ER+ Breast Cancer: Reversal of Antiestrogen Resistance by Manipulation of the PI3K/mTOR pathway

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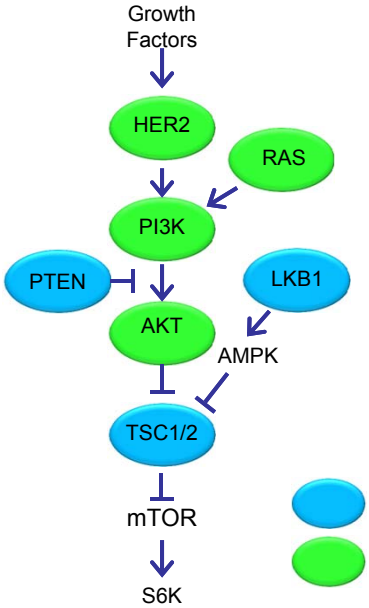
The PI3K pathway is a therapeutic target in cancer

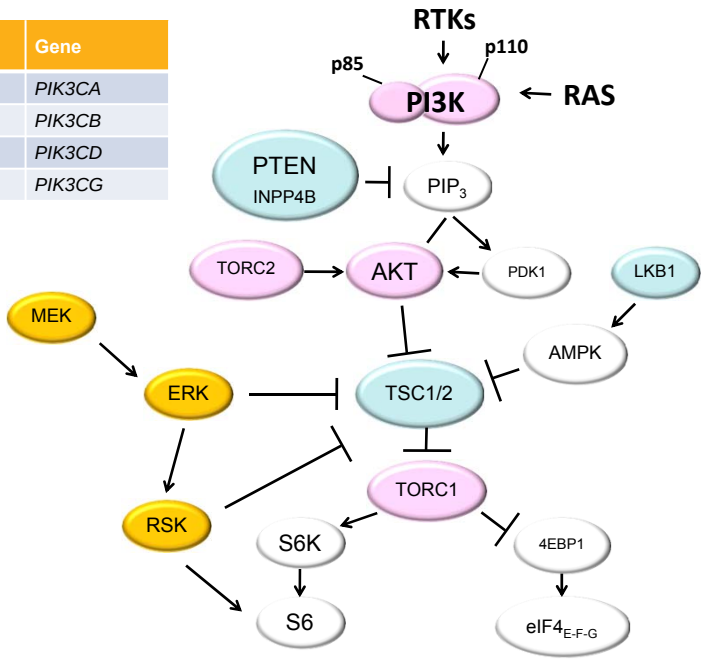


PI3K is the pathway most commonly mutated in human cancer, including breast cancer

Confers malignant transformation, tumor cell invasion, enhanced angiogenesis and survival, and drug resistance

Mechanisms of activation include amplification/ mutation of oncogenes, mutations in PIK3CA and AKT, and loss of tumor suppressors PTEN and LKB1

Class	Catalytic Isoform	Gene
IA	P110α	*PIK3CA*
IA	P110β	*PIK3CB*
IA	P110δ	*PIK3CD*
IB	P110γ	*PIK3CG*



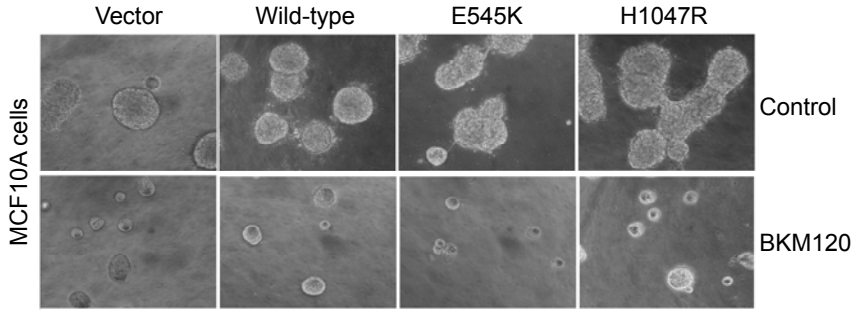
PIK3CA (p110α) mutations are gain-of-function oncogenes

Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110α (*PIK3CA*)

John E. Burke, Olga Perisic, Glenn R. Masson, Oscar Vadas, and Roger L. Williams[1]

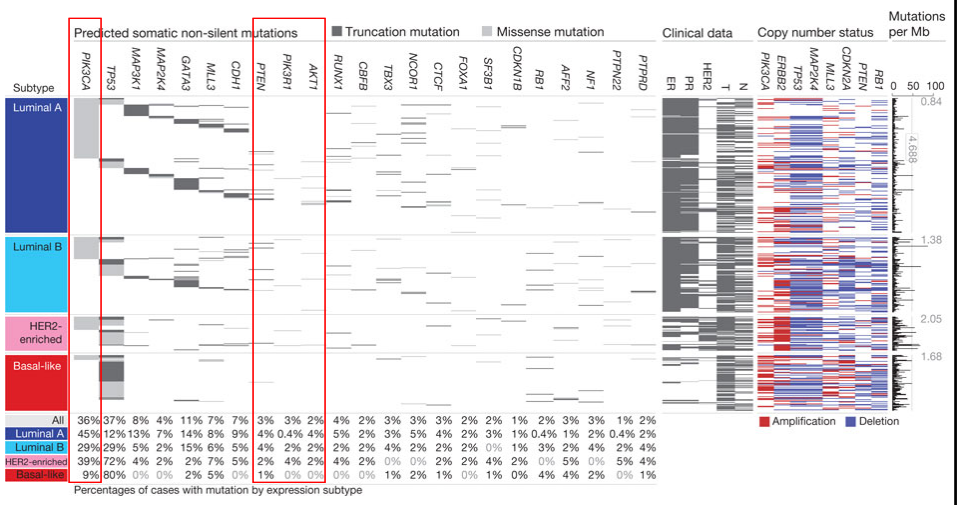
Laboratory of Molecular Biology, Medical Research Council, Cambridge CB2 0QH, United Kingdom

PNAS 109:15259-64, 2012



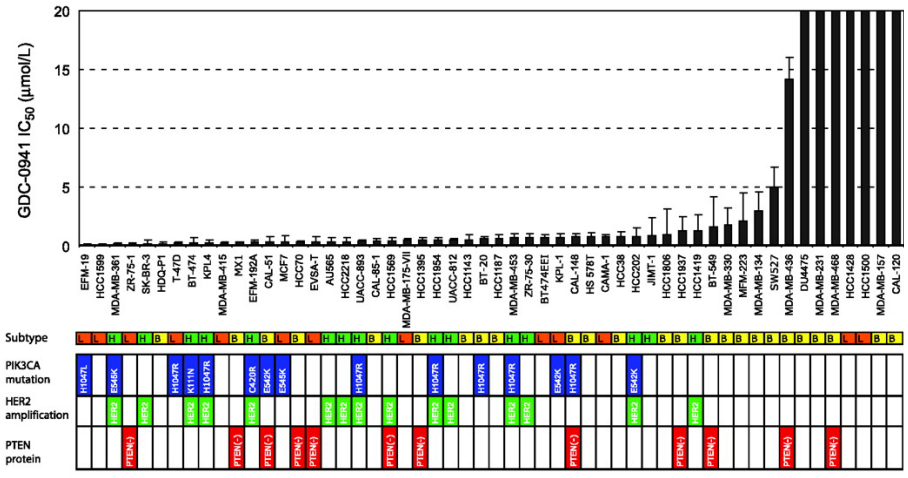
Chakrabarty *et al. Oncogene* 2010

TCGA: PI3K pathway mutations are the most common somatic alterations in breast cancer, particularly in ER+ tumors



DC Koboldt *et al. Nature* 000, 1-10 (2012) doi:10.1038/nature11412

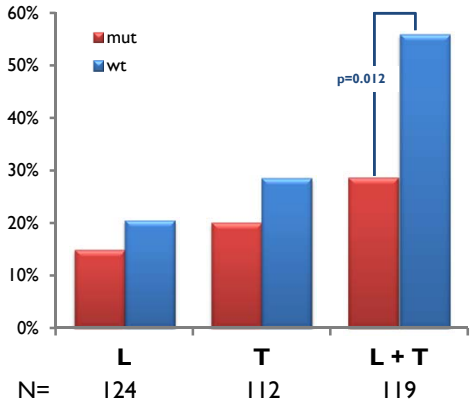
PIK3CA mutant and HER2-overexpressing br ca cells depend on p110α and are very sensitive to PI3K inhibitors



O'Brien *et al. Clin. Cancer Res.* 16:3670, 2010

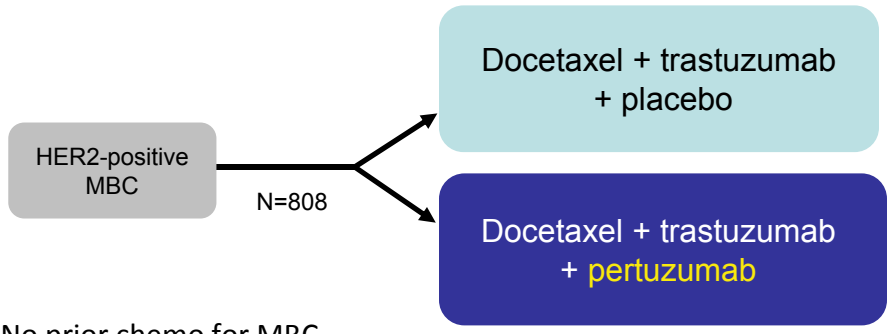
PIK3CA mutations are associated with resistance to anti-HER2 therapies (Neo-ALTTO)

- For each treatment arm, the pCR rate was lower for patients with a PIK3CA mutation
- The difference was statistically significant in the combination arm



Baselga *et al.* ECCO 2013

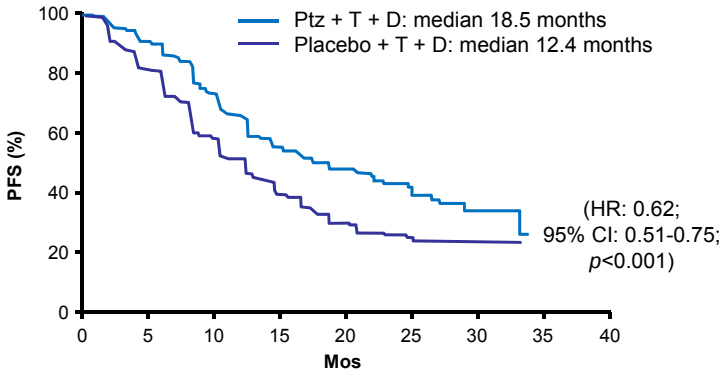
CLEOPATRA: Phase III Trial of Docetaxel + Trastuzumab vs. Docetaxel + Trastuzumab + Pertuzumab



- No prior chemo for MBC
- 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

CLEOPATRA: Combination of trastuzumab and pertuzumab is superior to trastuzumab



Ptz + T+ D	402	345	267	139	83	32	10	0	0
Pbo + T + D	406	311	209	93	42	17	7	0	0

Baselga *et al. NEJM* 366:109, 2012

Shorter median PFS observed with mutated *PIK3CA* while treatment effect is maintained

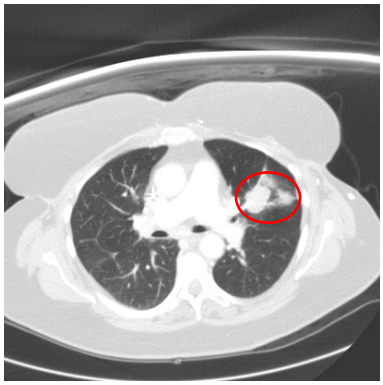
	Pla+T+D			Ptz+T+D			
PIK3CA status	Patients, n	Events	Median, months	Patients, n	Events	Median, months	HR (95% CI)
Mut	90	63	8.6	86	45	12.5	0.64 (0.43, 0.93)
WT	191	101	13.8	190	83	21.8	0.67 (0.50, 0.89)
Overall	406	242	12.4	402	191	18.5	0.62 (0.51, 0.75)

- The prognostic impact of *PIK3CA* mutations cannot be attributed to a specific mutation, nor to mutation(s) in a specific exon, based on the available dataset
  - 182 mutations detected overall (32%)
    - Exon 7: 12; exon 9: 39; exon 20: 131

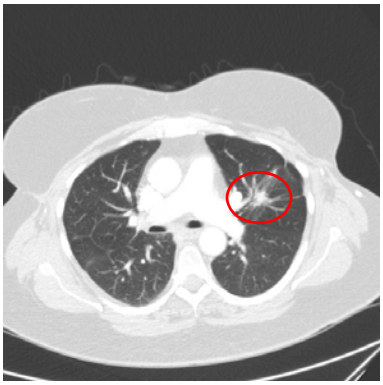
Mut, mutated; WT, wild-type

Prolonged complete response to PI3K inhibitor XL147 + trastuzumab (HER2/PIK3CA^{H1047R} breast cancer)

Baseline

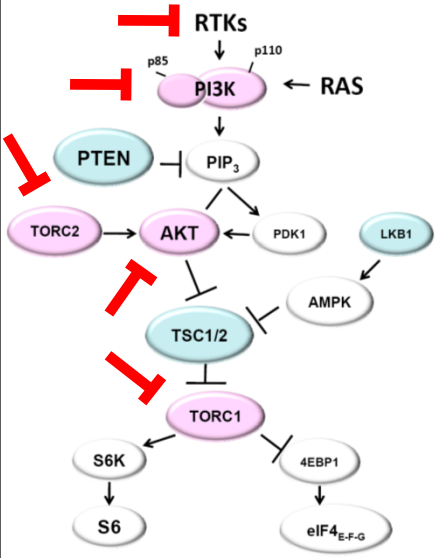


After Cycle 6



Previously treated with chemotherapy (adjuvant), trastuzumab, lapatinib, and T-DM1; this was 6th line of therapy for metastatic disease

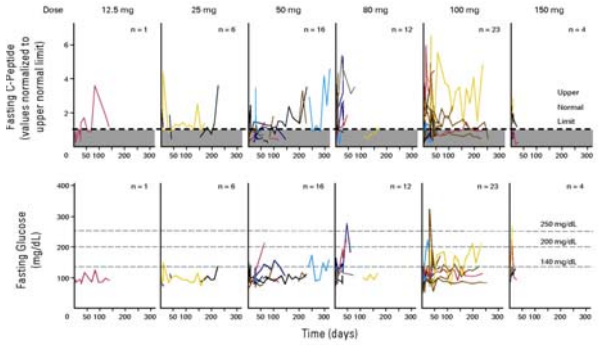
PI3K pathway inhibitors



Drug	Source	Target(s)
BYL719	Novartis	PI3Kα
GDC-0032	Genentech	PI3Kα
MLN-1117	Millenium	PI3Kα
Idelalisib	Calistoga	PI3Kδ
XL-147	Exelixis/Sanofi	Pan-PI3K
Buparlisib	Novartis	Pan-PI3K
GDC-0941	Genentech	Pan-PI3K
PKI-587	Pfizer	Pan-PI3K
XL-765	Exelixis/Sanofi	PI3K/mTOR
BEZ235	Novartis	PI3K/mTOR
GDC-0980	Genentech	PI3K/mTOR
PF-4691502	Pfizer	PI3K/mTOR
MLN-128	Millenium	TORC1/2
CC-223	Celgene	TORC1/2
AZD2014	AstraZeneca	TORC1/2
AZD5363	AstraZeneca	AKT (catalytic)
MK-2206	Merck	AKT (allosteric)
GDC-0068	Genentech	AKT (catalytic)

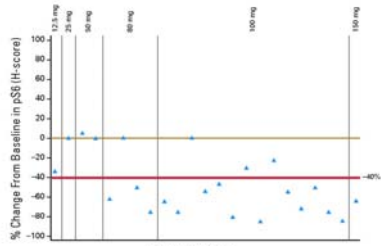
- What is the best approach to effectively inhibit the PI3K/AKT/TOR pathway?
  - The way this pathway is regulated suggests a combination of inhibitors will be necessary

Treatment with pan-PI3K inhibitor elevates circulating insulin levels



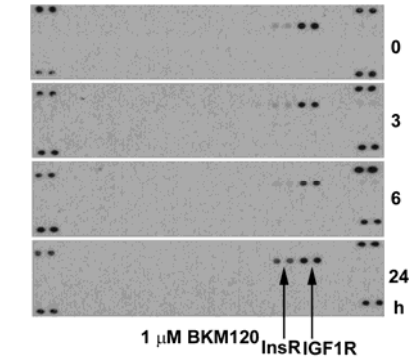
AKT stimulates GLUT4 in muscle and fat cells to allow clearance of glucose from serum

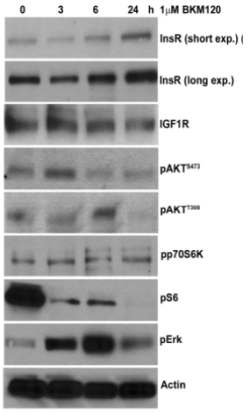
AKT stimulates glucose storage as gycogen in the liver



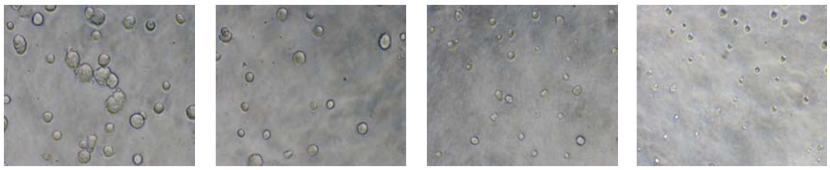
Bendell J C et al. JCO 2012;30:282-290

Pan-PI3K inhibitor induces upregulation of total and P-InsR in ER+ breast cancer cells

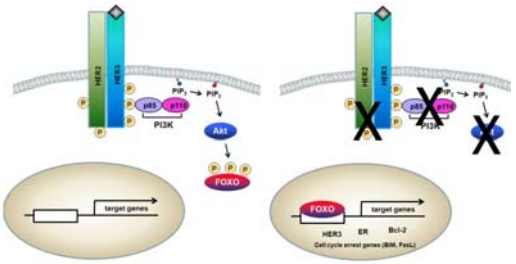




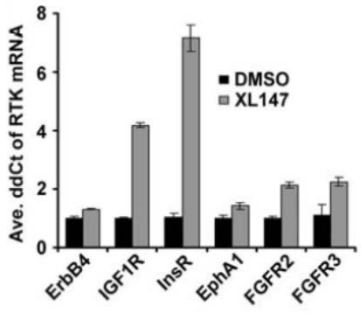
Control | InsR siRNA | BKM120 | BKM + InsR siRNA

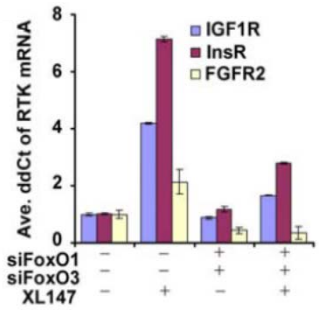


Inhibition of PI3K/AKT reactivates RTKs, ERα, BCL2



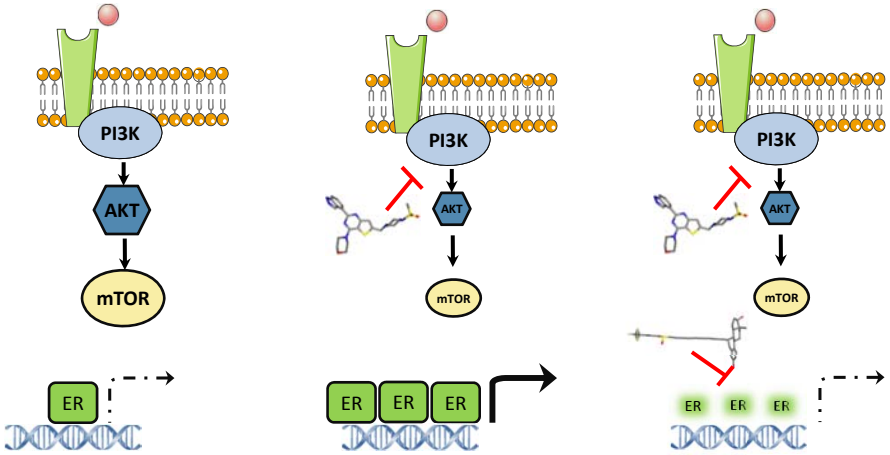
BT474



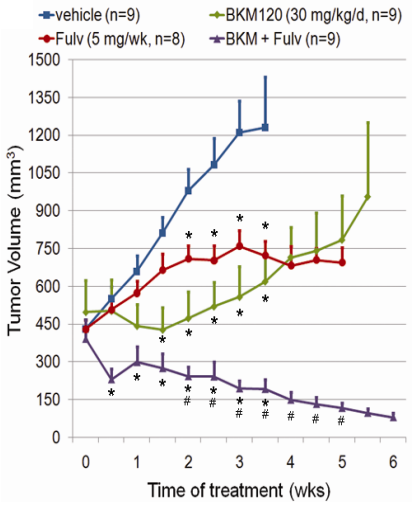


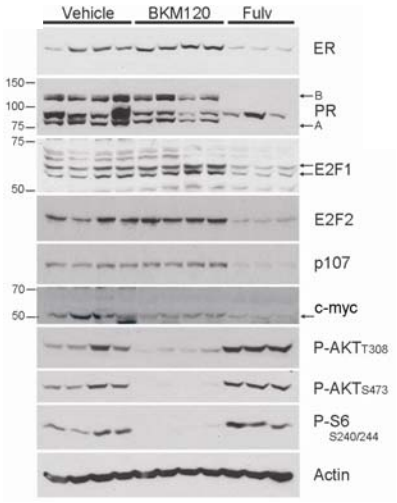
Chakrabarty *et al. PNAS* 109:2718-23, 2012

ER levels and function increase upon inhibition of PI3K/AKT: A rationale for combination therapy



Combined inhibition of ER and PI3K induces complete regressions of ER+/PIK3CA-mutant br ca xenografts





Miller *et al. Cancer Discovery* 1:338, 2011

Single-agent BKM120 (buparlisib) MTD defined as 100 mg/day

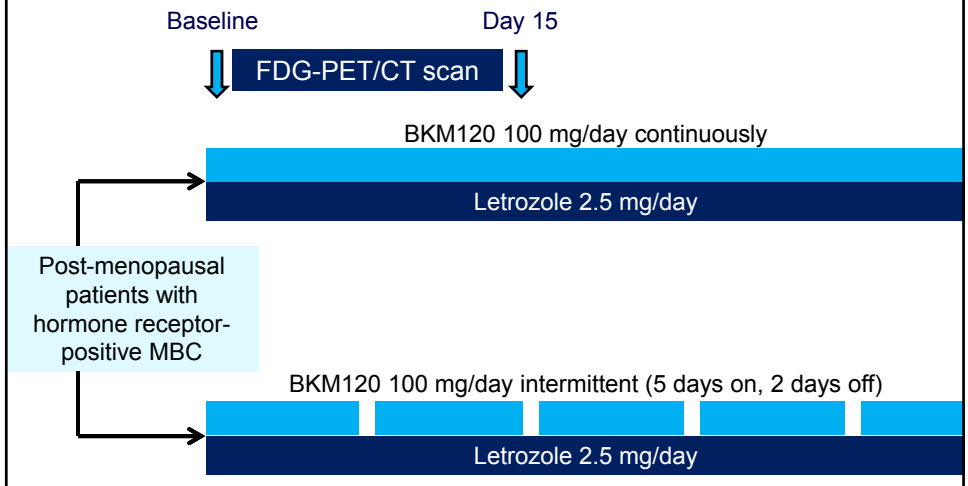
- Phase 1A, dose-escalation study of single-agent buparlisib in advanced solid tumors (NCT01068483)[1]
  - Single-agent MTD defined as 100 mg/day
- Subanalysis of patients with mBC (n = 21)
  - Single-agent buparlisib well tolerated at doses of 12.5–150 mg/day[1]
  - Few patients had grade 3/4 AEs
  - Most frequent treatment-related (≥10%) grade 3 AEs: fatigue/asthenia, elevated transaminases, hyperglycemia and diarrhea
  - The only treatment-related grade 4 AE was hyperglycemia
    - Observed in one patient at 150 mg/day
  - All-grade mood disorders were reported
  - No patient experienced QTc prolongation

Treatment-related AEs (≥10%) in mBC

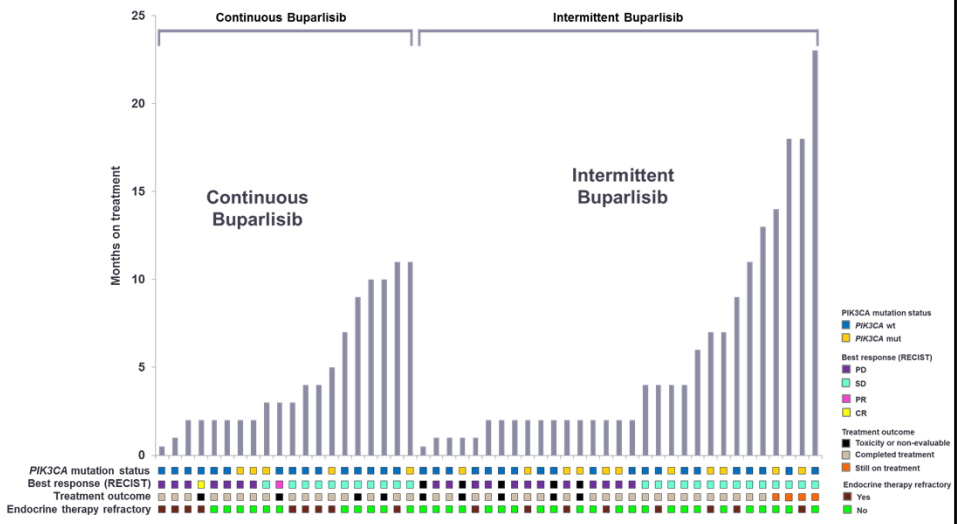
Preferred term, n (%)	All patients n=21	
	All-grade	Grade 3
Nausea	9 (43)	0
Fatigue/asthenia	9 (43)	3 (14)
Anxiety	8 (38)	1 (5)
Diarrhea	8 (38)	2 (10)
Hyperglycemia	7 (33)	2* (10)
Rash	7 (33)	1 (5)
Decreased appetite	6 (29)	0
Depression	6 (29)	0
Pruritus	6 (29)	1 (5)
Stomatitis	5 (24)	0
Affective disorder	4 (19)	1 (5)
Increased AST	4 (19)	1 (5)
Increased transaminases	4 (19)	3 (14)
Abdominal pain	3 (14)	0
Increased	3 (14)	0
Irritability	3 (14)	0
Tremor	3 (14)	0
Vomiting	3 (14)	0

*One additional patient had Grade 4 hyperglycemia.
AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; mBC, metastatic breast cancer; MTD, maximum-tolerated dose.
1. Rodon J, *et al. SABCS* 2011; abstr P3-16-01.

Letrozole + BKM120 (Ingrid Mayer, PI)

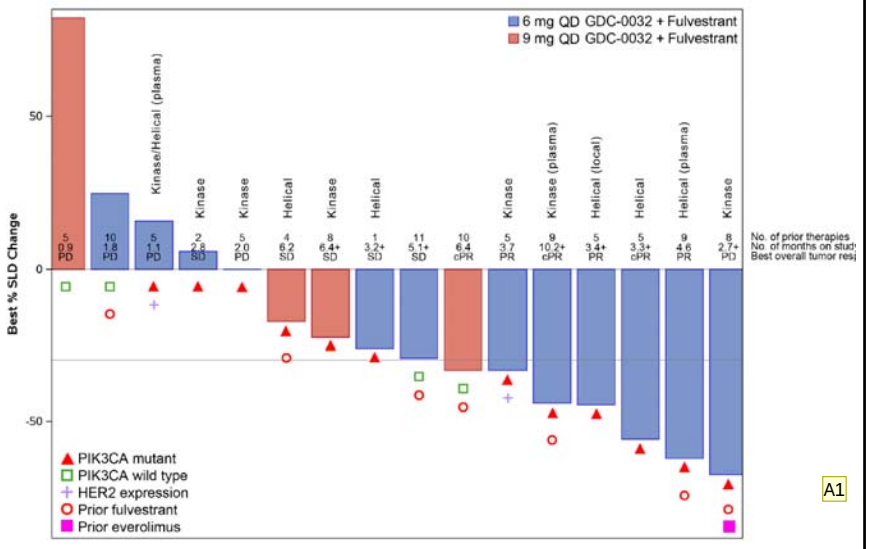


Clinical benefit from PI3K inhibitors does not correlate with presence of PIK3CA hot spot mutations



Mayer I, *et al. J Clin Oncol*. 2014 Mar 24. [Epub ahead of print]

Anti-tumor activity of PI3Kα inhibitor GDC-0032 in combination with fulvestrant



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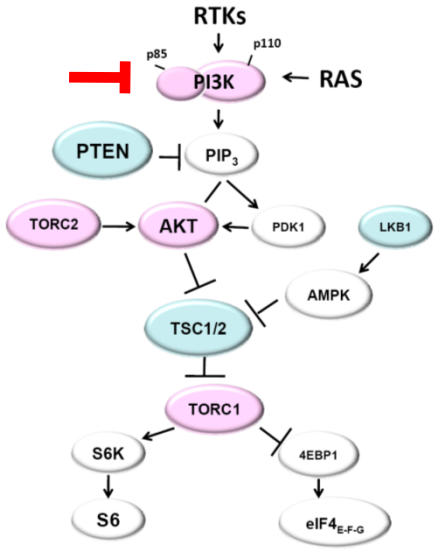
Juric D…Baselga J. SABCS 2013. Abstract PD1-3.

Slide 22

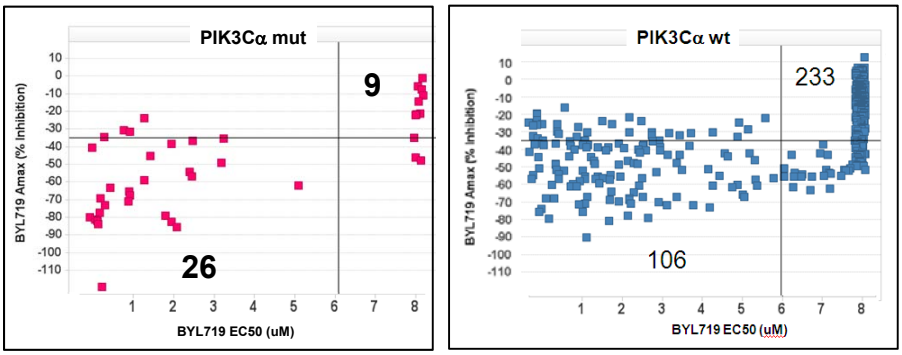
A1 Do we have any other info for this reference?
Author, 5/28/2014

PI3K pathway inhibitors



Drug	Source	Target(s)
BYL719	Novartis	PI3Kα
GDC-0032	Genentech	PI3Kα
MLN-1117	Millenium	PI3Kα
Idelalisib	Calistoga	PI3Kδ
XL-147	Exelixis/Sanofi	Pan-PI3K
Buparlisib	Novartis	Pan-PI3K
GDC-0941	Genentech	Pan-PI3K
PKI-587	Pfizer	Pan-PI3K
XL-765	Exelixis/Sanofi	PI3K/mTOR
BEZ235	Novartis	PI3K/mTOR
GDC-0980	Genentech	PI3K/mTOR
PF-4691502	Pfizer	PI3K/mTOR
MLN-128	Millenium	TORC1/2
CC-223	Celgene	TORC1/2
AZD2014	AstraZeneca	TORC1/2
AZD5363	AstraZeneca	AKT (catalytic)
MK-2206	Merck	AKT (allosteric)
GDC-0068	Genentech	AKT (catalytic)

PI3Kα (p110α)-specific inhibitor BYL719: *PIK3CA* mutation predicts sensitivity



***p*=1x10^{-6} by Fisher's Exact Test (two-tailed)**

- *PIK3CA* mutation/amplification (but not PTEN loss) is associated with sensitivity (lower IC_{50})
- HER2 amplification is also associated with sensitivity to BYL719

MTD of Single Agent BYL719 Defined as 400 mg/day

- Ph 1, open-label, dose escalation and expansion study of BYL719 in *PI3KCA*-altered advanced solid tumors (single-agent arm; NCT01219699)
- As of February 15, 2013, 102 patients had received BYL719
- Four (44%) patients had DLTs during dose escalation
  - All at BYL719 450 mg once-daily dose
- MTD of BYL719 QD declared as 400 mg/day
- Four (10%) patients had DLTs in the dose-expansion cohort
  - All were in the 400 mg once-daily cohort
- Five (29%) patients treated with twice-daily doses of BYL719 had DLTs
  - One (14%) at 150 mg and four (80%) patients at 200-mg dose

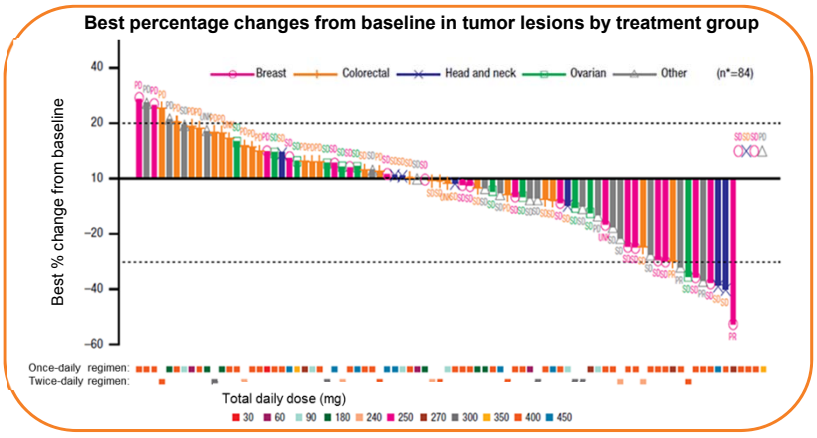
AEs (≥25%) suspected to be related to BYL719

AE, n (%)	All patients N=102
Hyperglycaemia	
All grade	50 (49)
Grade 3/4	25 (25)
Nausea	
All grade	44 (43)
Grade 3/4	3 (3)
Decreased appetite	
All grade	38 (37)
Grade 3/4	2 (2)
Diarrhea	
All grade	36 (35)
Grade 3/4	3 (3)
Rash and hypersensitivity	
All grade	35 (34)
Grade 3/4	8 (8)
Asthenia and fatigue	
All grade	35 (34)
Grade 3/4	2 (2)
Vomiting	
All grade	28 (28)
Grade 3/4	2 (2)

AE, adverse event; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha.
Data cut-off: February 15, 2013.
Gonzalez-Angulo AM, *et al. ASCO* 2013. #2531.

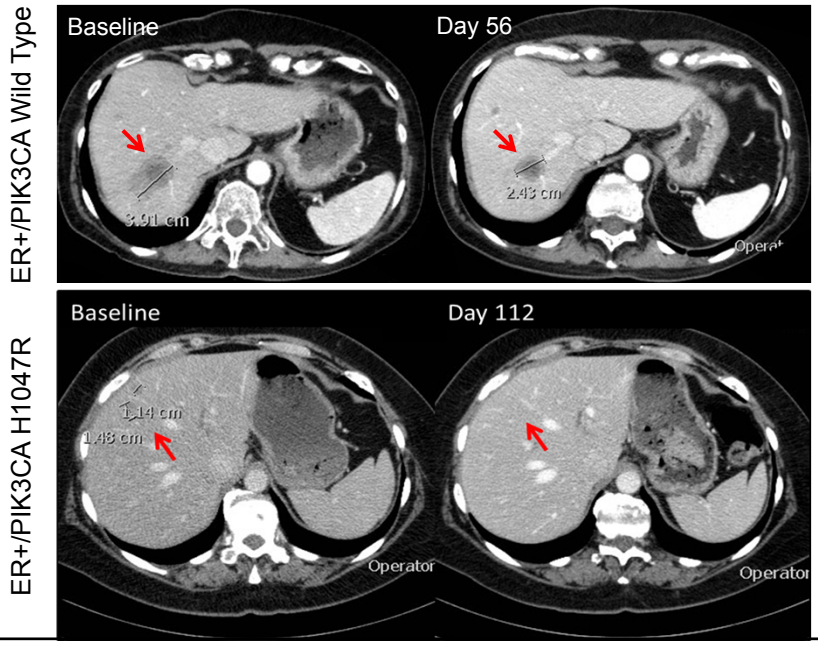
Single agent p110α-specific inhibitor BYL719 is active against PIK3CA mutant cancers

- PRs were observed in nine (9%) patients treated at ≥270 mg/day
  - Four confirmed PRs: one at 270 mg once daily in a patient with breast cancer
  - Five unconfirmed PRs: one at 400 mg once daily in ER+ breast cancer

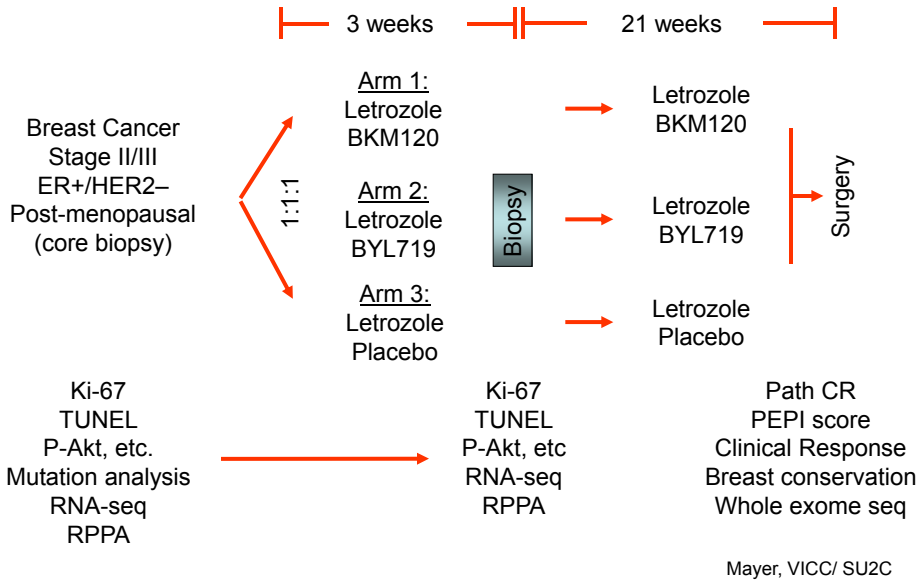


Gonzalez-Angulo AM, *et al. ASCO* 2013. #2531.

PI3Kα inhibitor BYL719 + letrozole induce partial responses in breast cancers with either WT or mutant PIK3CA

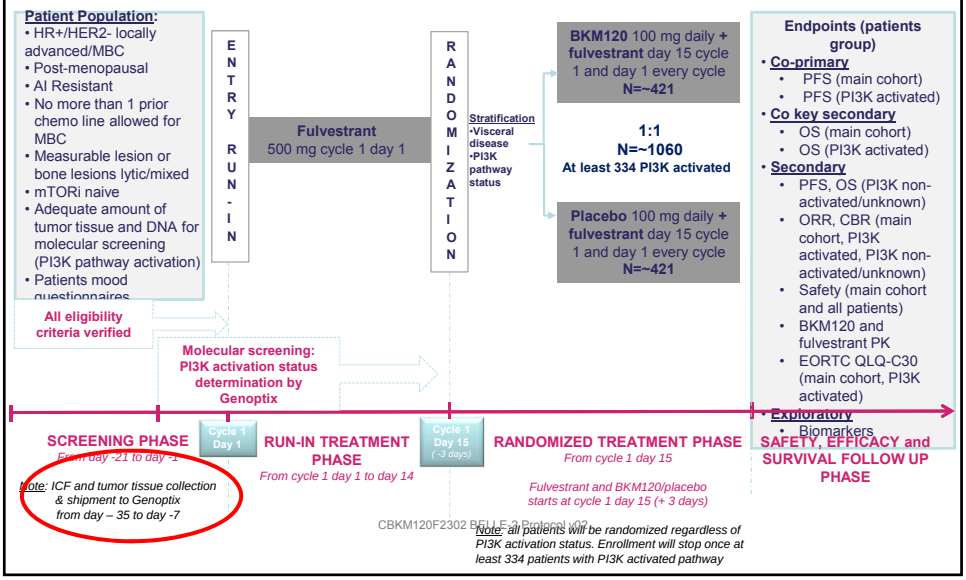


A phase II neoadjuvant trial of letrozole ± pan-PI3K inhibitor BKM120 or PI3Kα inhibitor BYL719 in patients with operable ER+ breast cancer

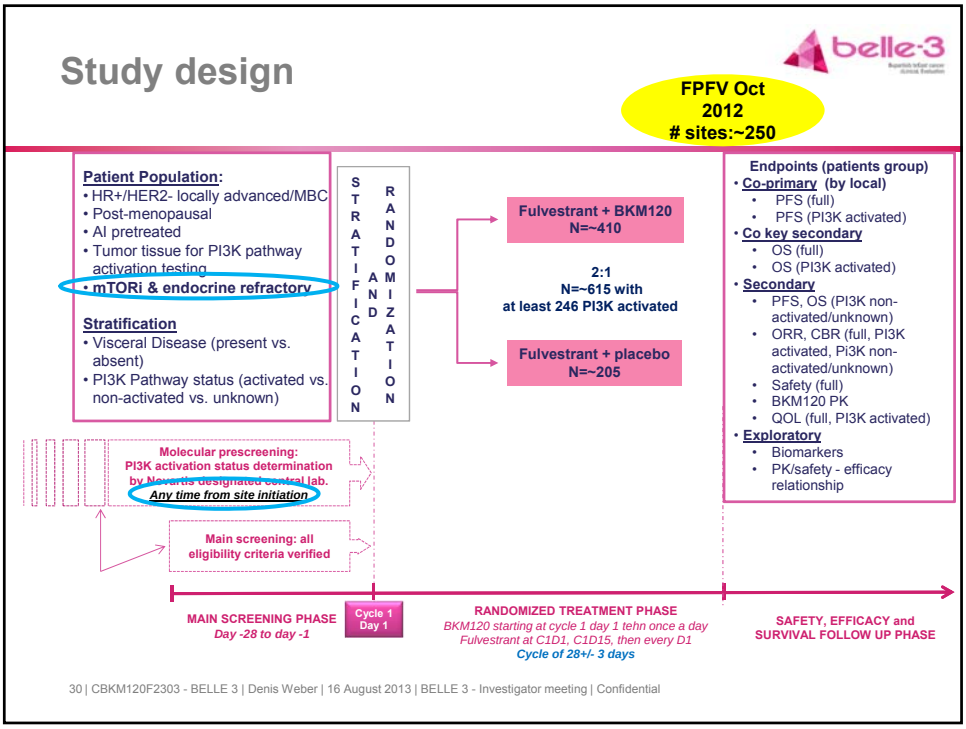


Mayer, VICC/ SU2C

CBKM120F2302 – BELLE-2
Study design overview



Study design



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

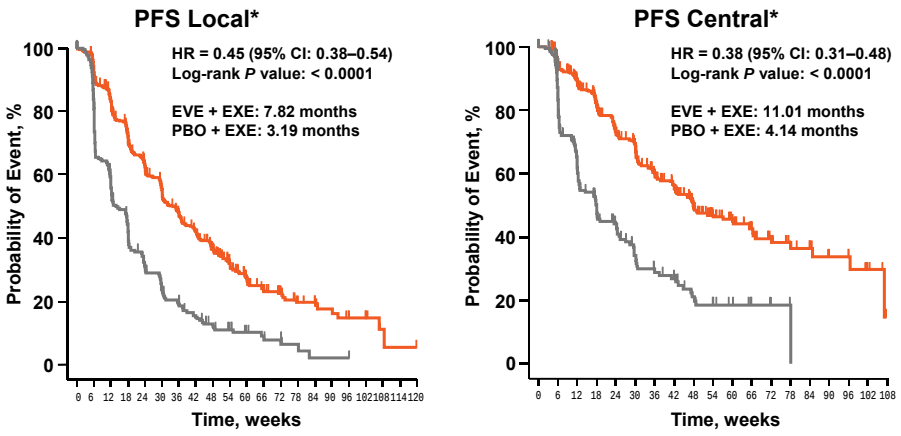
Placebo 10 mg PO daily + Exemestane 25 mg PO daily n = 239

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

- **Key Baseline Characteristics**

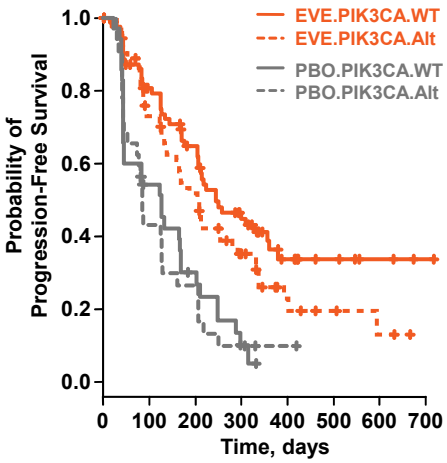
Median age, years	62
Race, %	
Caucasian	75
Asian	20
Visceral involvement, %	56
Bone metastases, %	77

BOLERO-2 Efficacy: Addition of Everolimus (EVE) to Exemestane (EXE) More Than Doubled Median PFS



Final PFS Analysis: 18-month Median Follow-up

BOLERO-2: Benefit from everolimus is maintained in regardless of PIK3CA mutations



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%)	

Hortobagyi GN, et al. *J Clin Oncol.* 2013;31(suppl): Abstract LBA509.

Clinical Implications

- It is likely PI3K inhibitors will be approved for the treatment of some subtype(s) of breast cancer in the next few years
- It is unclear whether pan-PI3K vs. isozyme specific inhibitors will be superior
- Clinical trials with PI3K inhibitors should at a minimum be enriched with patients with somatic alterations in the PI3K pathway
- In HER2+ and ER+ breast cancers, PI3K inhibitors should be used in combination with HER2-HER3 antagonists and antiestrogens, respectively