IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

Pre-IMPAKT Training Course

Basics in Cancer Cell Biology

Kinases

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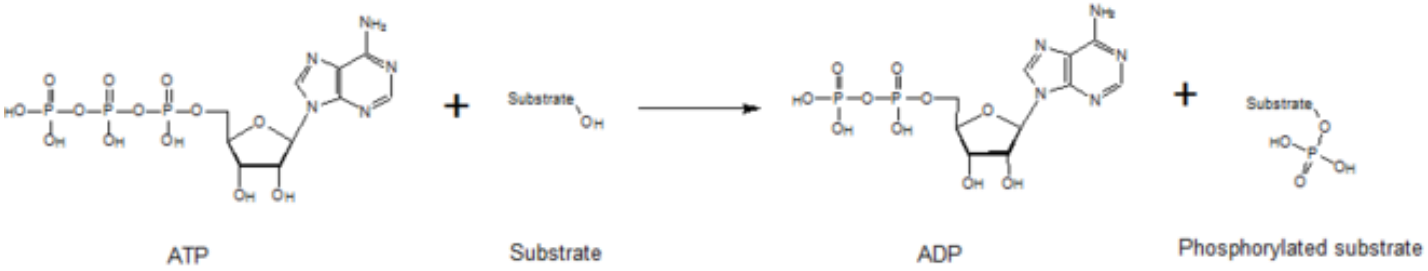
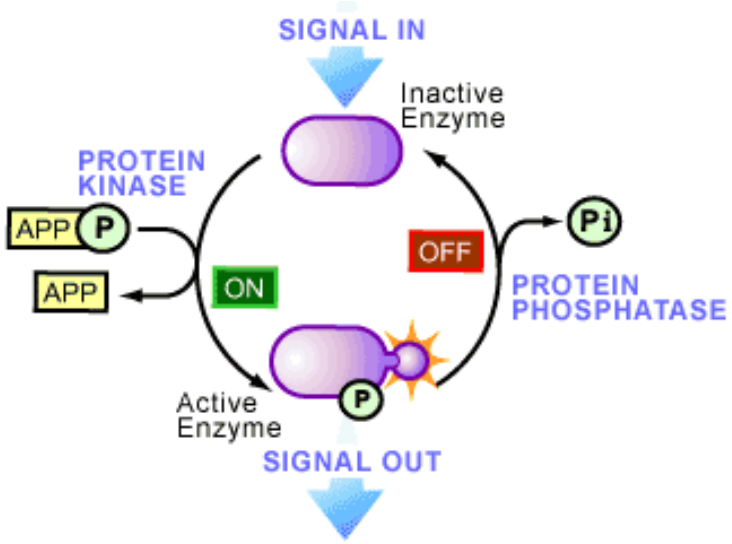
Barcelona

Kinases

- Etymology: Gk, *kinesis,* motion; *ase,* enzyme
- Transfers a phosphate group (≠phosphatase)

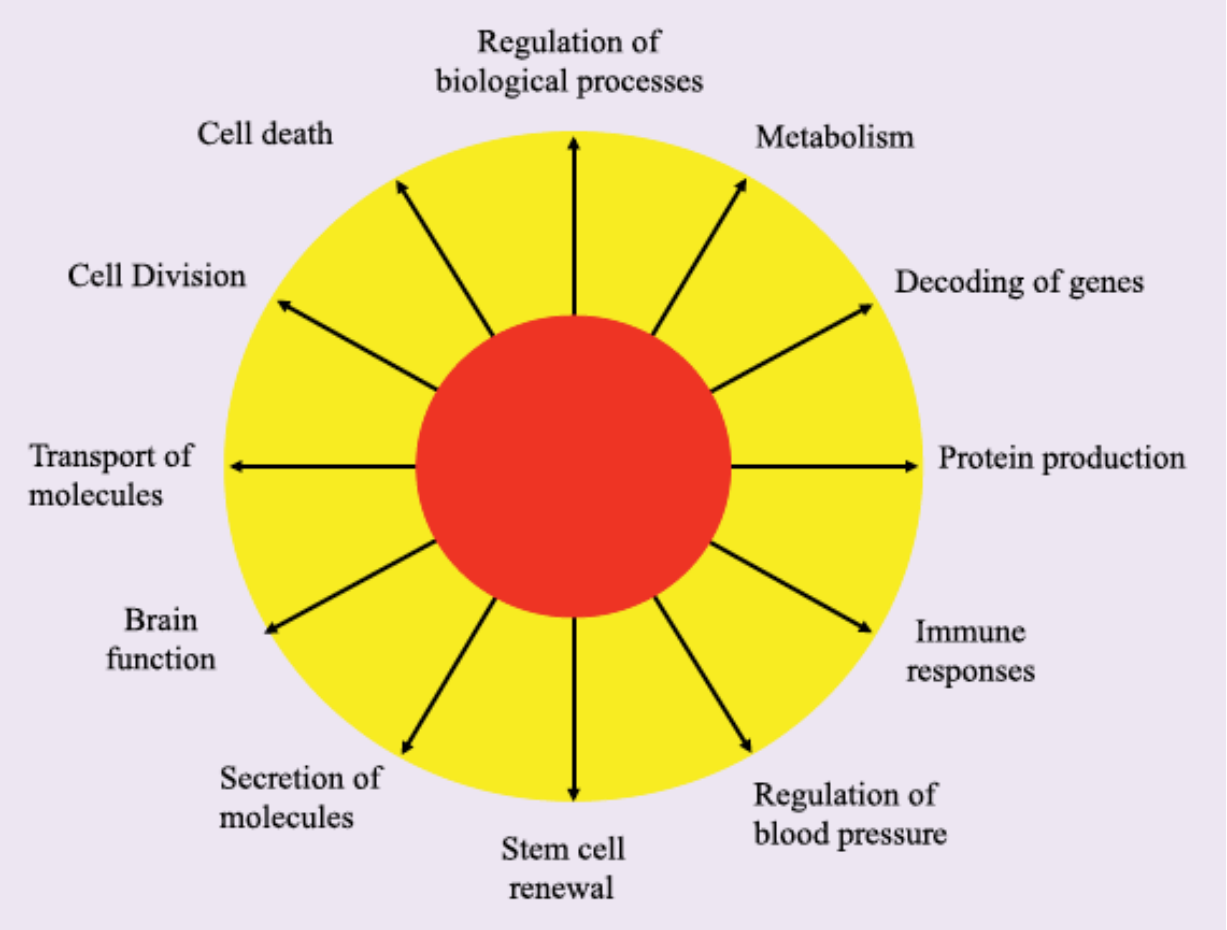


- Transmit signals

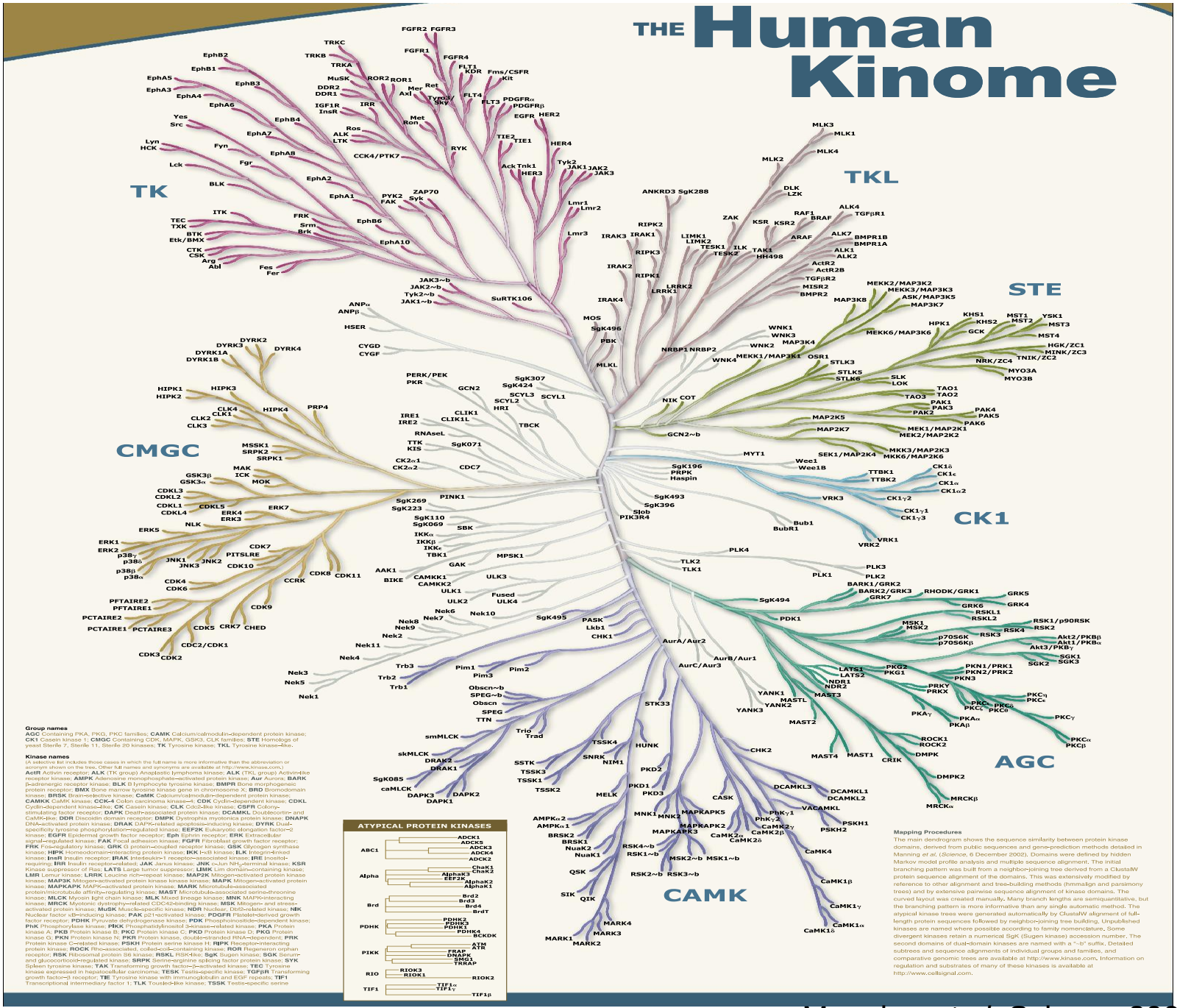


Kinases

- Regulate cellular processes



Cohen & Alessi ACS Chem Biol 2013



Manning *et al*, Science 2002

Kinases

- Mutations in kinases can cause disease and cancer

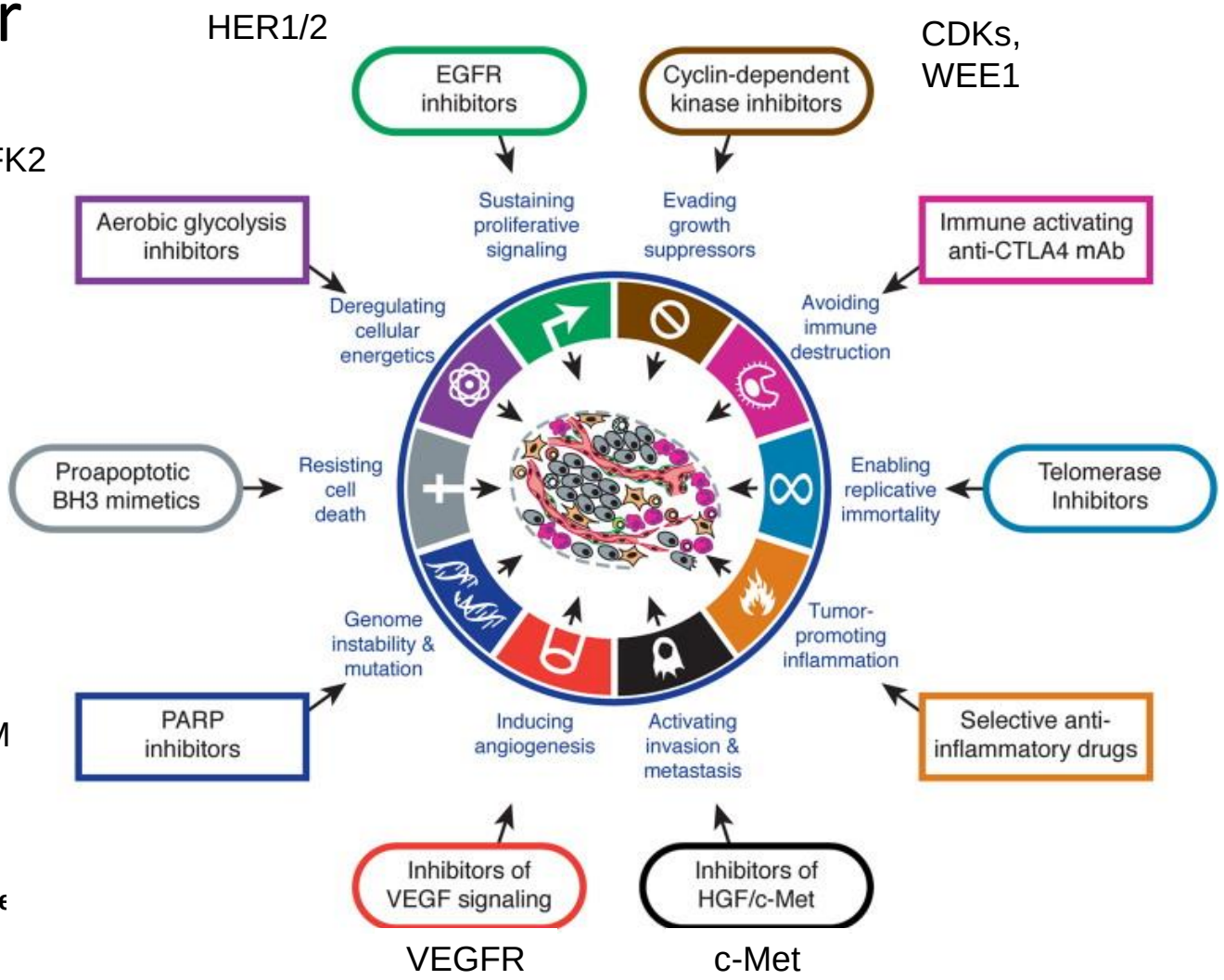
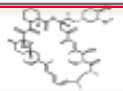
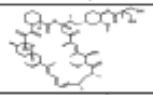
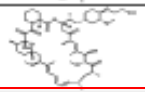
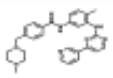
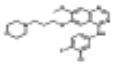
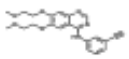
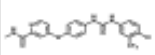
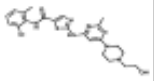
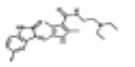
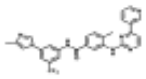
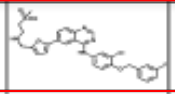
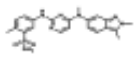
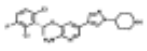
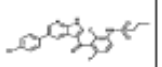
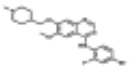
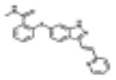
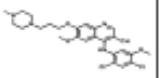
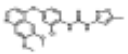
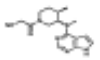
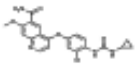
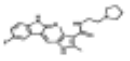
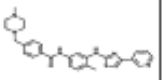
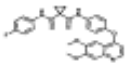
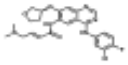
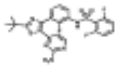
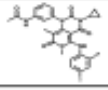


Table 1. Small Molecule Inhibitors of Protein Kinases Approved for Clinical Use or in Advanced Clinical Trials

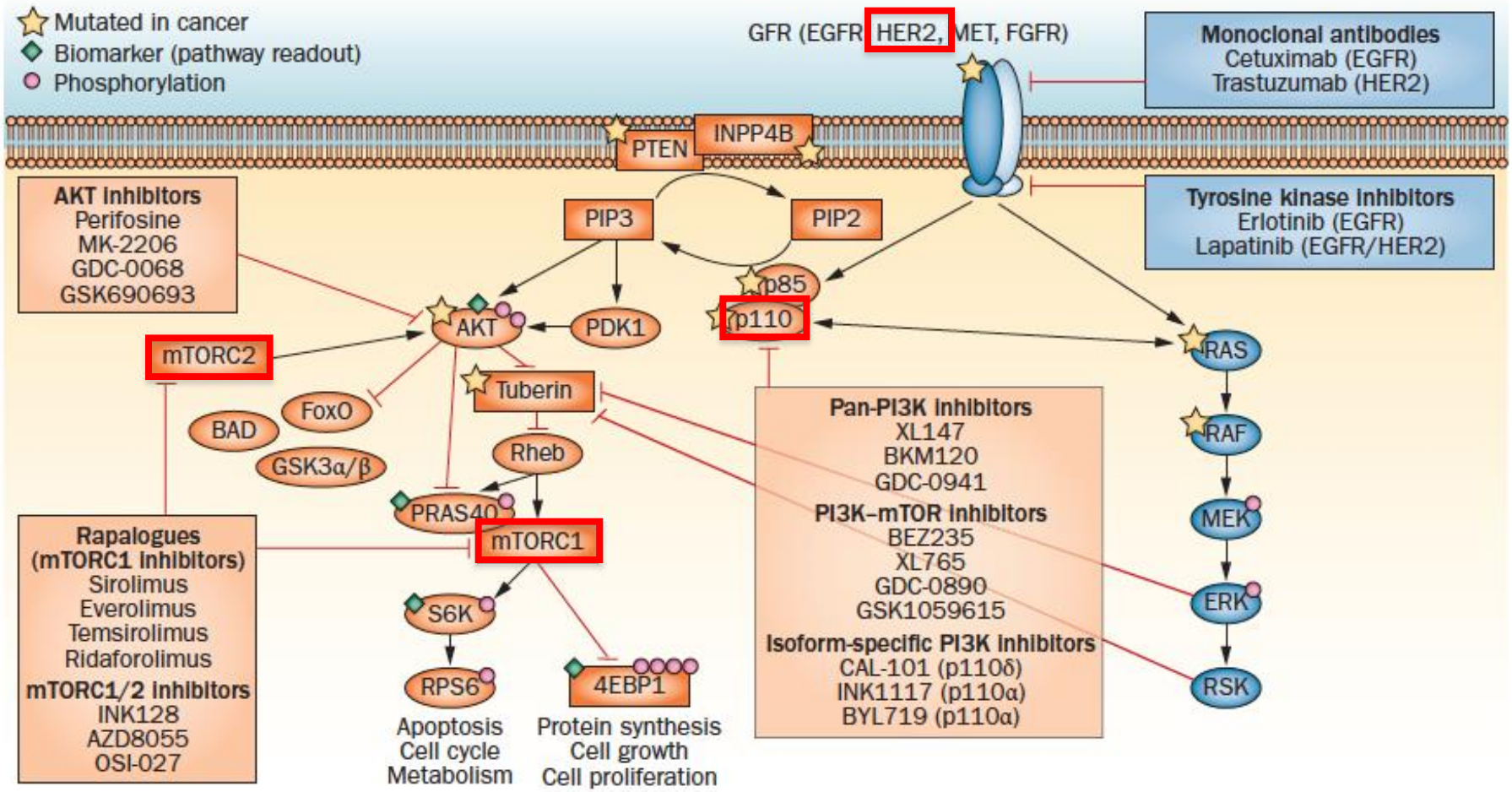
Name	Structure	Reported target	Company	Approved for clinical use
Eril		ROCK	Eisai	1995 cerebral vasospasm (Japan)
Rapamune		mTOR	Wyeth Pfizer	2000 kidney transplantation
Temsirolimus		mTOR	Wyeth Pfizer	2007 advanced renal cell carcinoma
Everolimus		mTOR	Novartis	2009 several cancers
Imatinib		Bcr-Abl c-KIT PDGFR	Novartis	2001 chronic myelogenous leukaemia
Gefitinib		EGFR	Astra Zeneca	2005 lung cancer
Erlotinib		ErbB1	Genetech Roche	2005 lung,pancreatic and others cancers
Sorafenib		Multiple Tyrosine kinases targeted	Onyx Bayer	2005 renal cancer
Dasatinib		Multiple Tyrosine-kinases targeted	Bristol Myers Squibb	2006 chronic myeloenous leukaemia, All
Sunitinib		Multiple Tyrosine-kinases targeted	SUGEN Pfizer	2006 renal cancer and GIST
Nilotinib		Bcr-Abl	Novartis	2007 chronic myelogenous leukaemia
Lapatinib		Her2 EGFR	GlaxoSmith Kline	2009 renal cancer
Pazopanib		VEGFR2 PDGFR c-KIT	GlaxoSmith Kline	2009 renal cancer
Ruxolitinib		JAKs	Incyte	2011 myelofibrosis
Crizotinib		ALK/Met	Pfizer	2011 NSCLC with Alk mutation

Name	Structure	Reported target	Company	Approved for clinical use
Vemurafenib		BRAF	Roche	2011 melanoma
Vadatinib		Multiple Tyrosine kinases targeted	Caprelsa IPR Pharms	2012 thyroid cancer
Axitinib		VEGFRs PDGFRB c-KIT	Pfizer	2012 renal cell carcinoma
Bosutinib		BcrAbi SRC	Pfizer	2012 chronic myelogenous leukemia
Tivozanib		VGFRs	AVEO Pharms	2012 kidney cancer
Tofacitinib		JAKs	Pfizer	2012 rheumatoid arthritis
Regorafenib		Multiple Tyrosine kinases targeted	Stivarga Bayer	2012 thyroid cancer
Lenvatinib		VEGFR2/ VEGFR2	Eisai	2012 thyroid cancer (Japan)
Toceranib		Multiple Tyrosine kinases targeted	Pfizer	2009 canine mastocytoma
Masivet Kinavet		c-KIT PDGFR	AB Science	2010 canine mastocytoma
Cabozantinib		VEGFRs KIT / Axl	Cometriq Exelixis	2012 canine thyroid cancer
Afatinib		Her2 EGFR	Boehringer Ingelheim	Not yet NSCLC
Dabrafenib		BRaf	GlaxoSmith Kline	Not yet metastatic melanoma
Trametinib		MEK1/2	GlaxoSmith Kline	Not yet metastatic melanoma

PI3Ki

Cohen & Alessi ACS Chem Biol 2013

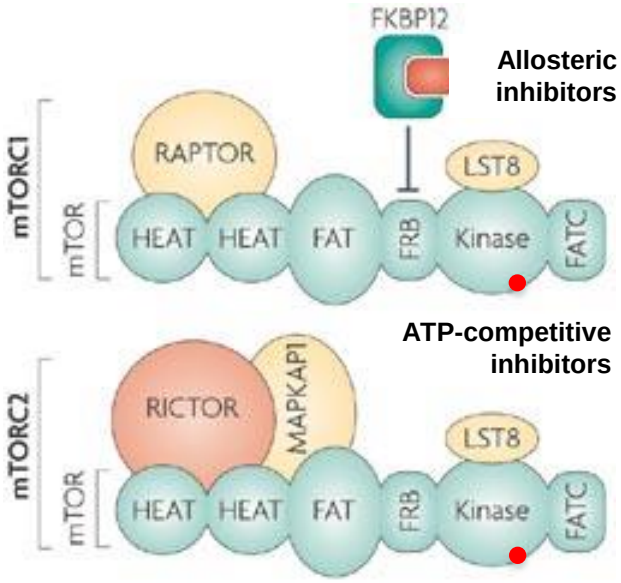
The HER2/PI3K/mTOR pathway

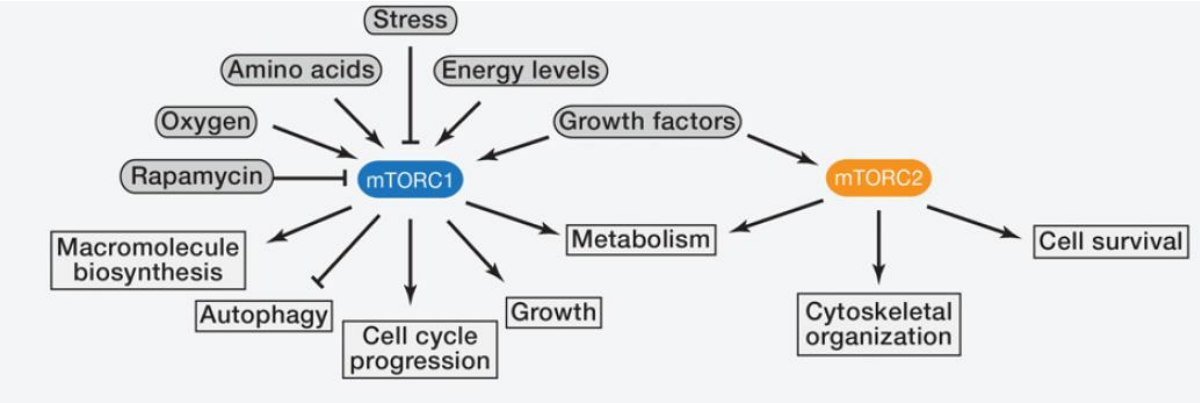


Rodon *et al*, NRCO 2012

mTOR complexes 1 and 2

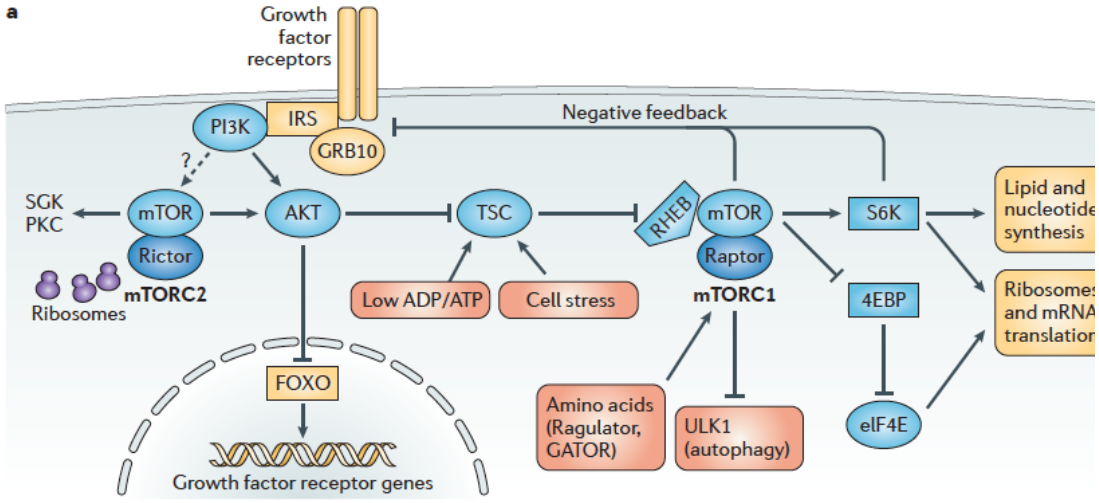
- Mammalian Target Of Rapamycin forms two complexes 1 and 2 with different binding partners and activity
- Allosteric vs kinase inhibitors have different mode of action, specifics in substrate inhibition and antiproliferative activity
- Blockade of mTOR disrupts negative feedbacks
- mTORC1, integrates various cellular signals and response

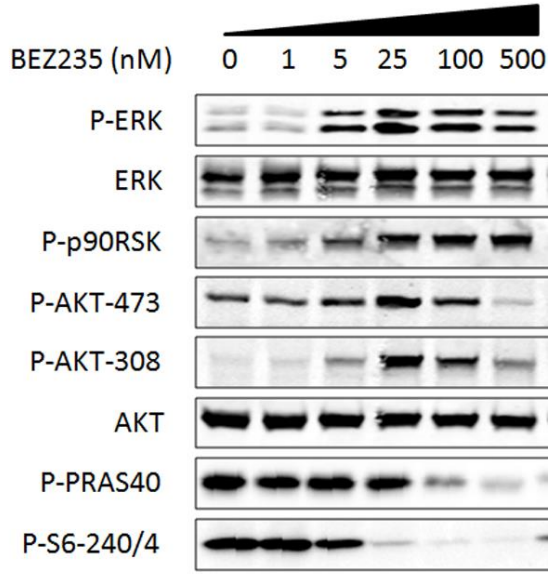




Thomson *et al*, NRI 2009
Laplante & Sabatini, Cell 2012

Allosteric mTORC1 and mTORC1/2 kinase inhibitors release feedback regulation on RTK/PI3K/ERK signalling





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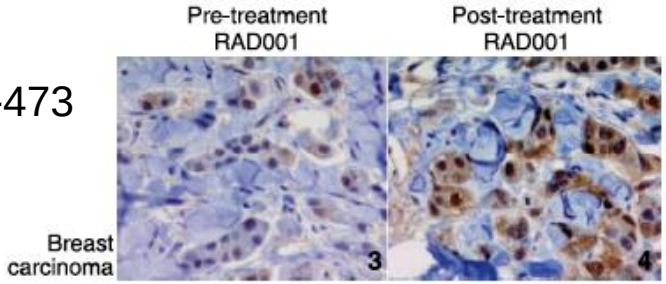
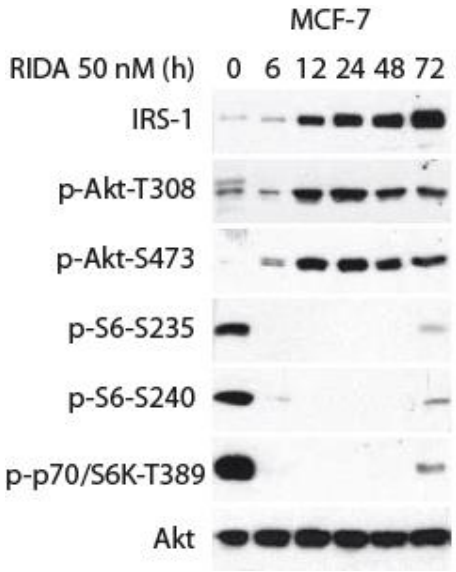
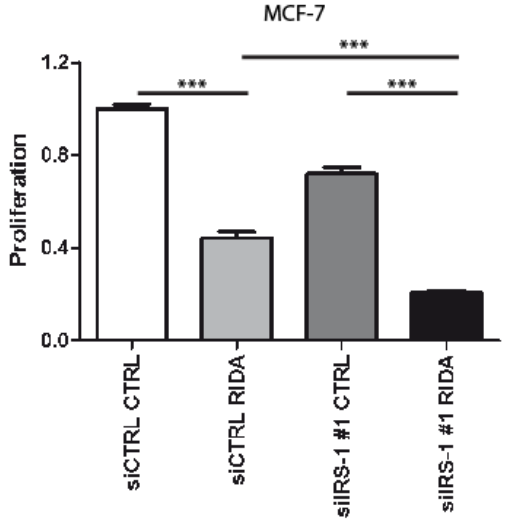


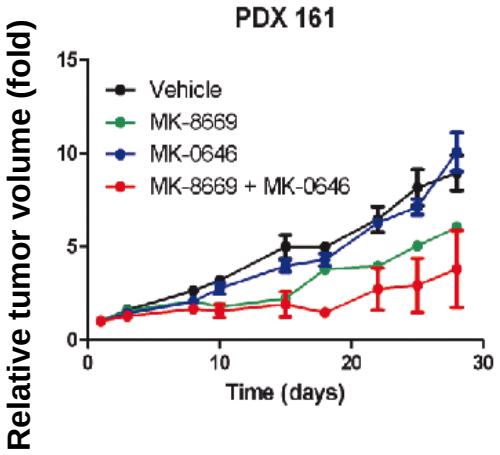
Fruman & Rommel, NRDD 2014
O'Reilly *et al*, Cancer Research 2006
Serra *et al,* Oncogene 2011

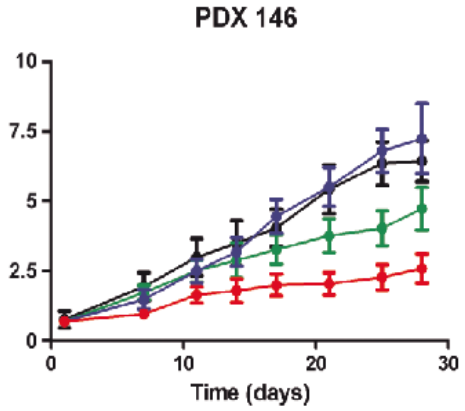
Inhibition of mTOR and IGF-1R is a promising strategy for Luminal B breast cancer treatment



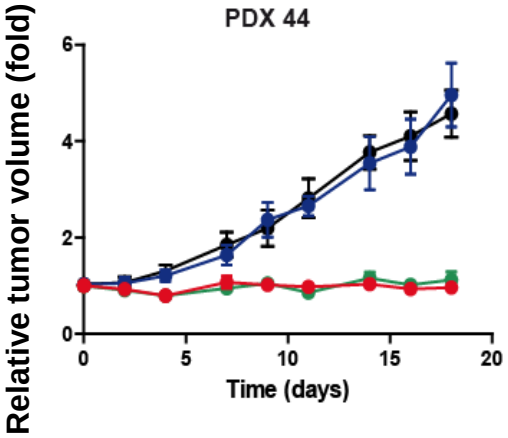


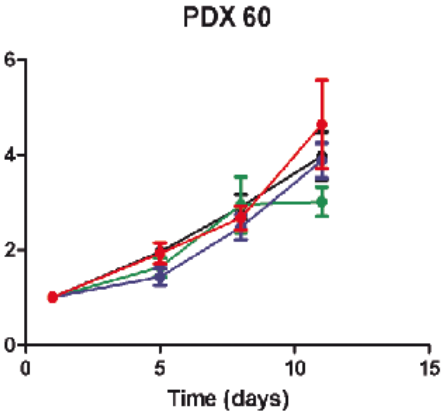
High IGF-1R





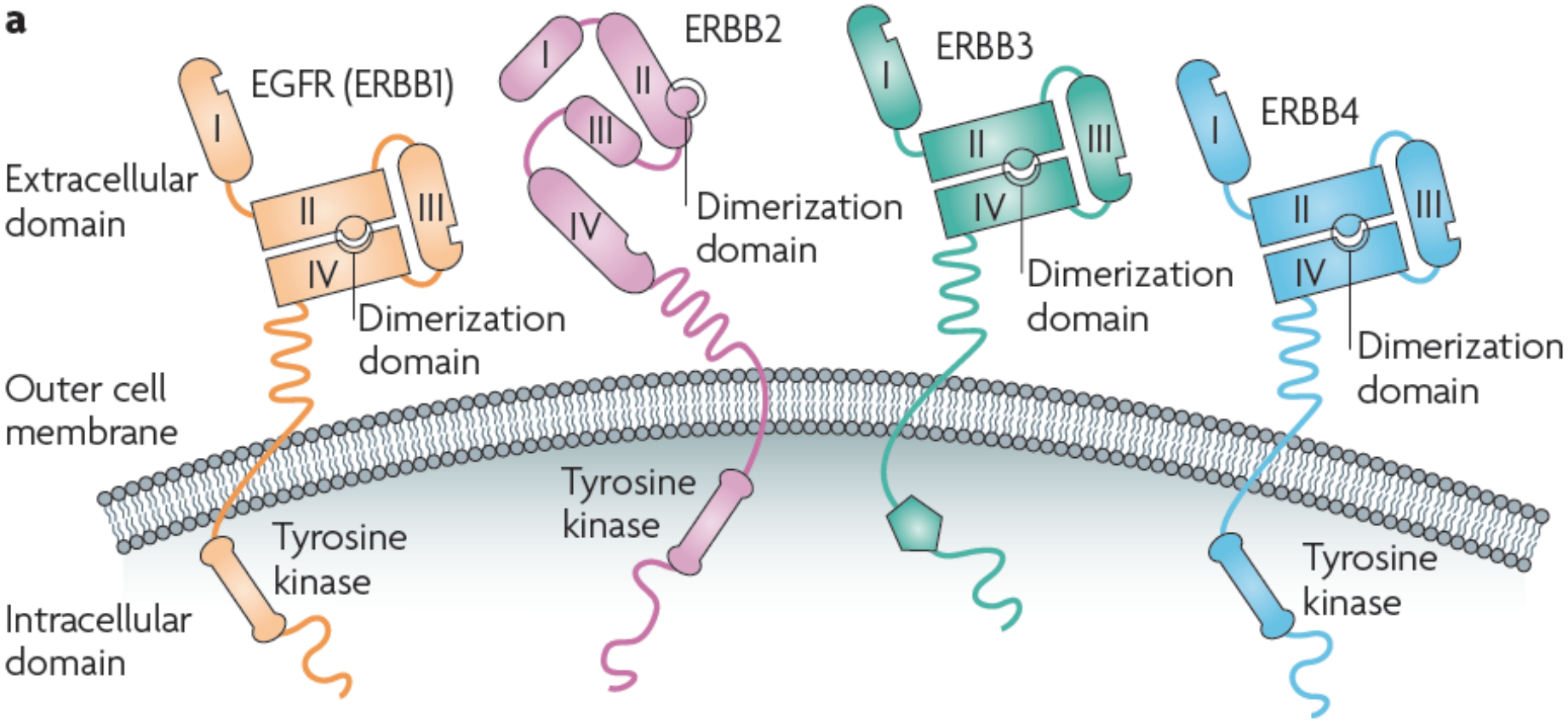
Low IGF-1R





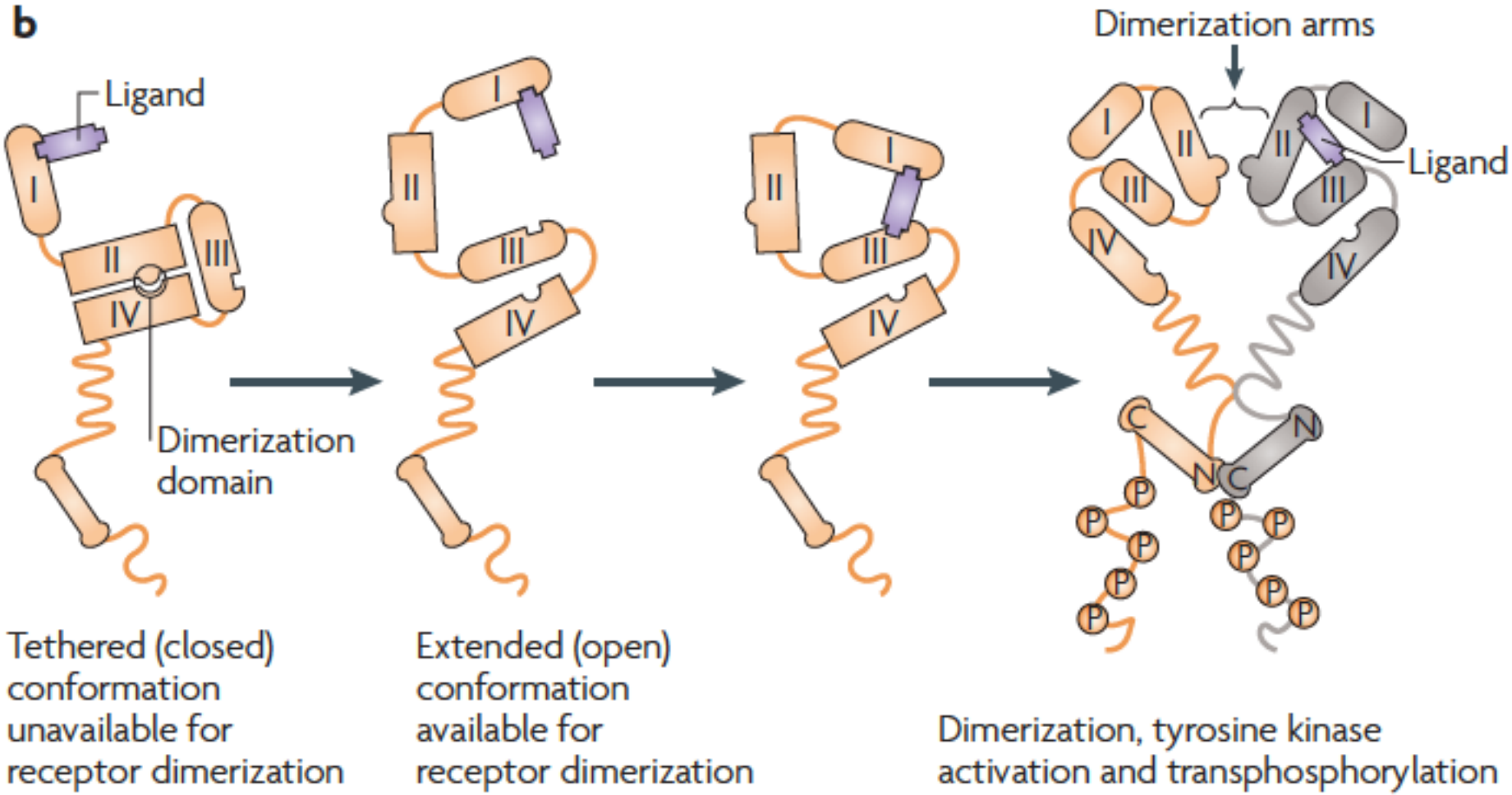
Martin Rivas, *unpublished data*

ERBB-family of receptor tyrosine kinases: ERBB2-ERBB3 potent oncogenic signalling



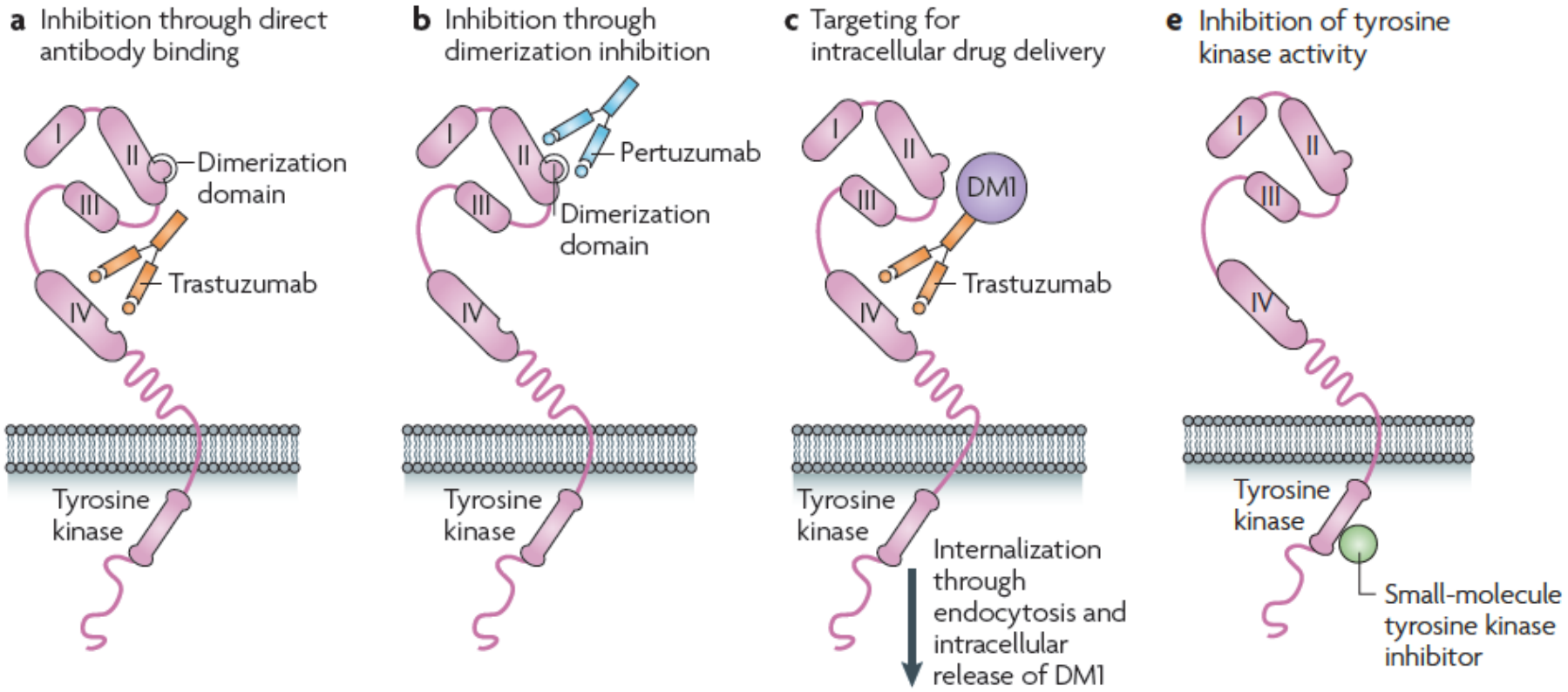
Baselga and Swain, NRC 2009

Activation of ERBB-receptor tyrosine kinases upon ligand binding



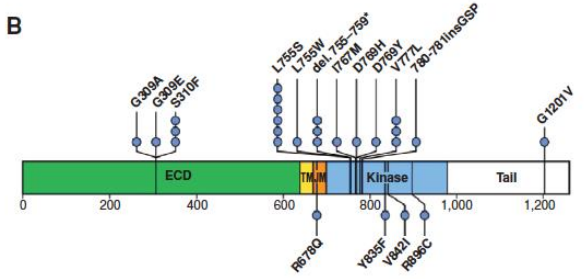
Baselga and Swain, NRC 2009

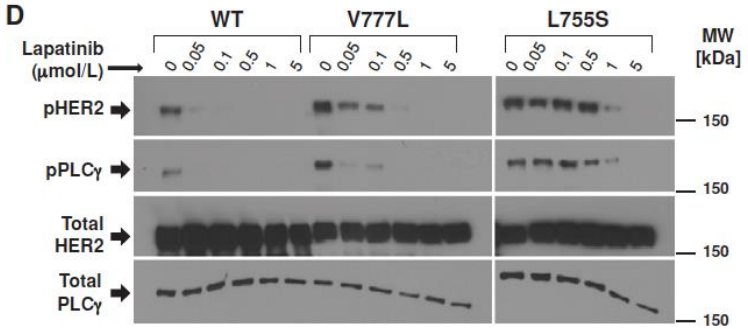
Blockade of ERBB2-receptor tyrosine kinase with monoclonal antibodies or small-molecule inhibitors

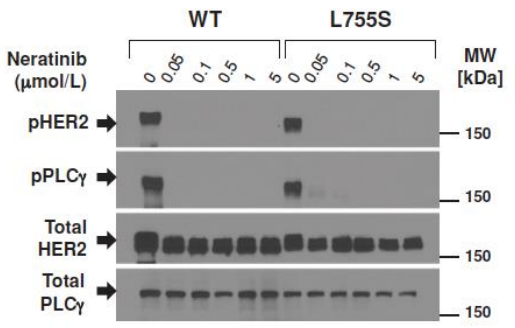


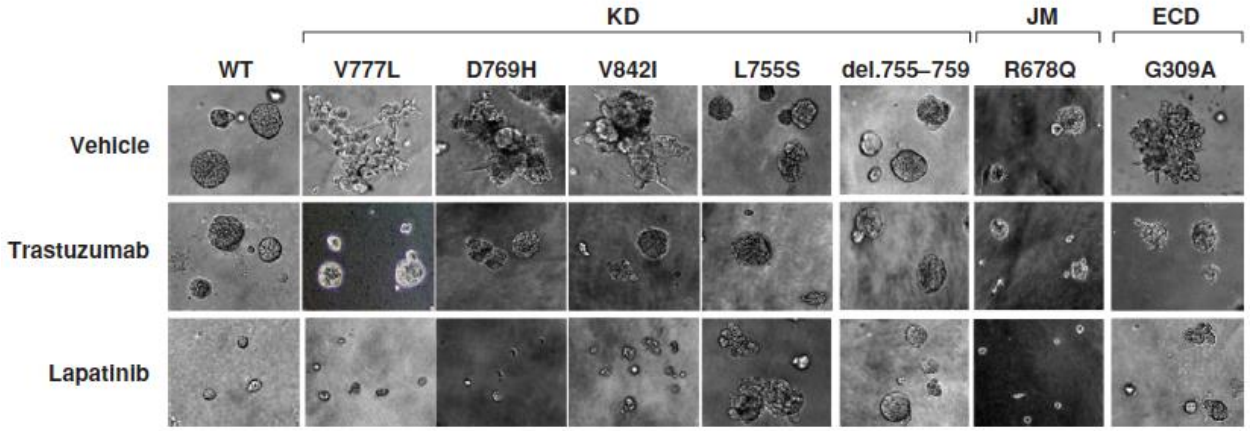
Baselga and Swain, NRC 2009

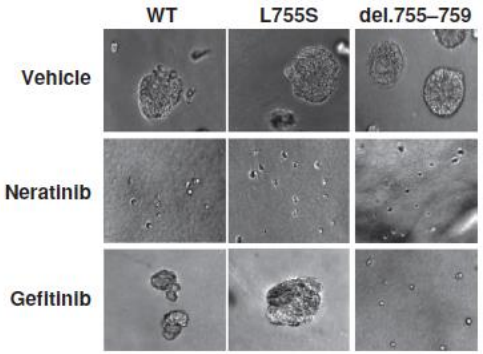
Reversible *vs* irreversible inhibition of ERBB2 in mutation-activated cancers







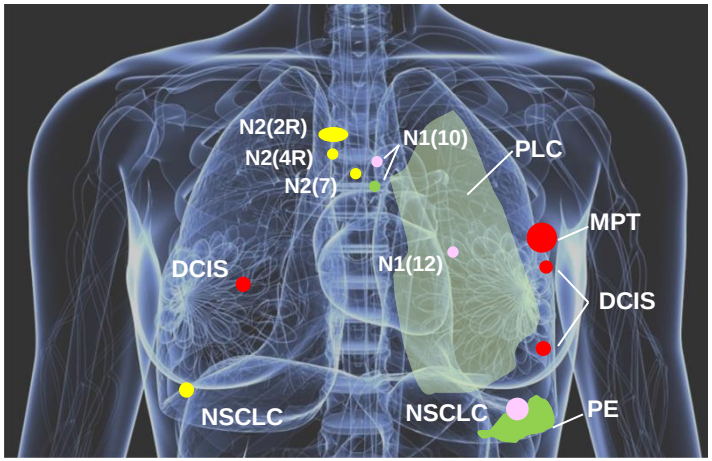




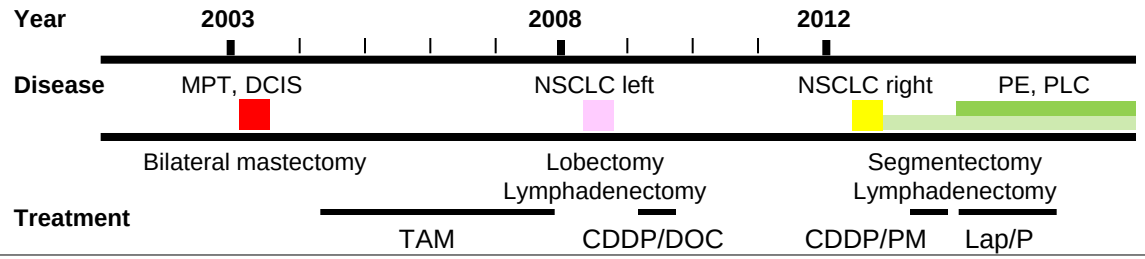
Bose *et al*, Can Disc 2013

CLINCAL RESPONSE TO A LAPATINIB-BASED THERAPY FOR A LI-FRAUMENI PATIENT WITH A NOVEL HER2-V659E MUTATION

A Tumor sites

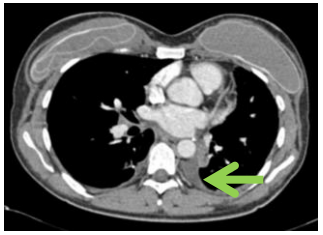


B Treatment timelines

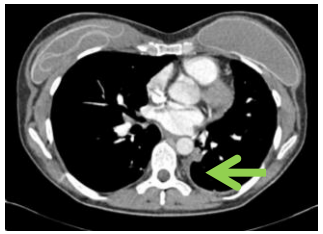


Radiologic response to lapatinib/paclitaxel in PE

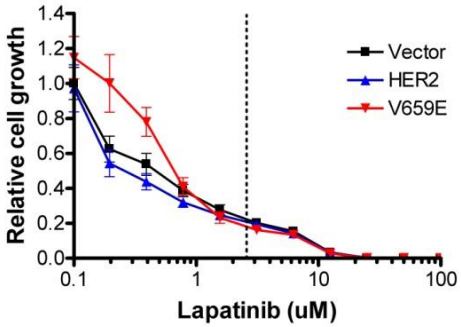
March 19, 2012

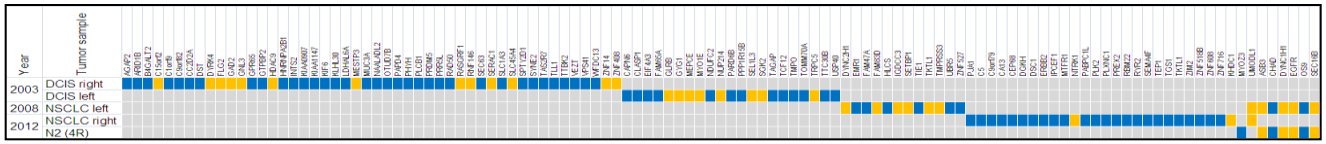


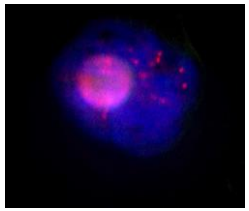
June 11, 2012



Antiproliferative activity of lapatinib

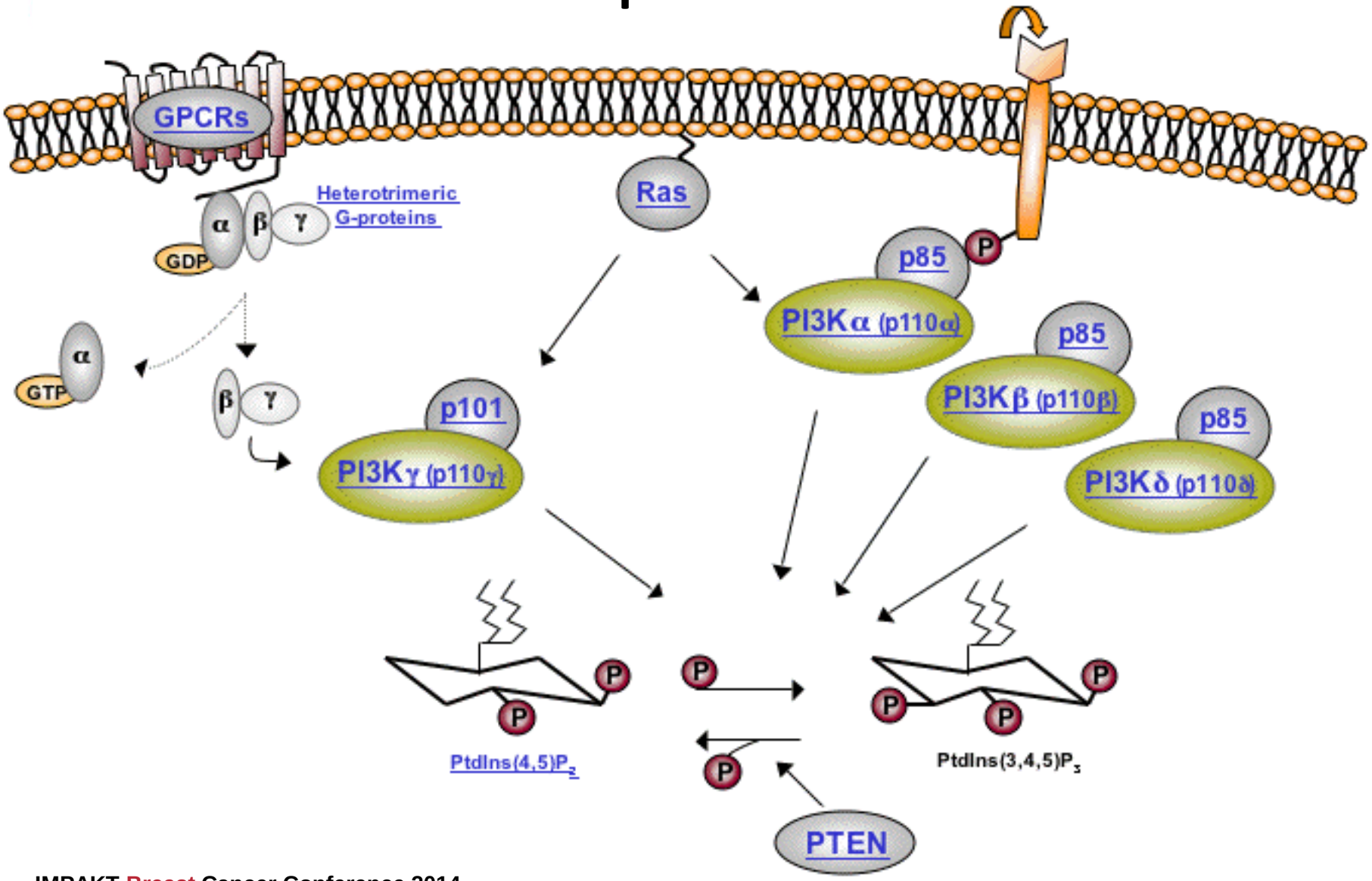






Serra et al *Cancer Discovery* 2013

PI3K lipid kinase



Clinical activity of PI3K-alpha inhibitors

Safety

- Median duration of exposure to BYL719 was 11.6 weeks (range: 0.7–60.7 weeks; **Figure 3**).

Figure 3. Duration of exposure to BYL719 and overall response by RECIST as per local review

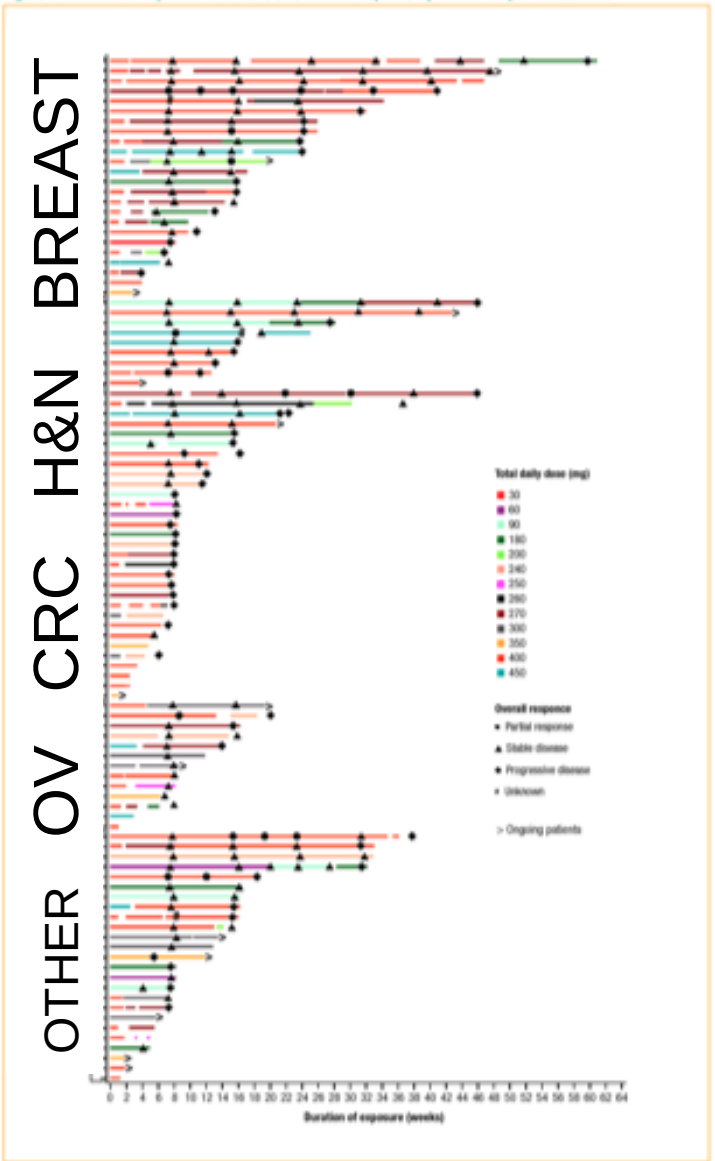
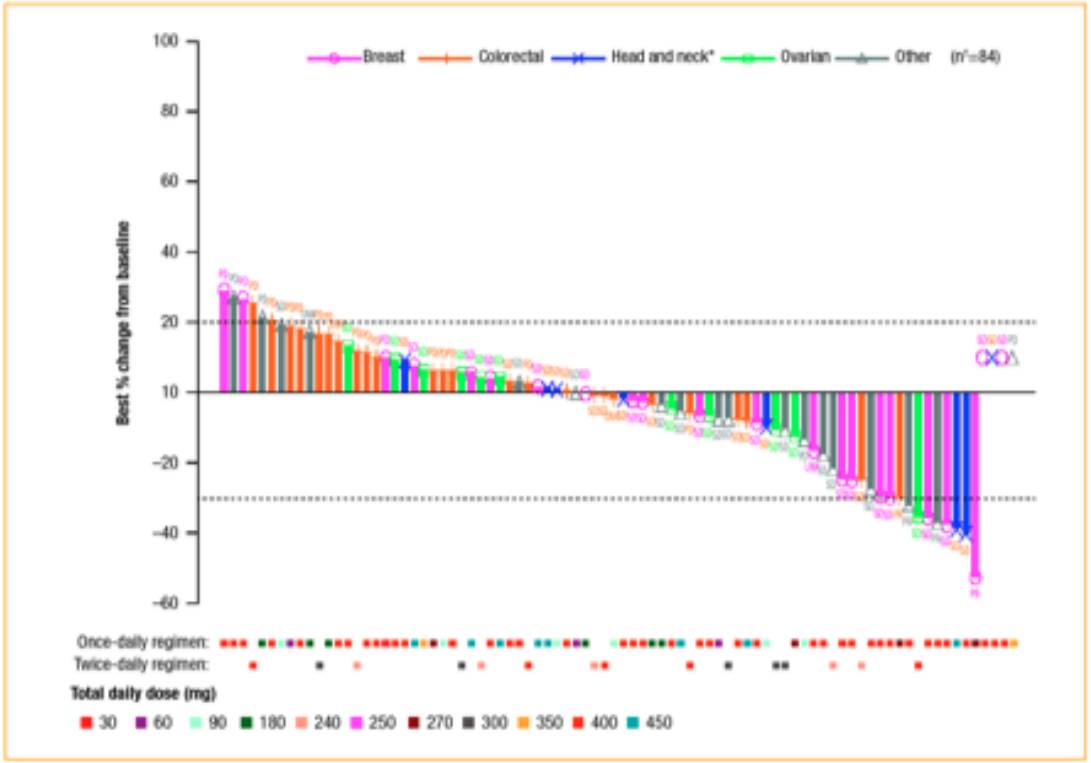


Figure 6. Best percentage change in sum of longest diameters and best overall response



Presented by Gonzalez-Angulo *et al*
at ASCO Annual Meeting 2012

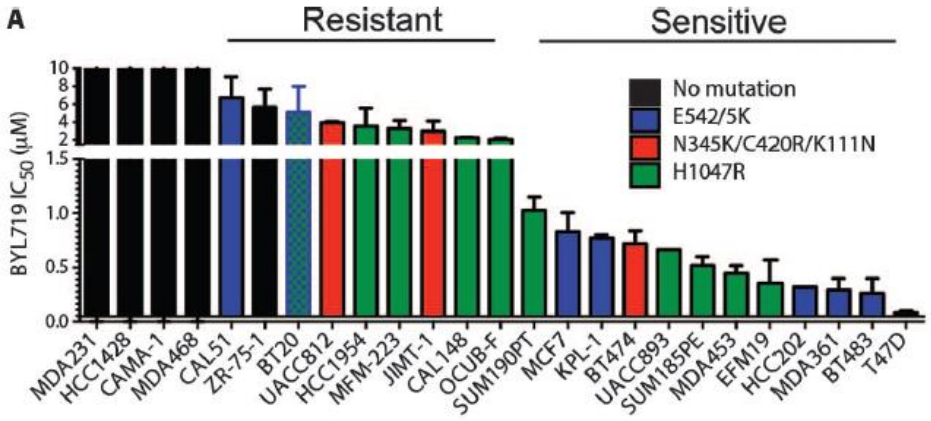
Mechanisms of resistance to PI3K inhibitors

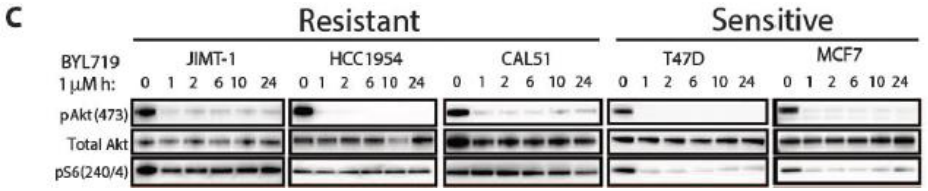
- Myc amplification (Liu et al Nat Med 2011)
- Notch 1 activation / myc (Muellner et al NCB 2011)
- Myc / eIF4E amplification (Ilic et al PNAS 2011)

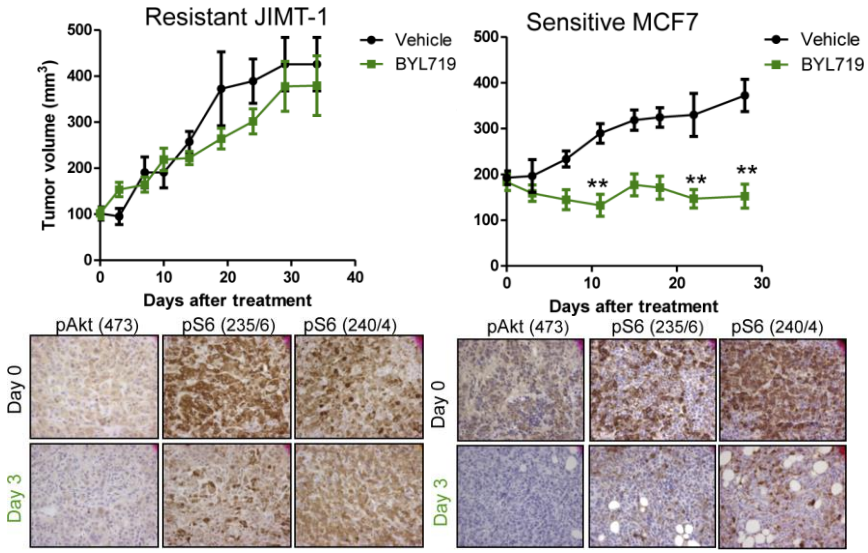
- Ras mutations (Ihle et al, Can Res 2009)
- RSK3/4 (Serra, Eichhorn et al JCI 2013)
- Amplification of mutant *PIK3CA* (Huw et al, Oncogenesis 2013)
- **Activation downstream of mTORC1 (Elkabets et al, STM 2013)**

- Feedback activation of JAK2/STAT5 (Britschgi et al Cancer Cell, 2012)
- Adaptive response Bcl2, EGFR, IGF1R (Muranen et al Cancer Cell 2011

PI3K-sensitive cell lines/tumors undergo complete PI3K-pathway inhibition upon PI3K blockade







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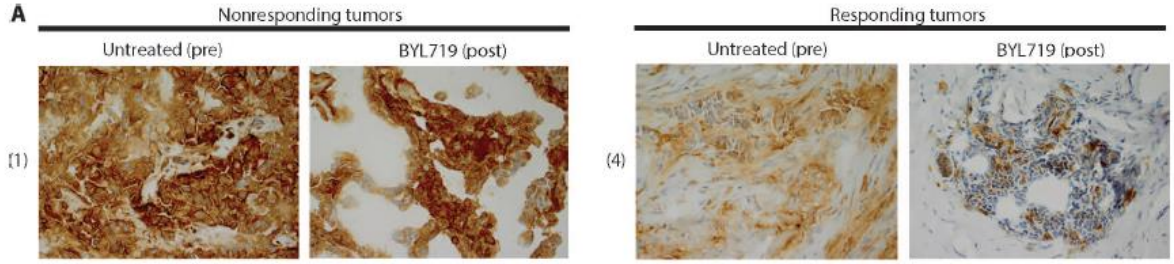

Elkabets *et al*, Science Translational Medicine 2012

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