VHIO

VALL D'HEBRON
Institut d'Oncologia

Medicina personalizada en el cáncer de mama

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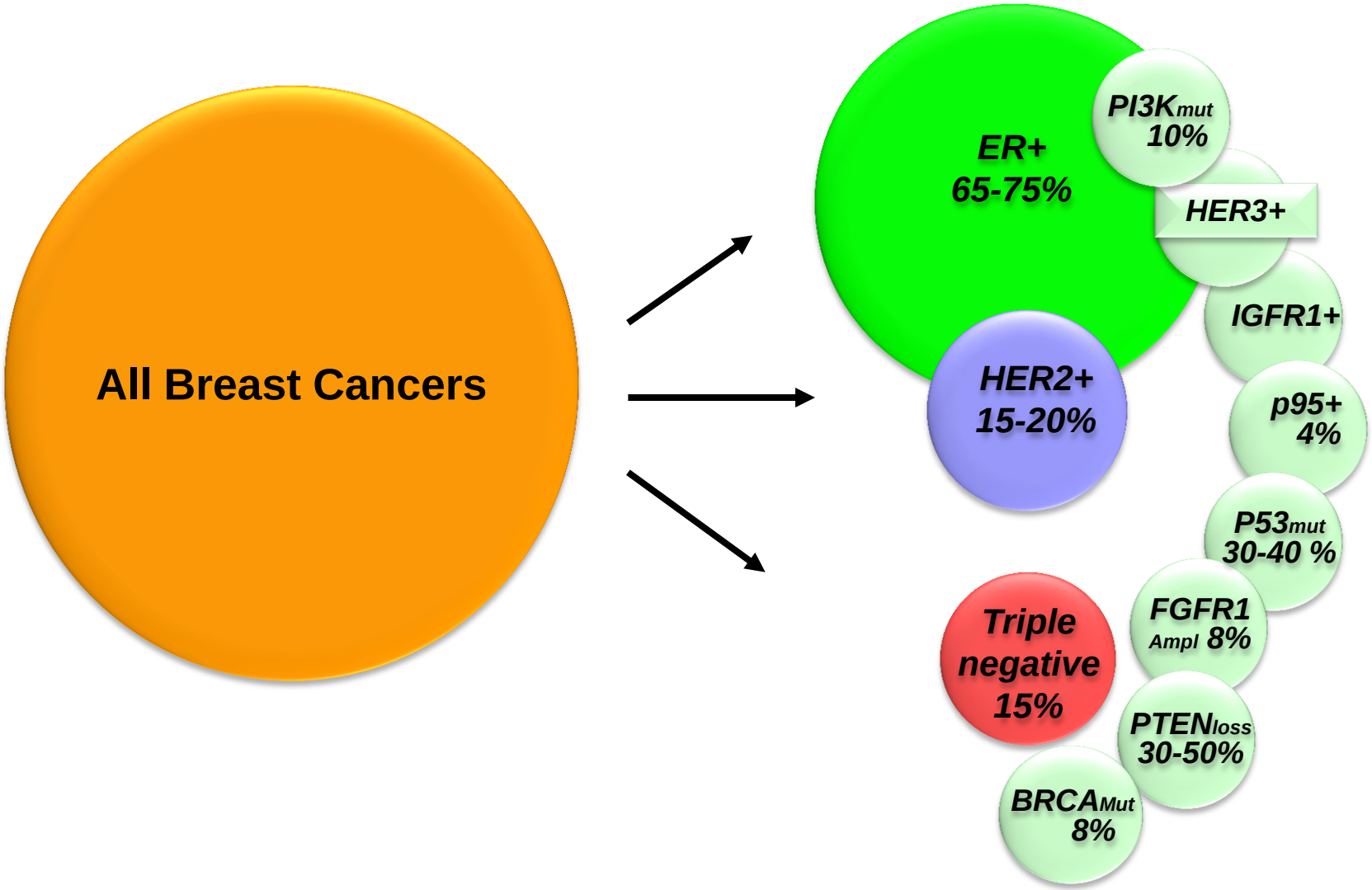
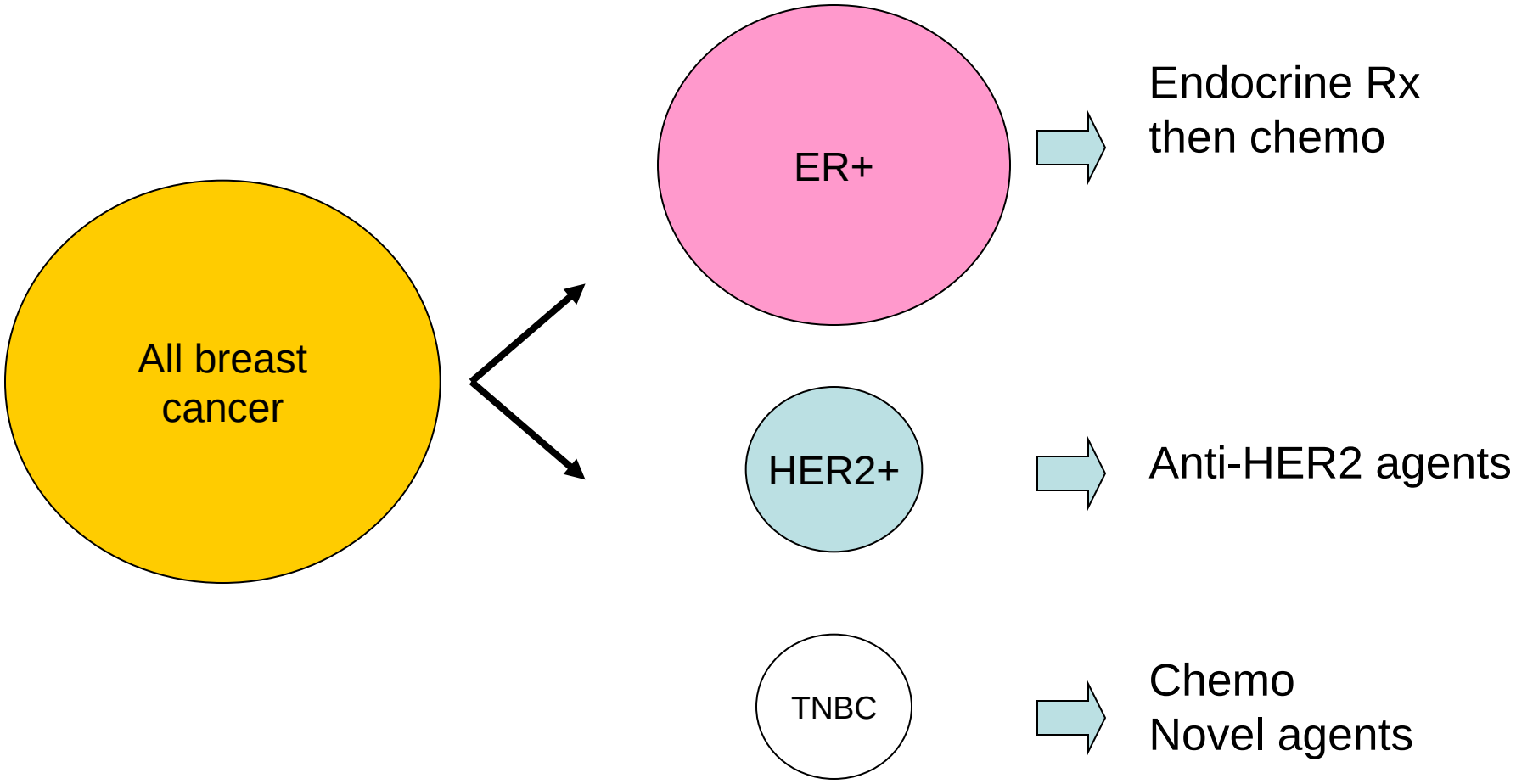
Breast Cancer Diseases – 201…



Breast Cancer Subsets and Treatments

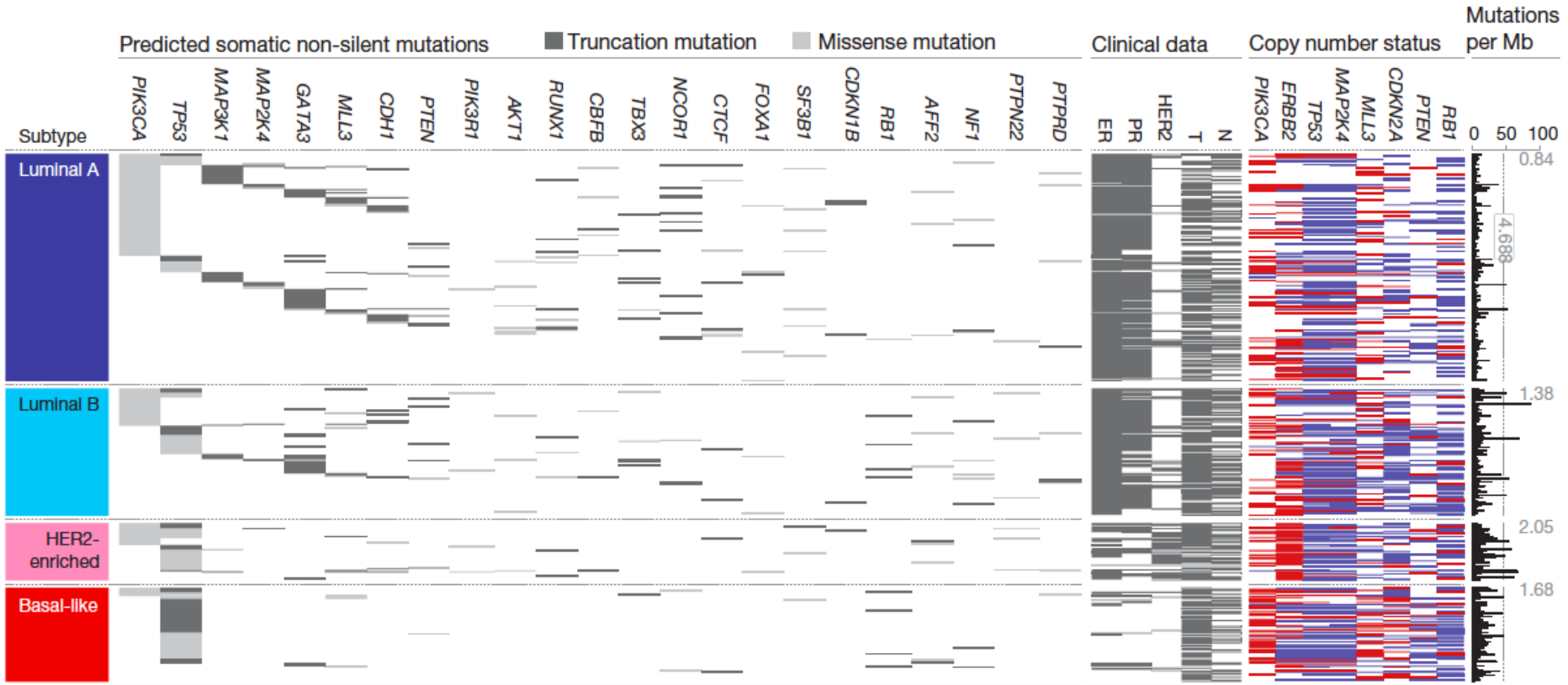


ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*



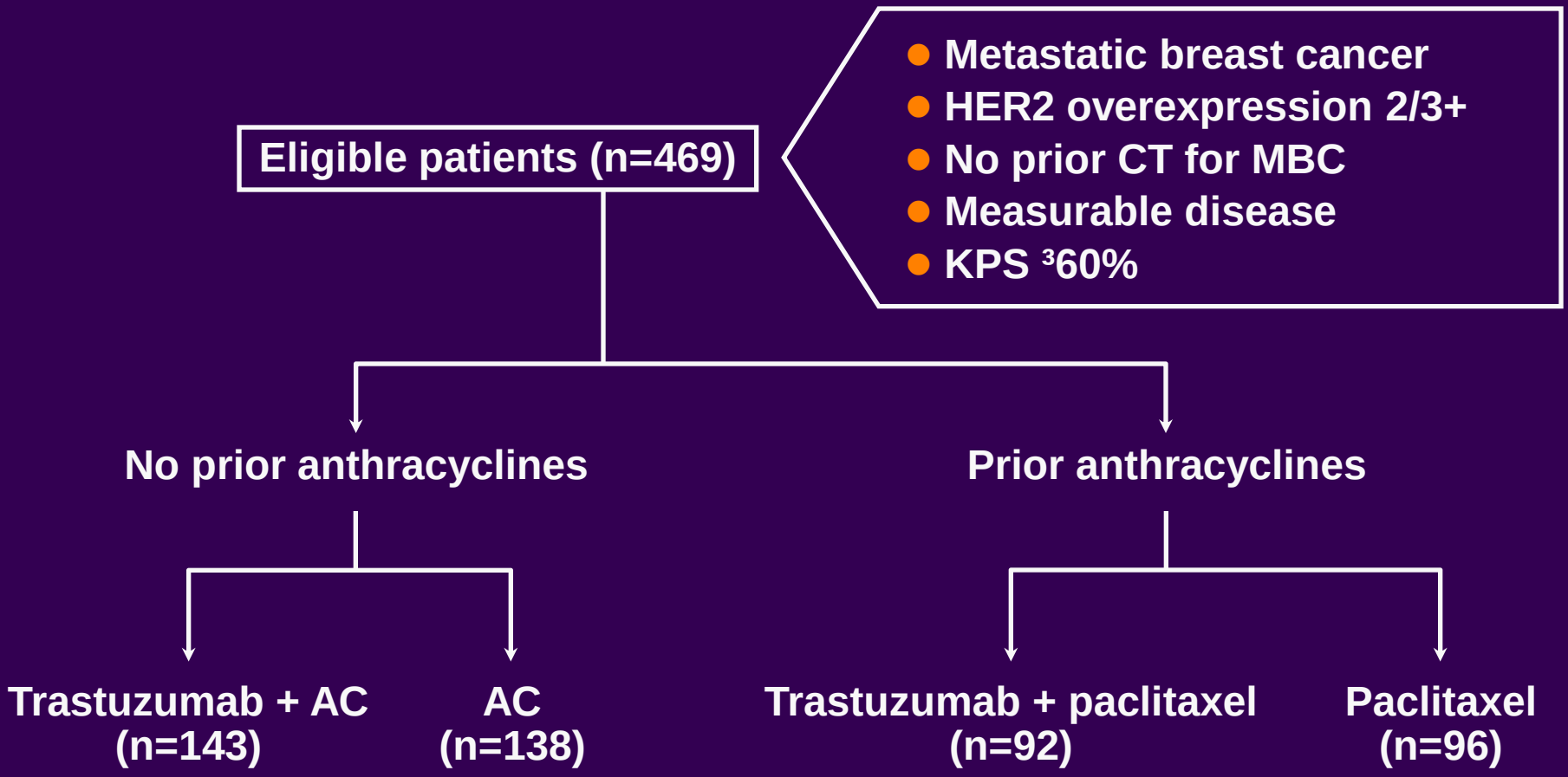
	PIK3CA	TP53	MAP3K1	MAP2K4	GATA3	MLL3	CDH1	PTEN	PIK3R1	AKT1	RUNX1	CBFB	TBX3	NCOR1	CTCF	FOXA1	SF3B1	CDKN1B	RB1	AFF2	NF1	PTPN22	PTPRD
All	36%	37%	8%	4%	11%	7%	7%	3%	3%	2%	4%	2%	3%	3%	3%	2%	2%	1%	2%	3%	3%	1%	2%
Luminal A	45%	12%	13%	7%	14%	8%	9%	4%	0.4%	4%	5%	2%	3%	5%	4%	2%	3%	1%	0.4%	1%	2%	0.4%	2%
Luminal B	29%	29%	5%	2%	15%	6%	5%	4%	2%	2%	2%	2%	4%	2%	2%	2%	0%	1%	3%	2%	4%	2%	4%
HER2-enriched	39%	72%	4%	2%	2%	7%	5%	2%	4%	2%	4%	2%	0%	0%	2%	2%	4%	2%	0%	5%	0%	5%	4%
Basal-like	9%	80%	0%	0%	2%	5%	0%	1%	0%	0%	0%	0%	1%	2%	1%	0%	1%	0%	4%	4%	2%	0%	1%

Percentages of cases with mutation by expression subtype

HER2+ MBC

Trastuzumab with chemotherapy in HER2 positive MBC

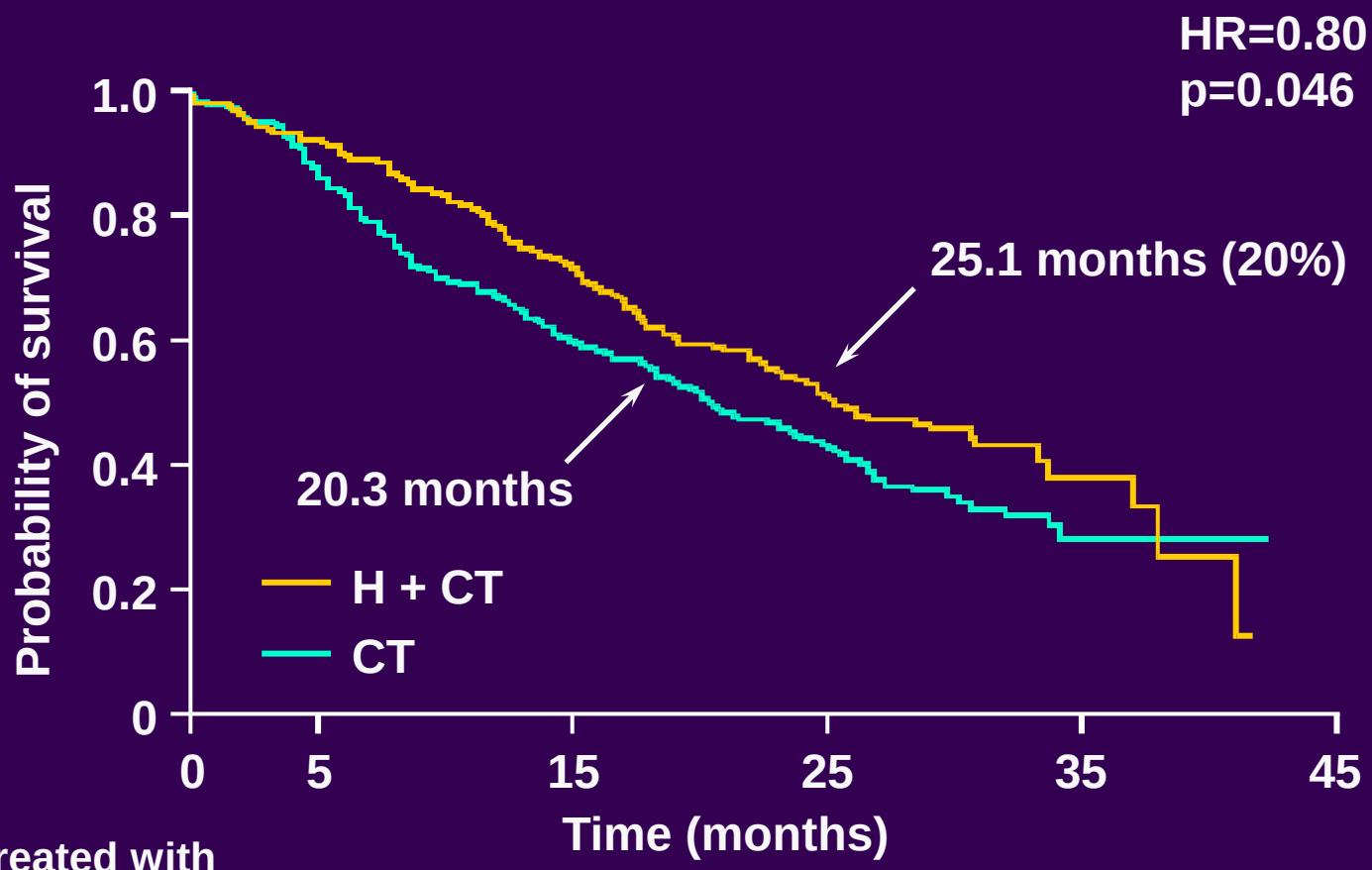
Design and enrolment



AC = doxorubicin/epirubicin + cyclophosphamide

Slamon DJ et al. N Engl J Med 2001

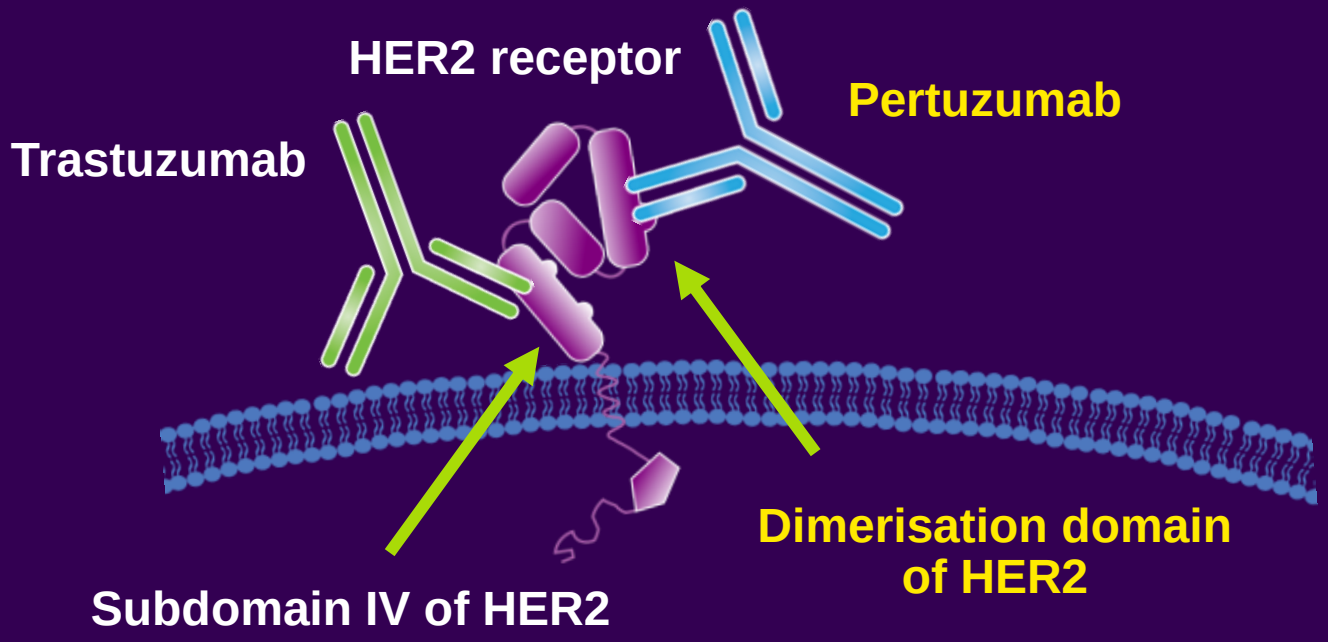
Overall survival



CT patients treated with trastuzumab after disease progression	24%	62%	65%	72%

Slamon DJ et al. N Engl J Med 2001

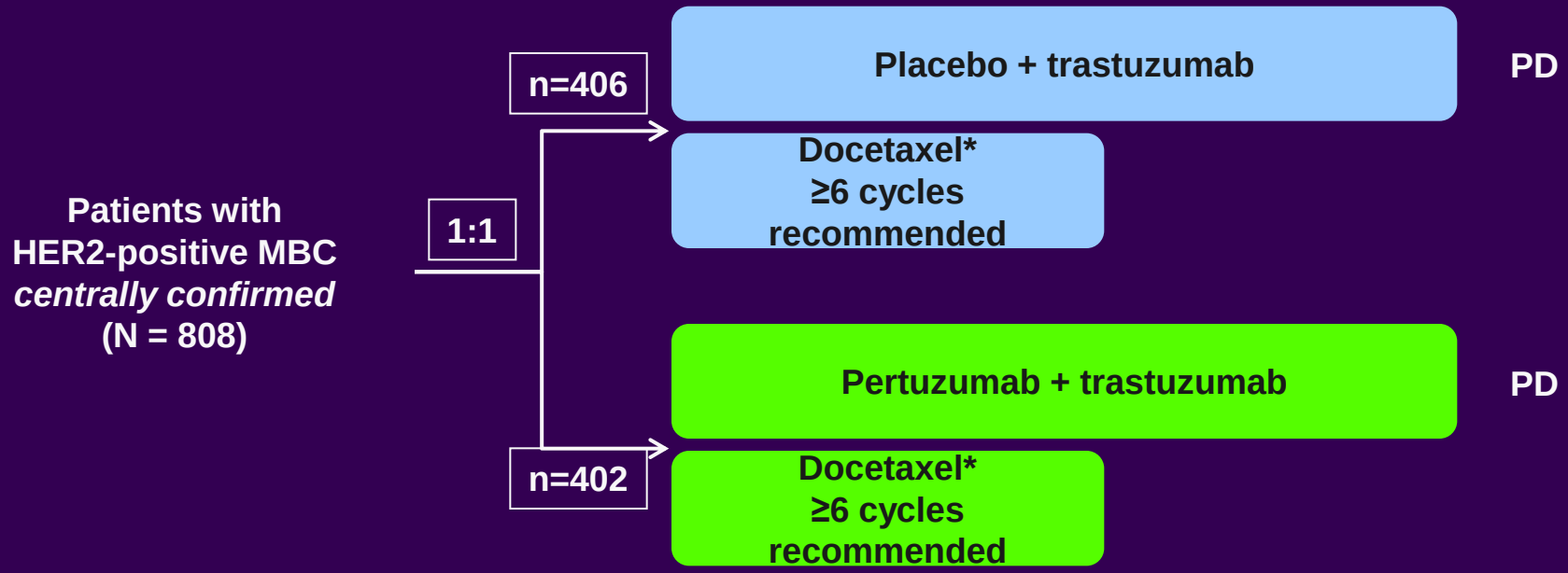
Pertuzumab and trastuzumab bind to different regions on HER2 and have synergistic activity



- Continually suppresses HER2 activity
- Flags cells for destruction by the immune system
- Does not inhibit HER2 heterodimerisation

- Inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER signalling
- Flags cells for destruction by the immune system

CLEOPATRA Study



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

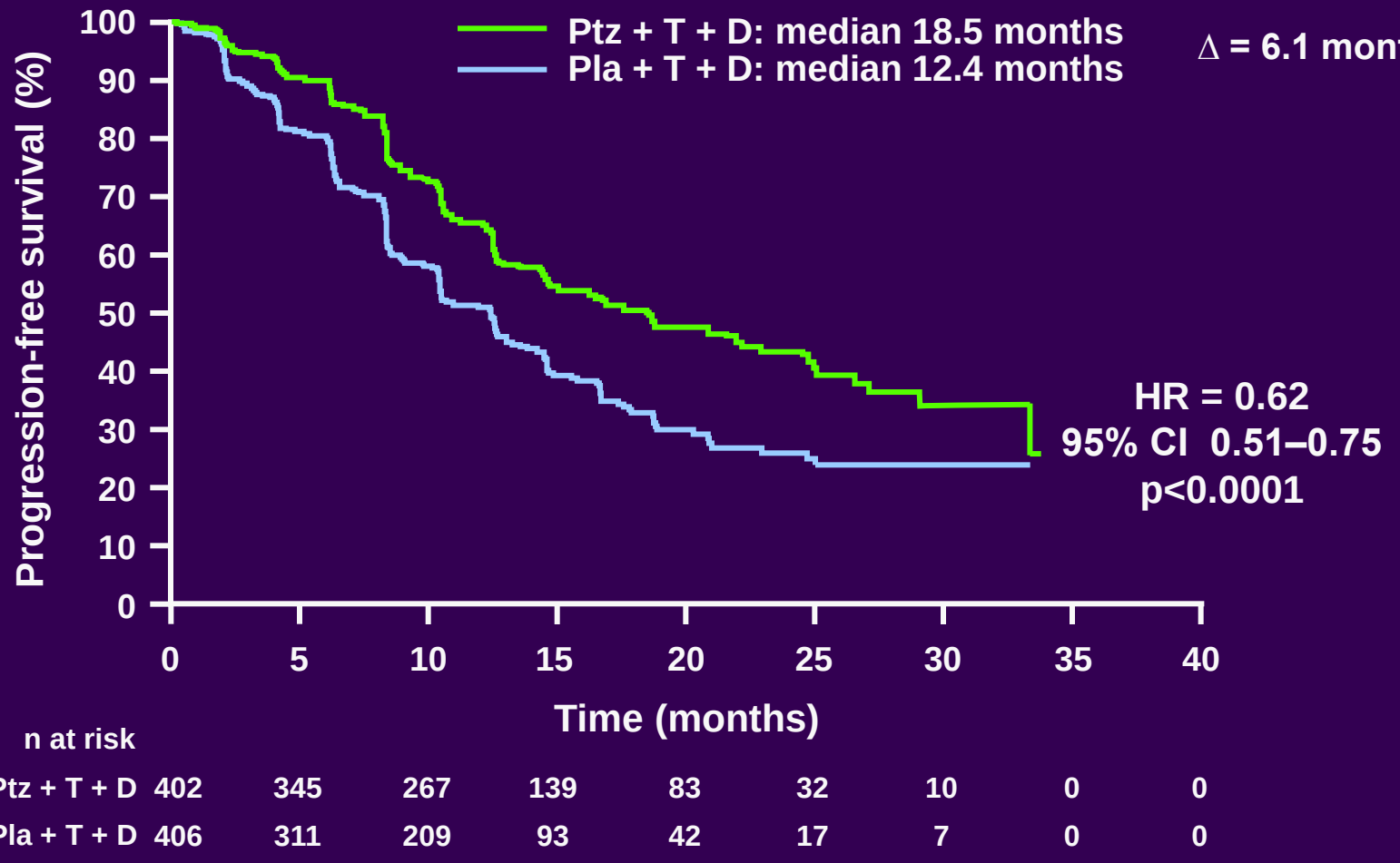
*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease

Baselga J, et al. NEJM 2012

Independently assessed PFS

Median follow-up: 19.3 months, n = 433 PFS events



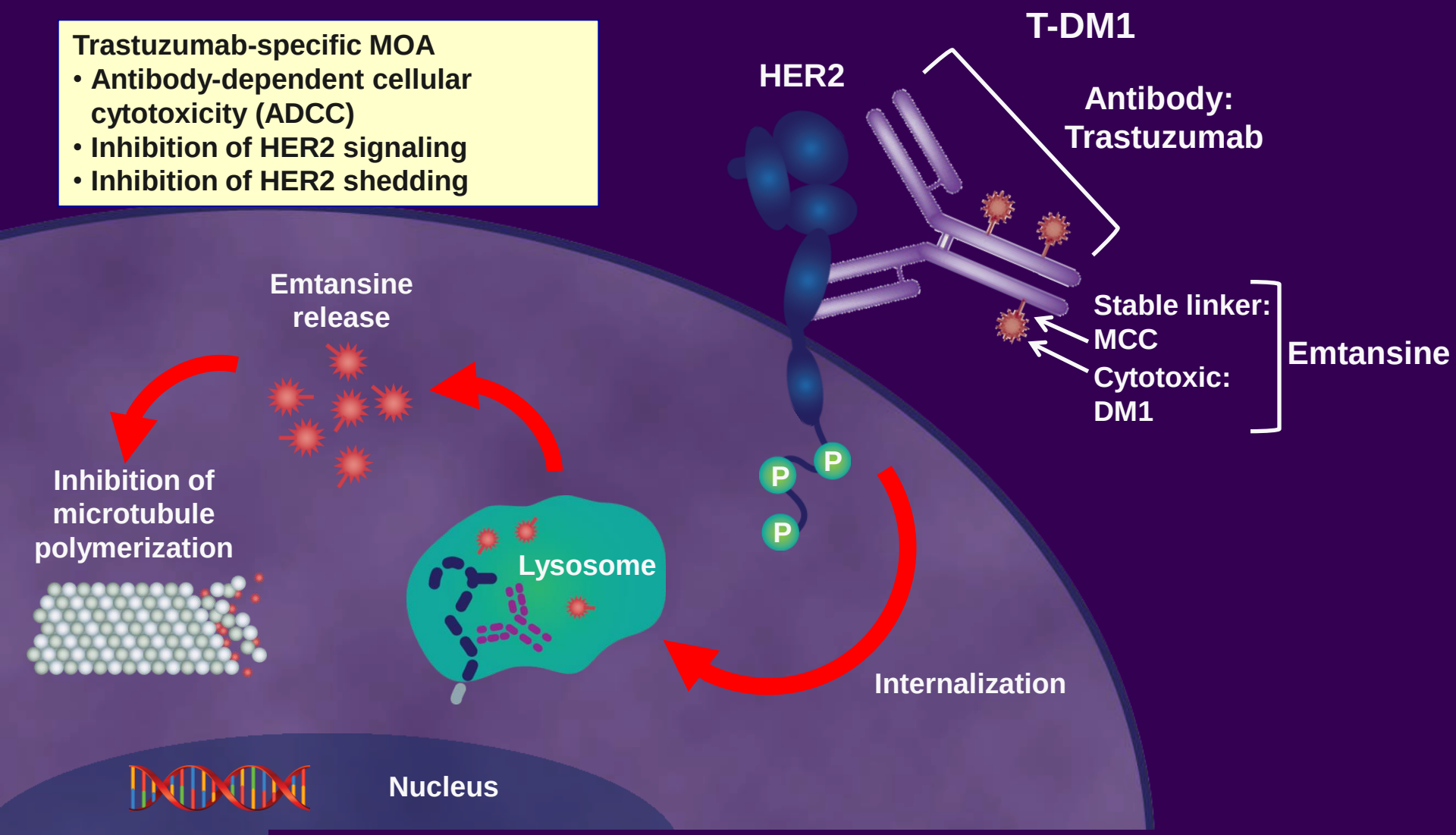
Stratified by prior treatment status and region

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga J, et al. NEJM 2012

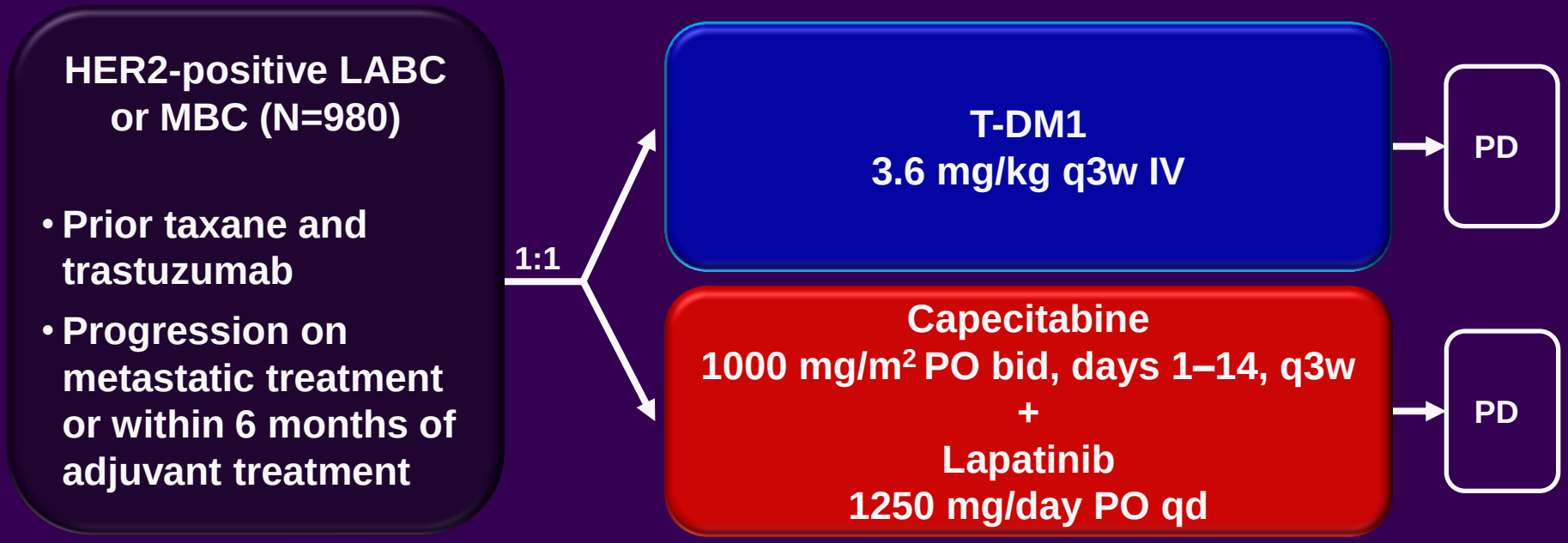
T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells

Trastuzumab-specific MOA
- **Antibody-dependent cellular cytotoxicity (ADCC)**
- **Inhibition of HER2 signaling**
- **Inhibition of HER2 shedding**



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

EMILIA Trial



- Primary endpoints: PFS by independent review, OS, and safety
- Key secondary endpoints: PFS by investigator, ORR, DOR
- Statistical considerations: Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints

Verma, et al. NEJM 2012

EMILIA Trial

After previous ASCO data, are these new data clinically relevant?

OS IMPROVEMENT ???

	Median (months)	No. of events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.475, 0.813)

P=0.0005

Efficacy stopping boundary P=0.0003 or HR=0.617

OS IMPROVEMENT

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

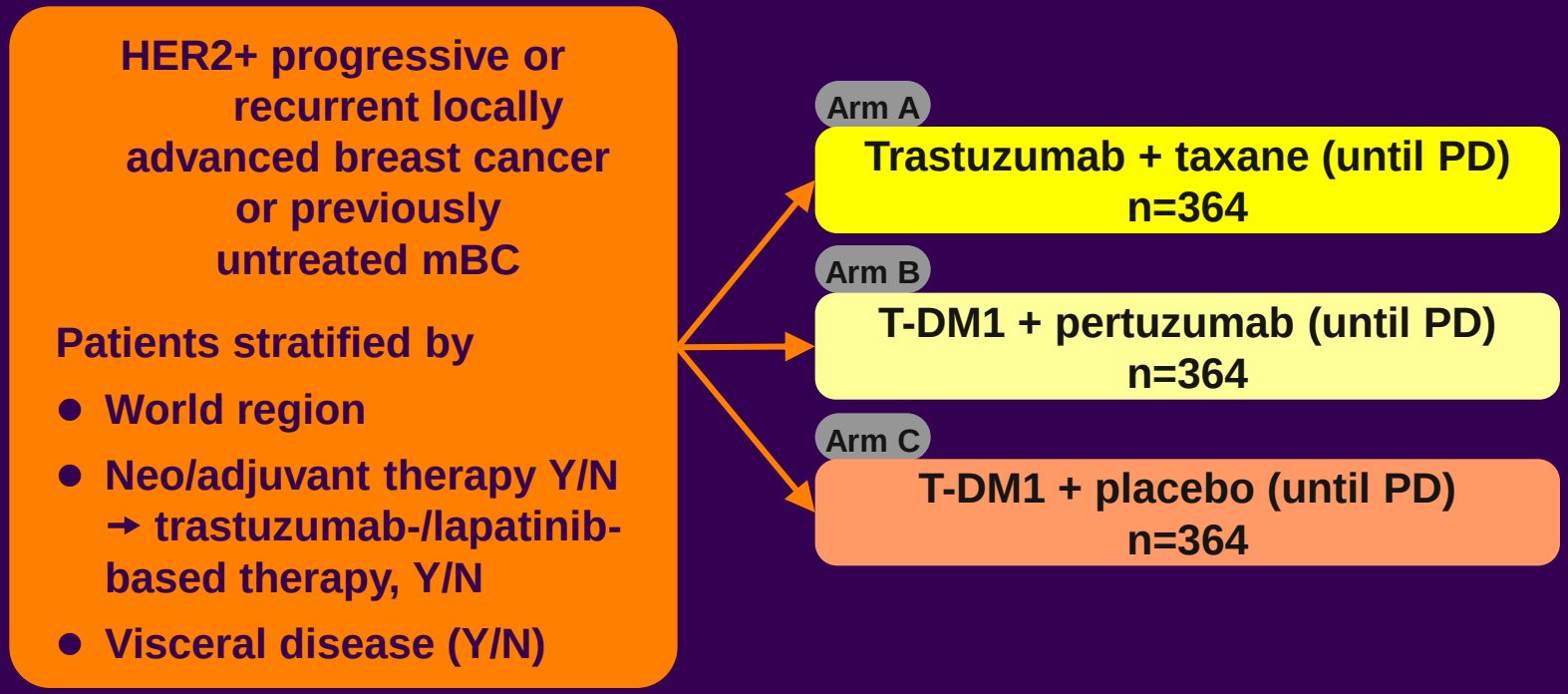
Stratified HR=0.682 (95% CI, 0.548, 0.849)

P=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727

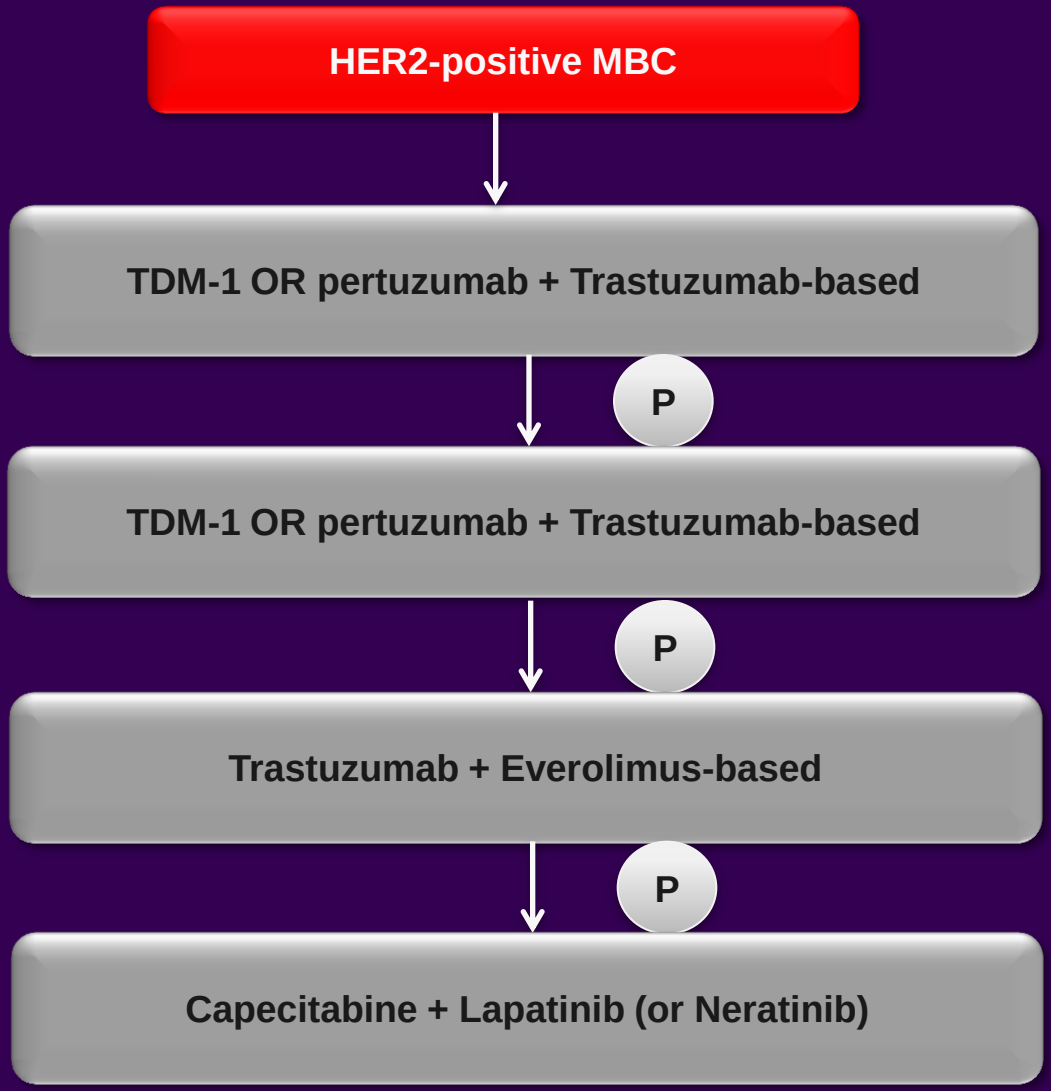
[1]Blackwell et al. ASCO 2012; [2]Verma et al. NEJM 2012

MARIANNE: phase III study of first-line T-DM1 ± pertuzumab versus SOC in HER2-positive MBC



- **Primary efficacy objective**
  - *PFS assessed by an IRF*
- **Primary safety objective**
  - *compare the safety of T-DM1 + pertuzumab or T-DM1 + placebo versus trastuzumab + taxane*

Near Future…


HER2-positive MBC
TDM-1 OR pertuzumab + Trastuzumab-based
P
TDM-1 OR pertuzumab + Trastuzumab-based
P
Trastuzumab + Everolimus-based
P
Capecitabine + Lapatinib (or Neratinib)

HER2 Status and Benefit from Adjuvant Trastuzumab in Breast Cancer

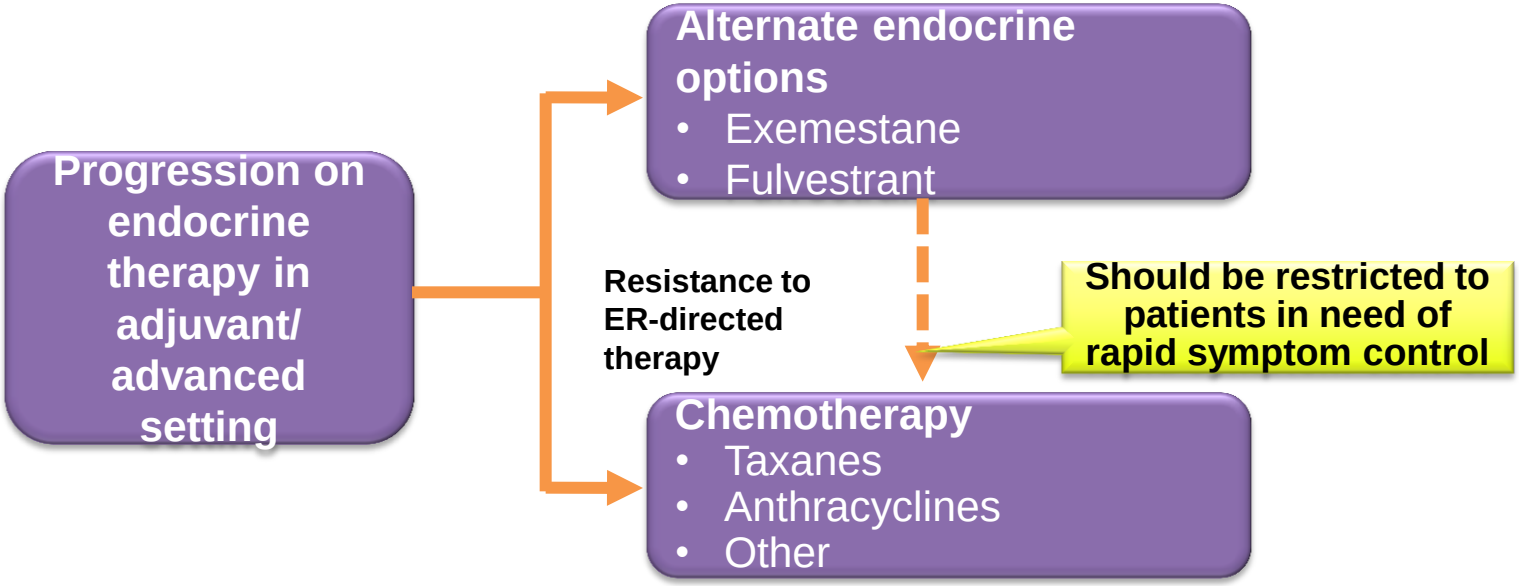
Table 1. Relative Risks of Disease Progression and Death among Patients in the ACTH Group as Compared with the ACT Group.*

End Point and Central HER2 Assay†	ACT	ACTH	Relative Risk (95% CI)	P Value	P Value for the Interaction
	no. of events/total no. of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37–0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14–0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43–0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01–0.64)	0.017	

Paik S, et al. NEJM 2008

HER2- MBC

HR+ ABC Treatment Paradigm* Progression After Endocrine Treatment



NCCN[1]	ABC-1[2]
Recommend 3 consecutive endocrine therapy regimens before switching to chemotherapy	No consensus following initial AI therapy; options include • Tamoxifen • Another AI • Fulvestrant • Megestrol acetate

AI, aromatase inhibitor; ER, oestrogen receptor; HR, hormone receptor; NCCN, National Comprehensive Cancer Center.
*Guidelines refer to postmenopausal HR+ advanced breast cancer, and recommend endocrine therapy for patients who are not in visceral crisis.

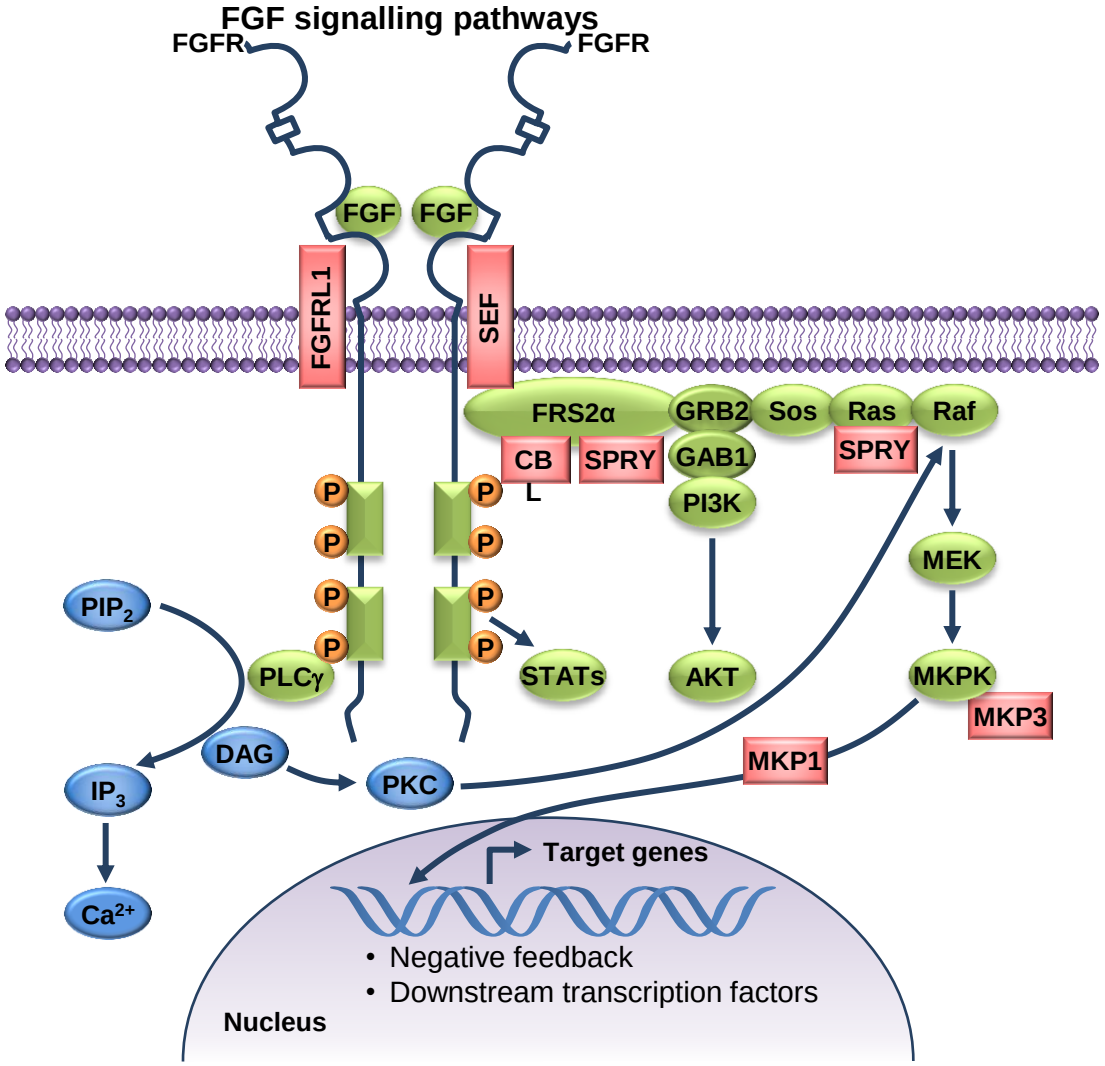
1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer*. V.3.2012;
2. Cardoso F, et al. *Breast*. 2012;21(3):242-252.

Some mechanisms of Resistance

- Tyrosine kinases and resistance to endocrine therapy
- Intracellular kinases and resistance to endocrine therapy
- CDK and other therapeutic targets

CDK, cyclin-dependent kinase.

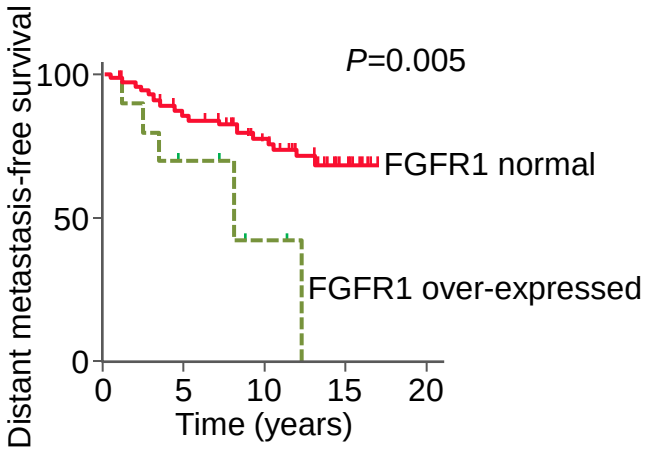
Fibroblast Growth Factor Signalling in ABC

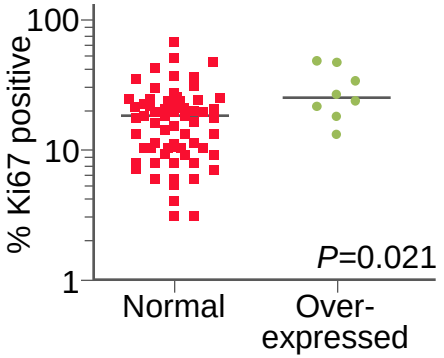


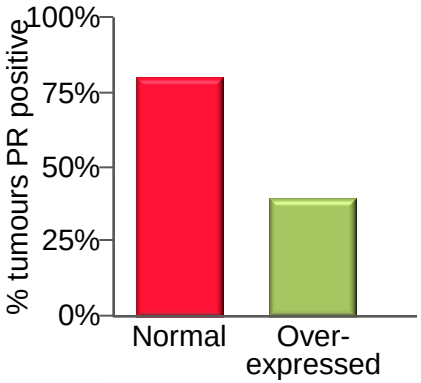
- 18 Ligands
- 4 Receptors
  - Transmembrane tyrosine kinases
  - MAPK activation
- *FGFR1* gene amplification in 10% of breast cancers

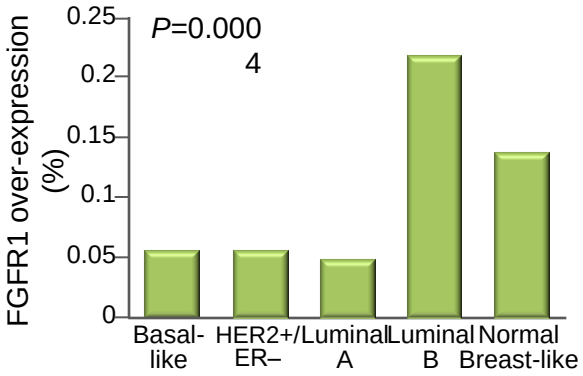
Turner N, et al. *Cancer Res*. 2010;70:2085-2094.

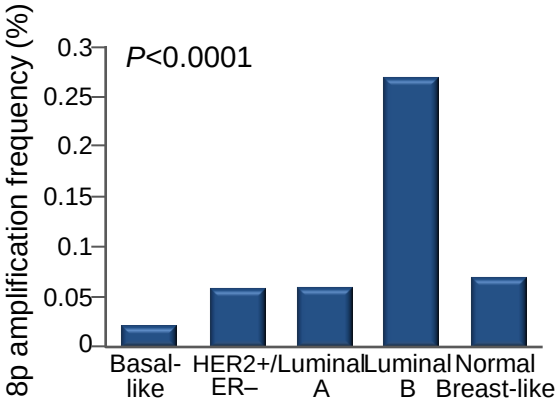
Association of *FGFR1* Amplification and Clinical Outcomes in HR+ Breast Cancer[1]











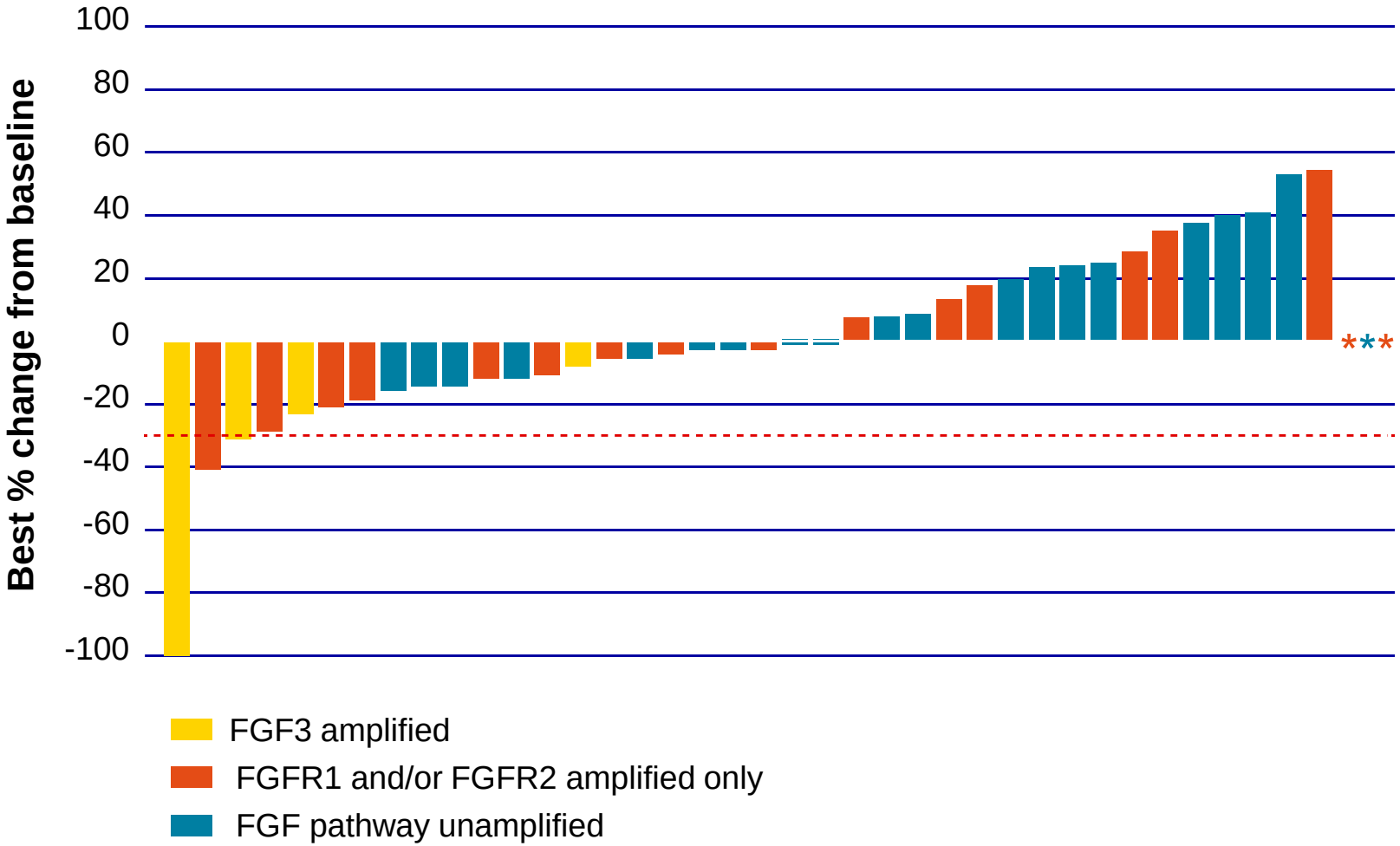
Ongoing Phase II trial will evaluate efficacy and safety of dovitinib combined with fulvestrant, in postmenopausal patients with HER2–/HR+ ABC after progression on prior endocrine therapy[2]

FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; HR, hormone receptor.

1. Turner N, et al. *Cancer Res*. 2010;70:2085-2094; 2. Clinicaltrials.gov. Accessed September 2012. Identifier number: NCT01528345

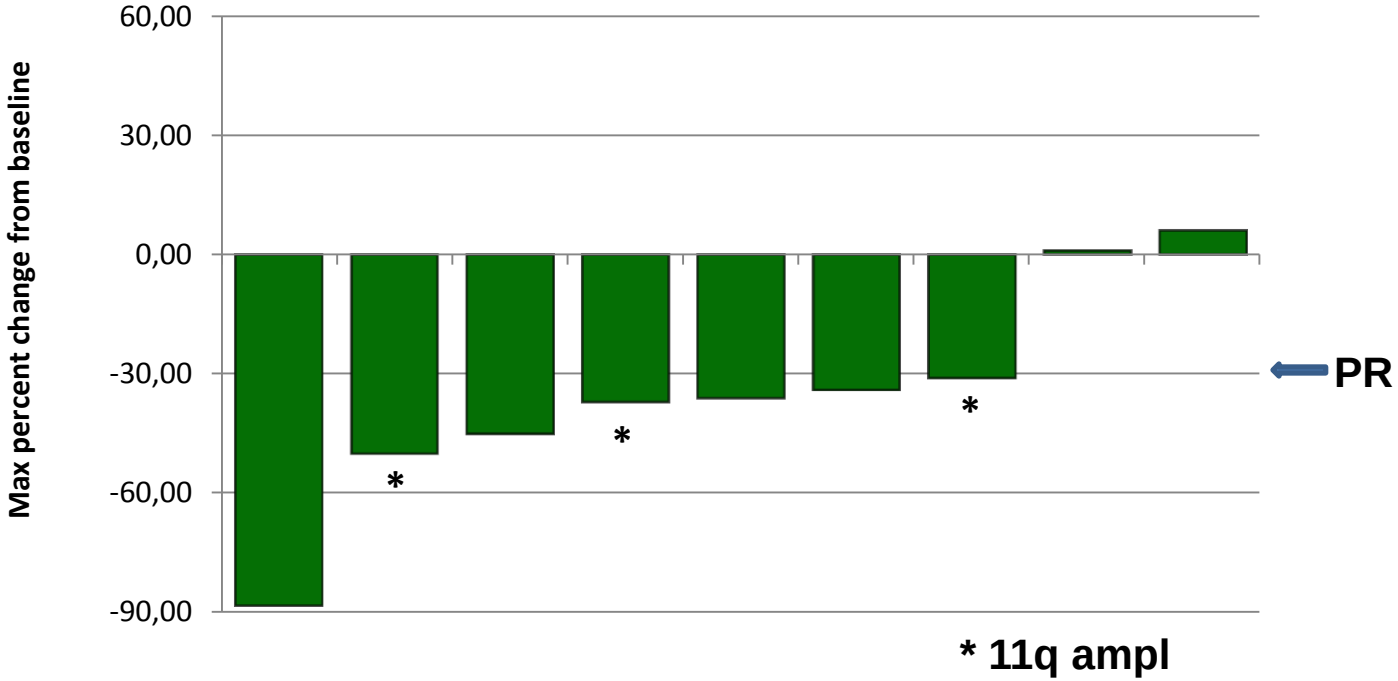
Dovitinib (TKI258) in Breast Cancer

A Multicenter, Open-Label Phase 2 Trial of Dovitinib, an FGFR1 Inhibitor, in *FGFR1*-Amplified and -Nonamplified Metastatic Breast Cancer



F Andre et al. ASCO 2012, Abst #508

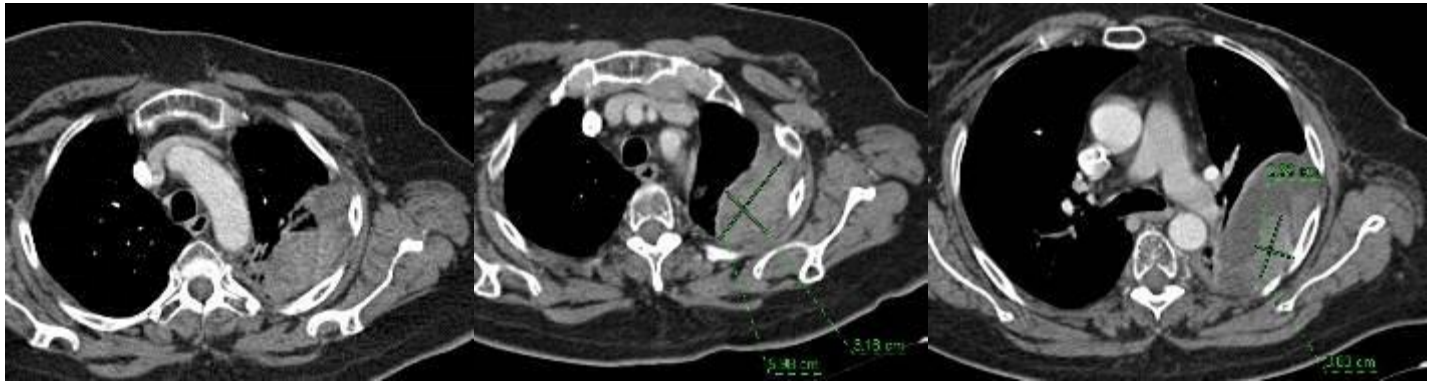
E3810:FGF+ Breast Cancer Patients with Measurable Disease



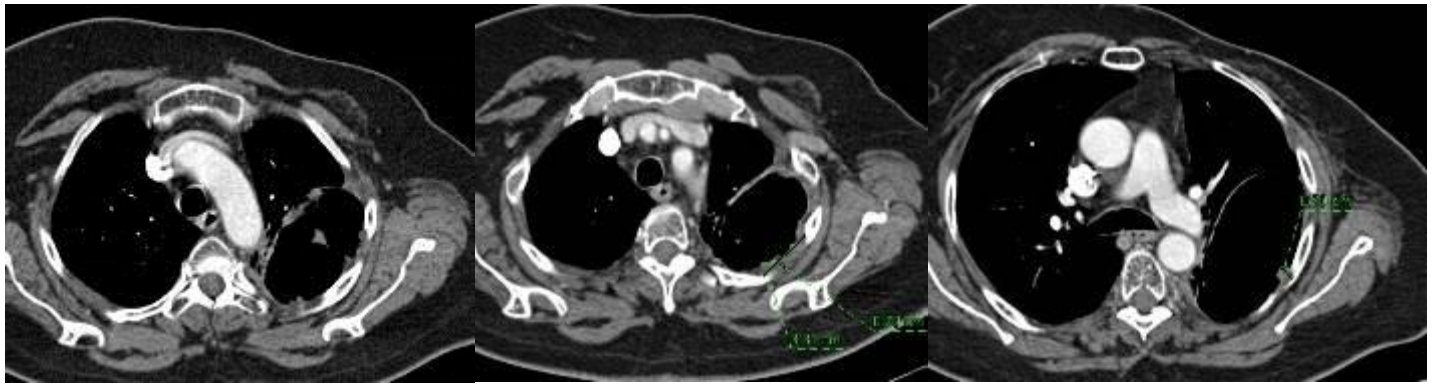
One patient with non-measurable target lesions and off study for PD not shown.

Patient 18032 (VHIO)

Baseline
Sept. 20, 2011



C3D1
Nov. 18, 2011



- **HR+/HER2-, *FGFR1* ampl (ratio 2.21) and CGH**
- Bone, lung and pleura metastases
- 14 prior treatment lines, including 5 Phase 1 trials
- E-3810 at 20 mg/day

Pivotal BOLERO-2 Study: Exemestane ± Everolimus in ABC Progressing After NSAIs

N=724

PMW with HR+ HER2– ABC refractory to LET or ANA, defined as

- Recurrence during or within 12 months after end of adjuvant treatment, or
- Progression during or within 1 month after end of treatment for advanced disease

Everolimus 10 mg/day + Exemestane 25 mg/day (n=485)

Placebo + Exemestane 25 mg/day (n=239)

Primary endpoint:
PFS

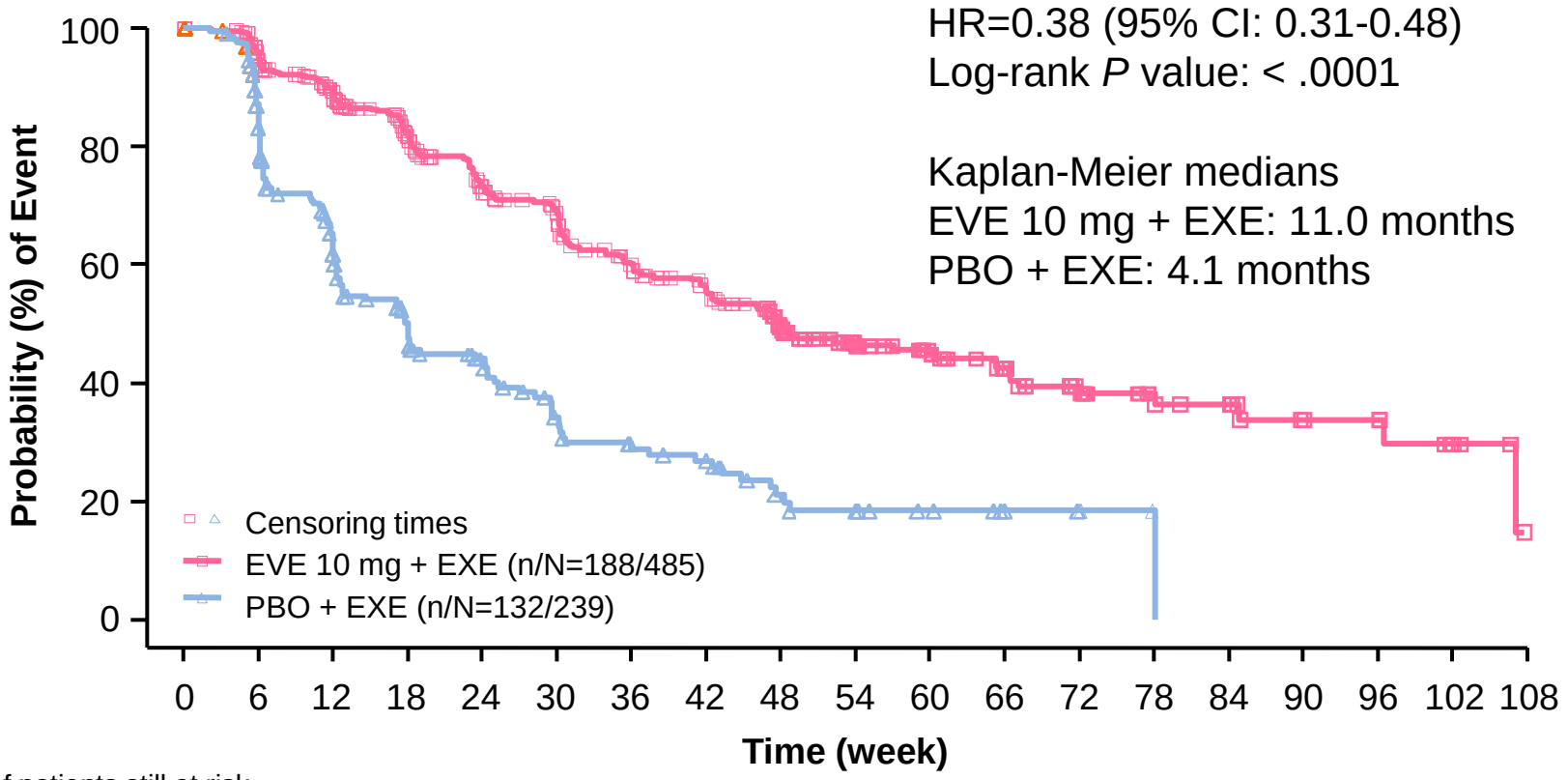
Secondary endpoints:
OS, ORR, CBR, safety, QoL, bone markers

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

ANA, anastrozole; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor; HR+, hormone receptor-positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; PMW, postmenopausal women; QoL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2: Primary Endpoint, PFS (18-Month Follow-up, Central Assessment)

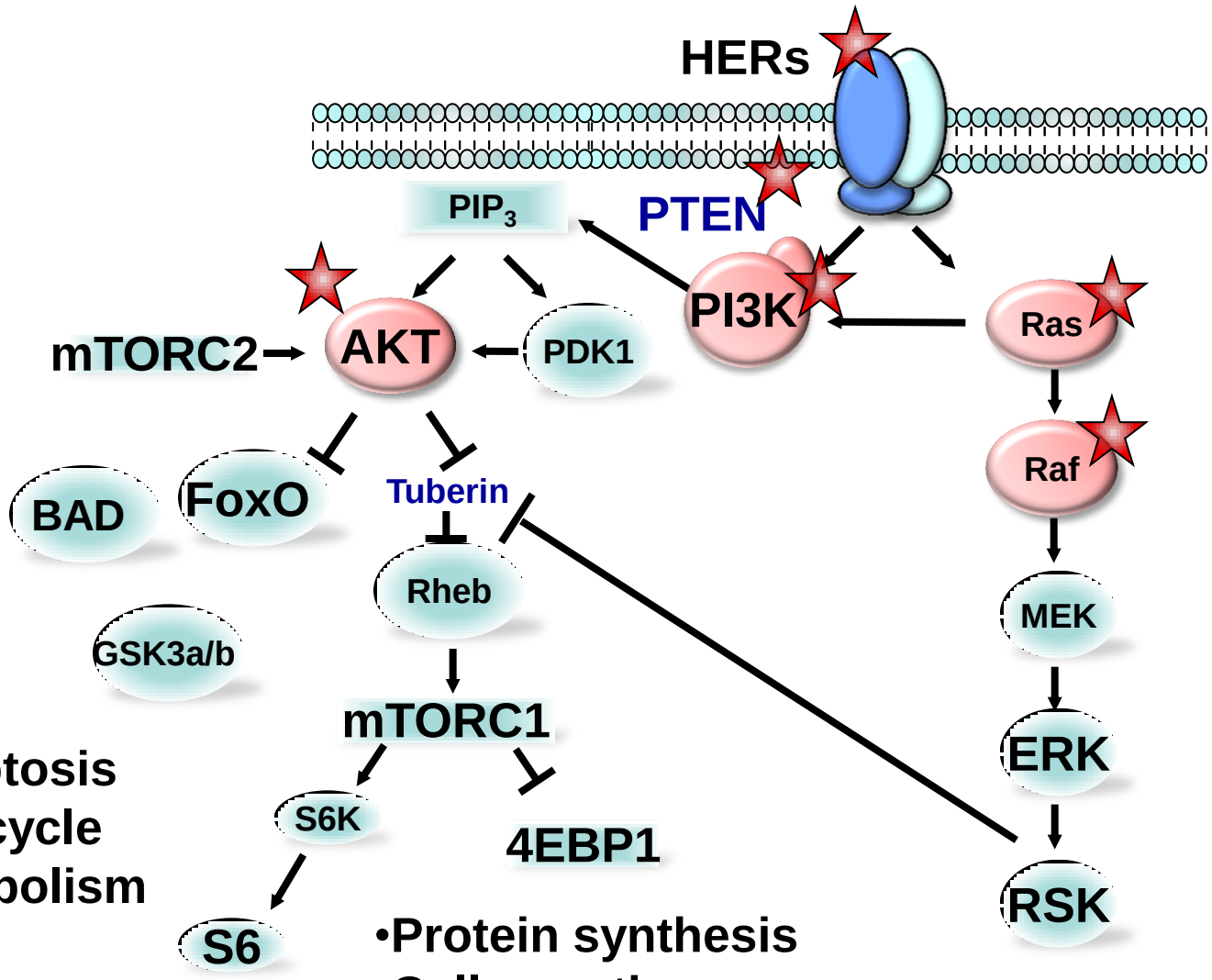


Number of patients still at risk

EVE 10 mg + EXE	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
PBO + EXE	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
Piccart M, et al. Presented at: ASCO 2012. Abstract 559 (poster).

The PI3K cascade regulates cell growth and survival



- Apoptosis
- Cell cycle
- Metabolism

- Protein synthesis
- Cell growth
- Cell proliferation

Frequent molecular alterations that activate the PI3K pathway

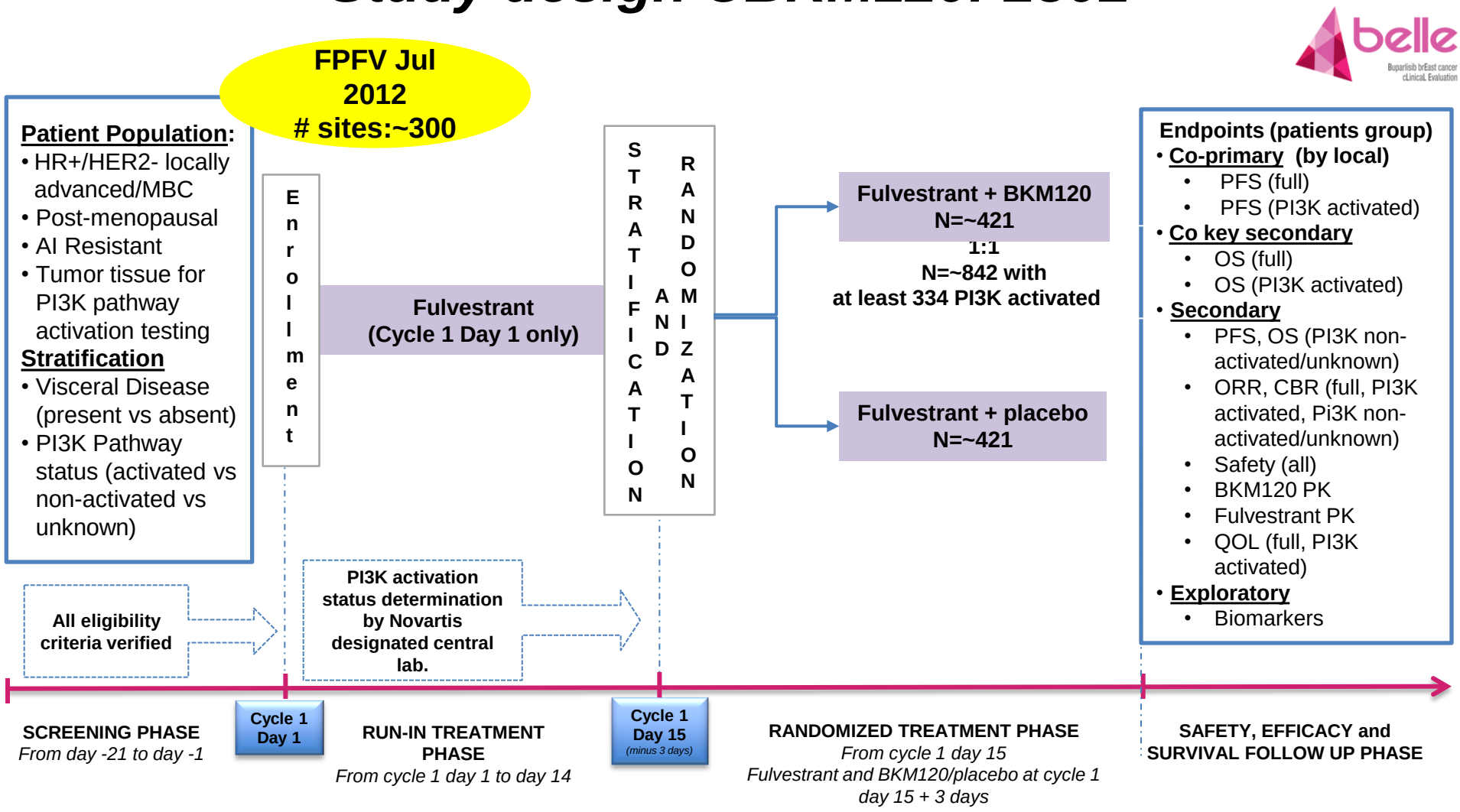
Clinical Activity of the first PI3K inhibitors Monotherapy

		BEZ235	BKM120	GDC0980 QD	GDC0941	PF-4691502	SF-1126	XL-147	XL-765¥	Σ
Breast	PR	1	1		2					4
	SD	4	1 a 3			1		1	1	8 - 10
	C								1†	1
NSCLC	PR	1						1		2
	SD					1		3	1	5
Mesothelioma	PR			*						0*
	SD			3					1	4
	actividad	1‡								1
Cervical ADK	PR				1					1

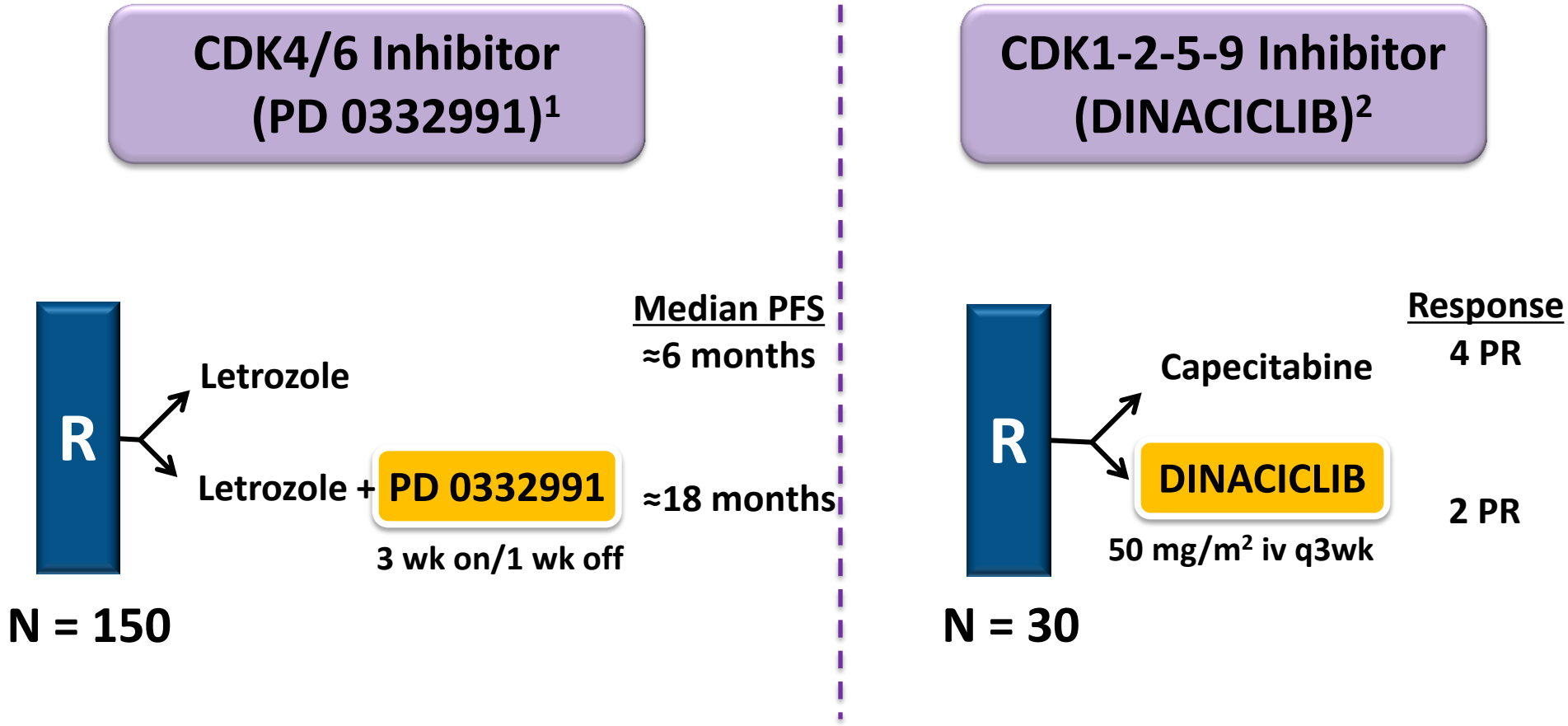
† Response in skin lesions
* 29% reduction
‡ <30% reduction (NOS)

BELLE2: Hormone Receptor Positive HER2 Neg Disease, mTORi naive

Study design CBKM120F2302



Targeting CDKs in Advanced Breast Cancer



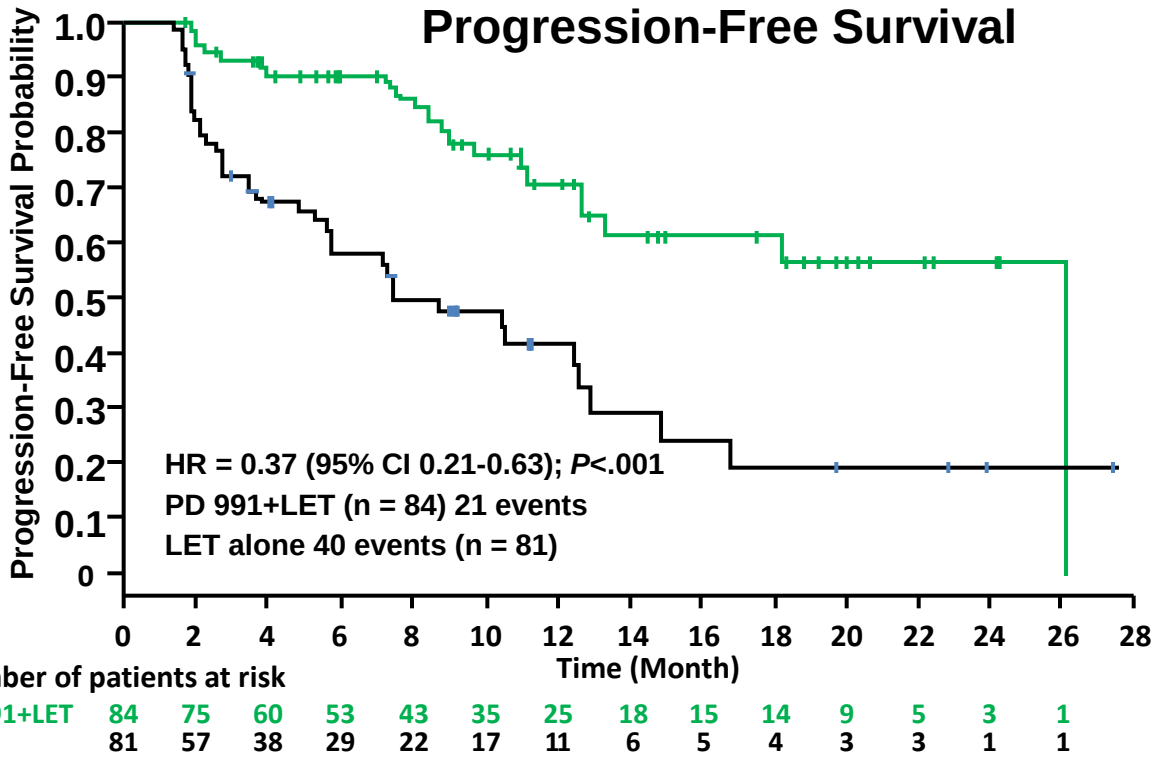
CDK, cyclin-dependent kinase; iv, intravenous; PFS, progression-free survival; PR, partial response; wk, week; R, randomised.

1. Finn RS, et al. IMPAKT Conference 2012; 2. Mito M, et al. AACR Conference 2012.

TRIO-18: PD991 + LET Significantly ⬆ PFS vs LET Alone

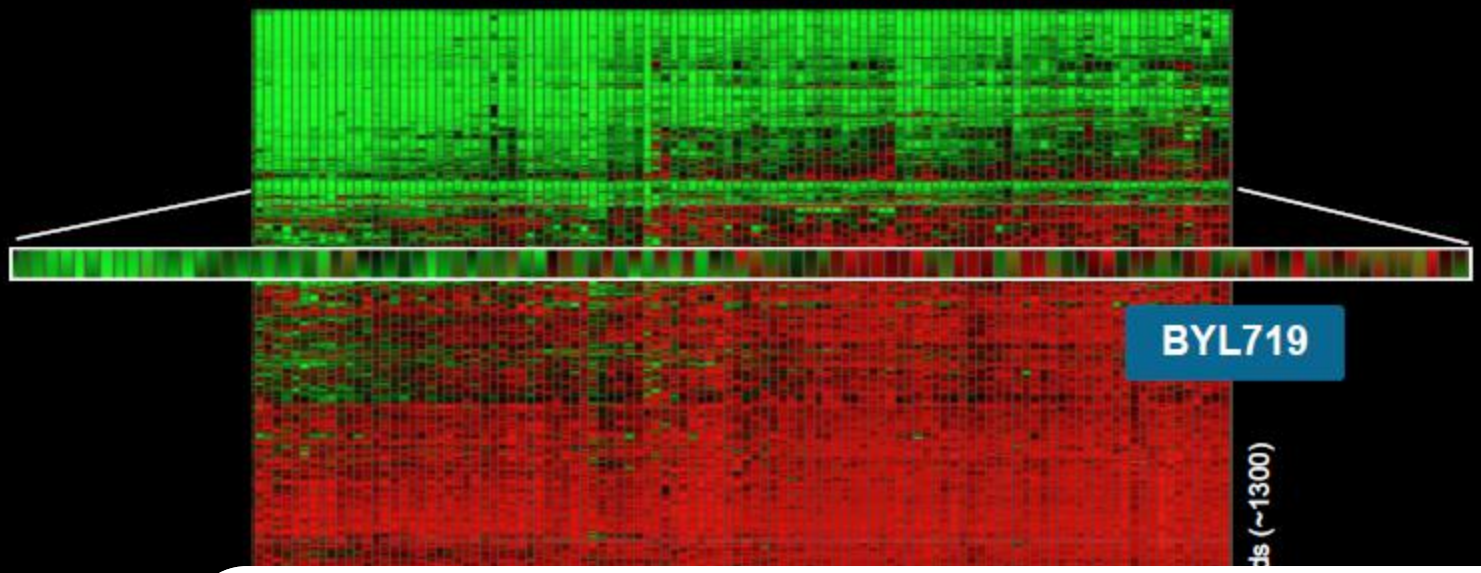
(RS Finn, abstract # S1-6)

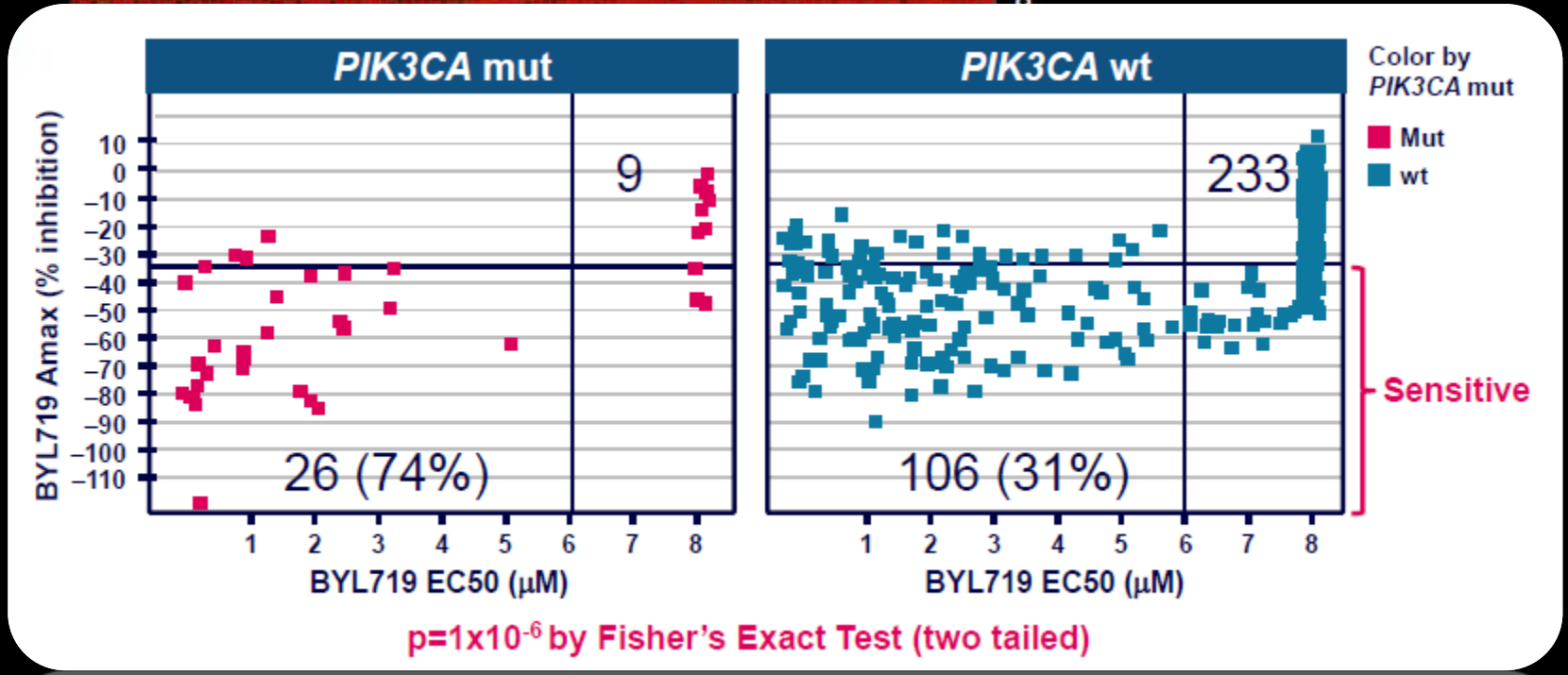
⇨ Oral Presentation



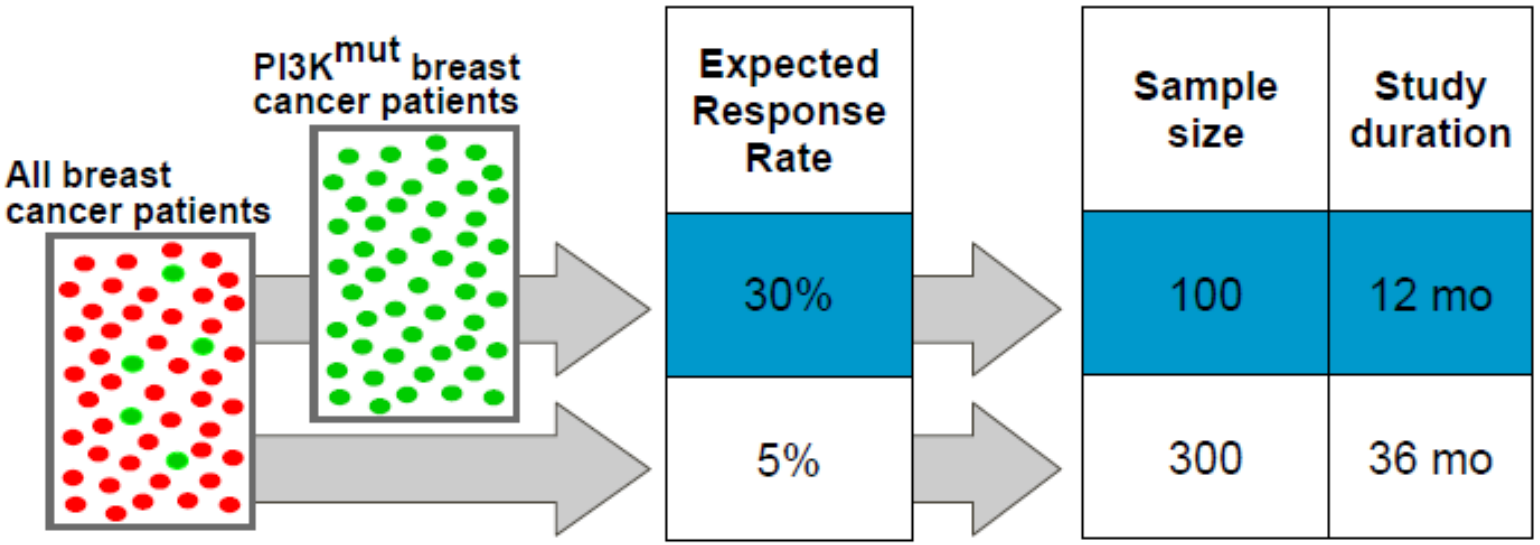
- Median duration of treatment was only 8.9 months for PD991+LET and 5.1 months for LET alone
- PFS for the letrozole-only arm was lower than expected from previous studies (usually ~9-10 mo)
- Conclusions from this study are preliminary; phase 3 trials are needed

	PD 991 + LET (n=83)			LET (n=77)		
Common AEs of Interest	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Neutropenia	19	46	5	1	1	0
Leukopenia	24	14	0	0	0	0
Alopecia	18	0	0	3	0	0
Thrombocytopenia	11	1	0	0	0	0


BYL719


PIK3CA mut
PIK3CA wt
Color by PIK3CA mut
Mut
wt
BYL719 Amax (% inhibition)
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
9
233
26 (74%)
106 (31%)
Sensitive
1
2
3
4
5
6
7
8
BYL719 EC50 (μM)
BYL719 EC50 (μM)
p=1x10-6 by Fisher's Exact Test (two tailed)

PI3K inhibitor development in breast cancer



Biomarker-driven selection will:

- Reduce trial size and associated costs by 67%
- Provide an unequivocal signal of efficacy by eliminating dilution effect of non-responders

BYL719, a next generation PI3K α-specific inhibitor: Preliminary safety, pharmacokinetics, and efficacy results from the first-in-human study

Dejan Juric[1], *Jordi Rodon*[2], *Ana M. Gonzalez-Angulo*[3], *Howard A. Burris, III*[4], *Johanna Bendell*[4], *Jordan D. Berlin*[5], *Mark R. Middleton*[6], *Douglas Bootle*[7], *Markus Boehm*[7], *Antonin Schmitt*[7], *Nicolas Rouyrre*[7], *Cornelia Quadt*[7], *Jose Baselga*[1]

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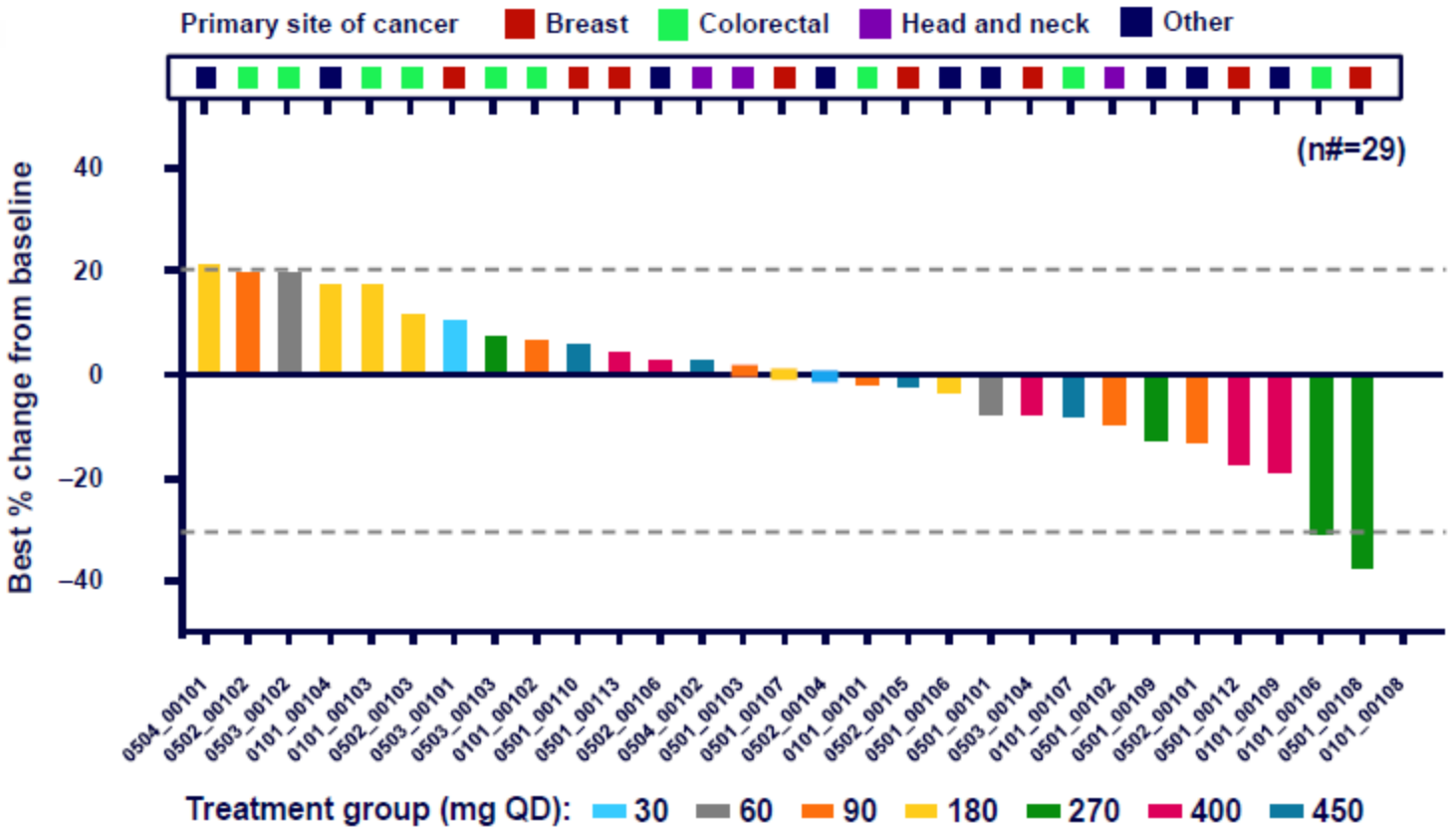
American Association for Cancer Research

Preliminary efficacy

Best percentage change from baseline in sum of longest diameters



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

Strategy no.1: No pre-selection

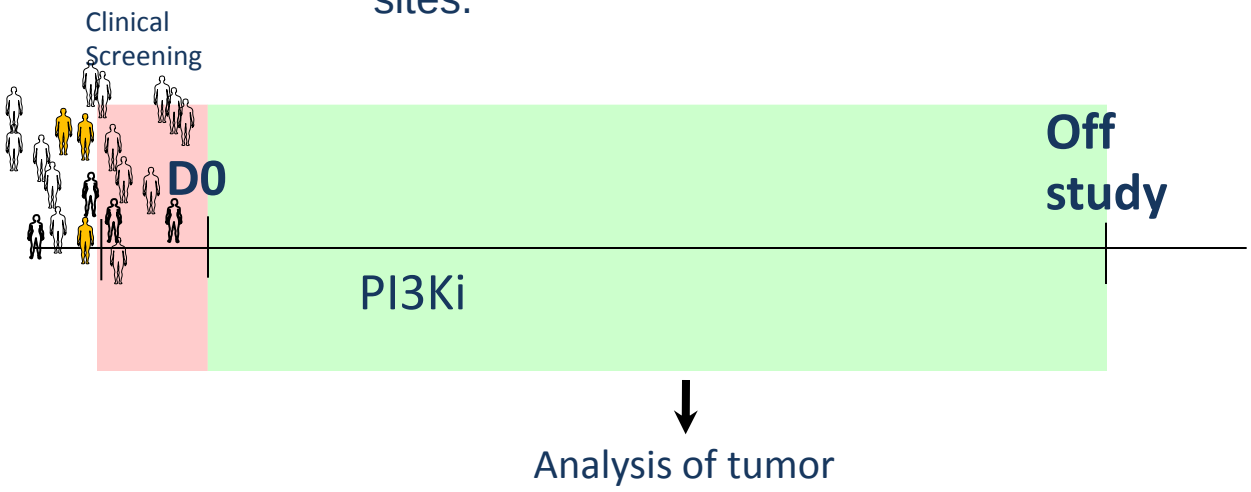
Basis: Alterations frequent enough so patients included in phase I trials are expected to harbor these alterations as frequently as described in the literature.

PROS:

- Selection of patients according to pathological methods may be easier and faster (good for fragile patients)
- Financial support of the Sponsor

CONS:

- The population of patients that participate in phase 1 trials is biased towards rare tumors
- Scant material may be an issue
- Low retrieval of tumor blocks from the sites.



Strategy no. 2: Prescreening before Phase I trial

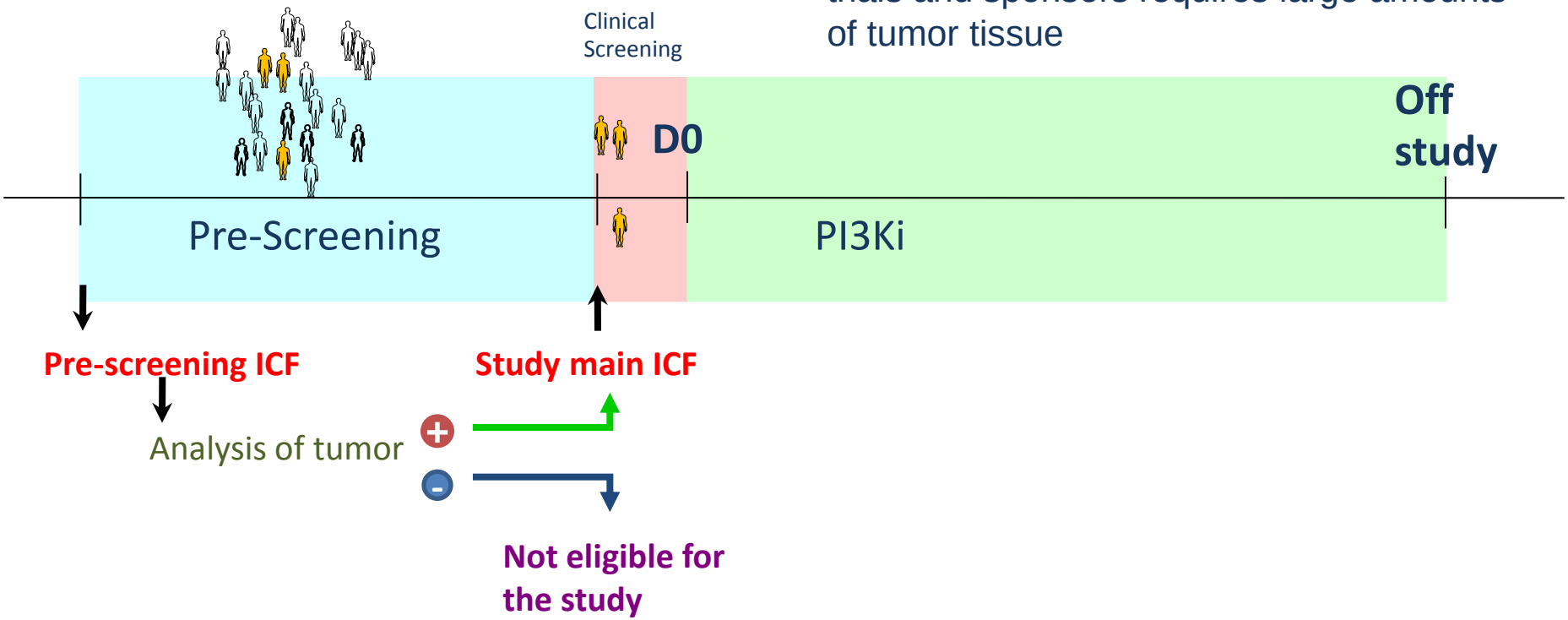
Basis: Prescreening tumors of patients referred to a phase I trial, by sending their tumor block to a central lab for analysis, before considering inclusion in a trial with a specific inhibitor.

PROS:

- Centralized labs guarantees state-of-the-art analysis
- Financial support of the Sponsor

CONS:

- The time to results and decision about inclusion may be unacceptable in phase 1
- High dropout rate should be expected
- Several analysis for several alterations, trials and sponsors requires large amounts of tumor tissue



Strategy no. 3: prescreening metastatic population

Basis: broad local prescreening of metastatic patients with a specific disease where the alterations are frequent. This information is used for decision making when disease progression is observed.

PROS:

- Patients may be considered for a clinical trial early on their disease (not so heavily pretreated)
- Patients have to sign only one Informed Consent for a general pre-screening program.
- No delay from time of progression on standard treatment to phase I trial enrollment

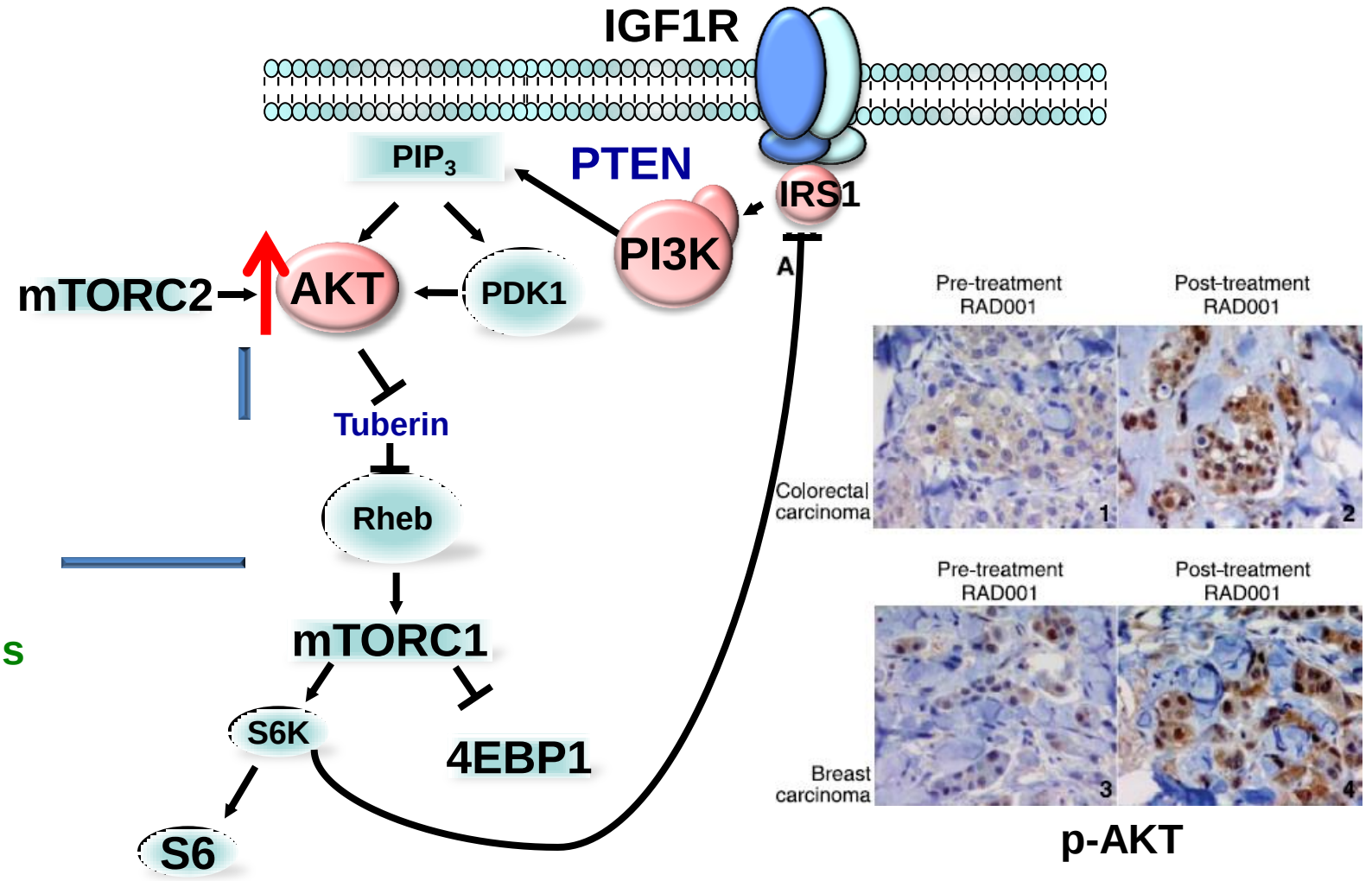
Broad evaluation of alterations using small amounts of tumor tissue with high-throughput techniques (including potential mechanisms of resistance)

CONS:

- Screening of patients that may never enter a trial
- Technologies for molecular analysis may evolve.
- Not covered by insurance or study budgets, requiring additional funding.

Understanding the mechanisms of resistance of resistance inhibitors (PI3K, …)

Rapalogs disturb a negative feedback activating Akt

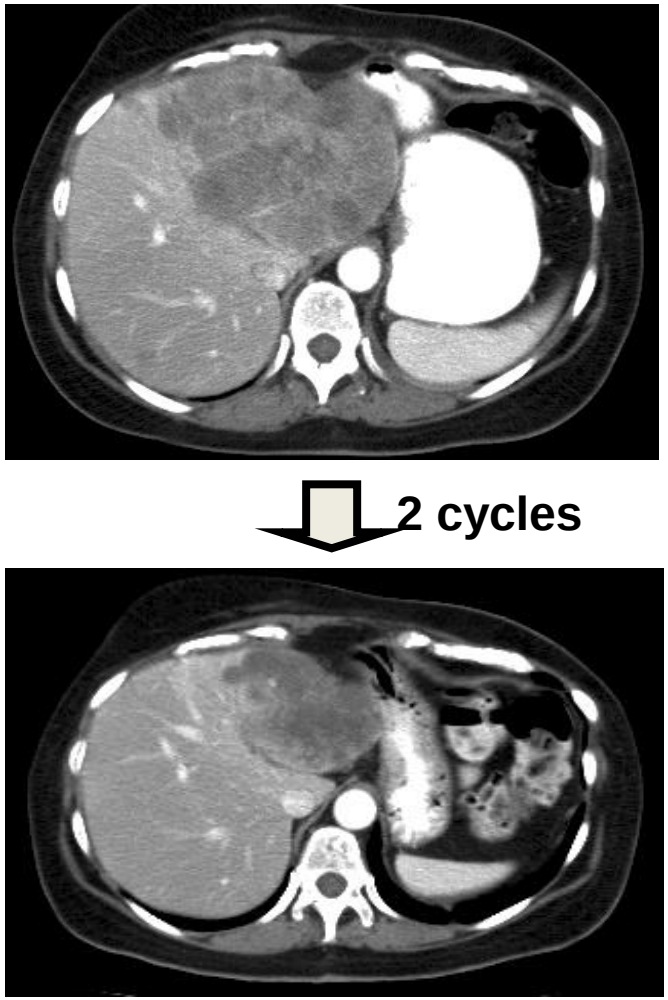


O'Reilly et al, Can Res 2006
Tabernero et al, J Clin Oncol 2008

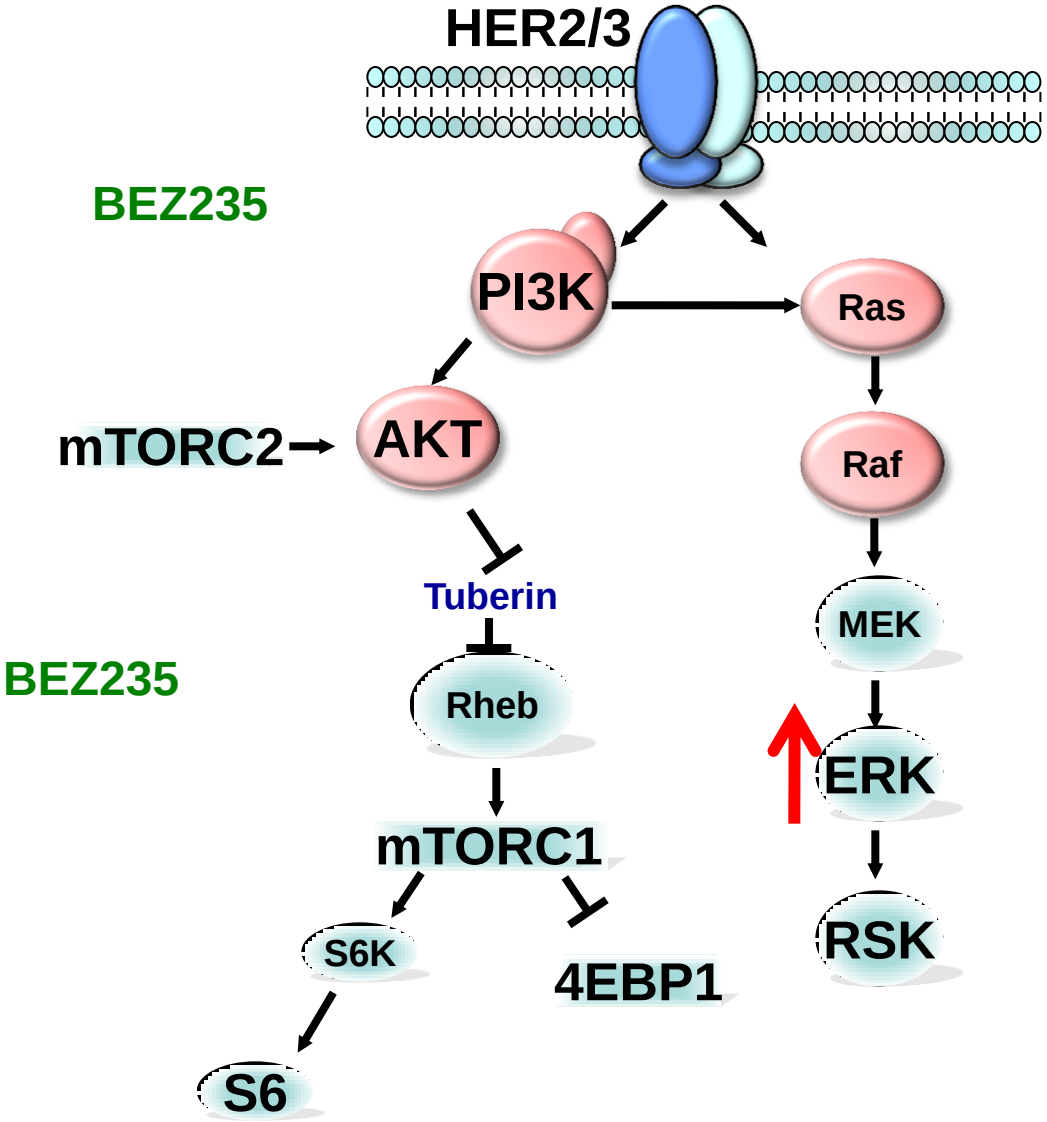
Example of a Partial Response to Ridaforolimus + Dalotuzumab

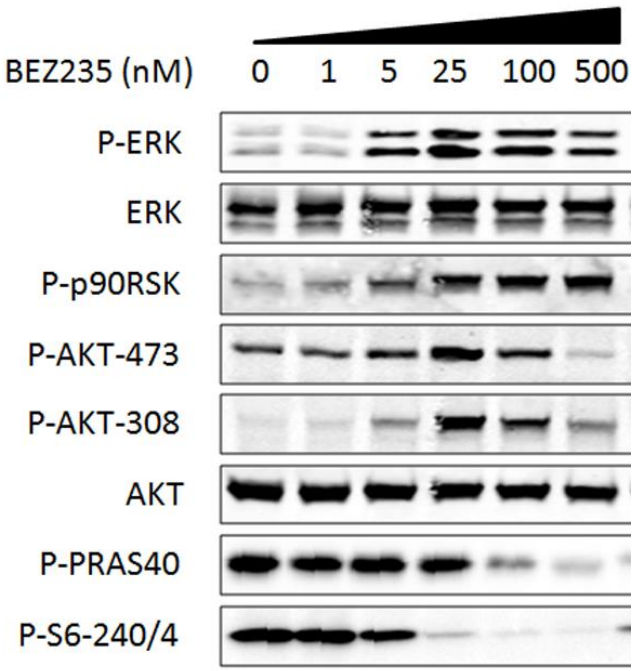
History

- 56 year-old female
  - Stage IV breast cancer
- ER+/PR+/HER2 neg, Ki67 20%
- Adjuvant chemotherapy. 4 prior chemotherapy regimens. 3 prior hormone therapies
- Patient remained on study treatment for 9 months before progression



PI3K/mTORC inhibition in HER2 overexpressing cells activates MAPK (and is HER2 dependant)

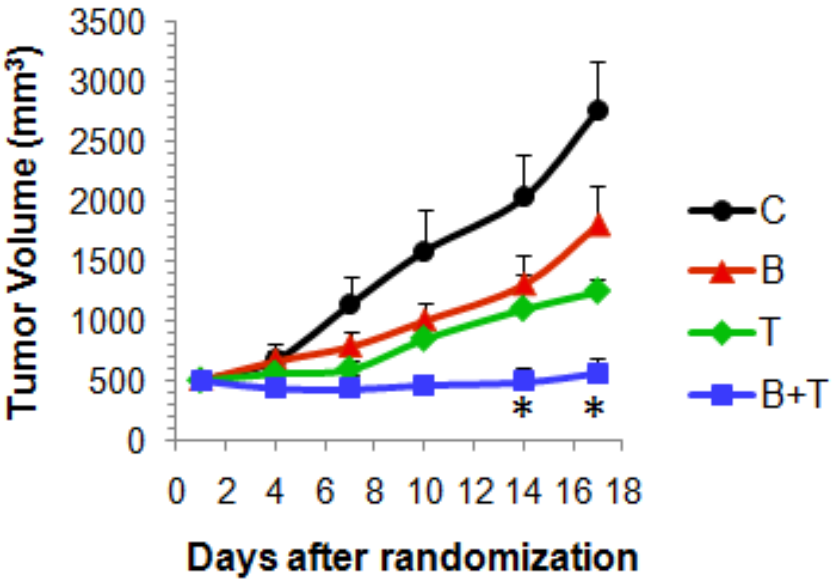




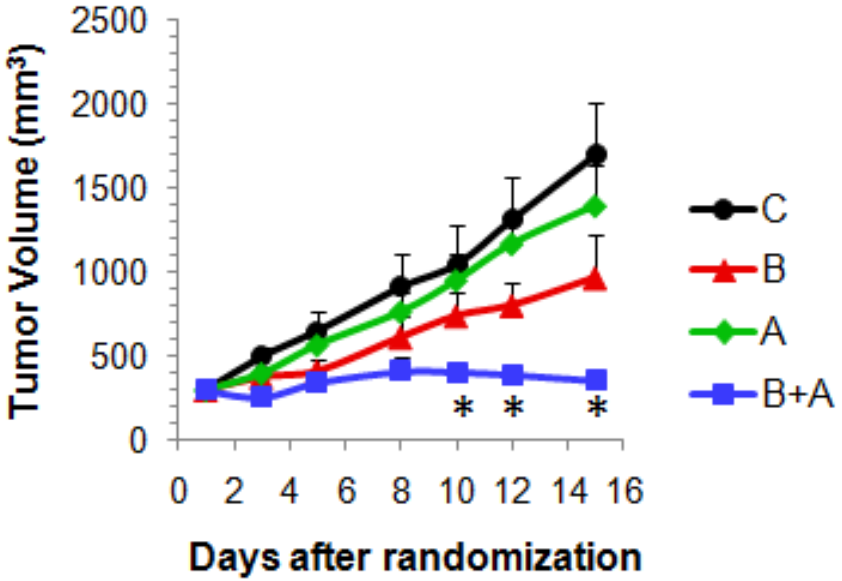
Serra et al, Oncogene 2011

Combination of PI3K/mTOR and HER2 inhibition or MEK inhibition shows enhanced anticancer activity

BEZ235 + trastuzumab



BEZ235 (PI3K/mTOR) + AZD6244 (MEK)



BT474-Tr xenografts

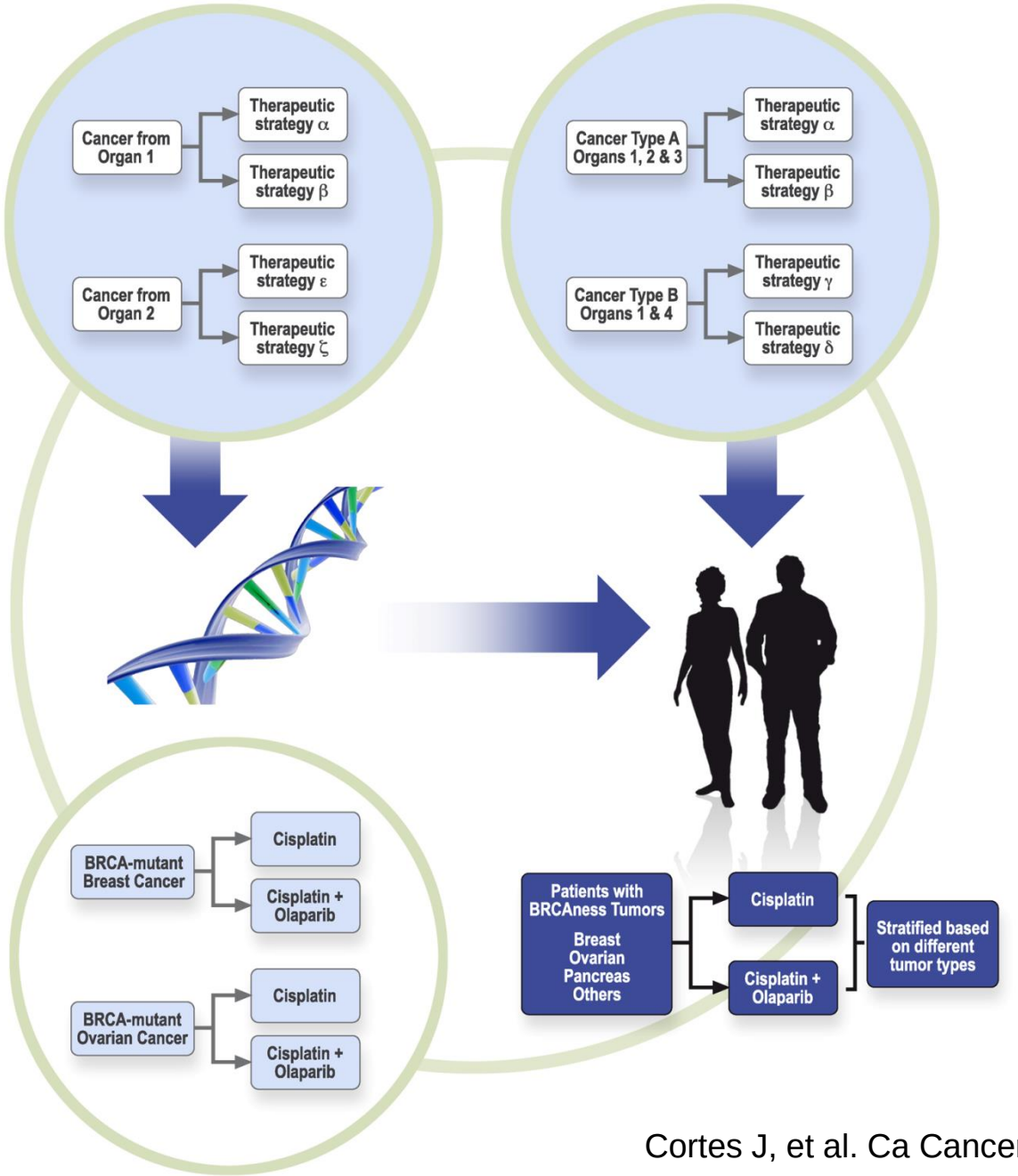
B- BEZ235 (20 mg/Kg QD); T- Trastuzumab (10mg/Kg, BIW)
B-BEZ235 (25 mg/Kg QD); A- AZD6244 (8mg/Kg QD)

Serra et al, Oncogene 2011

Clinical trials with PI3K inhibitors + MEK inhibitors

- BKM120 + GSK1120212
- BKM120 + MEK162
- BYL719 + MEK162
- GDC0941 (PI3K inh) + GDC0973 (MEK inh) (Shapiro, ASCO 2011)
- PF-04691502 + PD-0325901
- GSK2126458 + GSK1120212
- GSK1120212 (AKT inh) + GSK2141795 (MEK inh) (Kurzrock, ASCO 2011)
- BAY80-6946 + BAY86-9766
- MK-2206 (AKT inh) + selumetinib (MEK inh) (Tolcher, ASCO 2011)

Reality or Fiction?



Cortes J, et al. Ca Cancer J Clin (In Press)