Overcoming Resistance in ER-Positive Disease

Targeting intrinsic subtypes of metastatic breast cancer: The spectrum of sensitivity to endocrine therapy

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ddp BRAS DRUG DEVELOPMENT PROGRAM

Disclosures

- Research Funding
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- Honoraria/Consultancy (Research Account)
  - Novartis, Pfizer, Roche, Sanofi

Case Presentation

- 54F initially perimenopausal L 5.2cm, grade 2, ductal, 1/14 LNs, ER 90%, PR 10%, HER2-negative
- Treated with MRM, ALND, adjuvant FEC-D, locoregional RT, tamoxifen and NCIC CTG MA.32 (metformin vs placebo)
- 2y after diagnosis presents with R pelvic bone pain, bone scan shows widespread lytic metastases, CT mediastinal lymphadenopathy and liver metastases

Case Presentation

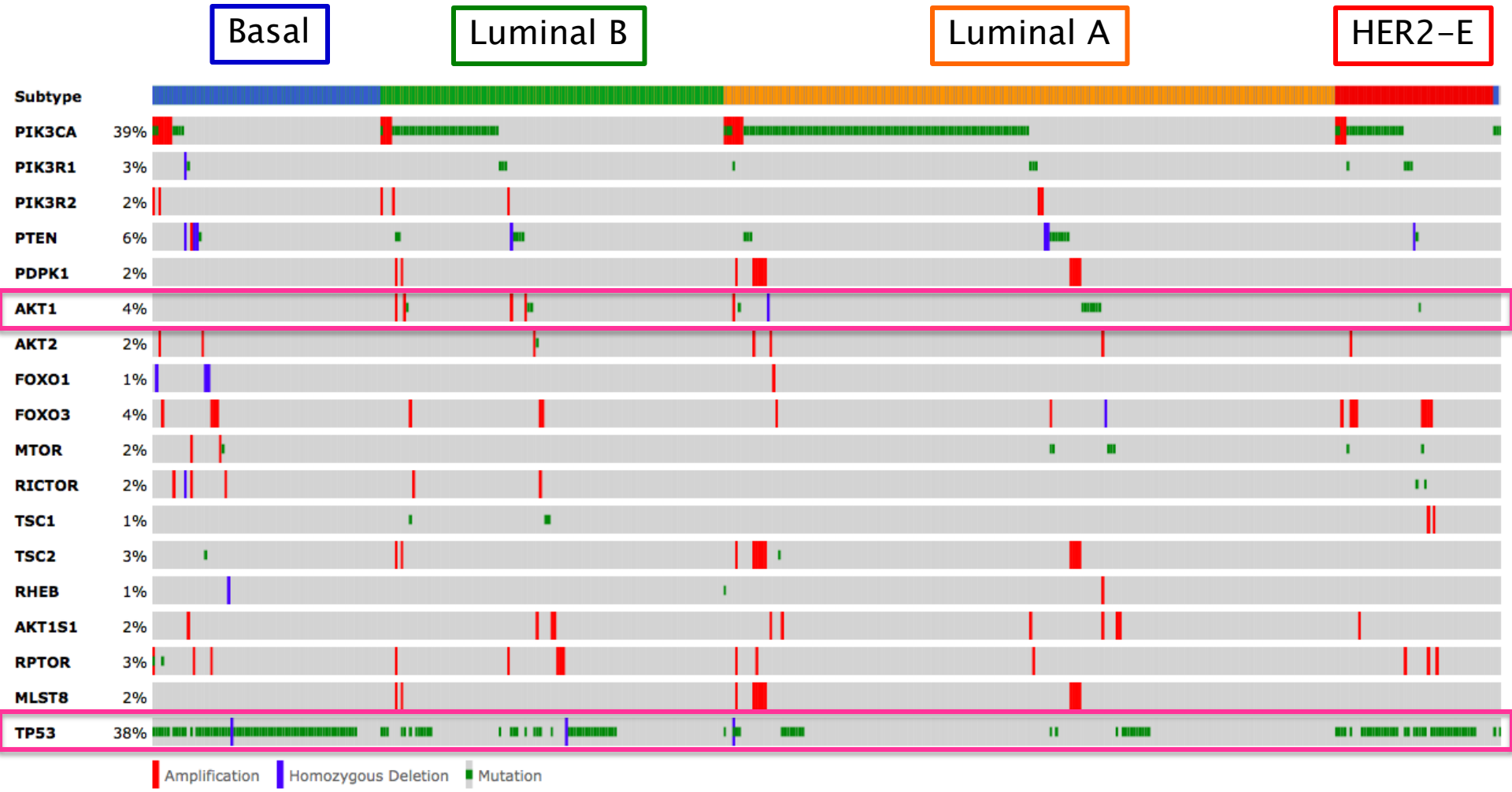
- Amenorrhea for 2+ years. ECOG PS 1. Started on letrozole and denusomab after palliative radiation to R ischium (20Gy/5F)

- Disease progression after 2 months with bilateral pleural effusions and increased size of liver metastases

- Liver biopsy = metastatic breast carcinoma
  - ER90%, PR10%, HER2-negative (FISH)
  - Targeted DNA sequencing (MiSeq – 48 genes)
    - *AKT1* (E17K) mutation
    - *TP53* (R306X) mutation

Hansen AR et al ESMO 2014 (Poster 1612P)

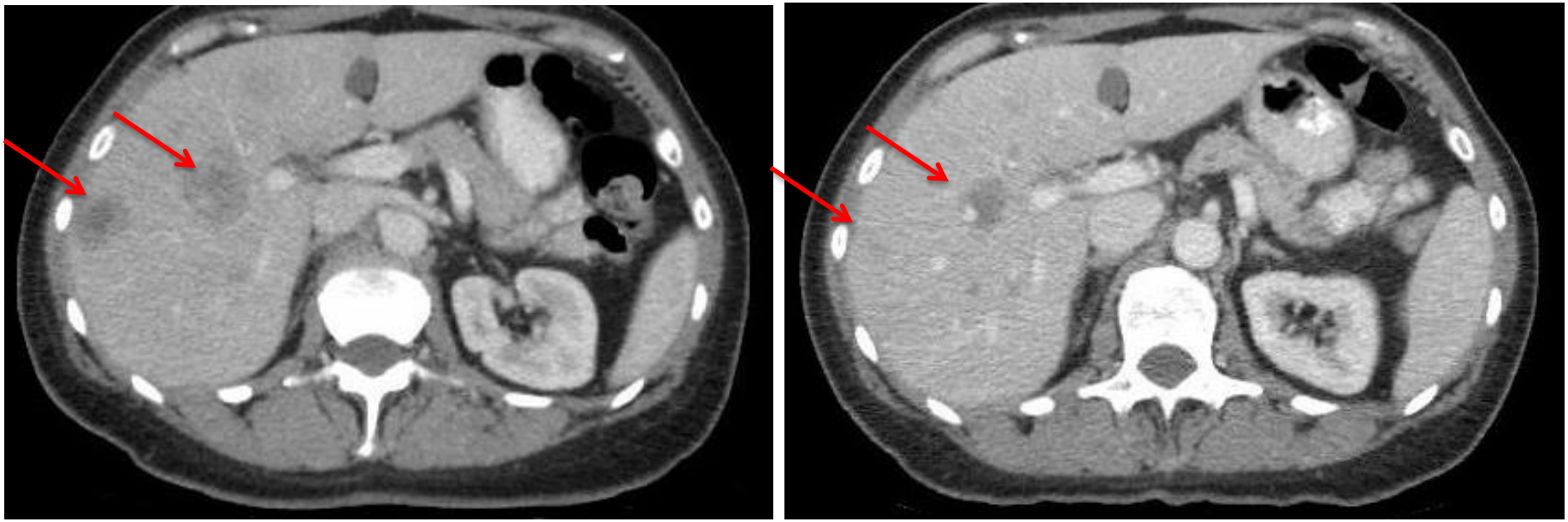
PI3K Pathway & TP53 Alterations – TCGA



The Cancer Genome Atlas Network. Nature 2012; 490:61-70.

Case Presentation

- Exemestane and Everolimus
  - Reduction of liver metastases and pleural effusion
  - Improvement in disease-related symptoms
  - Grade 1 macular papular rash, grade 1 diarrhea, and grade 1 fatigue
  - Minor reduction in target lesions



April 2013

June 2013

BOLERO-2 Trial Design

BOLERO-2
N = 724
- **Postmenopausal women**
- **Advanced Breast Cancer**
- **NSAI-refractory disease**
  - Recurrence during/within 12 mo of adjuvant treatment **or**
  - Progression during/within 1 mo of treatment for advanced disease

R 2:1

Everolimus 10 mg PO daily + Exemestane 25 mg PO daily **n = 485**

Placebo 10 mg PO daily + Exemestane 25 mg PO daily **n = 239**

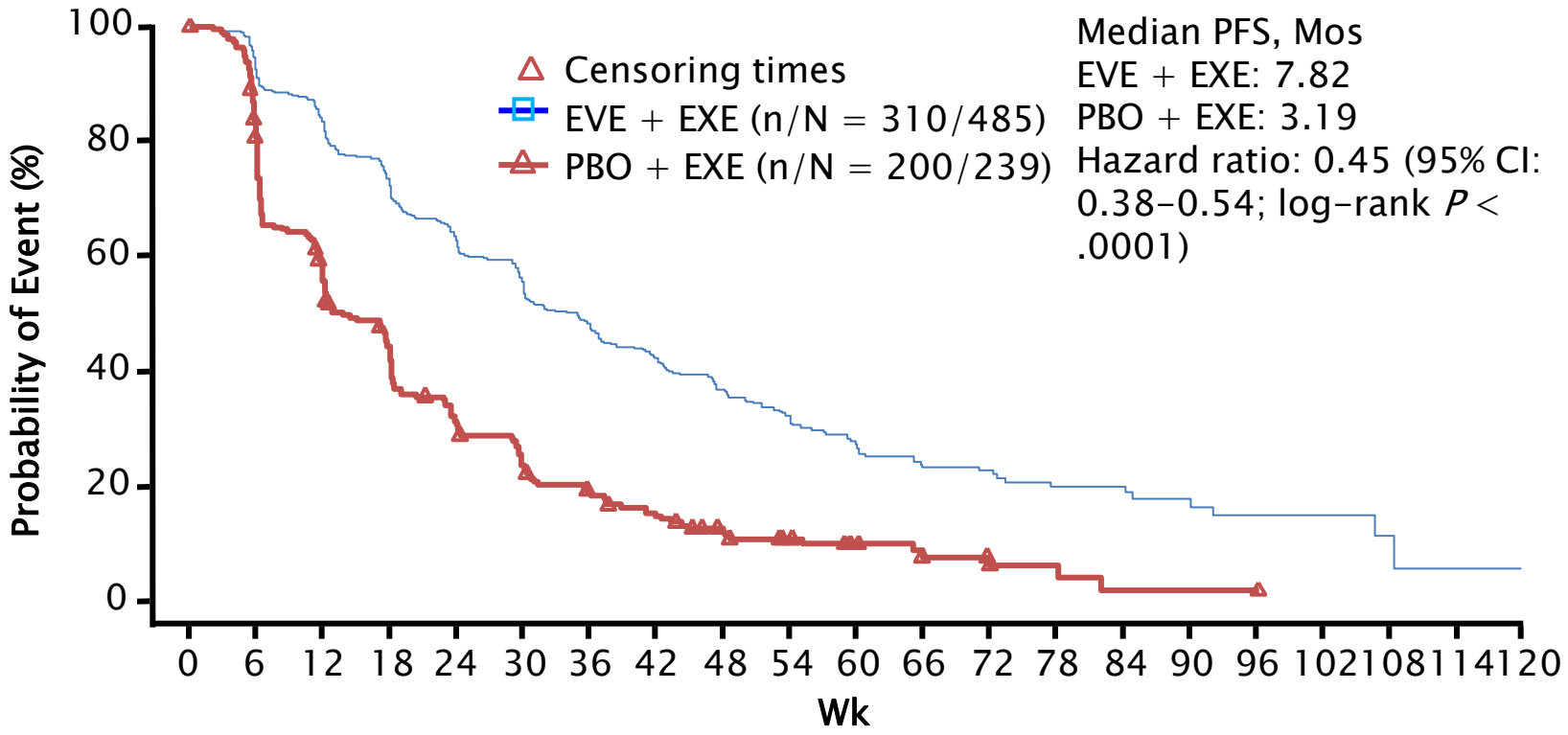
- **Primary Endpoint:**
  PFS by local assessment

- **Key Baseline Characteristics**

Median age, years	62
Race, %	
Caucasian	75
Asian	20
Visceral involvement, %	56
Bone metastases, %	77

Baselga J, et al. *N Engl J Med* 2012;366(6):520-29.
Hortobagyi G, et al. ASCO 2013; LBA509.

BOLERO-2 Trial: Progression Free Survival at 18 months F/U



Patients at Risk, n

EVE + EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

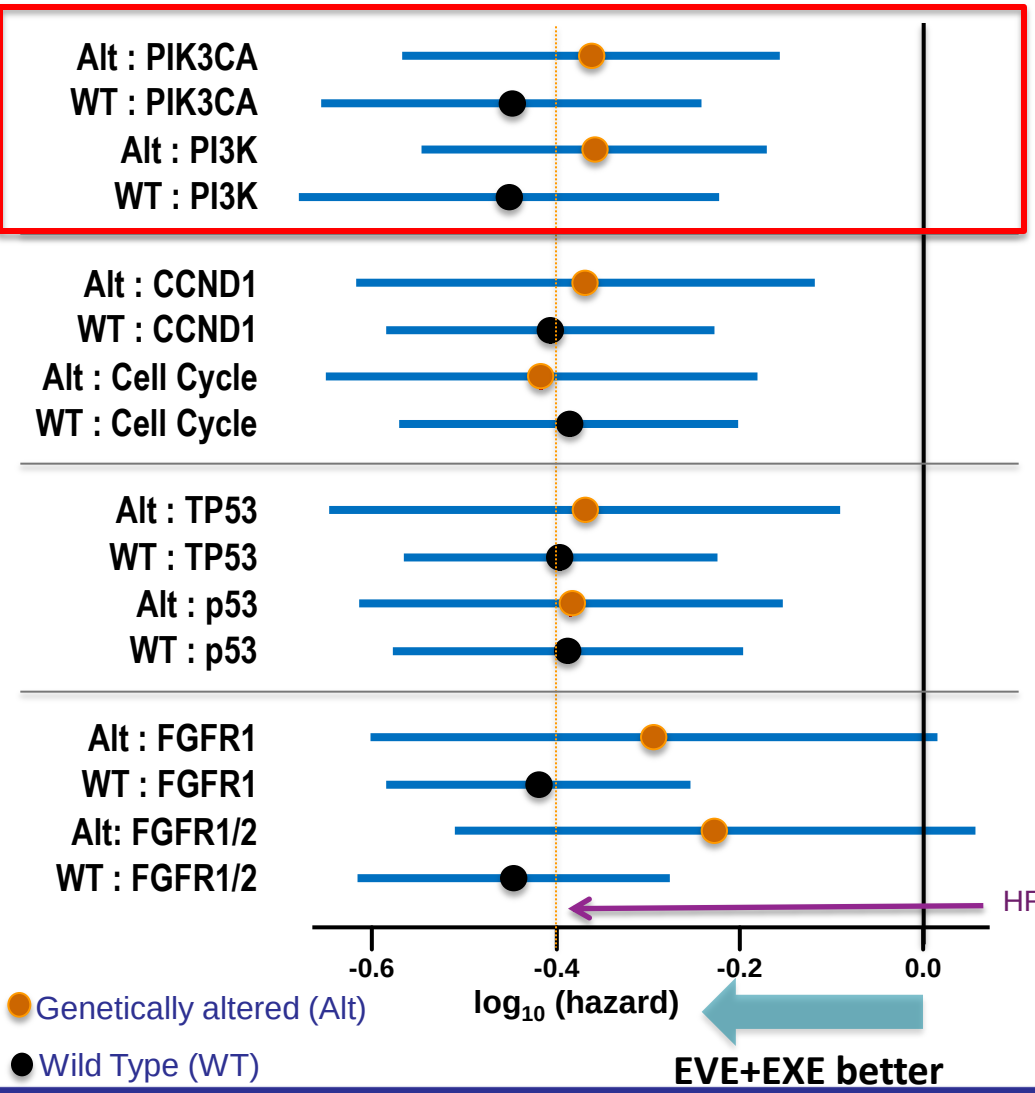
Piccart-Gebhart M, et al. ASCO 2012. Abstract 559.

BOLERO-2 Trial: Adverse Events at 18 months F/U

	Everolimus + Exemestane (n = 482)			Placebo + Exemestane (n = 238)		
		Grade			Grade	
Adverse Event, %	All	3	4	All	3	4
Total	100	44	9	91	23	5
Stomatitis	59	8	0	12	< 1	0
Rash	39	1	0	7	0	0
Fatigue	37	4	< 1	27	1	0
Diarrhea	34	2	< 1	19	< 1	0
Nausea	31	< 1	< 1	29	1	0
Appetite decreased	31	1	0	13	1	0
Noninfectious pneumonitis	16	3	0	0	0	0
Hyperglycemia	14	5	< 1	2	< 1	0

Impact on Treatment by Genetic Status

The Most Frequently Altered Single Genes and Pathways

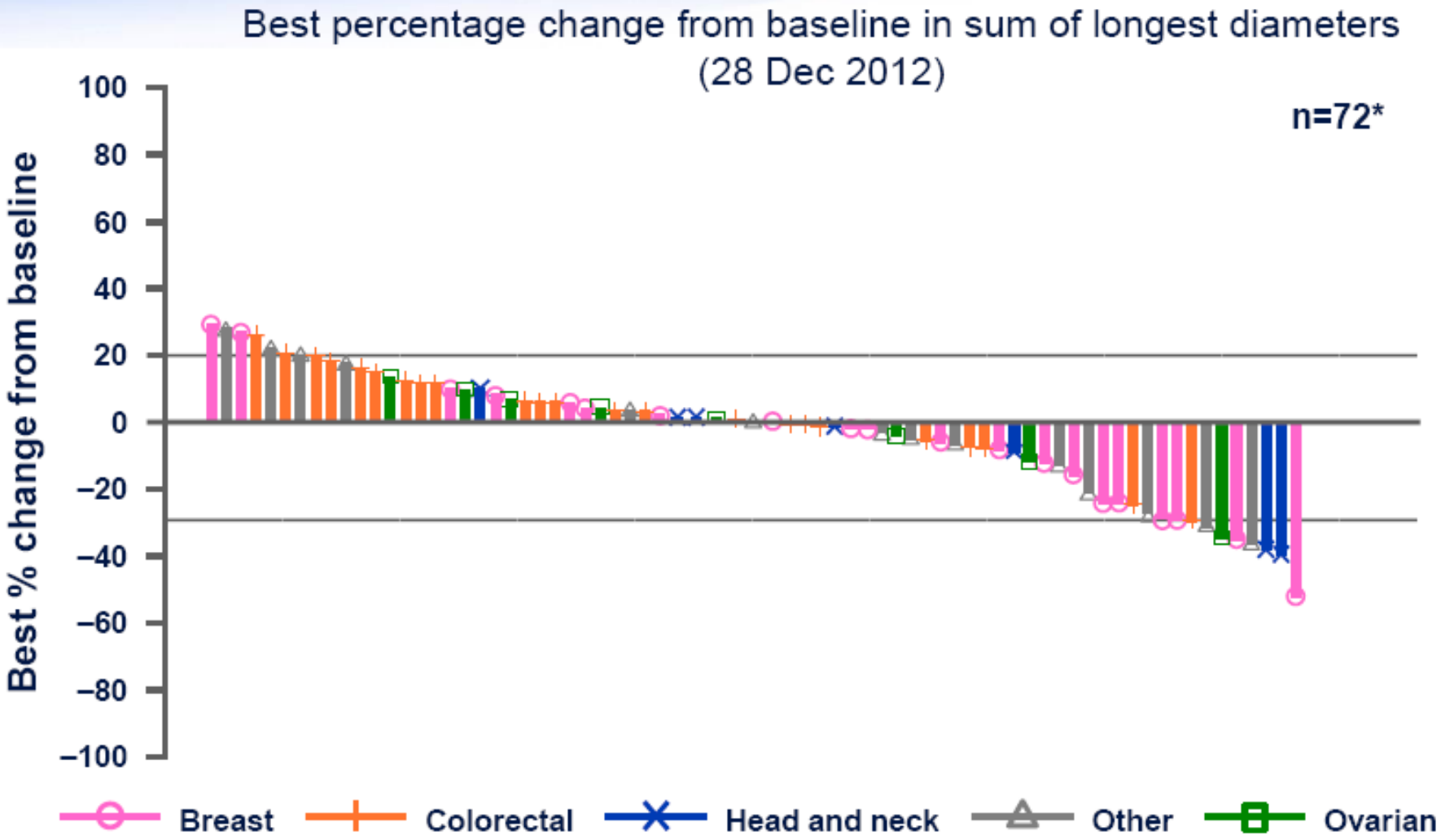


Positive treatment effect in favor of everolimus across the various genetic marker subgroups

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%)

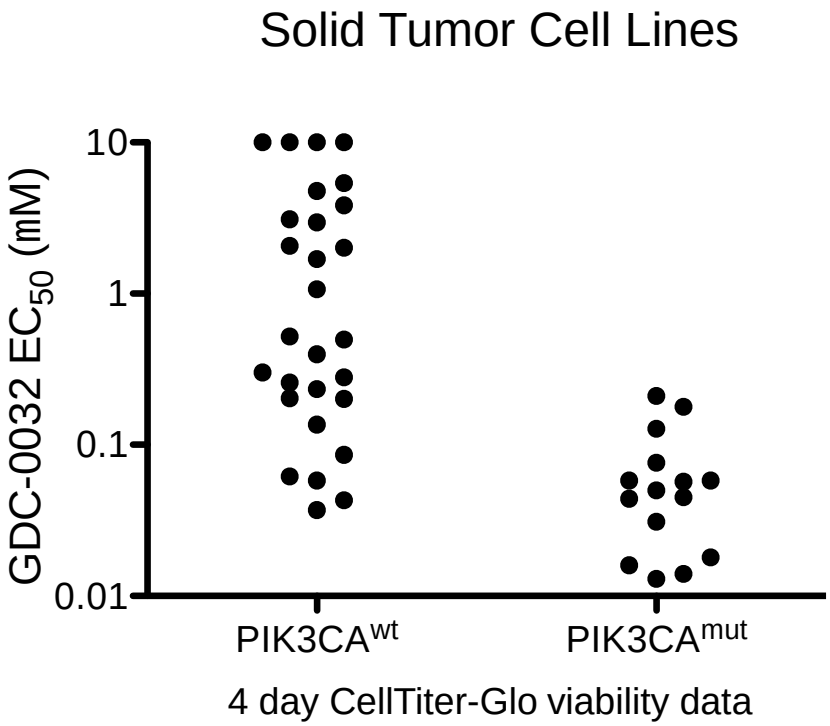
Preliminary clinical activity of BYL719 (by cancer type)

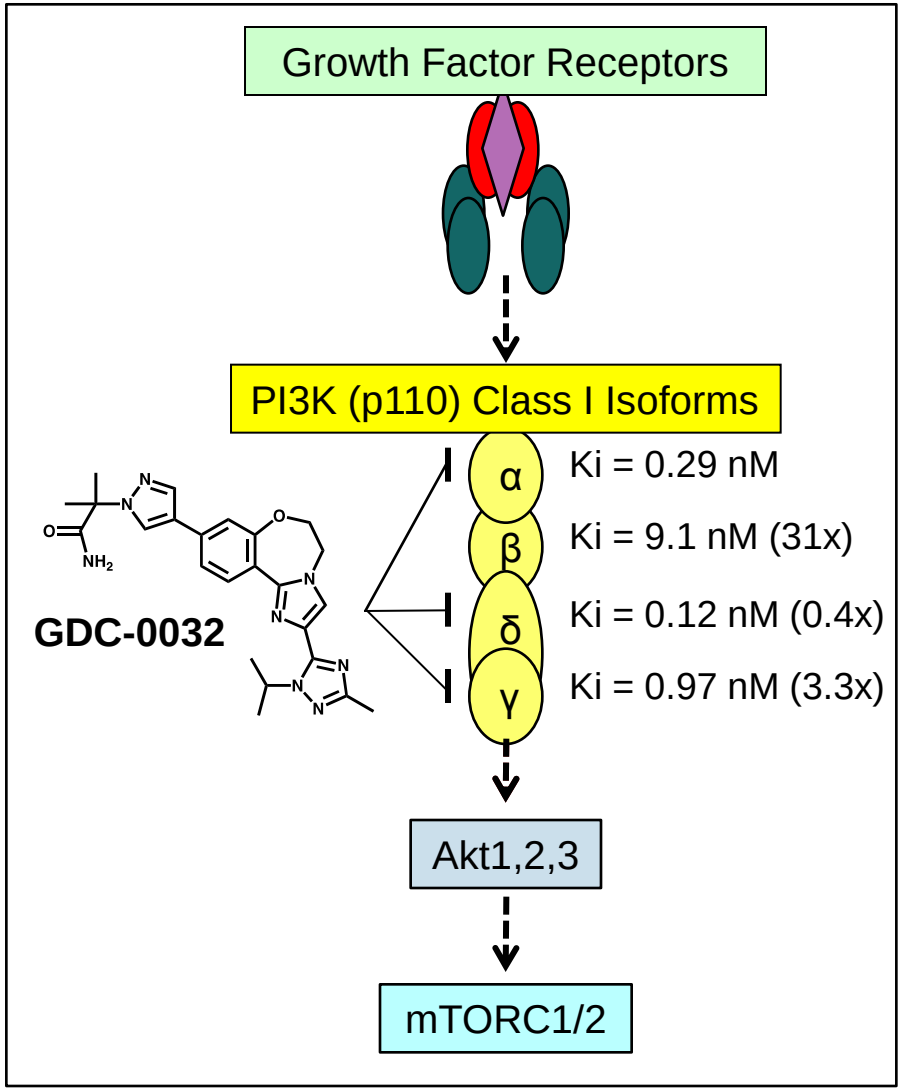


*Patients with missing best percentage from baseline and unknown best overall response are not included.

Rodon J et al AACR 2013.

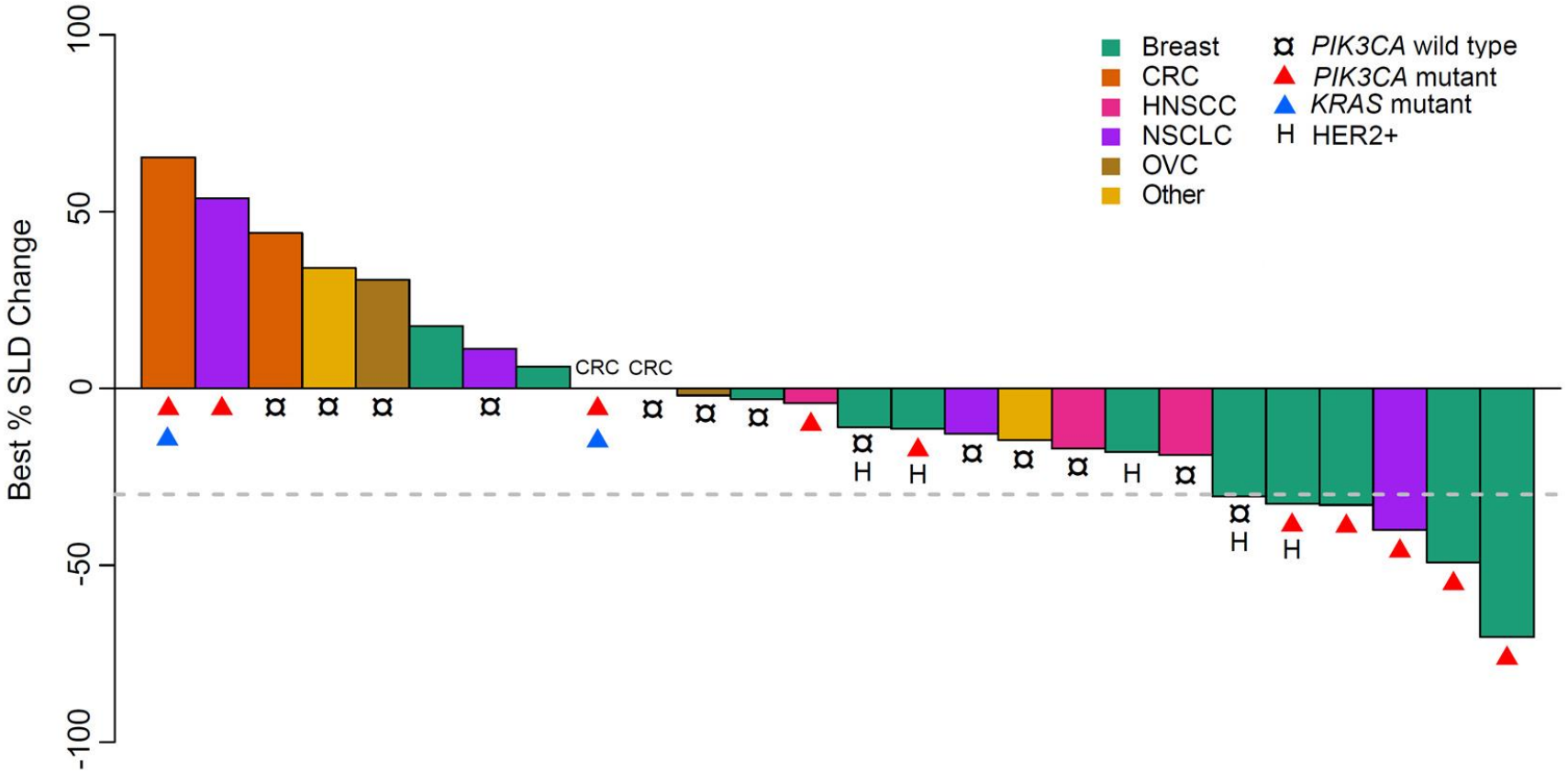
GDC-0032 is a PI3K inhibitor that spares the p110 beta isoform





Juric D et al. AACR 2013.

Preliminary efficacy in GDC-0032 Phase I study

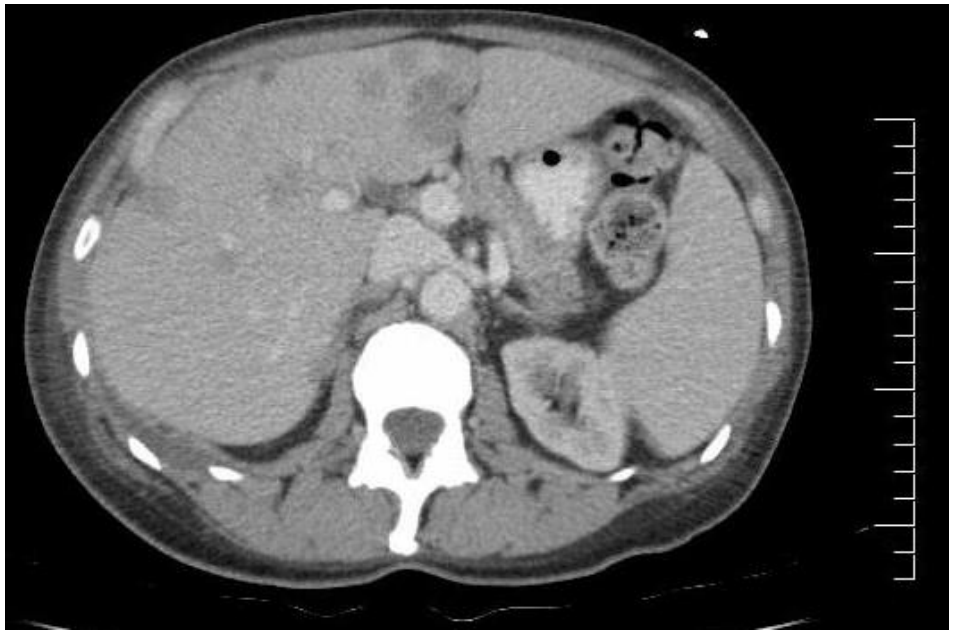


- Promising preliminary clinical activity in *PIK3CA* mutant cancers, especially breast cancer.
- *PIK3CA* mutant solid tumors: 5 cPR (at 3-12 mg QD) and 4 SD out of 12 pts
- *PIK3CA* mutant breast cancer: 4 cPR (RECIST -30 to -70%) and 2 SD out of 6 pts

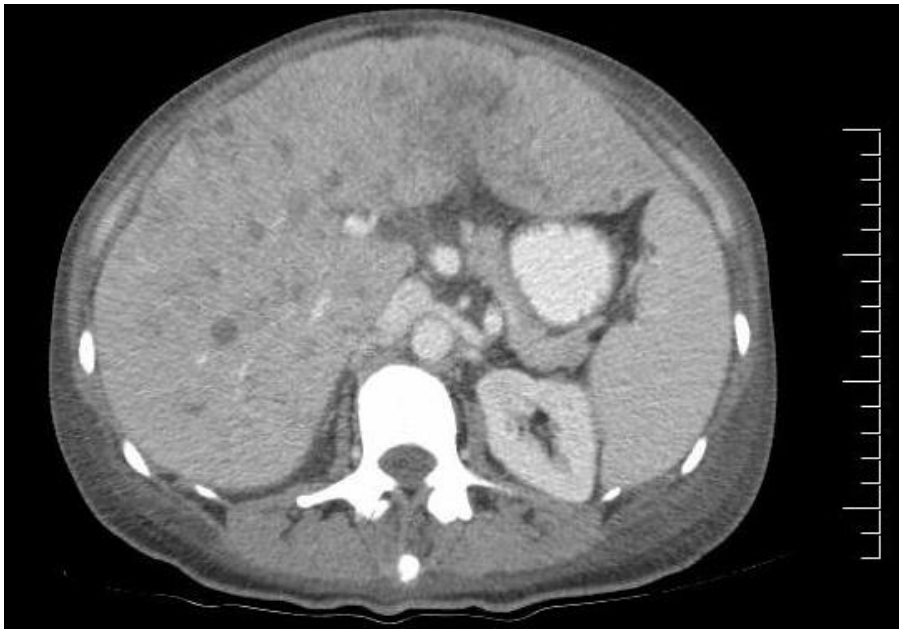
Pts shown had measurable disease with pre-treatment and on-study tumor assessments as of 30 Nov 2012

Case Presentation

- Progressed after 8 months on Everolimus and Exemestane with extensive liver disease
- Brief response to capecitabine for four months
- Rapid progression with fulminant liver failure and death



March 2014



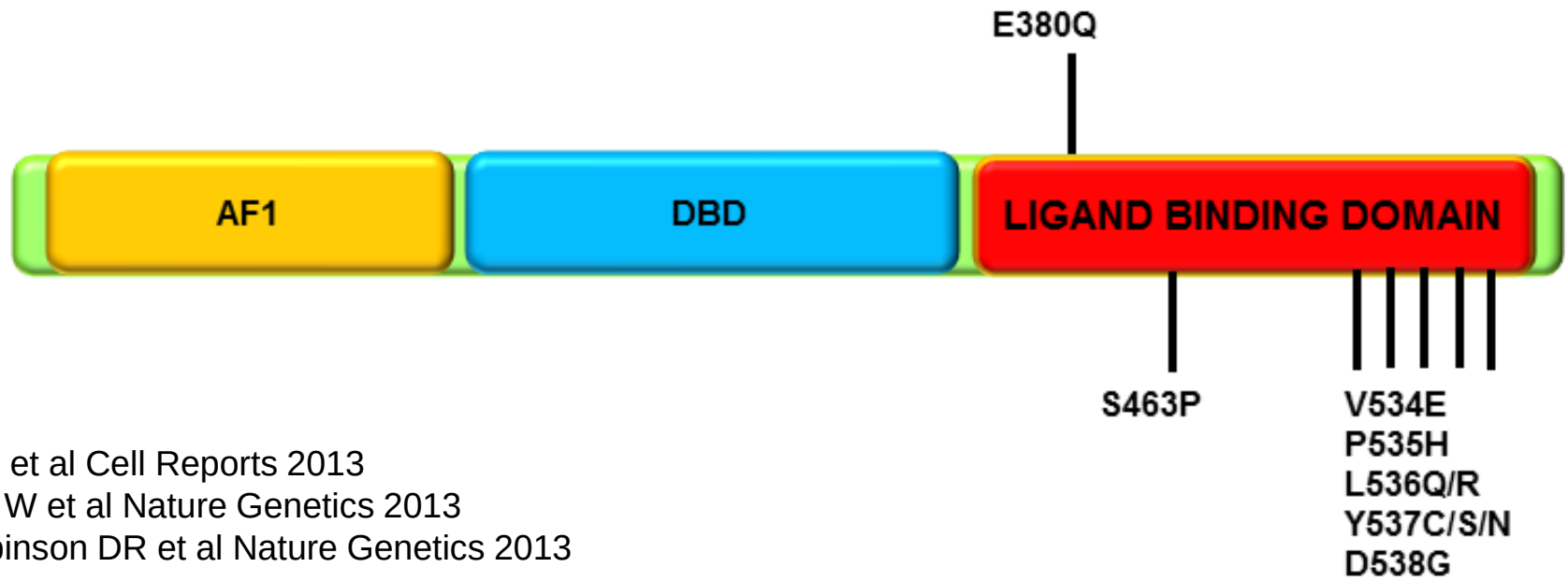
July 2014

Other Potential "Druggable" Targets for Endocrine Resistance

- *ESR1* mutation
- Cyclin/CDK/Rb
- FGF–FGFR signalling
- *ERBB2* mutation

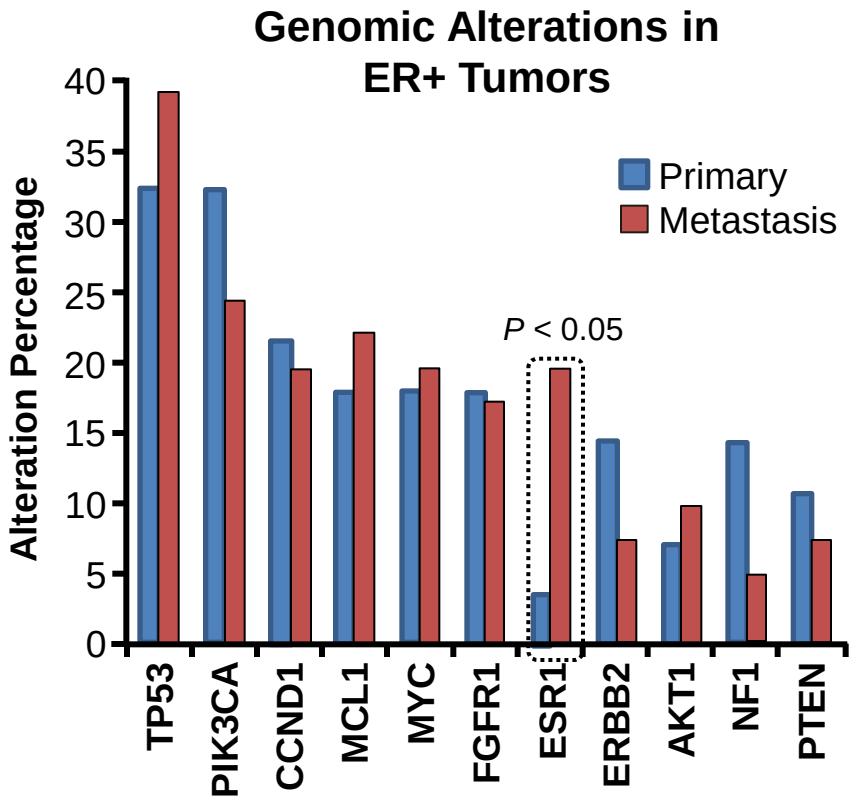
ESR1 Mutations

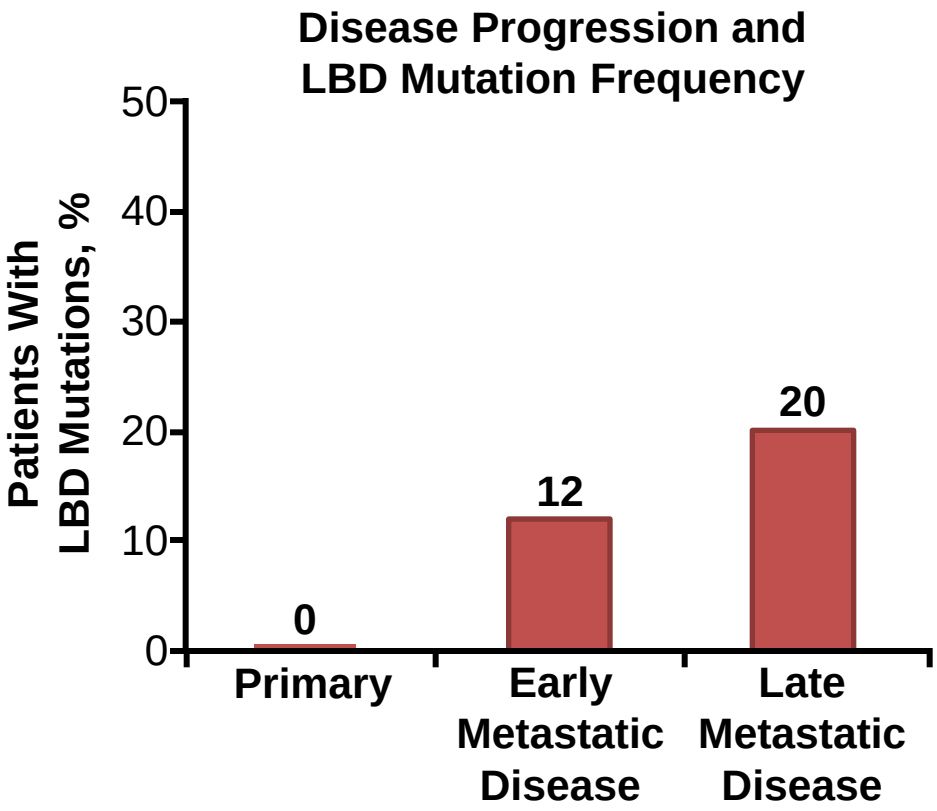
- Identified in metastatic ER+ breast cancers after anti-estrogen treatment
- Rare in primary tumors
- Produce ligand-independent activation of ER
- May be suppressed by higher doses fulvestrant than can be achieved in the clinic



Li S et al Cell Reports 2013
Toy W et al Nature Genetics 2013
Robinson DR et al Nature Genetics 2013

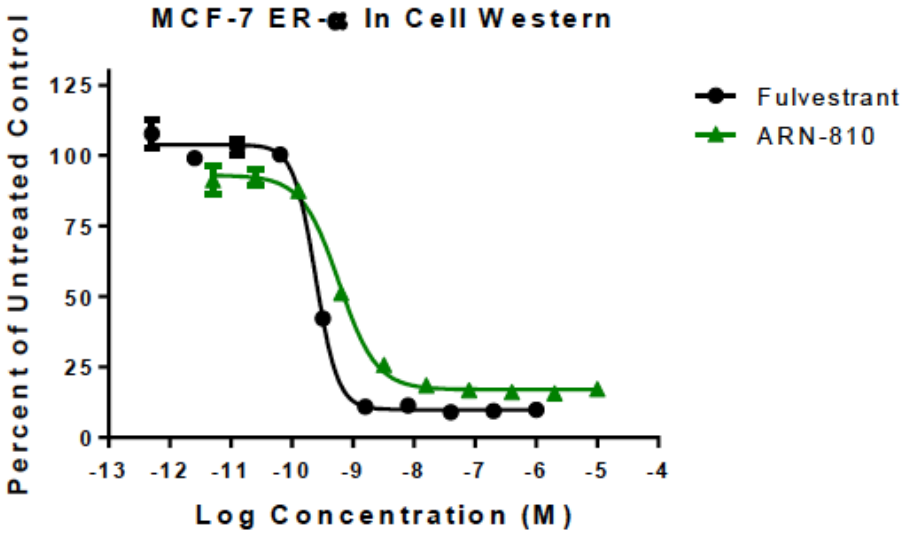
ESR1 mutations are enriched in metastatic ER+ breast cancer



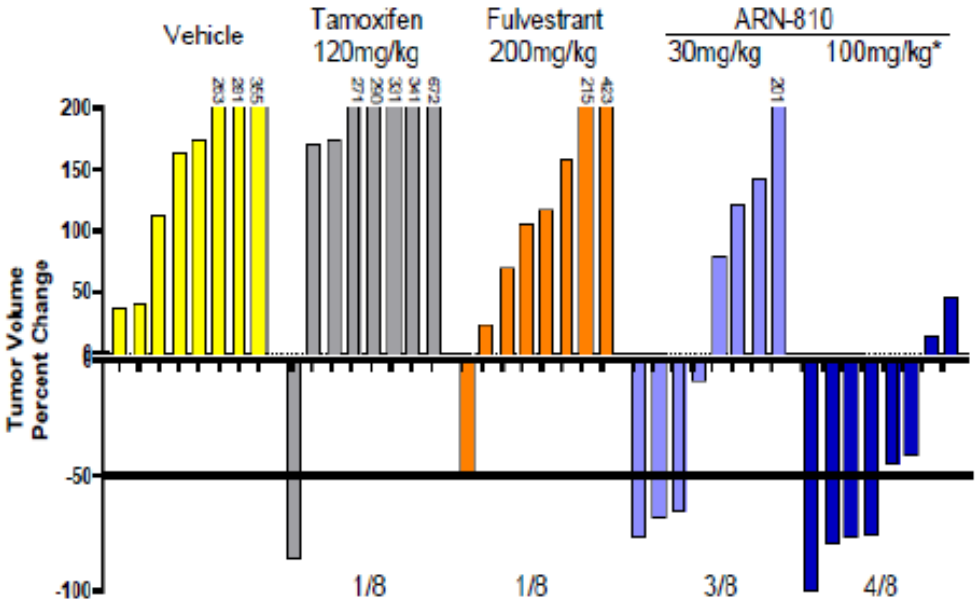


Jeselsohn RM et al. SABCS 2013.

ARN-810: Orally Bioavailable Selective Estrogen Receptor Down-Regulator (SERD)



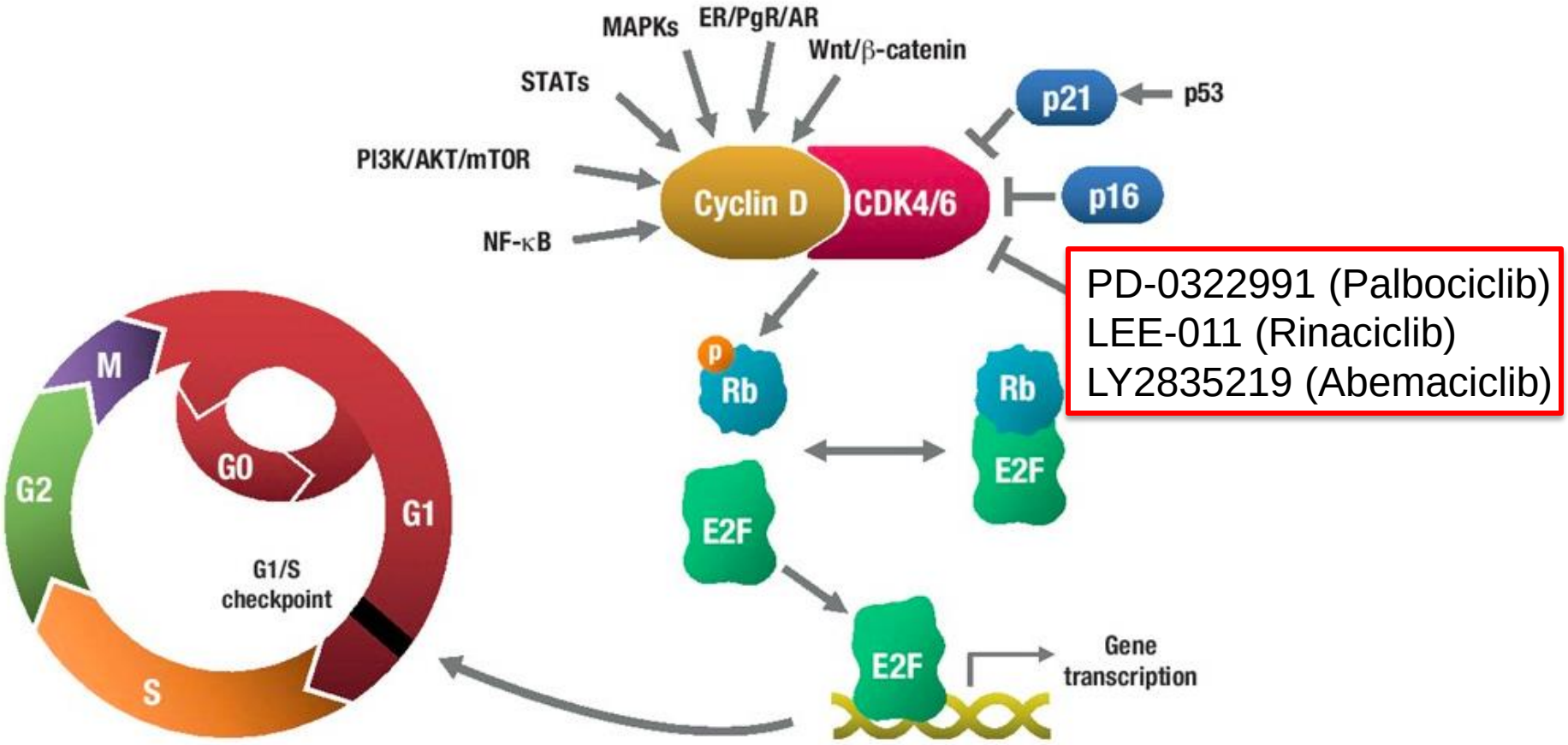
ARN-810: IC_{50} = 0.6 nM



ARN-810 exhibits anti-tumor activity in a tamoxifen-resistant MCF-7 model

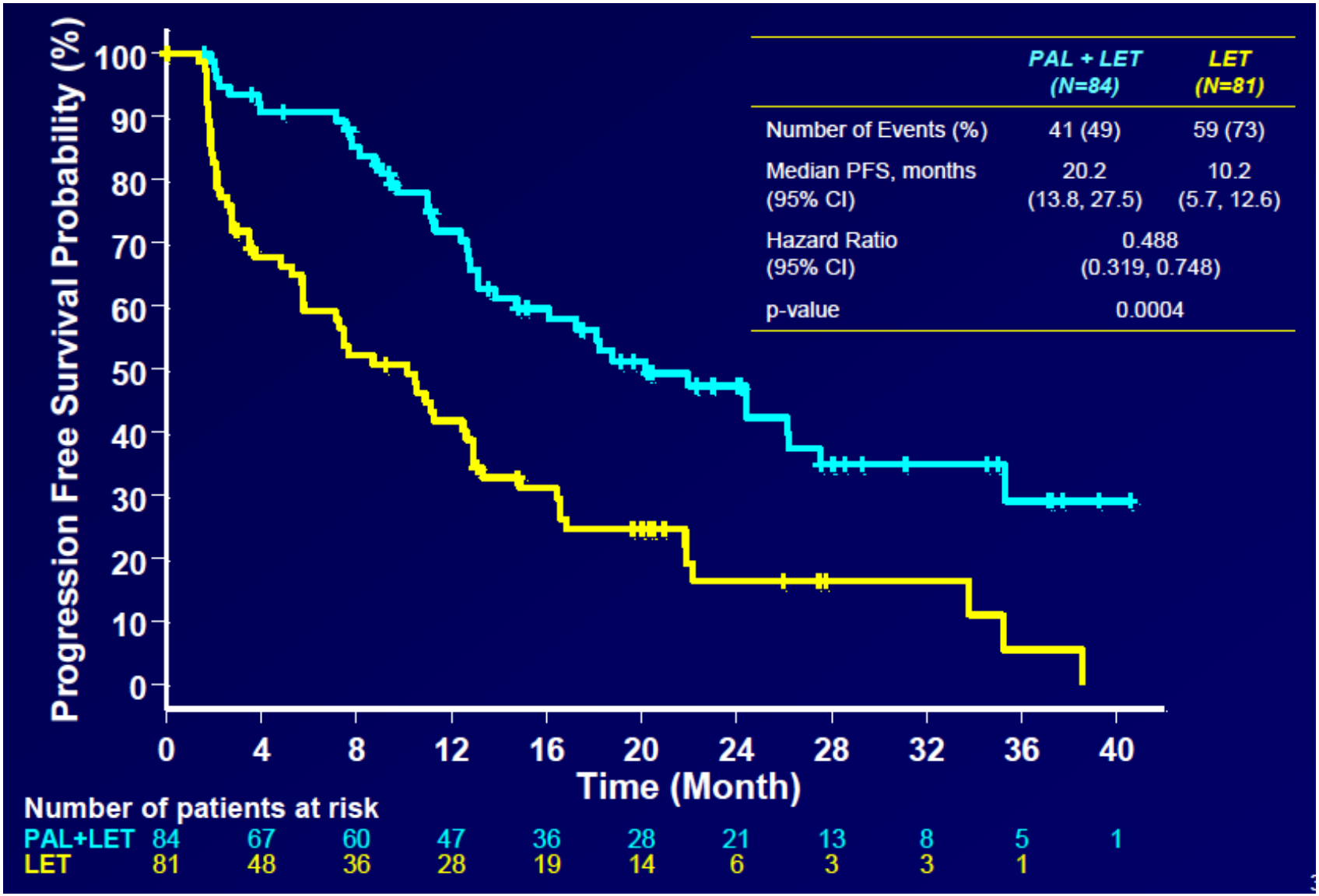
Mayer I et al. SABCS 2013.

Cyclin/CDK/Rb: Key Pathway in Cell Cycle Progression



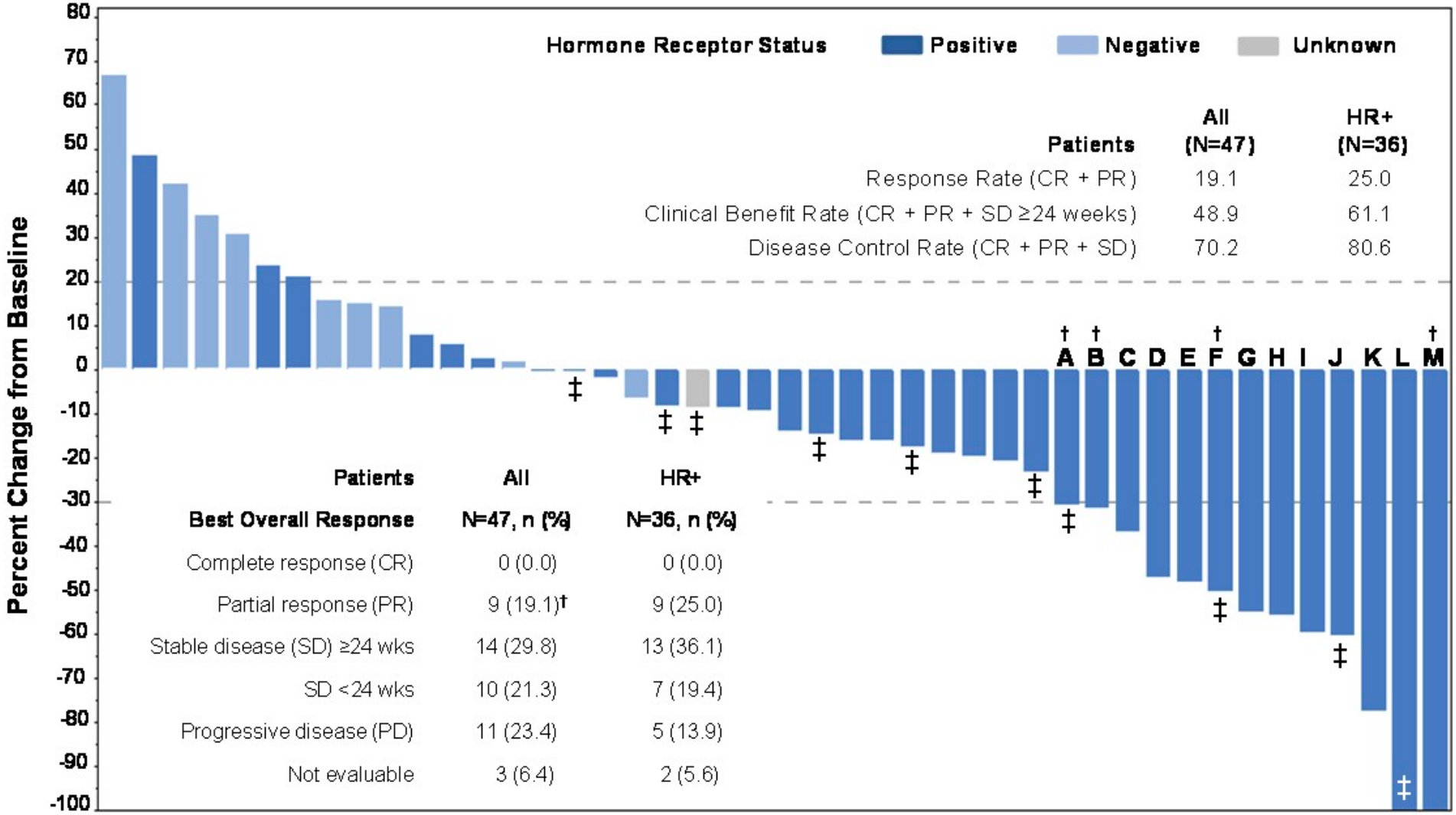
adapted from Infante JR et al. ASCO 2014

PALOMA-1: Progression Free Survival



Finn RS et al AACR 2014

LY2835219 (Abemaciclib): Waterfall Plot Phase I Trial (Breast Cancer Patients)



Patients	All (N=47)	HR+ (N=36)
Response Rate (CR + PR)	19.1	25.0
Clinical Benefit Rate (CR + PR + SD ≥24 weeks)	48.9	61.1
Disease Control Rate (CR + PR + SD)	70.2	80.6

Patients	All	HR+
Best Overall Response	**N=47, n (%)**	**N=36, n (%)**
Complete response (CR)	0 (0.0)	0 (0.0)
Partial response (PR)	9 (19.1)†	9 (25.0)
Stable disease (SD) ≥24 wks	14 (29.8)	13 (36.1)
SD <24 wks	10 (21.3)	7 (19.4)
Progressive disease (PD)	11 (23.4)	5 (13.9)
Not evaluable	3 (6.4)	2 (5.6)

†4 additional patients with unconfirmed PR were classified as stable disease and are not included in calculation of response rate

‡ Patient progressing on endocrine therapy before study entry and continued on that specific therapy

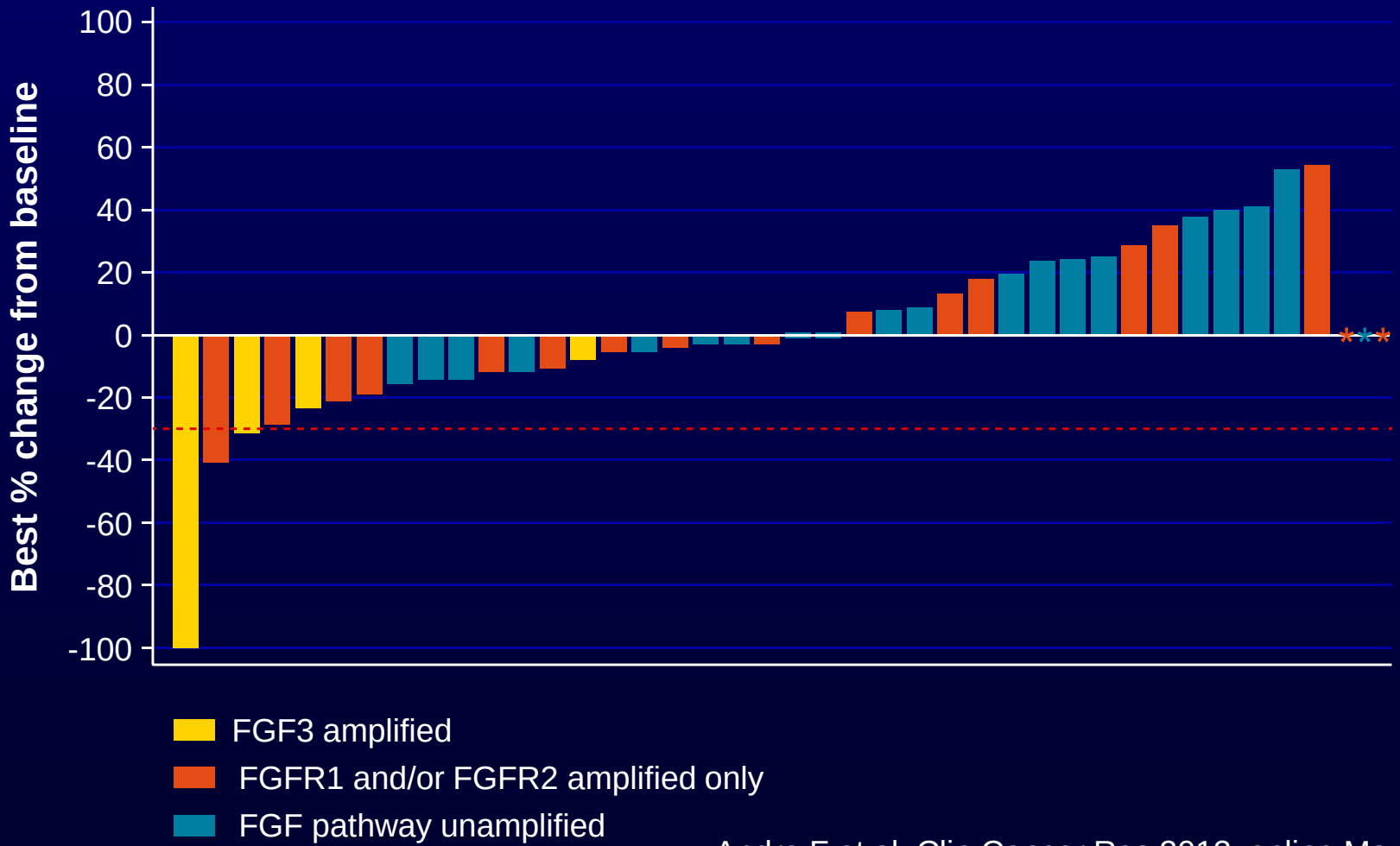
Patnaik A et al ASCO 2014

Fibroblast Growth Factor (FGF) Pathway Alterations in ER+ Breast Cancer: TCGA

Alteration	Luminal A	Luminal B	Targeted Drugs
FGF pathway			
FGFR1 amplification	10%	16%	Dovitinib Lucitanib BGJ398 AZD4547 JNJ-42756493
FGFR2 amplification	4%	8%	
FGF3 amplification	12%	28%	

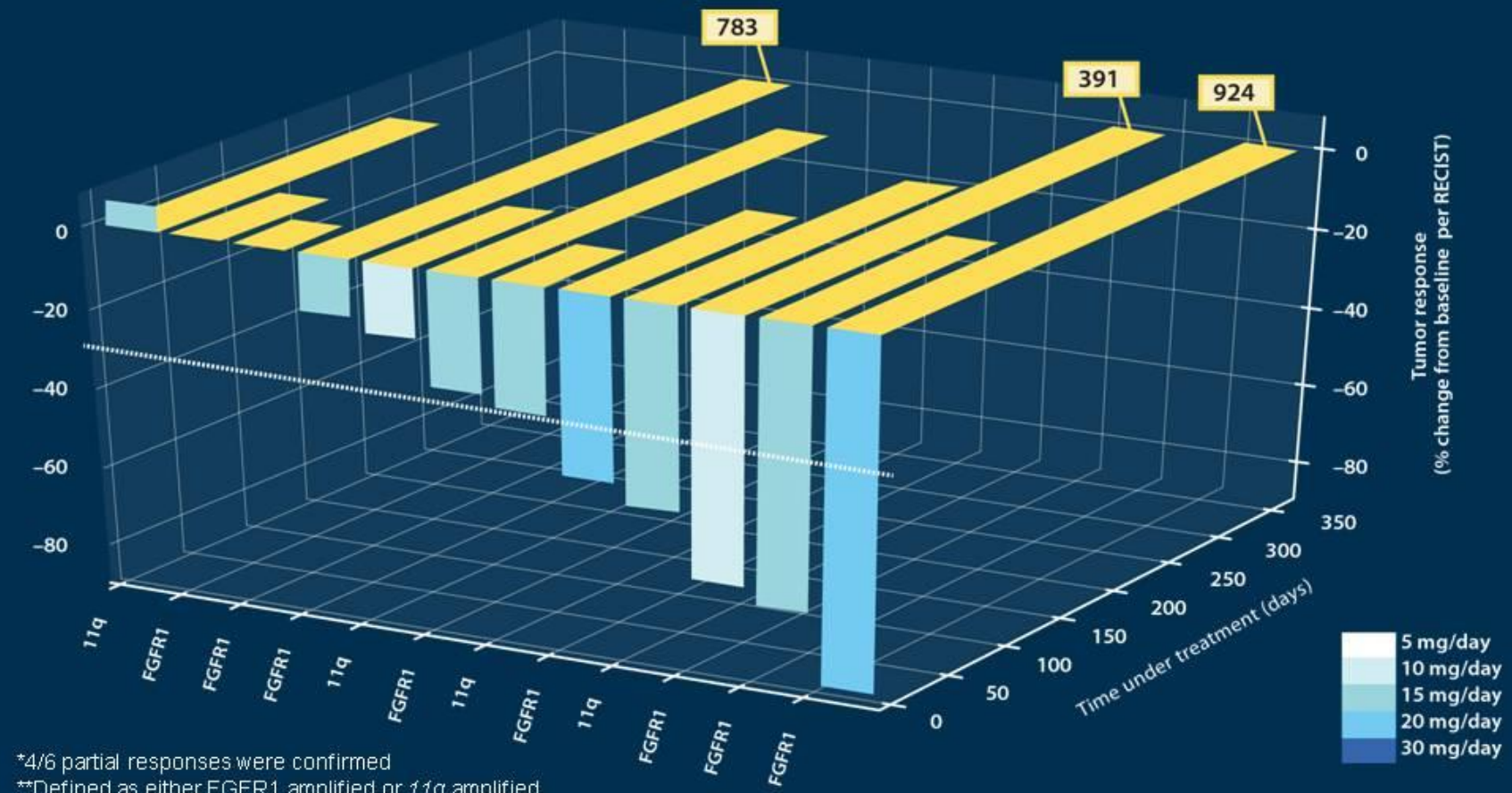
The Cancer Genome Atlas Network. Nature 2012; 490:61-70.

Dovitinib Activity in HR+ Patients With Known Measurable Disease and FGF Status



Andre F et al. Clin Cancer Res 2013; online May 8, 2013.

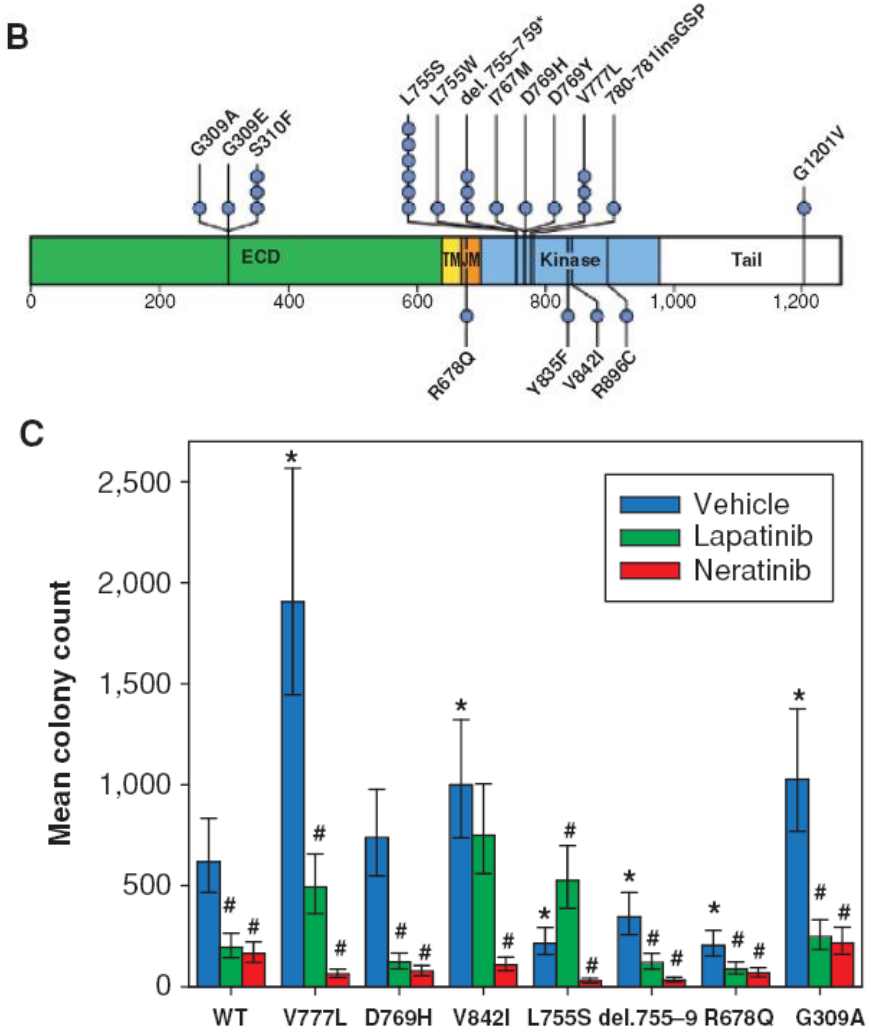
Lucitanib has 50% PR rate* in FGF-amplified breast cancer patients



*4/6 partial responses were confirmed
**Defined as either FGFR1 amplified or *11q* amplified

Presented By Jean-Charles Soria at 2014 ASCO Annual Meeting

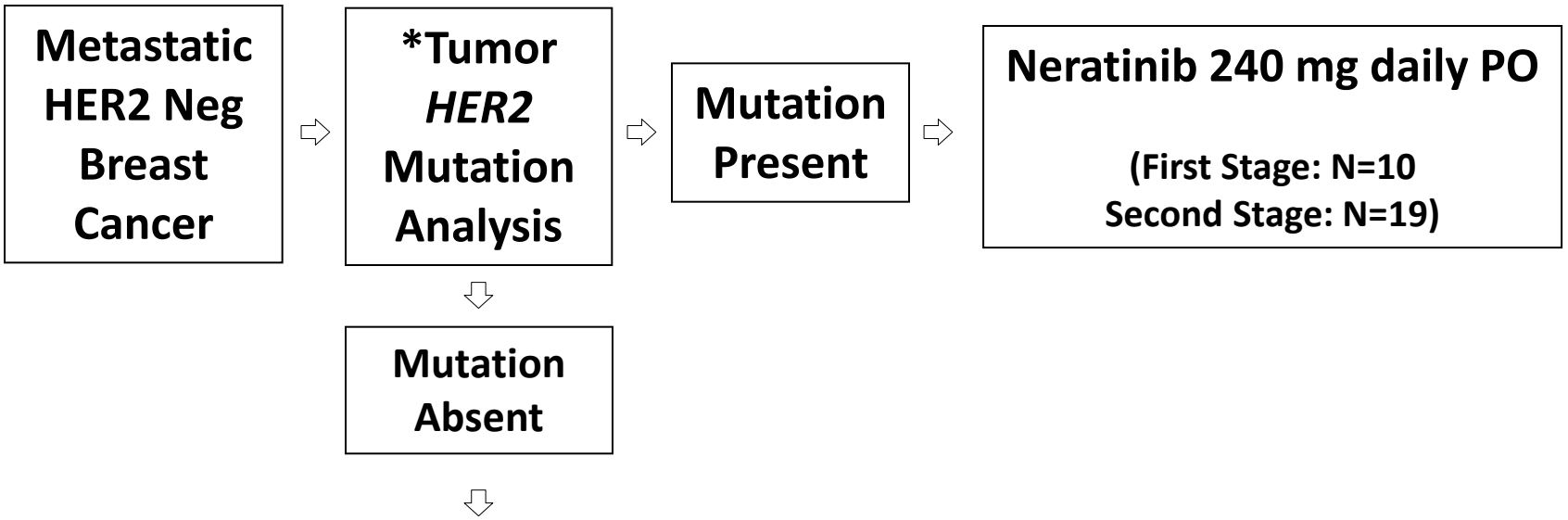
ERBB2 Mutation as an Oncogenic Driver in HER2 non amplified ER+ Breast Cancers



- ERBB2 mutation 1.6% of non-HER2 amplified breast cancers
- More common in lobular
  - Co-mutation with *CDH1* (E-cadherin) (6/27)
- May be enriched in metastatic breast
- Cell lines resistant to reversible HER2 TKI, sensitive to irreversible HER2 TKI

Bose R et al Cancer Discovery 2013. 3(2):1-14.
Ross J et al CCR 2013. 19(10); 2668–76

Washington University Phase II Trial



***Centrally tested at WU@GPS**

Primary Objective: Clinical Benefit Rate (CR+PR+SD≥6mos)

PI: Cynthia Ma

Summary

- Everolimus/Exemestane is an option for AI-resistant disease
  - Patient selection & monitoring is important
- Targeting PI3K, ESR1, CDK4/6, FGFR, and ERBB2 are being actively investigated to overcome endocrine resistance
- New drug development will be increasingly focussed on subpopulations of ER+ breast cancer