Steps forward in targeted therapy of breast cancer

Phase Ib/II study of BKM120 in combination with trastuzumab

Phase I study of E3810 with expansion in *FGFR1* amplified breast cancer

SAFIR trial – molecular screening

Dr Nicholas Turner
Royal Marsden Hospital and Institute of Cancer Research

The Royal Marsden NHS Foundation Trust

ICR The Institute of Cancer Research 1909 2009

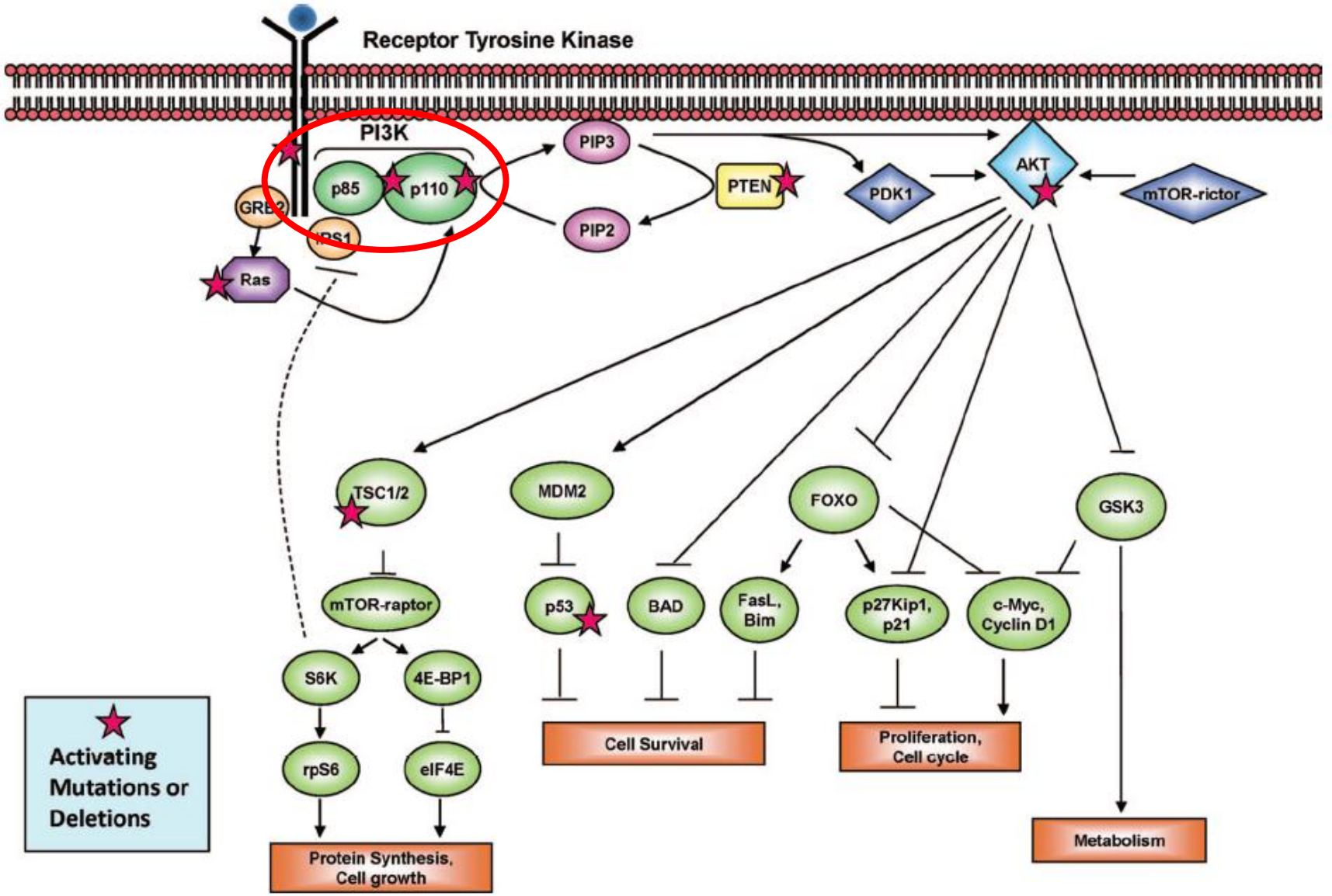
Disclosure relevant to discussion

Nicholas Turner

Honoraria

Novartis
AstraZeneca
EOS

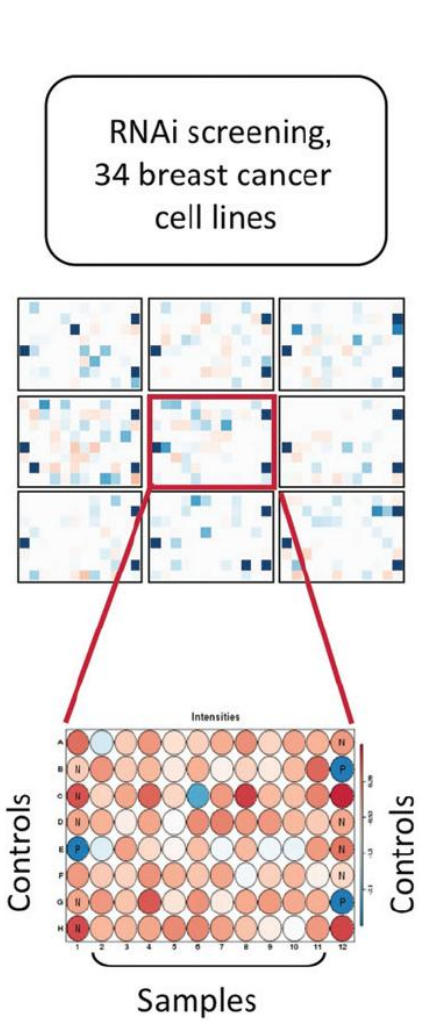
Background: PI3K-Akt pathway

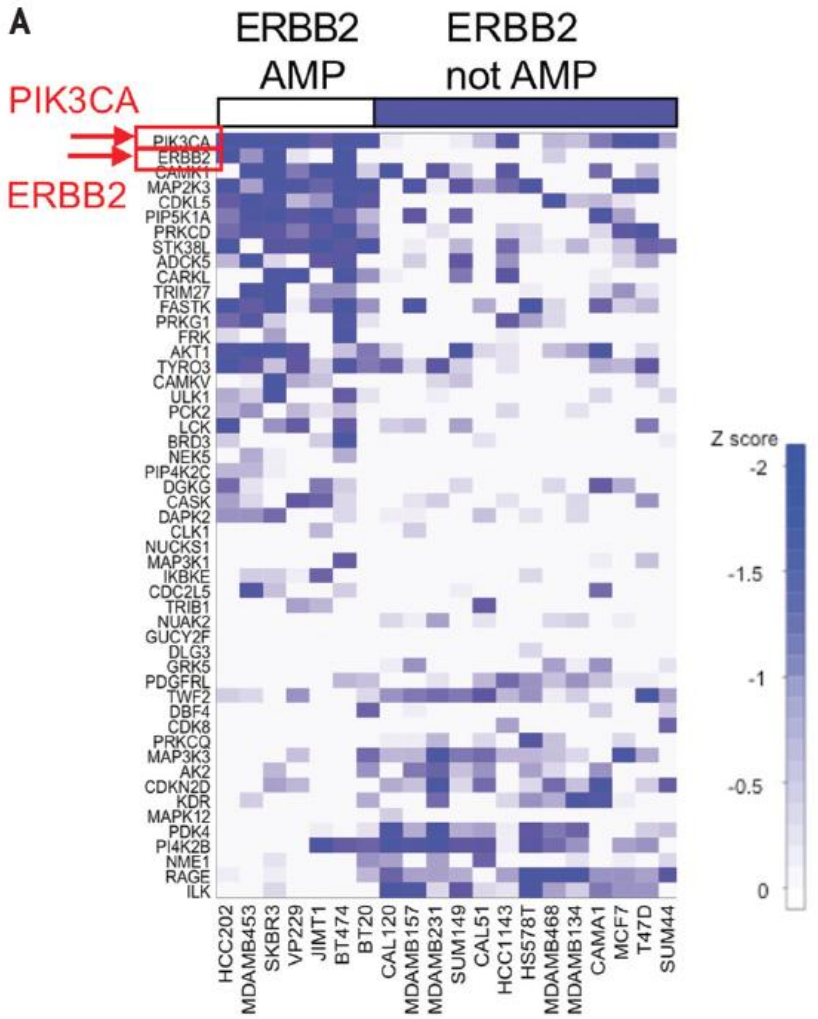


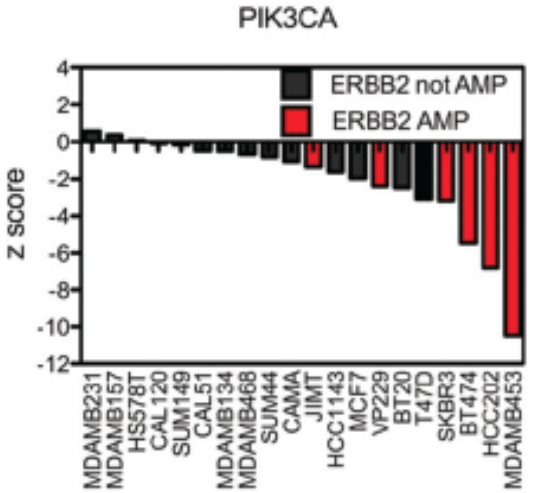
PIK3CA mutated in ~30% HER2 amplified cancers

Baselga J The Oncologist 2011

HER2 (ERBB2) amplified breast cancer is dependent on PI3 kinase signalling





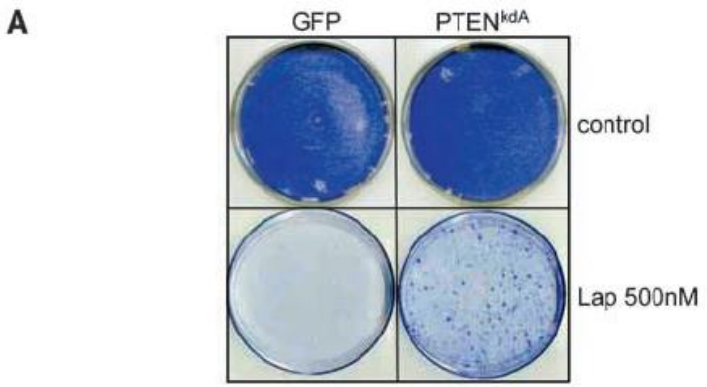


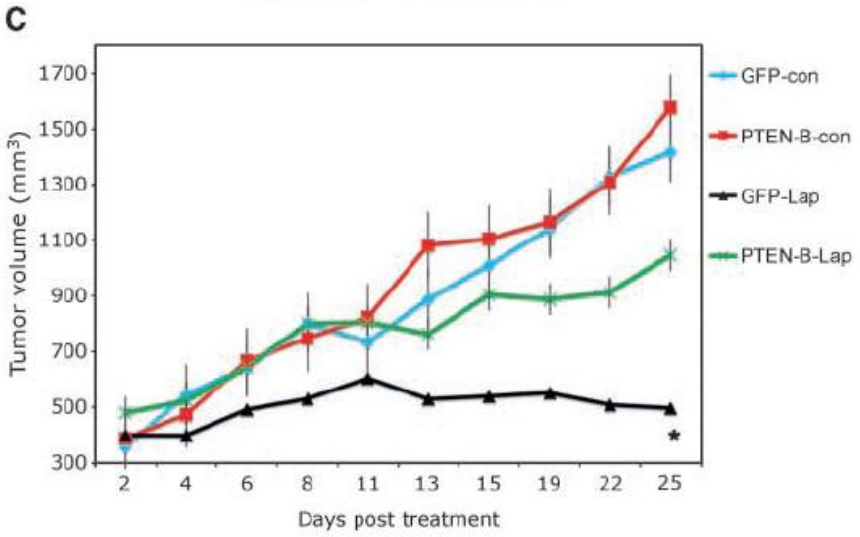
Brough et al Cancer Discovery 2012

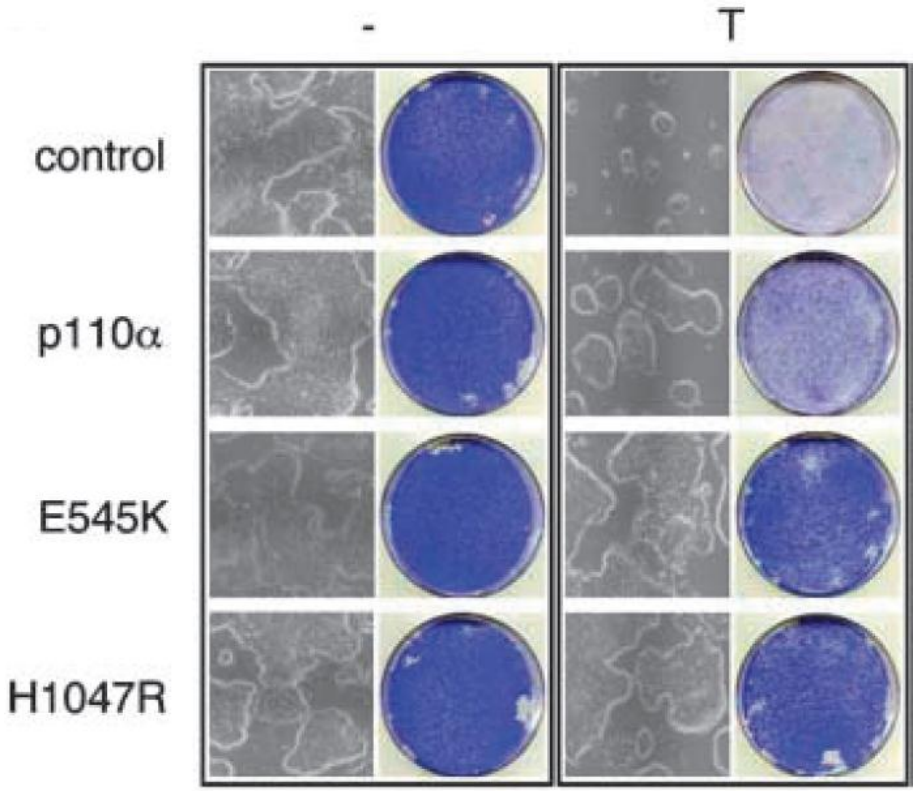
Activation of PI3 kinase pathway induces resistance to HER2 targeting

Loss of PTEN

Mutation of *PIK3CA*

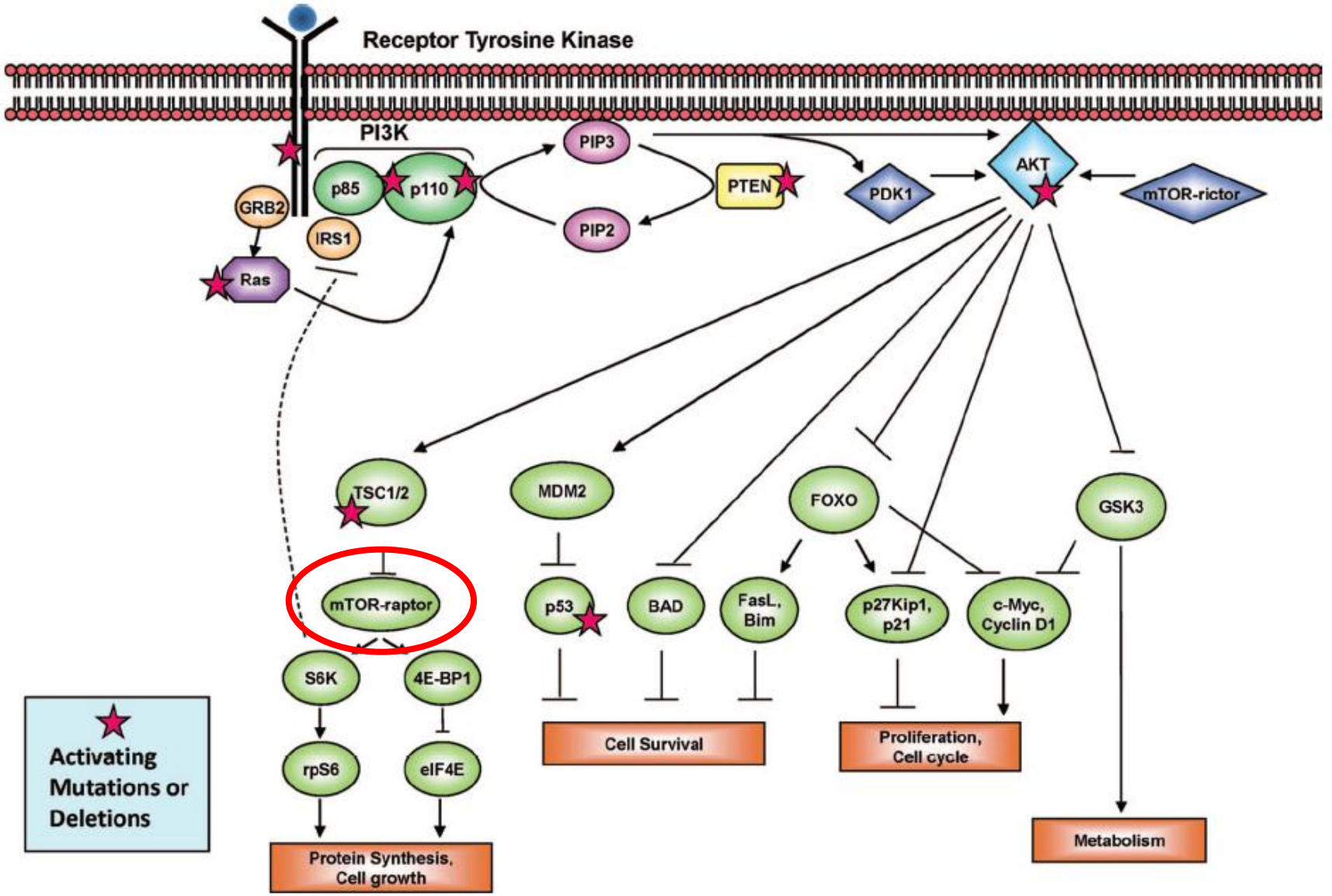






Eichhorn et al Cancer Res 2008

Background: PI3K-Akt pathway



PIK3CA mutated in ~30% HER2 amplified cancers

Baselga J The Oncologist 2011

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ORIGINAL REPORT

Phase I/II Study of Trastuzumab in Combination With Everolimus (RAD001) in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy

Phuong K. Morrow, Gerburg M. Wulf, Joe Ensor, Daniel J. Booser, Julia A. Moore, Peter R. Flores, Yan Xiong, Siyuan Zhang, Ian E. Krop, Eric P. Winer, David W. Kindelberger, Jeanna Coviello, Aysegul A. Sahin, Rodolfo Nuñez, Gabriel N. Hortobagyi, Dihua Yu, and Francisco J. Esteva

47 patients resistant to trastuzumab

Treated with traztuzumab + mTOR inhibitors everolimus

15% (7/47) partial response

Ph Ib/II study of BKM120 plus trastuzumab in patients with trastuzumab-resistant HER2+ advanced breast cancer

Barbara Pistilli[1], Ander Urruticoechea[2], Stephen Chan[3], Hyo Sook Han[4], Guy Jerusalem[5], Anthony Kong[6], Qinhua Ru[7], Sophie Ruquet[8], David Sternberg[7], Cristina Saura[9]

[1]Macerata Hospital, Macerata, Italy; [2]Catalan Institute of Oncology, Barcelona, Spain; [3]Nottingham University Hospital, Nottingham, UK; [4]Moffitt Cancer Center, Tampa, FL; [5]C.H.U. Sart-Tilman, Liege, Belgium; [6]Oxford University Hospitals NHS Trust, Oxford, UK; [7]Novartis Oncology, Florham Park, NJ; [8]Novartis Oncology, Paris, France; [9]Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Trial summary

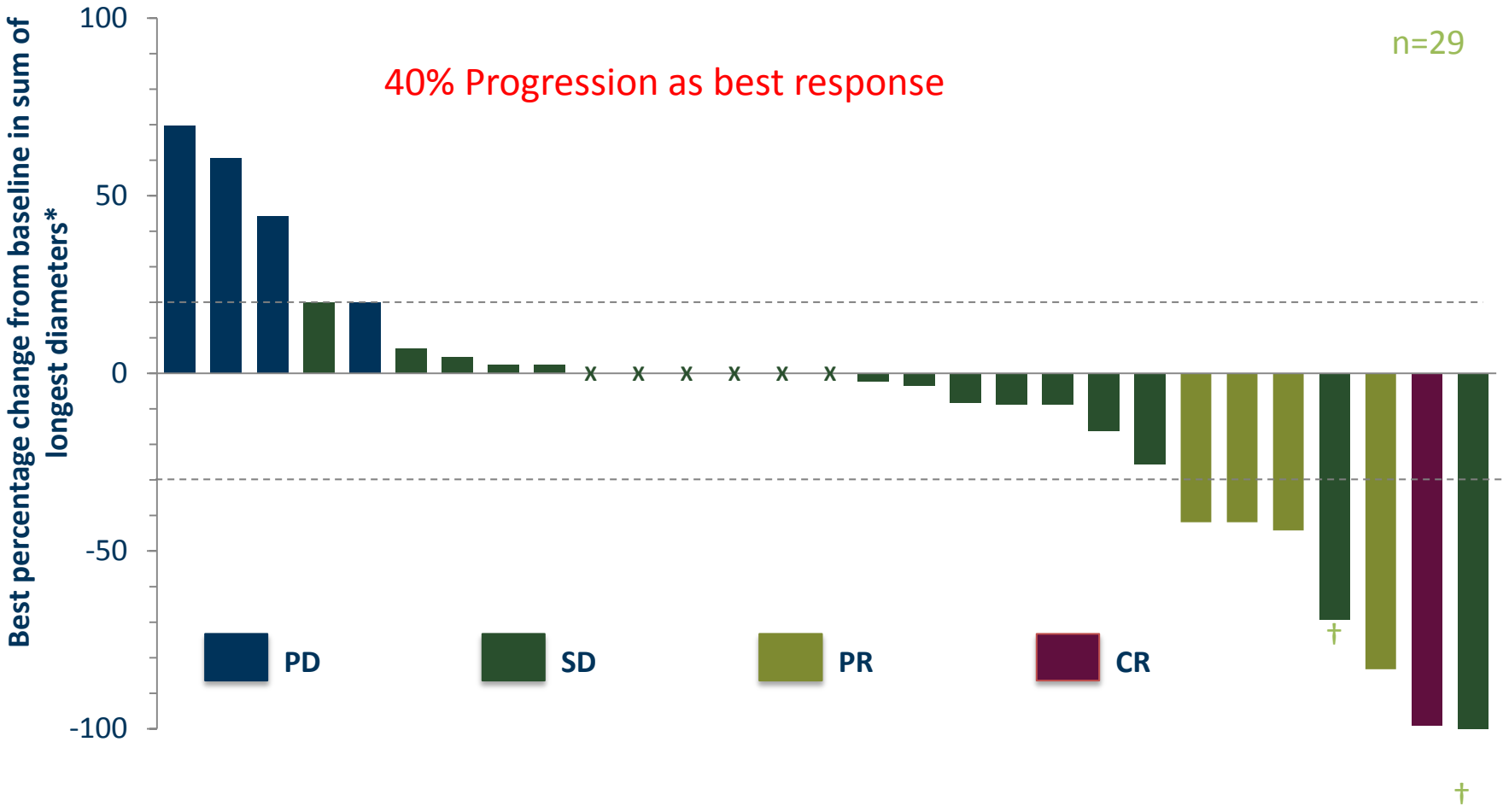
BKM120 Pan-PI3 kinase inhibitor in combination with trastuzumab

Trastuzumab resistant pre-treated disease
median 2.5 prior lines of HER2 directed therapy

50 Patients (with another 3 who never received BKM120)

Combination generally well tolerated

Clinical efficacy of BKM120 plus trastuzumab



Response rate 10%

Median exposure to drug 9 weeks

BKM120 and trastuzumab – who benefits?

Benefit appears to be only a relatively small proportion of patients – but in those patients an impressive level of activity

Strongly suggests biomarkers to guide future development

Full analysis of *PIK3CA* mutations required

BKM120 and trastuzumab – who benefits?

Response rate comparable with that reported for everolimus-trastuzumab

Responders on BKM120 - trastuzumab - same subset (or not) that responds to everolimus-trastuzumab?

Bolero 1 and 3 pivotal trials awaiting reporting

HER2 amplified cell lines are specifically reliant on the alpha catalytic subunit (*PIK3CA)*

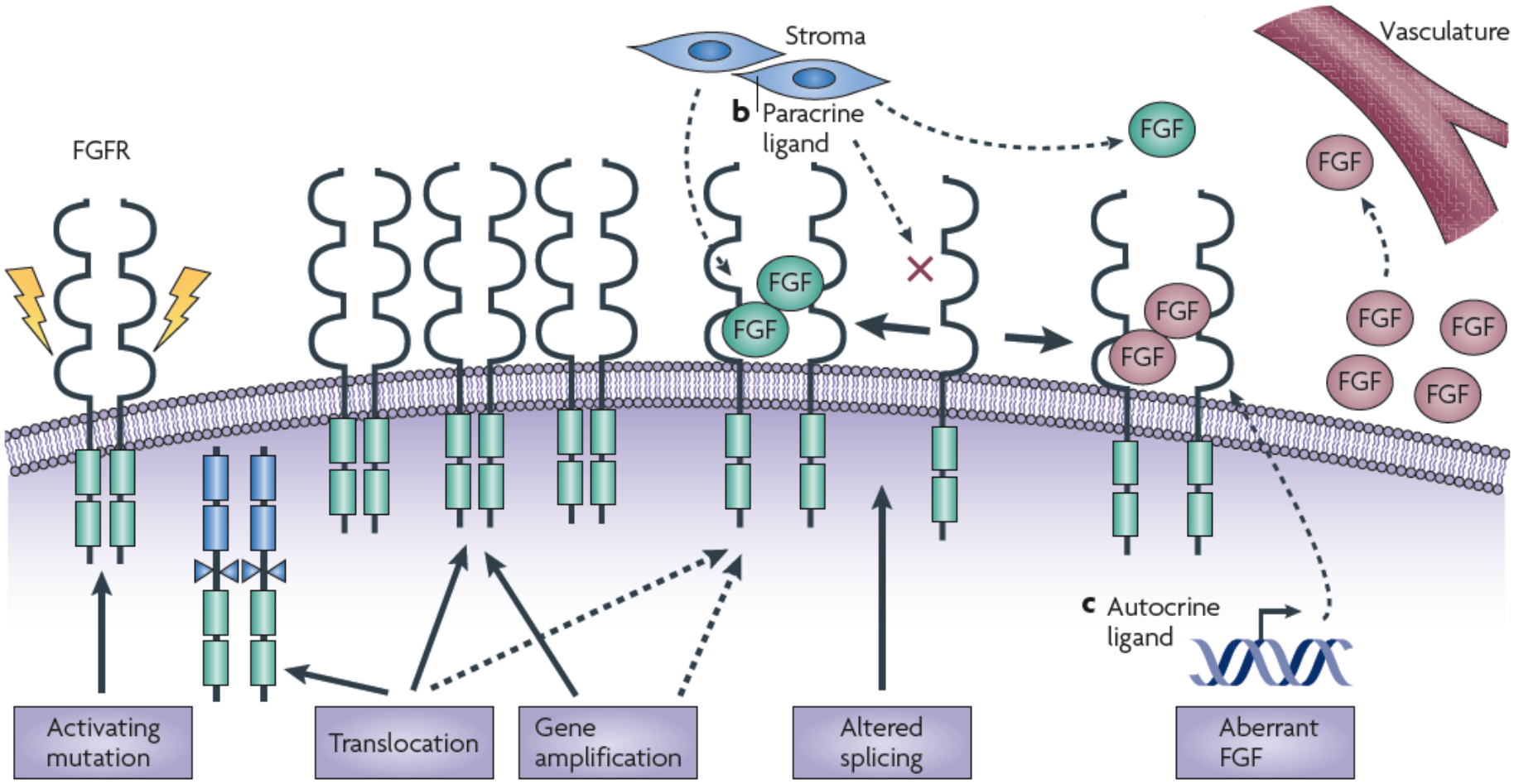
-could higher responses be achieved with alpha specific PI3K inhibitors?

Activation of FGFR signalling in cancer

Ligand independent signalling

Ligand dependent signalling

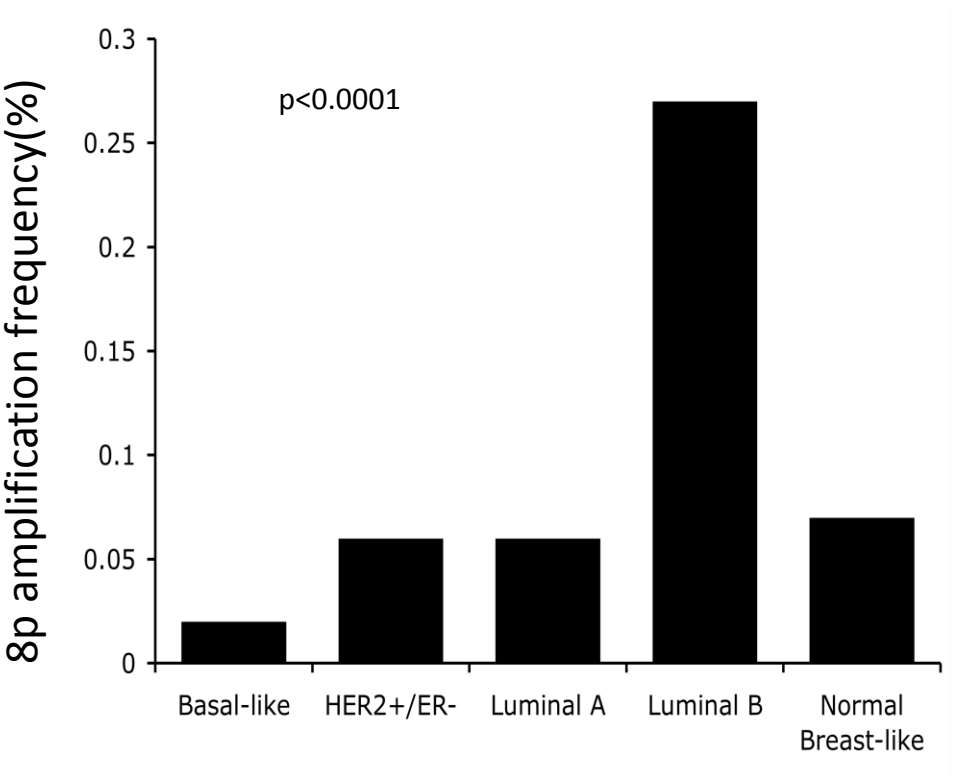
Angiogenesis



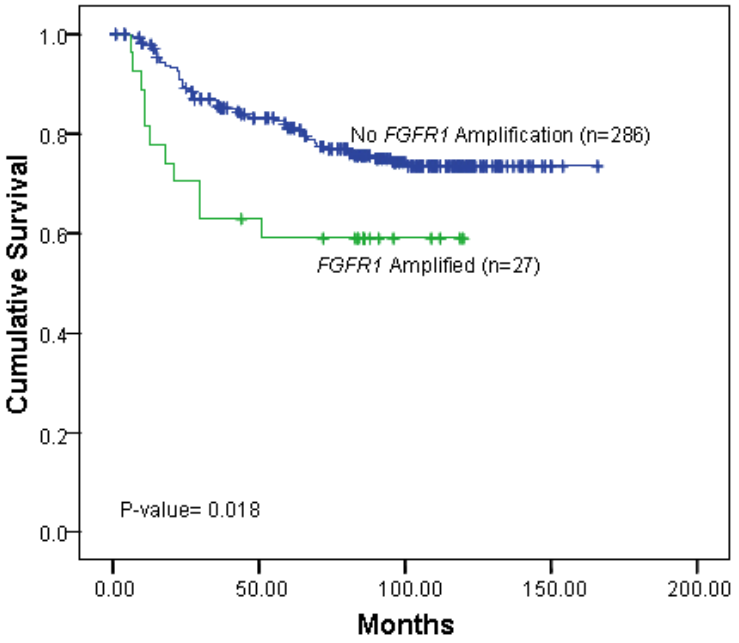
Turner and Grose Nat Rev Cancer 2009

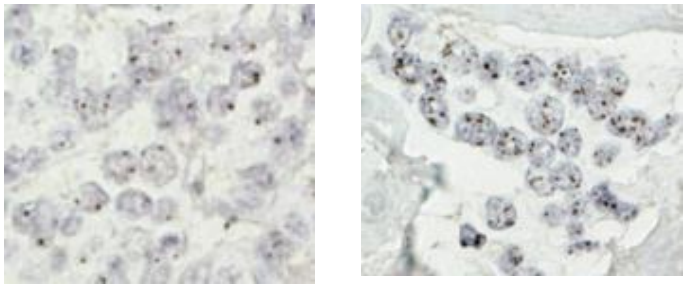
FGFR1 amplification in luminal B type breast cancer

Amplification in Luminal B subtype



Disease free survival

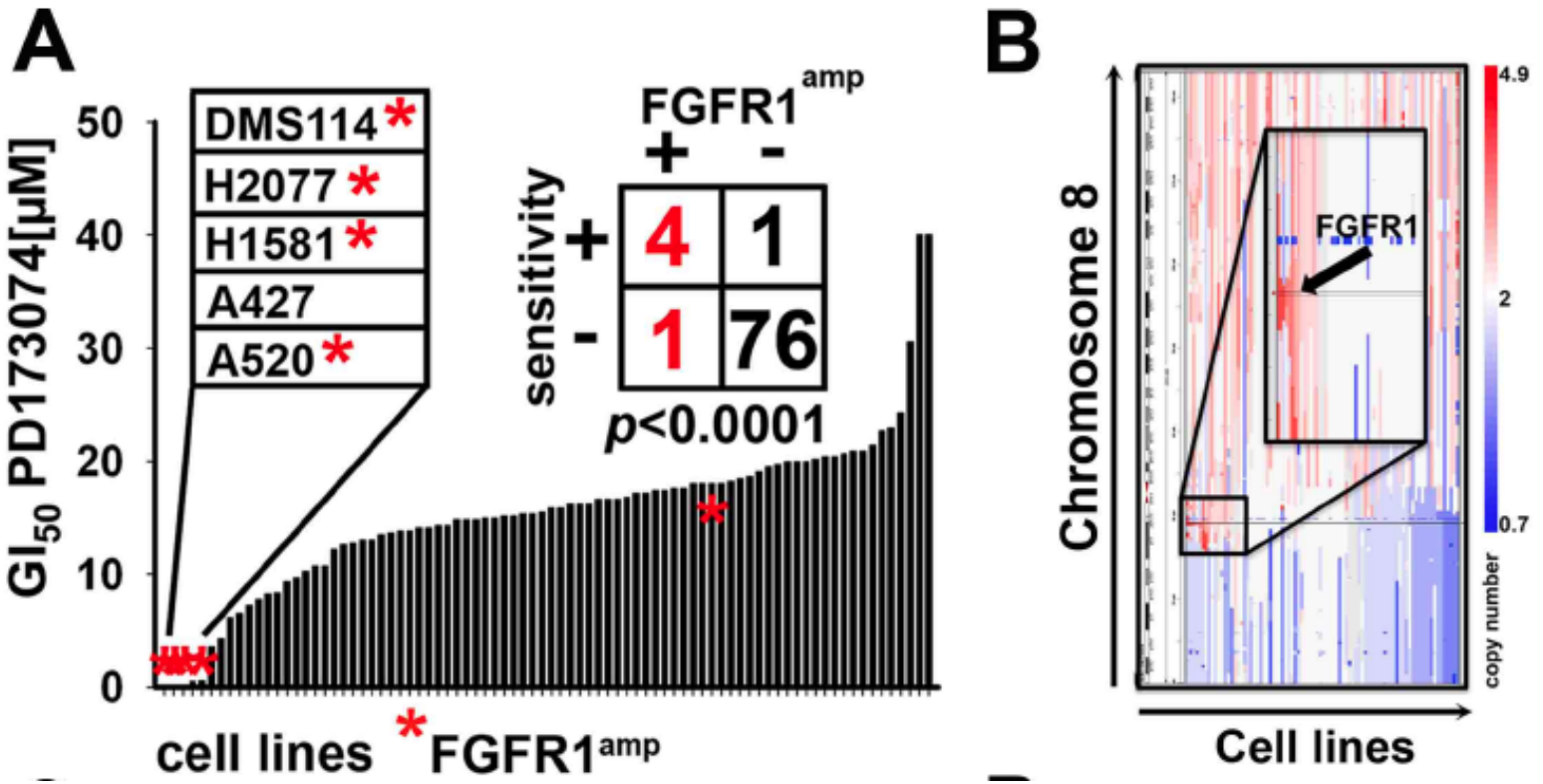


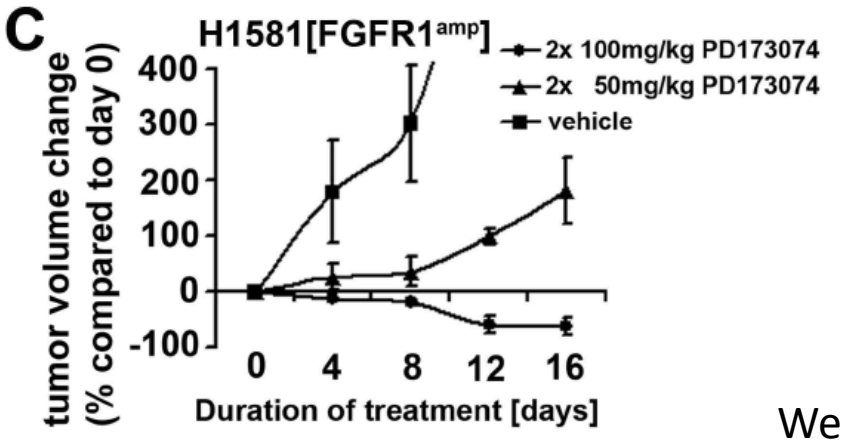


Turner et al Cancer Res 2010

El-Sheikh et al BCR 2007

FGFR1 is amplified in squamous lung cancer





Weiss et al Science Trans Med 2011

Significant antitumor activity of E-3810, a novel FGFR and VEGFR inhibitor, in patients with *FGFR1* amplified breast cancer

R. Dienstmann, F. Andrè, J.C. Soria, J. Tabernero, F. De Braud, R. Cereda, R. Bahleda, A. Hollebecque, A. Delmonte, M.G. Camboni

Breast Cancer Patients
Best Overall Response

	FGF+				Antiangiogenic sensitive			
	Evaluable	PR	SD	PD	Evaluable	PR	SD	PD
Breast cancer	10	7*@	1	2	2		1	1
ER+/PR+, HER2-	4	3		1	1			1
ER+/PR-, HER2-	3	2	1					
ER+/PR+, HER2+					1		1**	
ER+/PR-, HER2+	1			1				
TPN	2	2						

Response rate

***FGFR1* amplified 4/9 patients**
11q amplified 3/3 patients

Estimate of Median PFS ~5 months

Discussion points

EOS3810 - highly efficacious

Tolerability profile

Is this just a simple story of oncogene addiction?

Expansion Cohorts - Overall Safety

		FGF+		Antiangiogenic Sensitive	
		20 mg (n=3)	15 mg (n=15)	20 mg (n=10)	15 mg (n=23)
Off for toxicity	Any Cy	-	2*	4**	4***
	@ C1	-	1	3	2
Dose decreased	Any Cy	3	8	7	12
	@ C1-2	2	5	6	10
Treatment interruption		3	8	7	15

Reasons for interruption/dose decrease: GI toxicity and asthenia (14 pts), proteinuria (10 pts), HTN (8 pts).
Other significant events: LVEF decrease (2 pts), asymptomatic amylase-lipase increase (2 pts)

At 15mg Dose 47% (18/38) patients dose decrease in first 2 cycles

Side effects of VEGFR and multi-kinase inhibition

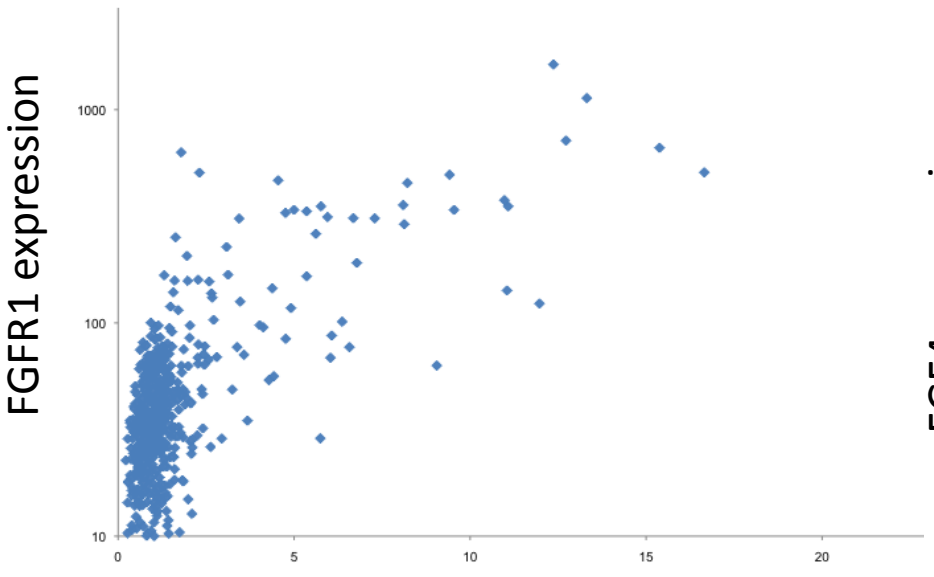
Further work on identifying a chronically tolerable dose/schedule

Why do 11q amplified patients respond?

11q amplicon CCND1, FGF3, FGF4, FGF19

3/3 patients respond to E-3810

But FGFs not frequently expressed from amplicon?



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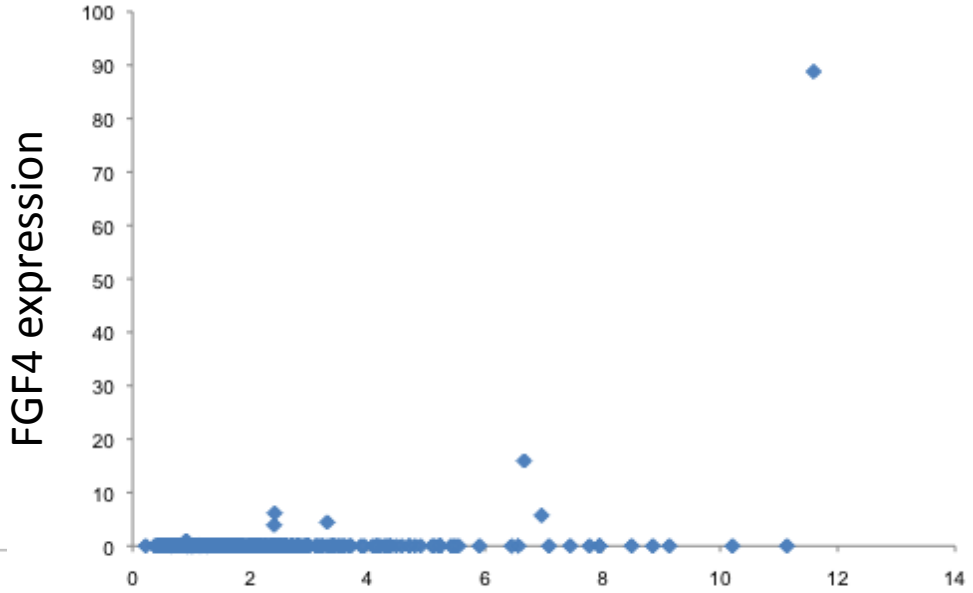
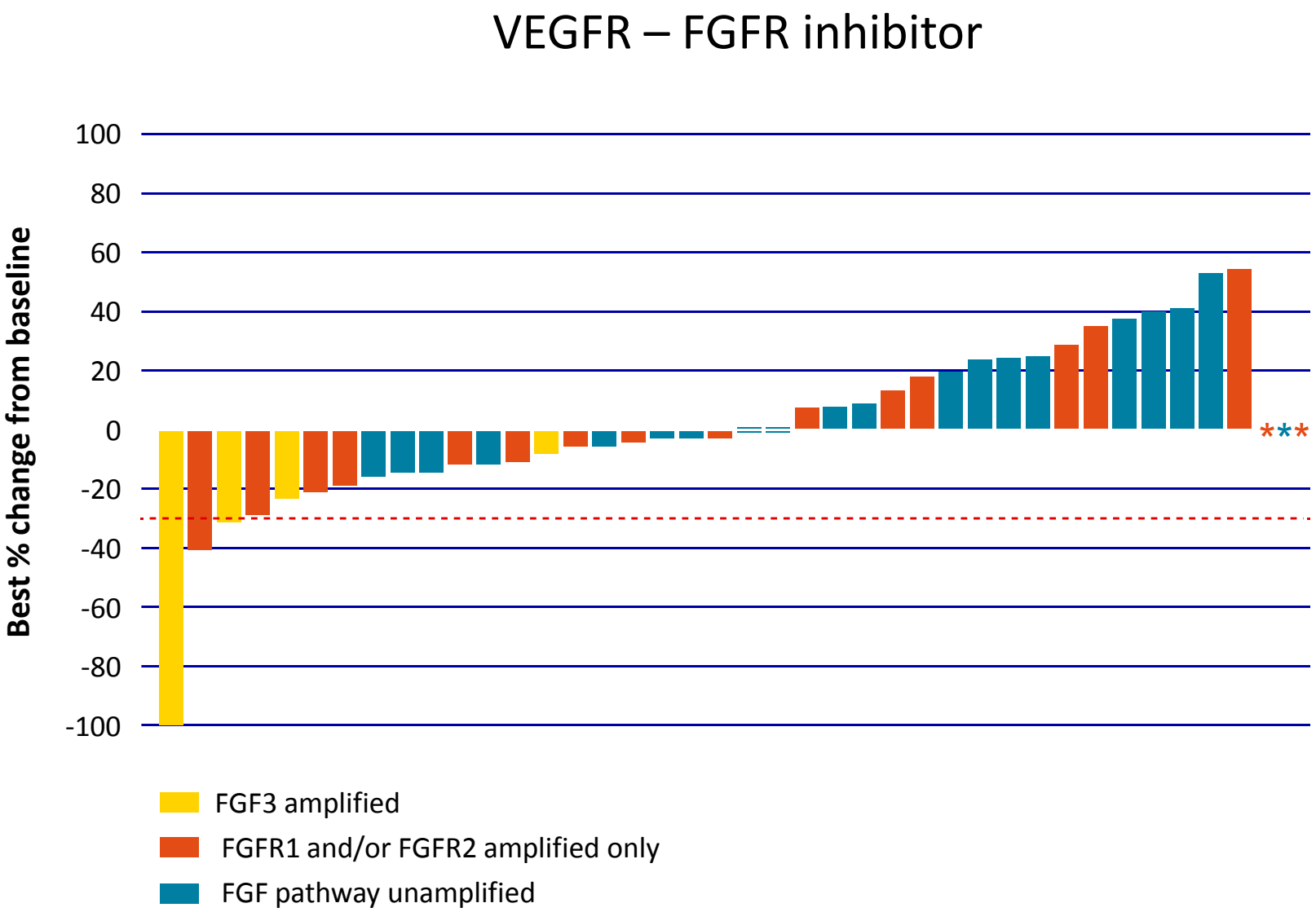


11q copy number

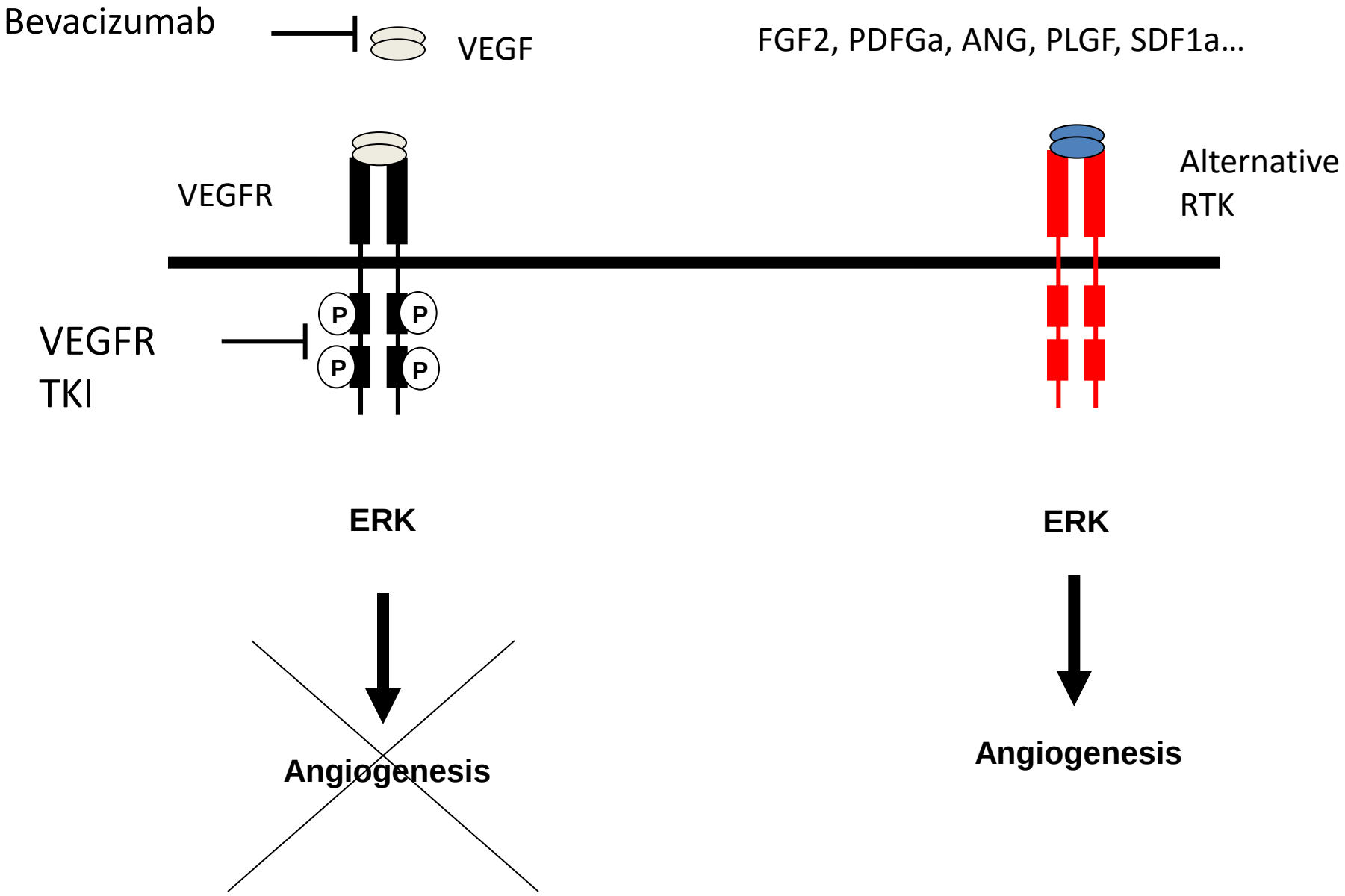
TCGA RNA Seq data

Phase II study of TKI258



Andre et al ASCO 2011

Target growth factor redundancy in angiogenesis



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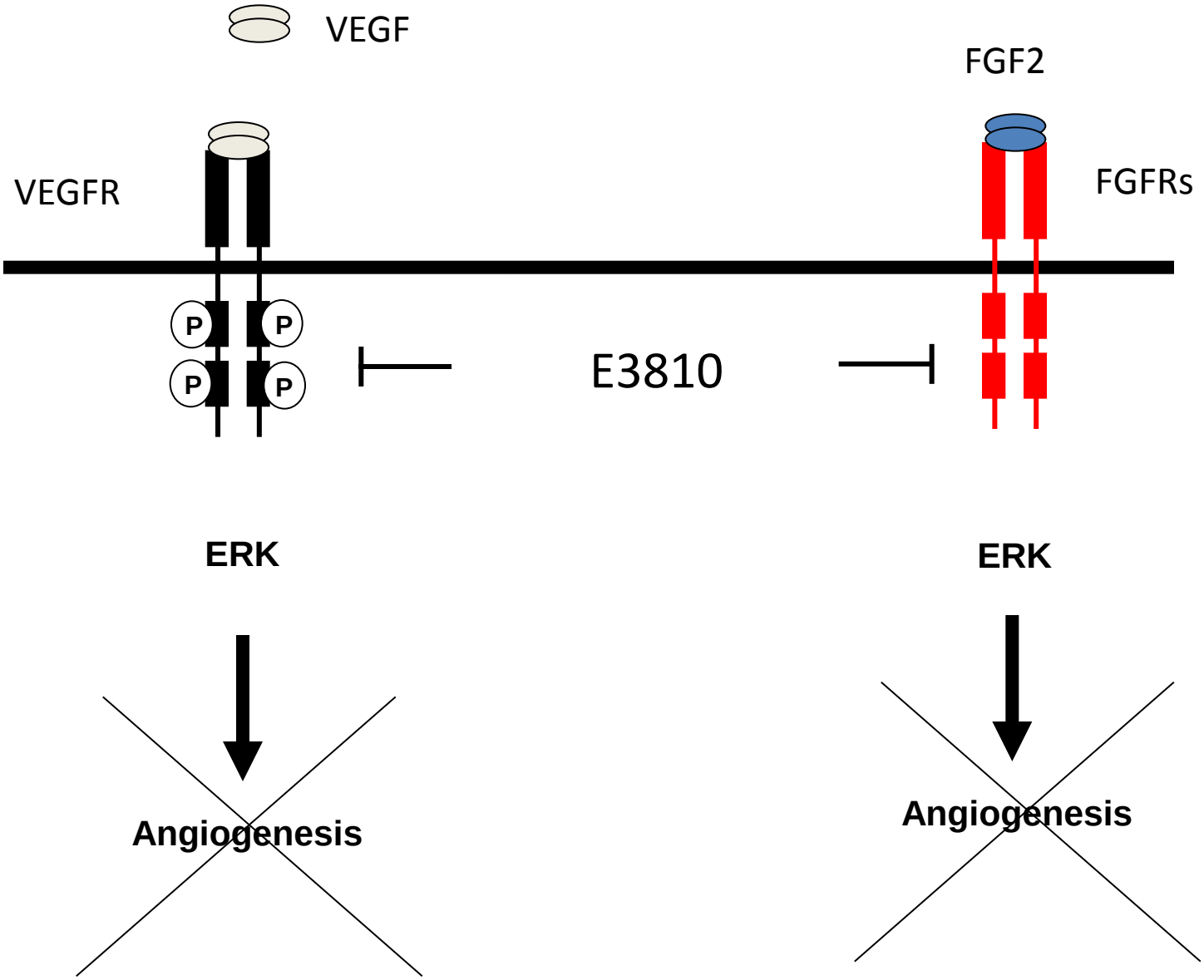
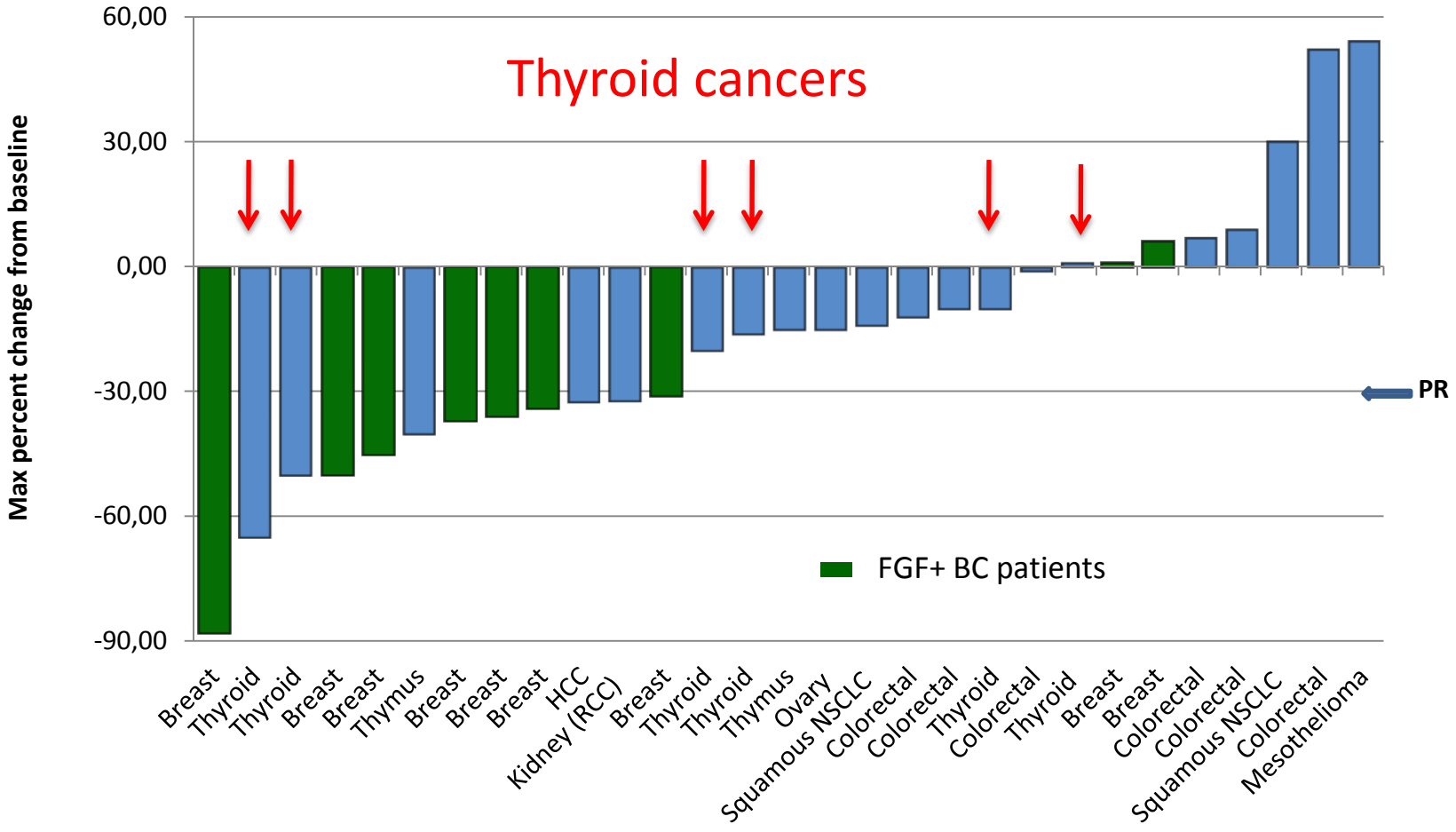


E3810 as an anti-angiogenic inhibitor



Is this just a simple story of oncogene addiction?

FGF2 is highly expressed in ER positive breast cancer stroma

Smith et al Ann Oncol 1999

FGF2 is expressed in an autocrine fashion by activated endothelium

Schweigerer et al Nature 1987

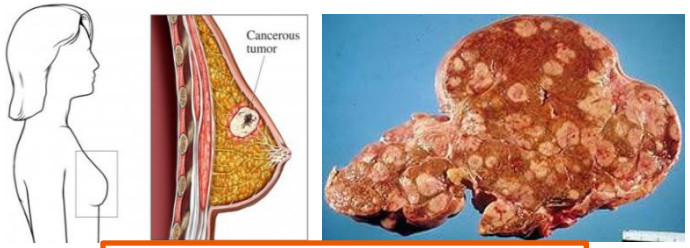
Is this a combined effect on angiogenesis and oncogene?

ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNICANCER SAFIR-01)

F. ANDRÉ, T. Bachelot, M. Campone, M. Arnedos, F. Commo, A. Gonçalves, C. Levy, J.-M. Ferrero, L. Lacroix, V. Dieras, F. Dalenc, D. Gentien, M. Lacroix-Triki, Q. Wang, J. Adelaide, M. Jimenez, H. Bonnefoi

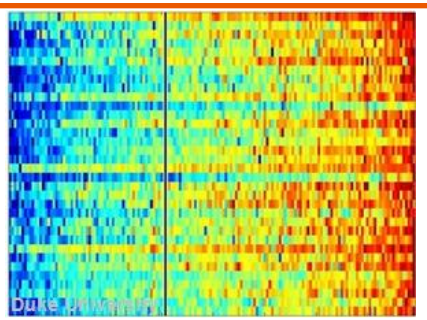
ESMO 2012, Vienna 1st october 2012

Personalized Medicine: To identify and target the right molecular pathway for each patient

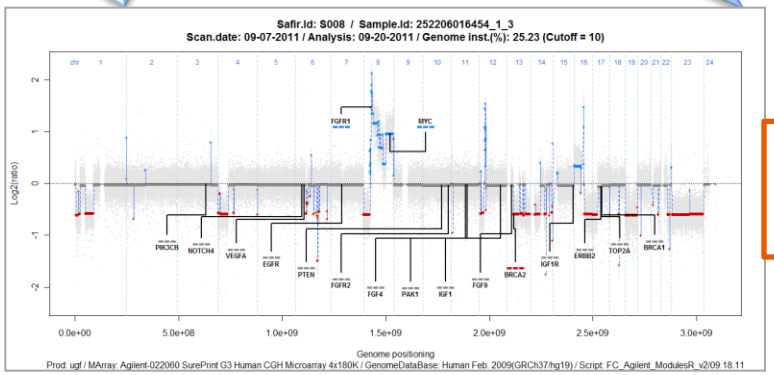


Biopsy metastases

Whole genome profiling



Identification of the Genomic Alteration



Targeted therapy according to the genomic profile

SAFIR01 Accrual