ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

PERSONALISED MEDICINE SYMPOSIUM

Distinctive features of the main classes:

mTOR, PI3K, dual inhibitors and AKT

Jordi **Rodon**

Sitges, Barcelona **28 February - 1 March 2014**

DISCLOSURE

I have served in Advisory Boards for Novartis and Lilly

OUTLINE

1. Introductory notes to the Pharmacology of the Pi3K pathway: **Family tree of PI3K-AKT-MTOR (PAM) inhibitors**
2. Personalized Medicine with PI3K pathway inhibitors? **Matching drug and genotype**.
3. **Drugs with unique properties.**

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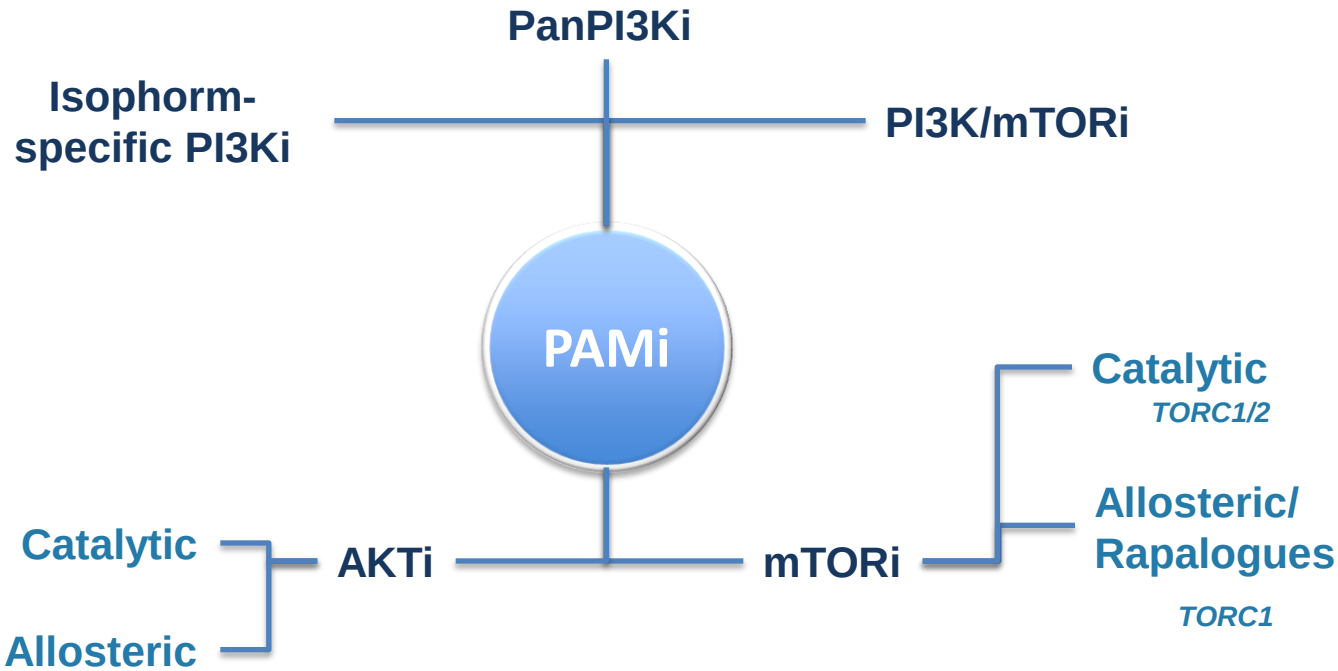
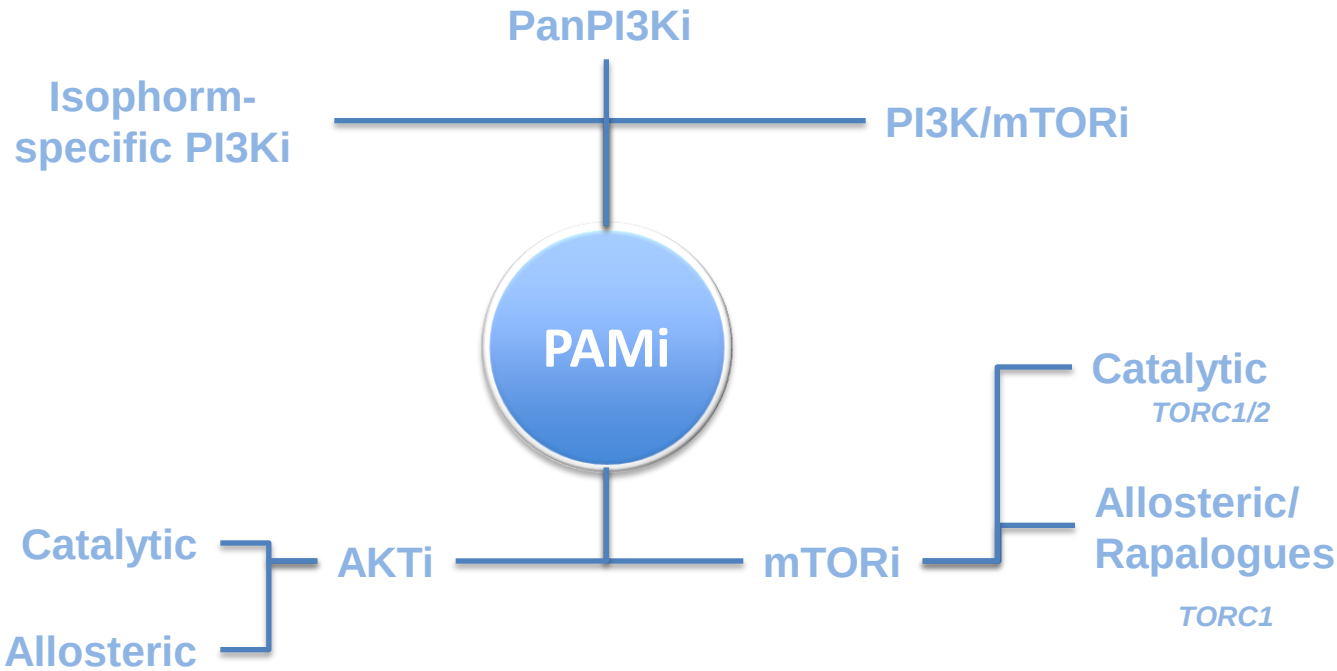
Family tree of PI3K-AKT-MTOR (PAM) inhibitors

- ESMO Signalling Pathways 2014

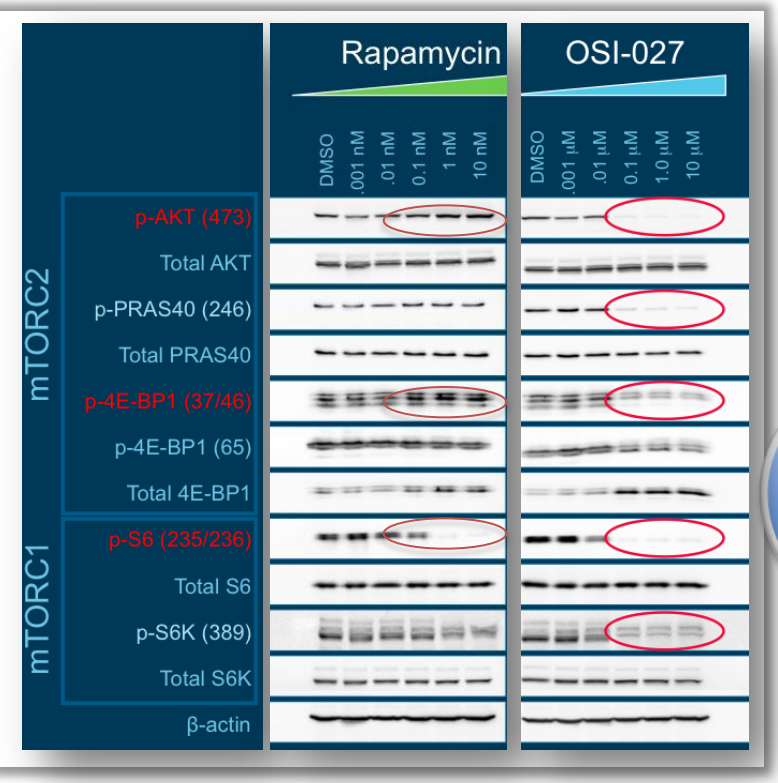


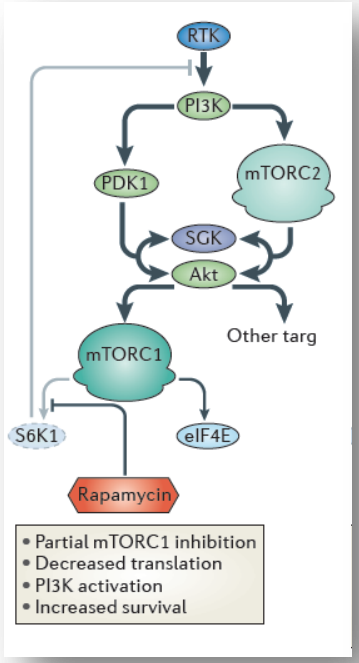
Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014

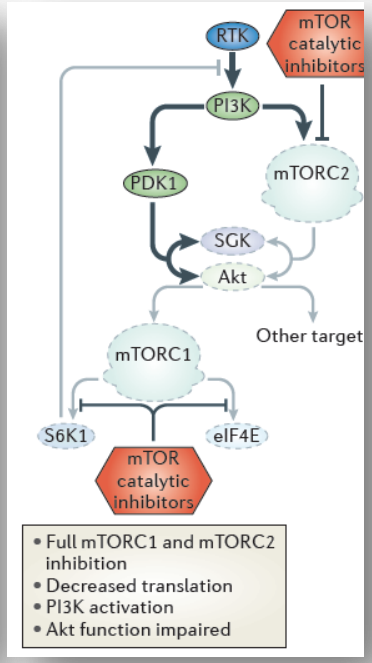


Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014

mTOR inhibitors







PAMi

mTORi

Catalytic
TORC1/2

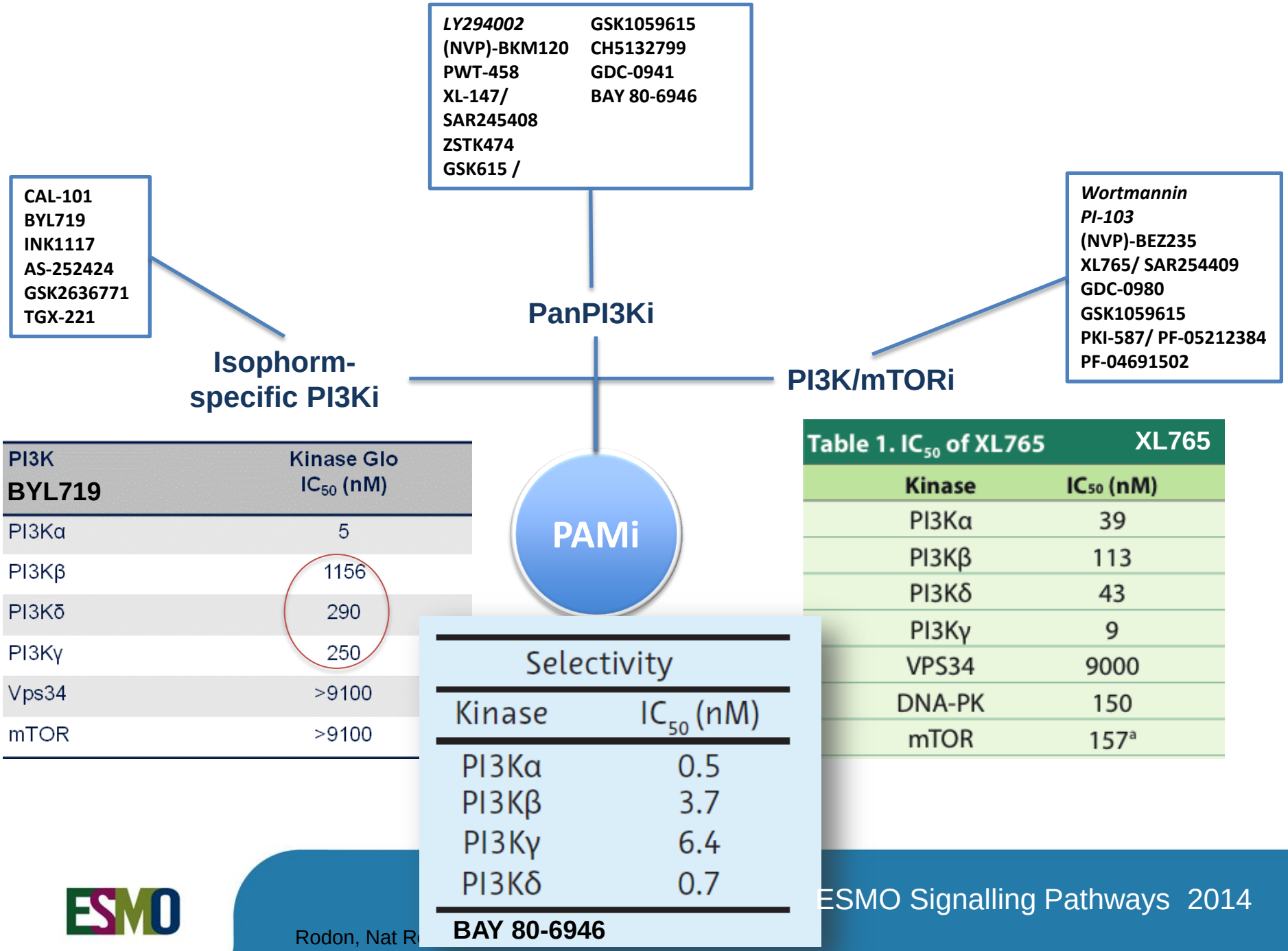
CC-115

AZD-8055
OSI-027
INK-128
PP-242
CC-223

Allosteric/ Rapalogues
TORC1

Rapamycin (Sirolimus)
CCI-779 (Temsirolimus)
RAD001 (Everolimus)
AP-23573 (Ridaforolimus)

Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014



PI3K BYL719	Kinase Glo IC_{50} (nM)
PI3Kα	5
PI3Kβ	1156
PI3Kδ	290
PI3Kγ	250
Vps34	>9100
mTOR	>9100

Selectivity	
Kinase	IC_{50} (nM)
PI3Kα	0.5
PI3Kβ	3.7
PI3Kγ	6.4
PI3Kδ	0.7

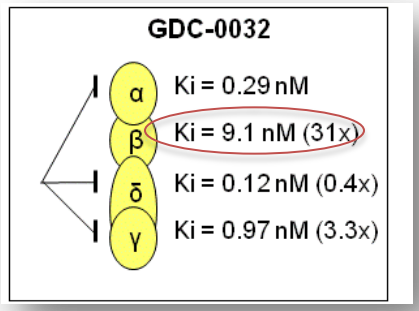
BAY 80-6946

Table 1. IC_{50} of XL765	XL765
Kinase	IC_{50} (nM)
PI3Kα	39
PI3Kβ	113
PI3Kδ	43
PI3Kγ	9
VPS34	9000
DNA-PK	150
mTOR	157[a]

Rodon, Nat R
Fruman, Nat Rev Drug Disc, 2014

Comparison of selectivity of some PI3K Inhibitors

Drug	p110α	p110β	p110δ	p110γ
BEZ235 (NVP-BEZ235, Dactolisib)	+	+	+	+
GDC-0941	+	+	+	+
ZSTK474	++	++	++	++
XL147	+			
TGX-221		+++		
GSK1059615	++++	++++	+++	+++
AZD6482	+	+	+	+
SAR245409 (XL765)	+	+	+	+
CAL-101 (Idelalisib, GS-1101)			+	
BKM120 (NVP-BKM120, Buparlisib)	+++	++	++	+
PF-05212384 (PKI-587)	++++			+++
GSK2126458 (GSK458)	+	+	+	+
GDC-0980 (RG7422)	+	+	+	+
CH5132799	+++	++	++	+++
PKI-402	+++	+++	++	++
PF-04691502	+++	+++	+++	+++
BAY 80-6946 (Copanlisib)	+	+		
GSK2636771		+		



PX-866: Irreversible PI3Ki

SF1126: Vascular Targeted Pan-PI3K/mTOR Inhibitor linked to an integrin-binding component

GDC0032

"Isophorm selective"

PanPI3Ki

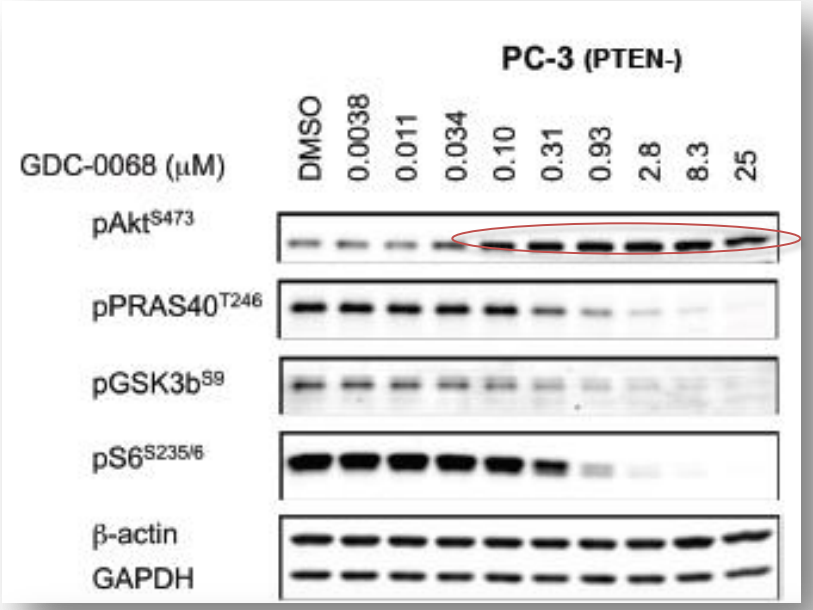
Isophorm-specific PI3Ki

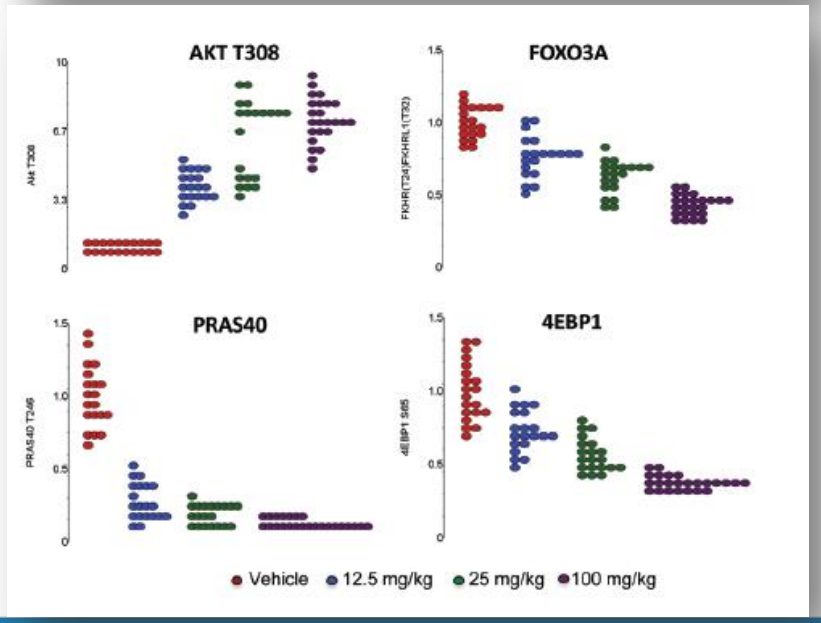
PI3K/mTORi

PAMi

Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014

AKT inhibitors



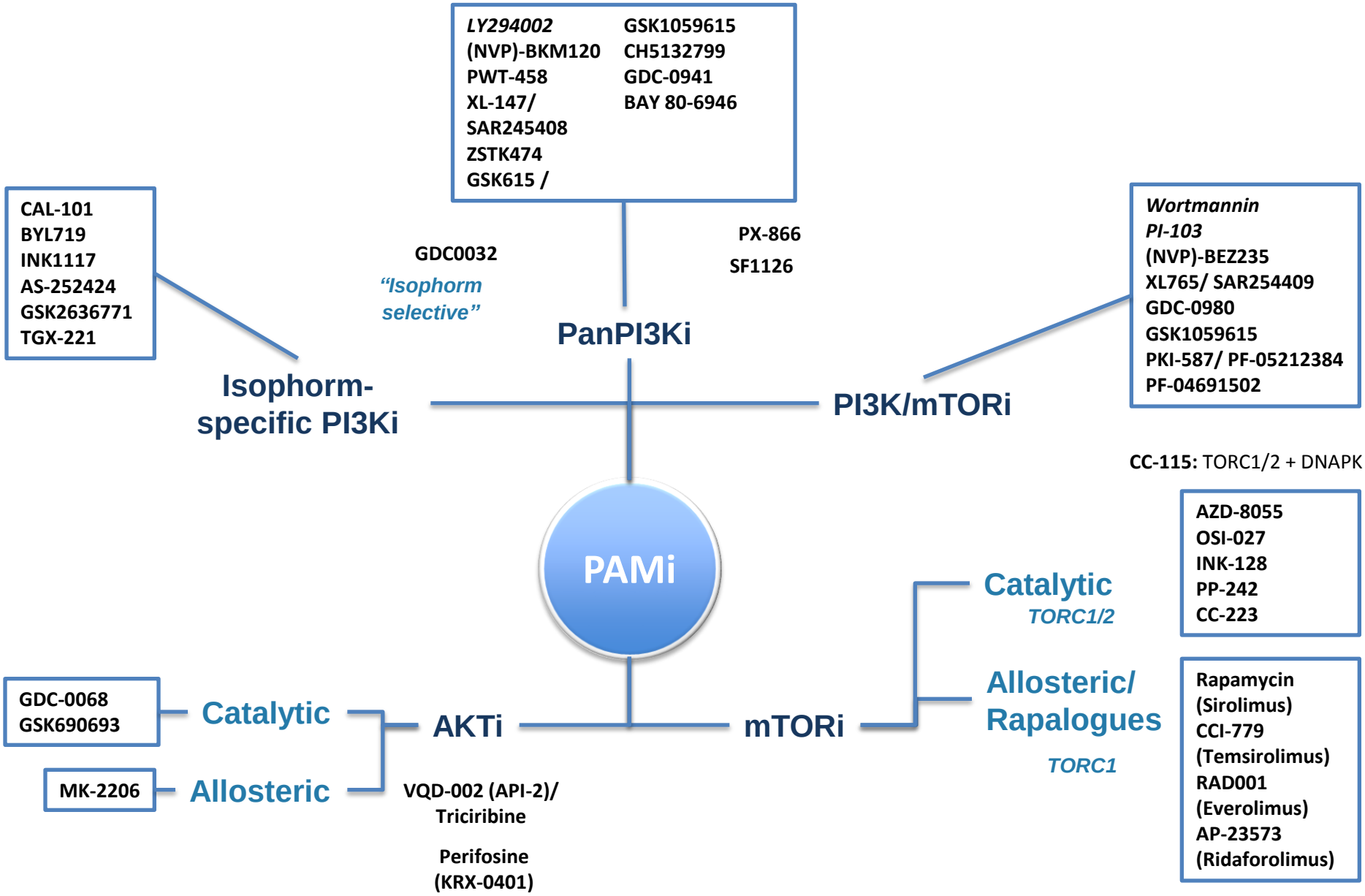


PAMi

AKTi

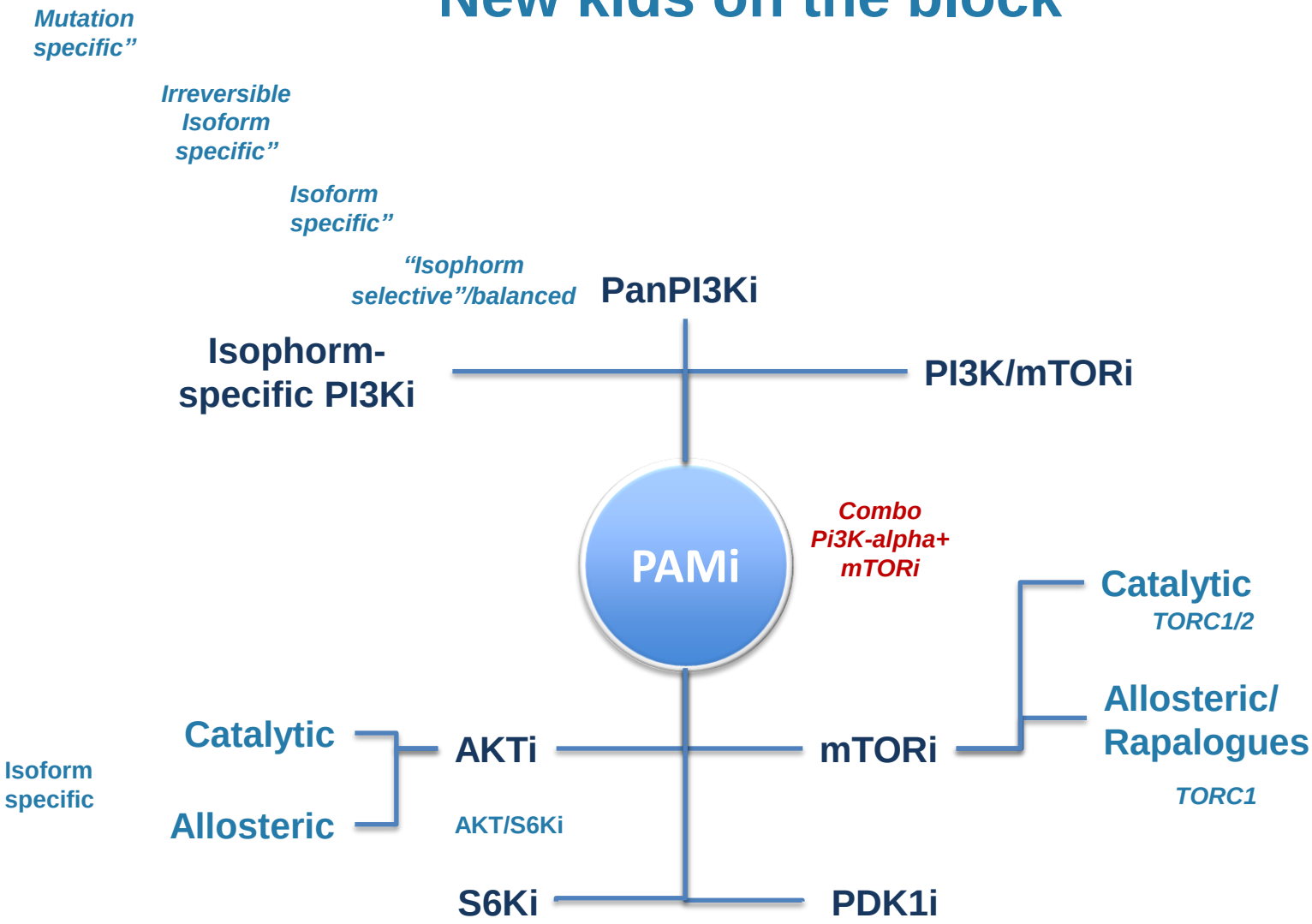
- Catalytic
  - GDC-0068
  - GSK690693
- Allosteric
  - MK-2206

Dose-dependent increase in a non-signaling hyper phosphorylated AKT (S473 and T308), and subsequent decrease in phosphorylated downstream targets



Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014

New kids on the block



Rodon, Nat Rev Clincal Oncol, 2013
Fruman, Nat Rev Drug Disc, 2014

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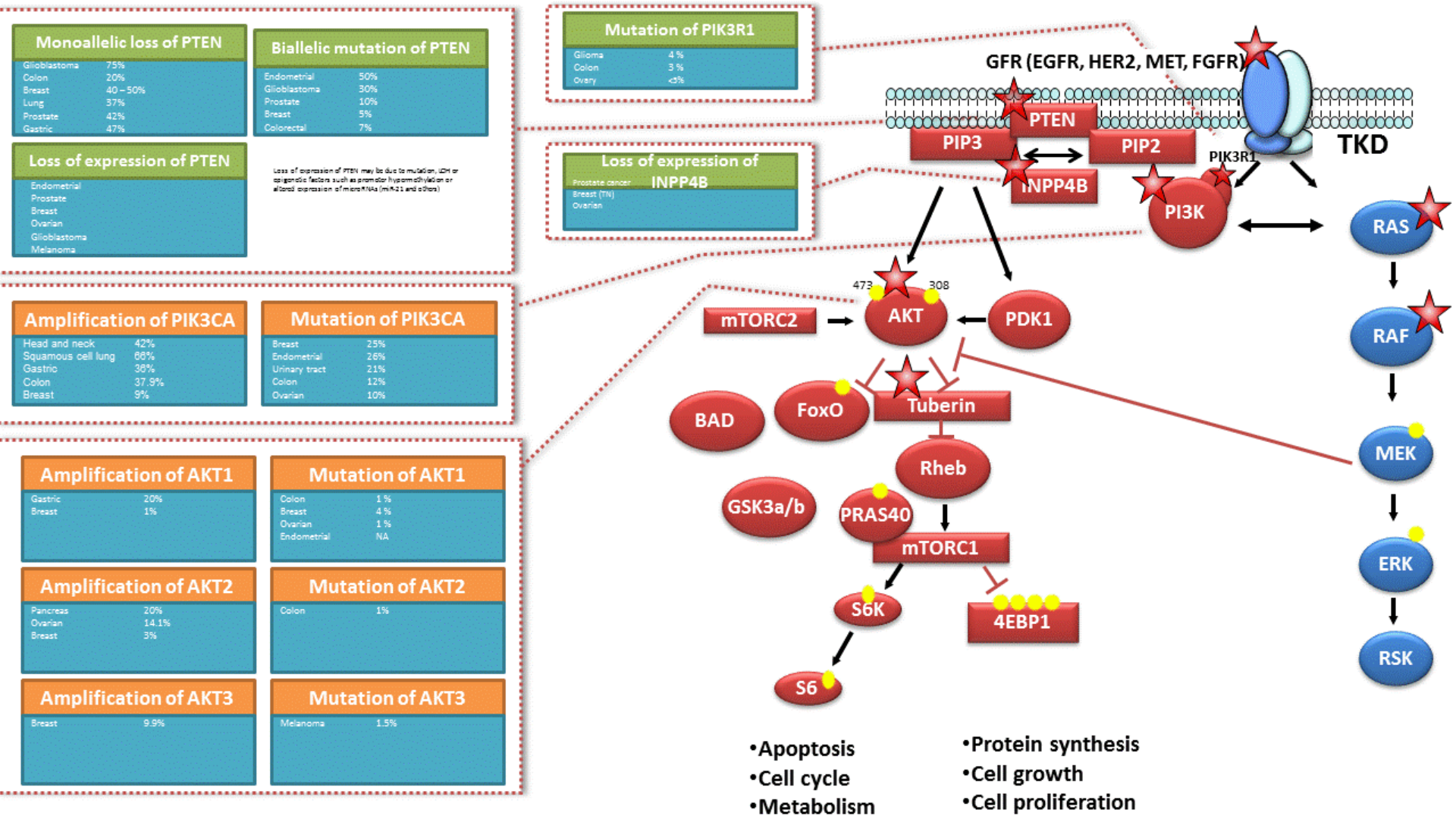
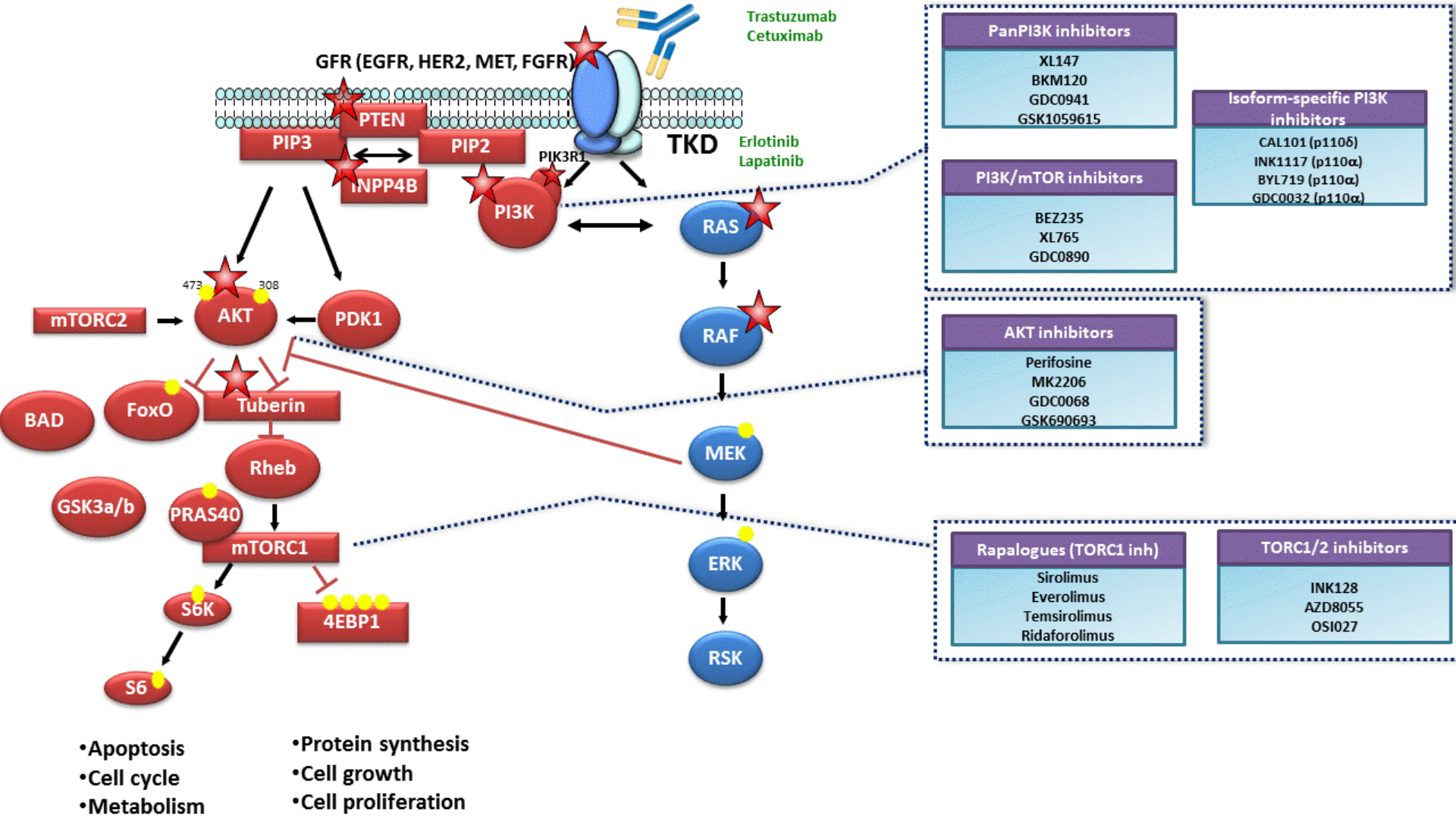
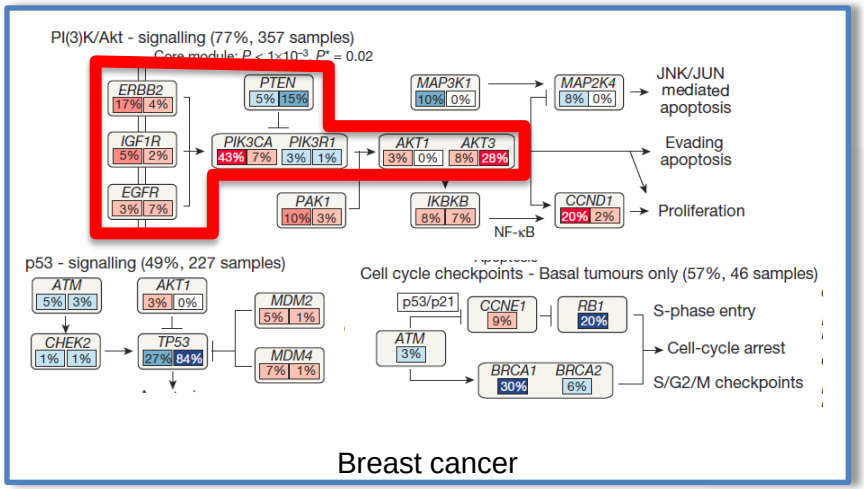
Matching Drug and Genotype?

- ESMO Signalling Pathways 2014

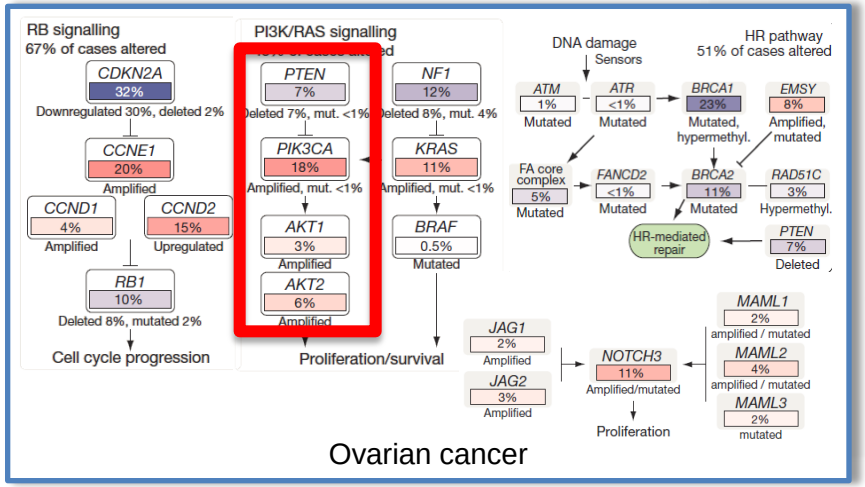

Monoallelic loss of PTEN
Glioblastoma 75%
Colon 20%
Breast 40 – 50%
Lung 37%
Prostate 42%
Gastric 47%
Biallelic mutation of PTEN
Endometrial 50%
Glioblastoma 30%
Prostate 10%
Breast 5%
Colorectal 7%
Loss of expression of PTEN
Endometrial
Prostate
Breast
Ovarian
Glioblastoma
Melanoma
Loss of expression of PTEN may be due to mutation, LOH or epigenetic factors such as promotor hypermethylation or altered expression of microRNAs (miR-21 and others)
Mutation of PIK3R1
Glioma 4 %
Colon 3 %
Ovary <3%
Loss of expression of INPP4B
Prostate cancer
Breast (TN)
Ovarian
Amplification of PIK3CA
Head and neck 42%
Squamous cell lung 66%
Gastric 36%
Colon 37.9%
Breast 9%
Mutation of PIK3CA
Breast 25%
Endometrial 26%
Urinary tract 21%
Colon 12%
Ovarian 10%
Amplification of AKT1
Gastric 20%
Breast 1%
Mutation of AKT1
Colon 1 %
Breast 4 %
Ovarian 1 %
Endometrial NA
Amplification of AKT2
Pancreas 20%
Ovarian 14.1%
Breast 3%
Mutation of AKT2
Colon 1%
Amplification of AKT3
Breast 9.9%
Mutation of AKT3
Melanoma 1.5%
GFR (EGFR, HER2, MET, FGFR)
PTEN
PIP3
PIP2
INPP4B
PIK3R1
TKD
PI3K
RAS
RAF
MEK
ERK
RSK
473
308
mTORC2
AKT
PDK1
BAD
FoxO
Tuberin
Rheb
GSK3a/b
PRAS40
mTORC1
S6K
4EBP1
S6
•Apoptosis
•Cell cycle
•Metabolism
•Protein synthesis
•Cell growth
•Cell proliferation


Trastuzumab
Cetuximab
GFR (EGFR, HER2, MET, FGFR)
PTEN
PIP3
PIP2
INPP4B
PIK3R1
TKD
Erlotinib
Lapatinib
PI3K
RAS
RAF
MEK
ERK
RSK
473
308
mTORC2
AKT
PDK1
BAD
FoxO
Tuberin
Rheb
GSK3a/b
PRAS40
mTORC1
S6K
4EBP1
S6
PanPI3K inhibitors
XL147
BKM120
GDC0941
GSK1059615
Isoform-specific PI3K inhibitors
CAL101 (p110δ)
INK1117 (p110α)
BYL719 (p110α)
GDC0032 (p110α)
PI3K/mTOR inhibitors
BEZ235
XL765
GDC0890
AKT inhibitors
Perifosine
MK2206
GDC0068
GSK690693
Rapalogues (TORC1 inh)
Sirolimus
Everolimus
Temsirolimus
Ridaforolimus
TORC1/2 inhibitors
INK128
AZD8055
OSI027
•Apoptosis
•Cell cycle
•Metabolism
•Protein synthesis
•Cell growth
•Cell proliferation

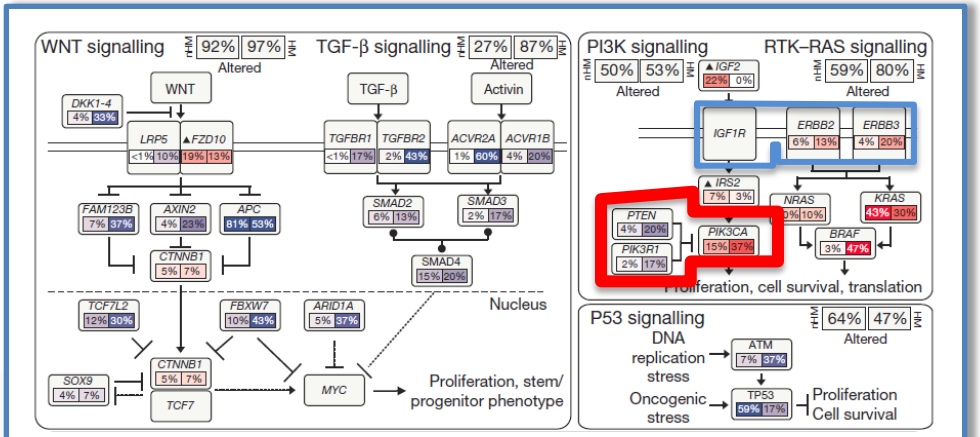
The Cancer Genome Atlas



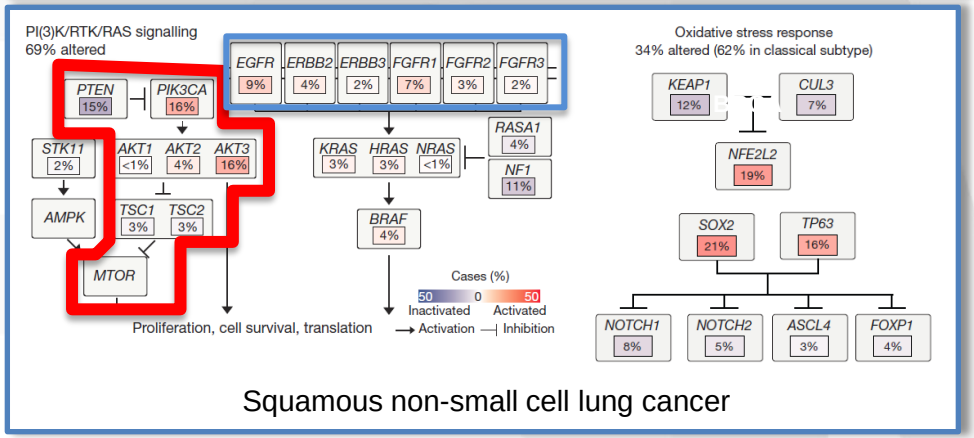
Breast cancer



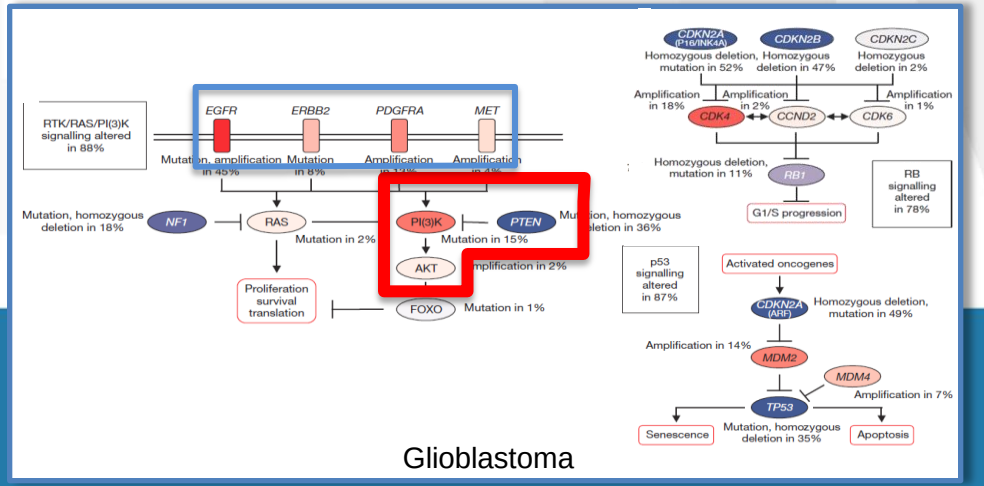
Ovarian cancer



Colorectal cancer



Squamous non-small cell lung cancer



Glioblastoma

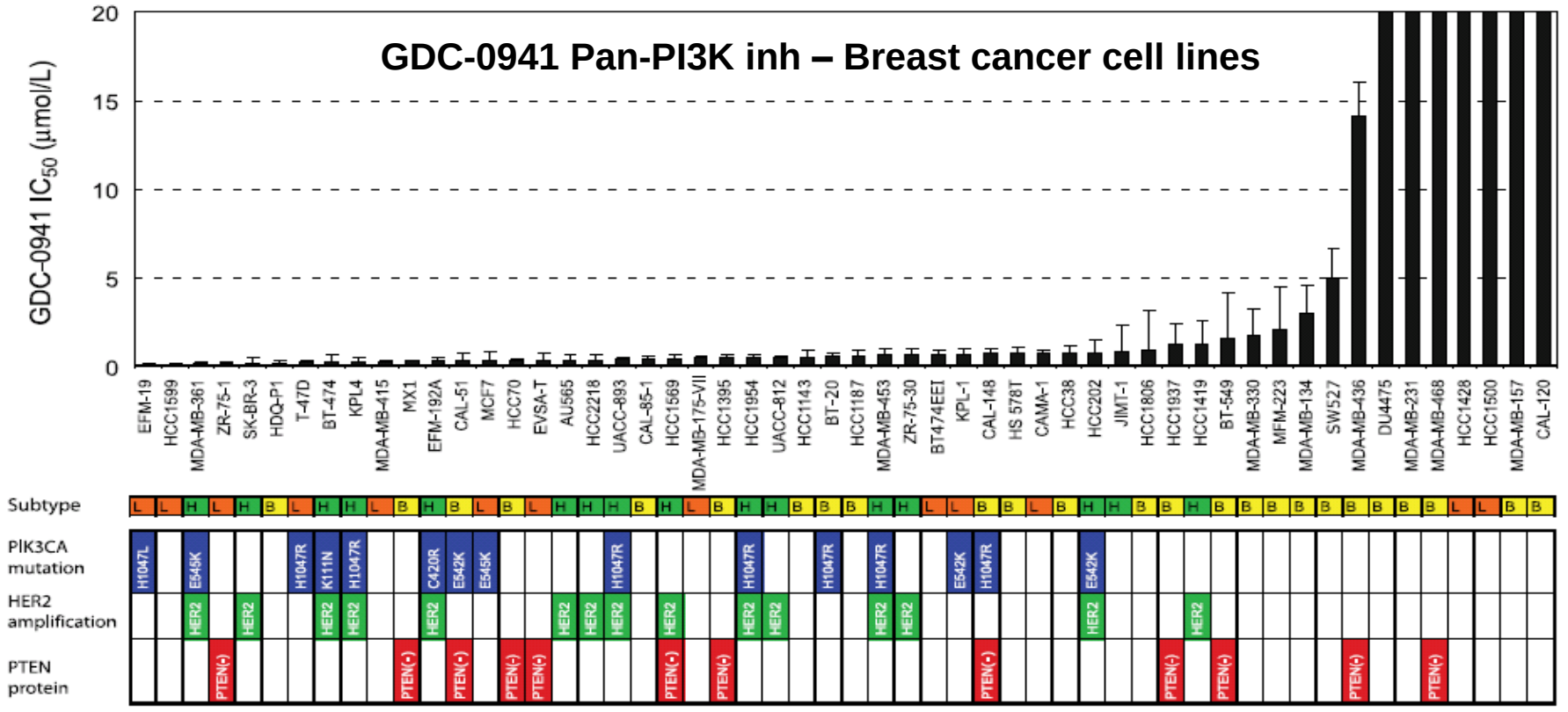
ESMO

Nature, October 2008
Nature, June 2011
Nature, July 2012
Nature, September 2012
Nature, October 2012

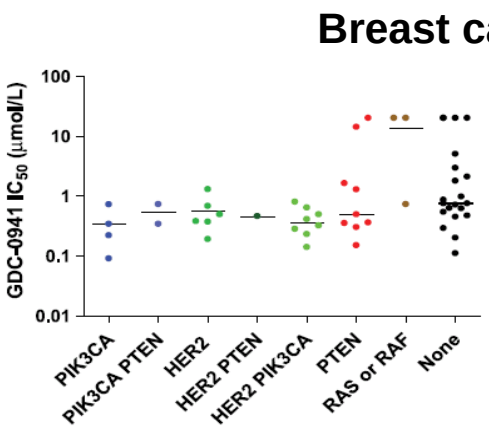
YES

Dienstmann, Molec Can Ther, 2014

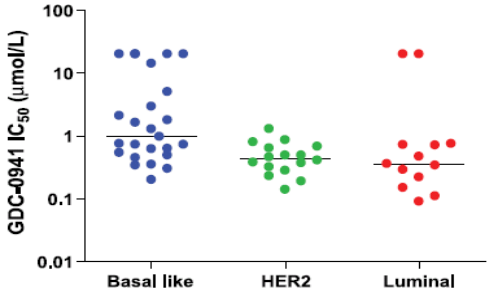
Predictors of sensitivity to pan-PI3K inhibitors



	α	β	δ	γ	mTOR
GDC-0941	+++	+++	+++	+++	-

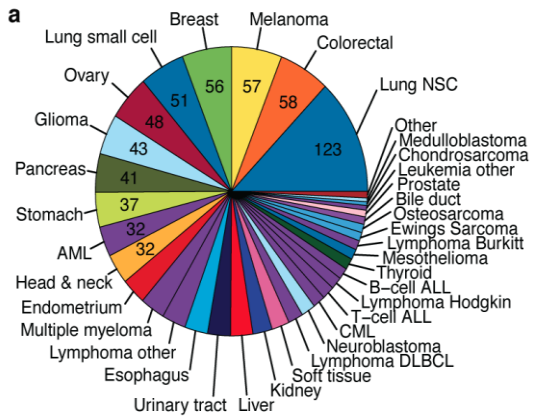


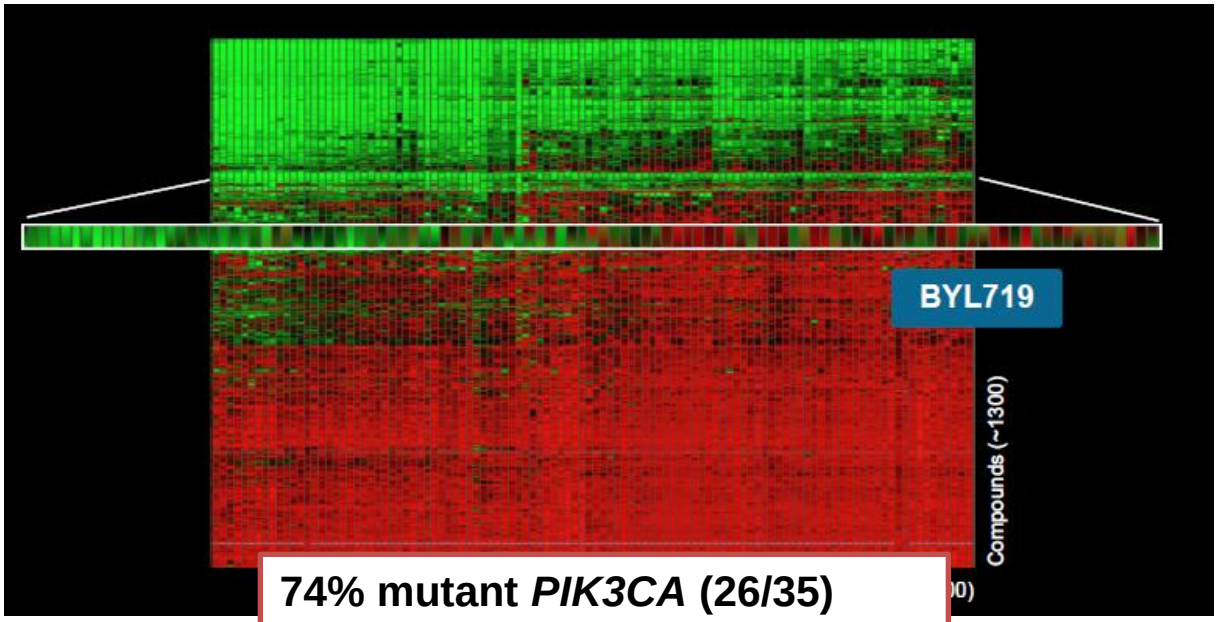
Breast cancer types



Predictors of sensitivity to PI3K-α selective inhibitors

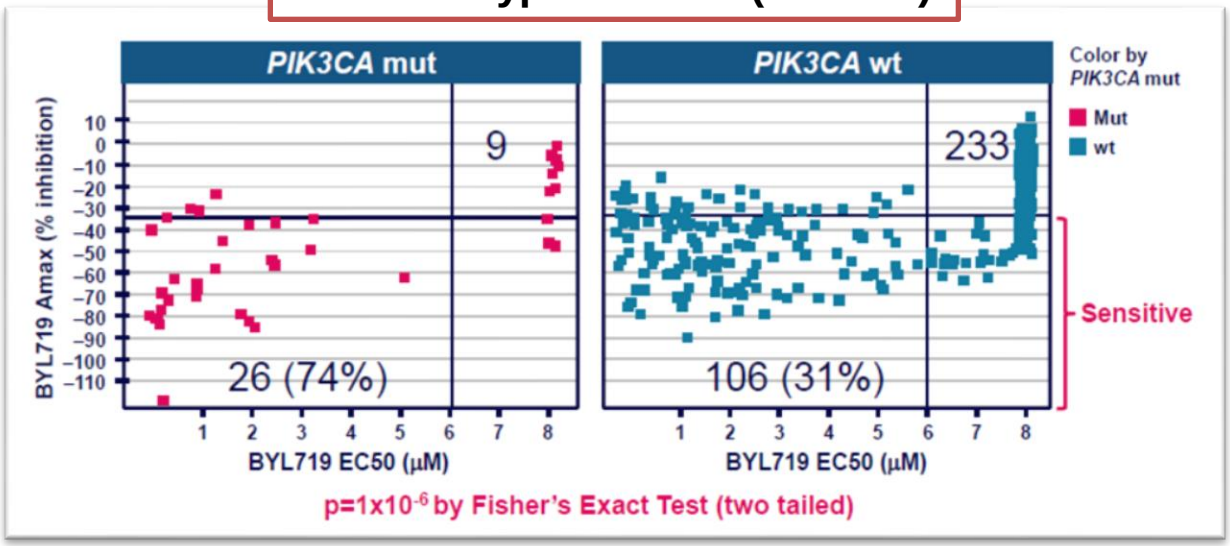
BYL719, PI3K alpha inhibitor





74% mutant *PIK3CA* (26/35)
31% wild type *PIK3CA* (106/339)

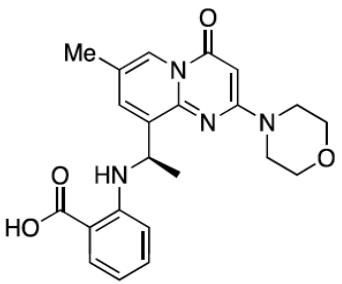
***PIK3CA* mutation and *PIK3CA* and *ERBB2* amplification associated with BYL719 sensitivity**



Barretina et al. Nature 2012
Huang et al. Proc AACR 2012

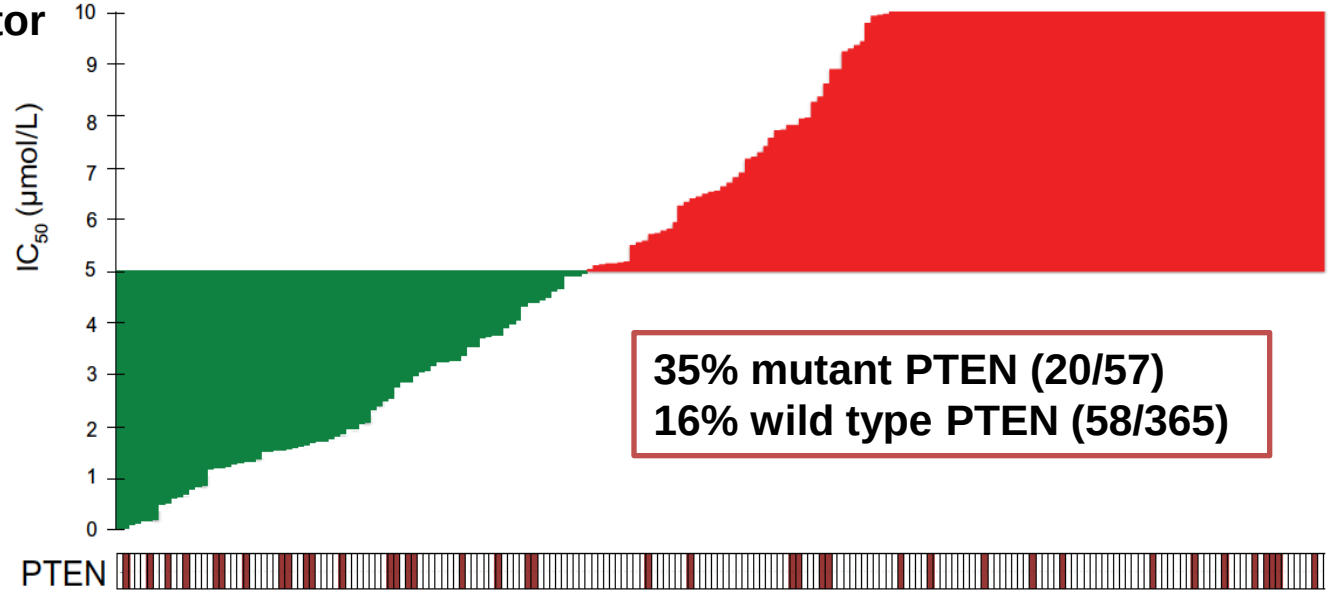
Predictors of sensitivity to PI3K-β selective inhibitors

KIN-193, a PI3K beta inhibitor



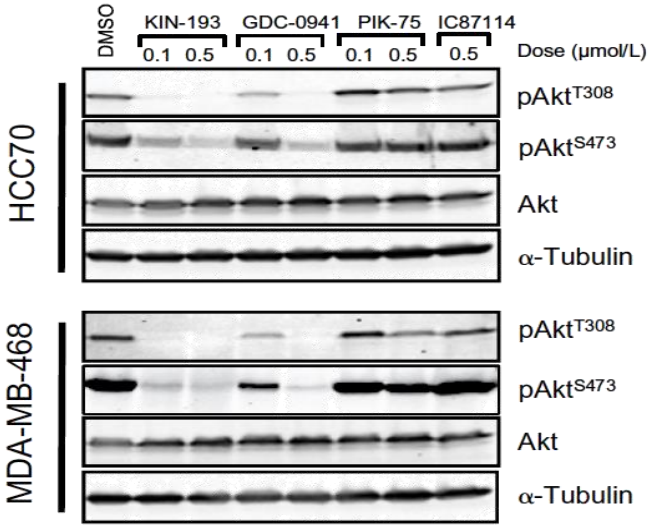
KIN-193

Kinase	IC_{50} (nmol/L)
PI3Kα	136
PI3Kβ	0.69
PI3Kδ	13.6
PI3Kγ	47.8
PI4Kα	8830
PI4Kβ	>10000
PI3K-C2α	>10000
PI3K-C2β	54.1
mTOR	3930
DNA-PK	53.7
hVPS34	3390



35% mutant PTEN (20/57)
16% wild type PTEN (58/365)

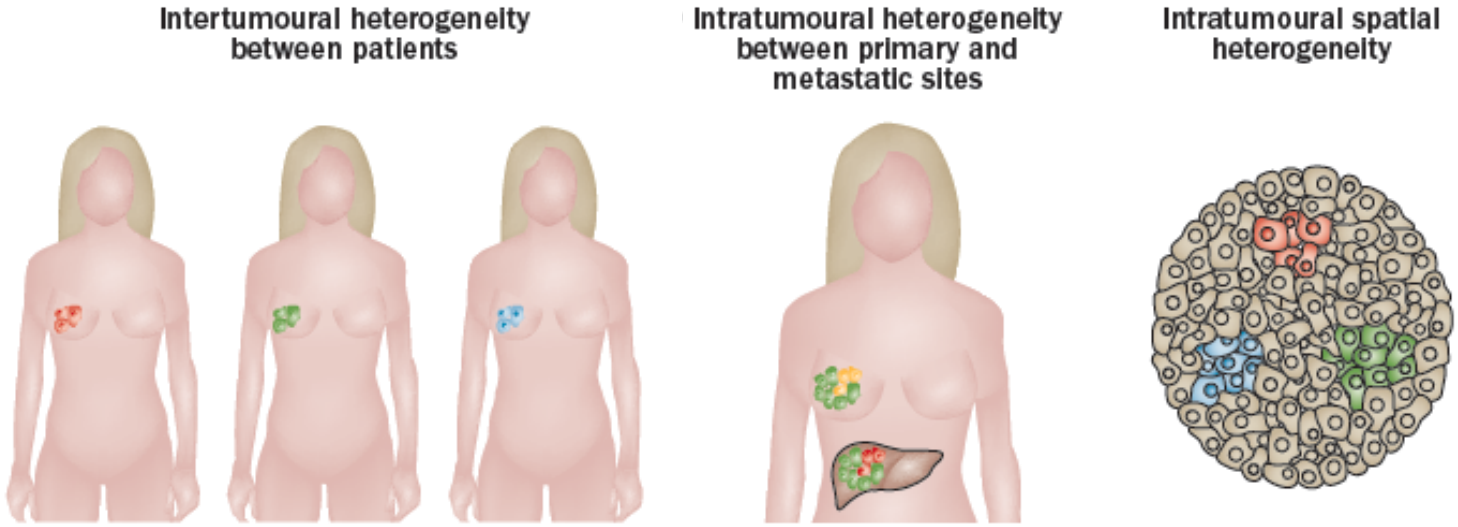
PTEN-negative cells

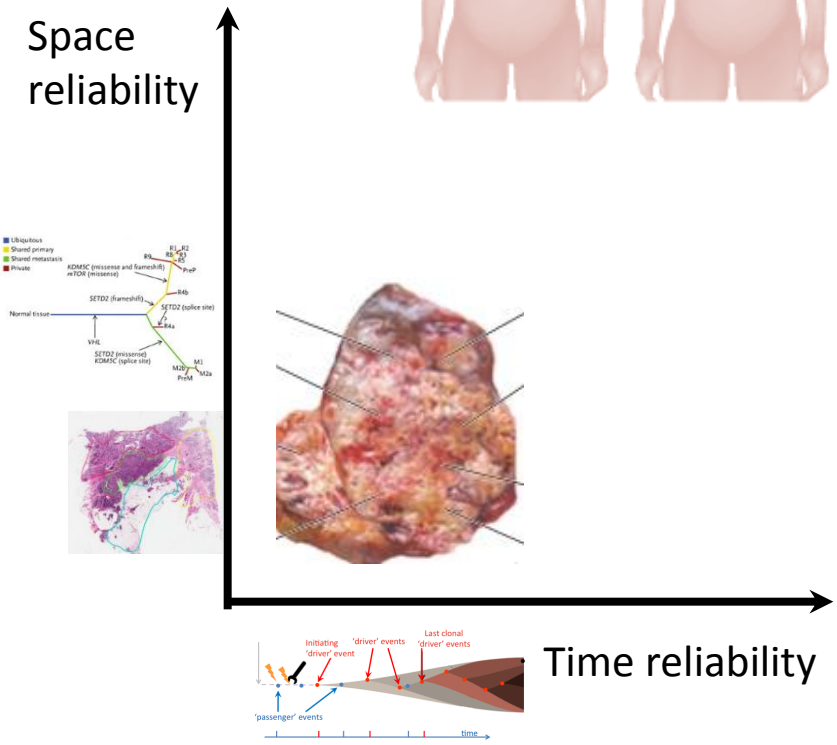


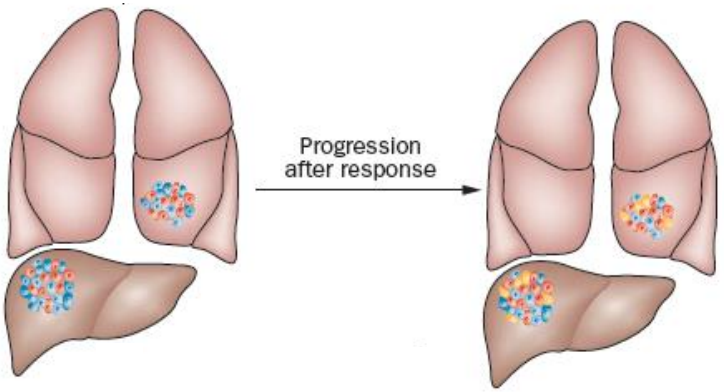
Ni J et al. Cancer Discovery 2012

NO

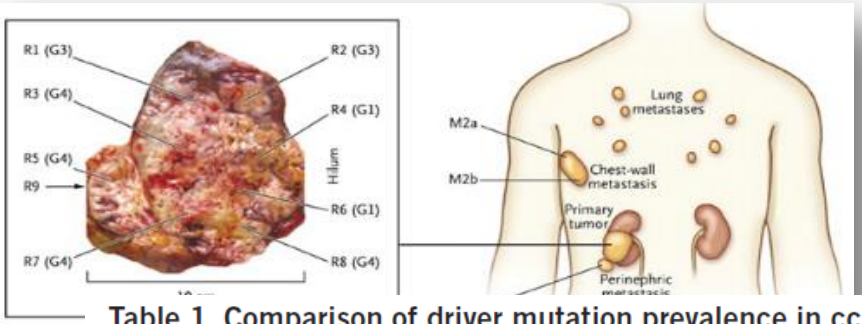
Dienstmann, Molec Can Ther, 2014


Intertumoural heterogeneity between patients
Intratumoural heterogeneity between primary and metastatic sites
Intratumoural spatial heterogeneity


Space reliability
Time reliability
Initiating 'driver' event
'driver' events
Last clonal 'driver' events
'passenger' events
time


Progression after response

Intra-patient tumor heterogeneity



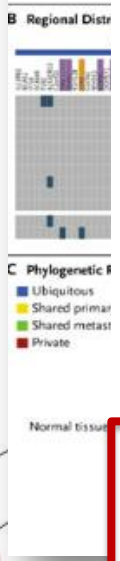
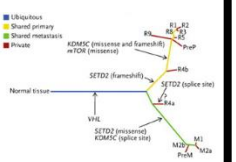
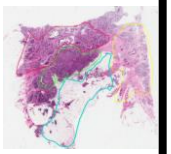


Table 1 Comparison of driver mutation prevalence in ccRCC samples

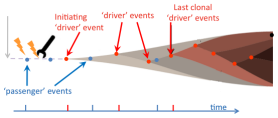
	Prevalence in TCGA samples (n = 102 samples)	Prevalence in all M-seq samples (n = 79 samples)	Prevalence in cases based on M-seq (n = 10 cases)	Prevalence cases/prevalence M-seq samples
PBRM1	42%	39%	60%	1.5
SETD2	18%	27%	30%	1.1
BAP1	21%	23%	40%	1.7
KDM5C	7%	11%	10%	0.9
TP53	5%	6%	40%	6.7
ATM	3%	4%	10%	2.5
ARID1A	6%	1%	10%	10.0
PTEN	5%	10%	20%	2.0
MTOR	9%	8%	10%	1.3
PIK3CA	3%	4%	20%	5.0
TSC2	2%	6%	10%	1.7
PI3K-mTOR pathway	18%	28%	60%	2.1

Space reliability





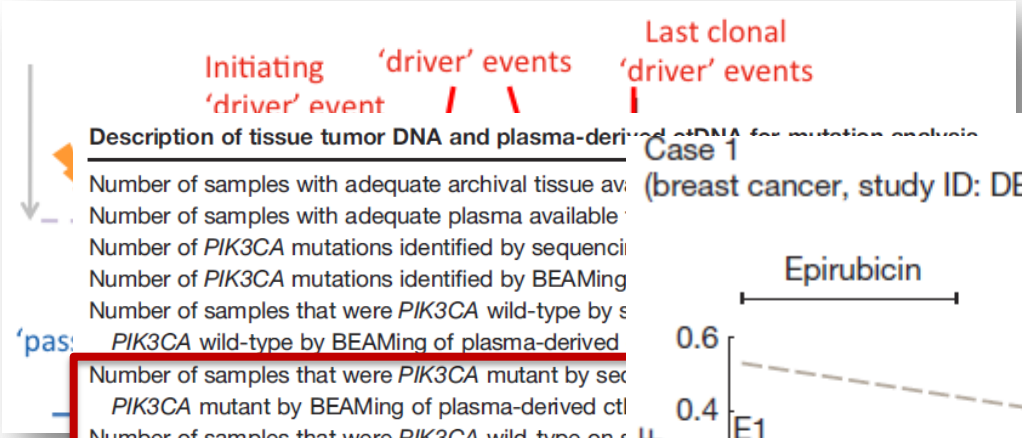
Time reliability

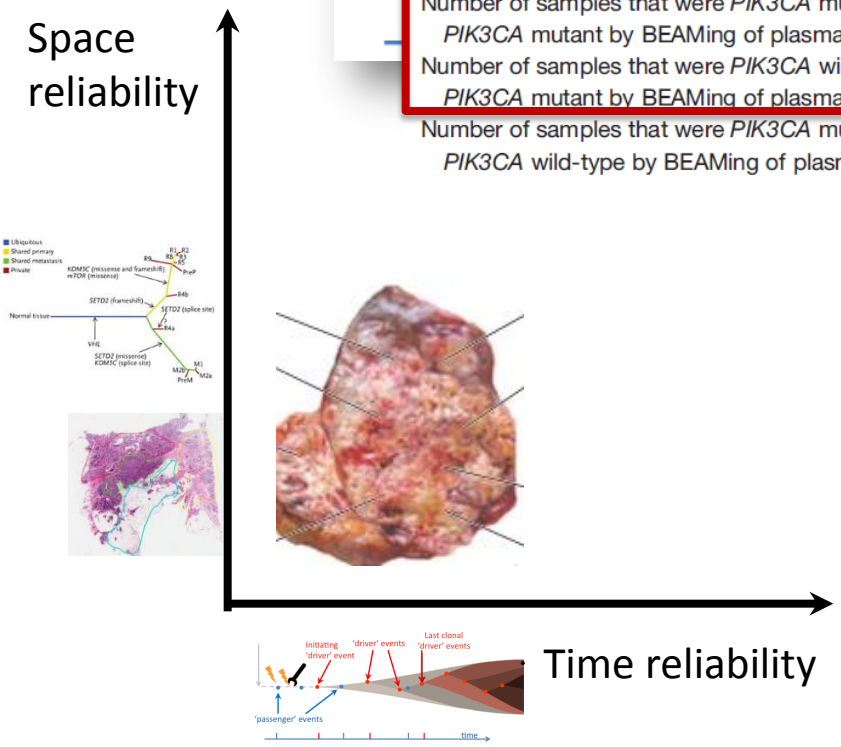


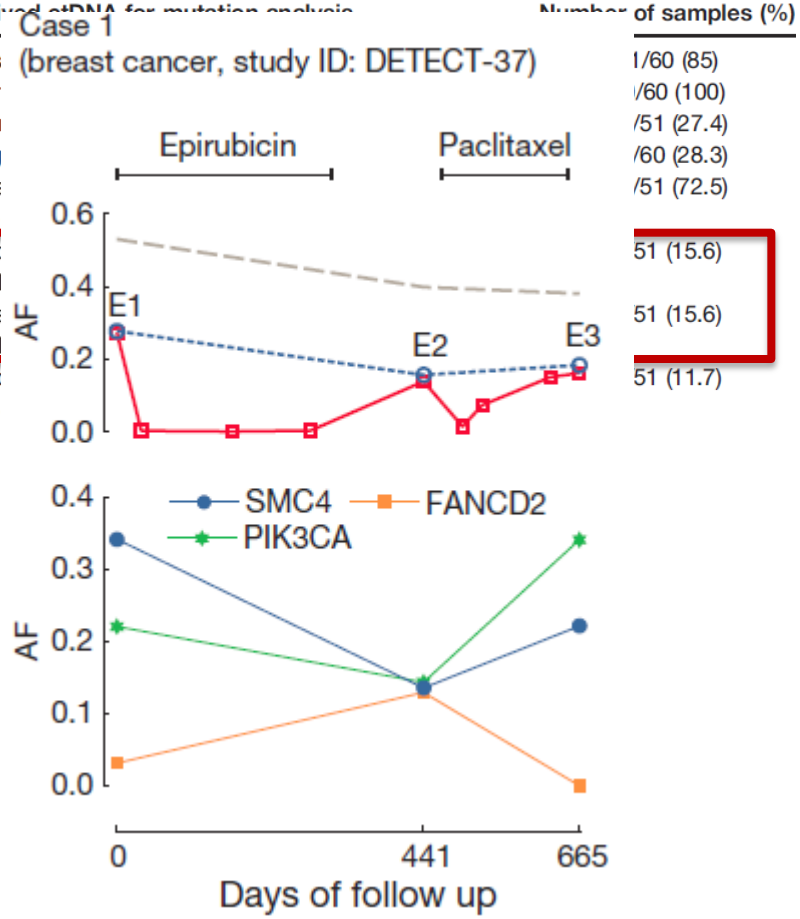
Gerlinger, N Engl J Med 2012

Gerlinger, Nat Gen, 2014

Temporal tumor heterogeneity and clonal evolution







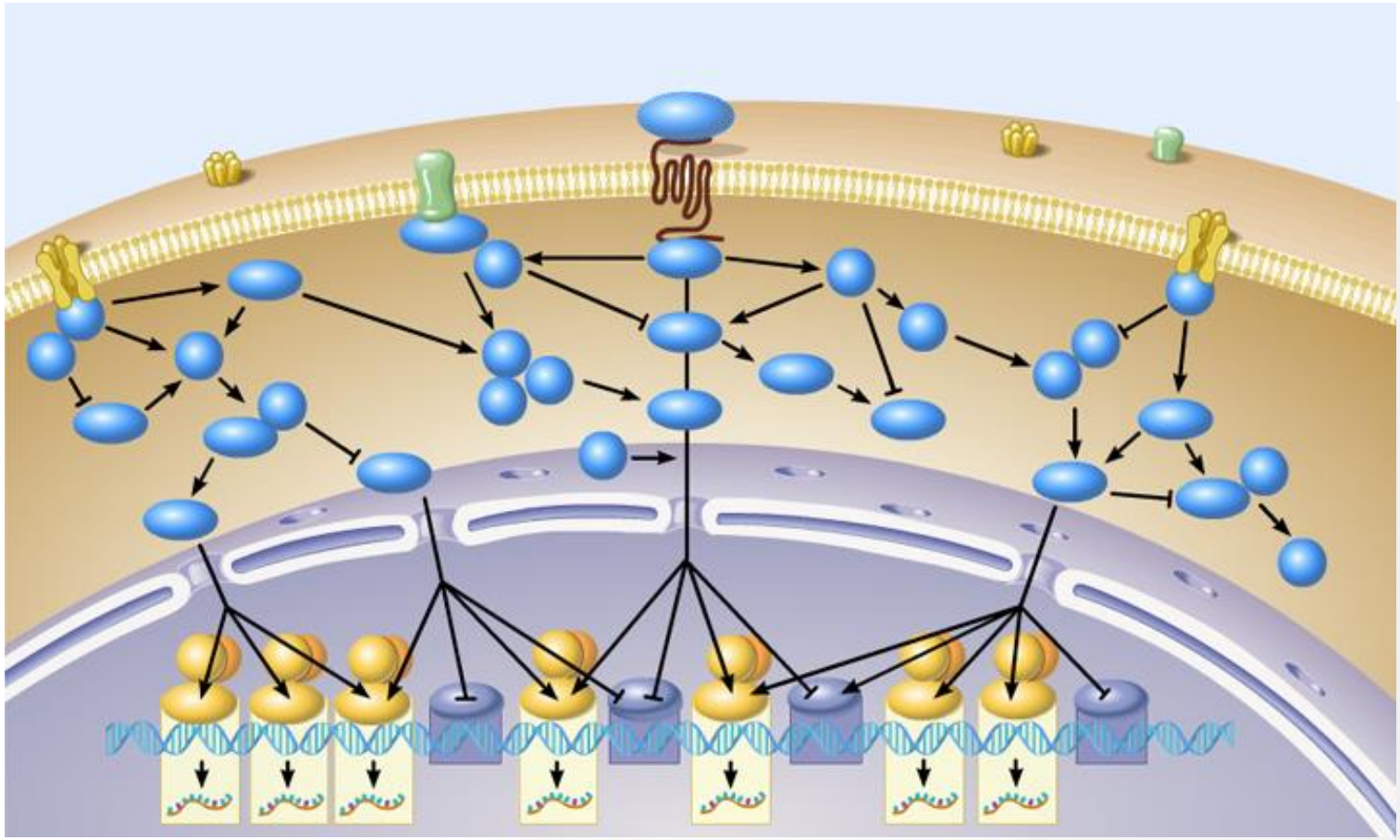
Murtaza. NATURE. VOL 497. 2 MAY 2013

Michaela J. Higgins Clin Cancer Res; 18(12) June 15, 2012

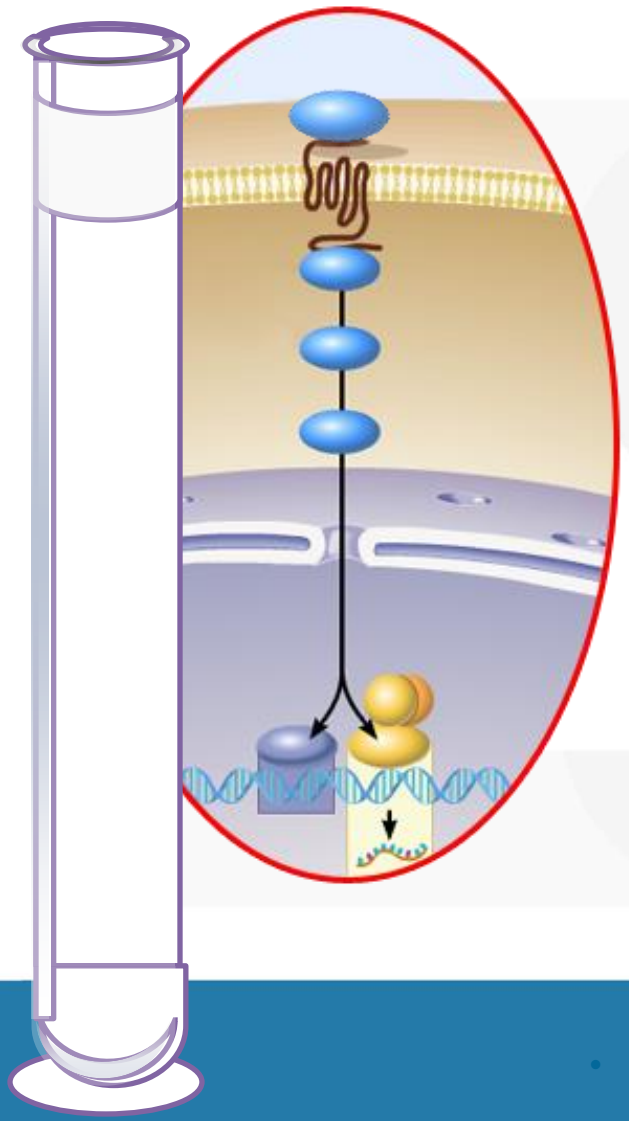
I do not know (yet)

Dienstmann, Molec Can Ther, 2014

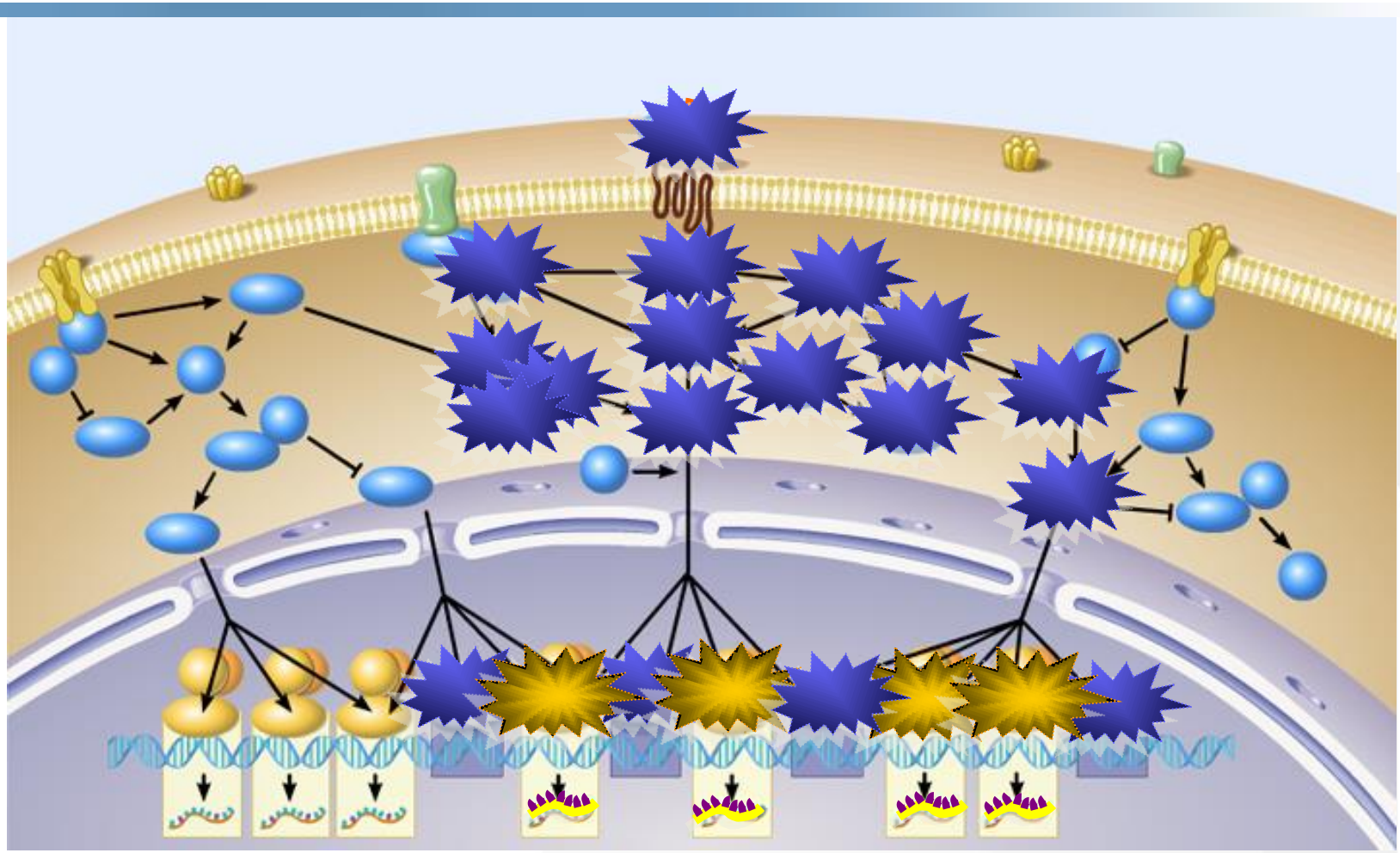
Conventional Drug Discovery Is Simplistic and Artificial

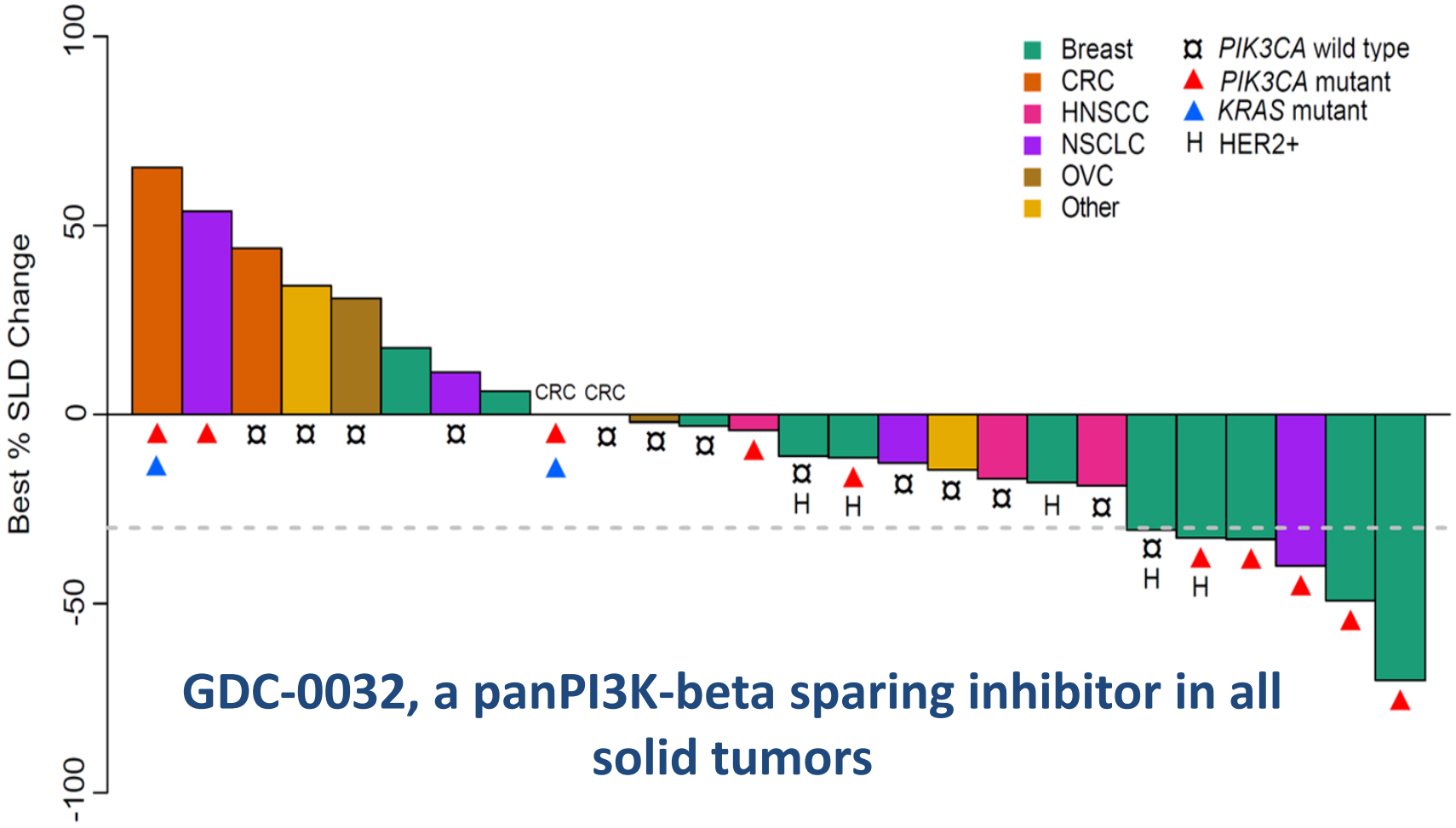


Conventional Drug Discovery Is Simplistic and Artificial



The Problem: Enormous Complexity of Real-Life Drug Action





GDC-0032, a panPI3K-beta sparing inhibitor in all solid tumors

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

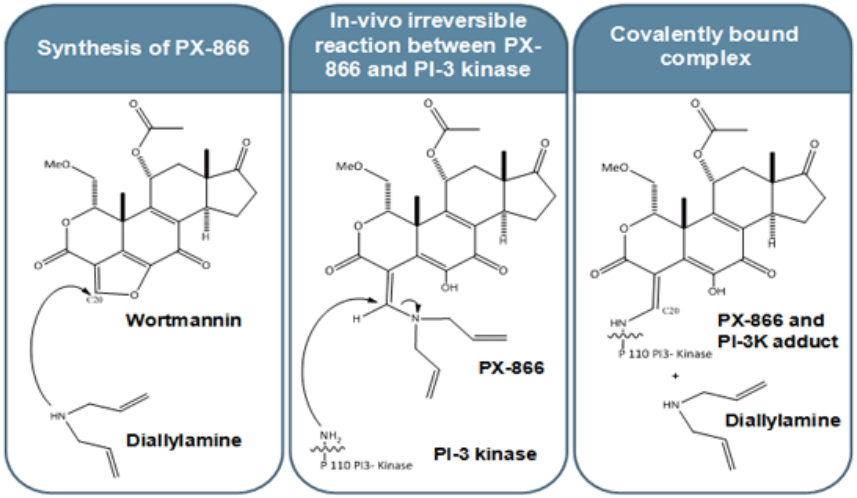
The Devil is in the Details:
Drugs with “unique” properties

The promise of PI3K irreversible inhibitors

PX866

Irreversible pan-PI3K inhibitor

- Preclinically: Inhibition of p-AKT (S473) was observed for up to 48 hours after PX-866 dosing in HT29 tumor models.



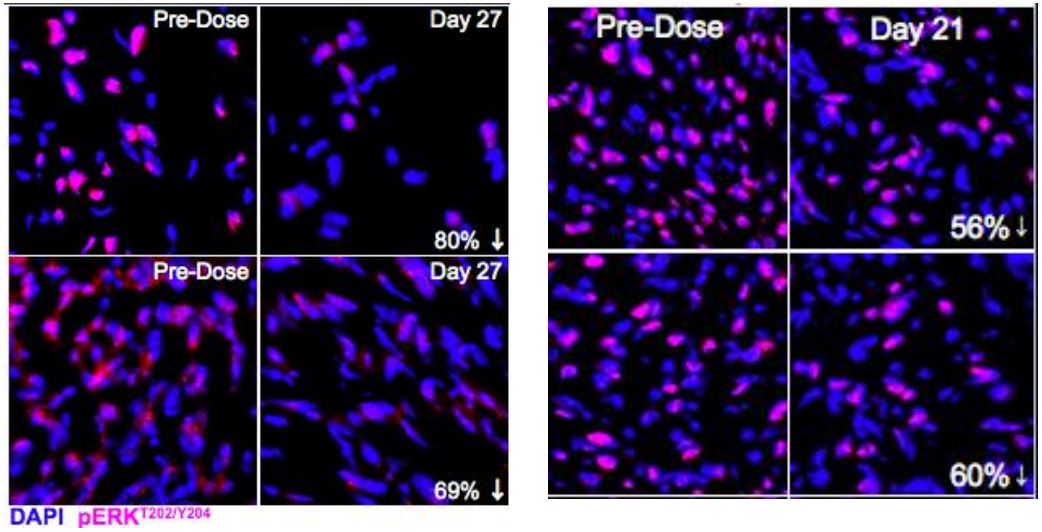
- Phase I trial:
  - DLTs of diarrhea
  - No hyperglycemia or skin toxicity
  - T 1/2+= 2.2-3.8 h
  - Inhibition of p-AKT was observed within 4 hours in 7 patients with p-AKT/T-AKT ratio decreases of 13% to 94%

Kd (nM)	PX-866	17-OH 866
PIK3CA WT	110	38
C420R	100	41
E542K	72	37
E545A	82	55
E545K	52	44
H1047L	85	56
H1047Y	110	83
I800L	980	320
M1043I	92	53
Q546K	81	44
mTOR	>30,000	>30,000

David S. Hong, Clin Cancer Res; 18(15) August 1, 2012

Off target effects

XL147 (panPI3Ki) and XL765 (PI3K/mTORi) and activity on MAPK.



XL765 **XL147**

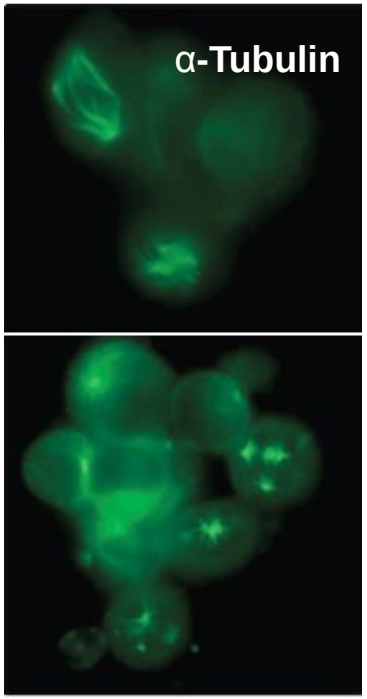
Similar pERK reduction in:

- Mucinous breast carcinoma (74%) and rectal carcinoma (62%) treated with XL765
- Merckel Cell and Leiomiosarcoma treated with XL147

BKM120 (panPi3Ki) and the antitubulin effect

Control

BKM120



BKM120 causes more cell death than other PI3k in vitro, irrespective of their level of PI3K addiction.

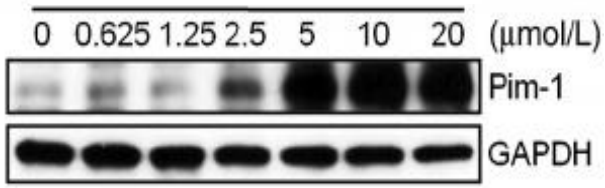
It displays tubulin-binding and microtubule-estabilizing activities, but at concentrations that may not be reached in the clinic

Shapiro, CCR 2013
Brachmann, S. M. Mol. Cancer Ther., 2012.

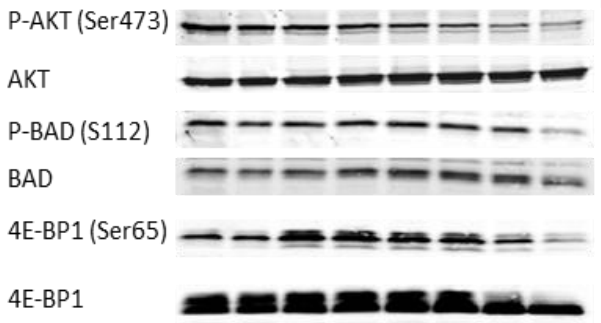
PI3K/PIM inhibitors

- PIM expression is regulated by JAK-STAT and NF-KB1 pathways
- Promote pro-survival signaling through regulation of BCL2 family
- Increased cap-dependent protein synthesis through phosphorylation and thus inhibition of translation repressor 4E-BP1 (By-pass Pi3K signaling)
- Cross-talk between PIM and PI3K.
- PIM Kinases are described as drivers of PI3k/AKT drug resistance

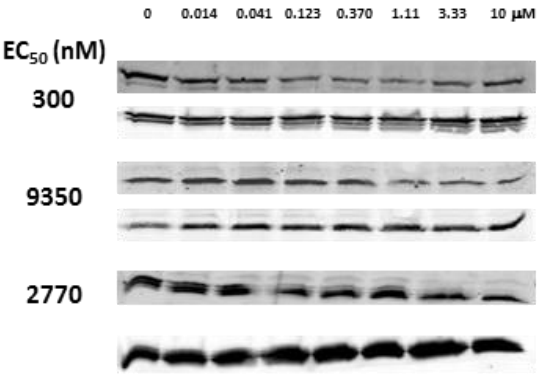
GSK690693, PI3K inhibitor



GDC-0941, panPI3K inhibitor



IBL202, panPI3K/PIM inhibitor



Pharmacological properties

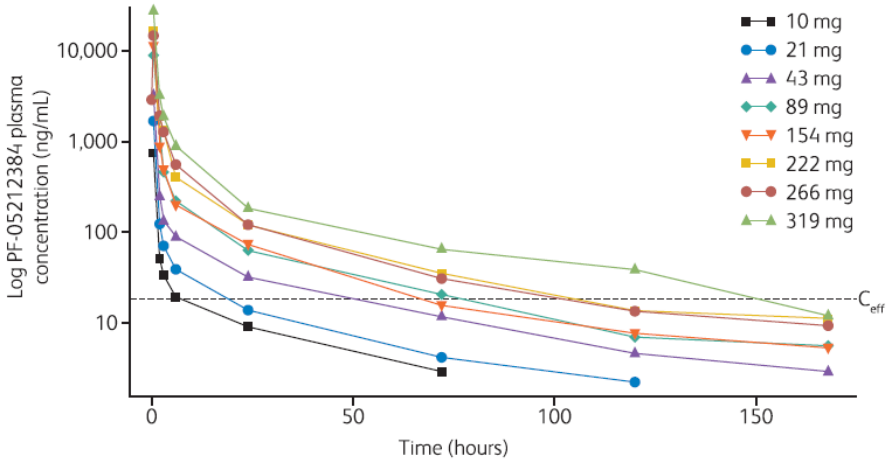
Intravenous PI3K inhibitors
(PF-05212384 and BAY 80-6946)

PF-05212384 is an intravenous, ATP-competitive, highly selective pan-class I isoform PI3K and mTOR inhibitor

The most common AEs (mucositis, hyperglycemia, and liver enzyme elevations) are known class-related effects of PI3K and mTOR inhibiton

Terminal $T_{1/2}$= 30-37 hours

Paired tumor biopsies at MTD group revealed a 35.9% reduction in pAkt S473



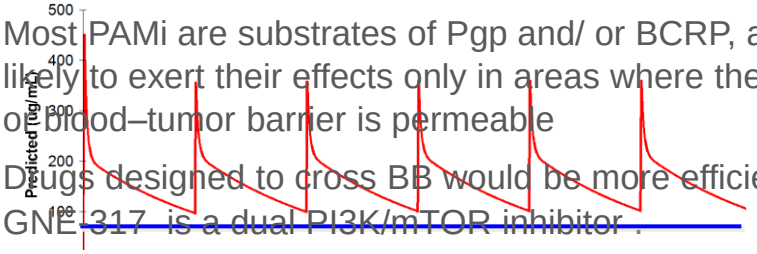
Brain-Penetrant PI3K Inhibitors
(BKM120, GDC0084)

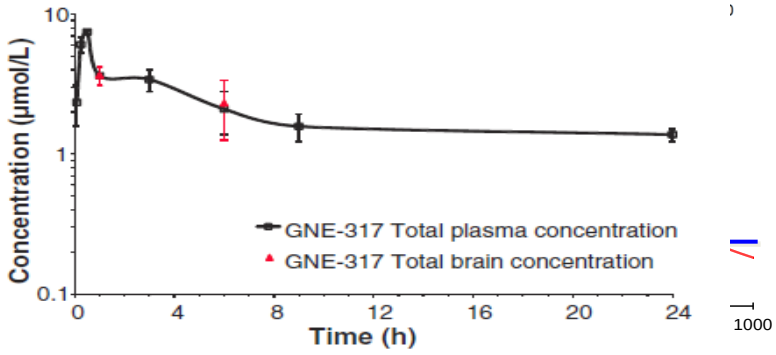
As per TCGA, 75% of Glioblastoma cases have alterations that activate the PI3K pathway

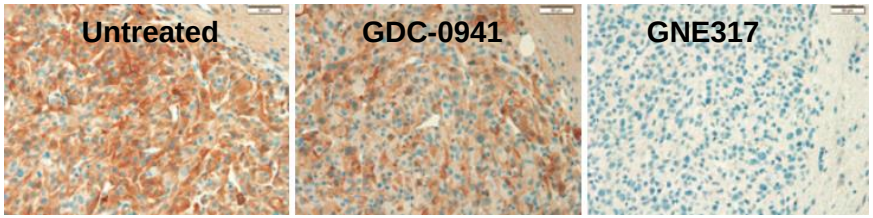
Most PAMi are substrates of Pgp and/ or BCRP, and are likely to exert their effects only in areas where the BBB or blood–tumor barrier is permeable

Drugs designed to cross BB would be more efficient.

GNE-317 is a dual PI3K/mTOR inhibitor .







Millham R, AACR 2011

Many lessons yet to be learn with Pi3K inhibitors…

But remember…

It is the Pharmacology, stupid!*

*Adapted from the famous “It’s the economy, stupid” at the presidential campaign for Bill Clinton against George H. W. Bush.