Institut de cancérologie
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Targeting kinases to reverse resistance to endocrine therapy

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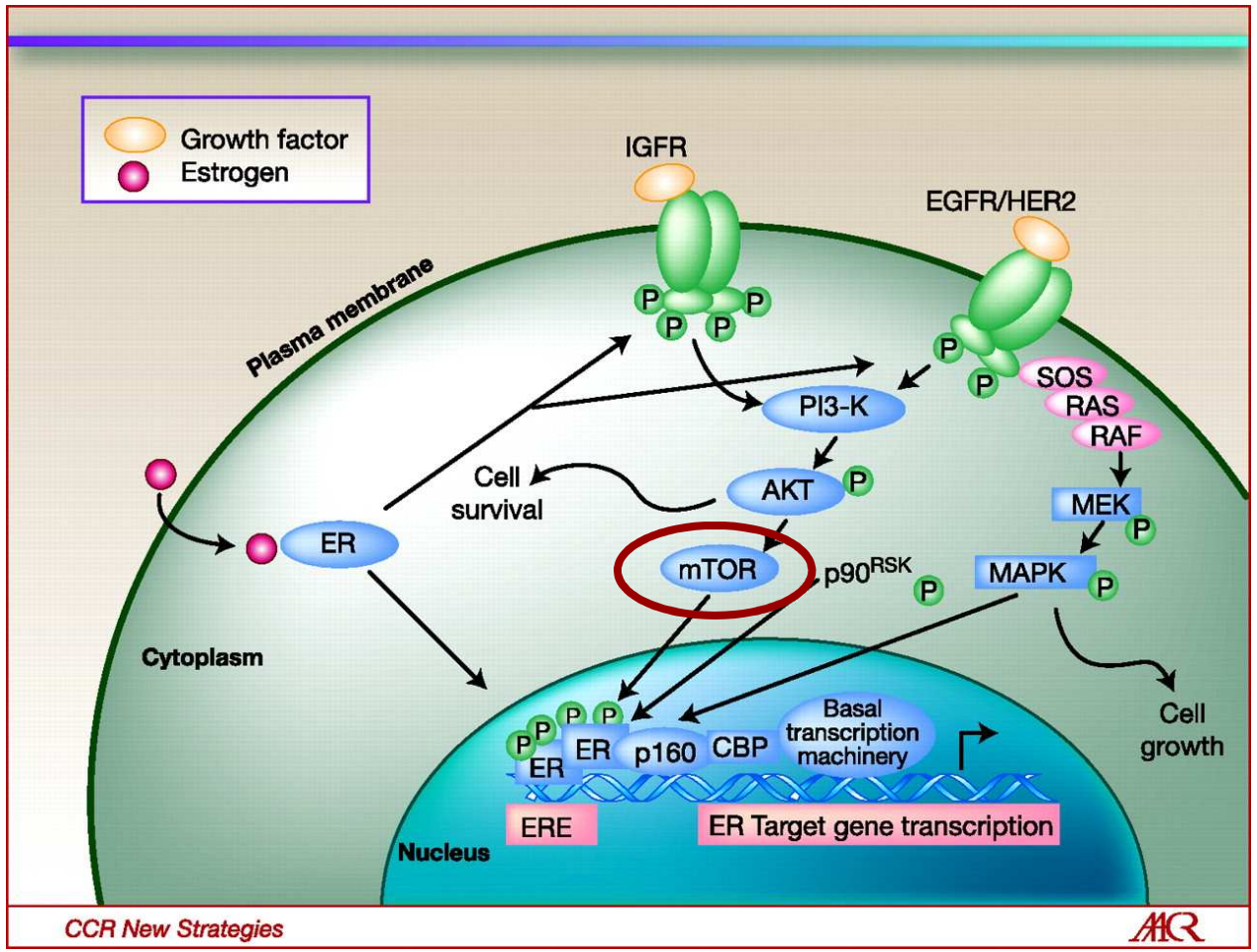
Outline

- mTOR inhibitors
- PI3K inhibitors
- Her inhibitors
- FGFR inhibitors
- CDK inhibitors

Mechanisms of resistance to endocrine therapy



Transmembrane
Tyrosine kinase

Second messengers

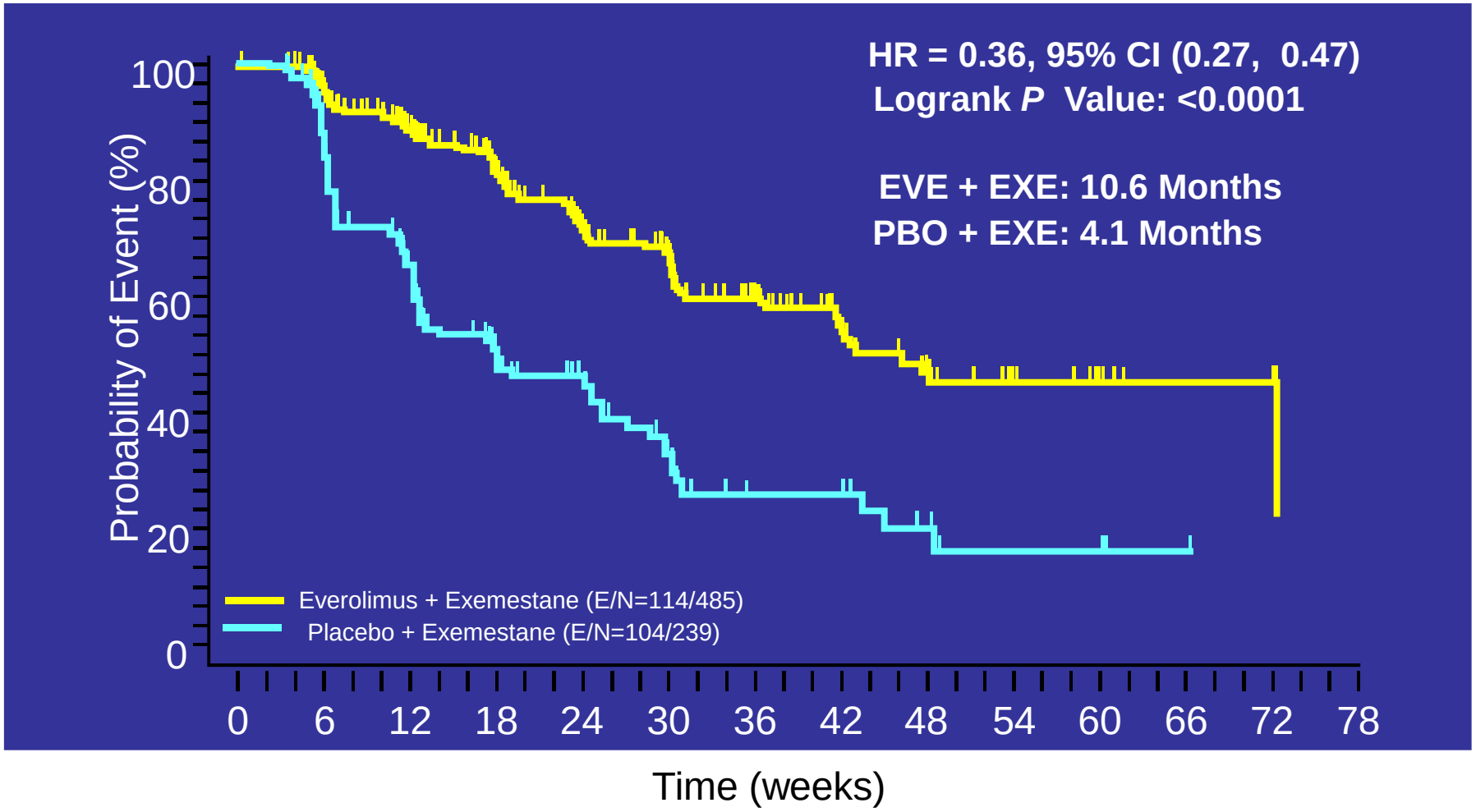
Johnston. Clin Cancer Res 2010

Overview of randomized trials testing everolimus in patients with Her2-/ER+ BC

Treatment	n	ratio
Letrozole +/- everolimus *(Baselga, J Clin Oncol, 2009)*	270	70% non responders Ki67 43 % (ratio: 0.61)
Tamoxifen +/- everolimus *(Bachelot, SABCS, 2010)*	111	0.53 (0.35-0.81)
Exemestane +/- everolimus *(Baselga, ECCO-ESMO, 2011)*	724	0.36 (0.27-0.47)

Three randomized trials report CONSISTENT data showing that Everolimus significantly improves efficacy endpoint when added to endocrine therapy

Everolimus efficacy on PFS in patients previously treated with endocrine therapy



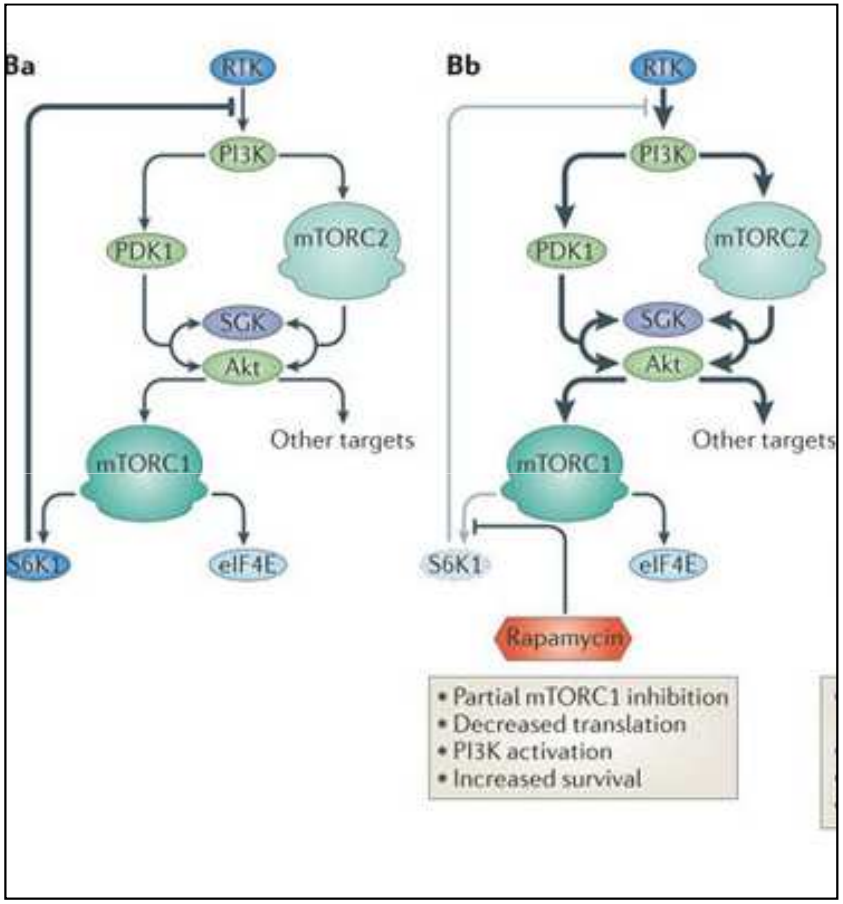
Presented by J. Baselga at the 2011 ECCO/ESMO, Abstract: 9LBA.

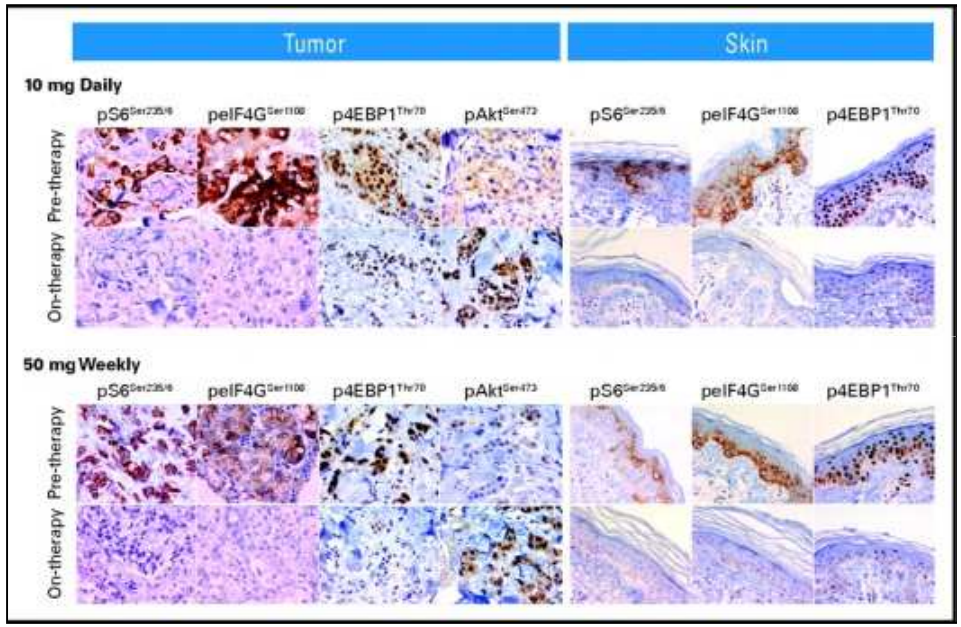
Latest major achievements in cancer treatment

Targeted Agents	Indication	Hazard Ratio (95% CI)
Gefitinib *(Maemondo, NEJM 2010)*	EGFRmut NSCLC	0.30 (0.22 to 0.41)
Trastuzumab *(Slamon, NEJM, 2001)*	Her2+++ mBC	0.51 (0.41–0.63)
Imatinib *(Ronald, Lancet , 2009)*	cKit+ GIST	0.35 (22-0.53)
Sunitinib *(Motzer, NEJM, 2007)*	kidney cancer (VHL-)	0.42 (0.32 to 0.54)
Everolimus	**AI-resistant BC**	**0.36 (0.27 to 0.47)**

Efficacy of everolimus is in the range of the most important recent advances in medical oncology… although no molecular selection was applied

Mechanisms of resistance to mTOR inh: Activating feedback loops





Tarbernero, J Clin Oncol

mTOR inhibition activates growth factor receptors and PI3 kinase
This feedback loop could mediate resistance to mTORC1 inh
Do IGF1R or PI3K inhibition sensitize to mTOR inhibitors ?

mTOR inhibitors and breast cancer

- mTOR inhibitors improve outcome in patients with ER+ metastatic breast cancer pretreated with endocrine therapy
- The understanding of resistance mechanisms allow to draw future combinations between mTOR and IGF1R, PI3K inhibitors
- 2nd and 3rd generations of mTOR inhibitors could improve results
- mTOR inhibitors are planned to be evaluated in the adjuvant setting

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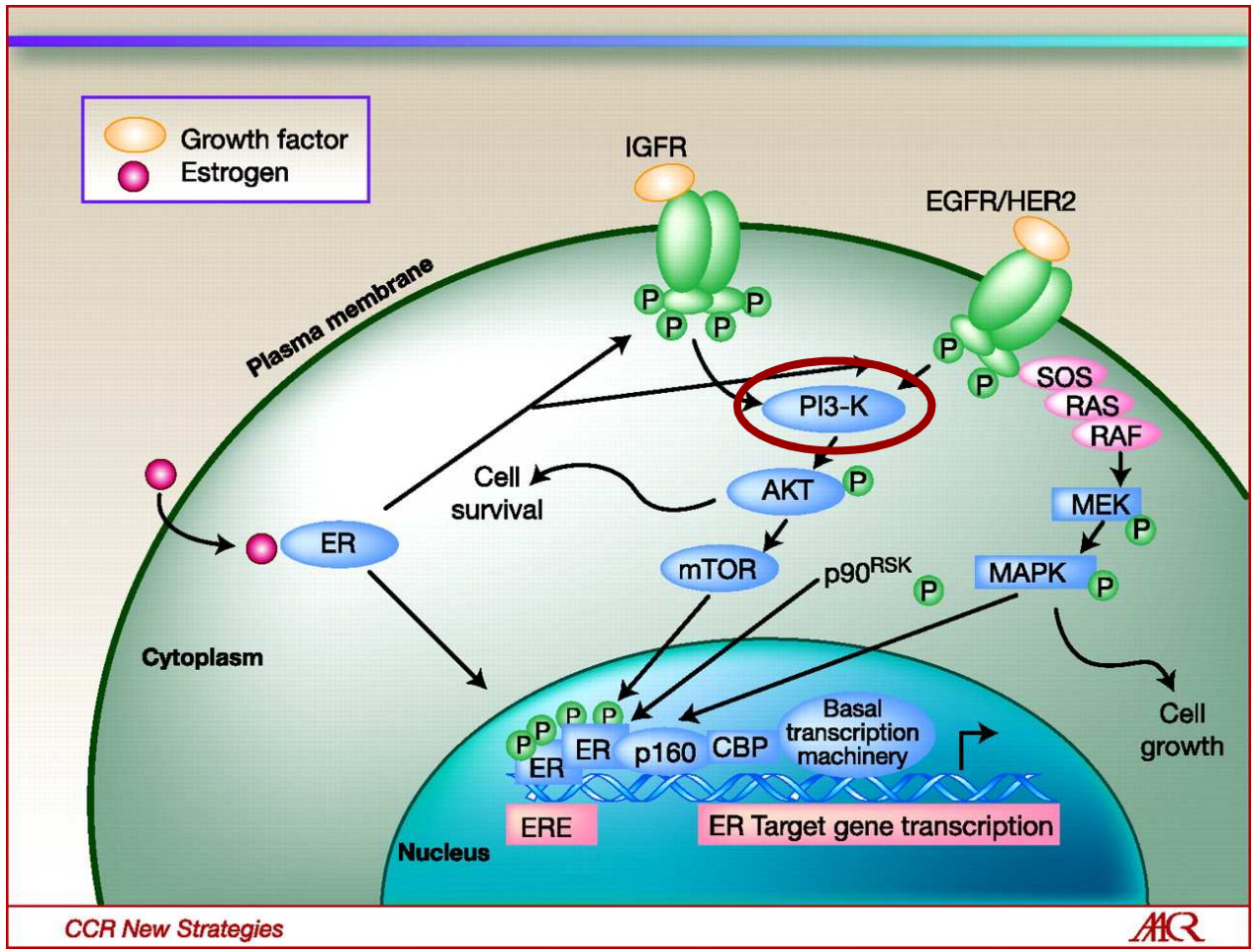


Transmembrane
Tyrosine kinase

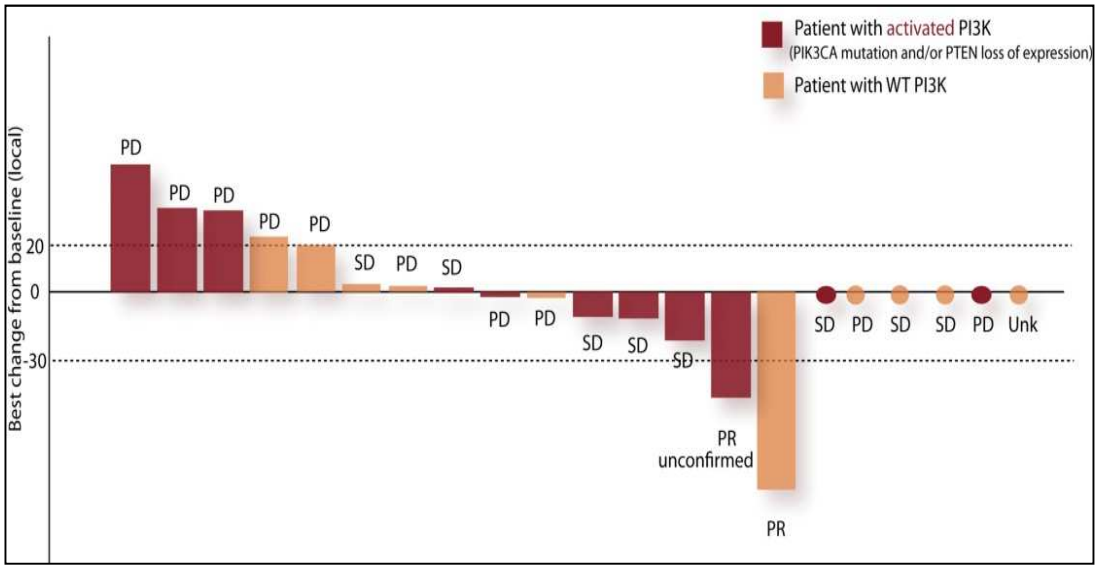
Second messengers

Johnston. Clin Cancer Res 2010

BKM120: Promising Preliminary Activity in MBC

Predictive role of PI3K pathway activation overall still unclear

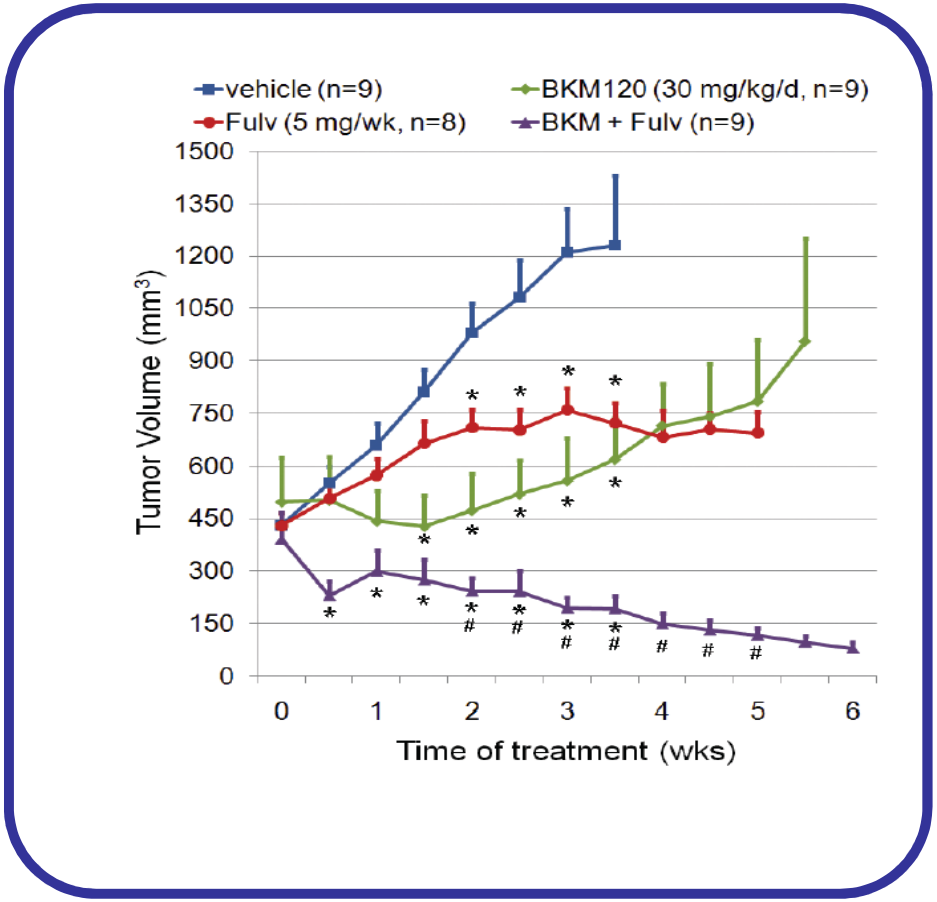
BKM120 – Single agent



Rodon *et al. ASCO* 2011

BKM120: Anti-tumor Activity in Preclinical Models of Breast Cancer

Fulvestrant treatment sensitizes long-term estrogen-deprived cells to BKM120[1]



Sanchez CG e*t al.* Breast Cancer Research;13 (2): Article R21

Rationale for PI3Ki in HR+ HER2- MBC

Frequency of mutations in the PIK3CA and PTEN genes

- Scientific and preclinical
  - Endocrine resistance frequently associated with enhanced growth factor signaling (PI3K pathway activation) (Miller TW, Cancer Discovery 2011)
  - Preclinical data support anti-estrogens and PI3Ki in AI-resistant models (Sanchez CG, Breast cancer Res 2011)

n = 547	**Mutation**	
	PIK3CA	PTEN
All breast tumors	117/547 (21.4%)	2/88 (2.3%)
HR+	**80/232 (34.5%)**	**2/58 (3.4%)**
ER+PR+	61/186 (32.8%)	1/48 (2.1%)
ER+PR–	19/41 (46.3%)	1/8 (12.5%)
ER–PR+	0/5 (0%)	0/2 (0%)

From Stemke-Hale, K. et al. Cancer Res 2008

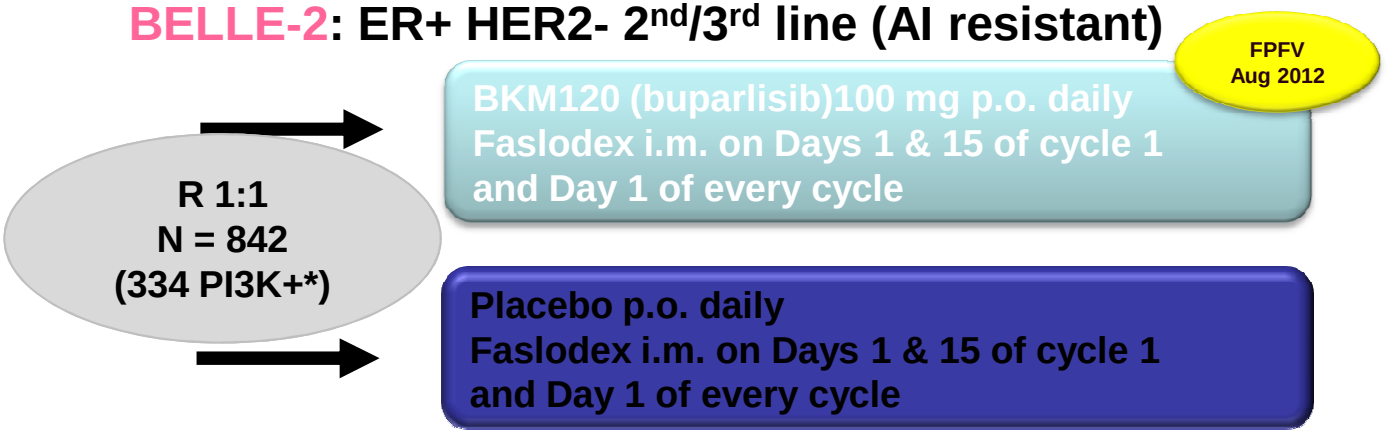
n = 1502	**Alterations**	
	PIK3CA mutation	PTEN loss
All breast tumors	356/1502 (23.7%)	435/1502 (29%)
HR+	**207/740 (28%)**	**214/740 (29%)**
ER+PR+	166/593 (28%)	NA
ER+PR–	28/107 (26%)	NA
ER–PR+	11/40 (27%)	NA

Gardner H. , Oncology Translational Laboratories, Novartis

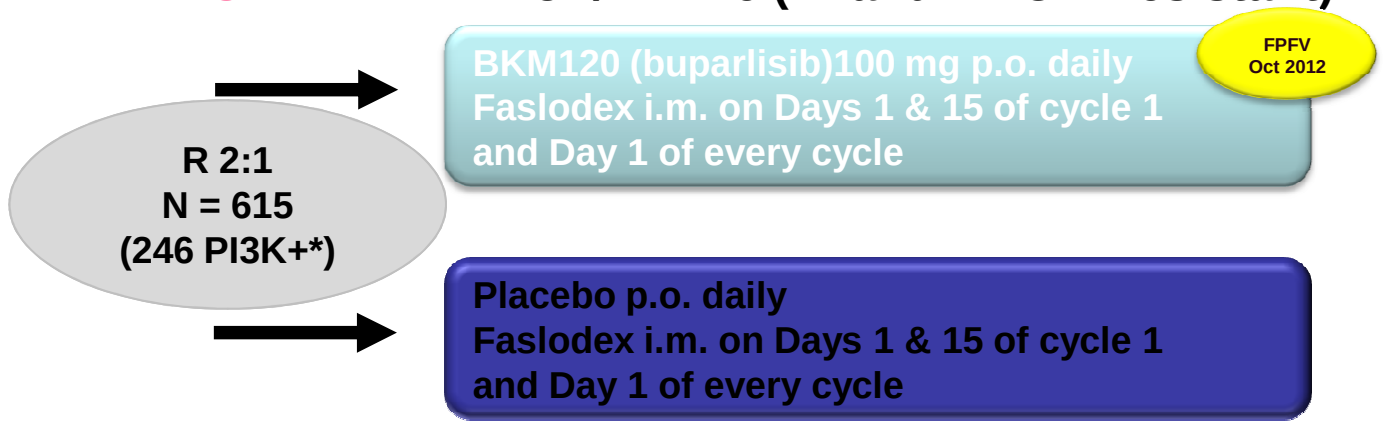
BKM120 in ER+ Breast Cancer Pivotal Trials

Stratification by PI3K status and co-primaries

BELLE-2: ER+ HER2- 2nd/3rd line (AI resistant)



BELLE-3: ER+ HER2- 3rd/4th line (AI and mTORi resistant)



*** PI3K+ is PI3K activation = PI3KCA mutation or PTEN mutation or PTEN loss of expression**

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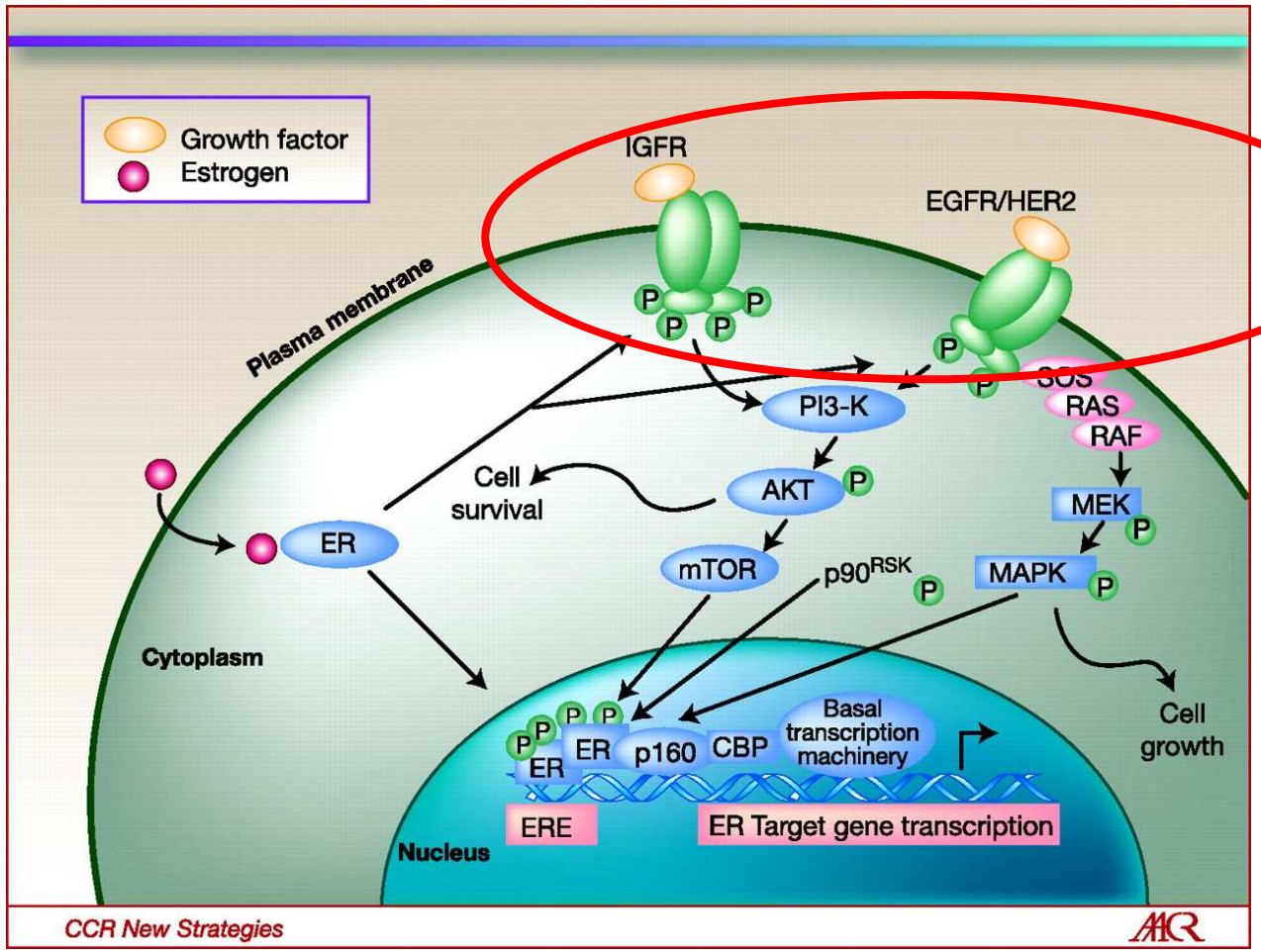
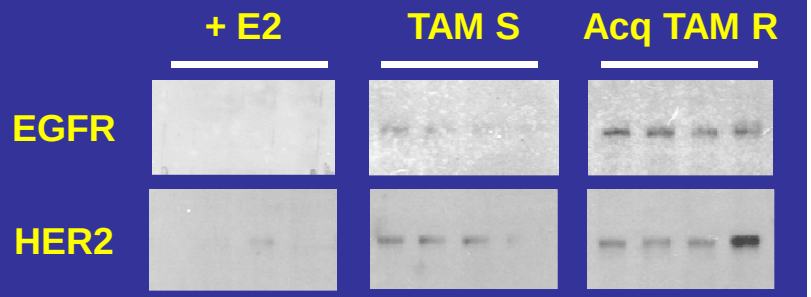
Mechanisms of resistance to endocrine therapy

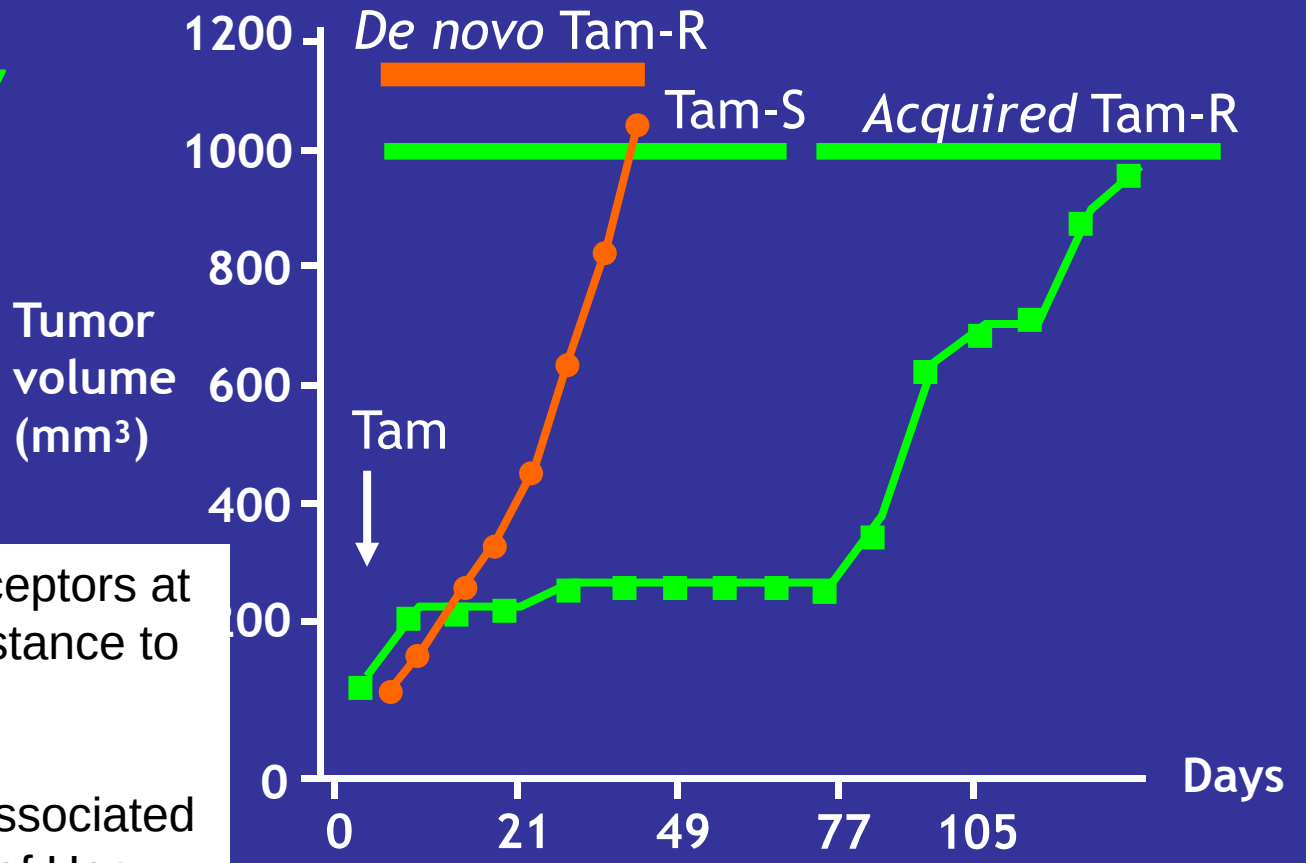


Transmembrane Tyrosine kinase

Johnston. Clin Cancer Res 2010

Her expression and resistance to ET



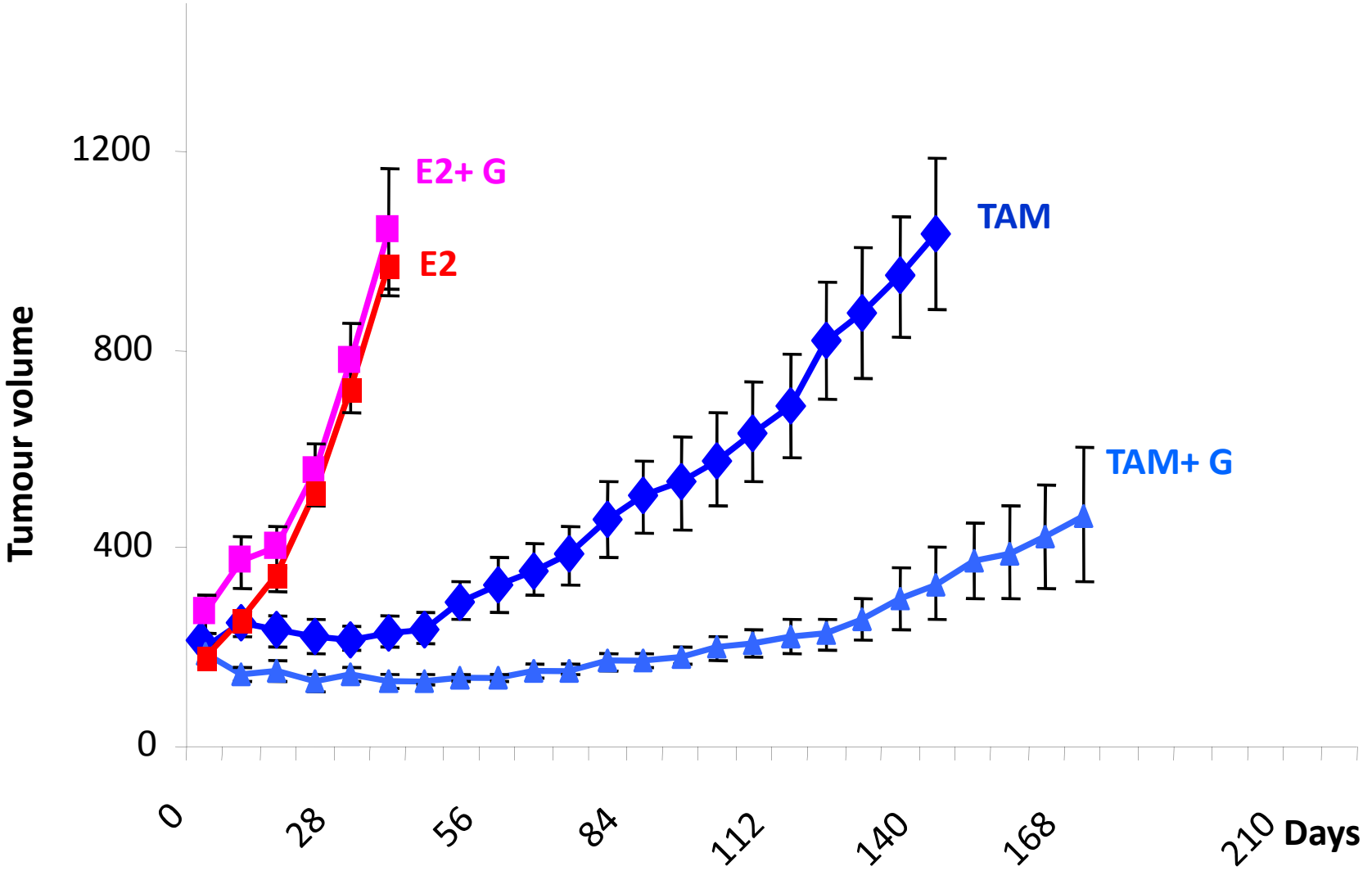


- Overexpression of Her receptors at baseline mediates 1ry resistance to ET in mice models

- Secondary resistance is associated with increased expression of Her

Osborne et al, JNCI 1994
slide S. Johntson

Gefitinib Effect on Acquired Tamoxifen Resistance in ER+ MCF-7 Tumors



Massarweh et al, Cancer Res., 2008 68; 826-33

Proof-of-concept trials

Osborne study

CTRC–AACR San Antonio Breast Cancer Symposium

Dec 2007

n = 206

- ER +ve advanced breast cancer
- Newly diagnosed

or

- 12 m post-adjuvant therapy

Tamoxifen 20 mg QD & Gefitinib 250 mg QD	Tamoxifen 20 mg QD & Placebo

Cristofanilli et al

ASCO

June 2008

n = 93

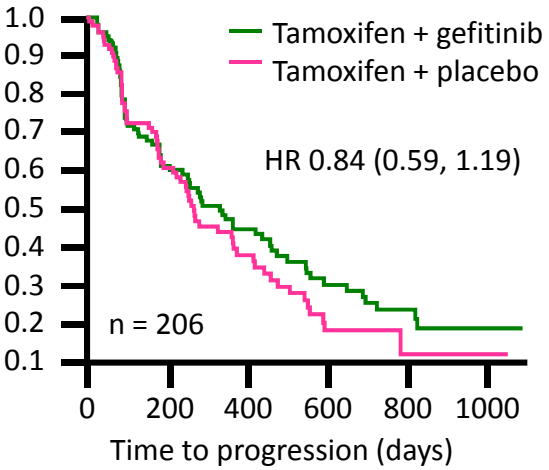
- ER +ve advanced breast cancer

Anastrozole 1 mg QD & Gefitinib 250 mg QD	Anastrozole 1 mg QD & Placebo

QD, once-daily

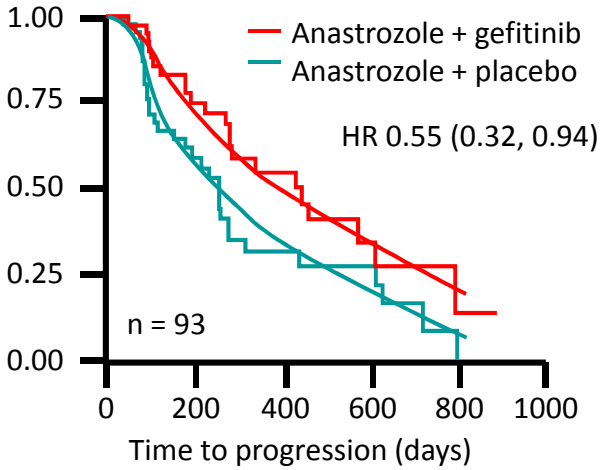
Phase II randomized trials suggest modest efficacy for EGFR inhibitors

Osborne study



Positive treatment effect for gefitinib in overall population

Cristofanilli et al



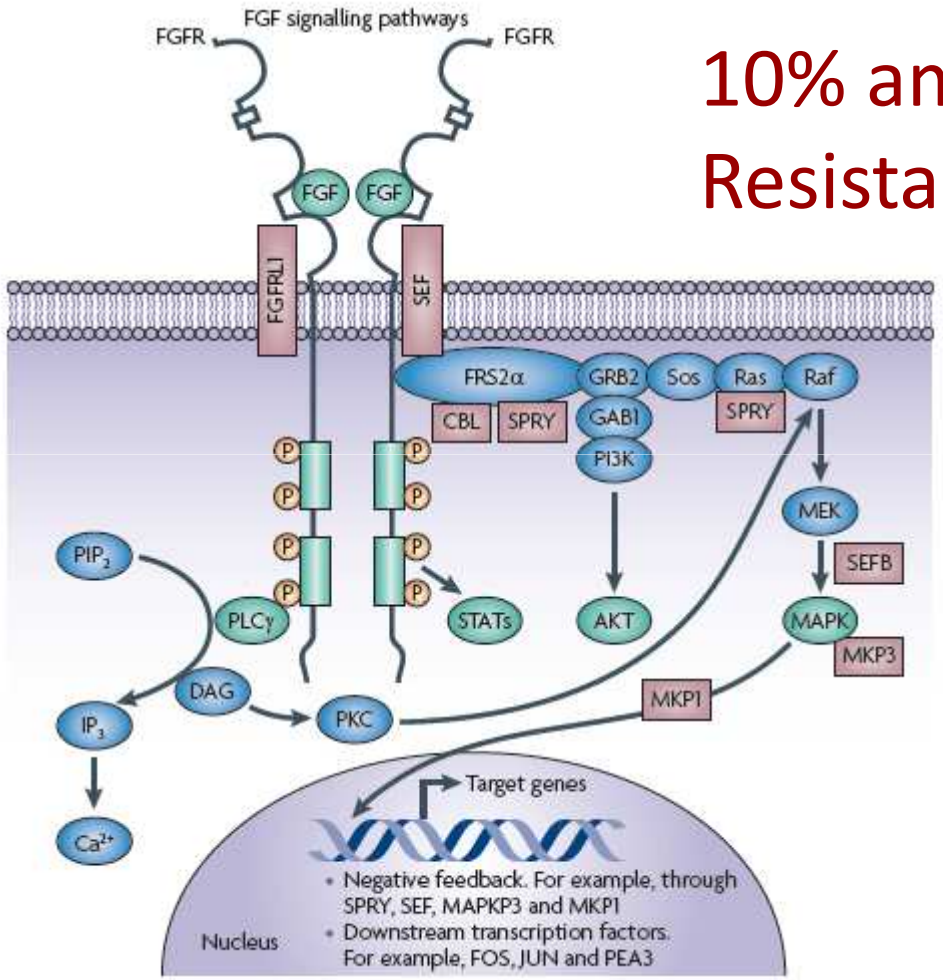
Her inhibitors

- Preliminary data suggest a potential activity
- New data are awaiting with a more potent Her inhibitor (AZ8931)

Outline

- mTOR inhibitors
- PI3K inhibitors
- Her inhibitors
- **FGFR inhibitors**
- CDK inhibitors

FGFR1 and breast cancer



10% amplification

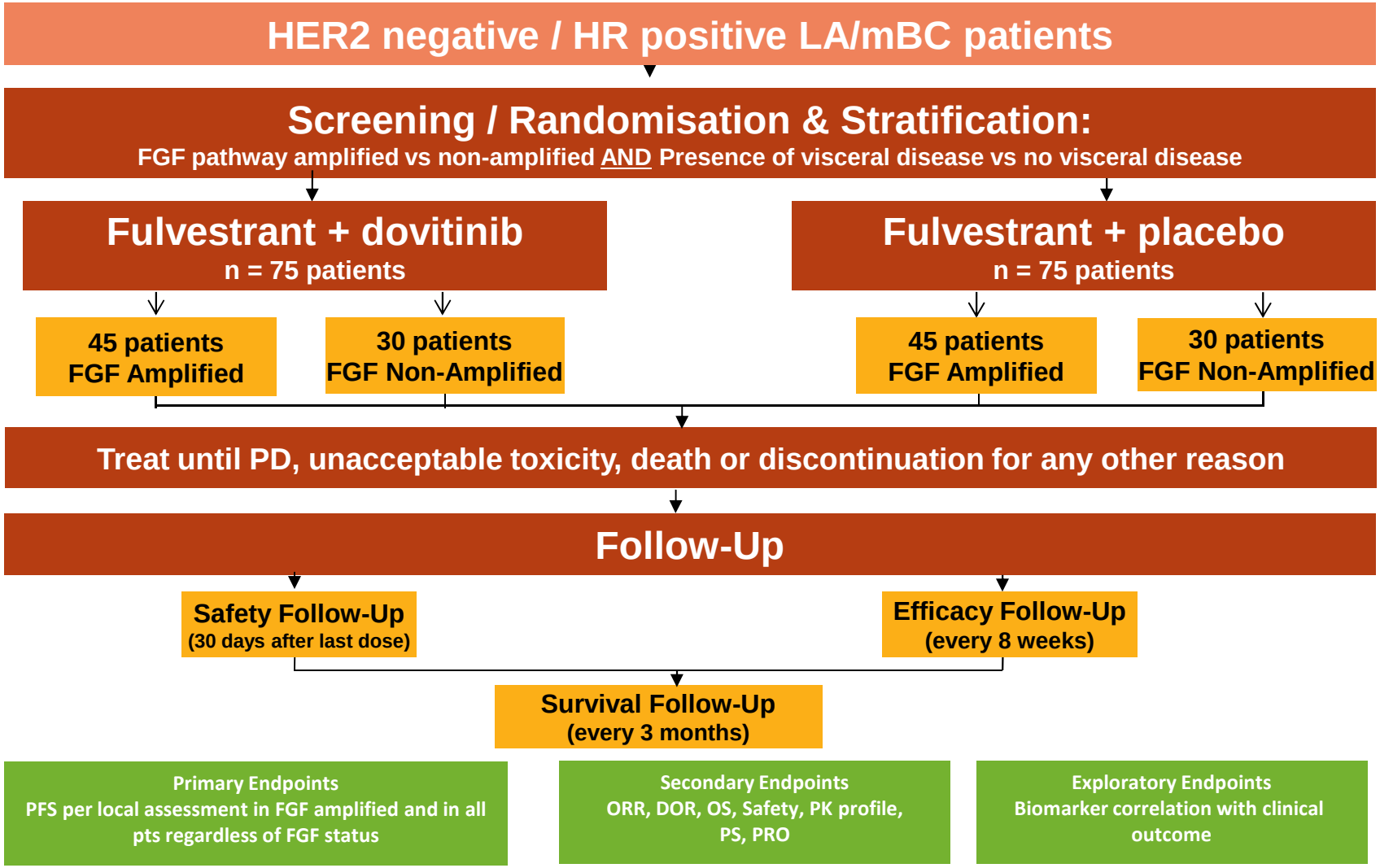
Resistance to ET

Efficacy Results of TKI258 in Patients With Measurable Disease (N=68)

	FGFR1+/HR+ (N = 20)	FGFR1−/HR+ (N = 31)	FGFR1−/HR− (N = 17)
Best overall RECIST response, n (%)			
PR not confirmed after 4 weeks (PRnc)	**3 (15)**	**–**	**–**
SD	9 (45)	15 (48)	4 (24)
PD	5 (25)	9 (29)	6 (35)
Unknown	3 (15)	7 (23)	7 (41)
PD per clinical evaluation but not RECIST	2	1	5
Not assessable	1	6	2
Clinical benefit (CR/PR/SD ≥24 weeks)	**3 (15)**	**1 (3)**	**2 (12)**
PRnc and/or SD ≥24 weeks	**5 (25)**	**1 (3)**	**2 (12)**
PFS median by Kaplan-Meier estimates, months [range]	3.6 [0–9.0]	3.5 [0–5.5]	2.1 [0–9.2]

Andre F, ASCO, 2011

Phase II randomized trial dovitinib (CTKI258A2210)



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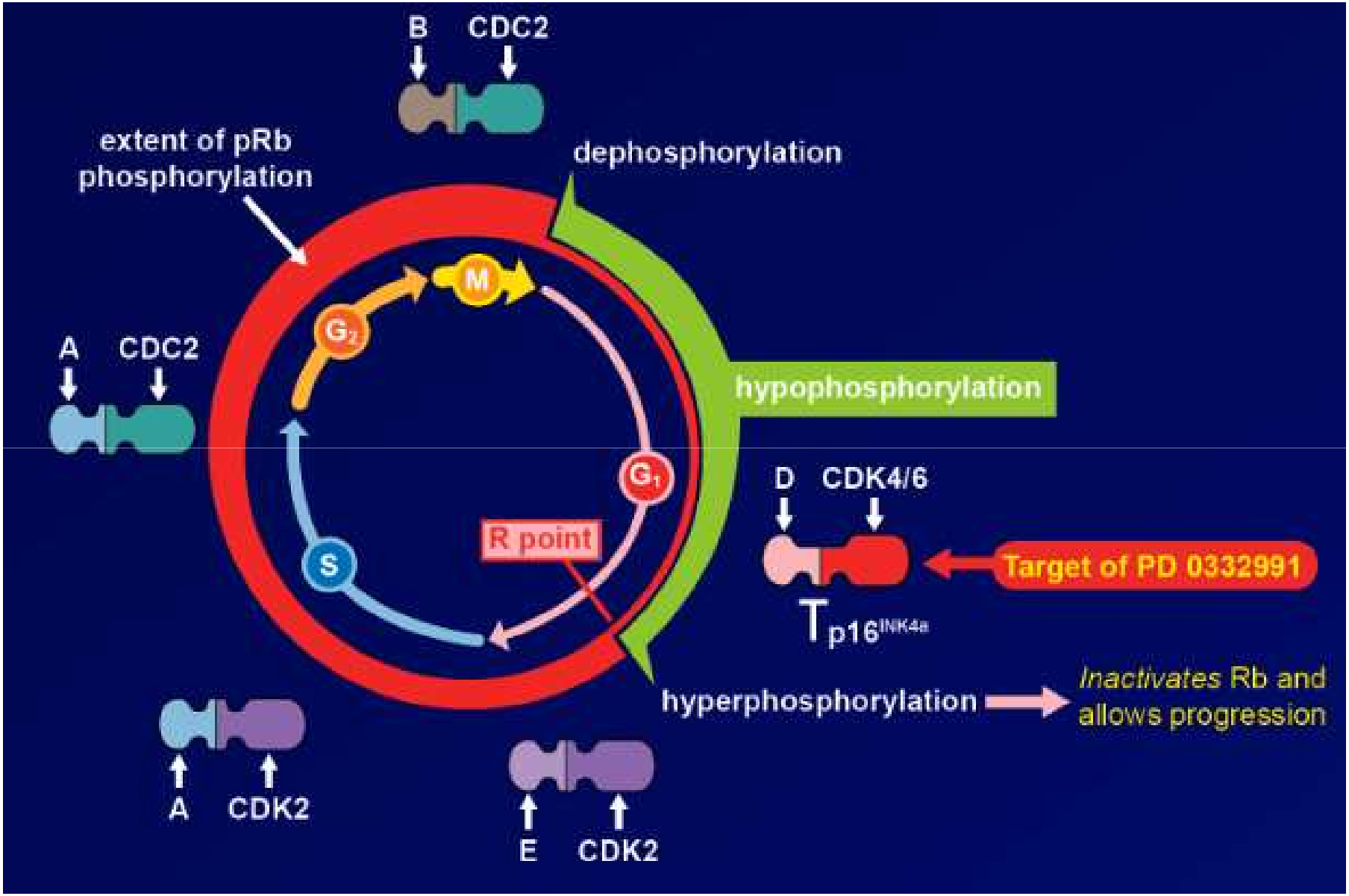
- **CDK inhibitors**


B CDC2
extent of pRb phosphorylation
dephosphorylation
M
G2
A CDC2
hypophosphorylation
G1
D CDK4/6
R point
S
Target of PD 0332991
Tp16INK4a
hyperphosphorylation
Inactivates Rb and allows progression
A CDK2
E CDK2

Abstract S1-6

Results of a Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (TRIO-18)

RS Finn,[1] JP Crown,[2] I Lang,[3] K Boer,[4] IM Bondarenko,[5] SO Kulyk,[6] J Ettl,[7] R Patel,[8] T Pinter,[9] M Schmidt,[10] Y Shparyk,[11] AR Thummala,[12] NL Voitko,[13] A Breazna,[14] ST Kim,[15] S Randolph,[15] DJ Slamon[1]

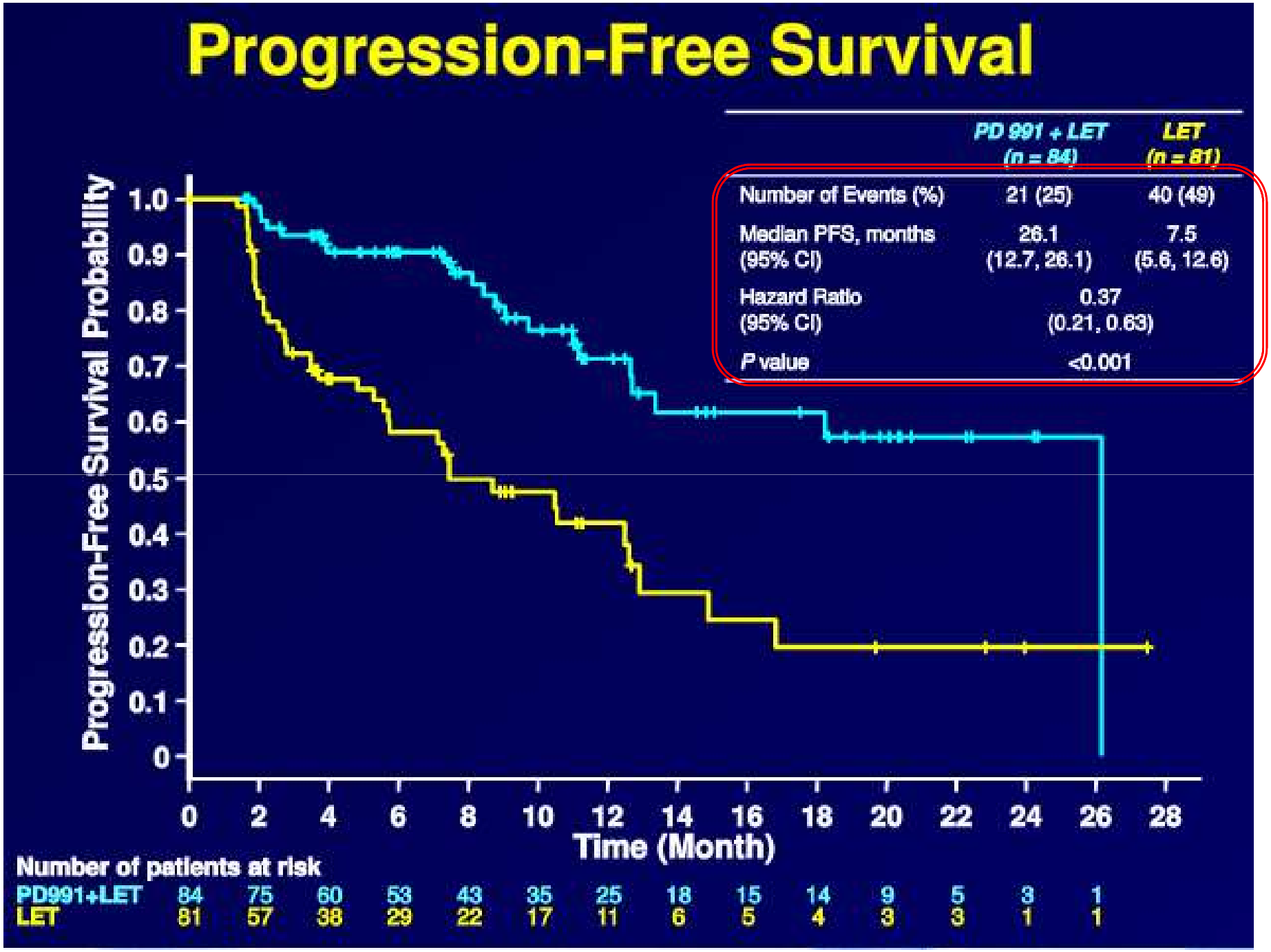
[1]University of California Los Angeles, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]Orszagos Onkologiai Intezet, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]University Hospital Mainz, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Henderson, NV, USA; [13]Kyiv City Clinical Oncology Center, Ukraine; [14]Pfizer Oncology, New York, NY, USA; [15]Pfizer Oncology, La Jolla, CA, USA

Presented at SABCS 2012; December 5, 2012; San Antonio, TX, USA

Baseline Characteristics (ITT)

	PD 991 + LET (n = 84)	LET (n = 81)
Median Age, years (range)	62 (41 – 89)	64 (38 – 84)
ECOG PS, n (%)		
0	46 (55)	45 (56)
1	38 (45)	36 (44)
Disease Stage		
Stage IIIB	3 (4)	6 (7)
Stage IV	80 (95)	75 (93)
Other	1 (1)	0
Disease Site		
Visceral	37 (44)	43 (53)
Bone only	18 (21)	12 (15)
Other (Non-Visceral)	29 (34)	26 (32)
Disease-Free Interval, n (%)		
>12 mos from adjuvant to recurrence	24 (29)	30 (37)
≤12 mos from adjuvant to recurrence or de novo advanced disease	60 (71)	51 (63)
Prior Systemic Treatment, n (%)		
None	44 (52)	37 (46)
Chemotherapy	34 (40)	37 (46)
Hormonal	26 (31)	28 (35)
Tamoxifen	23 (27)	24 (30)
Anastrozole	8 (10)	11 (14)
Letrozole	2 (2)	1 (1)
Exemestane	4 (5)	2 (2)

Progression-Free Survival



Conclusion

- mTOR inhibitors reverse resistance to endocrine therapy and improve outcome
- CDK4 inhibitors are highly promising:
  - Validation studies are ongoing
  - Development in ET-resistant patients is ongoing
- PI3K inhibitors are being developed
  - Role of PIK3CA mutations is unclear
- FGFR inhibitors are being developed
  - Development is facing challenges since incidence of FGFR1 amplification is rare