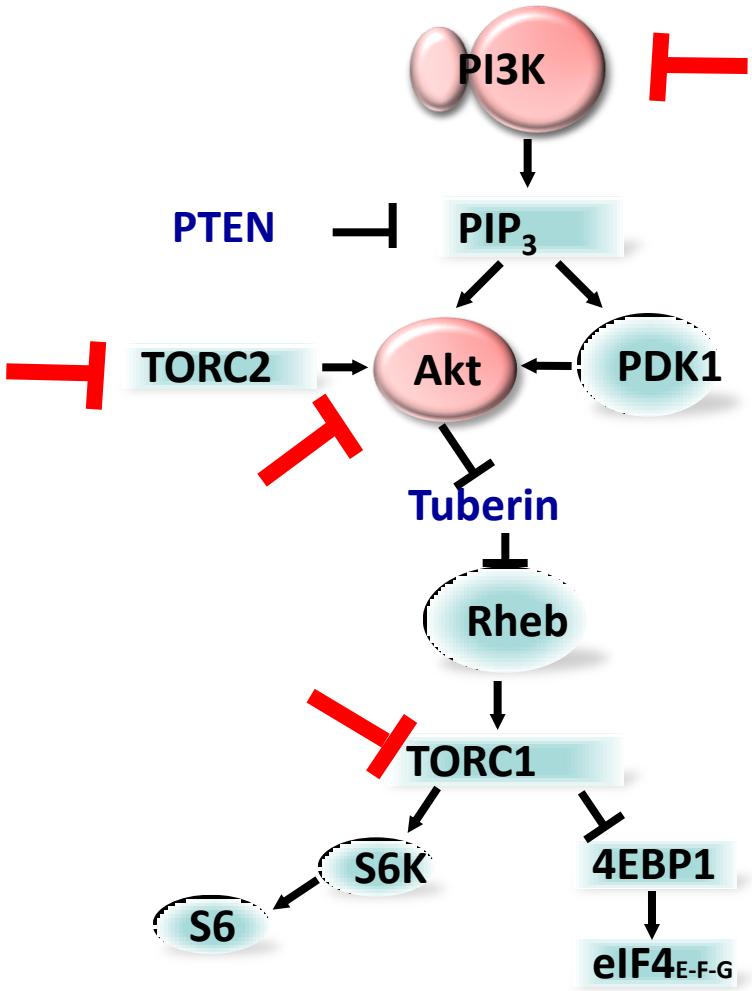
Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)

PI3K pathway inhibitors in clinical trials



Agent	Target
BYL719	PI3Kα
INK-1117	PI3Kα
GDC-0032	PI3Kα,δ,ϒ
XL-147	Pan-PI3K
BKM120	Pan-PI3K
GDC-0941	Pan-PI3K
PKI-587	Pan-PI3K
XL-765	PI3K / mTOR
BEZ-235	PI3K / mTOR
PF-4691502	PI3K/mTOR
AZD8055	mTOR (catalytic)
INK 128	mTOR (catalytic)
MK-2206	AKT1,2,3
GDC-0068	AKT

PI3K pathway inhibitors in clinical trials



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BKM120XUS13T (Mayer)

Summary of Phase Ib BKM120 + letrozole in ER+ MBC

ER+ HER2– MBC

FPFV: Jan2011

Arm A: BKM120 100 mg QD (N=20)

Arm C: BKM120 100 mg 5/7 days (N=31)

Arm B: BEZ235 400 mg BID (N=20)

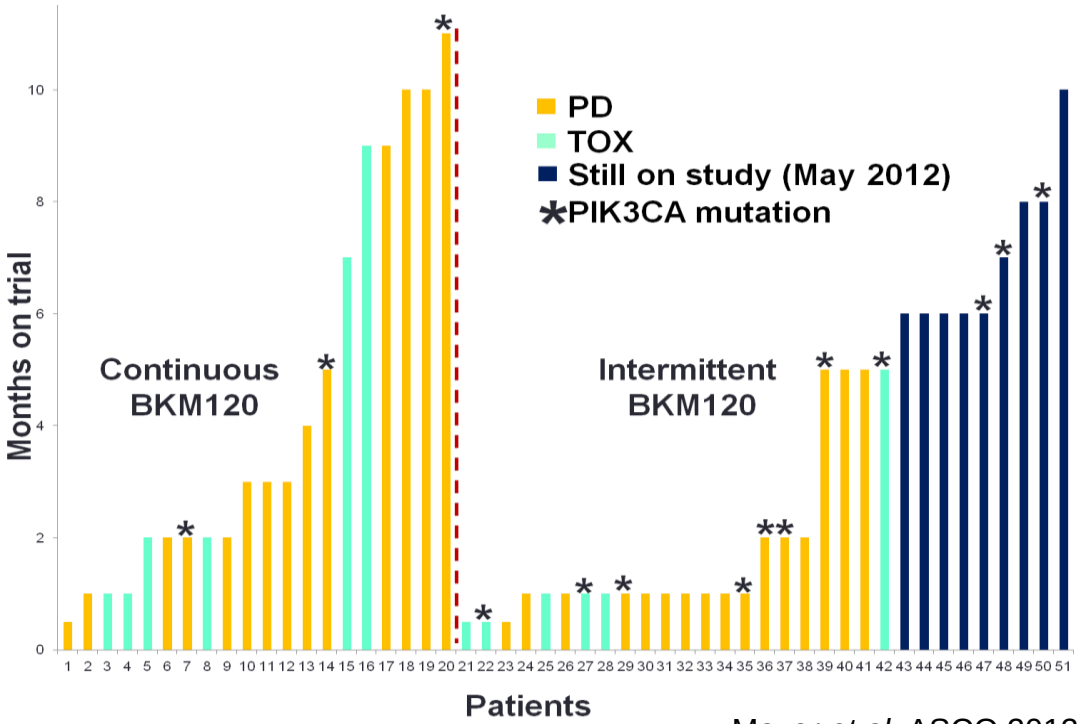
Endpoints
Primary:
- Toxicity

Secondary:
- Anti-tumor effect

Exploratory
- *PIK3CA* mut
- PTEN/Akt1
- FDG-PET/CT

Current Status:
- 43/51 pts progressed on an AI
- **DLTs:** 1 in Arm A (G3 transaminitis); 1 in Arm C (G3 depression)
- **Arm A:** 1 CR, 1 PR; CBR 6 (30%)
- **Arm C:** CBR 9 (29%), all still ongoing
- Arm C better tolerated overall

	Continuous	Intermittent
Hyperglycemia	10%	–
Fatigue	5%	–
Transaminitis	15%	9%
Anxiety	5%	–
Depression	5%	3%
Rash	5%	3%



Mayer *et al.* ASCO 2012

BKM BELLE-2
Study design overview

FPFV July 2012
29 countries
~300 sites
30pts/month

Patient Population:
- HR+/HER2- locally advanced/MBC
- Post-menopausal
- AI Resistant
- No more than 1 prior chemo line allowed for MBC
- Measurable lesion or bone lesions lytic/mixed
- mTORi naive
- Adequate amount of tumor tissue for molecular screening (PI3K pathway activation testing)
- Mood questionnaires

ENTRY RUN-IN

Fulvestrant
500 mg cycle 1 day 1

RANDOMIZATION

Stratification
- **Visceral disease**
- **PI3K pathway status**

BKM120 100 mg daily **+ fulvestrant** day 15 cycle 1 and day 1 every cycle
N=~421

1:1
N=~842
At least 334 PI3K activated

Placebo 100 mg daily **+ fulvestrant** day 15 cycle 1 and day 1 every cycle
N=~421

Endpoints (patients group)
- **Co-primary**
  - PFS (full)
  - PFS (PI3K activated)
- **Co key secondary**
  - OS (full)
  - OS (PI3K activated)
- **Secondary**
  - PFS, OS (PI3K non-activated/unknown)
  - ORR, CBR (full, PI3K activated, PI3K non-activated/unknown)
  - Safety (full)
  - BKM120 and fulvestrant PK
  - EORTC QLQ-C30 (full, PI3K activated)
- **Exploratory**
  - Biomarkers

All eligibility criteria verified

Molecular screening: PI3K activation status determination by Genoptix

SCREENING PHASE
From day -21 to day -1

Note: tumor tissue collection & shipment to central lab from day – 21 to day -7

Cycle 1 Day 1

RUN-IN TREATMENT PHASE
From cycle 1 day 1 to day 14

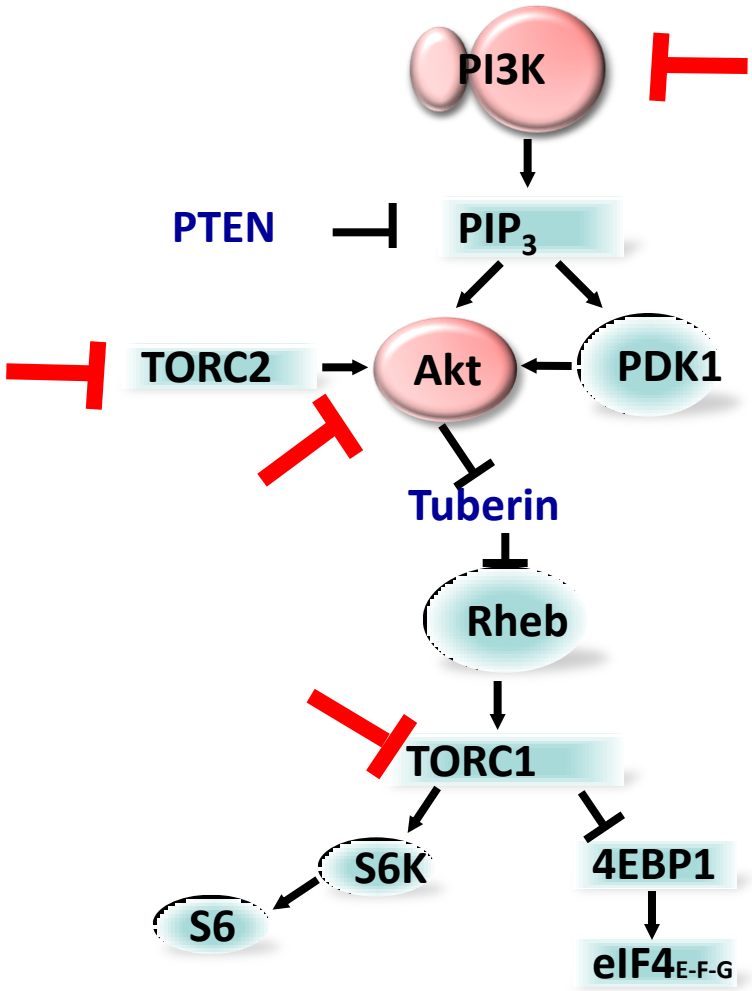
Cycle 1 Day 15
(-3 days)

RANDOMIZED TREATMENT PHASE
From cycle 1 day 15
Fulvestrant and BKM120/placebo start at cycle 1 day 15 (+3 days)

Note: all patients will be randomized regardless of PI3K activation status. Enrollment will stop once at least 334 patients with PI3K activated pathway

SAFETY, EFFICACY and SURVIVAL FOLLOW UP PHASE

PI3K pathway inhibitors in clinical trials



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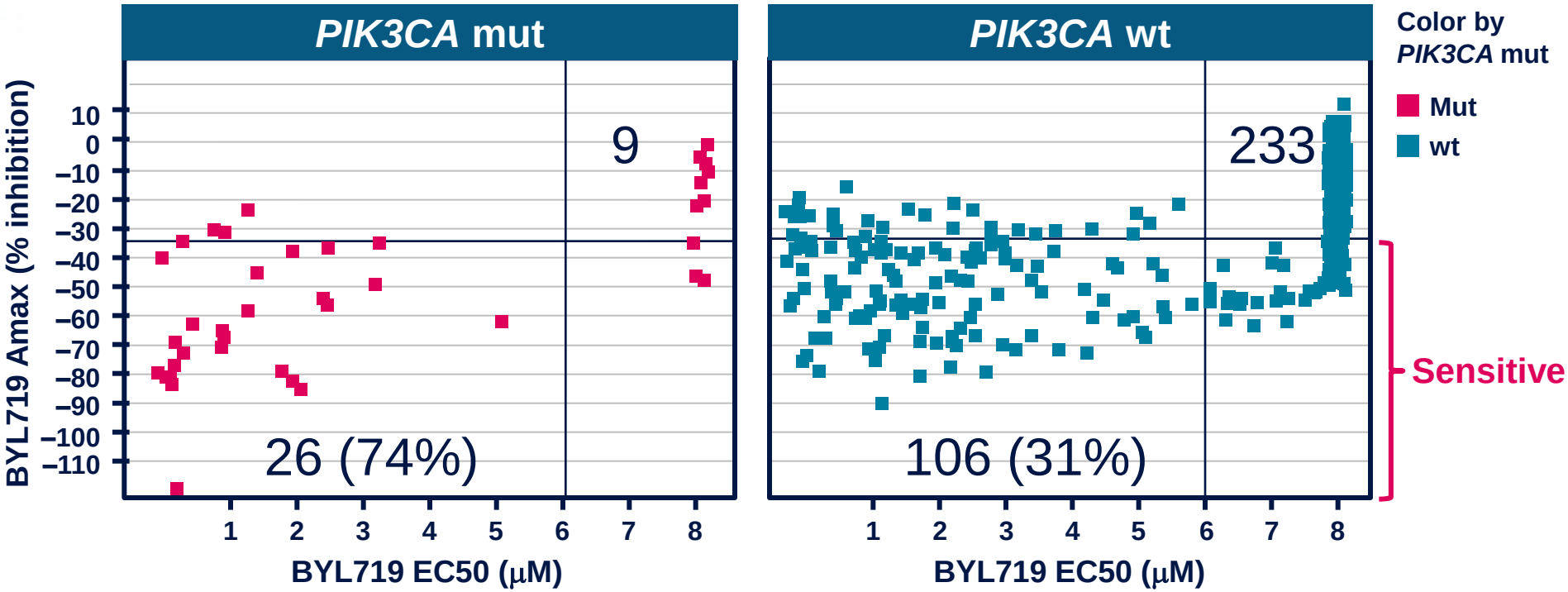
BYL719 displays preferential sensitivity in *PIK3CA* mutated cell lines



$p=1x10^{-6}$ by Fisher's Exact Test (two tailed)

- *PIK3CA* mutation is associated with sensitivity across different tumor types
- Amplifications of *PIK3CA* or *ERBB2* are also associated with BYL719 sensitivity (p=0.001)

Juric D, et al. Presented at AACR Annual Meeting, March 31 – April 4, 2012

BYL719 Phase I: Study design

Dose-escalation phase (completed)

Oral, once-daily BYL719, 28-day cycle (n=36)

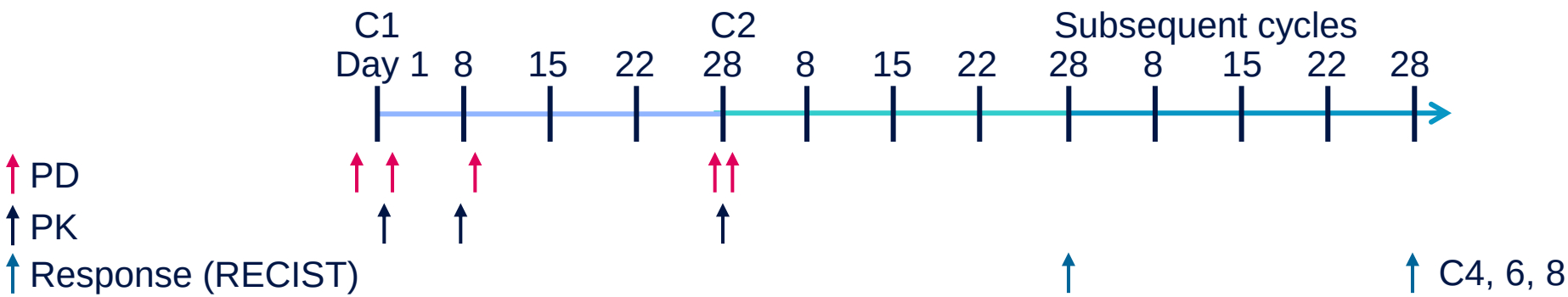
30 mg/day
60 mg/day
90 mg/day
180 mg/day
270 mg/day
400 mg/day
450 mg/day

Dose levels

→ Declaration of MTD →

MTD expansion phase (ongoing)

400 mg QD BYL719 (approximately 45 patients) in *PIK3CA*-altered solid tumors

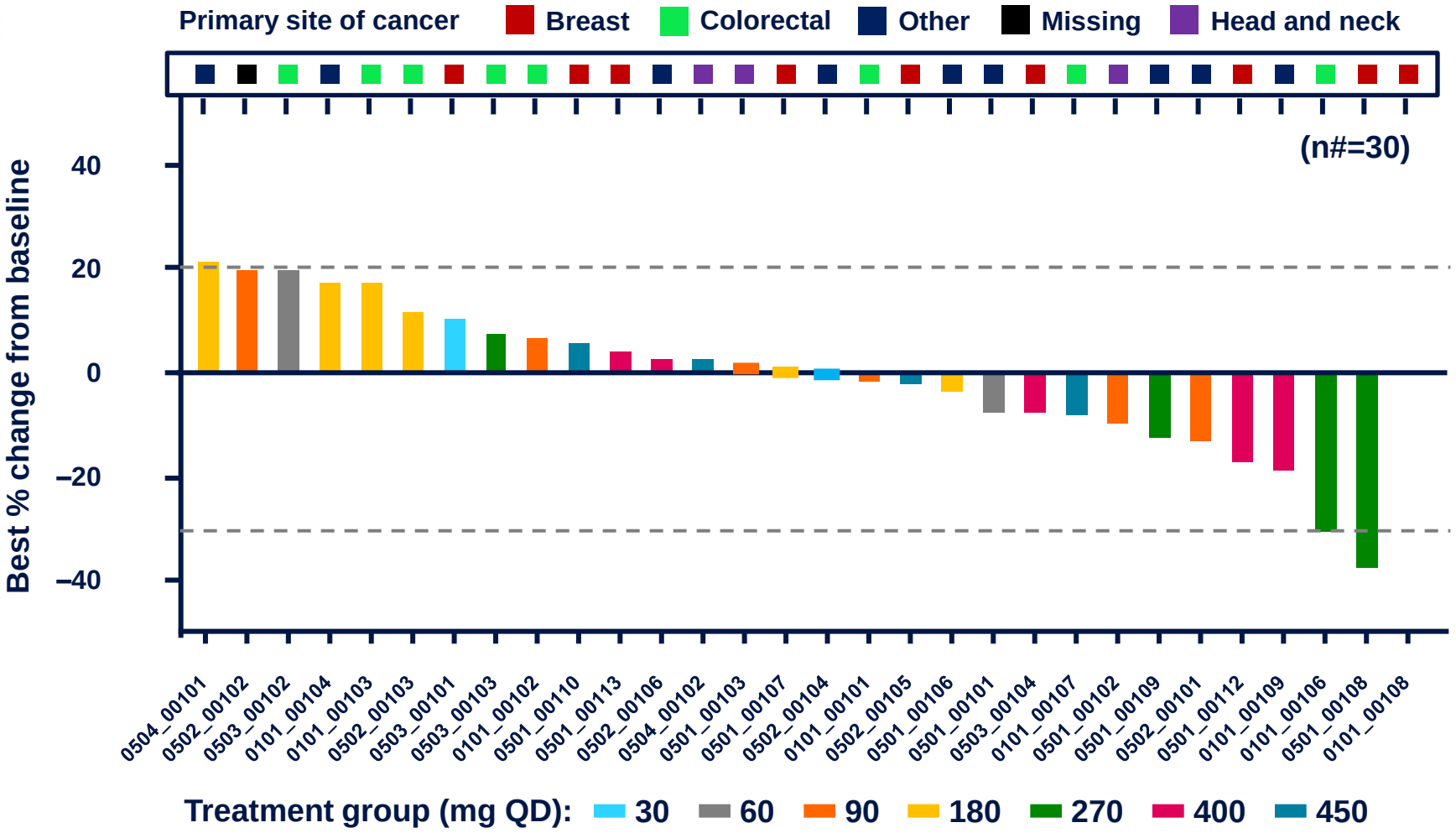


36 patients were enrolled in the dose-escalation phase; data are reported for 35 patients as of 2 January, 2012

Juric D, et al. Presented at AACR Annual Meeting, March 31 – April 4, 2012

Preliminary efficacy

Best percentage change from baseline in sum of longest diameters



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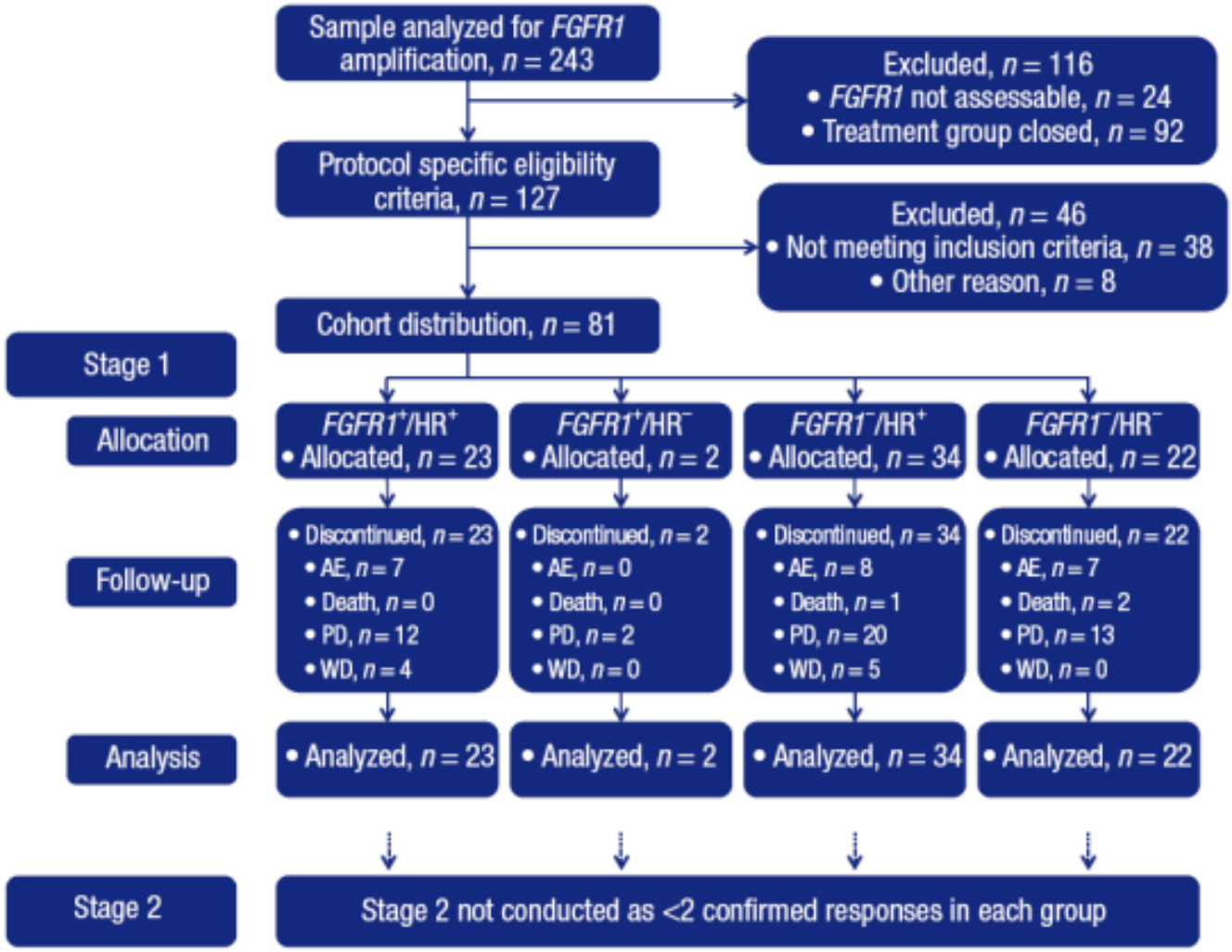
Phase II Study of Dovitinib (TKI258) in patients with HER2 – breast cancer (Andre et al)



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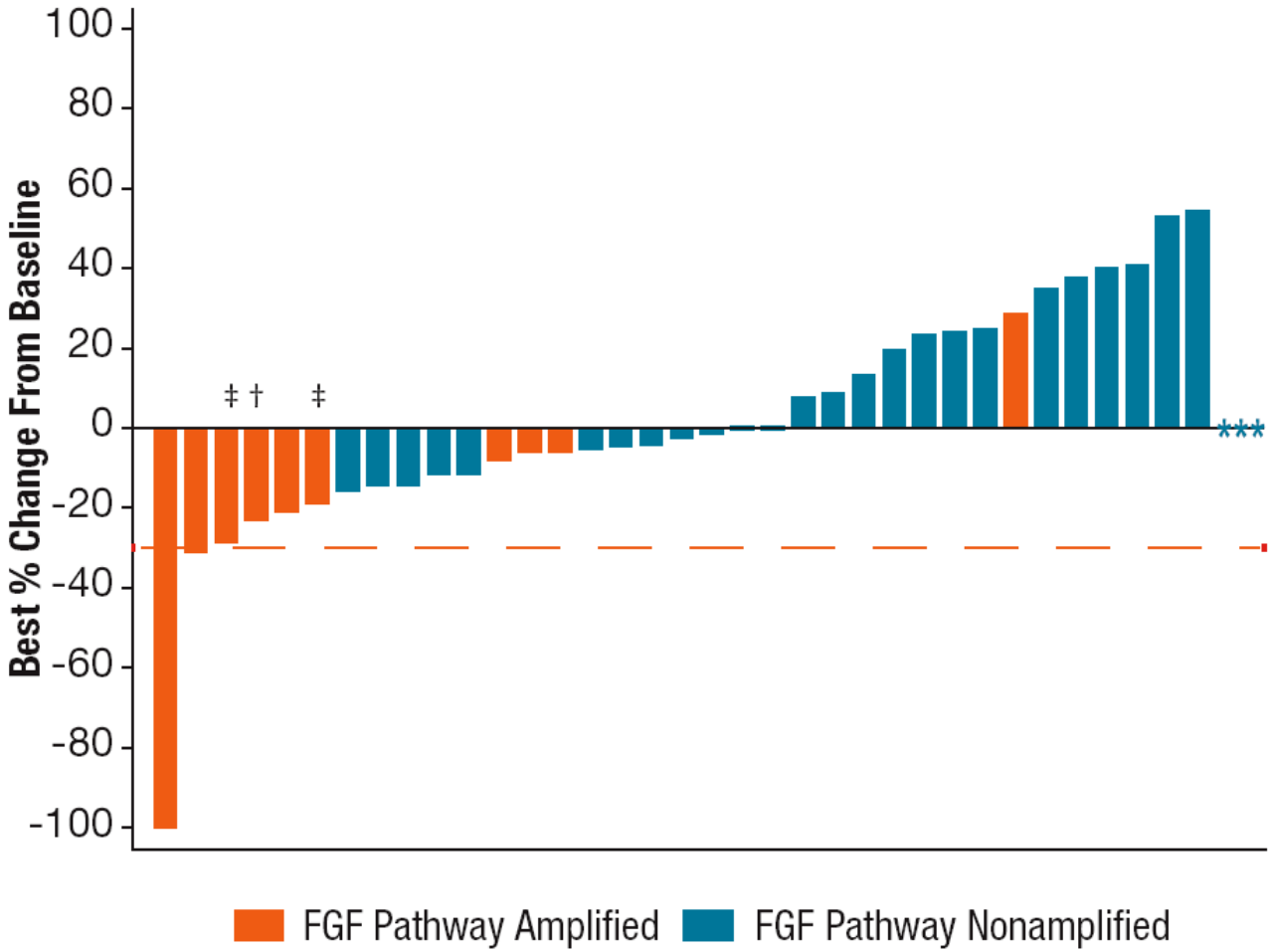
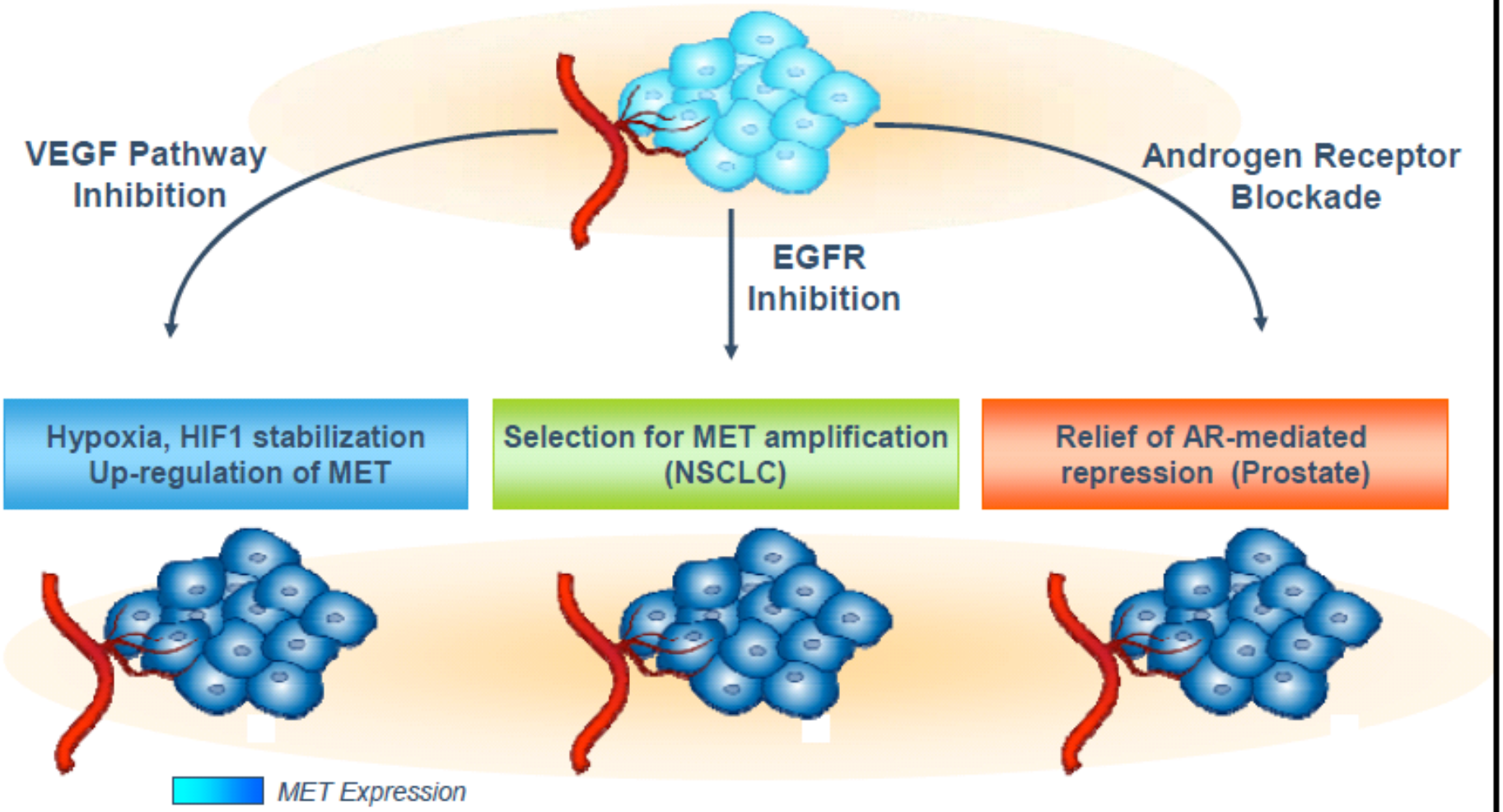
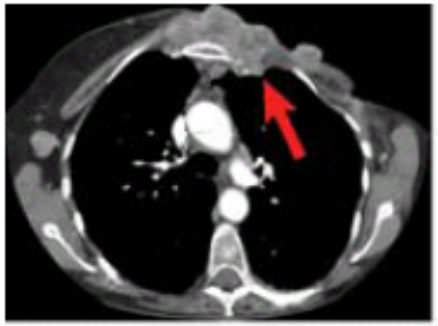


HR⁺ FGF-pathway–amplified (red bars; *FGFR1*, *FGFR2*, or *FGF3* amplification by qPCR) or FGF-pathway–nonamplified (blue bars) patients.

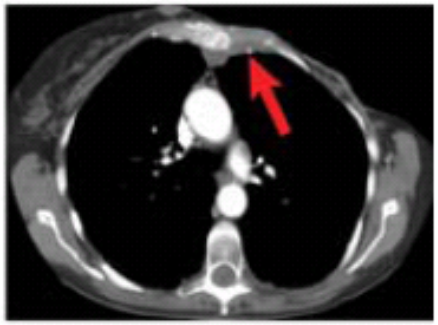
Up-regulation of MET as a Response to Treatment



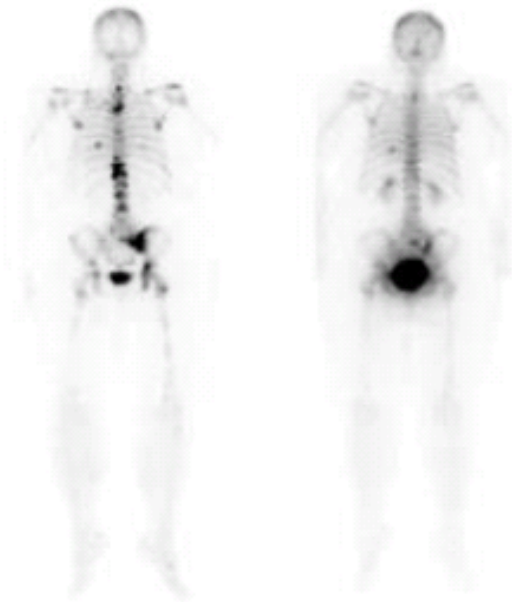
Breast Cohort: Effects in Soft Tissue and Bone Metastases



Screening



Week 12



Screening Week 6

Response in chest wall lesion in a patient with invasive ductal carcinoma

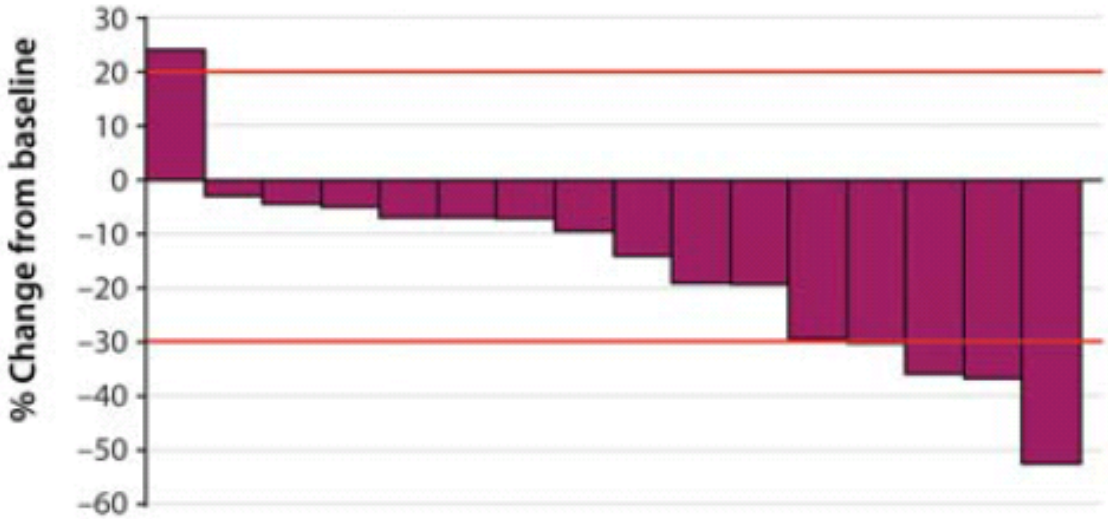
Prior anticancer treatment: 5-FU/epirubicin/ cyclophosphamide, docetaxel, gemcitabine/carboplatin

Bone scan resolution in patient with invasive ductal carcinoma; Concurrent 29% reduction of a tumor lesion and a 82% reduction in plasma CTx levels.

Prior anticancer treatment: radiotherapy, paclitaxel/adriamycin, hormonal therapy, ixabepilone

Breast Cohort: XL184 Achieves Tumor Shrinkage in the Majority of Patients

Best Radiological Time Point Response in Patients with ≥ 1 Post-Baseline Tumor Assessment (N = 16)



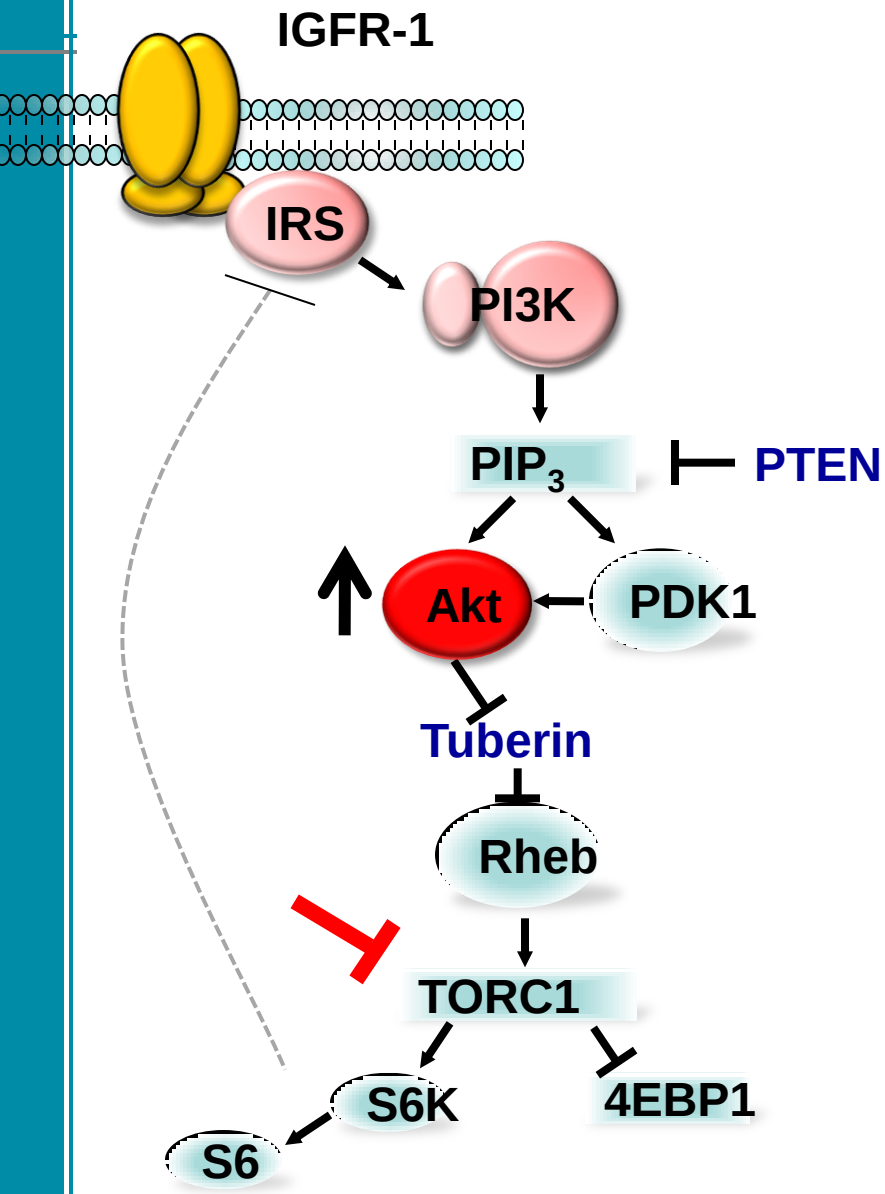
Overview of Breast Cancer Responders

Patient	Histology	Receptor Status	Site of Target Lesions	Number of Prior Treatments	Most Recent Prior Treatment (Best Response)	Time on XL184 (weeks)
1	Invasive lobular	ER+/PR–/ HER2+	lymph node	3	fulvestrant (UNK)	25+
2	Invasive ductal	ER+/PR+/ HER2 (ND)	liver	2	paclitaxel (UNK)	18+
3	Invasive ductal	ER+/PR–/ HER2–	lung and lymph nodes	3	exemestane/bosutinib (SD)	18+
4	Invasive ductal	ER+/PR+/ HER2 (ND)	chest wall	3	carboplatin/gemcitabine (UNK)	17

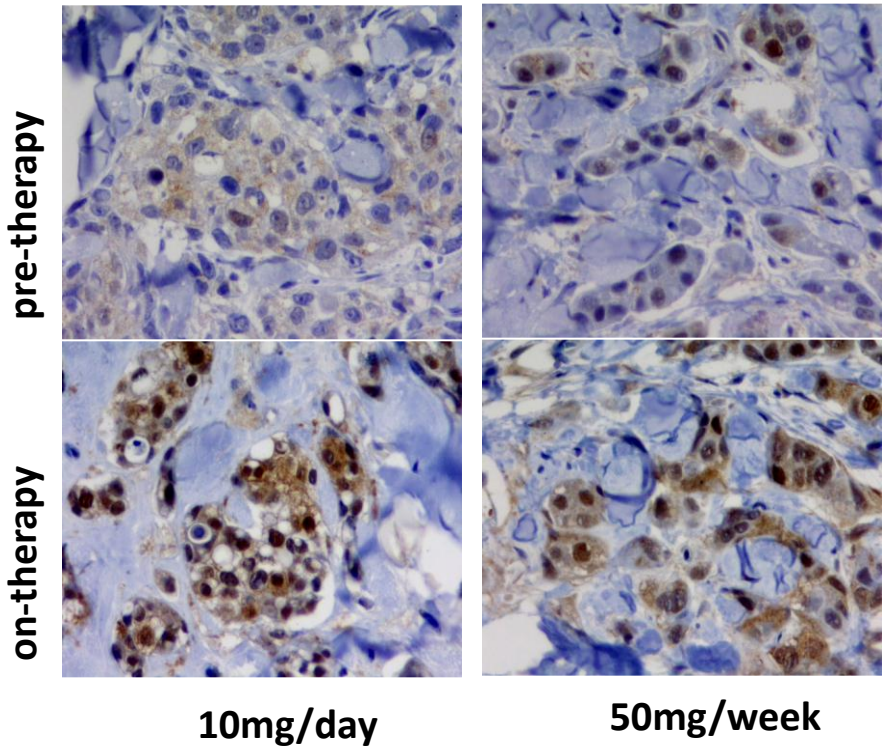
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; ND, not determined SD, stable disease; UNK, unknown

PI3K Compensatory Pathways

Rapalogs Activate Akt

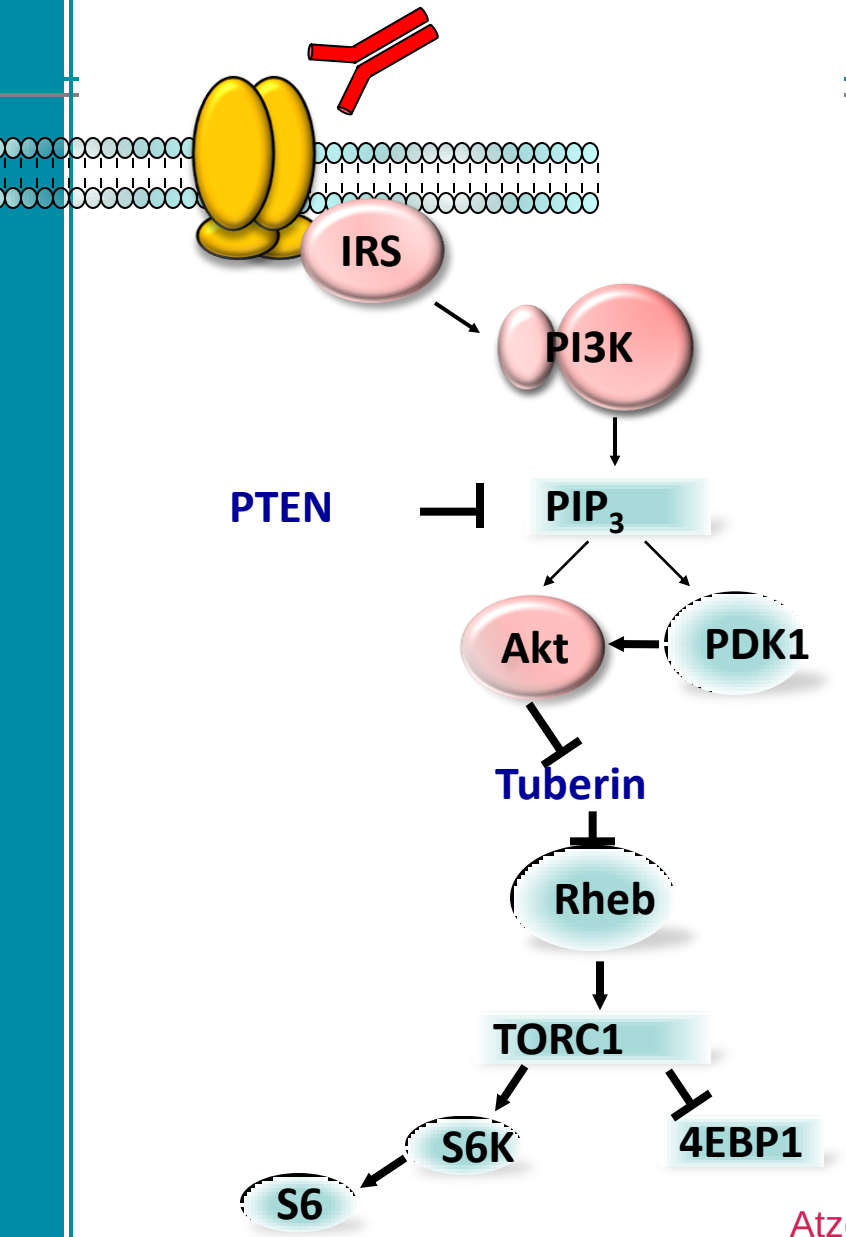


Phase I Everolimus Study
Tumor pAkt

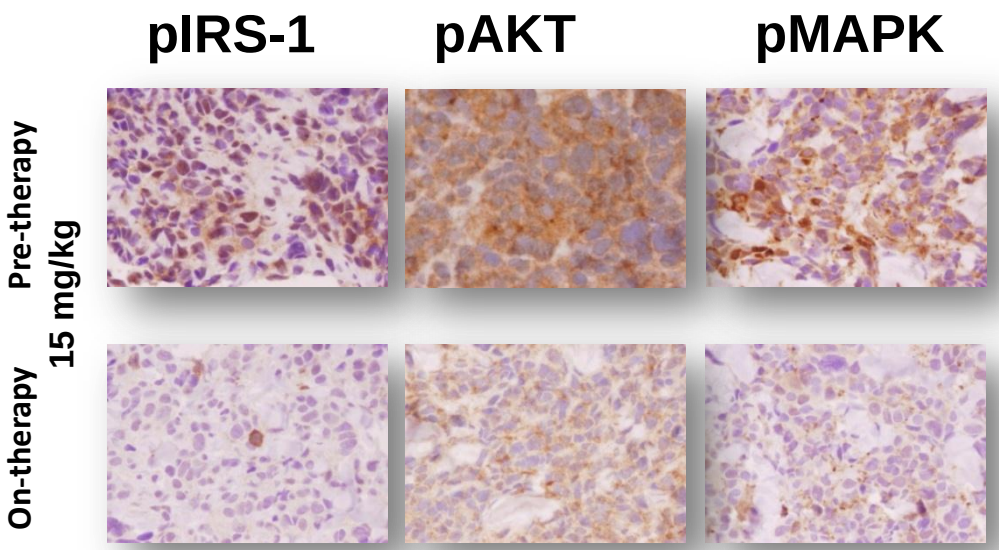


Tabernero *et al*. J. Clin Oncol. 2008

PI3K Compensatory Pathways



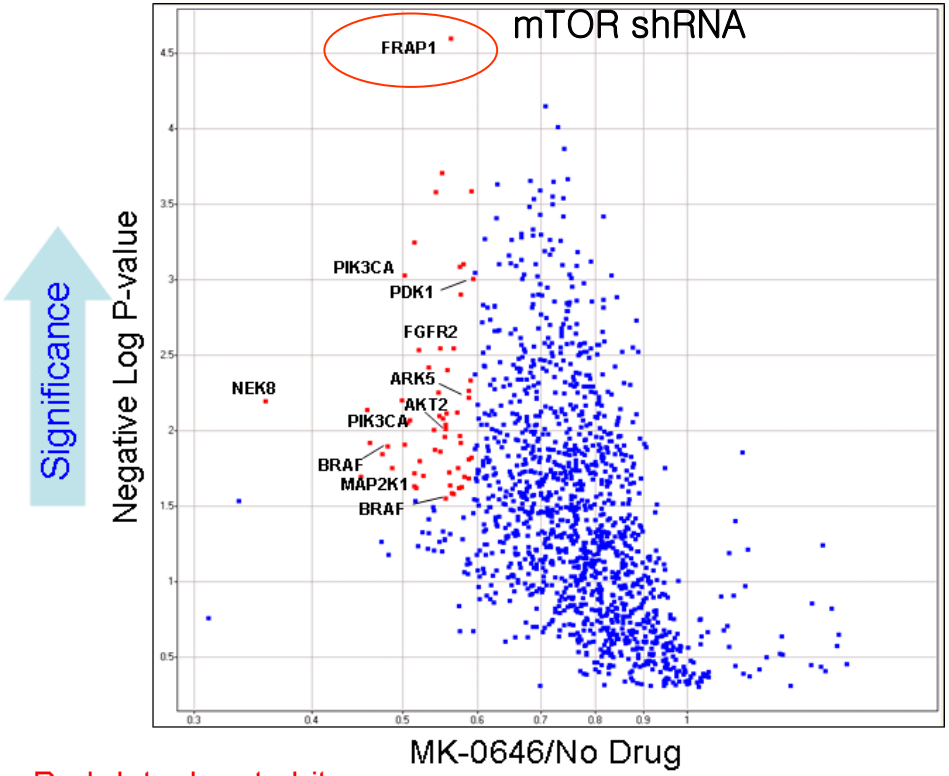
Phase I study of MK-0646 (P001)
Pre- and post-treatment tumor tissue



Atzori *et al*. CCR 2011

Science-Driven Rationale for combined mTOR and IGFR1 Targeted Therapy

Dalotuzumab Enhancer Screen



Red dots denote hits

shRNA=small hairpin RNA

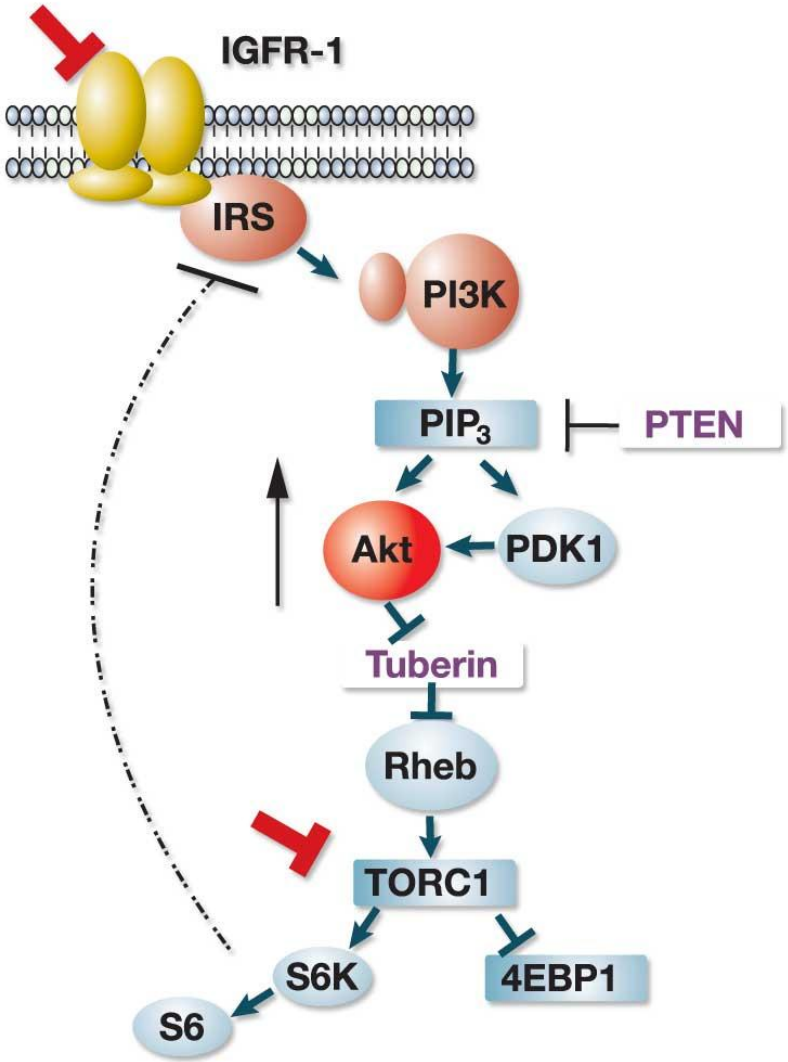
- mTOR is top hit in dalotuzumab enhancer screen
- IGF1R is top hit in ridaforolimus enhancer screen

- Ridaforolimus activates AKT signaling in cell lines
- Combined treatment with ridaforolimus and dalotuzumab *in vitro*:
  1. Knockdown of pAKT
  2. Enhanced knockdown of pS6

     Both dependent on IGFR expression

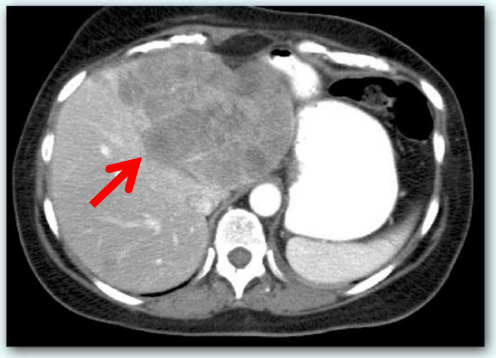
Phase I clinical trial of the combination of IGF-1R MAb (dalotuzumab) plus mTOR inh. (ridaforolimus)

Suppress IGF-1R plus mTOR to prevent compensation by tumor cells

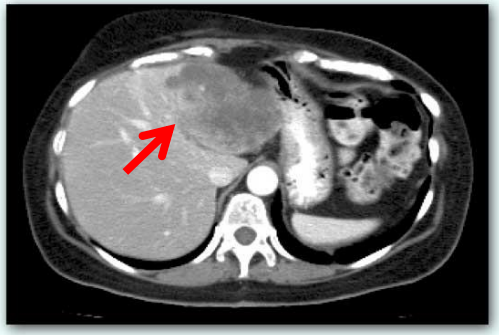


Patient had received 7 prior treatments

Before therapy



2 months later



Di Cosimo. ASCO 2010. abst. 3008

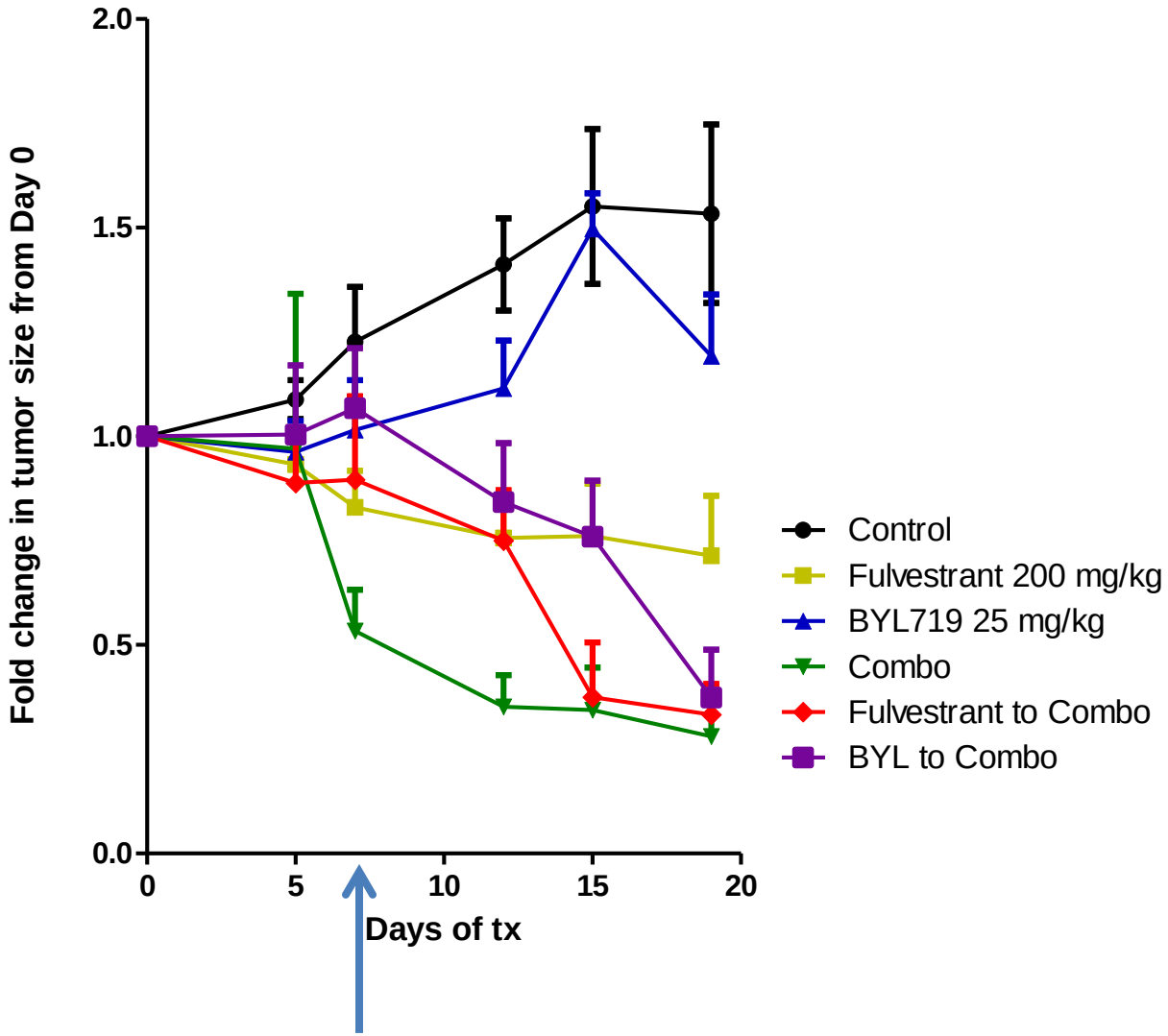
Evidence of anti-tumor activity in breast cancer

Breast Cancer Subpopulation	N	FDG-PET PR (EORTC)		PFS ≥ 6 months		Tumor Marker		RECIST PR	
		n	%	n	%	n	%	n	%
Triple Negative	2	0		0		0		0	
HER2+	3	3		0		2		0	
ER+	18	2		4		6		3	
ER+/high proliferation	11	2		4		5		3	
ER+/low proliferation	5	0		0		0		0	
ER+/unk proliferation	2	0		0		1		0	
All breast cancer	23	5	21.7	4	17.3	8	34.8	3	13.0

- Overall, 10 of 23 (**43%**) breast cancer patients showed objective evidence of anti-tumor activity
  - **6 of 11 (54%) patients with ER+/high proliferation breast tumors**
  - **0 of 5 patients with ER+/low proliferation breast tumors**

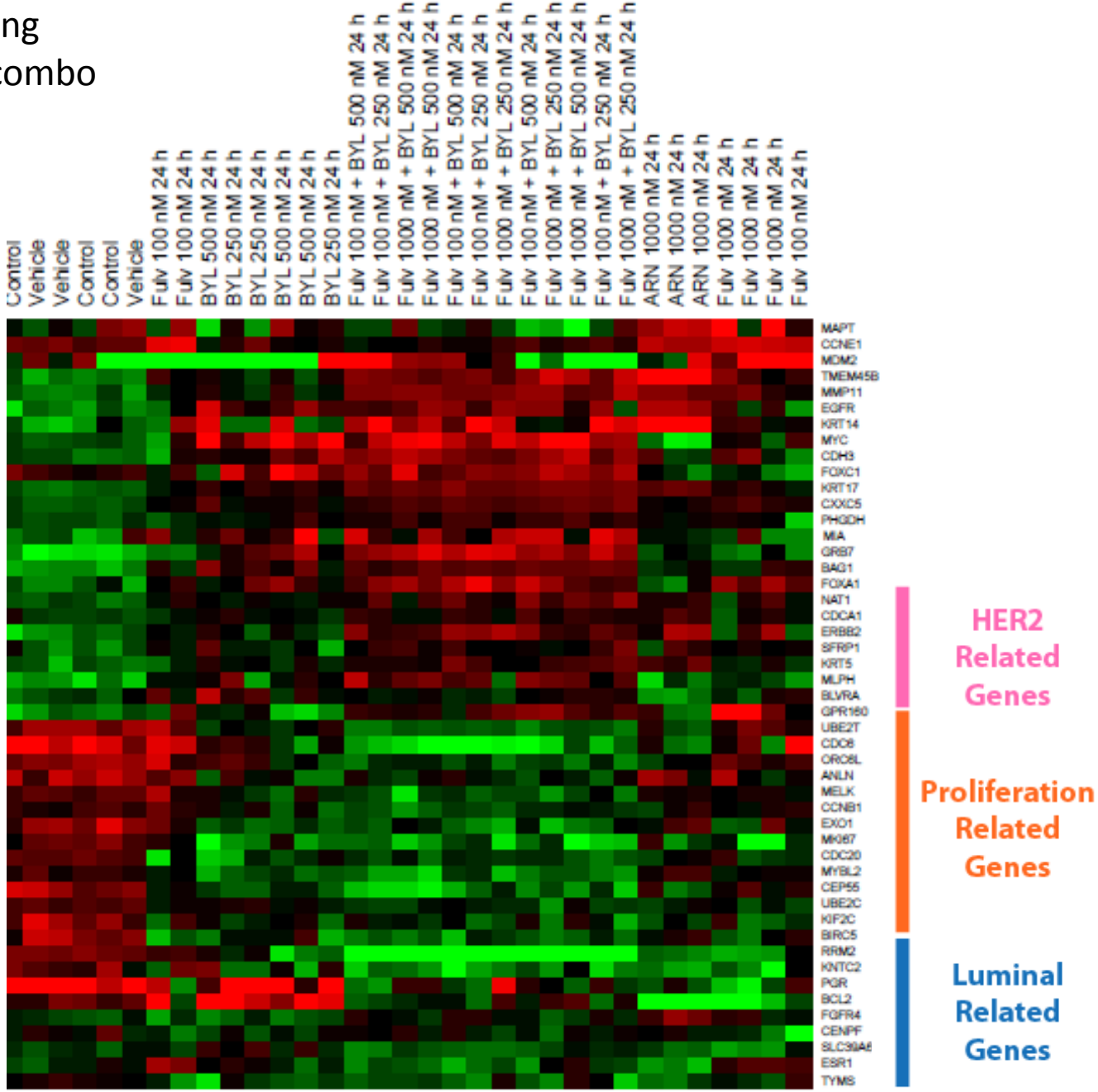
Di Cosimo. ASCO 2010. abst. 3008

Combined Fulvestrant and BYL in MCF7 xenografts

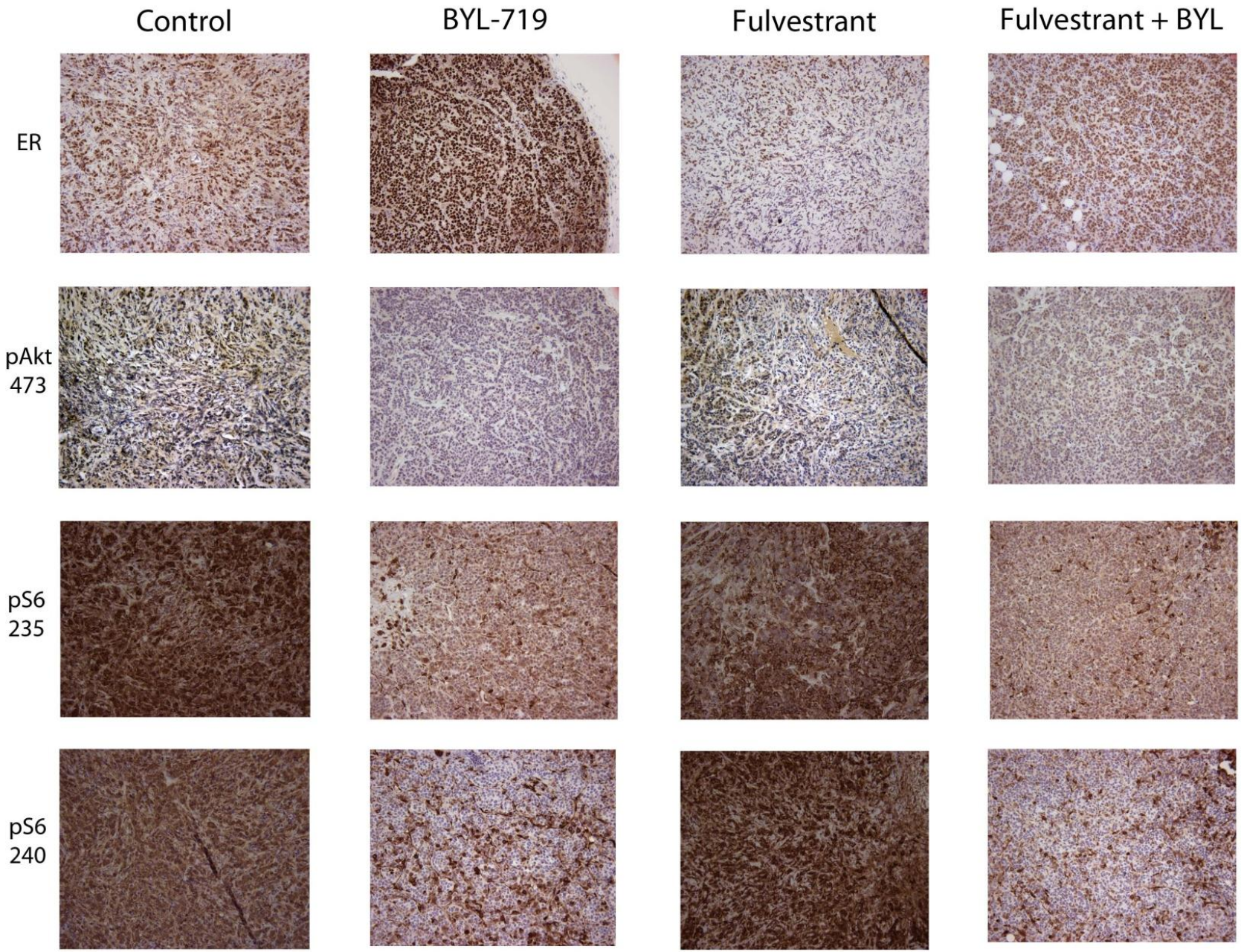


Day 7: combo initiated on single agent fulvestrant and BYL arms

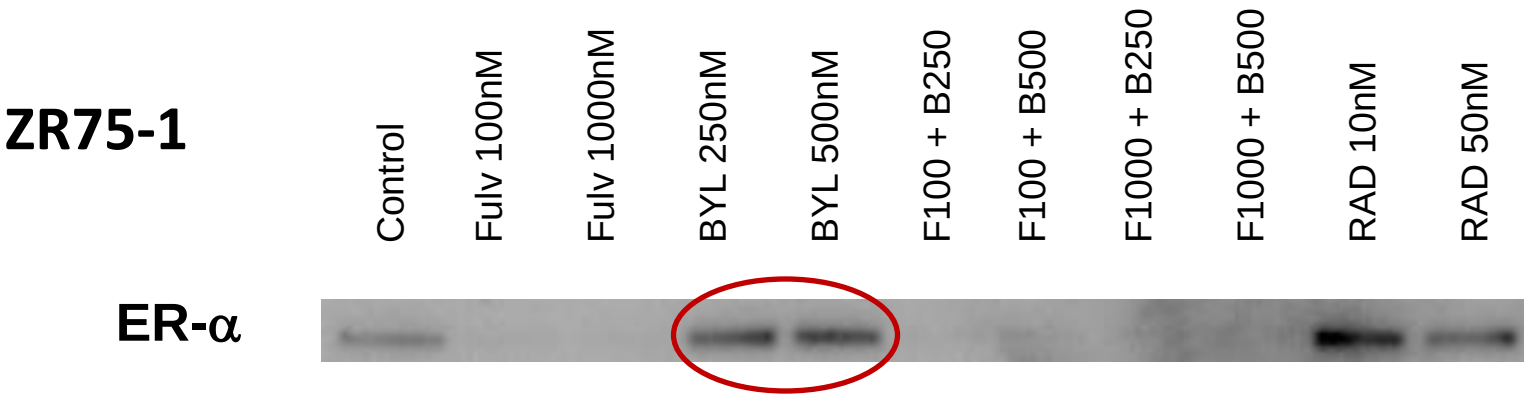
PAM50 obtained comparing BYL719, Fulvestrant and combo treated MCF7 cells.



BYL treatment of MCF7 xenografts induce ER expression in vivo



PI3K/mTOR inhibition induces ER expression



Targeting the PI3K-mTOR Pathway in Breast Cancer
Summary

- Addition of everolimus to exemestane prolongs PFS in patients with ER+ HER2- breast cancer refractory to initial non-steroidal aromatase inhibitors
- Newer, more potent PI3K inhibitors under clinical development. PI3Kα inhibitors have shown activity in PI3Kα mutant tumors
- Inhibition of compensatory pathways with targeted agents likely to reproduce the results of the BOLERO-2 study in other indications and conditions
- IGF-1R + mTOR showing activity. Randomized studies under way
- FGFR inhibitors have shown activity in FGFR amplified tumors
- Cabonzatinib showing activity in patients with bone disease
- Early studies with ER degraders