Current Trends & Future Directions in Bedside to Bench Translational Research in ER+ Breast Cancer

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- Stock options
  - Provista, Y-TRAP
- Scientific Advisory Board
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Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- **Short presurgical** (aka, ‘window’) and neoadjuvant therapeutic trials
- Biopsy and molecular profiling of recurrent (drug-resistant) metastases
- Interrogation of exceptional responders to targeted therapies

Endocrine Resistance: Mechanisms and Targeted Therapies

Mechanisms	Targeted Therapies
HER2 amplification	➢ Trastuzumab, lapatinib, T-DM1
ESR1 mutations, fusions	➢ Fulvestrant (?), novel ER degraders, CDK4/6 inhibitors
Ligand-independent ER	➢ CDK4/6 inhibitors, fulvestrant
PIK3CA mutations	➢ TORC1, pan-PI3K, and PI3Kα inhibitors
FGFR pathway alterations	➢ FGFR inhibitors
HER2 mutations	➢ Neratinib
NF1 mutations/deletions	➢ MAPK pathway inhibitors

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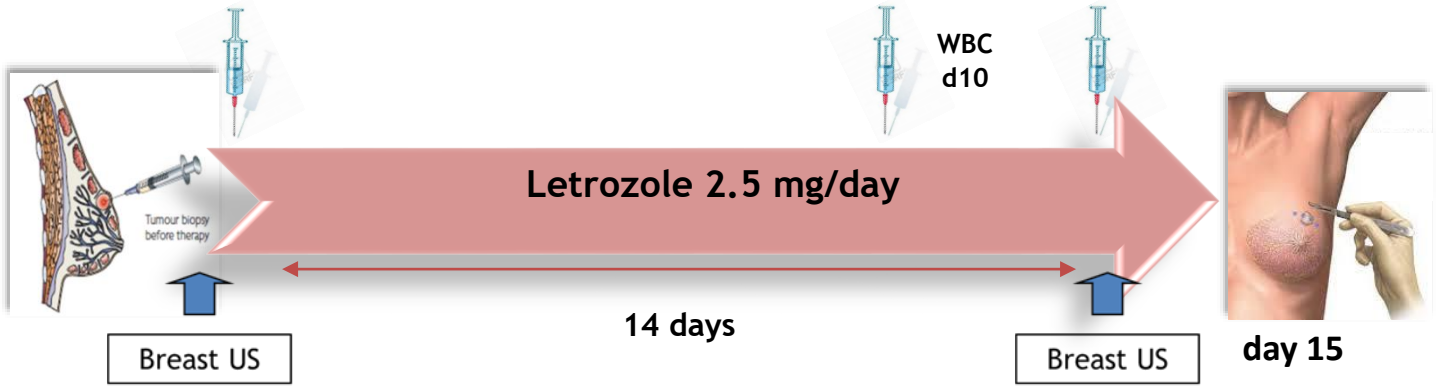
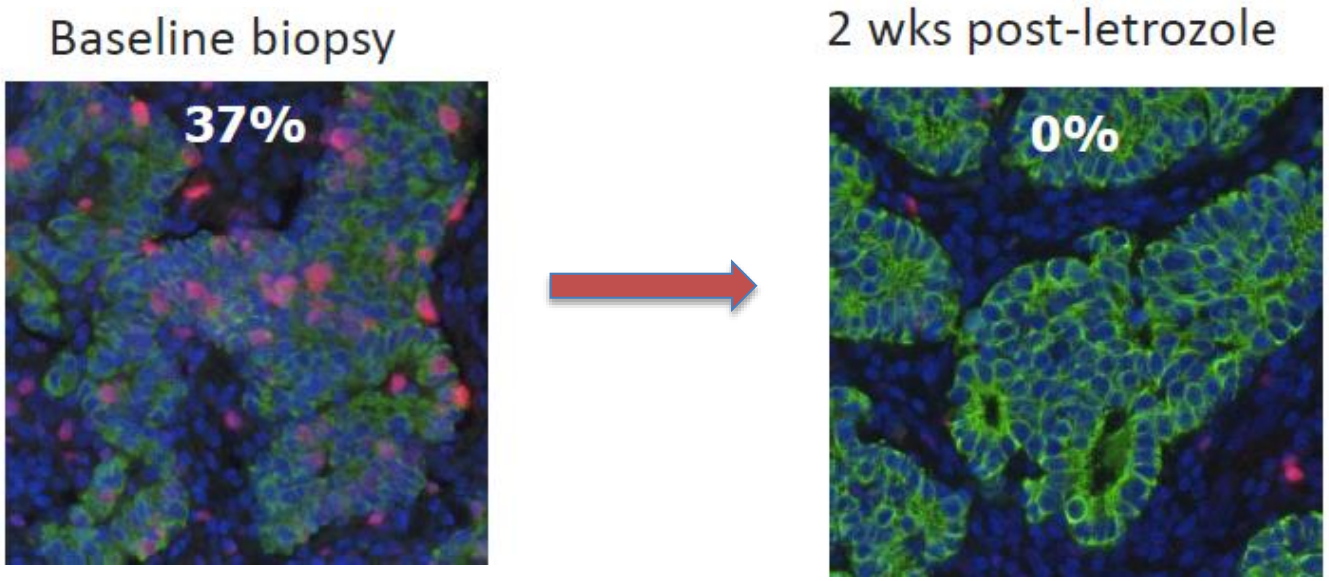
Profiling ER+ breast cancer to discover mechanisms of resistance





Glitnane et al Science Trans Med 2017

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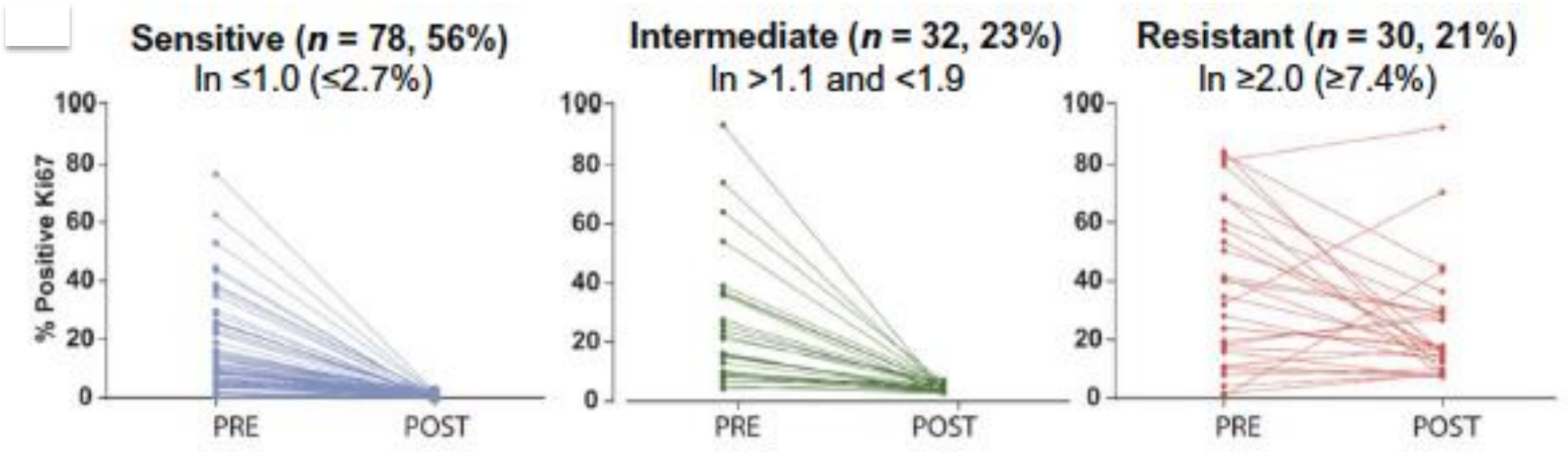
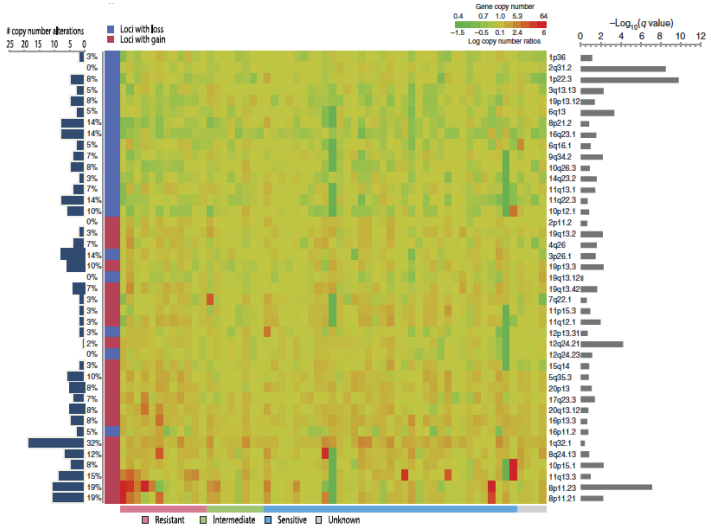
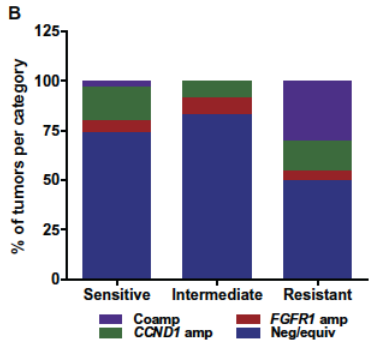
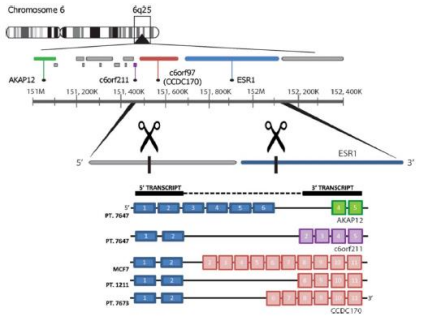




Amplification
CCND1 and FGFR1

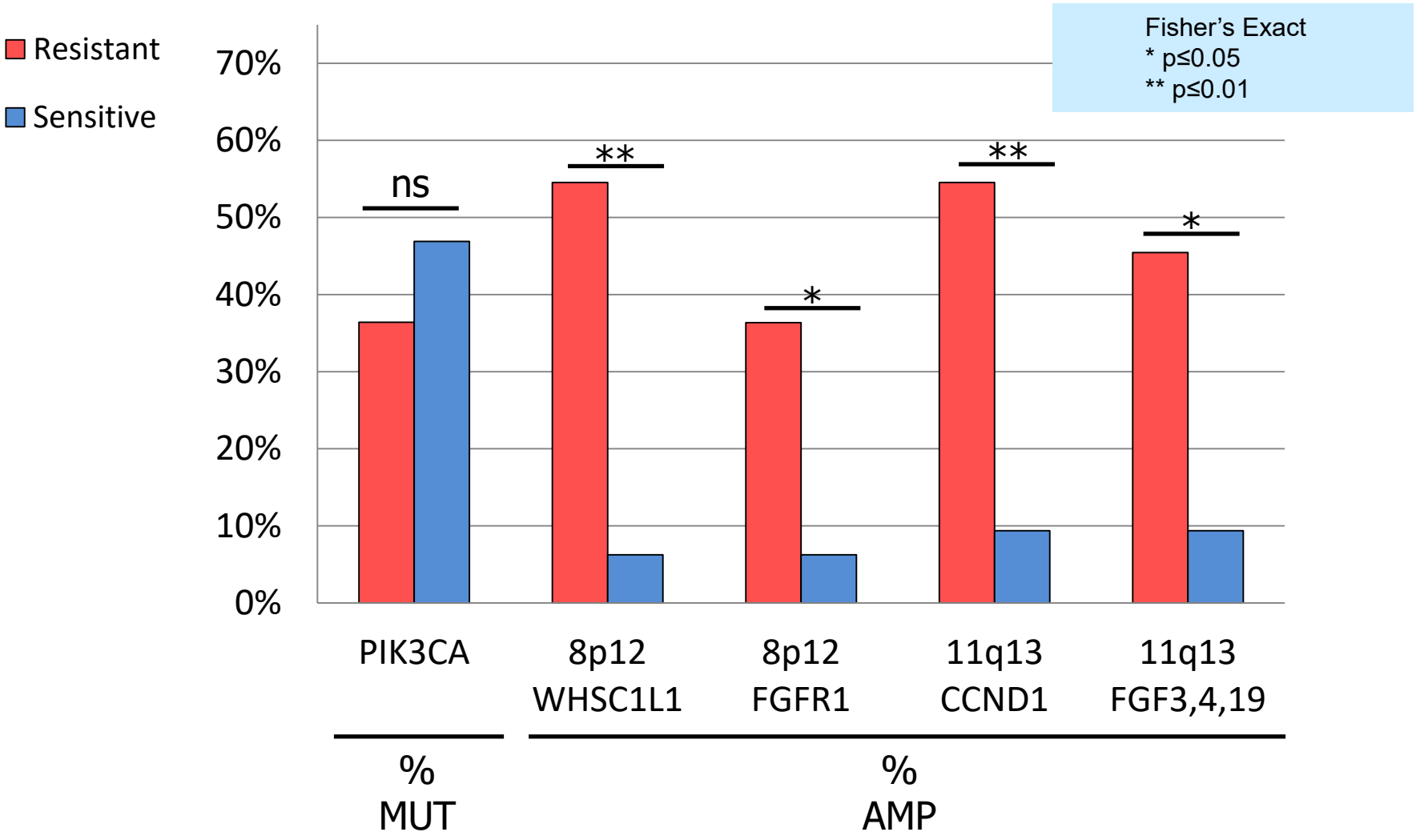


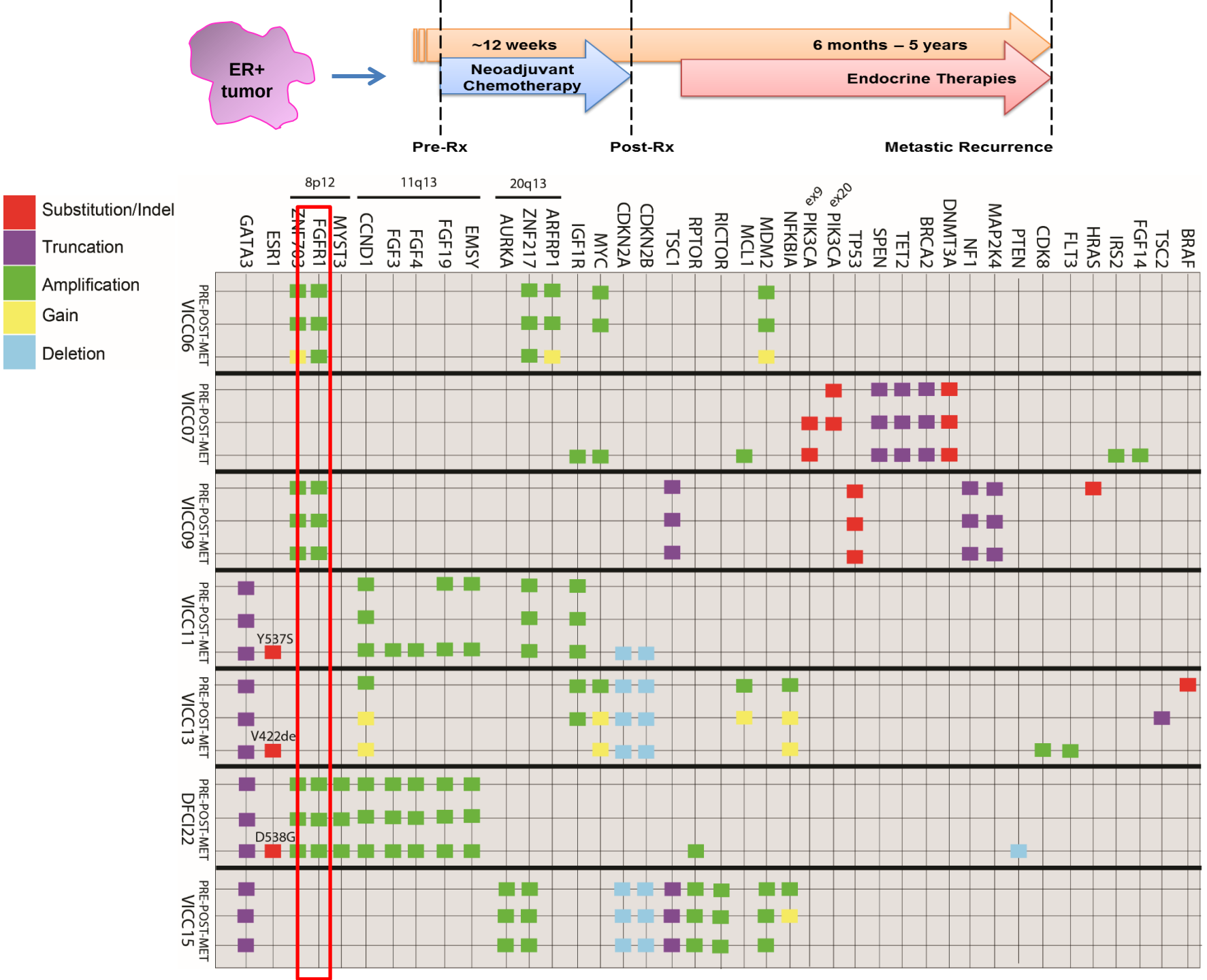
ESR1 fusions

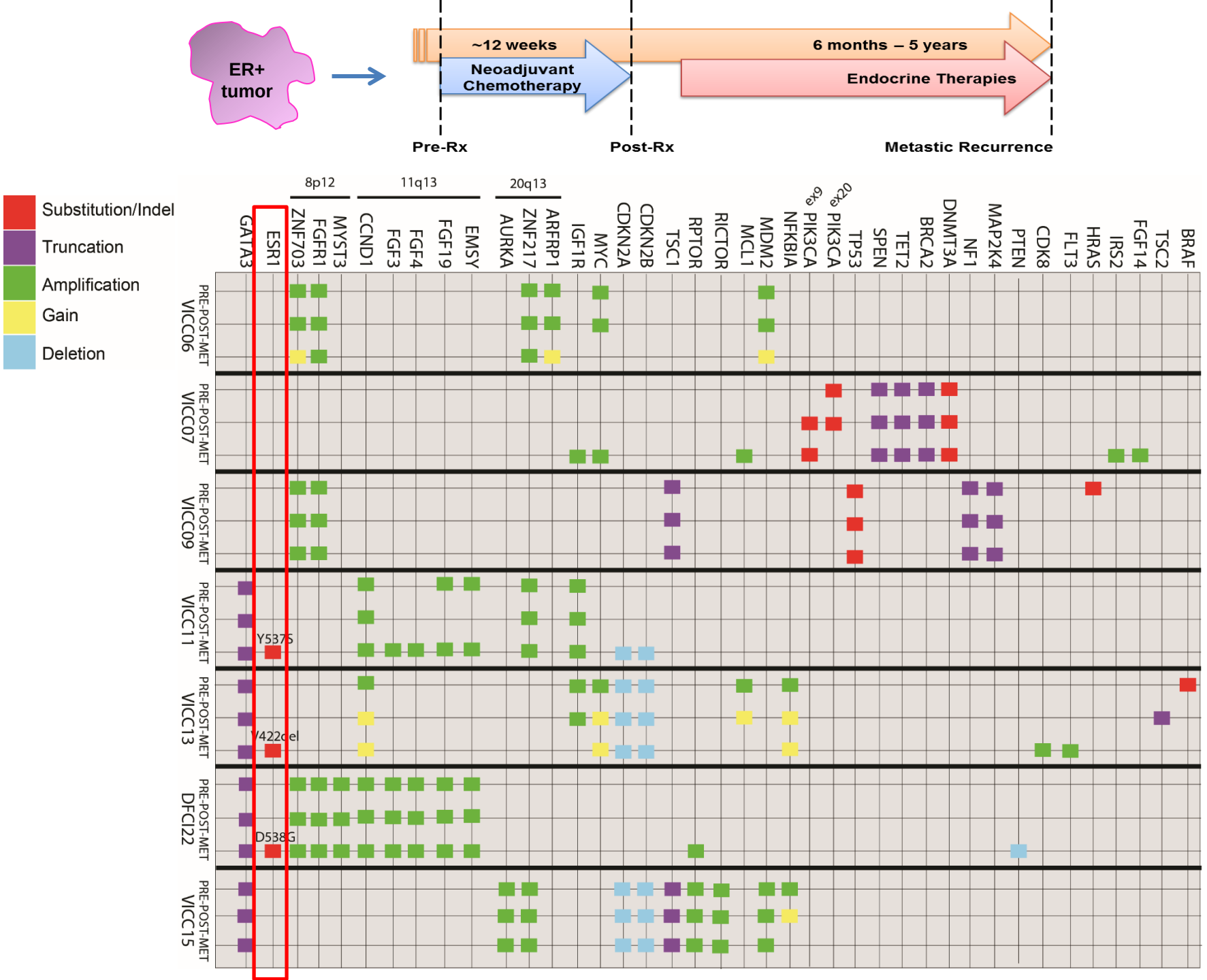


Glitnane et al Science Trans Med 2017

Most frequent recurrent somatic alterations associated with resistance to estrogen deprivation (letrozole)




ER+ tumor
~12 weeks
Neoadjuvant Chemotherapy
6 months – 5 years
Endocrine Therapies
Pre-Rx
Post-Rx
Metastic Recurrence
Substitution/Indel
Truncation
Amplification
Gain
Deletion
8p12
11q13
20q13
GATA3
ESR1
ZNF703
FGFR1
MYST3
CCND1
FGF3
FGF4
FGF19
EMSY
AURKA
ZNF217
ARFRP1
IGF1R
MYC
CDKN2A
CDKN2B
TSC1
RPTOR
RICTOR
MCL1
MDM2
NFKBIA
PIK3CA ex9
PIK3CA ex20
TP53
SPEN
TET2
BRCA2
DNMT3A
NF1
MAP2K4
PTEN
CDK8
FLT3
HRAS
IRS2
FGF14
TSC2
BRAF
PRE-POST-MET
VICC06
VICC07
VICC09
VICC11
VICC13
DFCI22
VICC15
Y537S
V422de
D538G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CCND1
FGF3
FGF4
FGF19
EMSY
AURKA
ZNF217
ARFRP1
IGF1R
MYC
CDKN2A
CDKN2B
TSC1
RPTOR
RICTOR
MCL1
MDM2
NFKBIA
PIK3CA ex9
PIK3CA ex20
TP53
SPEN
TET2
BRCA2
DNMT3A
NF1
MAP2K4
PTEN
CDK8
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VICC07
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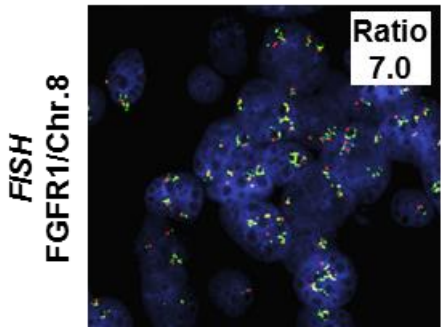
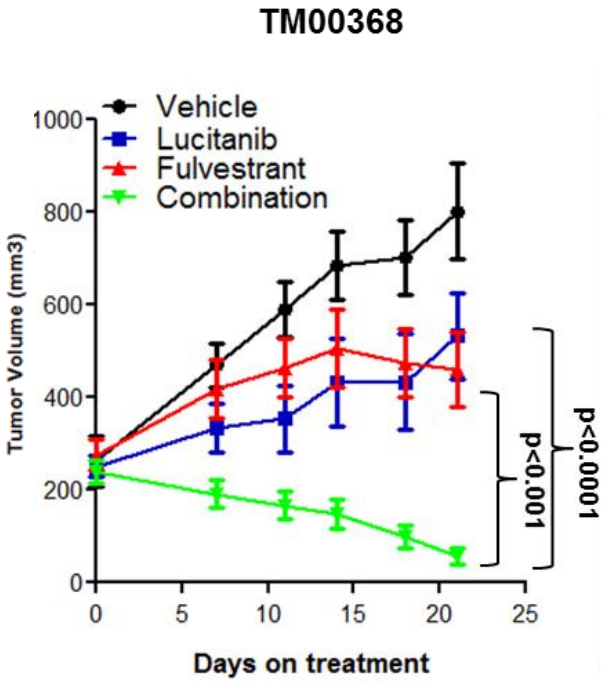
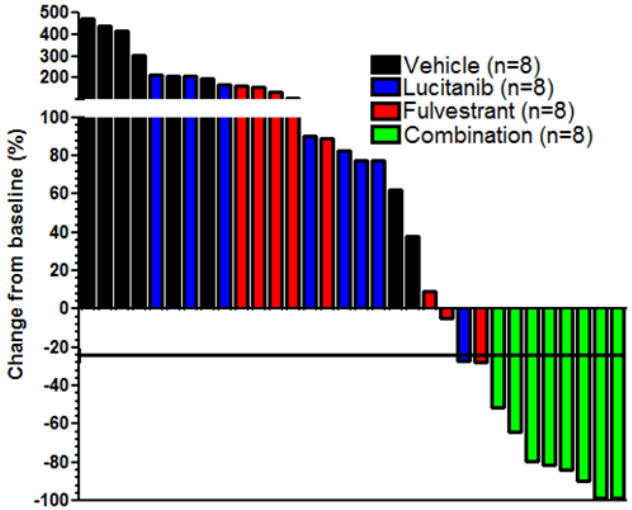
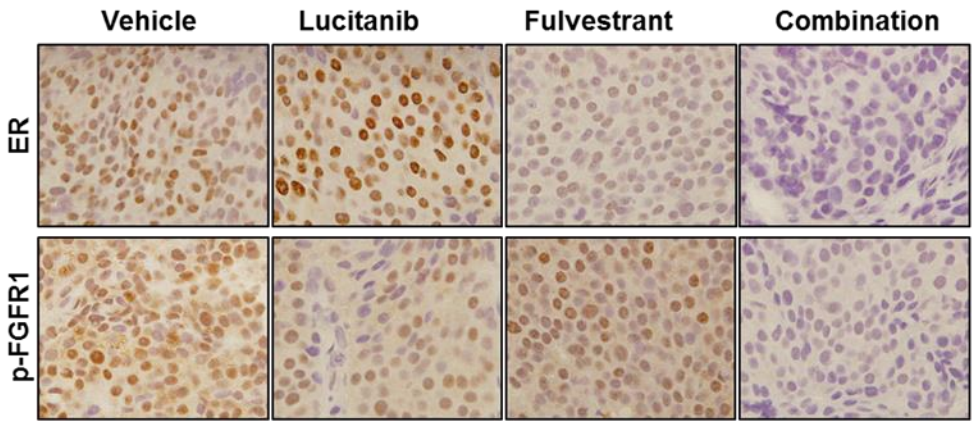
VICC11
VICC13
DFCI22
VICC15
Y537S
V422del
D538G

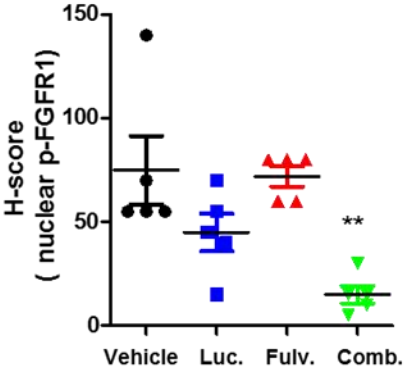
ER+/FGFR1-amplified PDXs do not shrink with fulvestrant alone but are potently inhibited by fulvestrant and FGFR TKI lucitanib

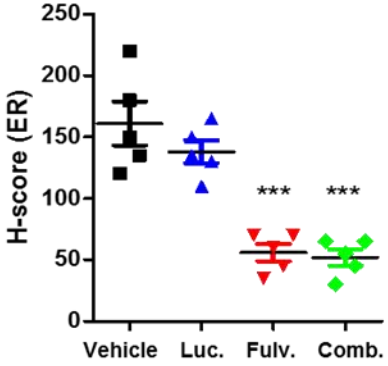








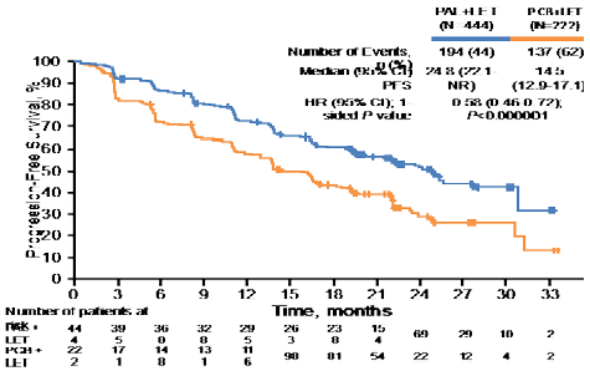




Formisano et al. Clin. Cancer Res. 2017

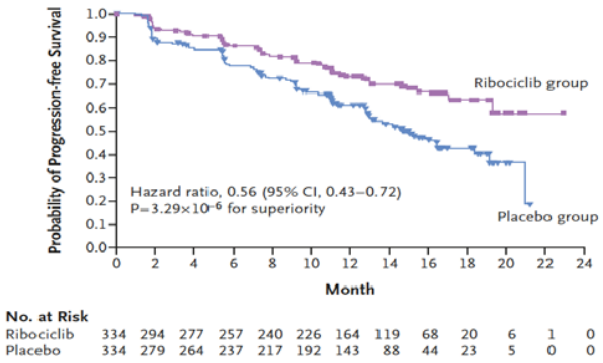
CDK4/6 inhibitors are first-line therapy in advanced ER+ breast cancer

PALOMA2



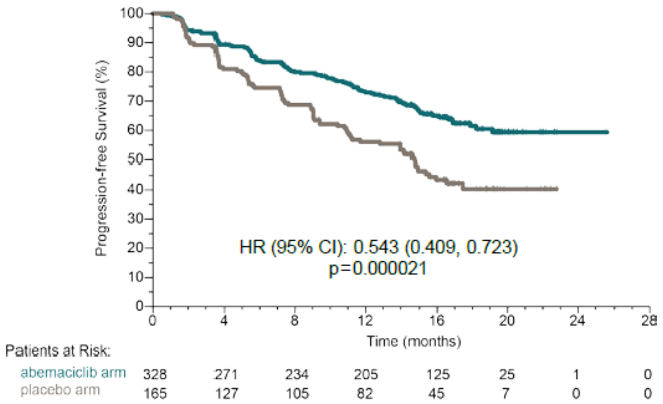
Finn *et al* NEJM 2016

MONALEESA2



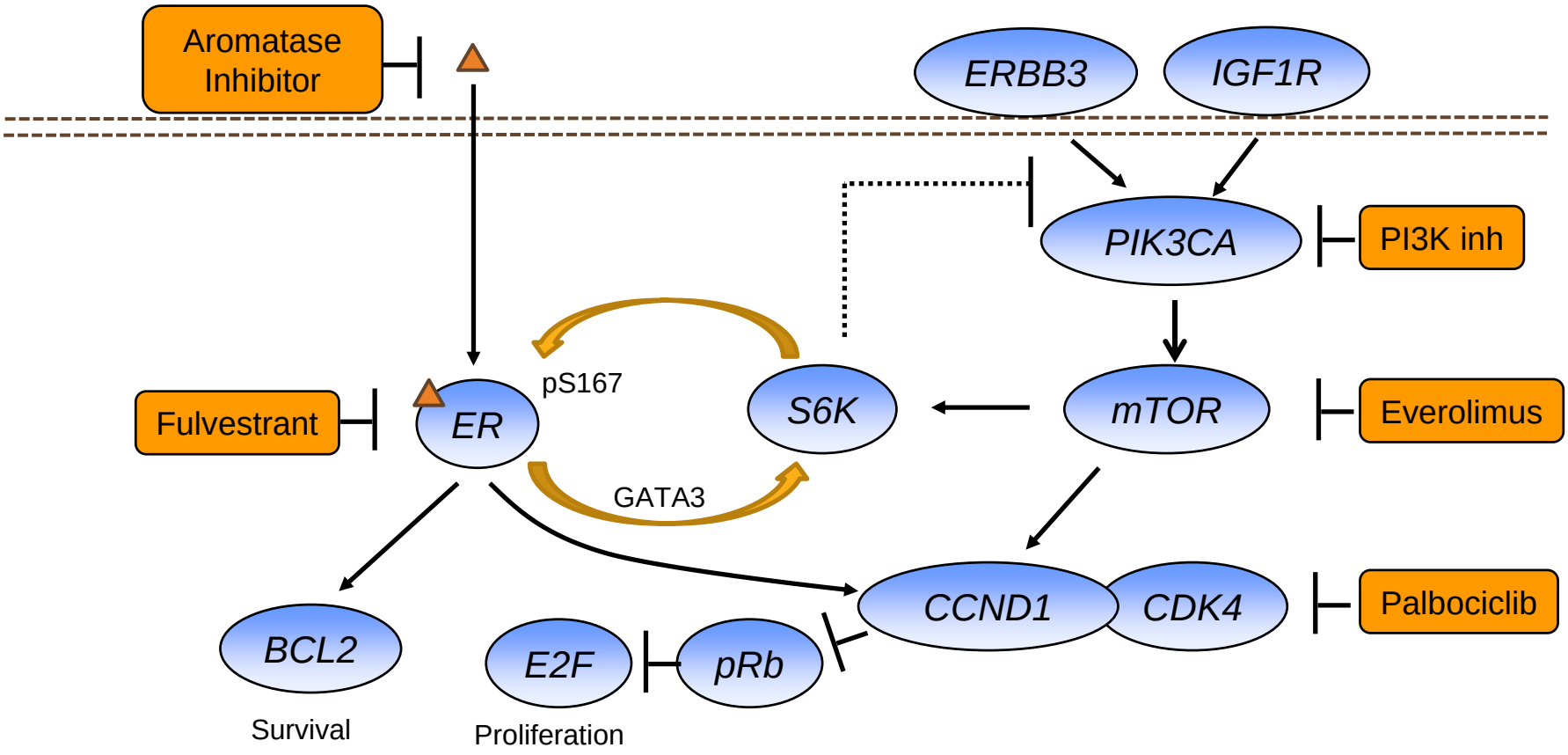
Hortobagyi *et al* NEJM 2016

MONARCH3



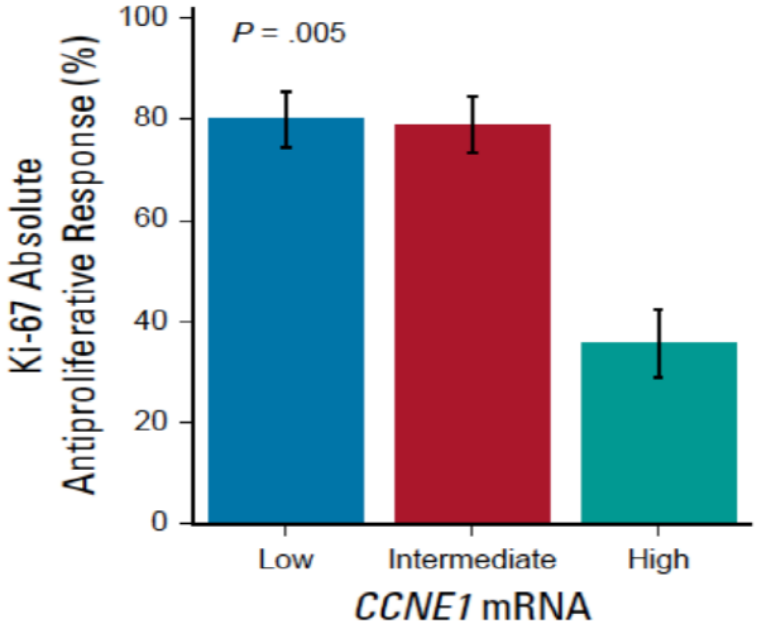
De Leo *et al* JCO 2017

Dual blockade of the ER pathway with ER and CDK4/6 inhibitors

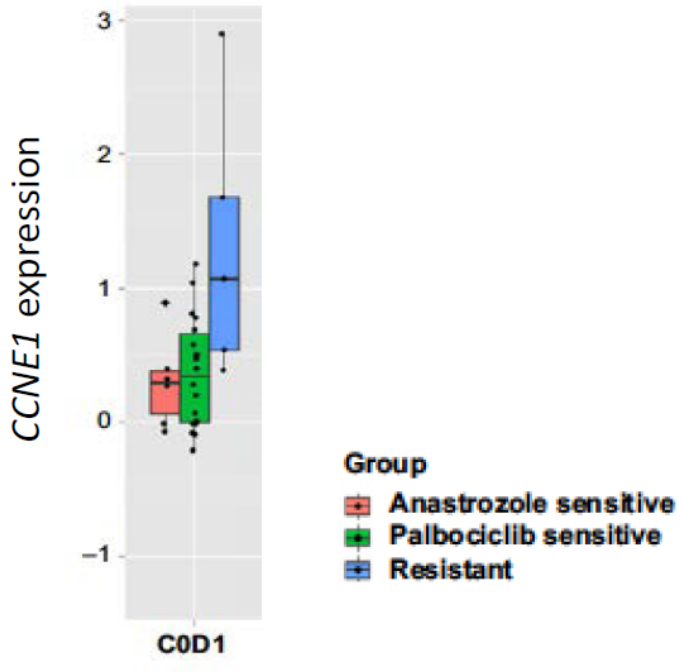


CCNE1 mRNA overexpression in presurgical studies correlates with resistance to CDK4/6 inhibitors

POP Trial
2 weeks Palbociclib



NeoPalAna
Anastrozole → Palbociclib



Arnedos *et al* Ann Oncol 2018, Turner *et al* JCO 2019

Ma C *et al* CCR 2017

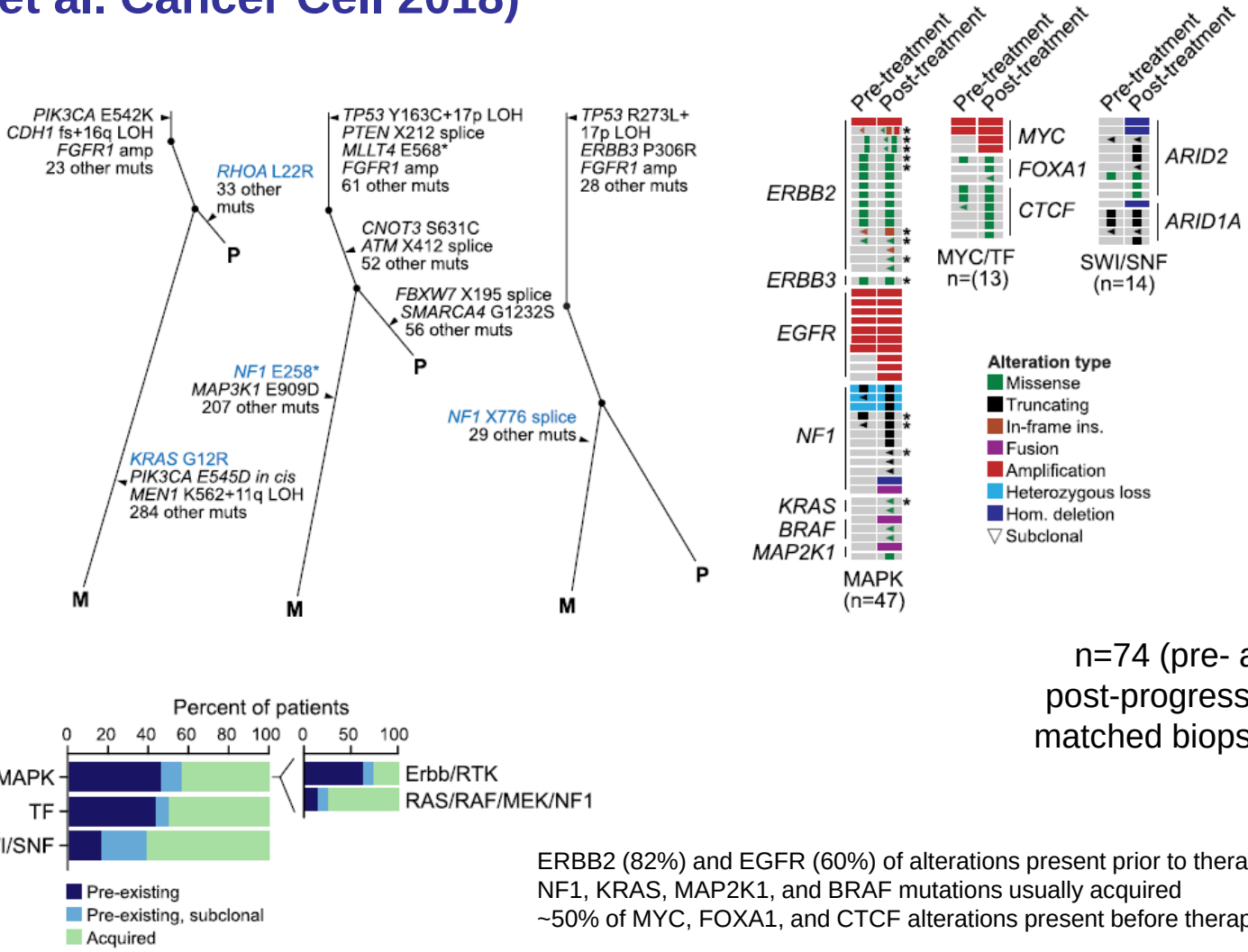
Implications

- Neoadjuvant and short term presurgical trials can be used as a platform to discover mechanisms of antiestrogen resistance
- And also to identify patients that can be considered for treatment with adjuvant targeted therapies (i.e., CDK4/6 inhibitors)

Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- Short presurgical (aka, ‘window’) and neoadjuvant therapeutic trials
- **Biopsy and molecular profiling of recurrent (drug-resistant) metastases – including plasma ctDNA**
- Interrogation of exceptional responders to targeted therapies

ER+ breast cancer evolution under endocrine therapy (Razavi et al. Cancer Cell 2018)



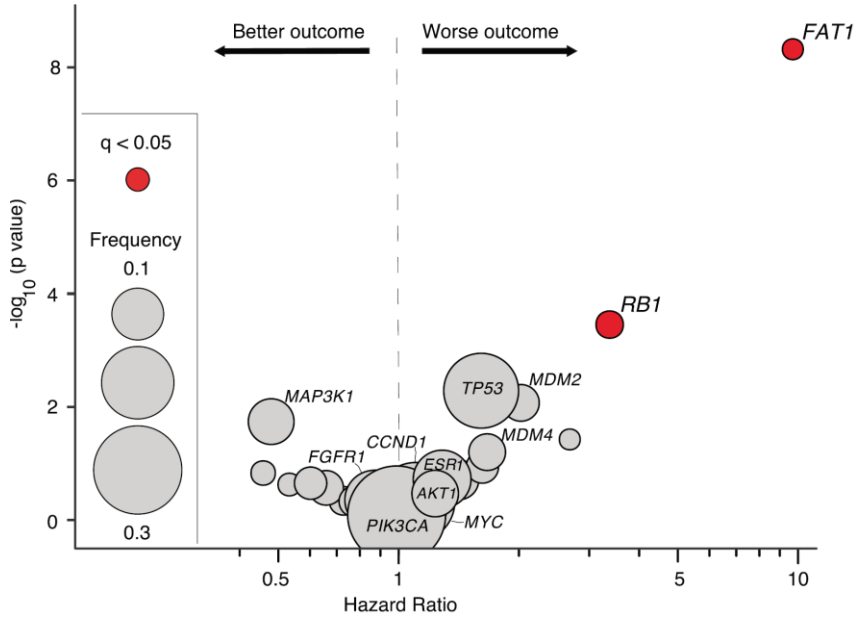
n=74 (pre- and post-progression matched biopsies

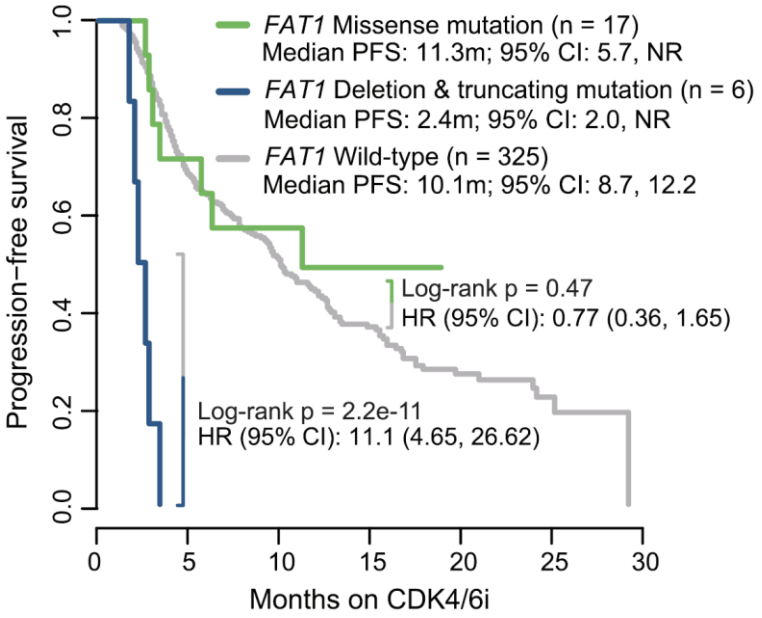
ERBB2 (82%) and EGFR (60%) of alterations present prior to therapy
NF1, KRAS, MAP2K1, and BRAF mutations usually acquired
~50% of MYC, FOXA1, and CTCF alterations present before therapy

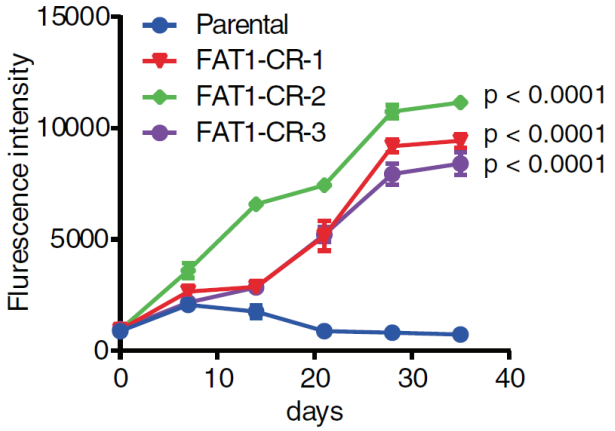
- WES in 30 treatment-naïve primary tumors, post-progression (hormonal therapy) specimen, and matched normal control
- Acquired mutations not found in primary tumors, including with higher depth sequencing using MSK-IMPACT (sensitivity to 1.3% of cancer cells)
- Additional targeted sequencing on matched pre- and post progression tumors from 44 additional patients
- Acquired mutations often subclonal

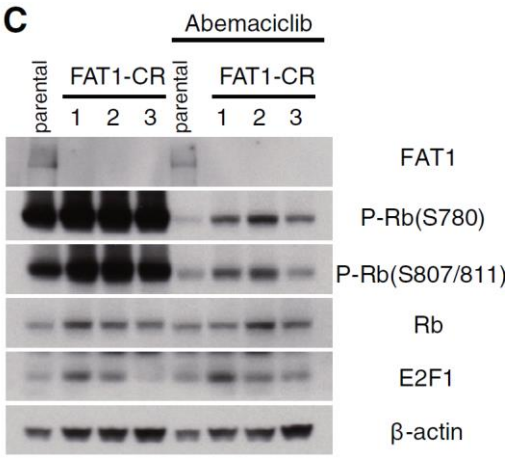
Cancer Cell

Loss of the FAT1 Tumor Suppressor Promotes Resistance to CDK4/6 Inhibitors via the Hippo Pathway



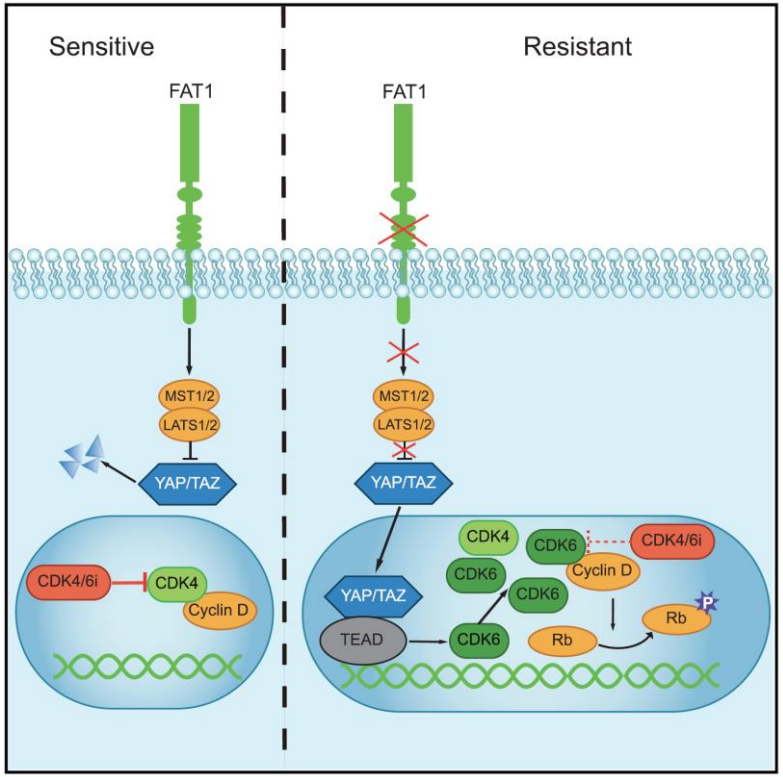


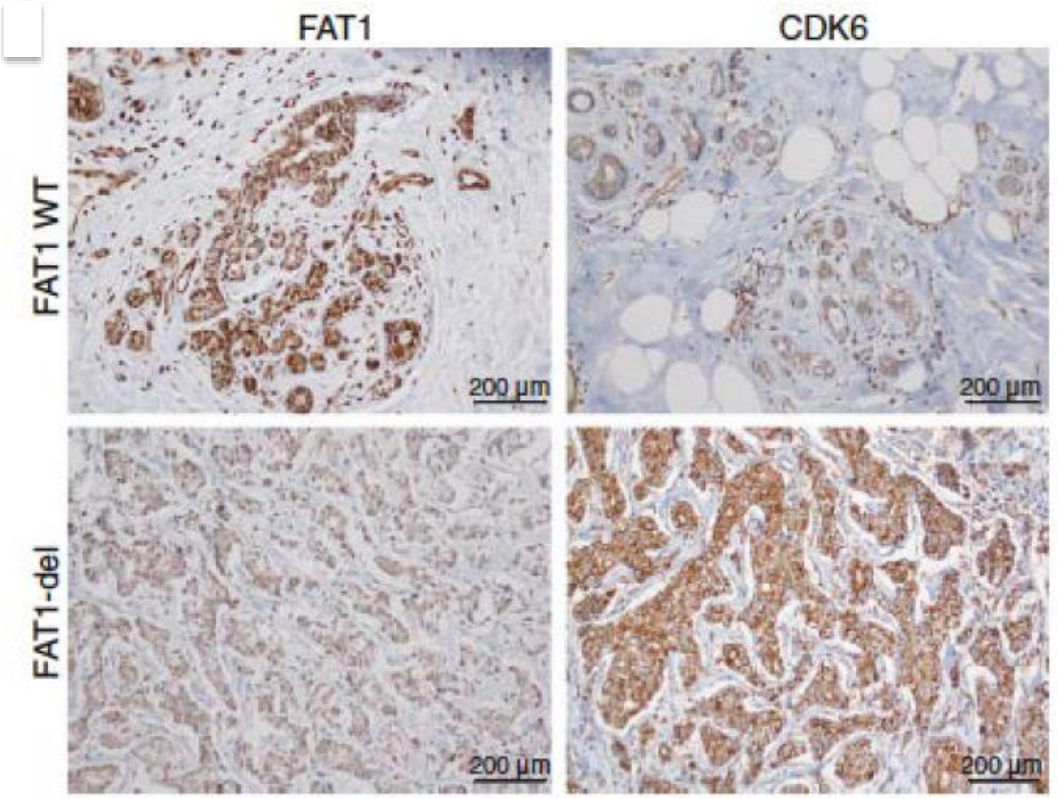




Li Z, ….. Chandarlapaty S. Cancer Cell 2018

Loss of FAT1 tumor suppressor promotes resistance to CDK4/6 inhibitors via Hippo pathway-dependent CDK6 overexpression





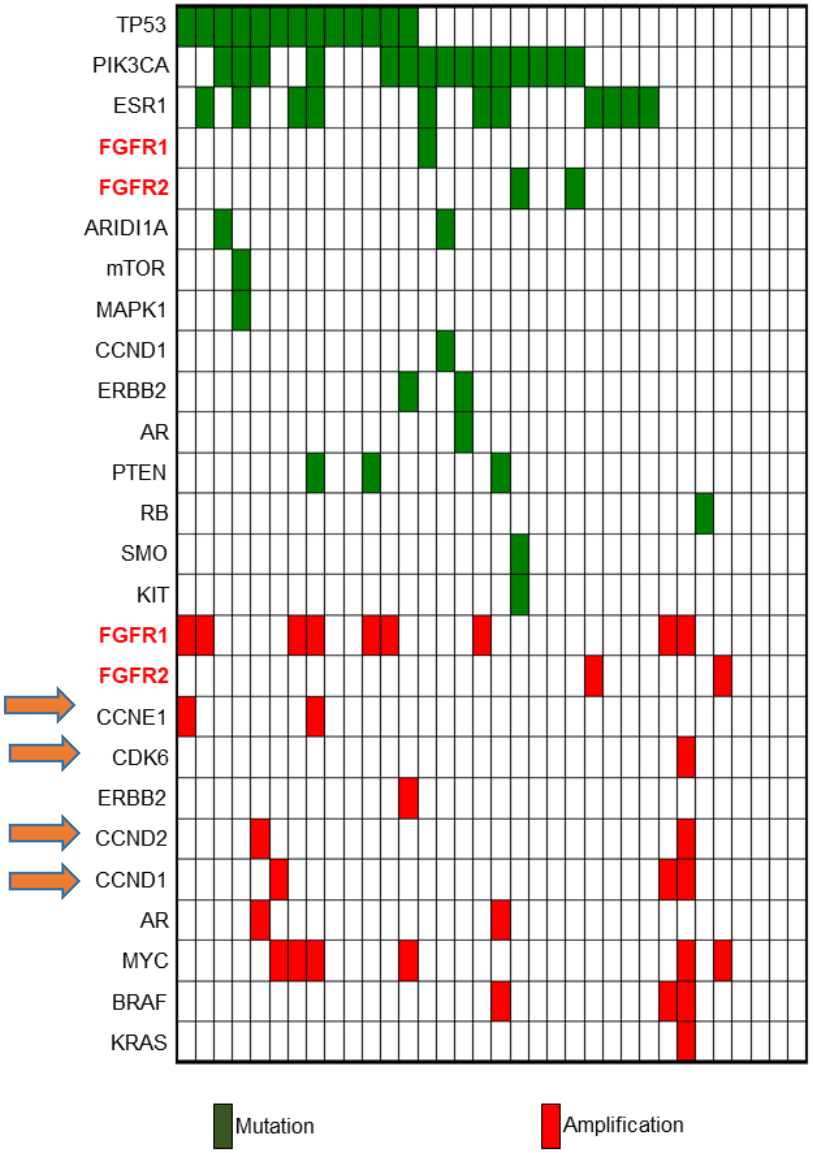
Li Z, ….. Chandarlapaty S. Cancer Cell 2018

FGFR pathway alterations in ctDNA are associated with progression on CDK4/6 inhibitors

ER+/HER2- (n=34) → Palbociclib + Endocrine therapy → Progression → Guardant 360

Guardant 360 (plasma tumor DNA):
14/34 (41%) FGFR pathway alterations:

9/34 FGFR1 amplification
2/34 FGFR2 amplification
1/34 FGFR1 mutation (N546K)
2/34 FGFR2 mutation (N549K, V395D)



Formisano *et al. Nature Communications* 2019

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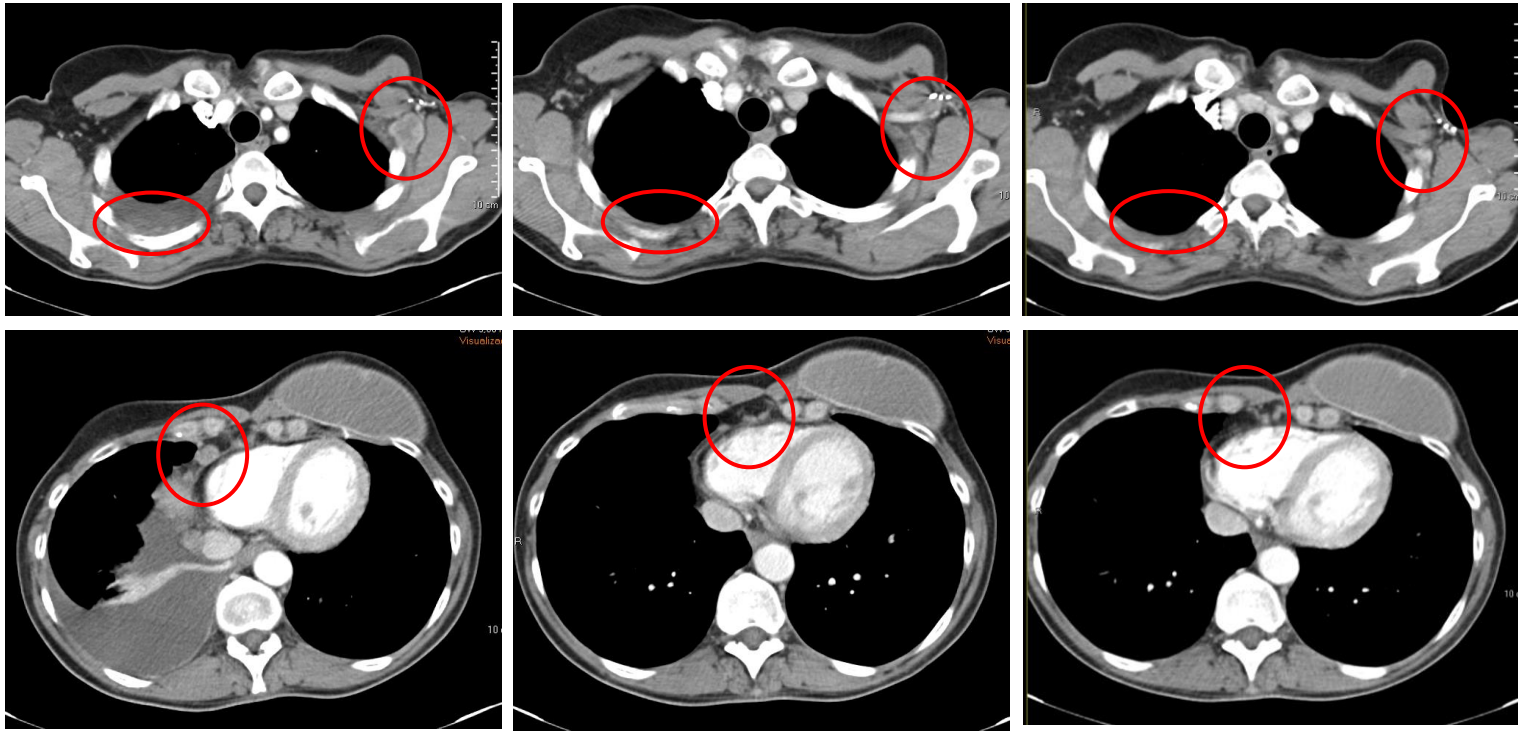
Extraordinary response of patient with breast cancer to HER2 (ERBB2) tyrosine kinase inhibitor neratinib

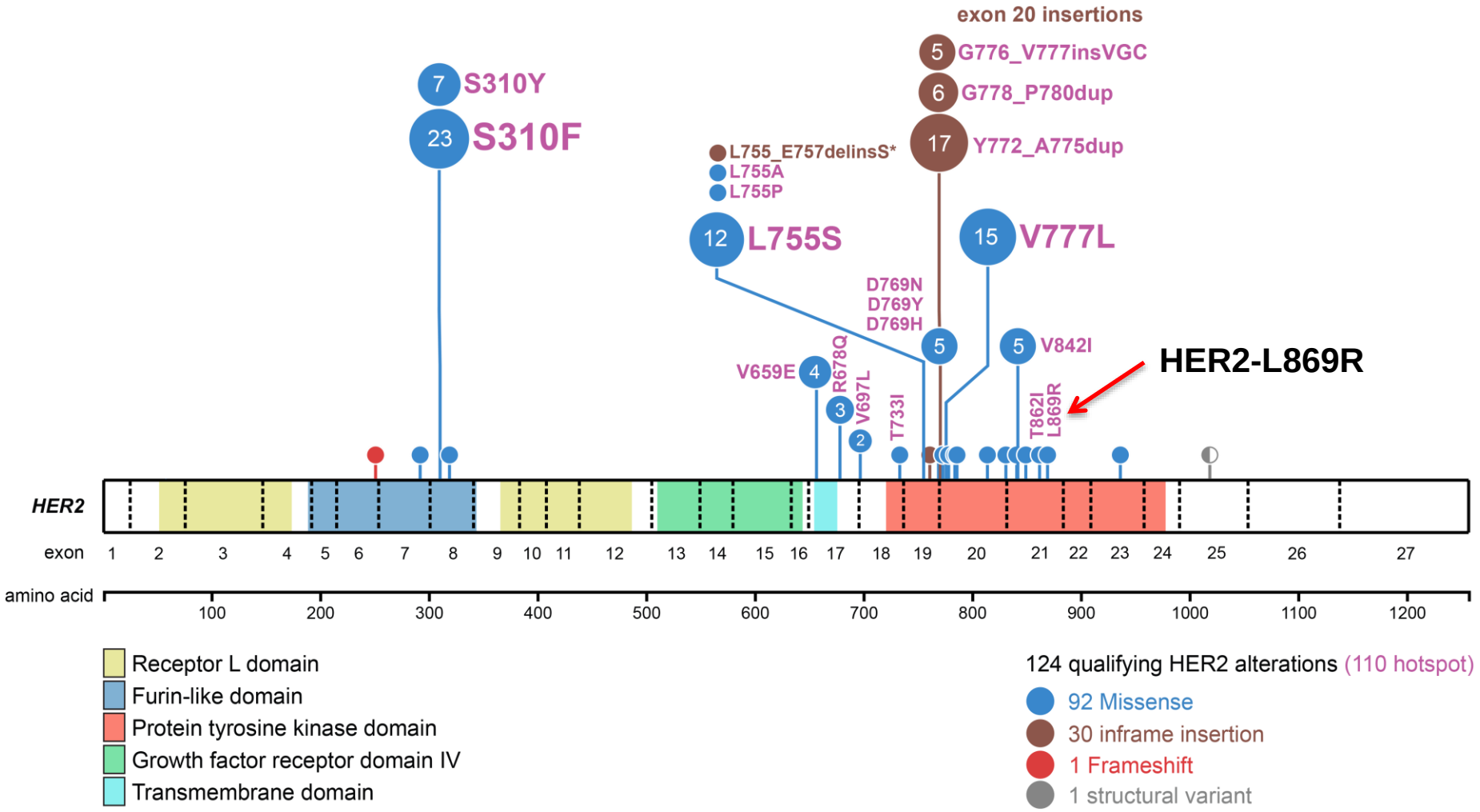
ERBB2 mutant (L755_E757delinsS) ER+/HER2– breast carcinoma



Baseline | 8 weeks | 16 weeks

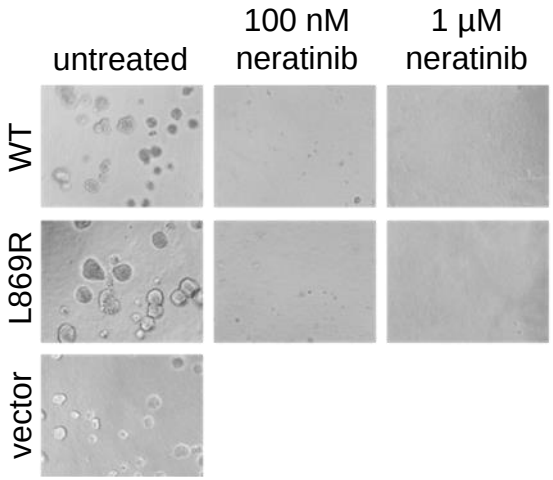
Confirmed PR: 70% reduction by RECIST following neratinib monotherapy

HER2 (ERBB2) mutations occur in 2-4% of breast cancers



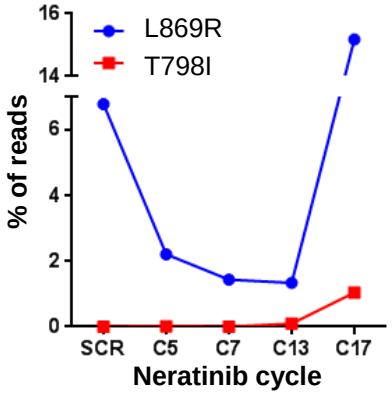
HER2-T798I gatekeeper mutation mediates acquired resistance to neratinib

HER2 L869R lobular breast cancer

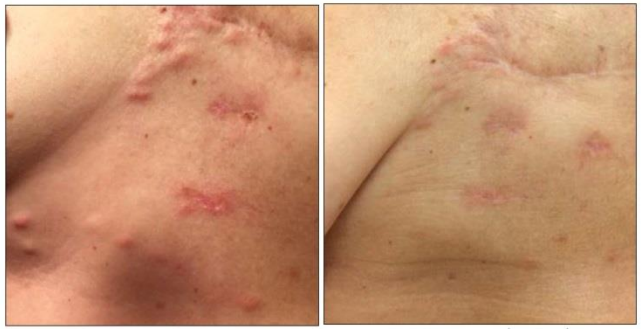


Progression on neratinib

HER2 L869R/T798I
Acquired resistance to neratinib

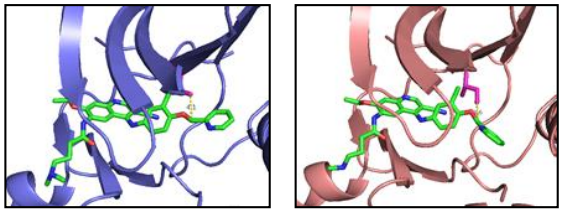


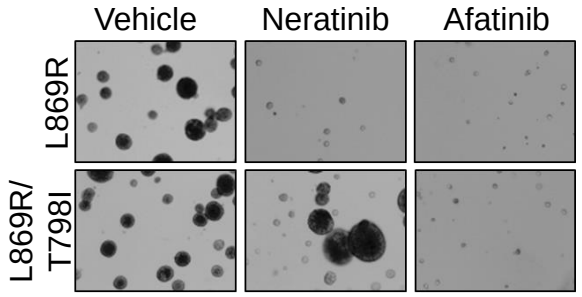
Neratinib clinical trial



Baseline

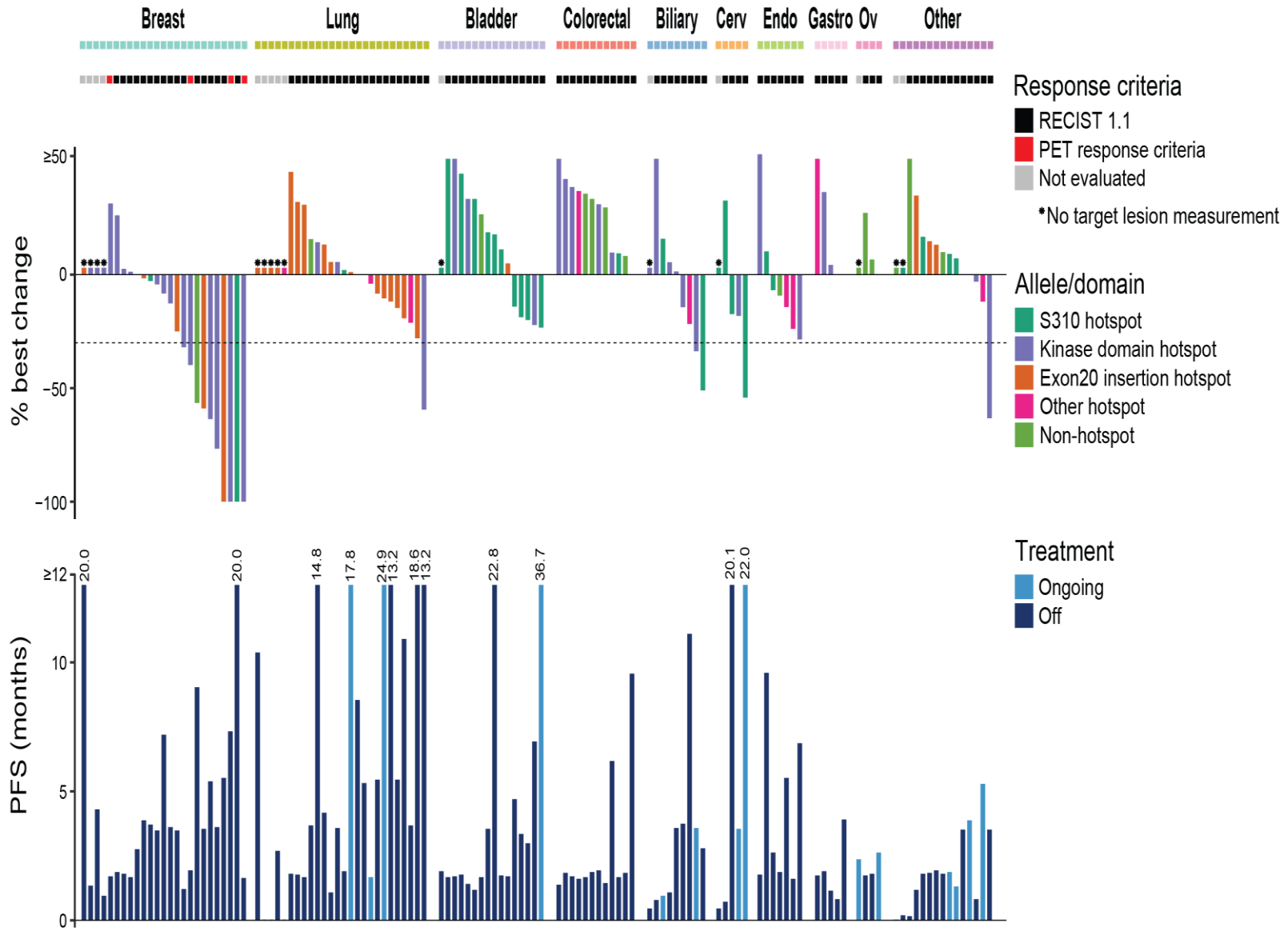
Post-Treatment (20 days)





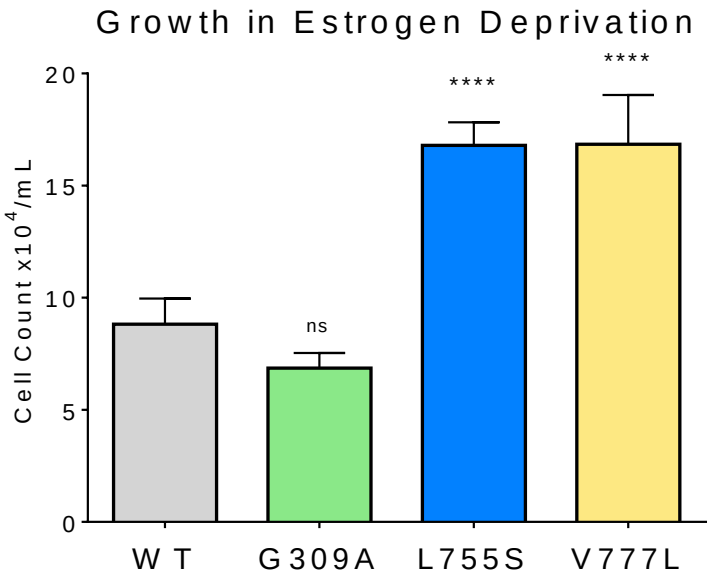
Hanker *et al. Cancer Discovery* 2017

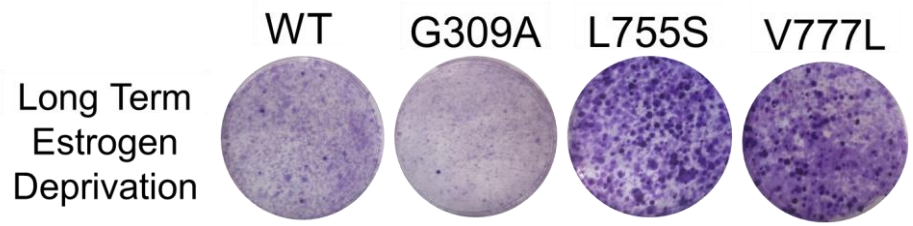
Efficacy in HER2-mutant tumors by cancer type

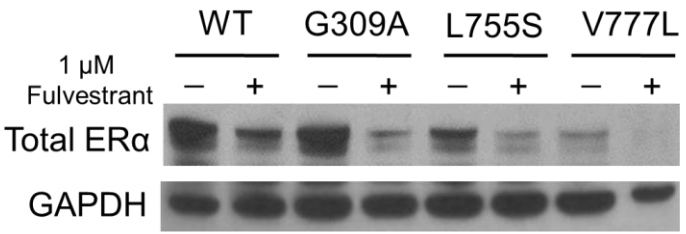


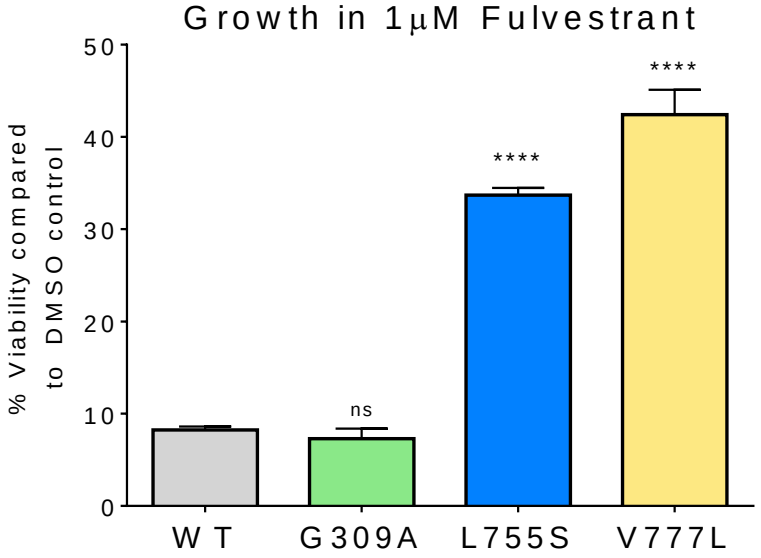
Hyman et al. Nature 2017

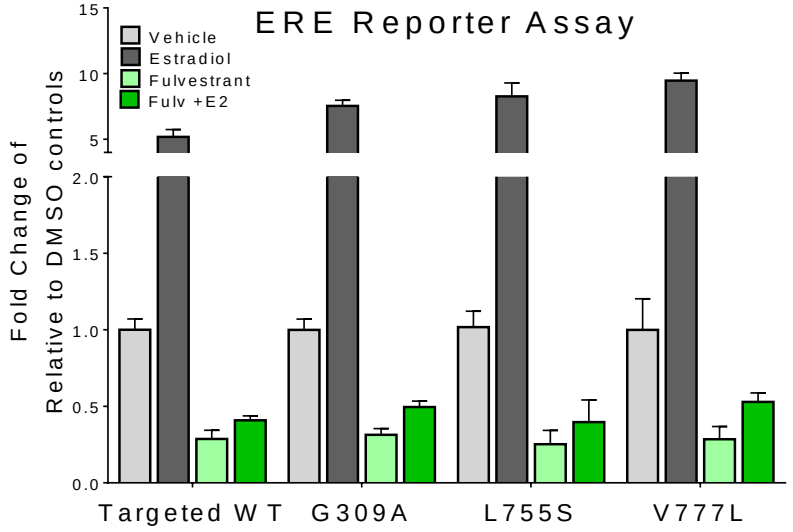
HER2 mutations confer resistance to estrogen deprivation and to fulvestrant



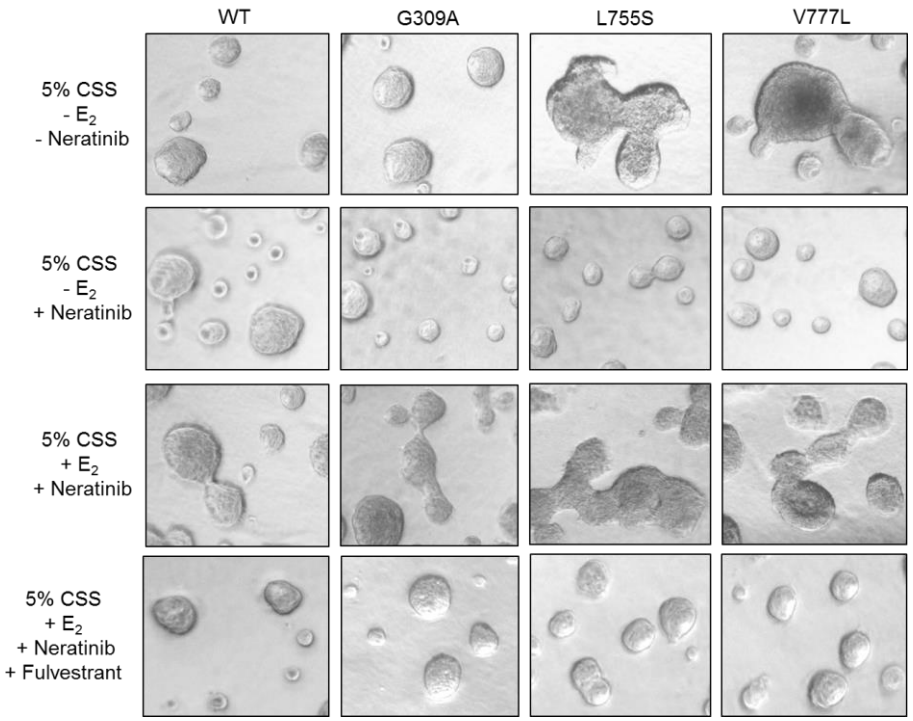


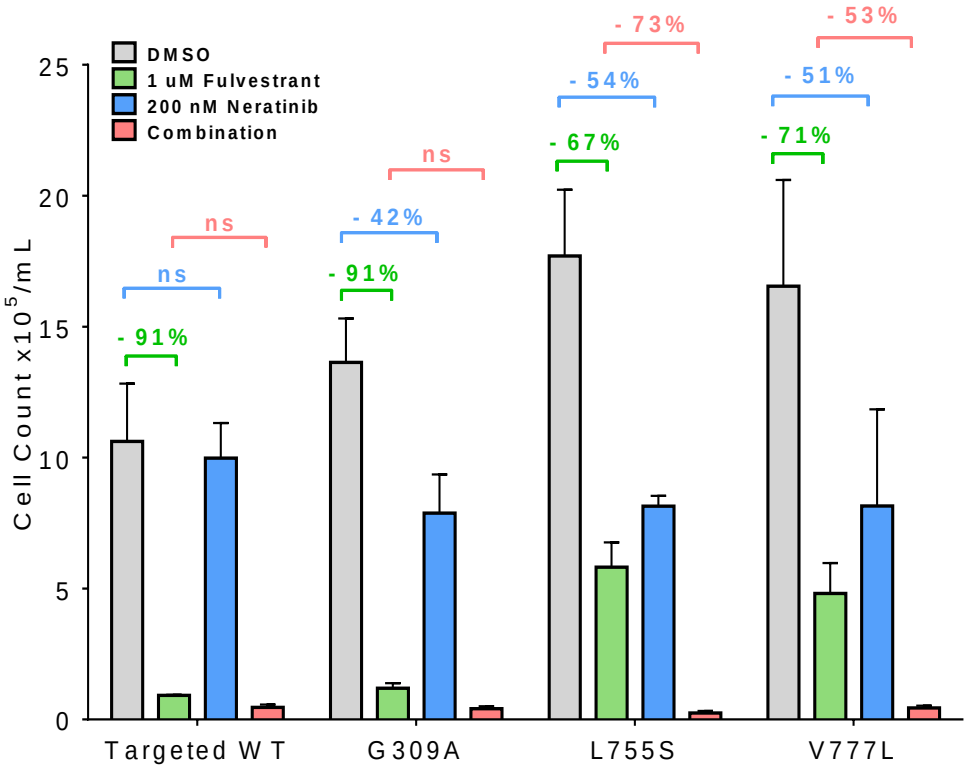






Estrogen rescues ER+/HER2 mutant cells: Combined blockade of HER2 and ER is required





Croessmann *et al. Clin. Cancer Res.* 2018

Figure 1

SUMMIT study design (Amendment 4)

Key inclusion criteria

- Documented *HER2* mutation (locally assessed)
- ECOG status of 0 to 2

***HER2*-mutant tumors**

Key exclusion criteria

- Prior treatment with any pan-HER TKI (eg, lapatinib, afatinib, dacomitinib, neratinib)
- Symptomatic or unstable brain metastases

Breast HR+ → **Neratinib + fulvestrant**

Breast HR–
Biliary tract
Cervical
Ovarian
Salivary gland
Solid tumors (NOS)
→ **Neratinib monotherapy**

Bladder → **Neratinib + Paclitaxel**

Neratinib: oral 240 mg daily
Fulvestrant: intramuscular 500 mg on day 1, 15 and 29; once every 28 days thereafter (labeled dose)
Paclitaxel: intravenous 80 mg/m^2 on day 1, 8 and 15; every 28 days
Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

Primary endpoint
- Objective response rate at first (8wks) post-baseline tumor assessment (ORR_8)

Secondary endpoints
- ORR (confirmed)
- Duration of response (DoR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

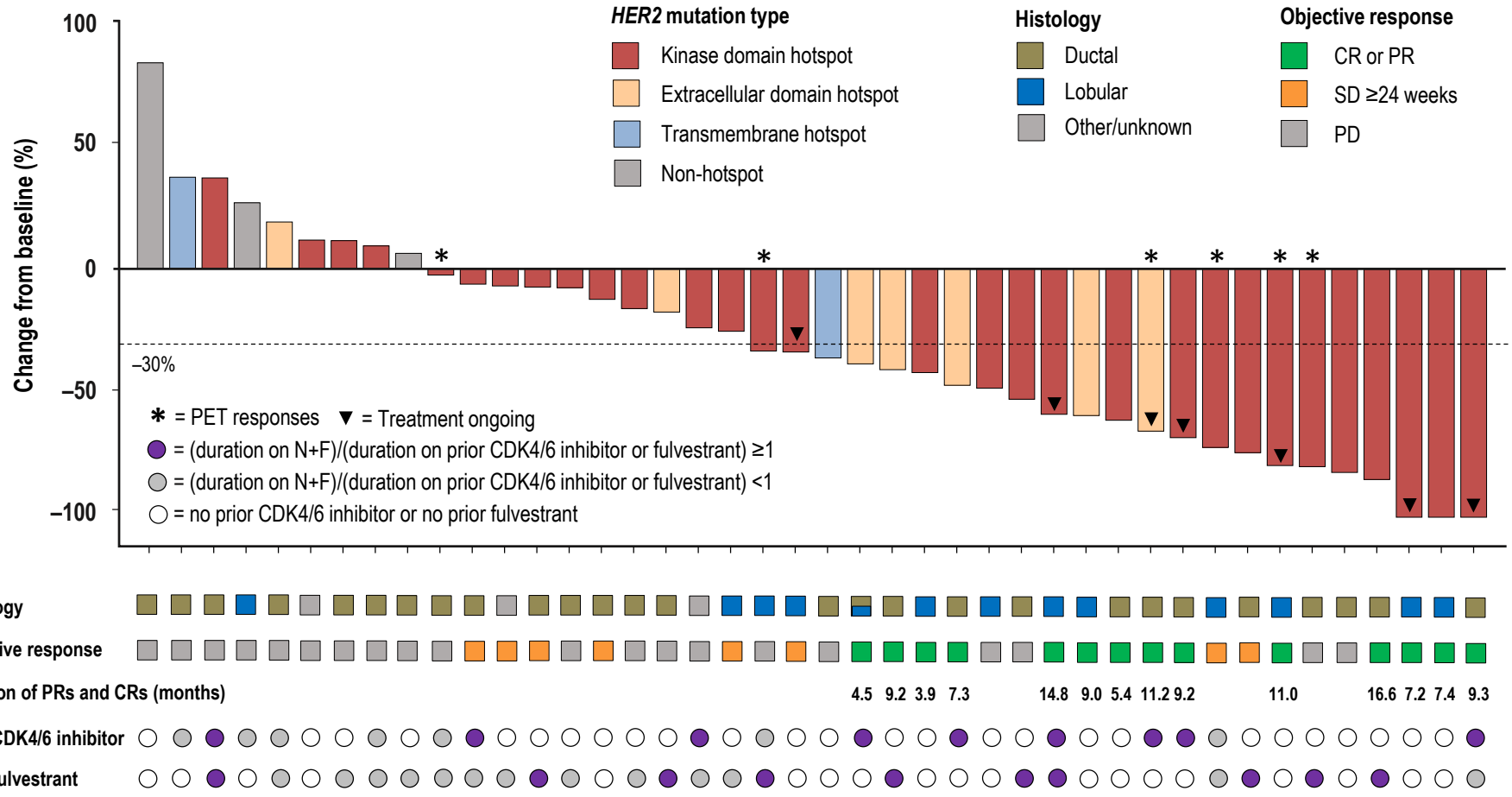
Simon 2-stage design
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments
- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods
- ORR_8, ORR, CBR: associated 95% CI
- Median PFS: KM estimate with 95% CI

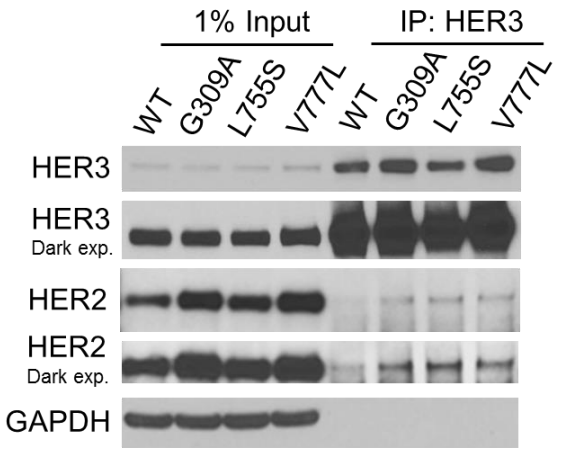
Figure 3

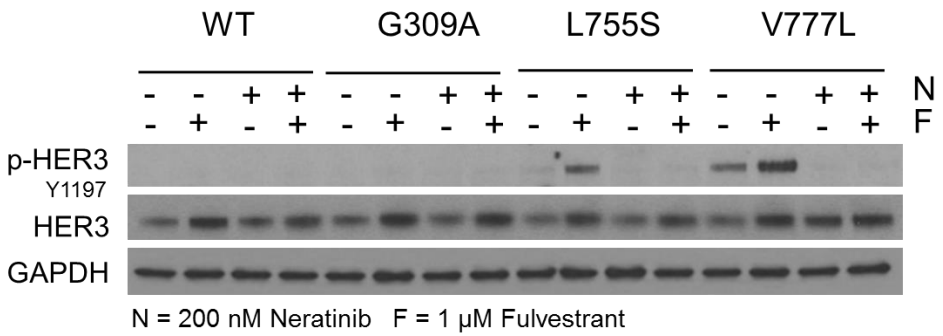
Waterfall plot – best % change in tumor size

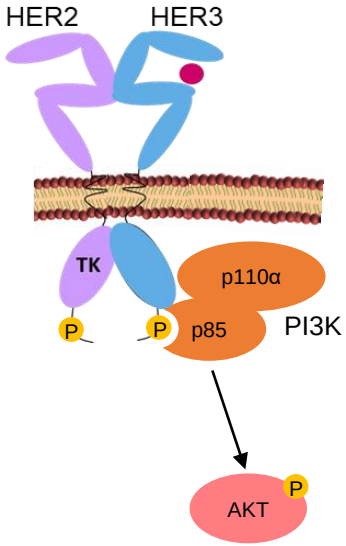


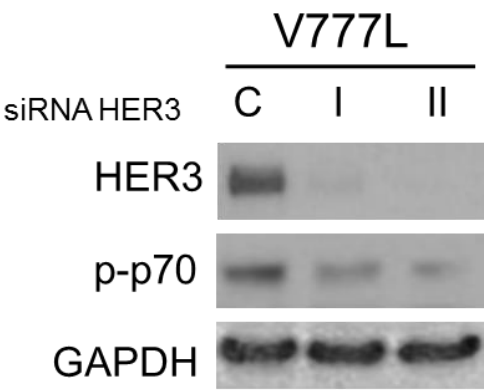
Not shown: 5 patients in whom no % change in tumor size could be calculated (n=1 died before first post-baseline assessment; n=1 ended treatment due to AEs before first post-baseline assessment; n=3 non-target lesions only)

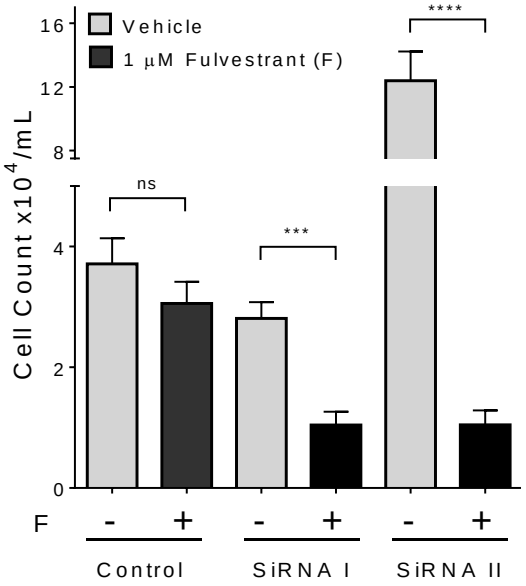
HER2 kinase domain mutations exhibit enhanced dimerization with HER3 (ERBB3)











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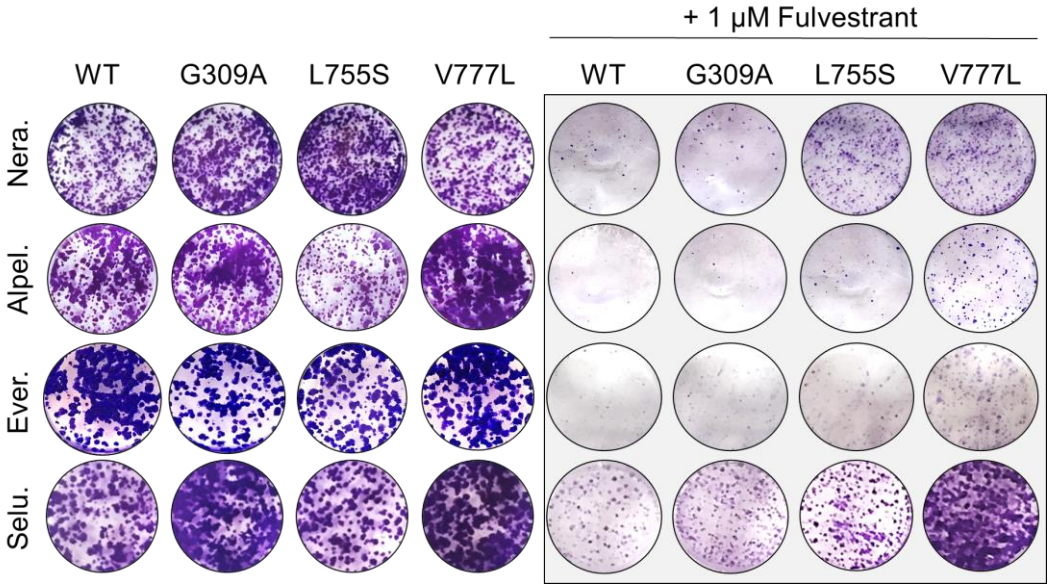
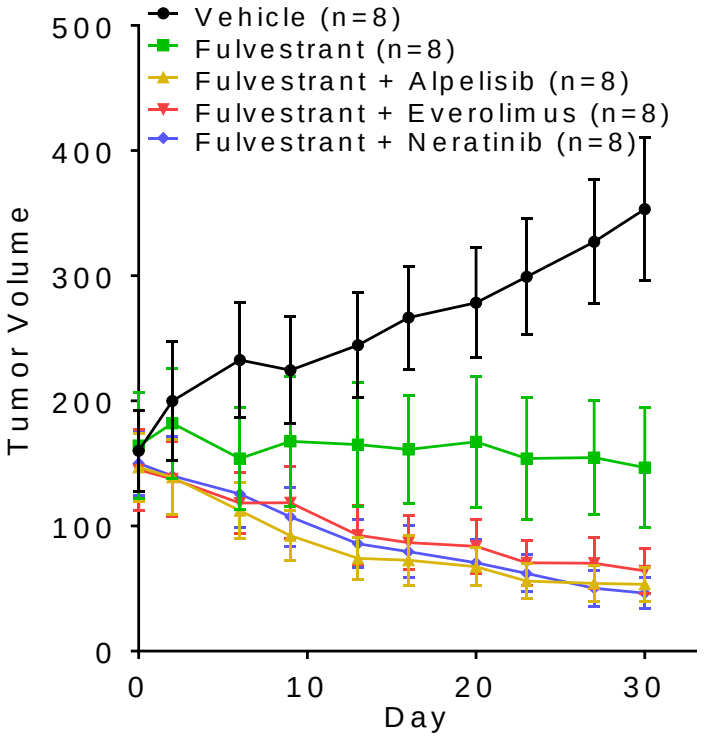
HER2 kinase domain mutations rely on PI3K/AKT/mTOR signaling

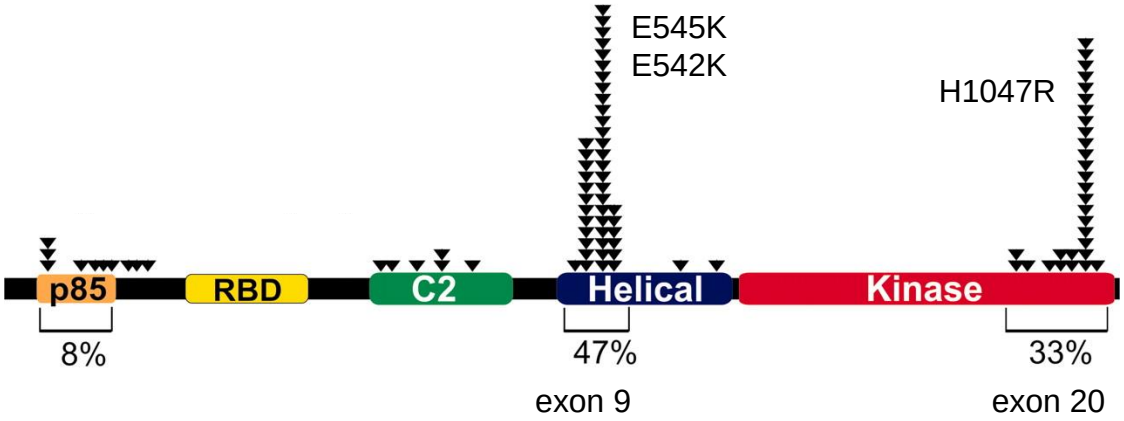


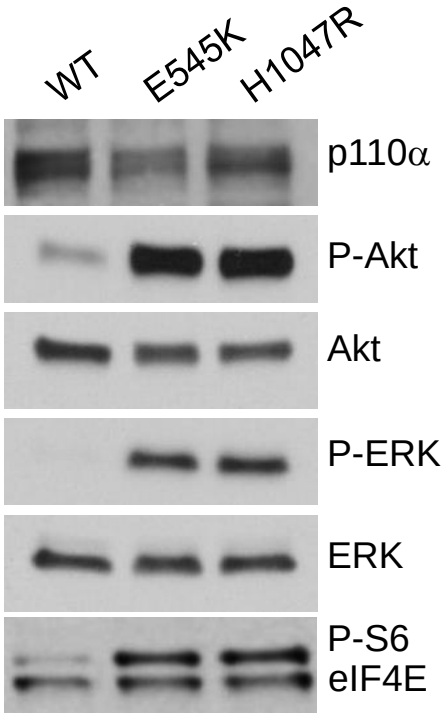


Endocrine Resistance: Mechanisms and Targeted Therapies

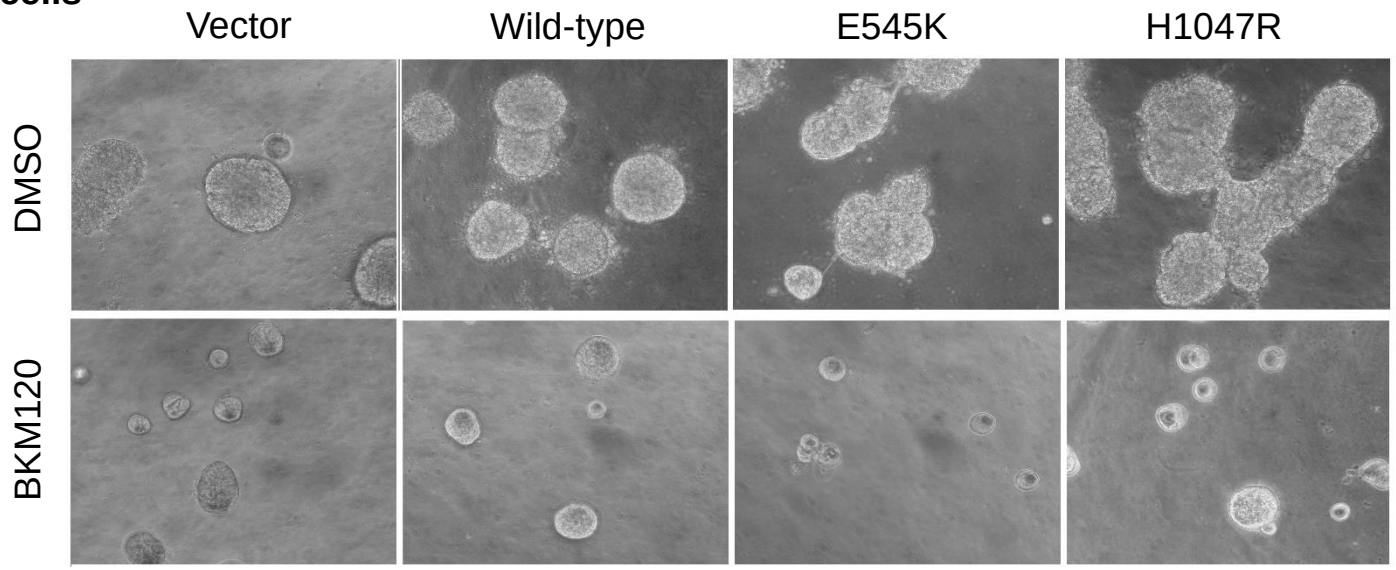
Mechanisms	Targeted Therapies
HER2 amplification	➢ Trastuzumab, lapatinib, T-DM1
ESR1 mutations, fusions	➢ Fulvestrant (?), novel ER degraders, CDK4/6 inhibitors
Ligand-independent ER	➢ CDK4/6 inhibitors, fulvestrant
PIK3CA mutations	➢ TORC1, Pan-PI3K, and PI3Kα inhibitors
FGFR pathway alterations	➢ FGFR inhibitors
HER2 mutations	➢ Neratinib
NF1 mutations/deletions	➢ MAPK pathway inhibitors

PIK3CA (p110α) mutations are gain-of-function oncogenes





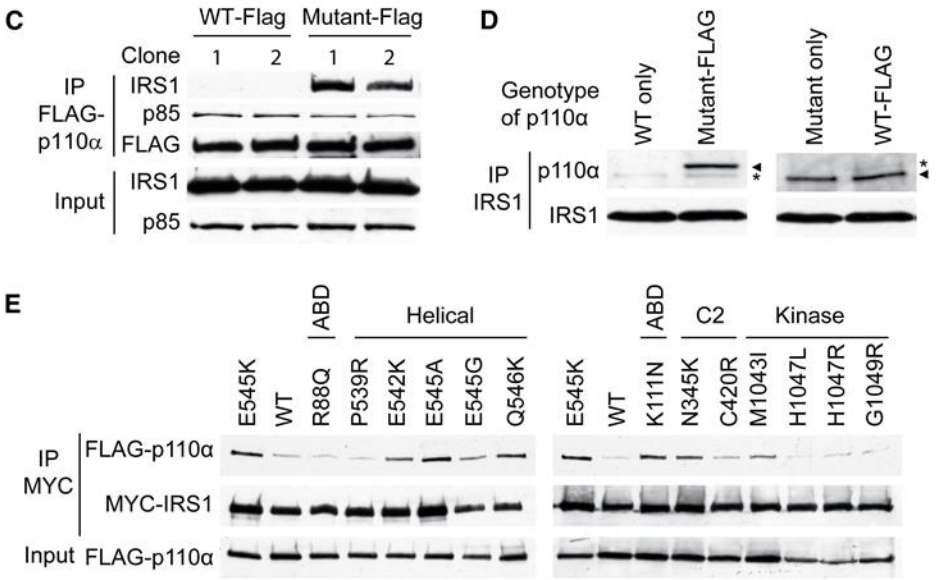
MCF10A cells

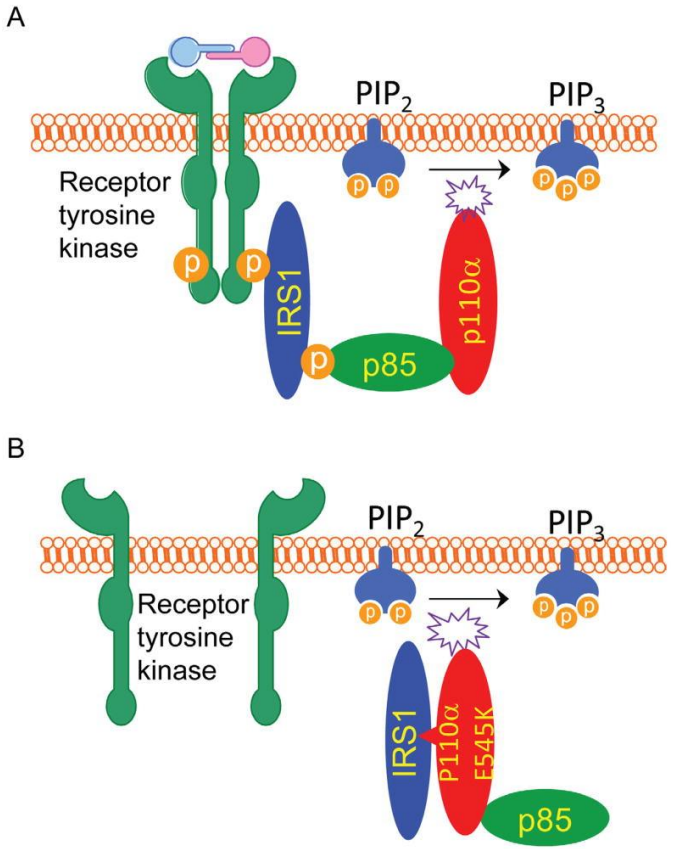


Chakrabarty *et al. Oncogene* 2010

Gain of interaction of p110α helical domain mutants with IRS-1 is required for its oncogenicity

DLD cells transfected with FLAG-p110α

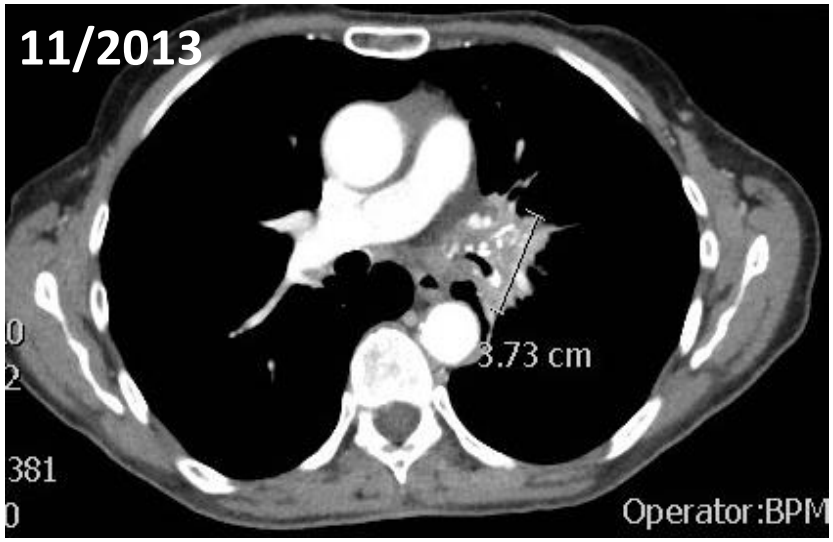


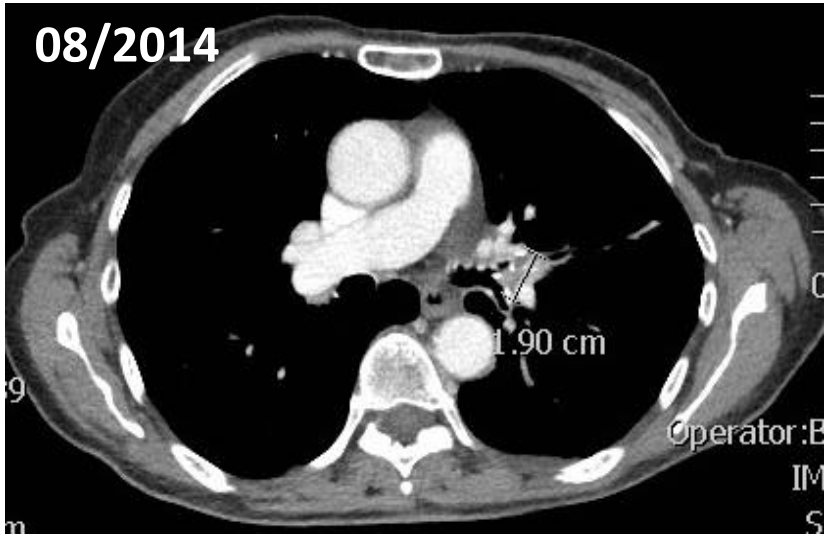


Hao et al. Cancer Cell 23:583-93, 2013

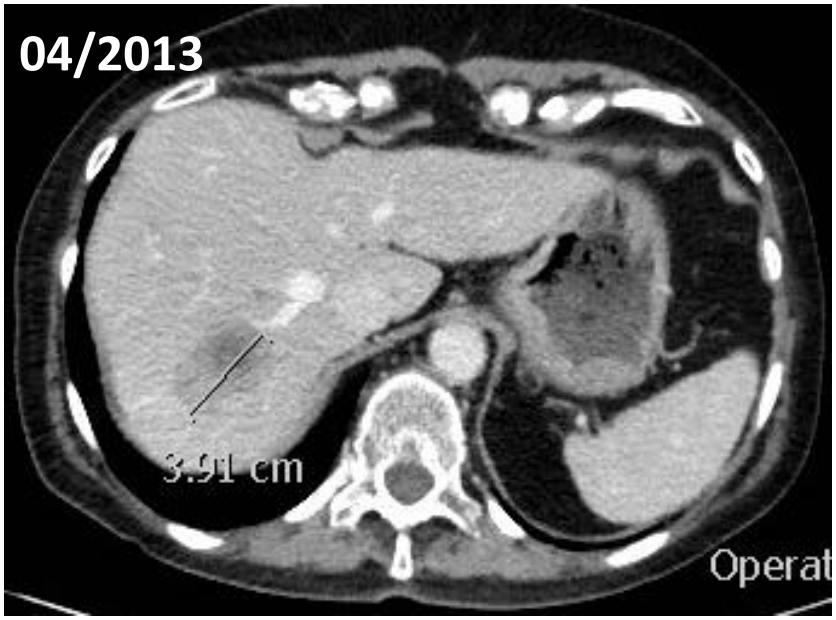
Combination of PI3Kα inhibitor alpelisib and letrozole is active against breast cancers with mutant PIK3CA

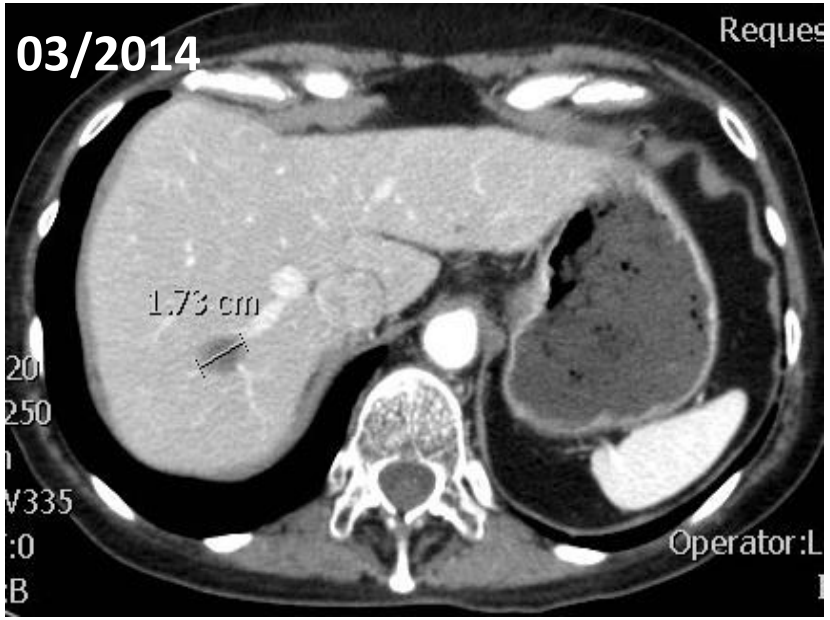
PIK3CA H1047R





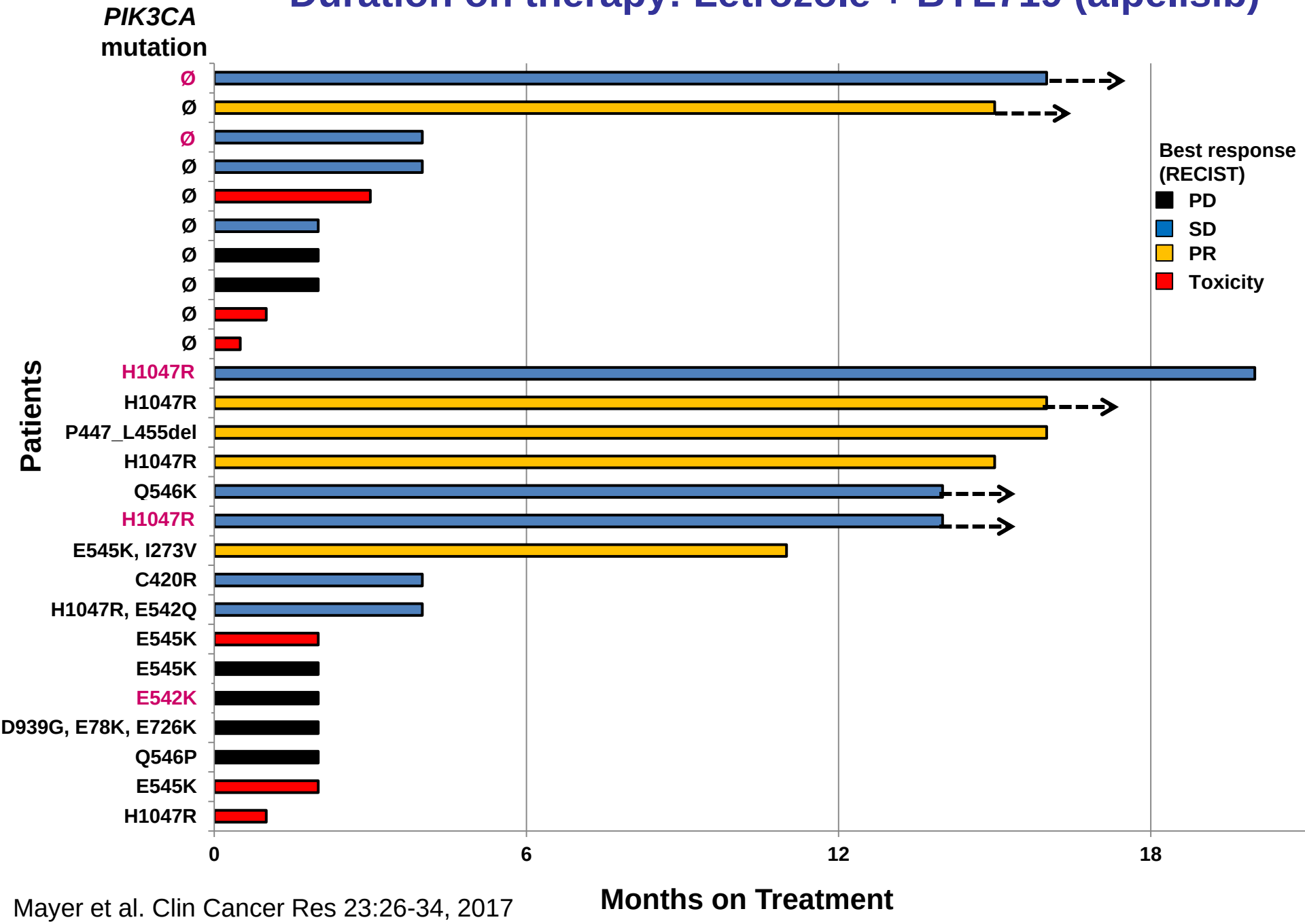
PIK3CA D447-L455_del





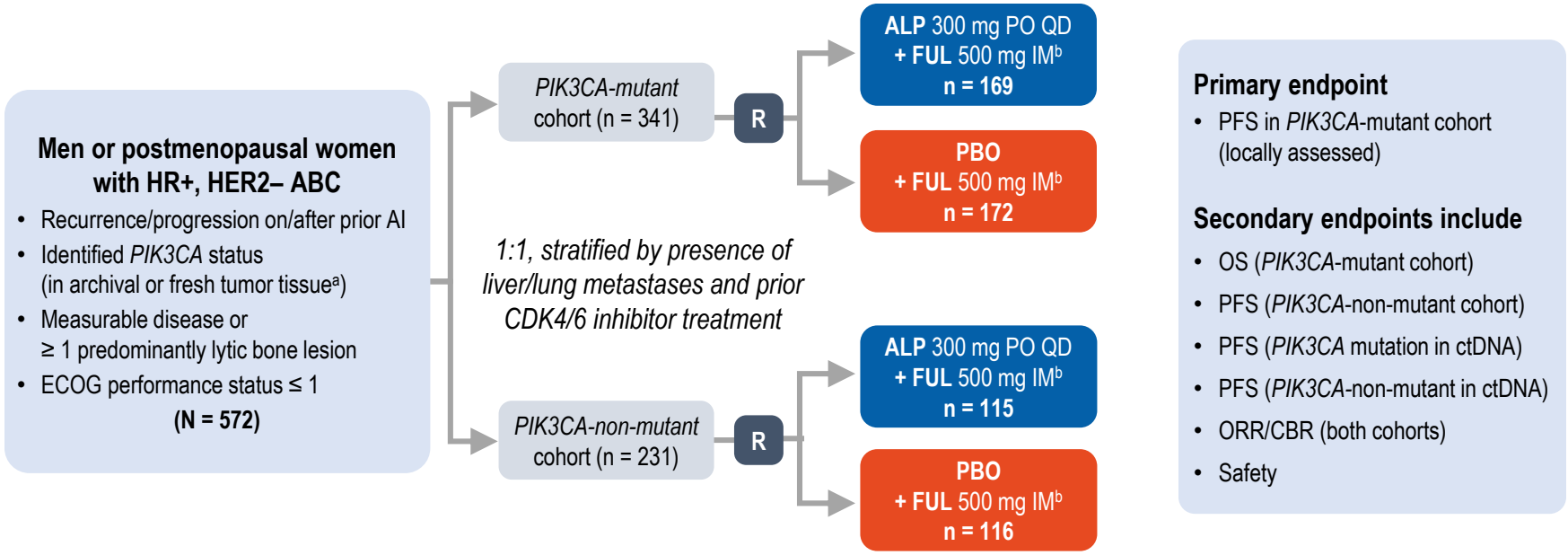
Mayer et al. Clin Cancer Res 23:26-34, 2017

Duration on therapy: Letrozole + BYL719 (alpelisib)



Mayer et al. Clin Cancer Res 23:26-34, 2017

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)[1]



- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

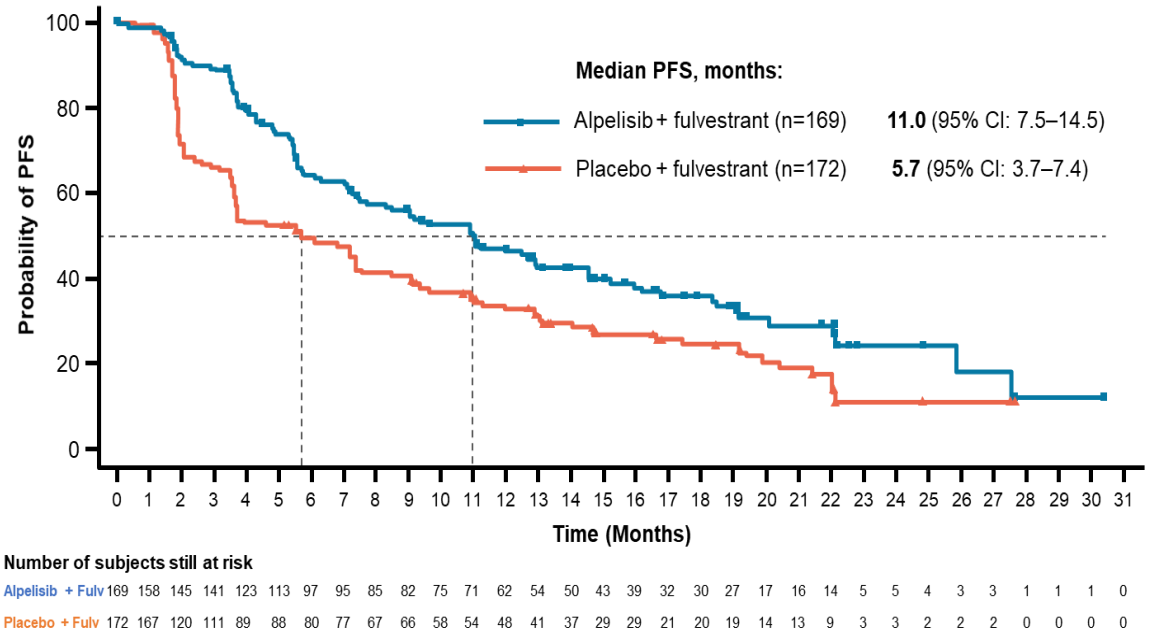
ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

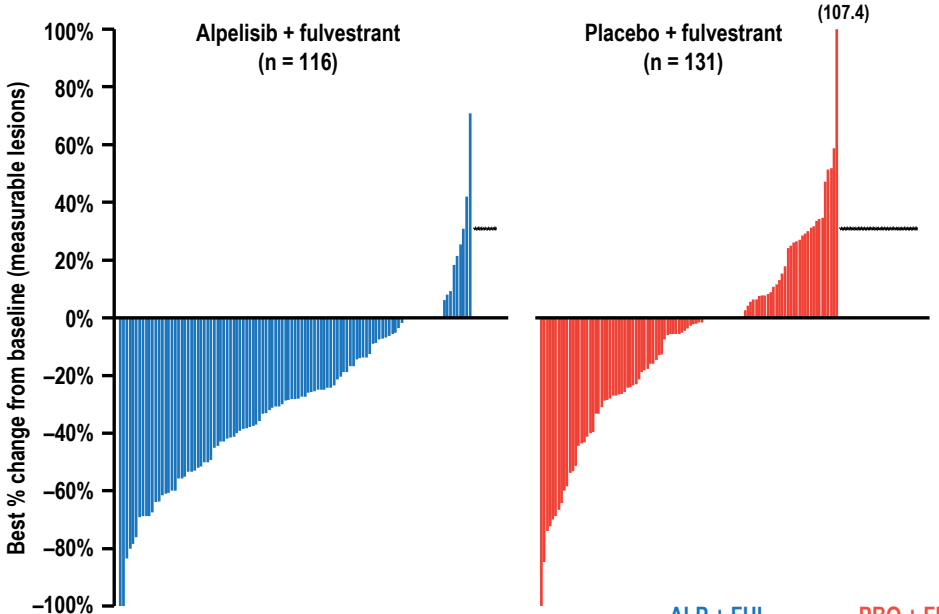
Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort[1,a]



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	0.00065	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

Best Percentage Change in Sum of Target Lesion Diameters Based on Local Investigator Assessment in *PIK3CA*-mutant Cohort[a,b]



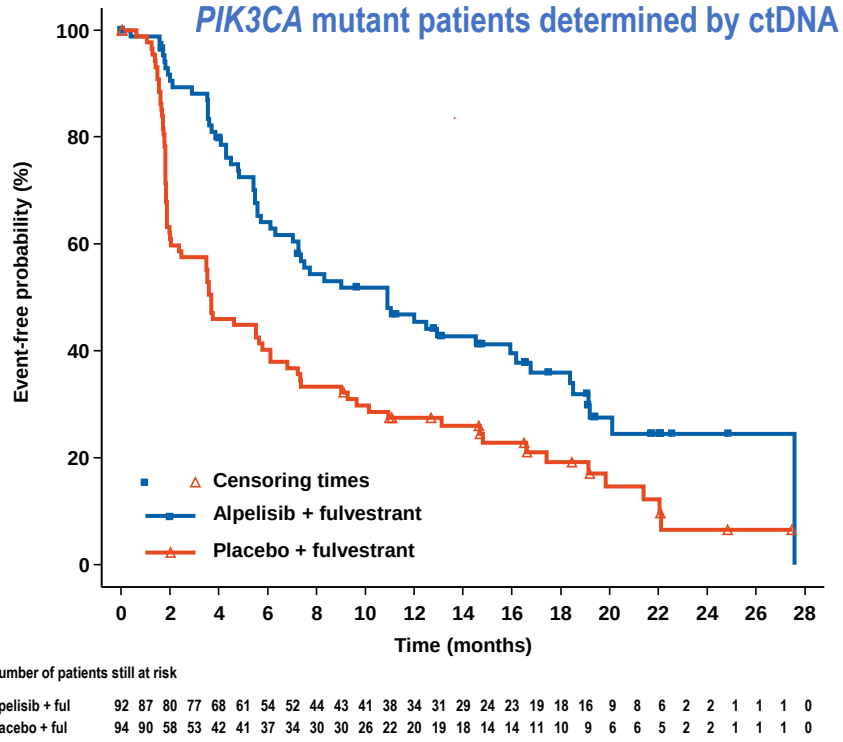
	ALP + FUL	PBO + FUL
Decrease in best percentage change from baseline	**75.86%**	**43.51%**
Increase/zero change in best percentage change from baseline	18.10%	35.88%
Percent change in target lesion contradicted by overall lesion response = PD	6.03%	20.61%

PD, progressive disease; UNK, unknown.

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator. Only patients with measurable disease at baseline are presented.

[a] Mutation status determined from tissue biopsy. [b] Change from baseline in sum of target lesion diameters.

Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status



	ALP + FUL		PBO + FUL		
	Event n/N (%)	Median PFS	Event n/N (%)	Median PFS	HR
Patients with *PIK3CA* mutation: tissue	103/169 (60.9)	11.0	129/172 (75.0)	5.7	0.65
Patients with *PIK3CA* mutation: plasma	57/92 (62.0)	10.9	75/94 (79.8)	3.7	0.55
Patients without *PIK3CA* mutation: tissue	49/115 (42.6)	7.4	57/116 (49.1)	5.6	0.85
Patients without *PIK3CA* mutation: plasma	92/181 (50.8)	8.8	103/182 (56.6)	7.3	0.80

ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; QD, once daily.

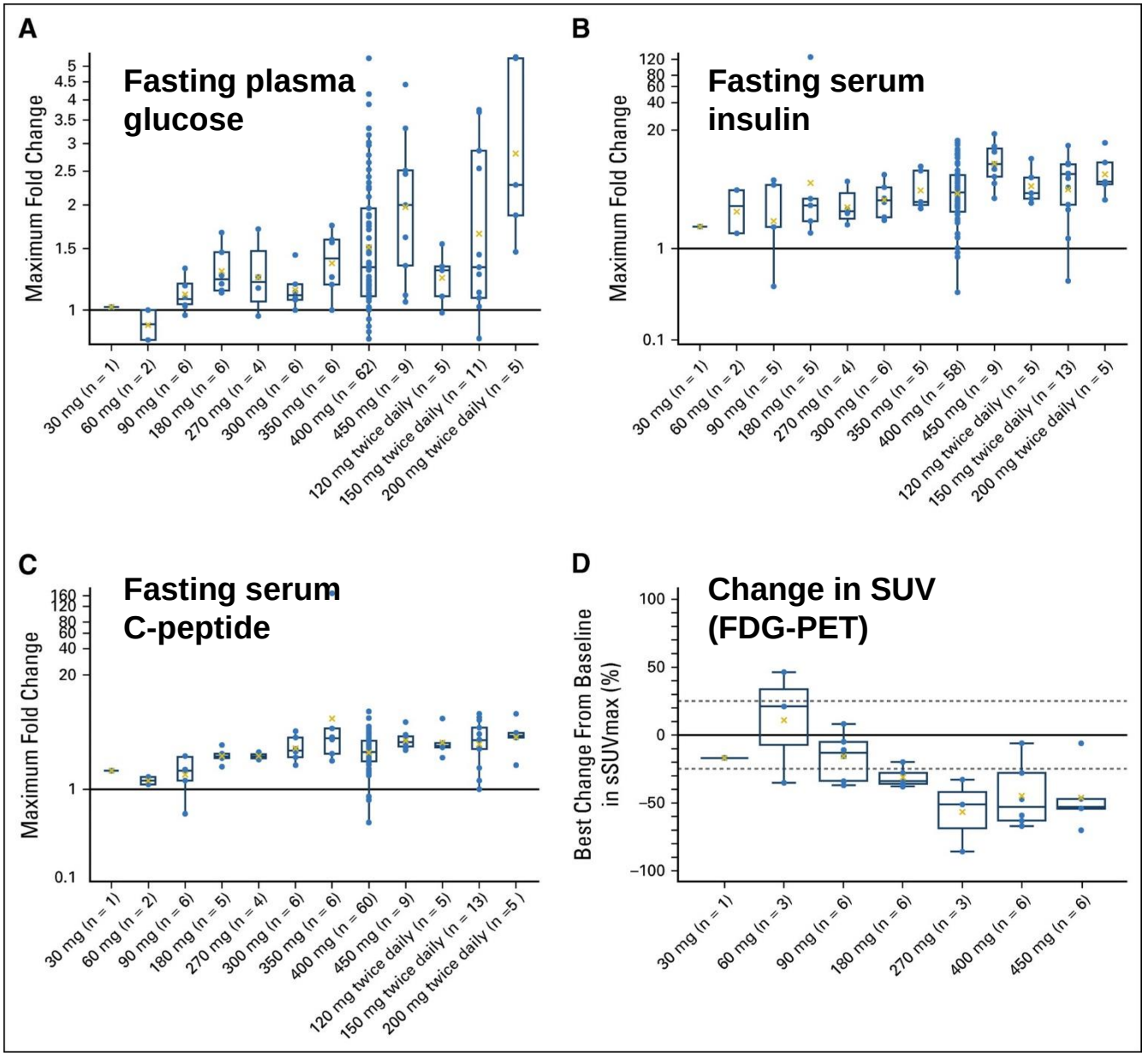
Adverse events in the total population

AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

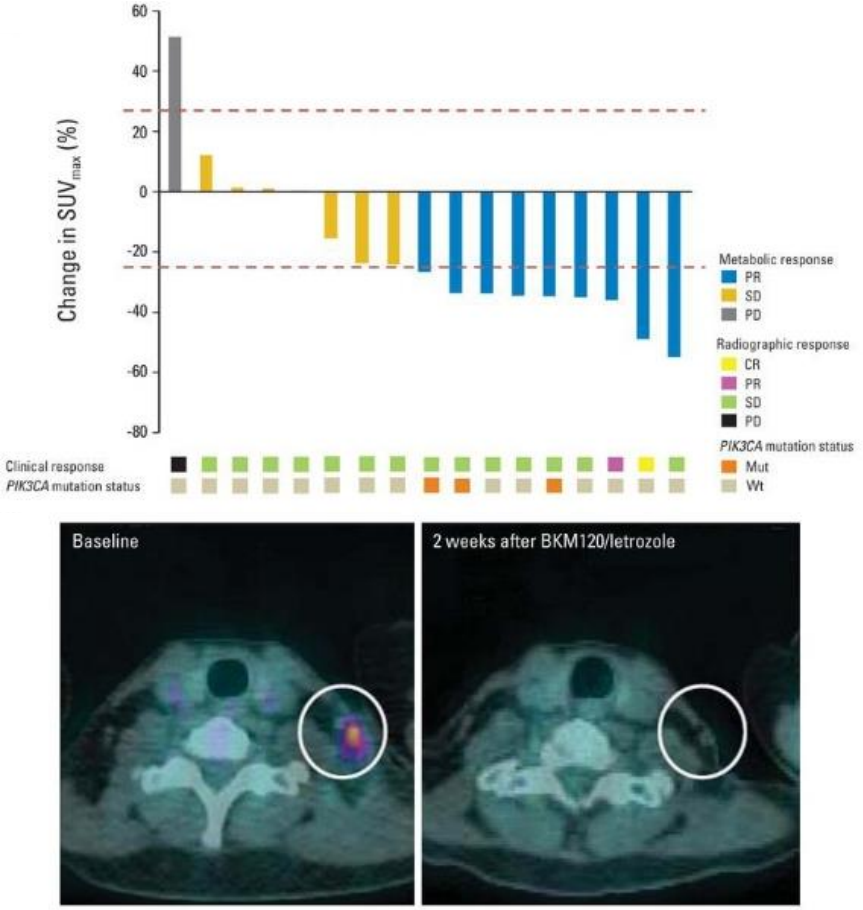
- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) due to rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash was observed in 14.1% of patients (all-grade) and 8.8% (grade 3) in the alpelisib arm, vs 1.7% and 0.3%, respectively, in the placebo arm
- The safety profile of the alpelisib group and the placebo group was similar in *PIK3CA*-mutant and *PIK3CA*-non-mutant cohorts

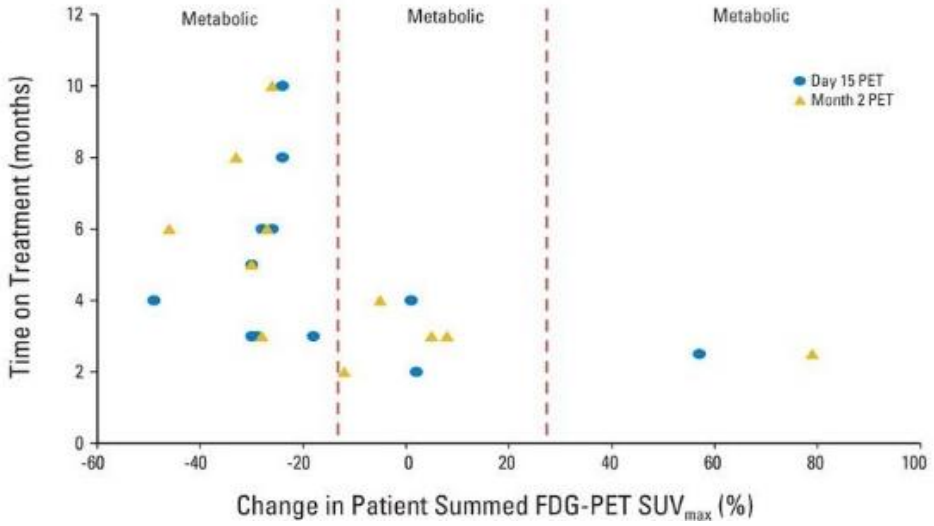
*Single preferred term of "rash" does not include preferred term of "maculopapular rash".

Inhibition of PI3Kα blocks glucose uptake and increases insulin levels (Juric et al. JCO 2018)



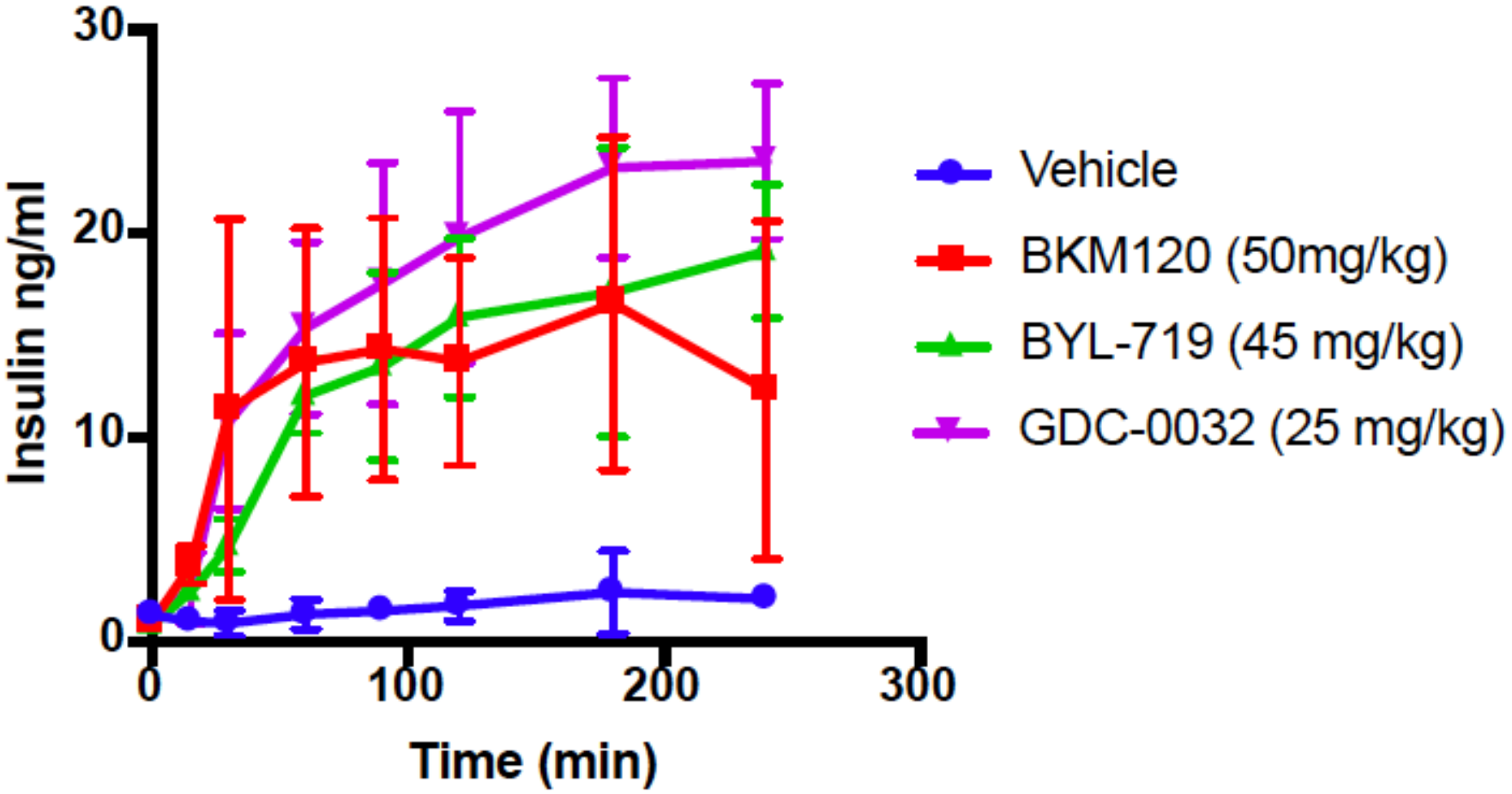
Reduction in FDG uptake by PET correlates with clinical benefit from pan- PI3K inhibitor buparlisib





Mayer et al. JCO 2014

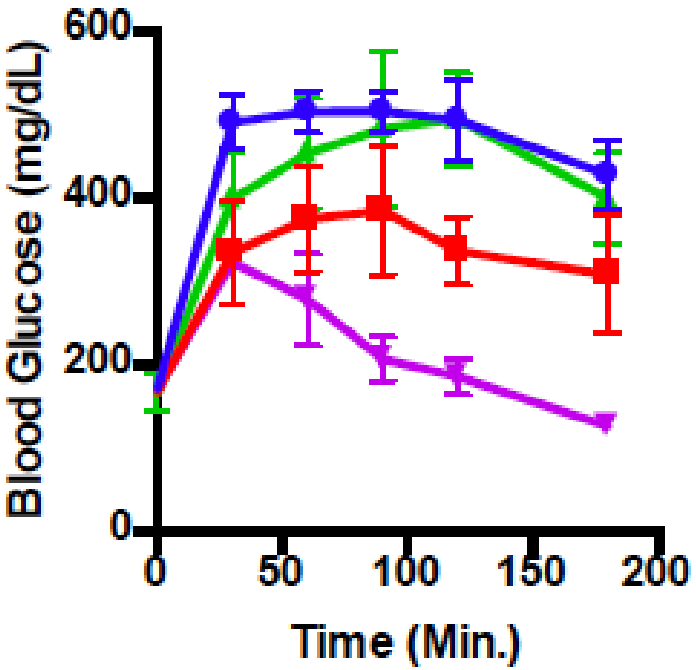
Insulin is highly elevated in the serum following treatment with PI3K inhibitors and remains high for hours

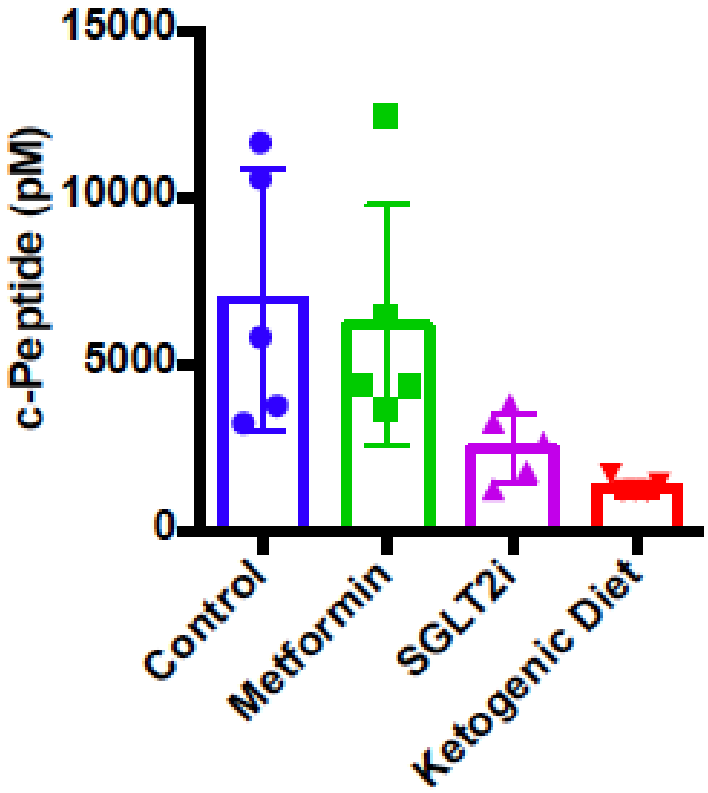


Hopkins B, ….. Cantley L. Nature 2018

Peak in serum glucose and serum insulin can be reduced by both a sodium-glucose transporter (SGLT) inhibitor and by a ketogenic diet. Metformin is not as effective.

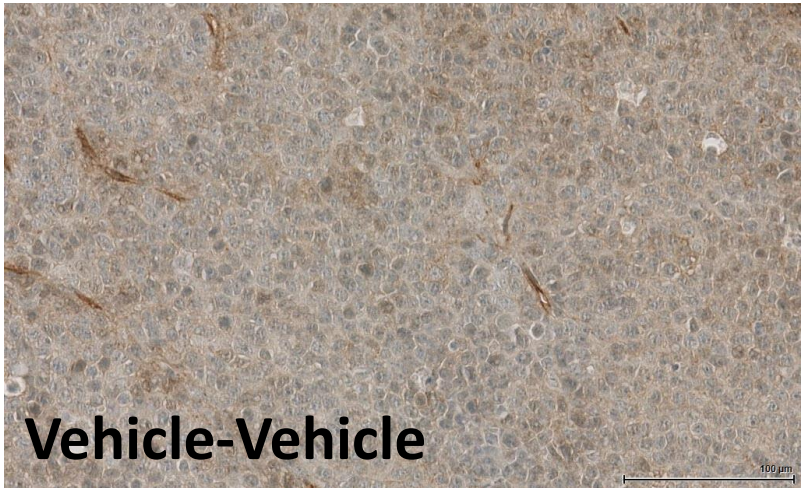
SGLTi → ↓ glucose reabsorption in the kidney
Ketogenic diet → depletes glycogen, ↓ gluconeogenesis

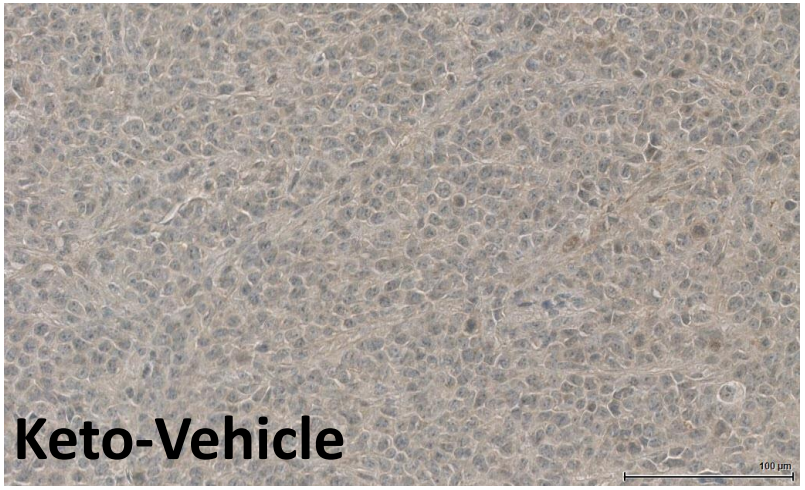




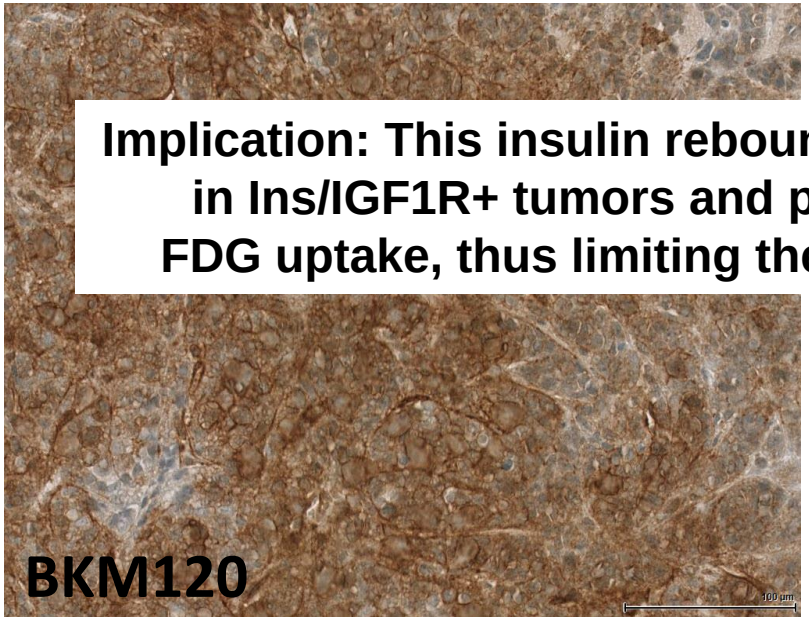
Hopkins B, ….. Cantley L. Nature 2018

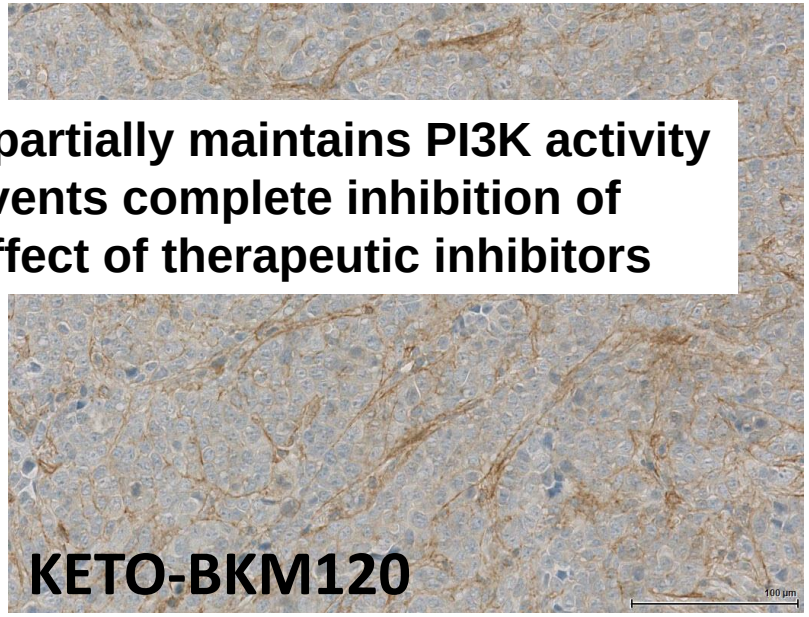
90 min post-dosing a PIK3CA mutant/PTEN-null endometrial tumor with BKM120, P-InsR increases and this increase is prevented when mice are on a ketogenic diet



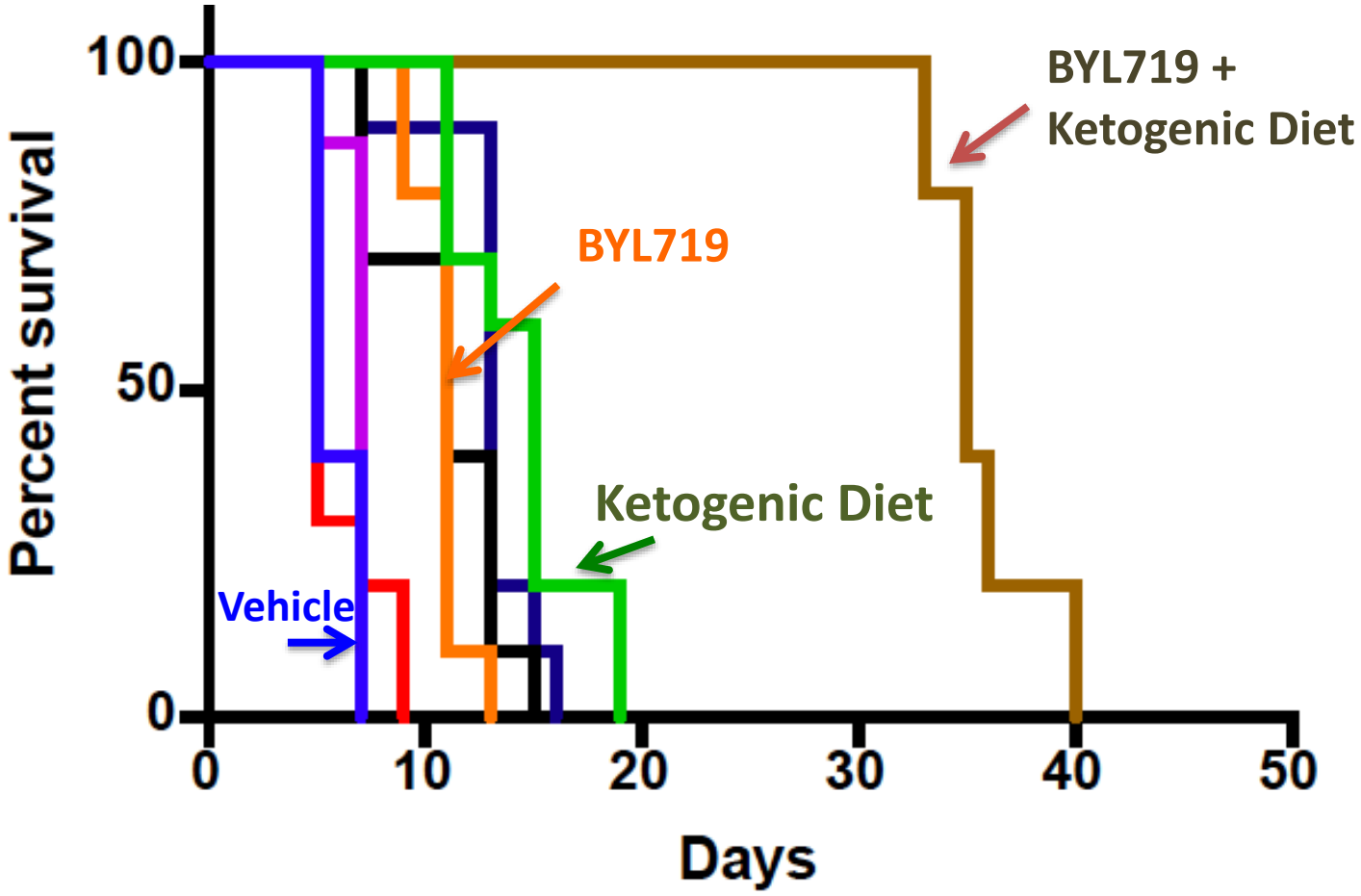


Implication: This insulin rebound partially maintains PI3K activity in Ins/IGF1R+ tumors and prevents complete inhibition of FDG uptake, thus limiting the effect of therapeutic inhibitors





A ketogenic diet markedly improves response to PI3K inhibitors in orthotopic allografts of murine KRAS-mutant/TP53 deleted pancreatic cancer



Reasons why therapeutic inhibition of PI3K in cancer has not had a better outcome

- Mutant PIK3CA is a weak oncogene
- Lack of optimal patient selection
- 'Dialing up' inhibition of PI3K causes severe rash and hyperglycemia, thus inhibition of PI3K is suboptimal and transient
- Use of pan-PI3K (± mTOR) inhibitors with poor tolerance
- Therapeutic inhibition of PI3K is followed by compensatory upregulation of several RTKs (ERBB receptors, Ins/IGF-IR, FGFRs), ERα, BCL2
- Lack of emphasis on combination trials
- Insulin production is increased upon inhibition of PI3K
- **Lack of mutant specific inhibitors**

Hanker et al. *Cancer Discovery* 2019

Approaches to Discover Mechanisms of Endocrine Resistance in ER+ Breast Cancer

- Short presurgical (aka, ‘window’) and neoadjuvant therapeutic trials
- Biopsy and molecular profiling of recurrent (drug-resistant) metastases
- Interrogation of exceptional responders to targeted therapies → trials with targeted therapies, all informed by metastatic tumor profiling
- **Big increase in combinations of targeted therapies with standard of care anti-ER therapy all informed by serially assessed tumor evolution**

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Saurabh Mendiratta, MS
Sumanta Chatterjee, PhD

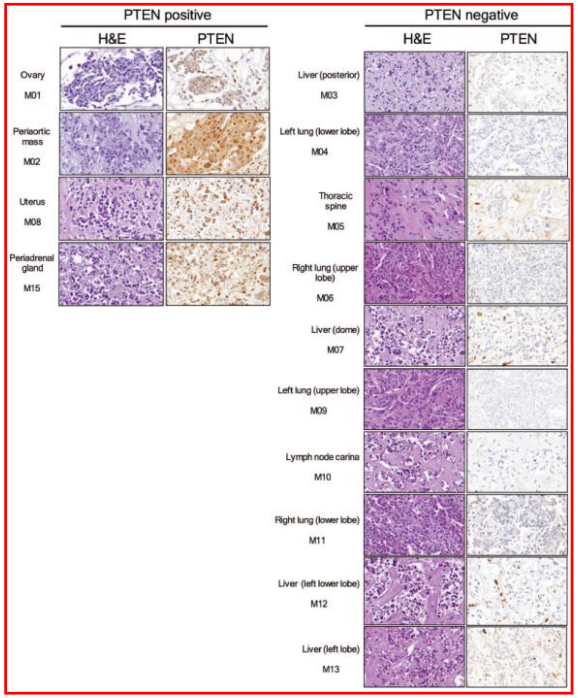
Weil Cornell
Lewis Cantley, PhD

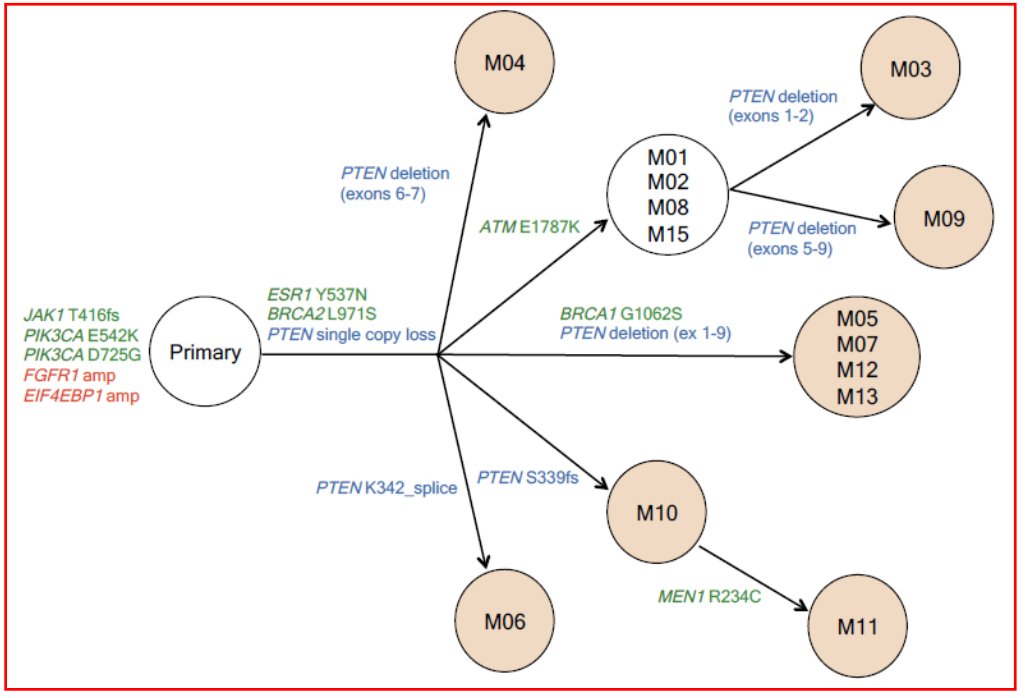
Puma Biotechnology
Al Lalani, PhD
Richard Cutler, PhD
Richard Bryce, MD

Guardant Health
Becky Nagy, PhD
Richard Lanman, MD

Novartis
Samit Hirawat, MD
Tetiana Taran, PhD

Convergent PTEN-null phenotype developed by parallel evolution under selective pressure with BYL719





Juric, Castel, Nature, 2014