Mutations in PIK3CA and ERBB2: resistance mechanism, therapeutic target, or both?

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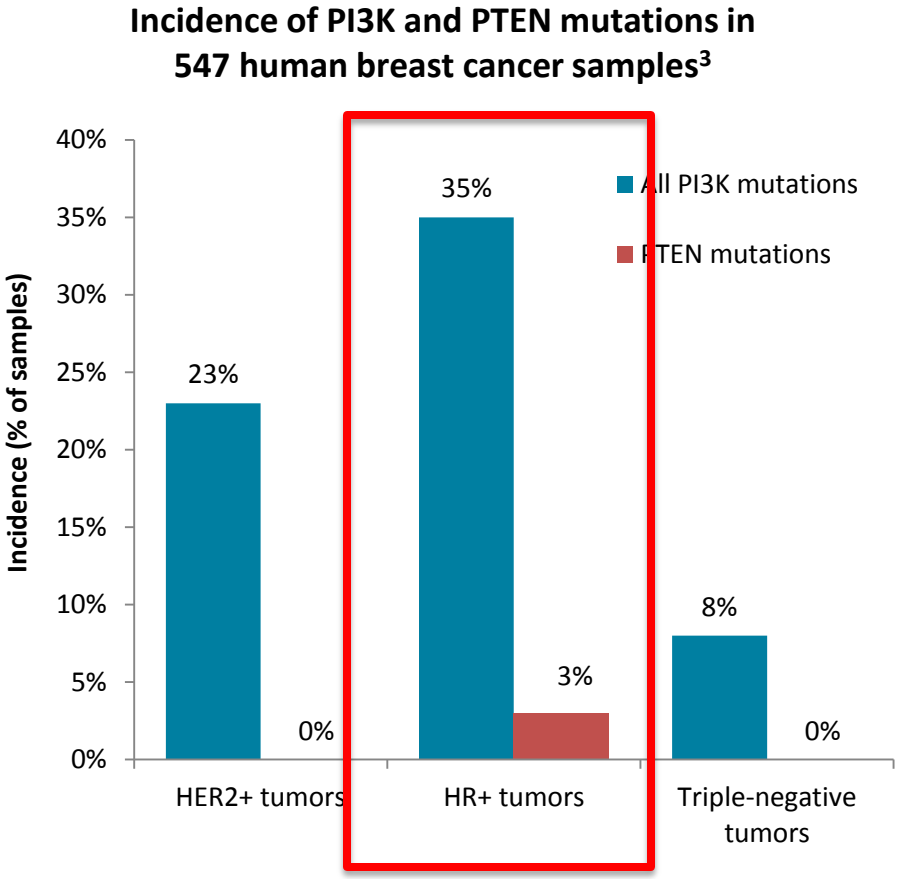
IMPAKT 2015

Agenda

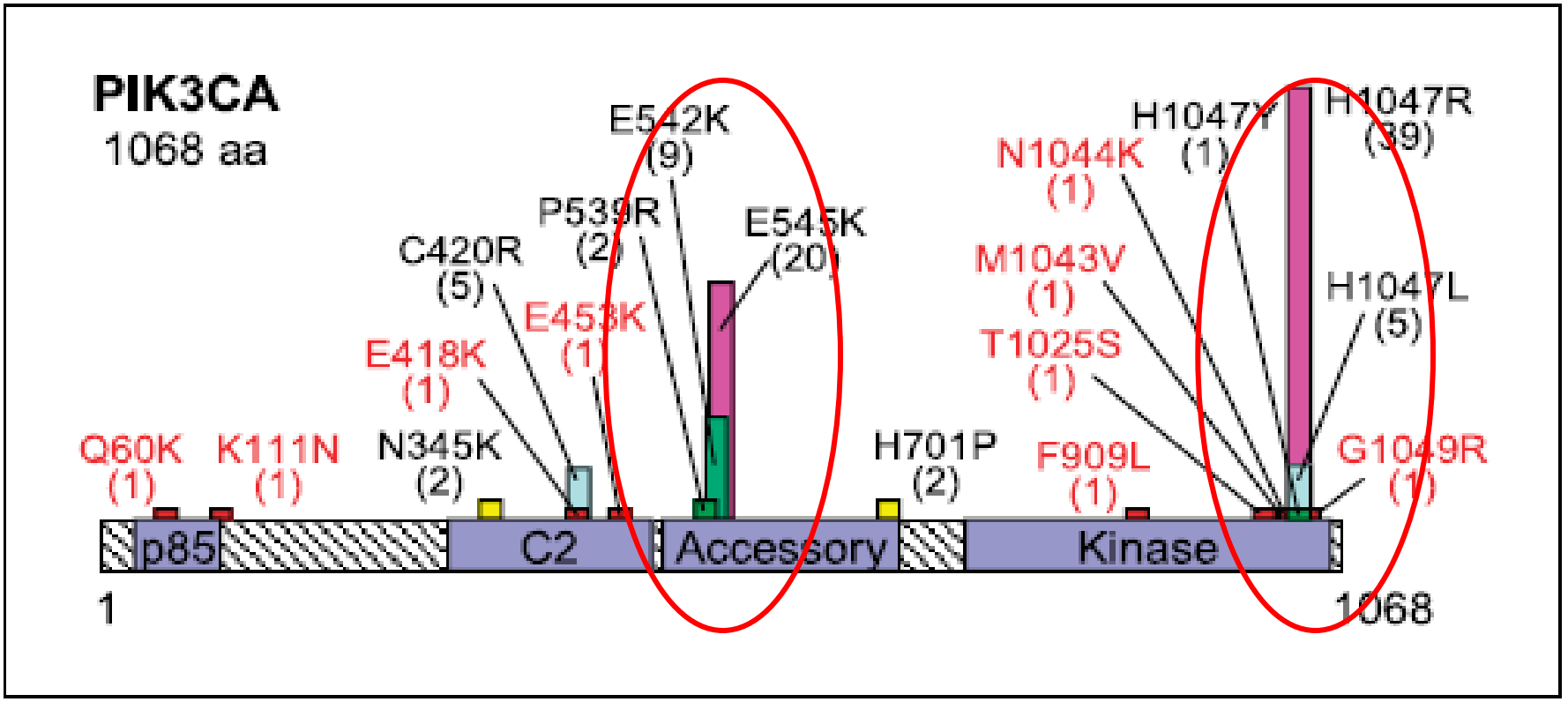
- The role of PI3-Kinase mutations in ER+ cancers
- The role of PI3-Kinase mutations in HER2+ cancers
- Significance of ERBB2 mutations in HER2-negative cancers
- ERBB2 as a resistance mechanism in HER2+ cancers

The PI3K/AKT/mTOR Pathway in Breast Cancer: Common Molecular Alterations



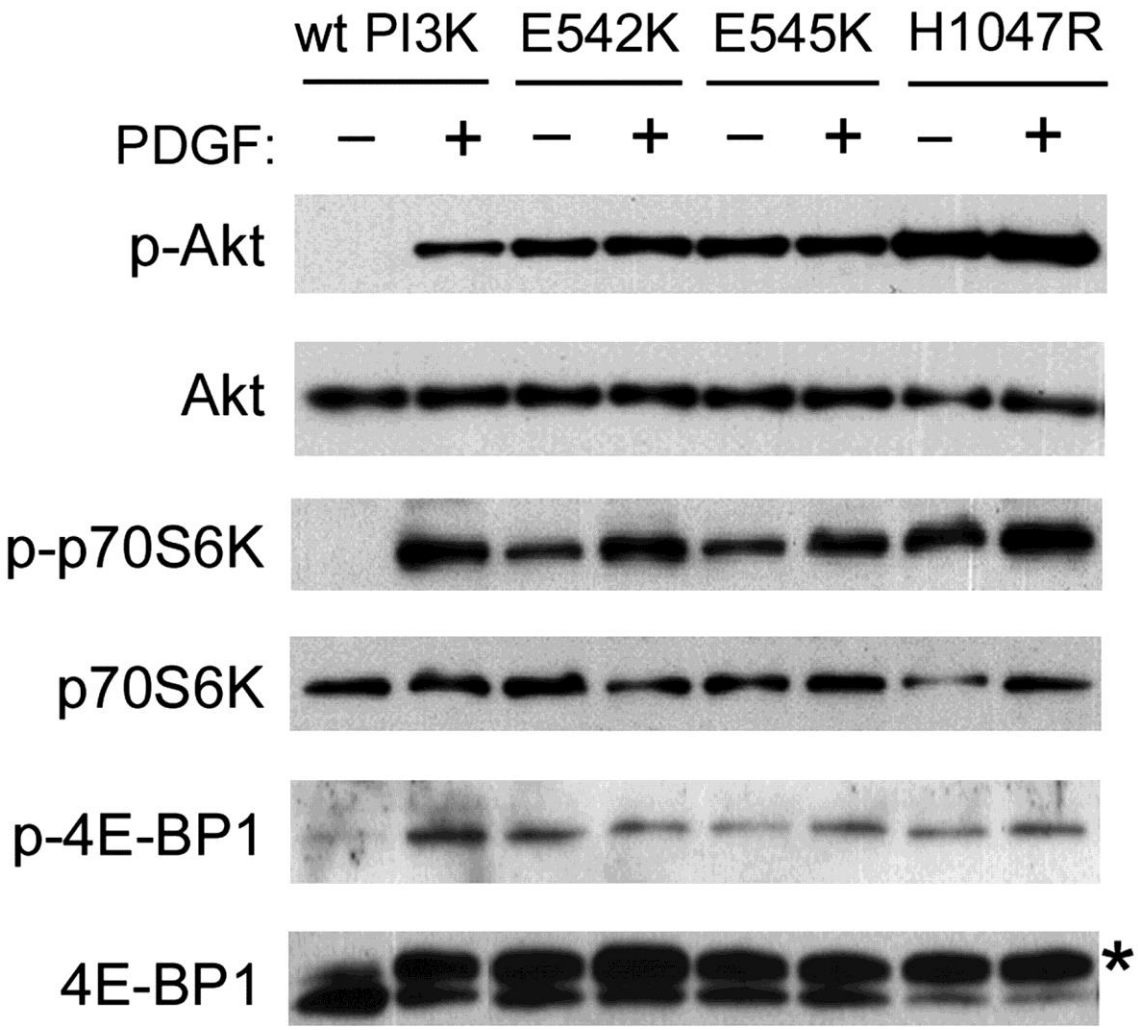
1. Liu P, *et al*. *Nat Rev Drug Discov* 2009;8:627–644;2. Baselga J. *Oncologist* 2011;16:Suppl 1:12–19;
3. Stemke-Hale K, *et al. Cancer Res* 2008;68:6084–6091.

Mutations in PIK3CA primarily occur in two hotspots



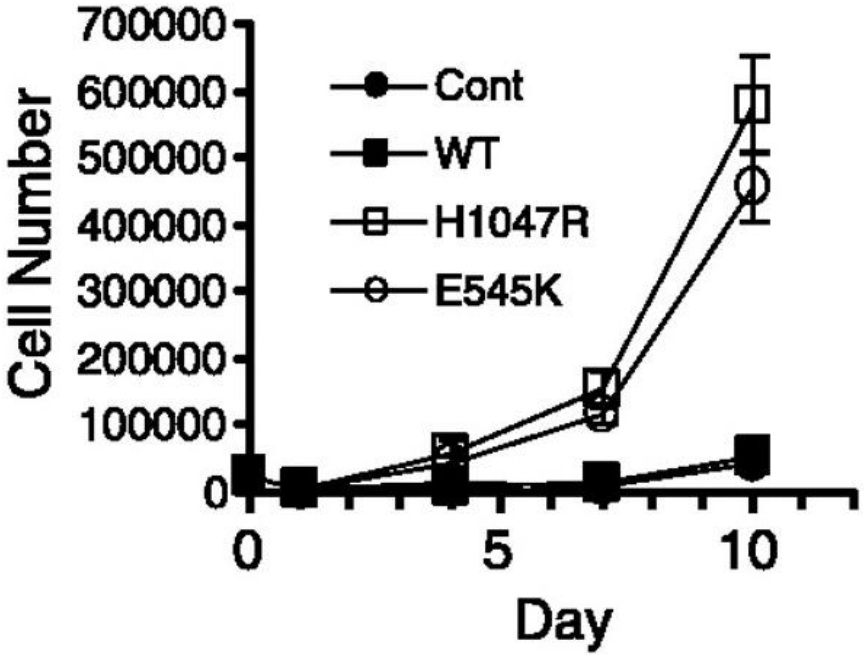
Saal et al, Canc Res 2005

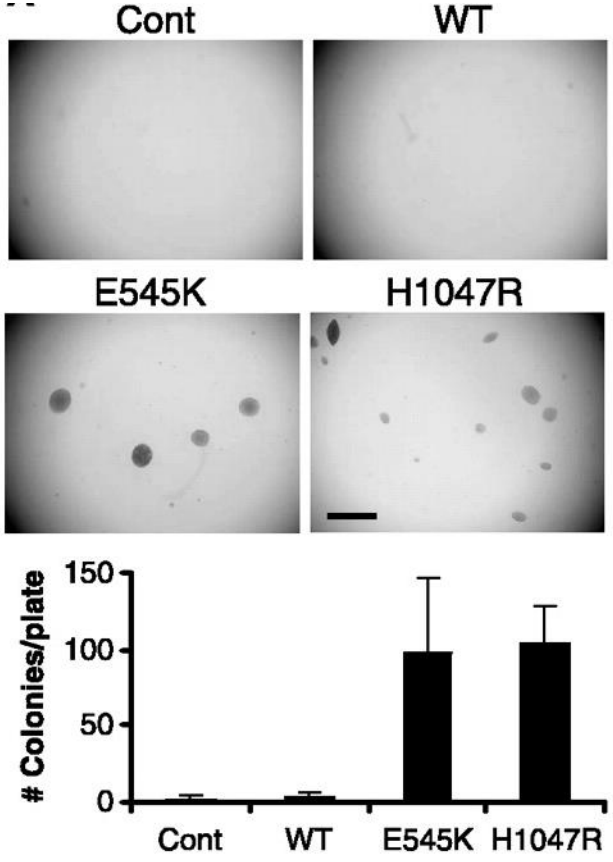
Mutations in PIK3CA result in constitutive activation of the kinase



Sohye Kang et al. PNAS 2005;102:802-807

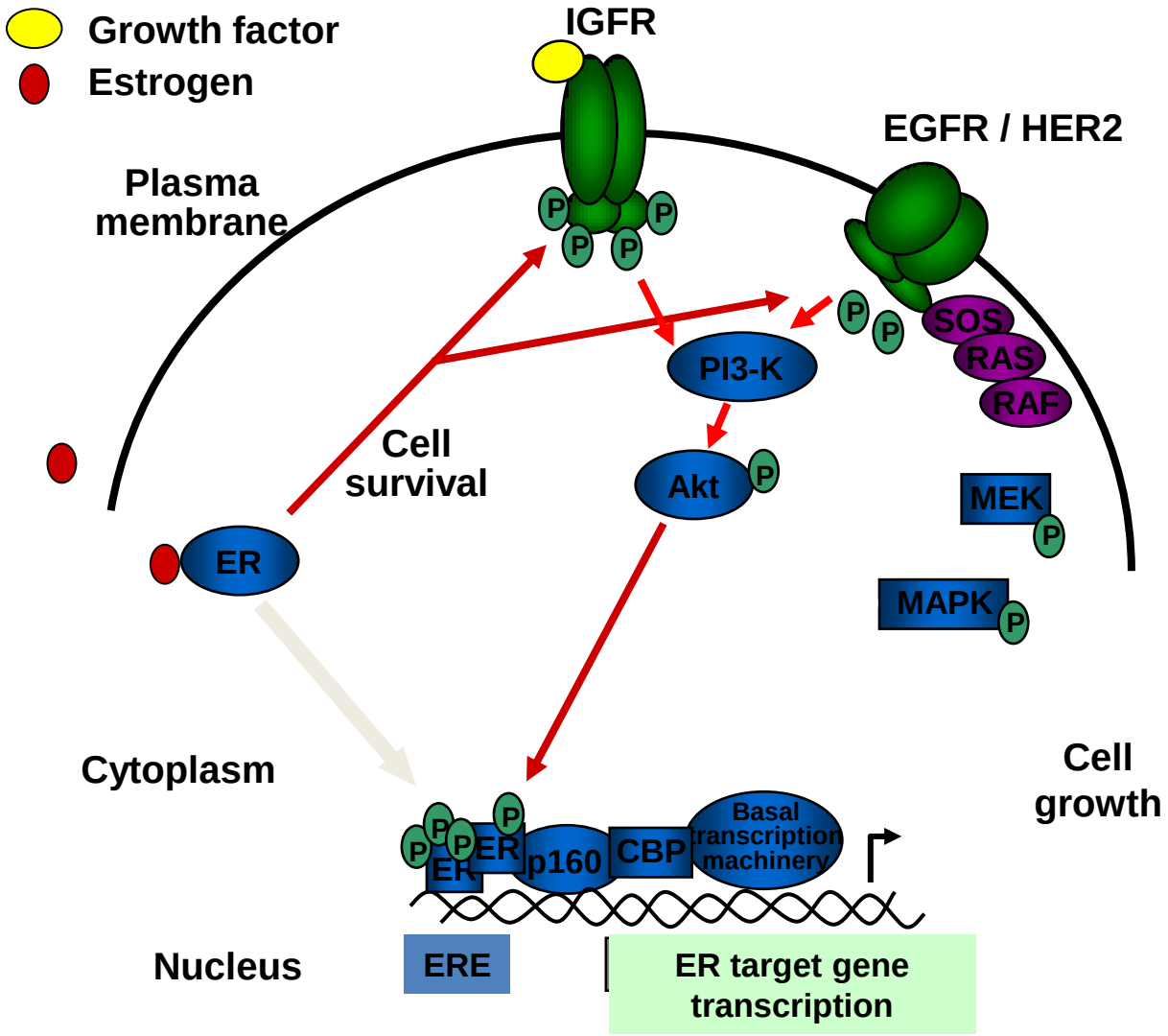
Mutant PI3K can transform MCF10A mammary epithelial cells





Isakoff et al, Canc Res 2006

Evidence of Cross-Talk Between ER and PI3-kinase mTOR pathways

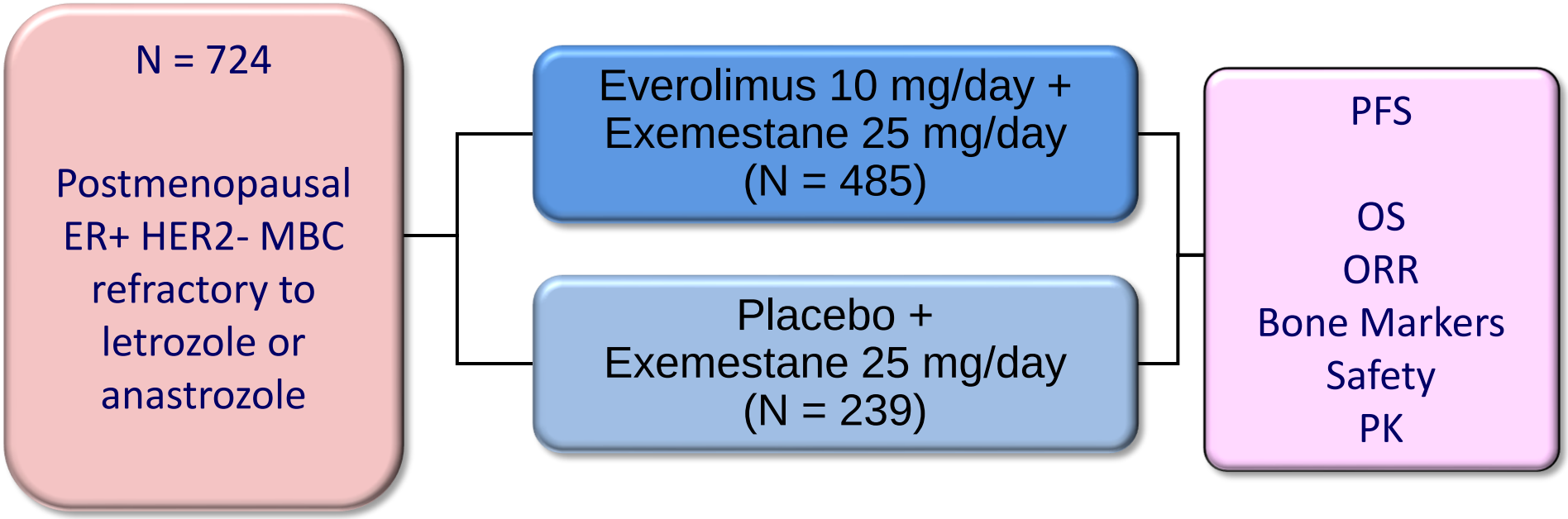


- **mTORC1 activates ER in a ligand-independent fashion**
- **Estradiol suppresses apoptosis induced by PI3K/mTOR blockade**
- **Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells**

Adapted from Johnston S. *Clin Cancer Res*. 2005;11:889S-899S

Baselga, ESMO 2011

BOLERO-2: Successful mTOR Inhibition

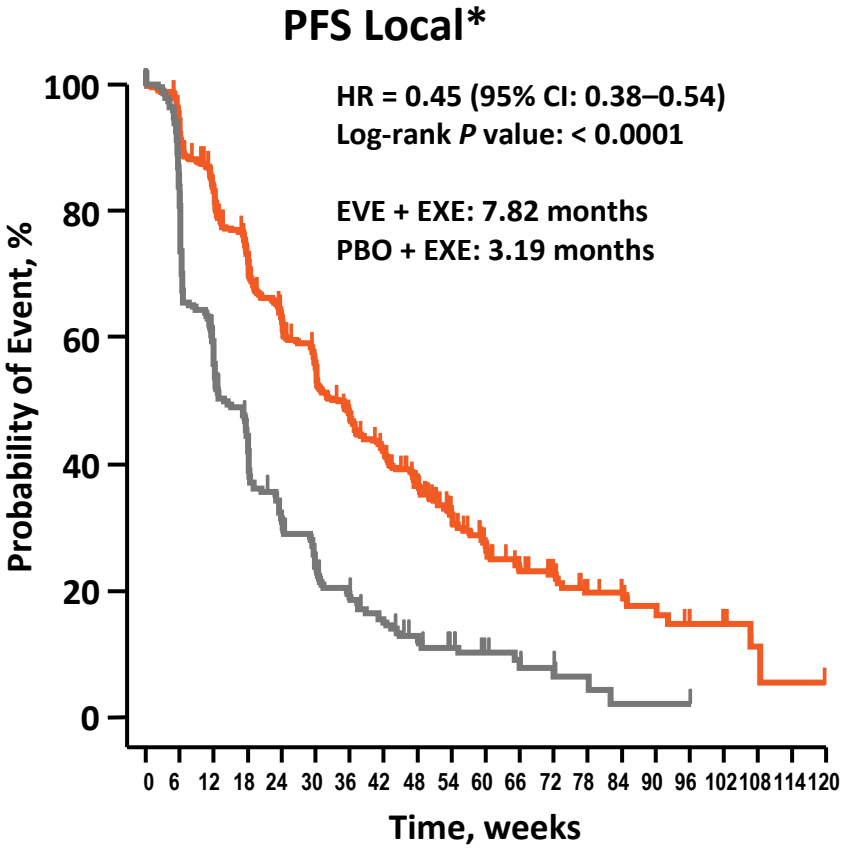


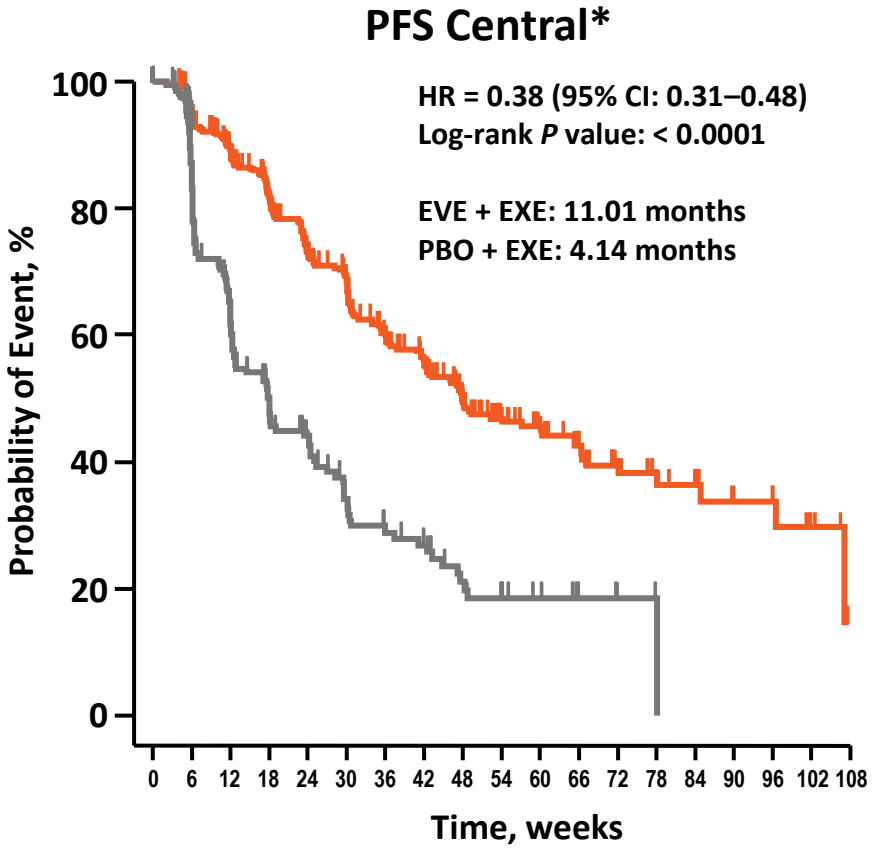
- Stratification:
    1. Sensitivity to prior hormonal therapy
    2. Presence of visceral disease
- No cross-over

Baselga et al, ESMO 2011

BOLERO-2 Efficacy:

Addition of Everolimus (EVE) to Exemestane (EXE) More Than Doubled Median PFS

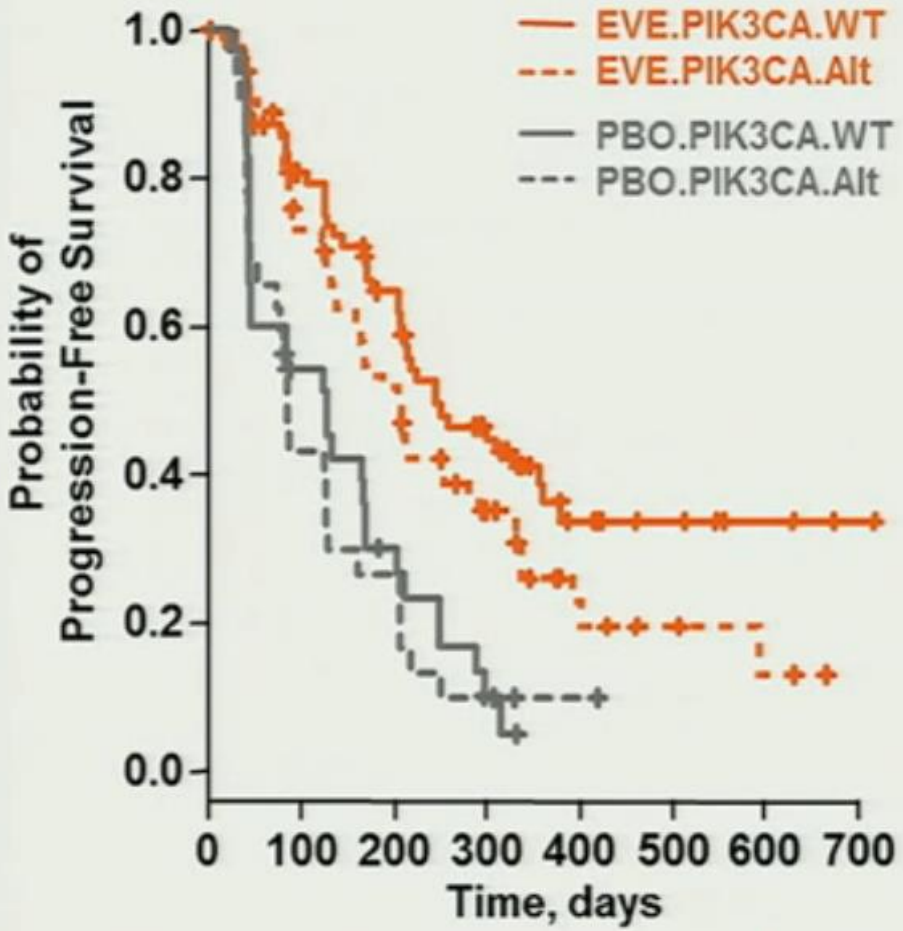




Final PFS Analysis at 18 mo: 4 month improvement in PFS over AI alone

Piccart M, et al. ASCO 2012; Abstract 559.

EVE Benefit Maintained in Patients Regardless of Gene Alterations in PIK3CA



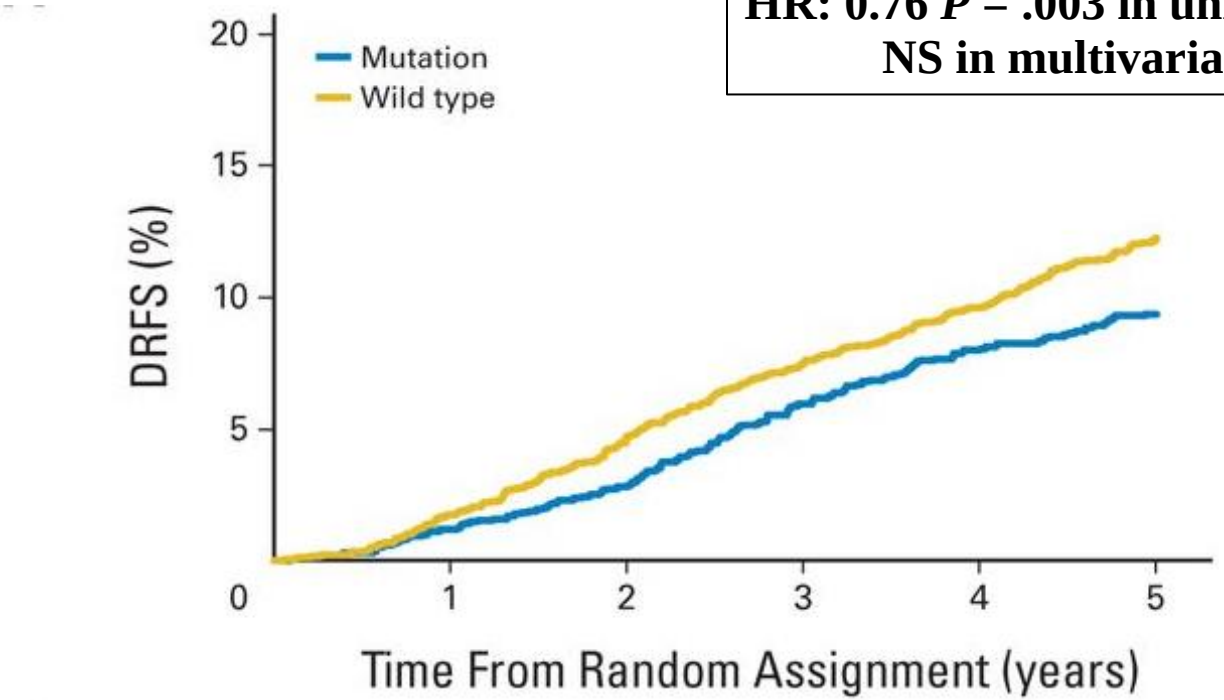
Study Arm	PIK3CA	Subgroup, n	PFS events, n (%)	HR (95%CI)
EVE	WT	83	44 (53%)	0.36 (0.22 - 0.57)
PBO	WT	36	31 (86 %)	
EVE	Alt	74	50 (68%)	0.44 (0.27 - 0.70)
PBO	Alt	34	28 (82%)	

Abbreviations: Alt, genetically altered; CI, confidence interval; EVE, everolimus; HR, hazard ratio; PBO, placebo; WT, wild type.

Hortobagyi et al, ASCO 2013

Impact of PI3KCA mutation status on DRFS in the TEAM (EXE vs Tam → EXE) trial

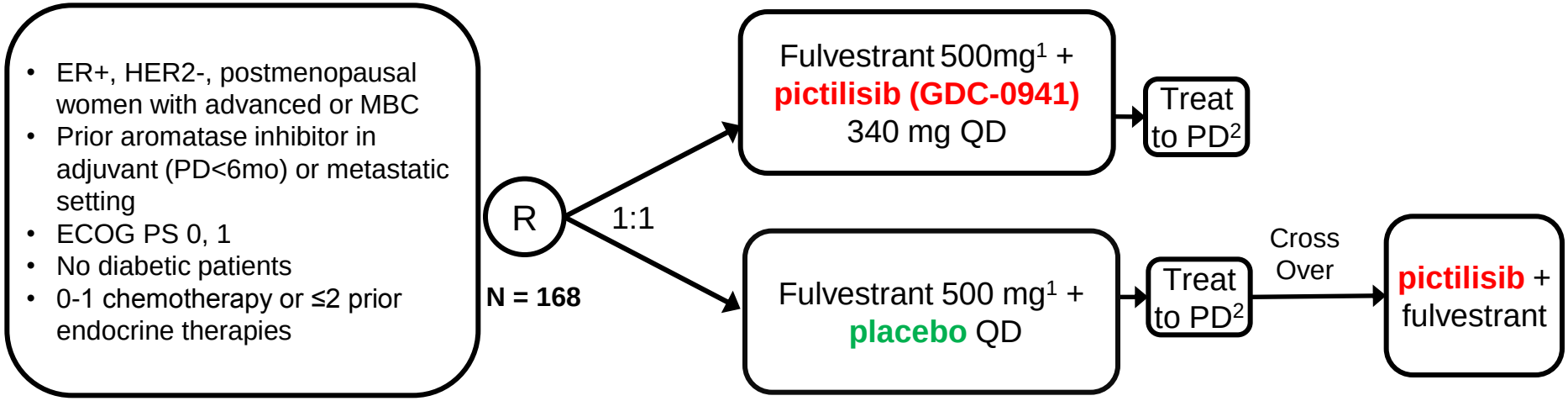
HR: 0.76 *P* = .003 in univariate analysis
NS in multivariate analysis



No. at risk						
Mutation	1,702	1,665	1,615	1,539	1,439	1,121
Wild type	2,570	2,490	2,394	2,287	2,153	1,640

Vicky S. Sabine et al. JCO 2014;32:2951-2958

FERGI Study Design – Part I

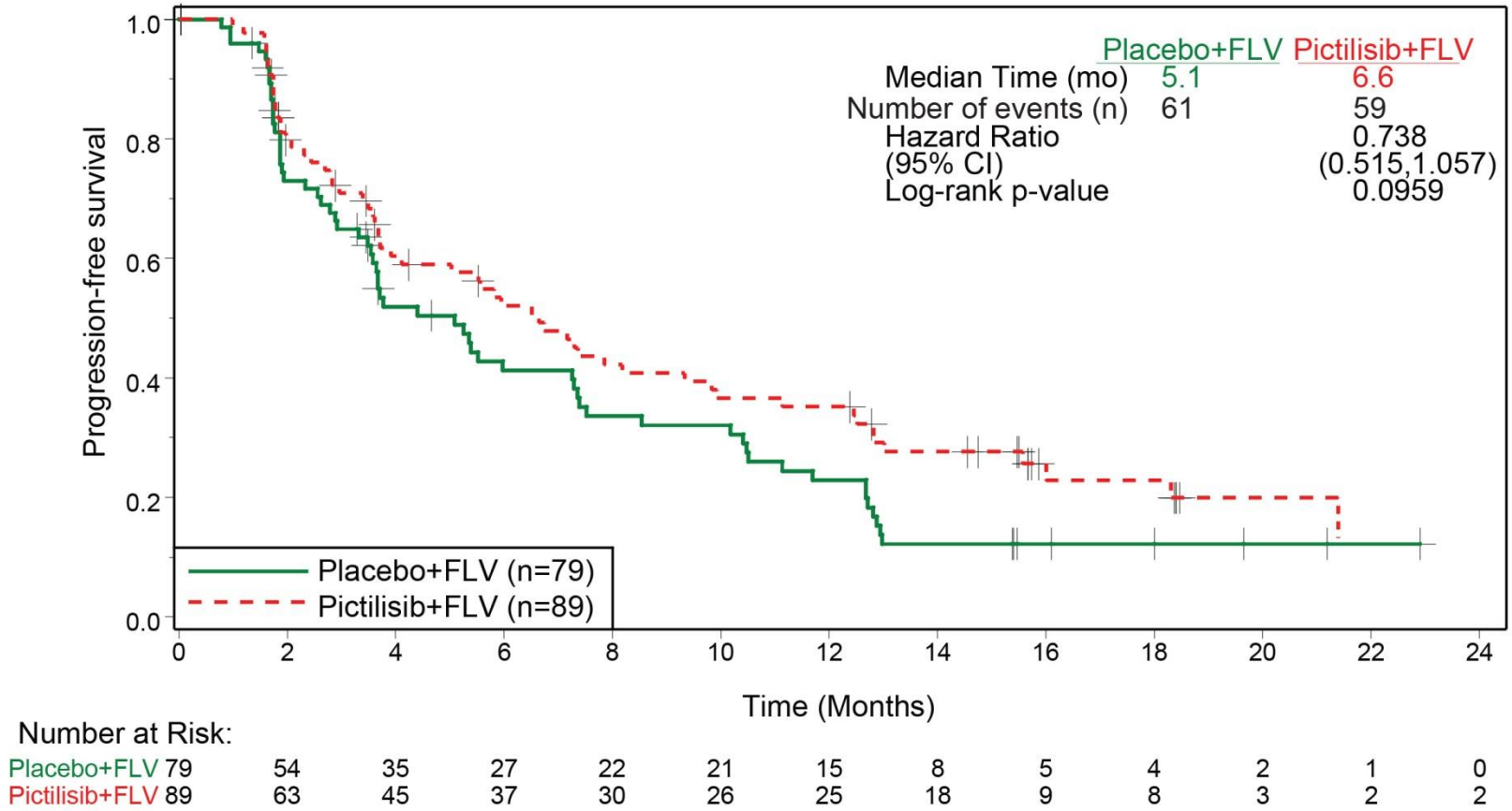


Stratification factors	1° objective	2° objectives
• *PIK3CA*-MT and *PTEN* loss[3] • Measurable disease • 1º vs. 2º resistance[4]	• PFS in the ITT • PFS in *PIK3CA*-MT pts • Safety	• Objective response rate • Duration of objective response • PK

[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

Progression-Free Survival in the ITT Population

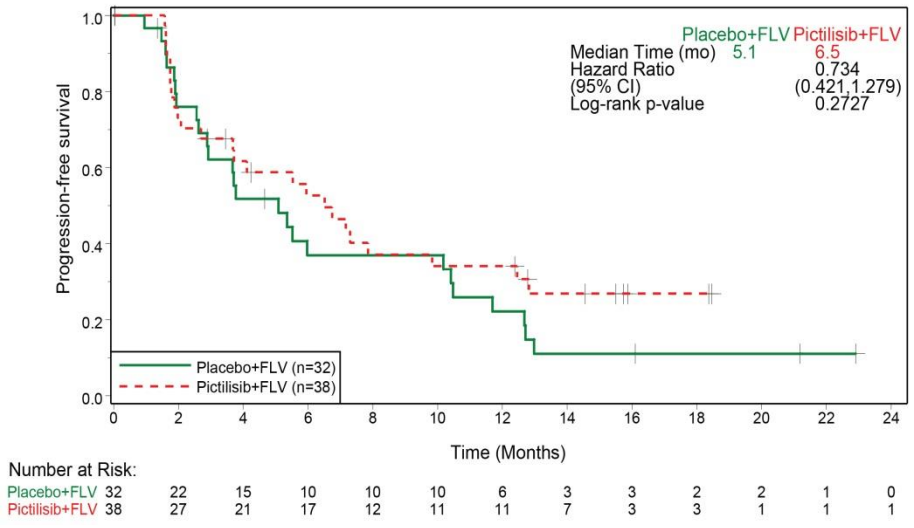


Number at Risk:

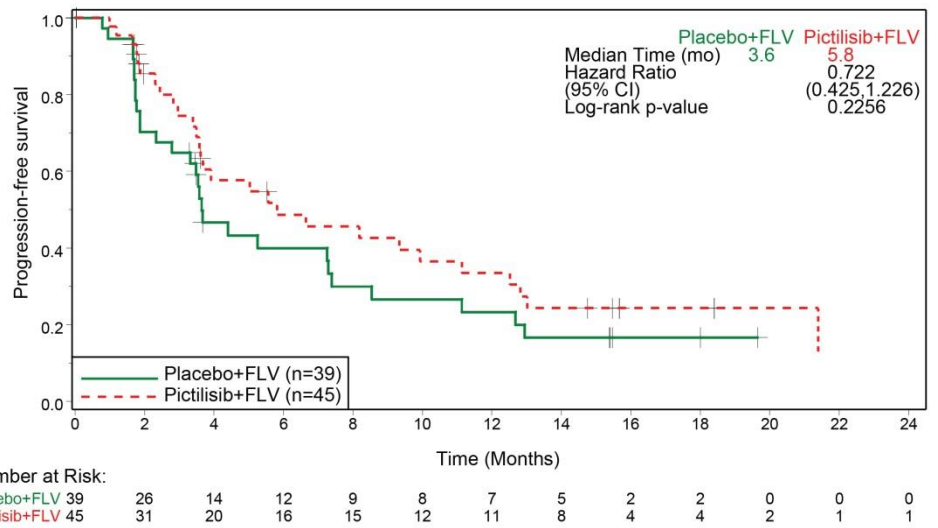
Placebo+FLV	79	54	35	27	22	21	15	8	5	4	2	1	0
Pictilisib+FLV	89	63	45	37	30	26	25	18	9	8	3	2	2

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

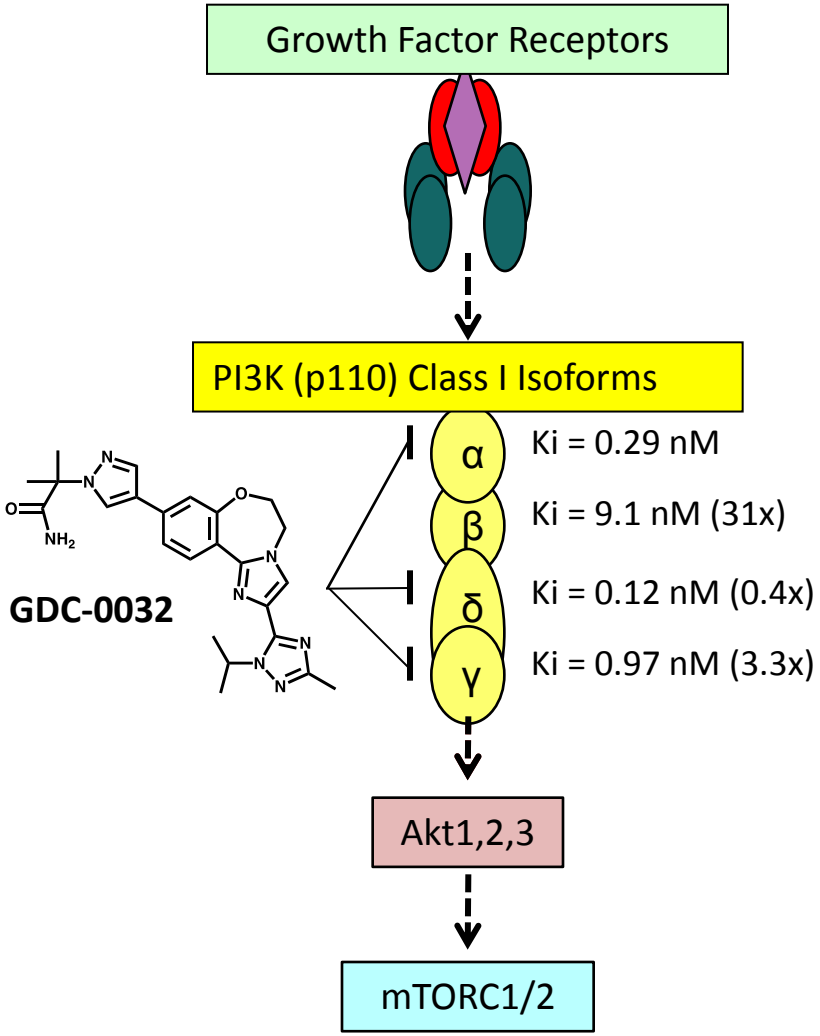
Patient Disposition

	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%)

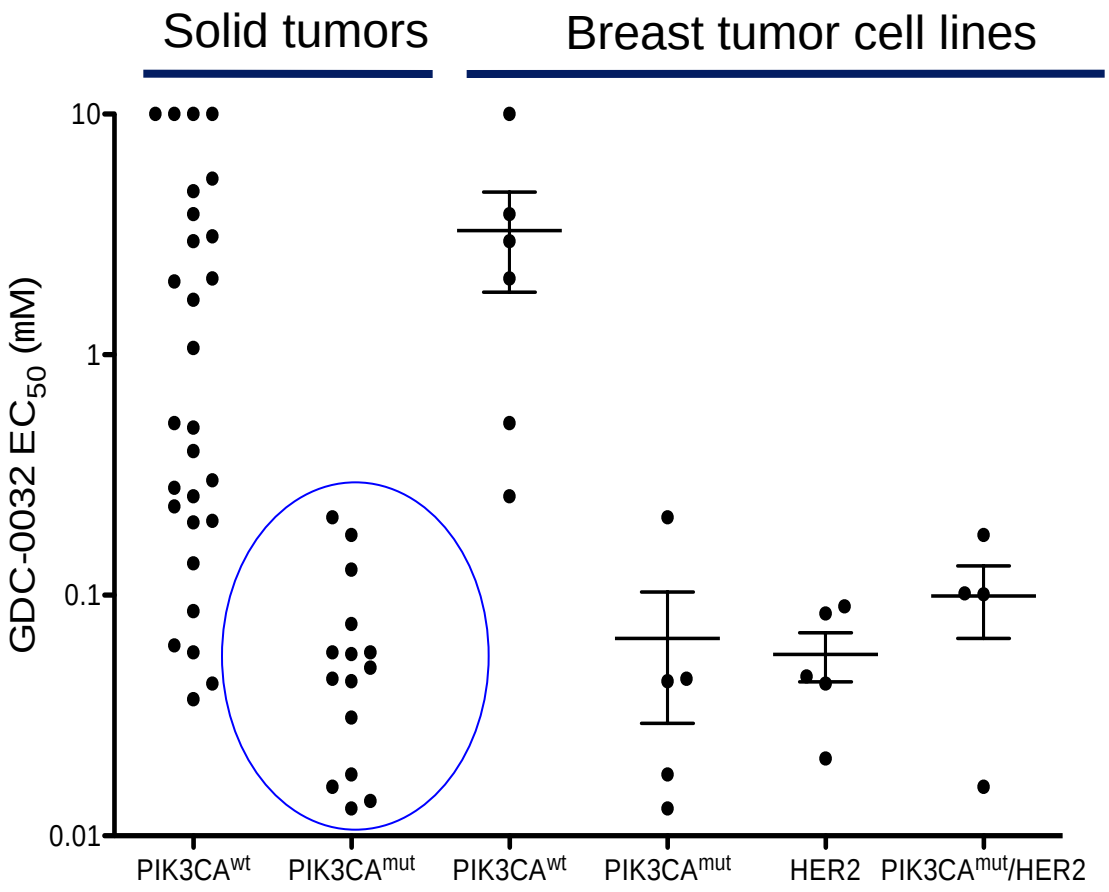
[1]From treatment discontinuation eCRFs
[2]From AE eCRFs

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

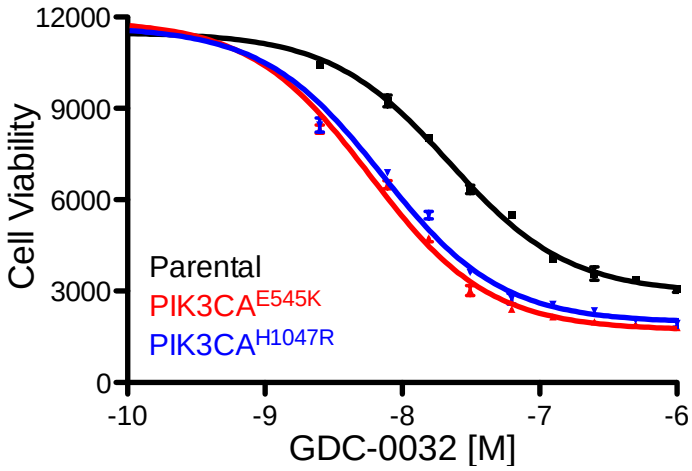
Taselisib (GDC-0032) is a PI3K inhibitor that spares the p110 beta isoform



Taselisib more potent against *PIK3CA*^{mut} mutant versus *PIK3CA*^{wt} cancer cell lines



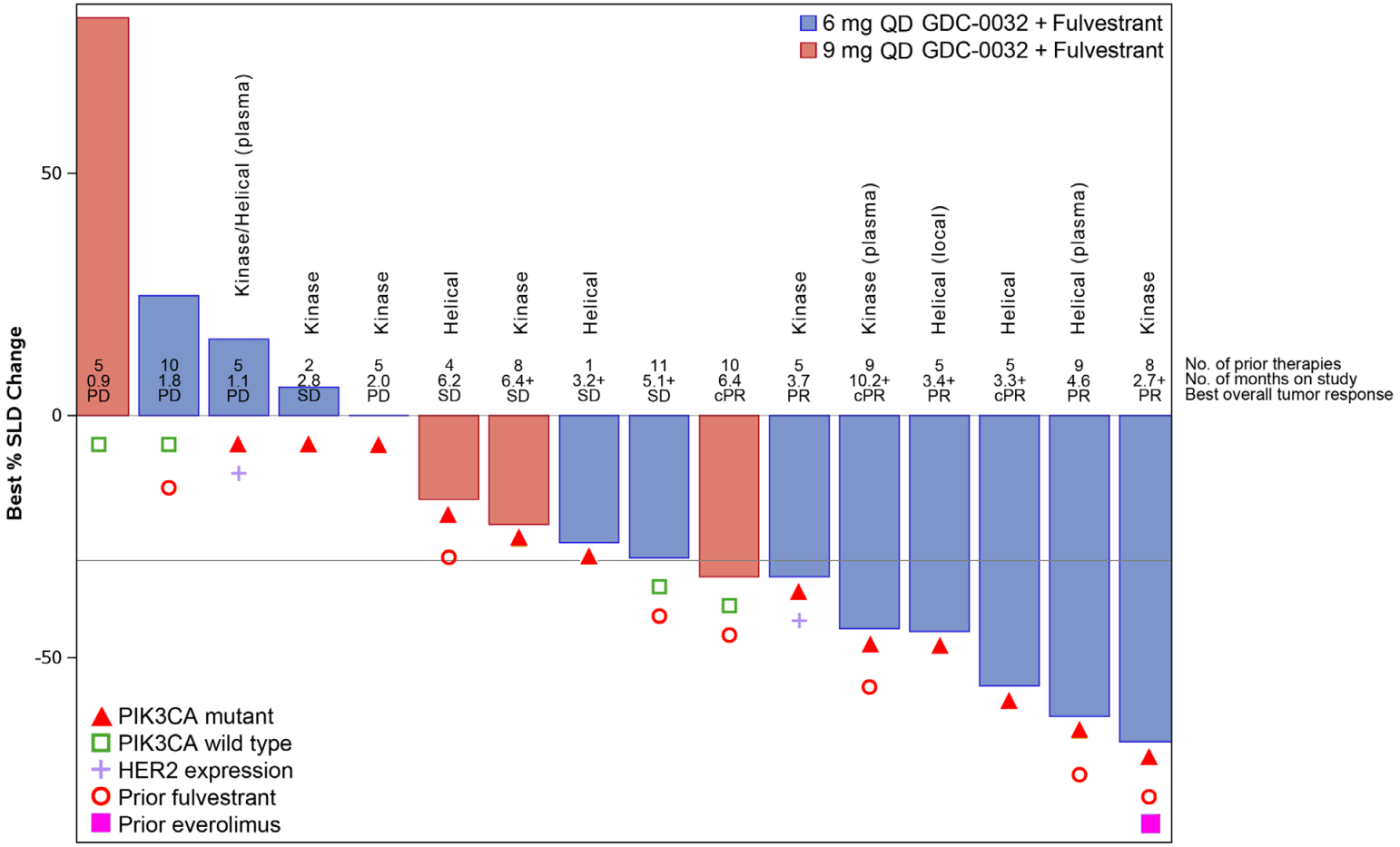
SW48 isogenic lines (*PIK3CA*^{mut} vs. *PIK3CA*^{wt})



PI3-kinase alpha encoded by *PIK3CA* gene

Juric et al, 2013

Anti-Tumor Activity Observed with Taselisib and Fulvestrant Combination

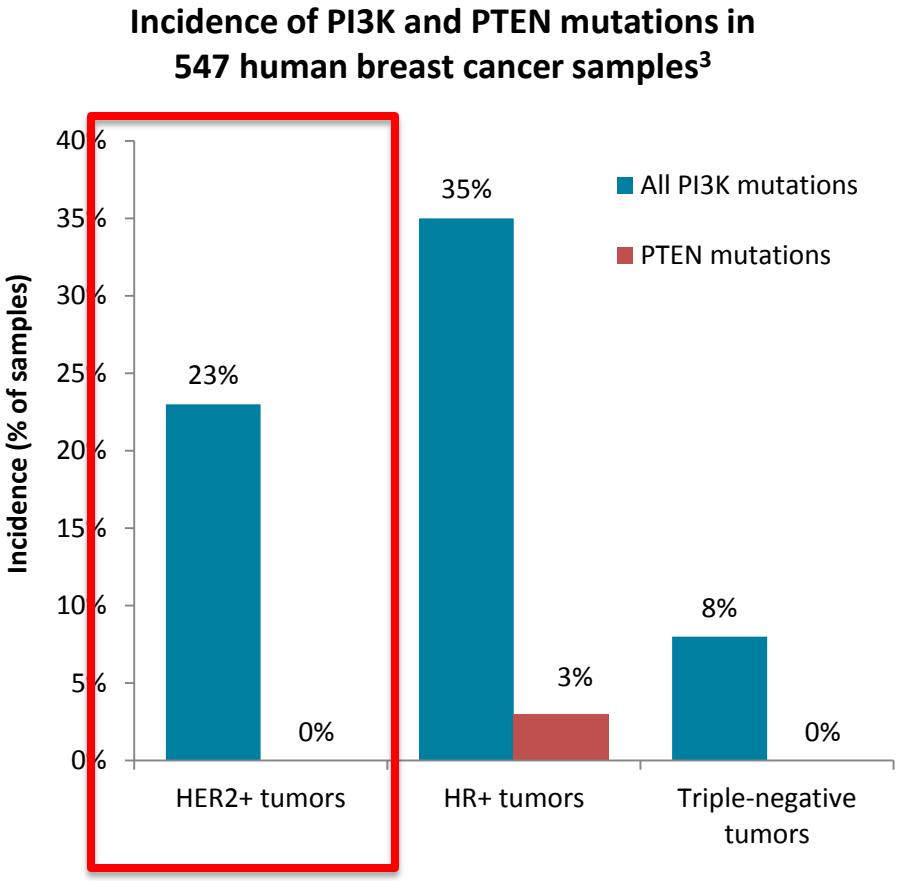


- Multiple partial responses observed in heavily pretreated HR+ breast cancer patients
- Anti-tumor activity observed in patients who had prior fulvestrant or everolimus
- Increased anti-tumor activity observed in patients with PIK3CA mutant breast cancer

Critical questions in HR+ breast cancer

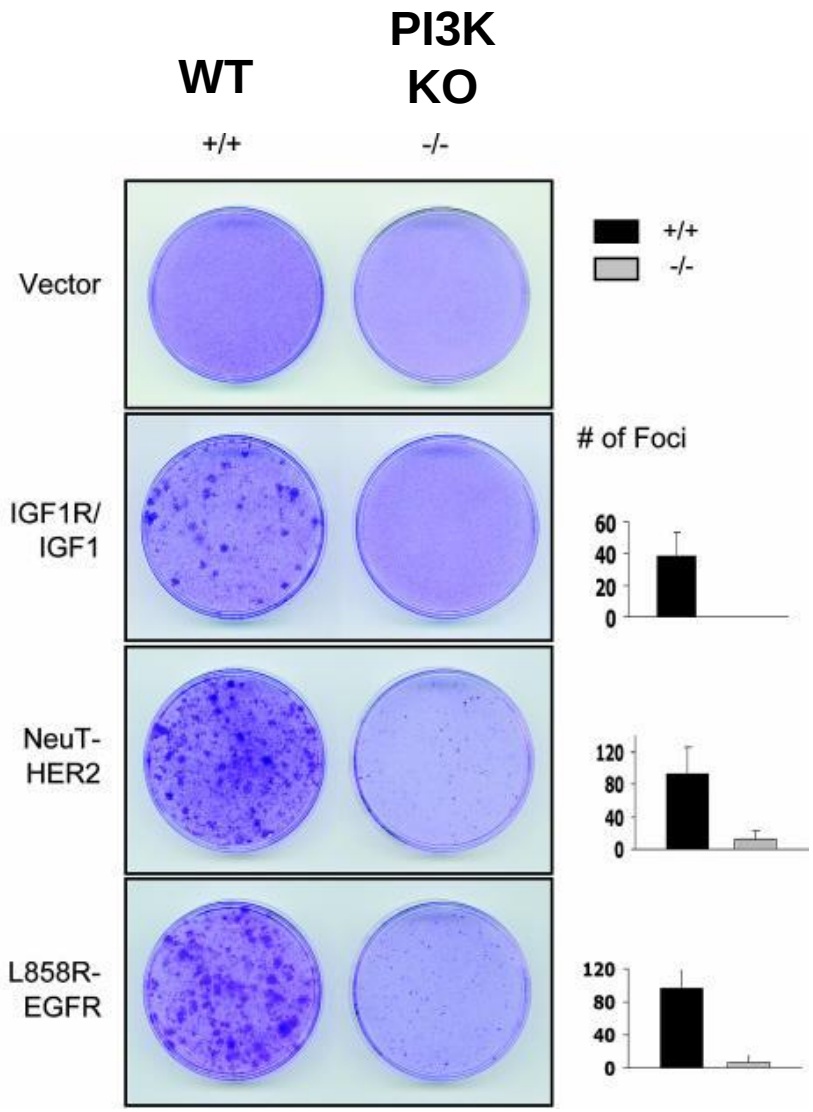
- Are PIK3CA mutations prognostic in HR+ breast cancer?
  - Largest data sets show no independent association with prognosis
- Are PIK3CA mutations associated with resistance to endocrine therapy in breast cancer?
  - No clinical data confirming mutations as cause of therapeutic resistance
  - Important question to test
- Do PIK3CA mutations predict response to PI3-kinase inhibitors
  - Not to pan-inhibitor
  - Possibly to alpha-selective inhibitors

The PI3K/AKT/mTOR Pathway in Breast Cancer: Common Molecular Alterations



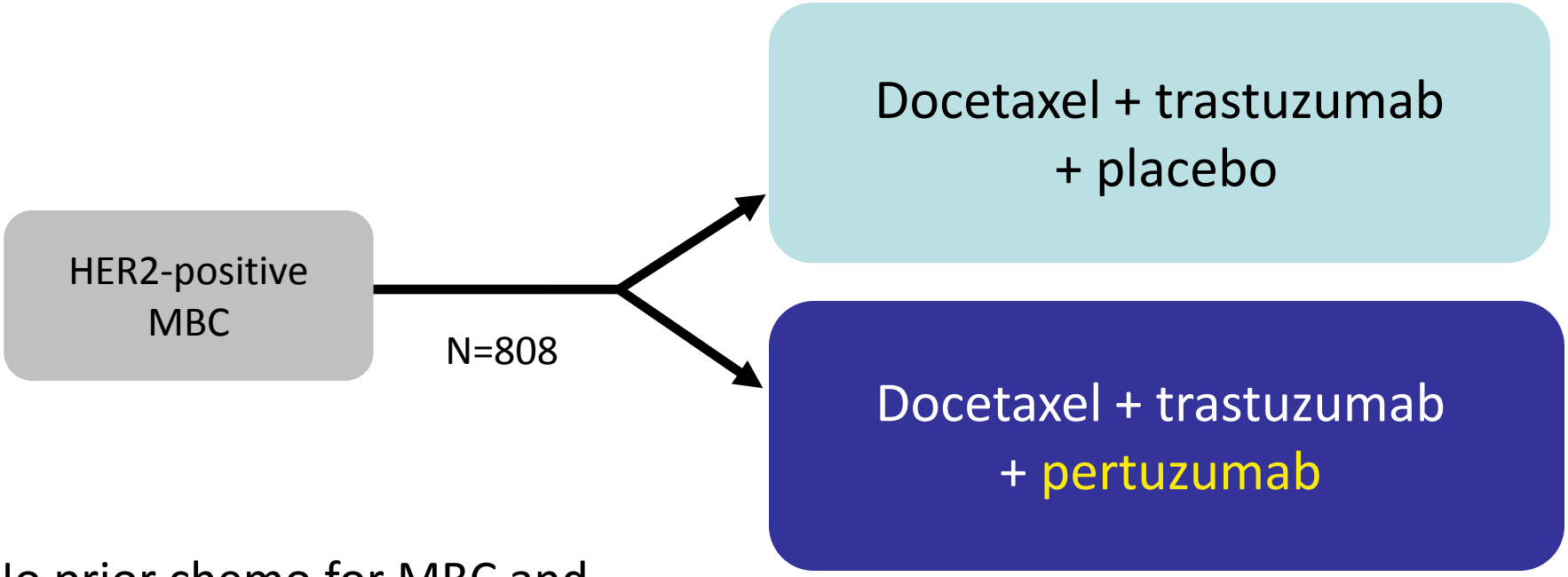
1. Liu P, *et al*. *Nat Rev Drug Discov* 2009;8:627–644;2. Baselga J. *Oncologist* 2011;16:Suppl 1:12–19;
3. Stemke-Hale K, *et al. Cancer Res* 2008;68:6084–6091.

PI3K is required for HER2 mediated transformation



Zhao et at, PNAS 2006

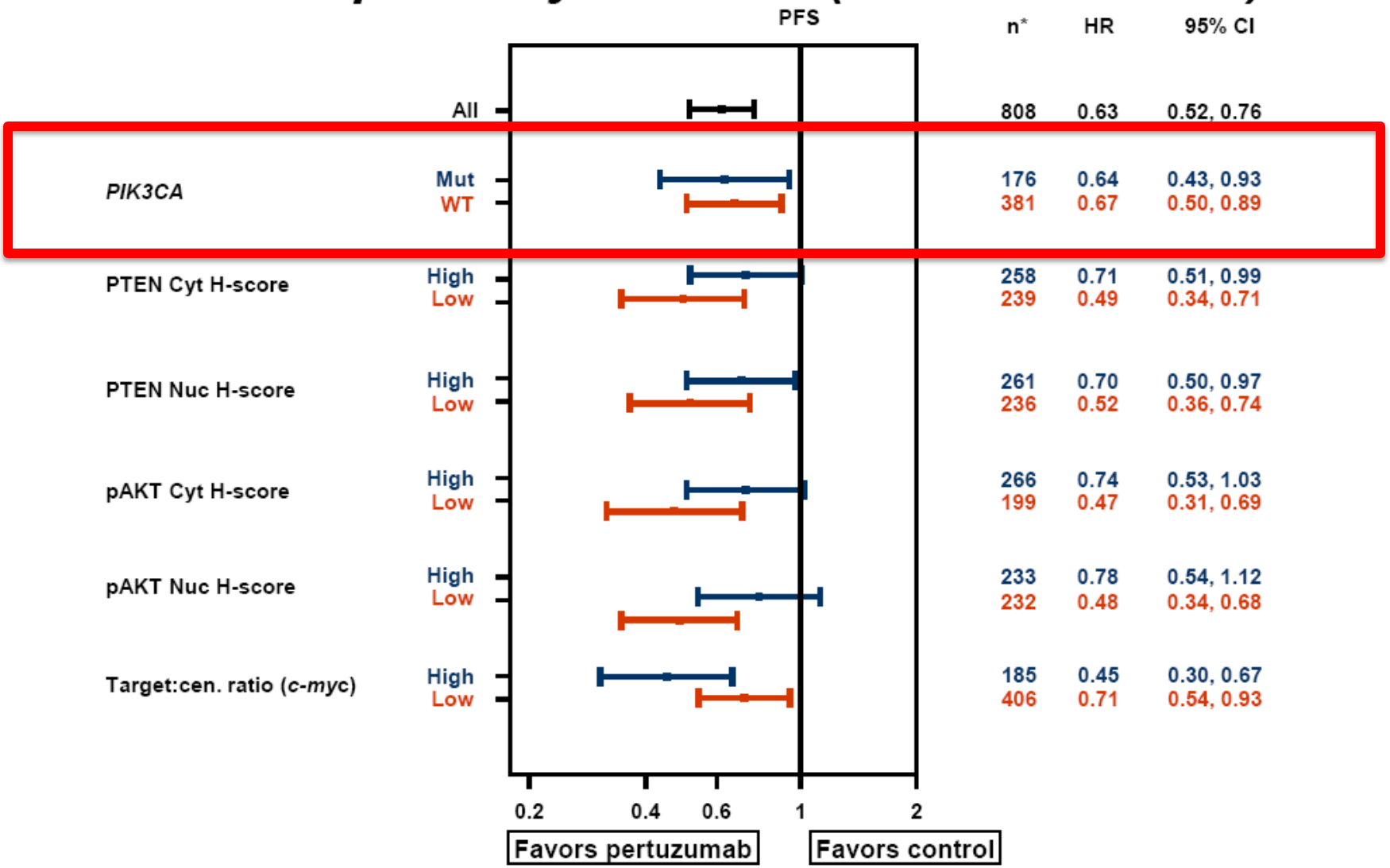
CLEOPATRA:
Phase III Trial of Docetaxel + Trastuzumab vs Docetaxel + Trastuzumab + Pertuzumab



- No prior chemo for MBC and >12mo from adjuvant trastuzumab/chemo
- Up to 1 prior hormone for MBC allowed
- ECOG 0-1
- LVEF >= 50%

Pts received a median of 8 cycles of docetaxel in both arms

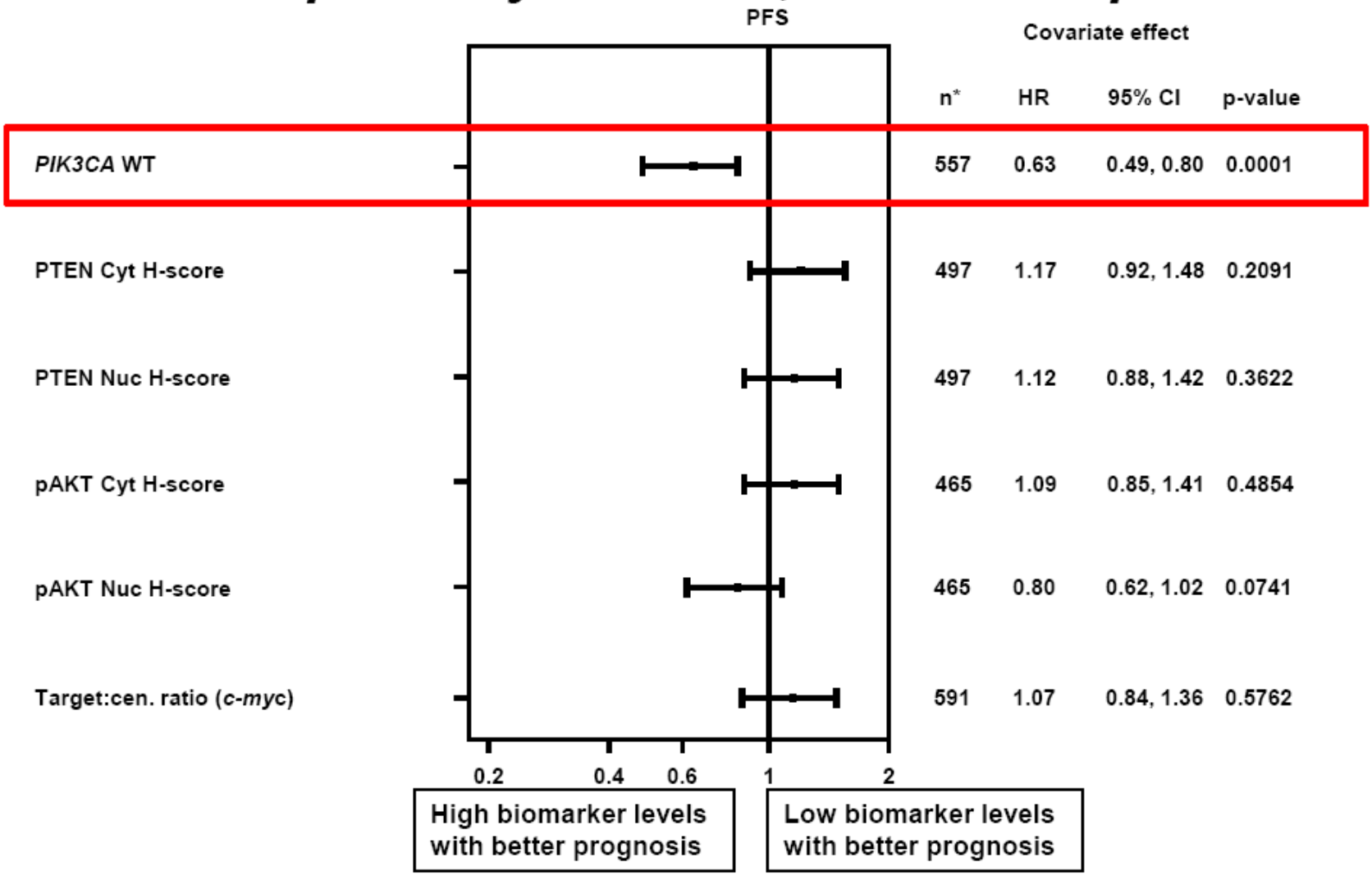
Predictive analysis of pertuzumab PFS benefit
Intracellular pathway markers (in tumor tissue)



* Not all of the 808 collected samples were assessable for each biomarker, due to tissue availability/technical issues

Cyt, cytoplasmic; Mut, mutated; Nuc, nuclear; WT, wild-type

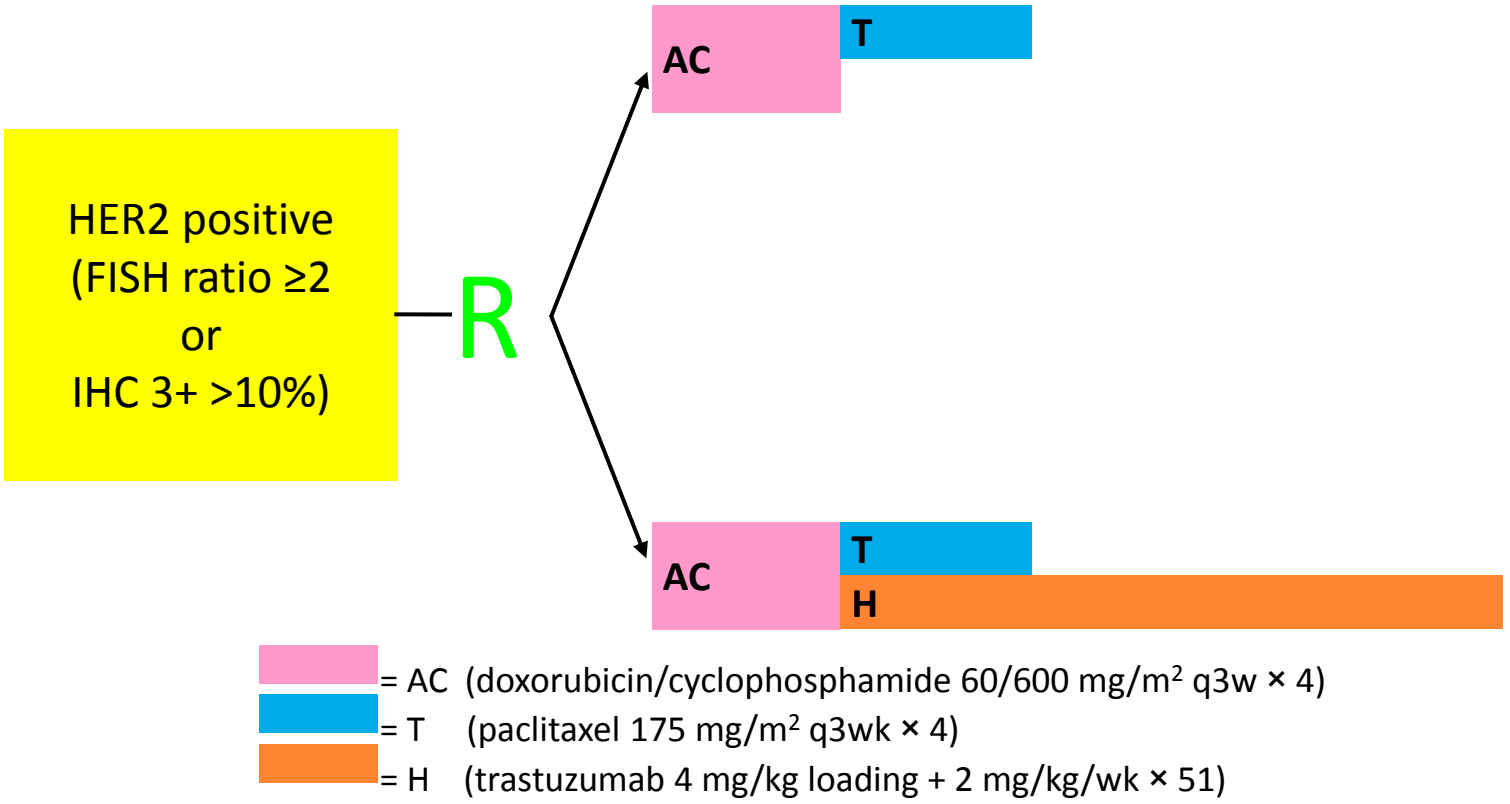
Prognostic effects independent of treatment arm
Intracellular pathway markers, both arms pooled



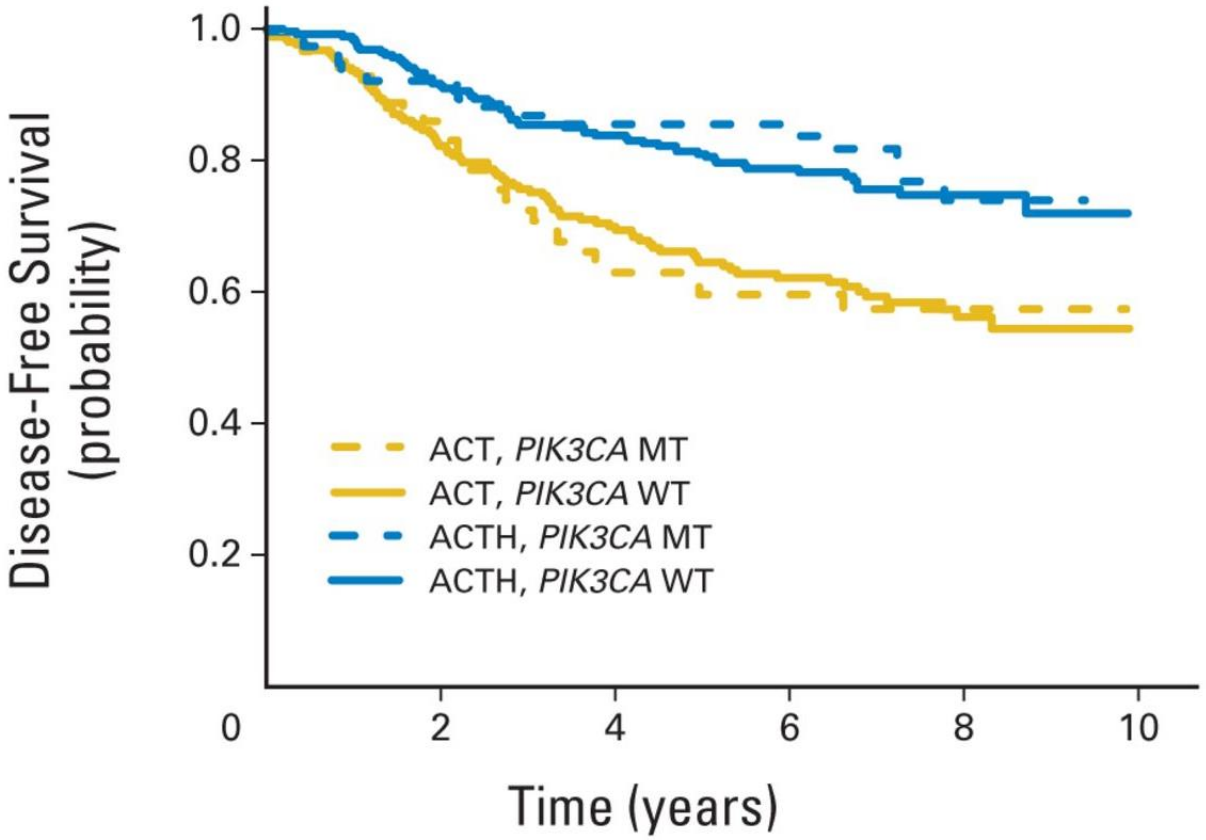
* Slide 11

The treatment benefit with the addition of pertuzumab was maintained in all cases
HR < 1.00 in all cases (p = 0.0003 – < 0.0001)*

NSABP B-31 trial design



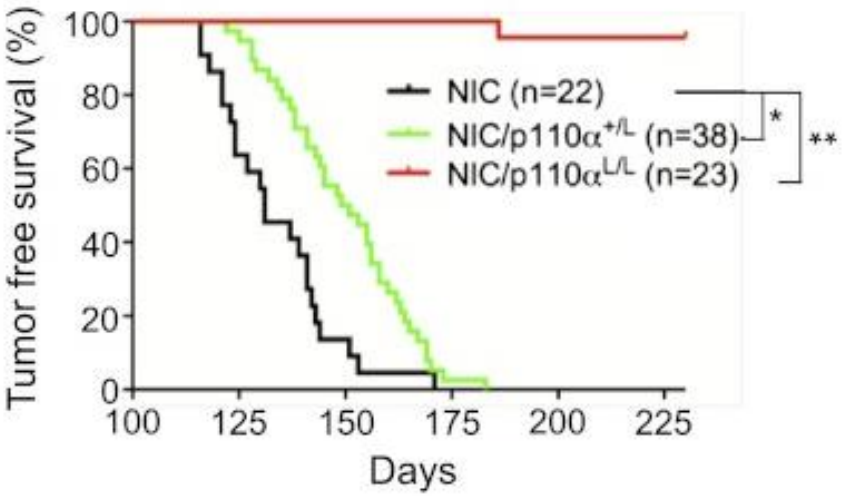
PIK3CA mutation status does not predict benefit of trastuzumab in NSABP B31

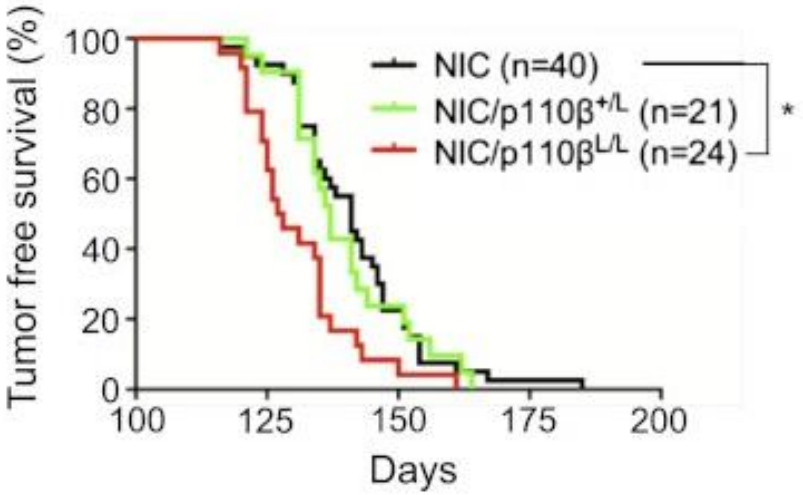


No. at risk						
ACT, *PIK3CA* MT	90	59	40	30	10	0
ACT, *PIK3CA* WT	251	167	131	97	45	0
ACTH, *PIK3CA* MT	76	70	65	49	21	0
ACTH, *PIK3CA* WT	254	232	209	155	54	0

Pogue-Geile et al. JCO 2015;33:1340

PI3k alpha, but not PI3k beta is required for HER2-mediated tumorigenesis

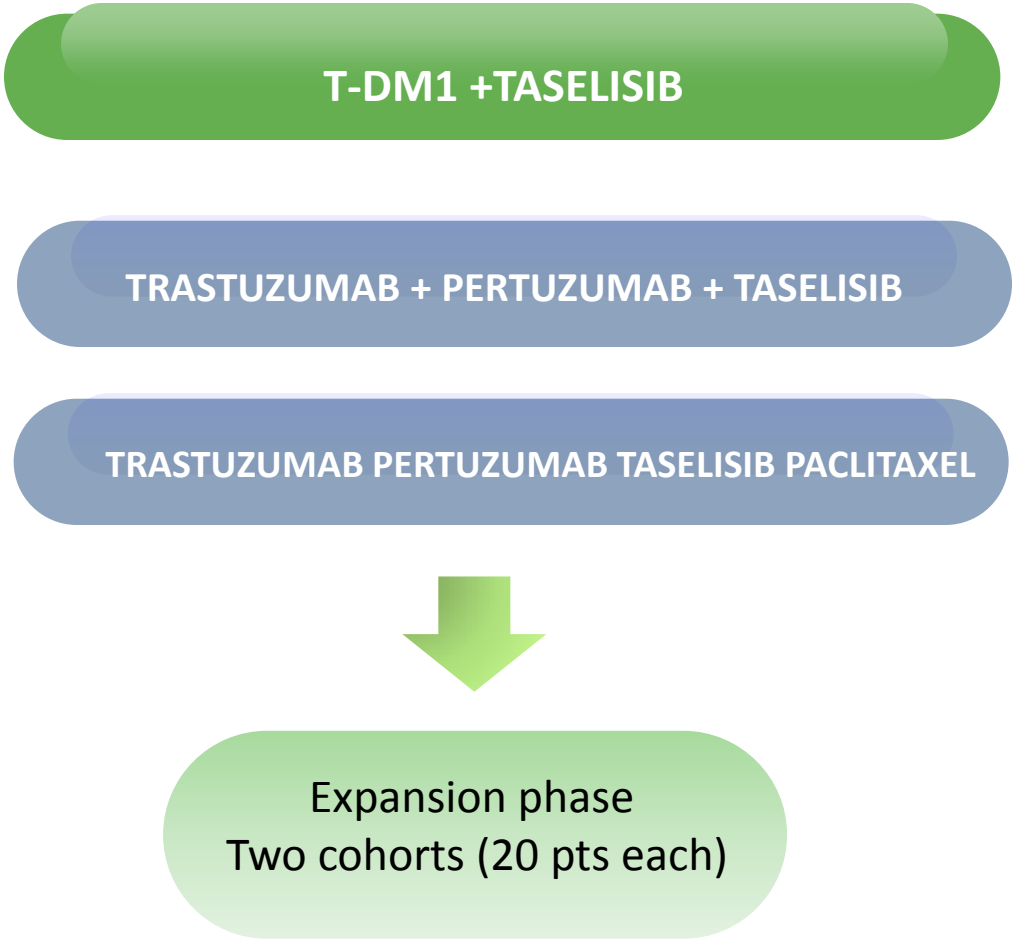




Utermark et al, Genes Dev. 2012; 26(14): 1573–1586.

Phase Ib study of taselisib in combination with anti-HER2 agents

- **Patients with HER2 metastatic breast cancer (any line)**
- **STUDY DESIGN: 3 + 3**
- **Three cohorts**



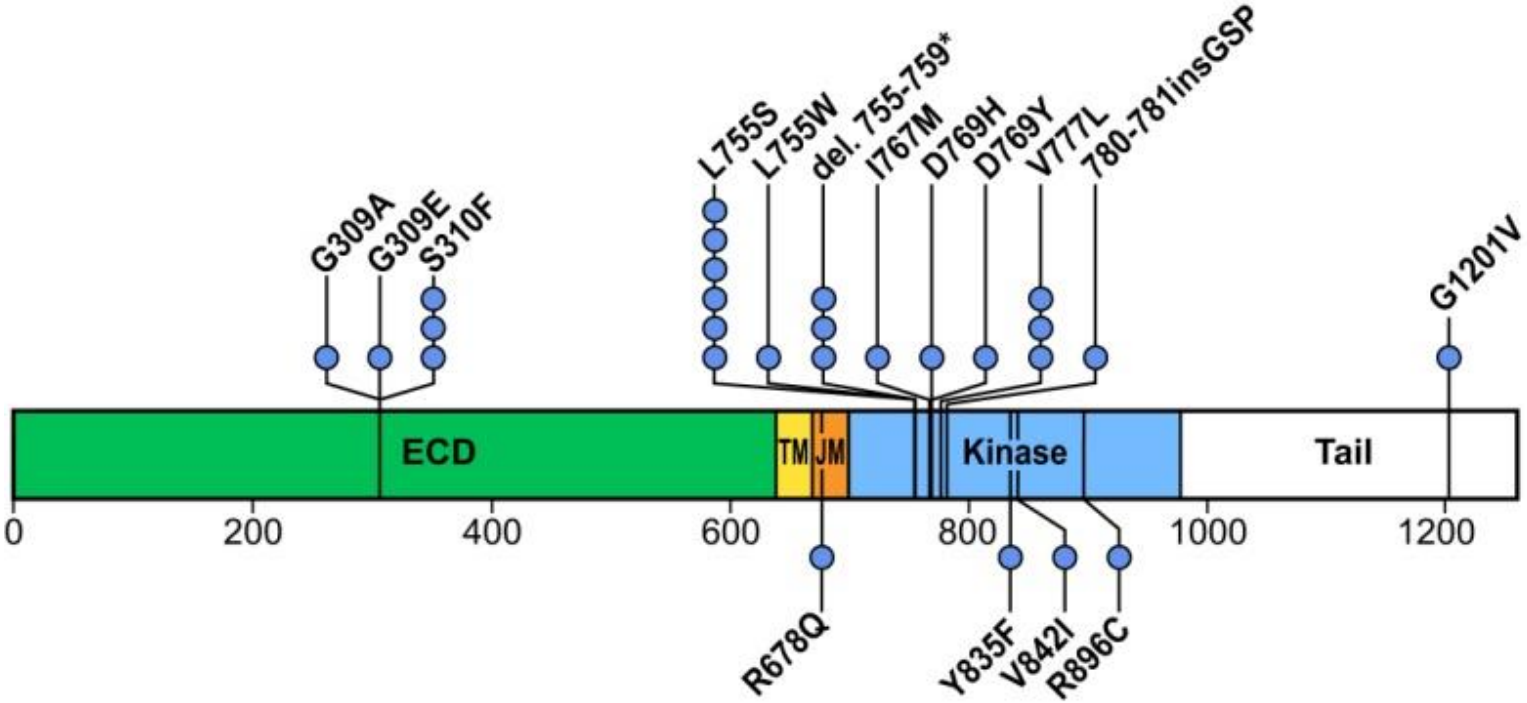
PI Metzger and Krop

Critical questions in HER2+ breast cancer

- Are PIK3CA mutations prognostic in HER2+ cancers?
  - In adjuvant setting does not appear to be prognostic
  - In advanced cancers, PIK3CA mutations associated with decreased PFS in 1st line setting
- Do PIK3CA mutations predict benefit of trastuzumab or pertuzumab?
  - In adjuvant setting, PIK3CA mutations not predictive of trastuzumab benefit
  - In MBC, no data on trastuzumab benefit. Does not predict benefit of pertuzumab
- Do PIK3CA mutations predict response to PI3-kinase inhibitors
  - No data yet
  - Important question to address

ERBB2 mutations

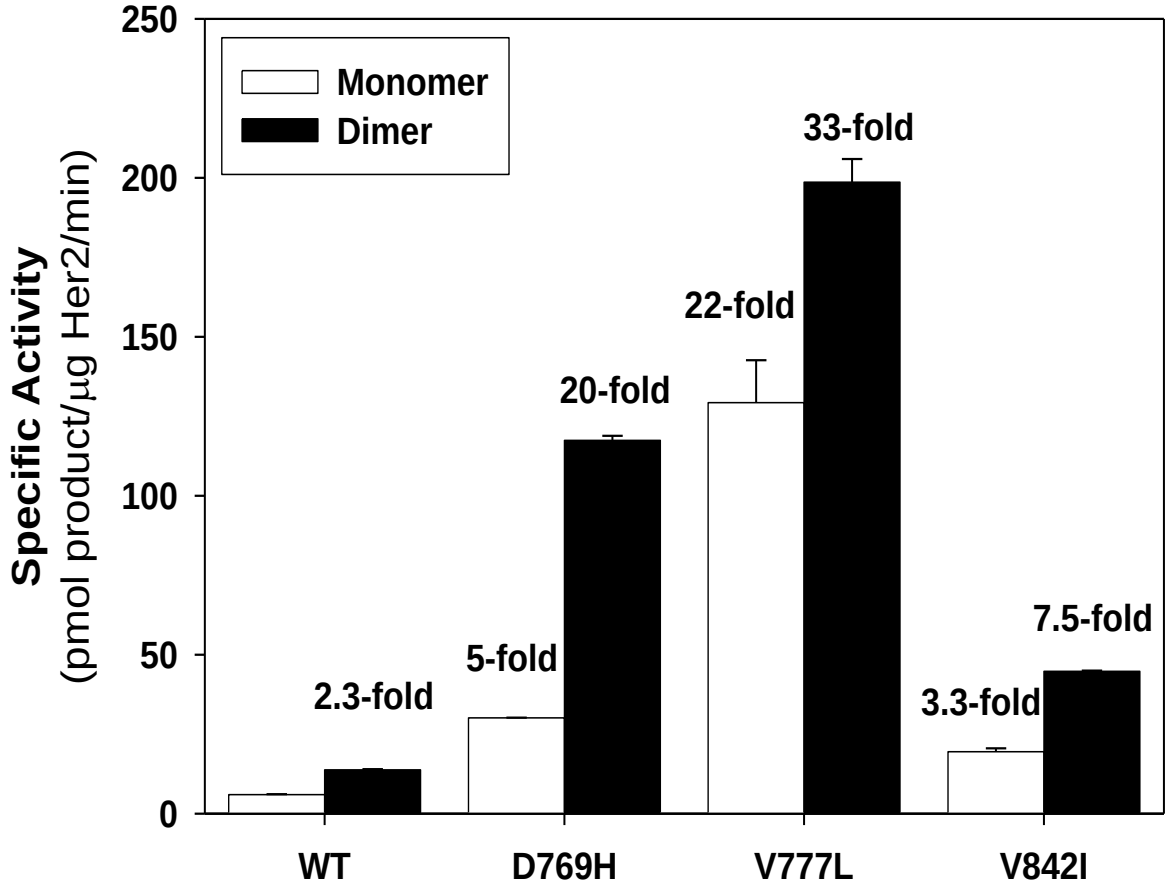
HER2 Somatic Mutations In HER2-negative breast cancer



- Overall rate of mutation 1.6%
- Enriched in ER+ and lobular BC
- Mutations clustered in kinase domain

Adapted from Bose et al, SABCS 2012

In vitro Kinase Activity of 3 HER2 Mutations



Fold increase is relative to WT HER2 monomer specific activity

Cell Growth Inhibition by Neratinib and Lapatinib

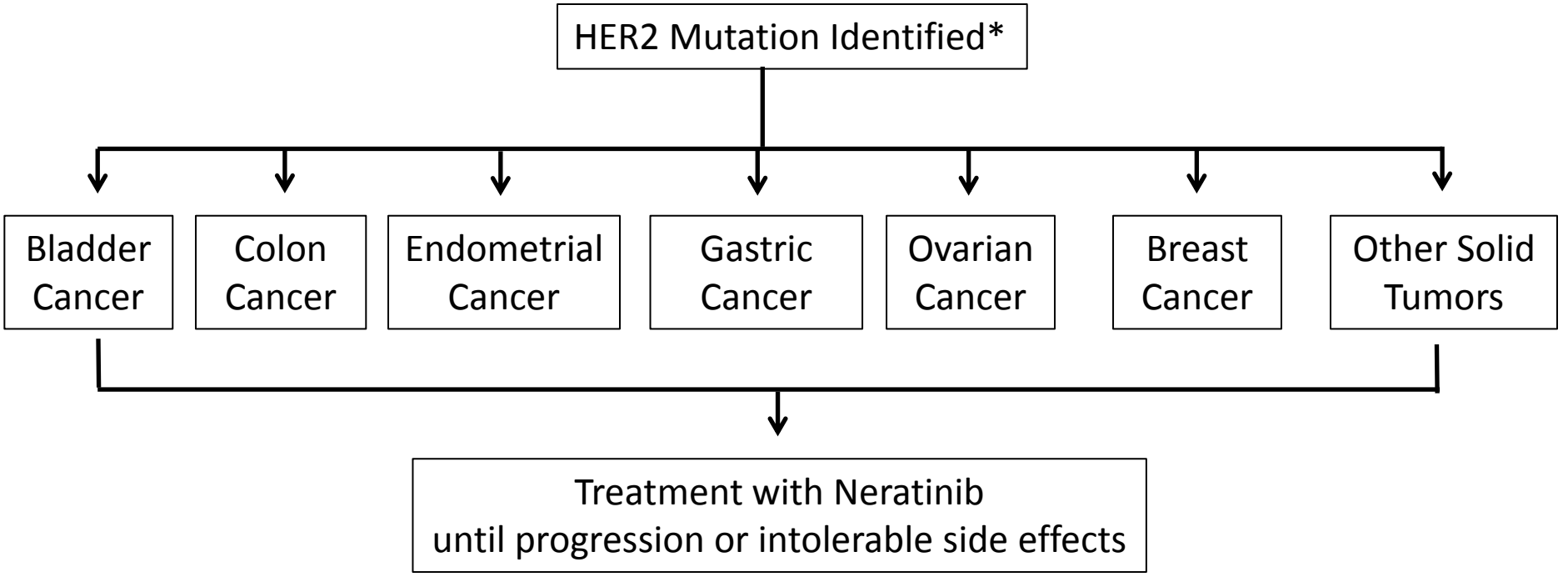
Table 1. Inhibition of cell growth by neratinib and lapatinib

	IC_{50} (nmol/L)	
	Neratinib	Lapatinib
MCF10A – HER2 WT	<2	400 ± 60
G309A	<2	470 ± 50
V777L	<2	1,040 ± 570
D769H	<2	980 ± 950
V842I	<2	650 ± 210
del.755–759	2.1 ± 0.2	660 ± 90
L755S	15 ± 6	>10,000
BT474 cells	<2	31 ± 2
MCF7 cells	>3,000	>10,000

NOTE: Cells were incubated with drugs for 6 days, and cell viability and number were measured using Alamar Blue.

Her2 gene amplified line

HER2 Mutation Basket Study Schema

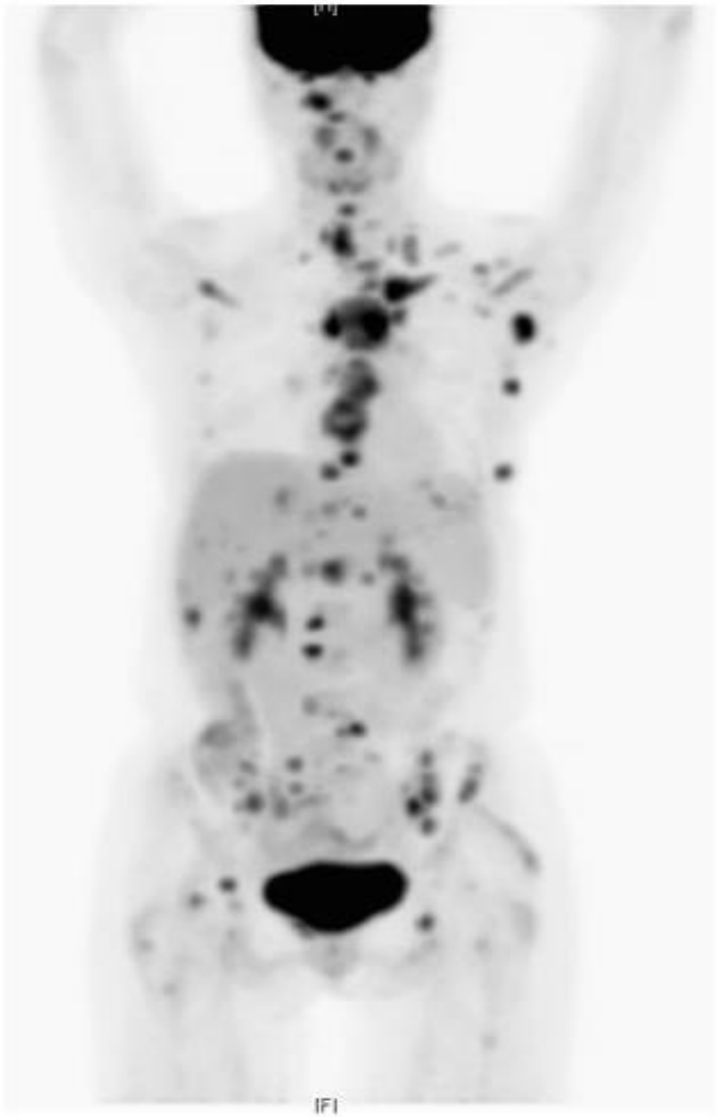


Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoints: PFS, OS

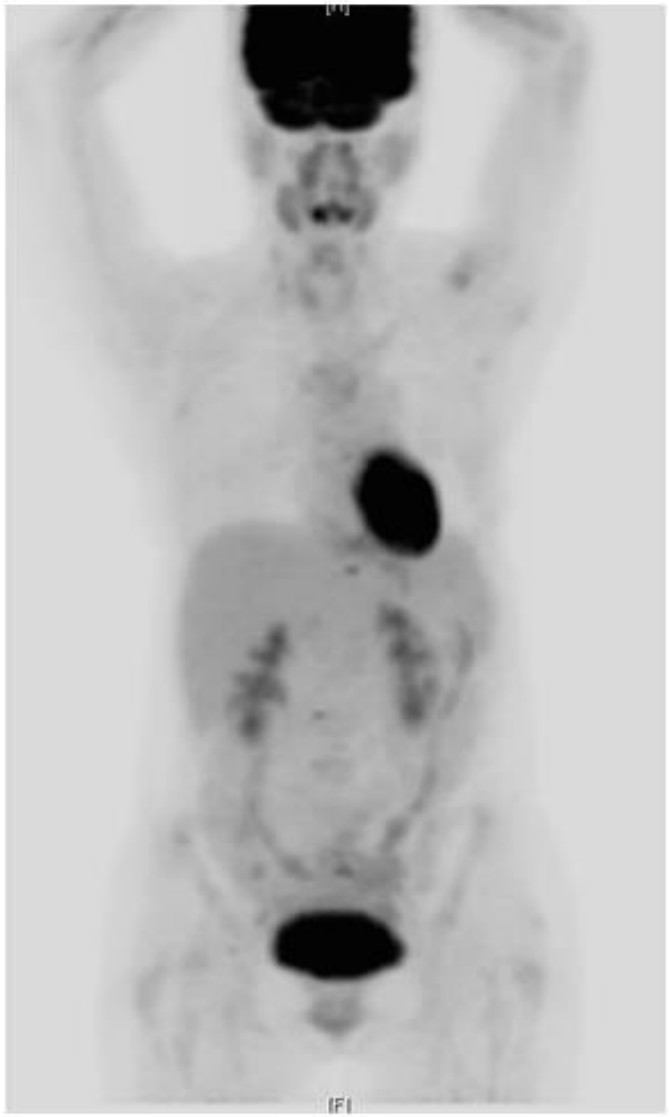
Multinational Study, MSKCC Lead Site
MSKCC Central Repository for All Biospecimens

*- Not limited to previously characterized activating mutations

ER positive, HER2 non-amplified, V777L Breast Cancer



Baseline



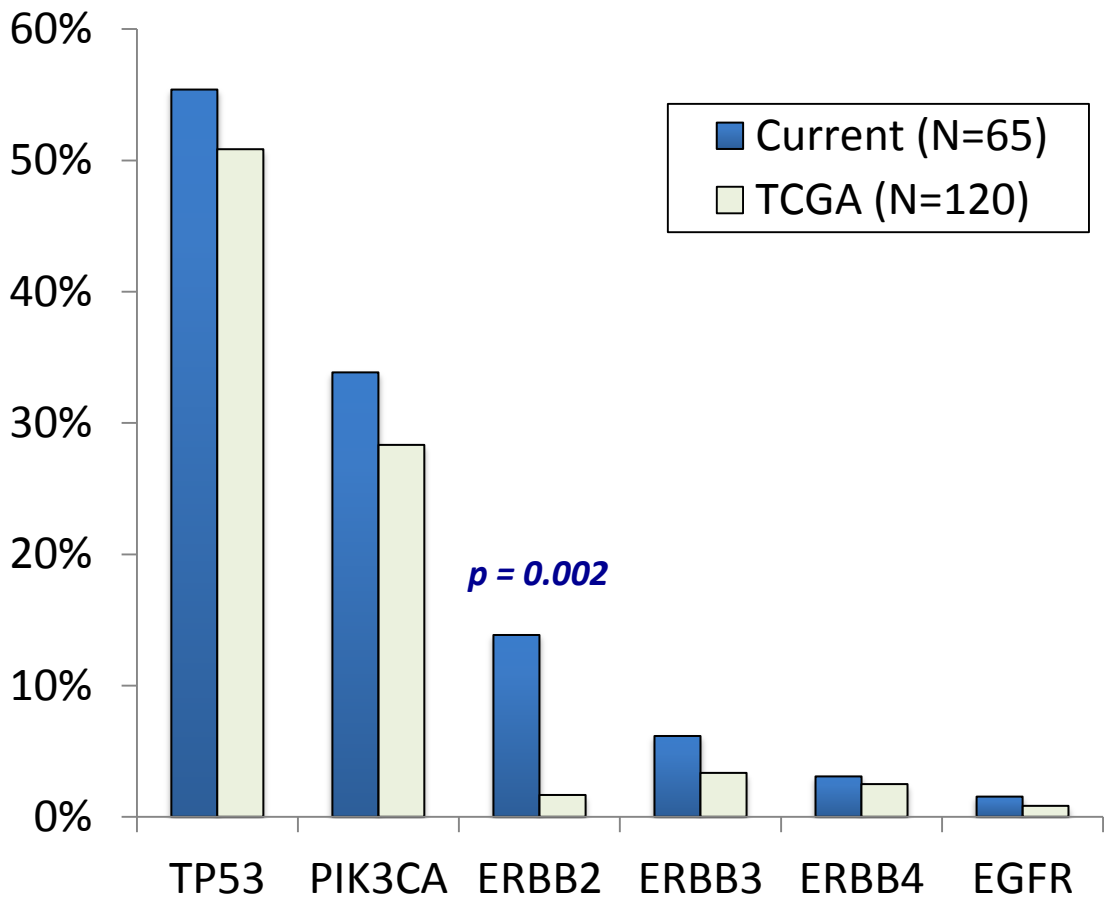
8 weeks

Courtesy of David Solit, MSKCC

Comparison of 65 Biopsies from Patients with Metastatic Disease to TCGA Data

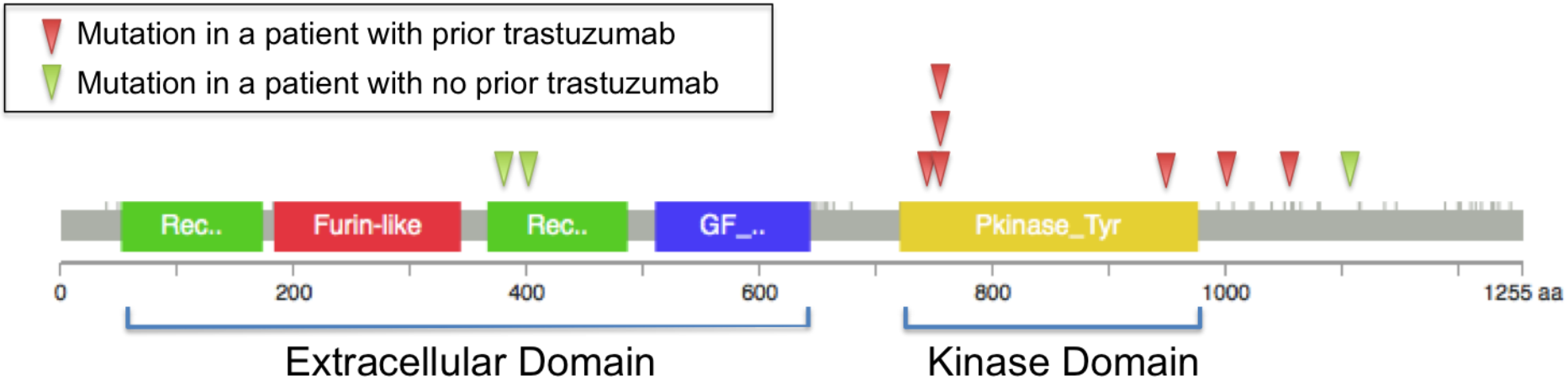
Compared to 120 primary, treatment-naïve HER2+ tumors sequenced in the TCGA study:

- There was no significant difference in the incidence of *TP53* and *PIK3CA* mutations (point mutations and indels) (55% and 34%, respectively).
- ***The incidence of ERBB2 (HER2) mutations was significantly increased (14% vs 2%, p = 0.002).***
- There was no significant difference in the mutation rates in ERBB3, ERBB4, and EGFR.



Nick Wagle et al

Somatic HER2 Mutations in Metastatic HER2+ Breast Cancer



- In 9/65 patients (14%), we identified a somatic HER2 mutation, 5 of which were in the kinase domain
- HER2 L755S (found in 3 patients) results in resistance to lapatinib and sensitivity to irreversible inhibitors (e.g. neratinib)[1]
- 2 novel kinase domain mutations, present at low allelic fractions, in patients who received prior trastuzumab
- 4 additional patients, 2 of whom received prior trastuzumab, had uncharacterized mutations in other domains of HER2 at low allelic fractions

[1]Kancha et al, PLOS One, 2011; Bose et al, Cancer Discovery, 2013

Mutations in PIK3CA and ERBB2: resistance mechanism, therapeutic target, or both?

- In HR+ cancers, available data do not support a substantial role for PIK3CA mutations as mechanism of resistance to targeted therapy or prognostic marker
  - May still predict benefit of isoform selective PI3-kinase inhibitors
- In HER2+ cancers, PIK3CA mutations do not appear to predict benefit of HER2-directed therapy
- HER2 kinase mutations may be therapeutic target in HER2-negative cancers and may be associated with resistance to trastuzumab in HER2-amplifed cancers