Avances en nuevos marcadores en cáncer y en biología tumoral AACR 2012

Federico Rojo
IIS-Fundación Jiménez Díaz

Roche

USCAP & AACR HIGHLIGHTS 2012

Guión de la presentación

- Avances en melanoma y BRAF
- Cáncer de mama: más allá de HER2
- NSCLC y EGFR
- Biología del cáncer: temas candentes

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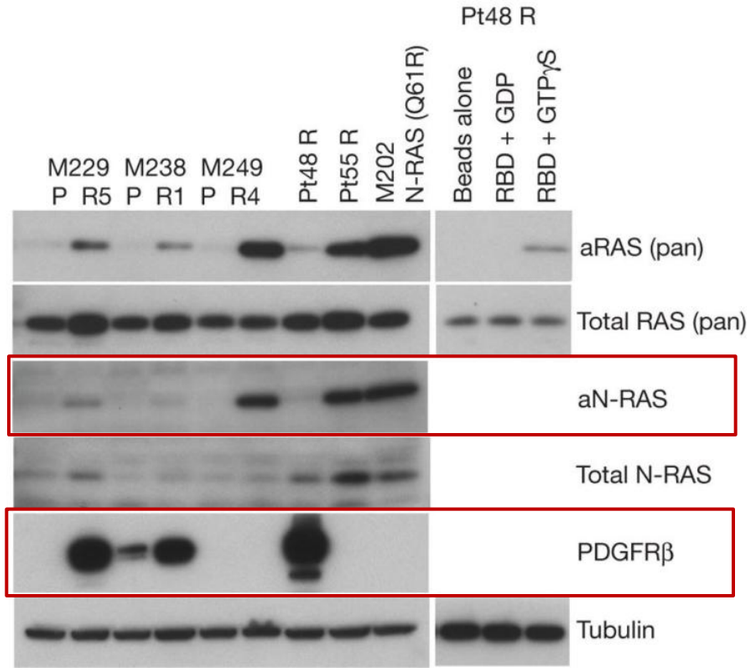
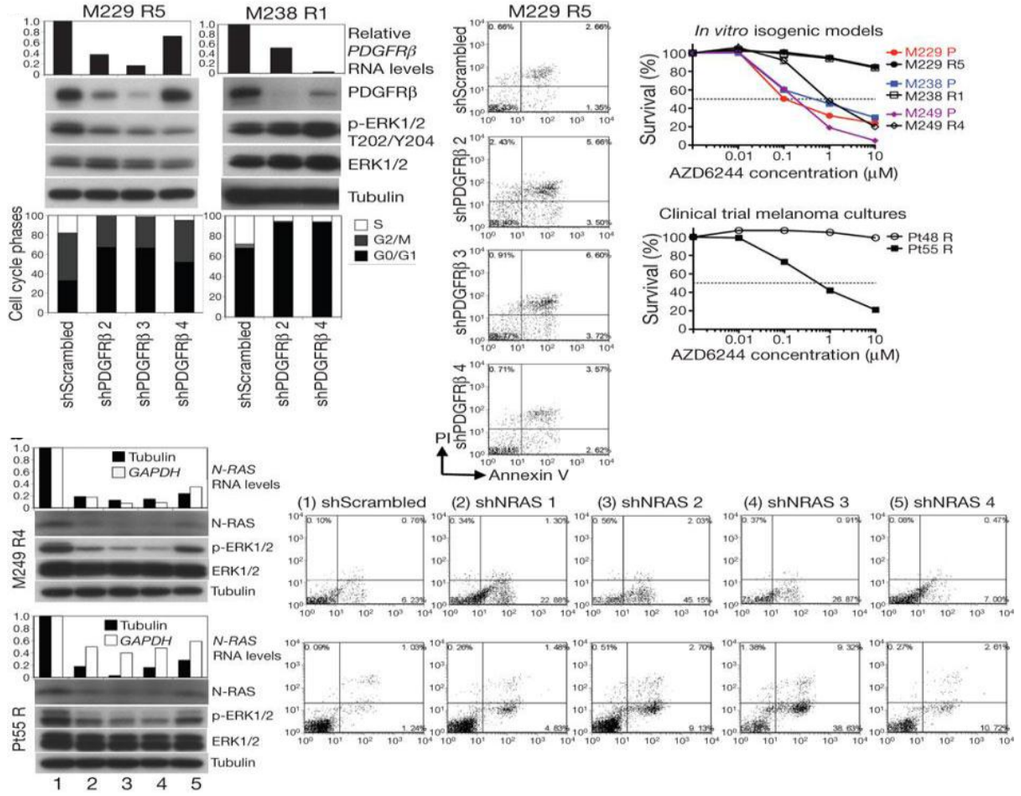
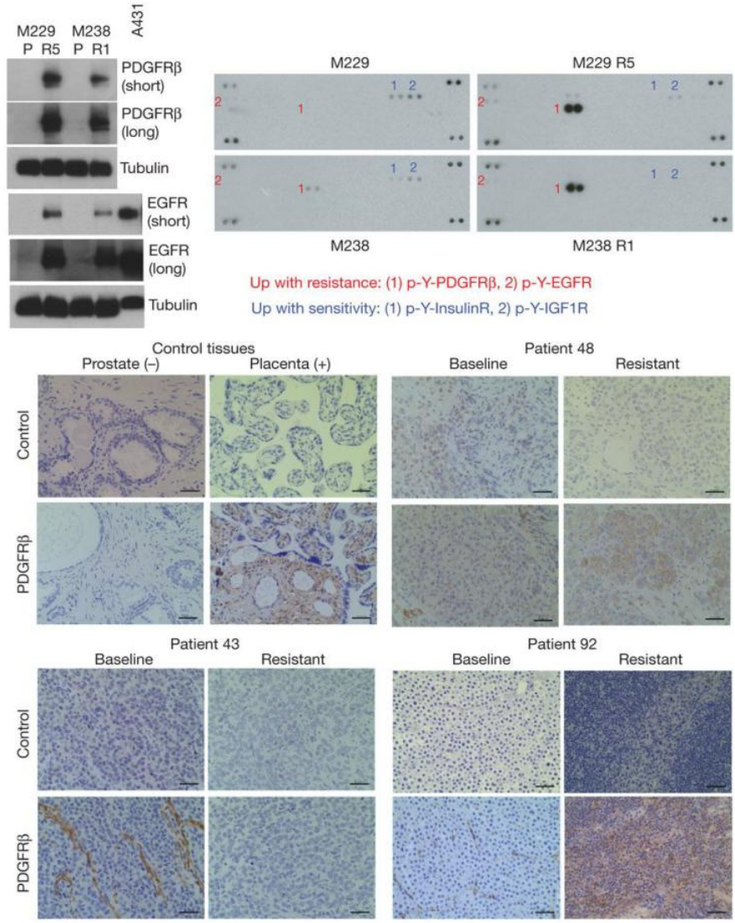
BRAF biomarkers of sensitivity

Targeting mutations in melanoma. *Smalley, KSM*

NRAS mutations in melanoma: How can we develop targeted therapies for these patients? *Davies, MA*







Resistance to Selective BRAF Inhibition Can Be Mediated by Modest Upstream Pathway Activation

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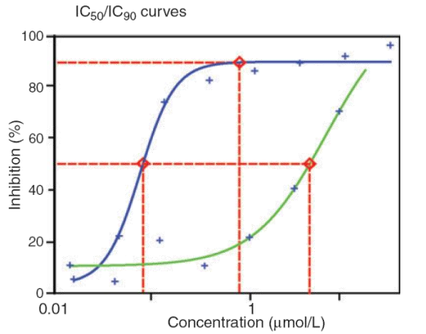

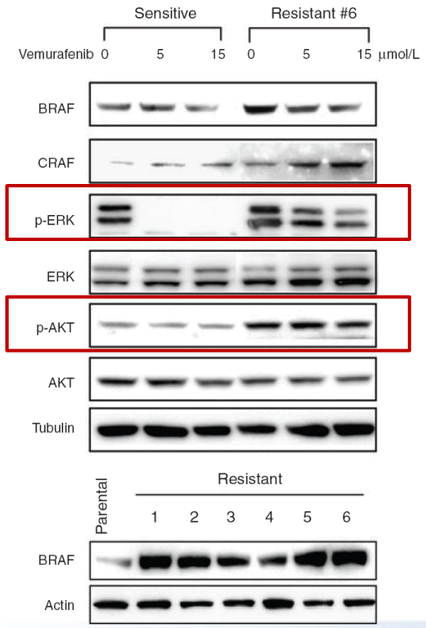

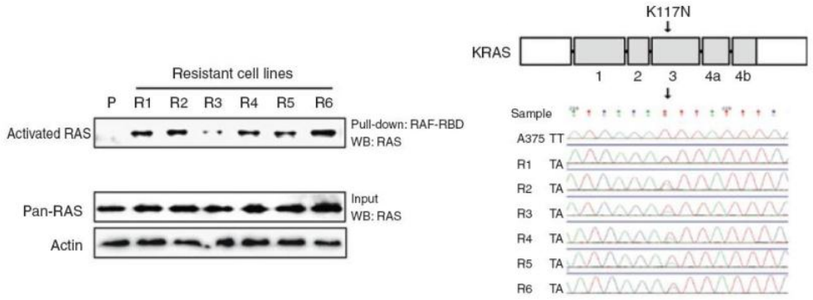

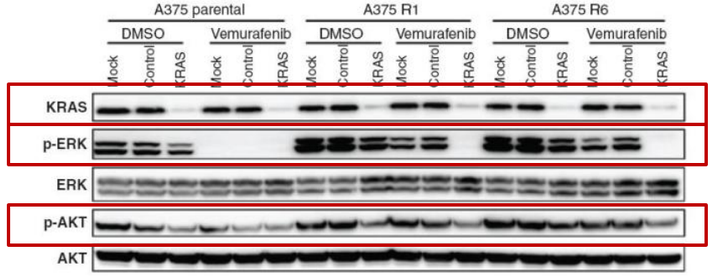

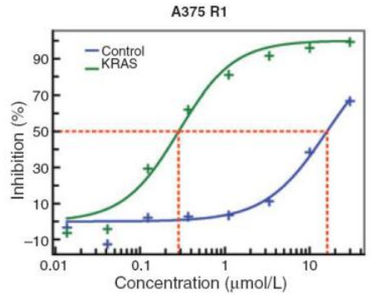

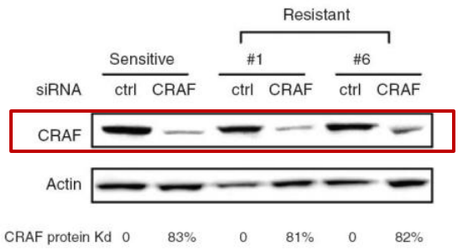

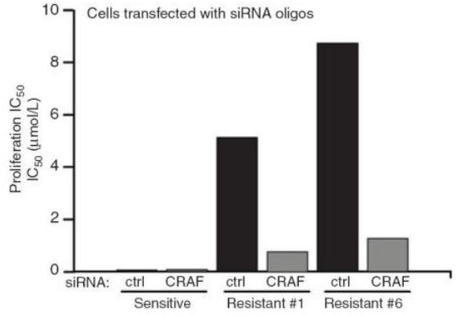

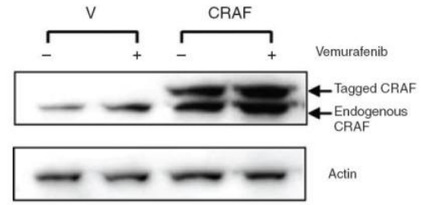

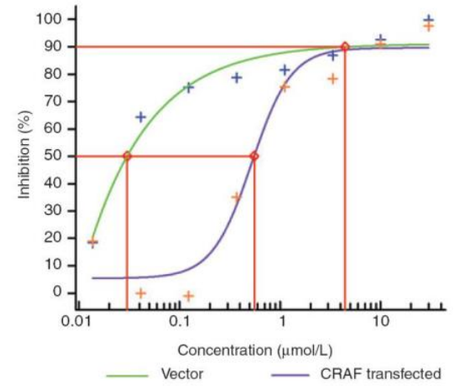

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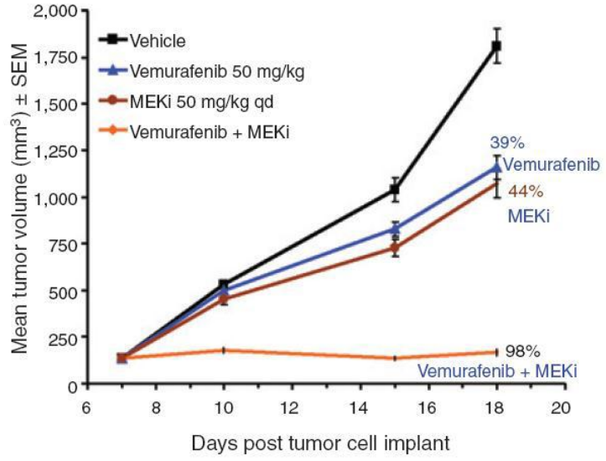
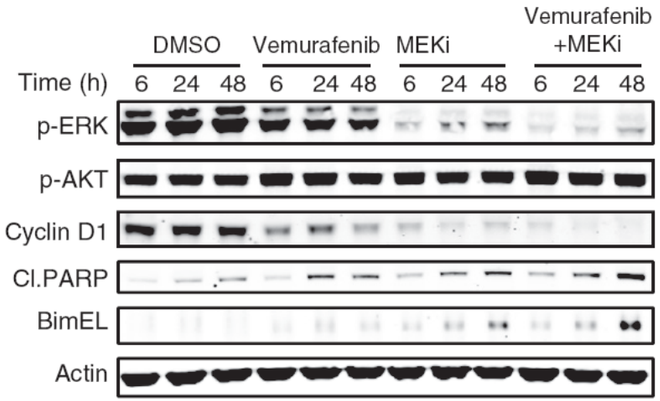
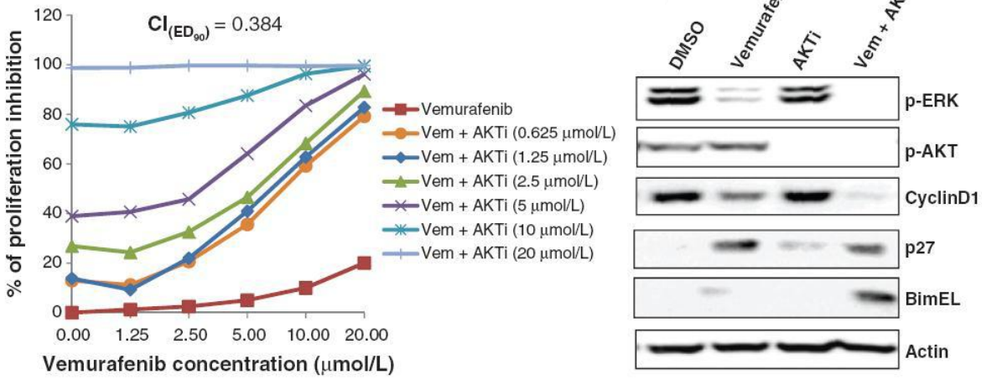


Dose group (mg/kg, qd)	TGI (%)	PR	ILS (%)
Vehicle	-	-	-
Vemurafenib (50)	39	-	22
MEKi (12.5)	11	-	0
MEKi (25)	18	-	22
MEKi (50)	44	-	33
Vemurafenib (50) + MEKi (12.5)	88	1/10	78
Vemurafenib (50) + MEKi (25)	92	-	78
Vemurafenib (50) + MEKi (50)	98	3/10	100





BRAF biomarkers of sensitivity

#2806 BRAF and MEK inhibitor profiling across 240 tumor cell lines to correlate with sensitivity and resistant biomarkers. Karen Bernards, Yulia Ovechkina, Jushun Cheng, John Kushleika, Alison Angione, James Hnilo, Christine O'Day.

- MEK1 mutations (MEKp124L/S, Emery, PNAS 2009; MEK1C121S, Wagle, JCO 2011)
- COT overexpression, CRAF activation (Johannessen, Nature 2010)
- NRAS mutation, PDFGR overexpression (Nazarian, Nature 2010)
- IGF1R overexpression (Villanueva, Cancer Cell 2010)
- BRAF amplification (Corcoran, Sci Signal 2010)

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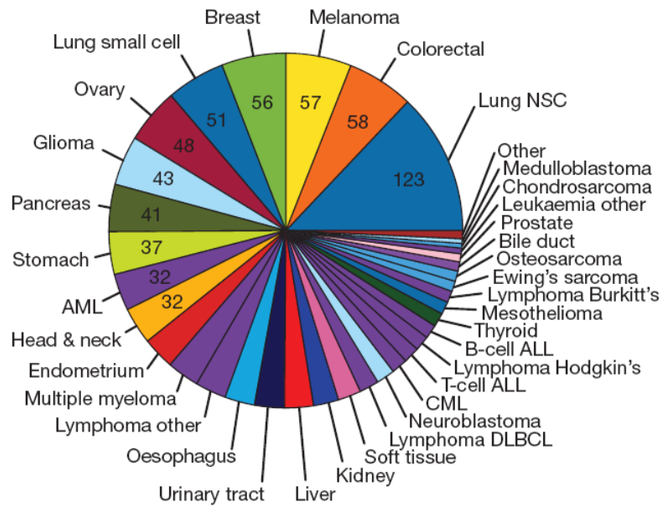
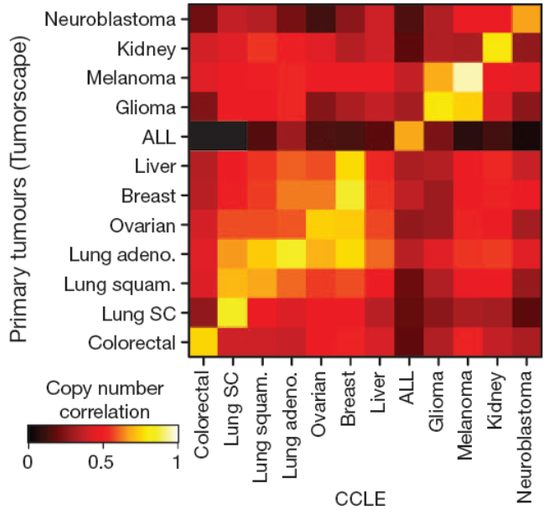
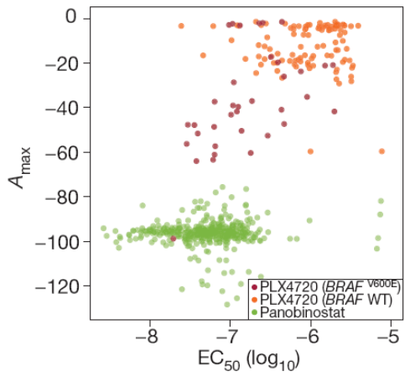
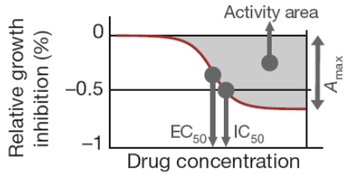
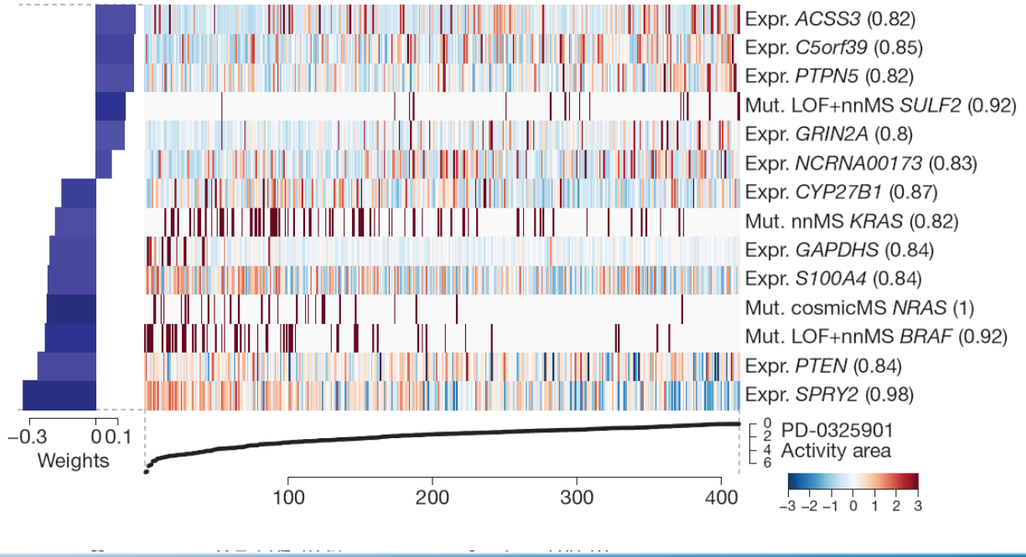






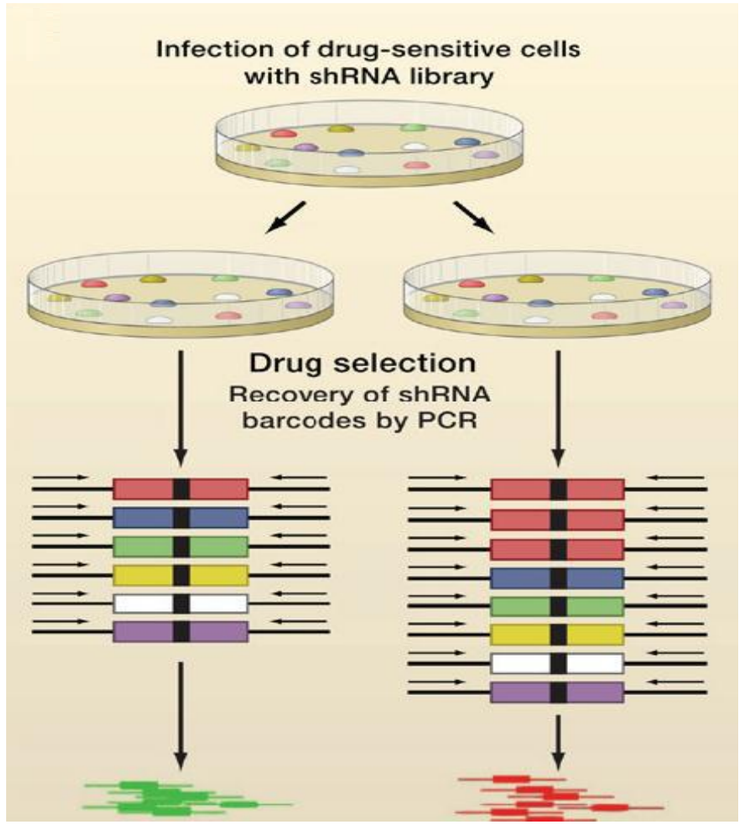


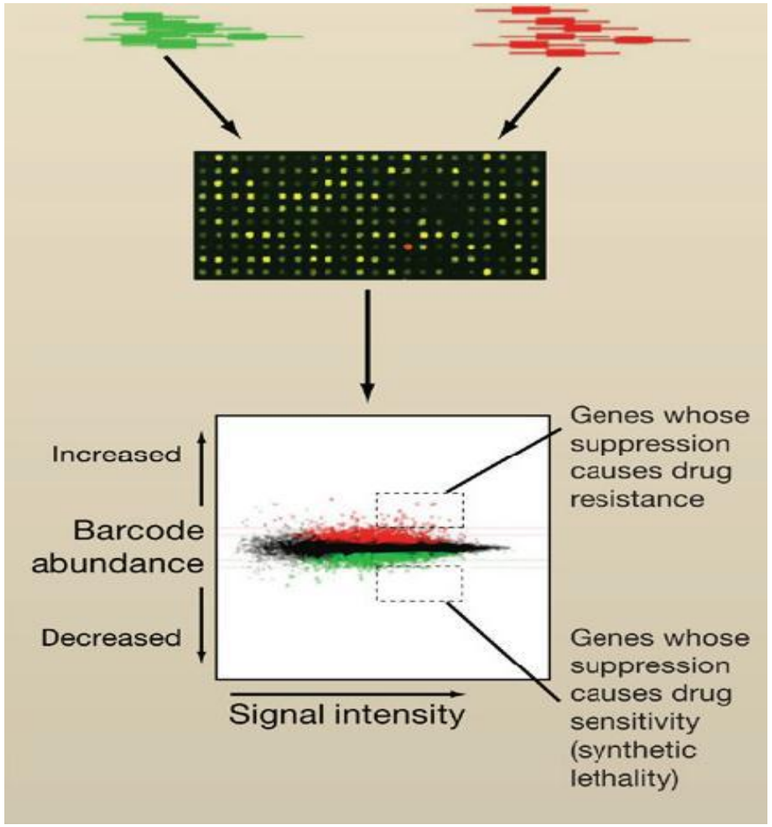


Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

#2156 Preclinical combinations of vemurafenib, a selective BRAF inhibitor, with other targeted therapies in BRAFV600E colorectal cancer models. *H Yang, B Higgins, K Kolinsky, J Li, R Margolis, Z Go, A Railkar, K Packman, G Bollag, F Su.*

#5608 Functional genetic screens to find modulators of sensitivity to inhibitors of the PI3K/mTOR pathway. *MS Van der Heijden, K Berns, MO Ports, R Bernards.*





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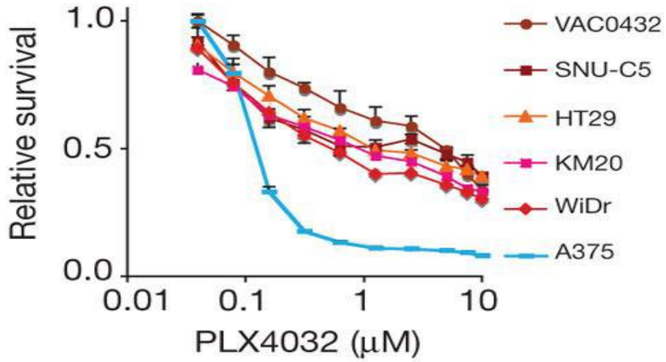

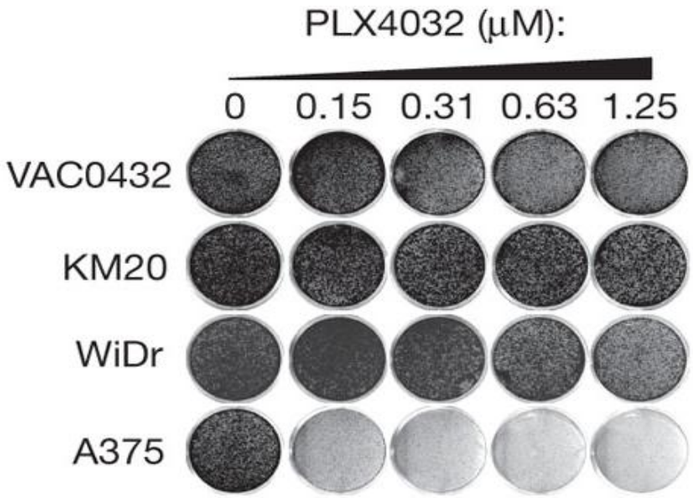

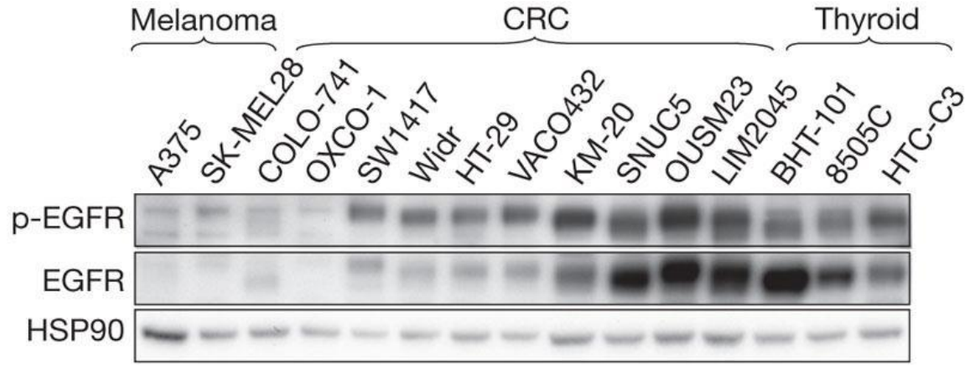

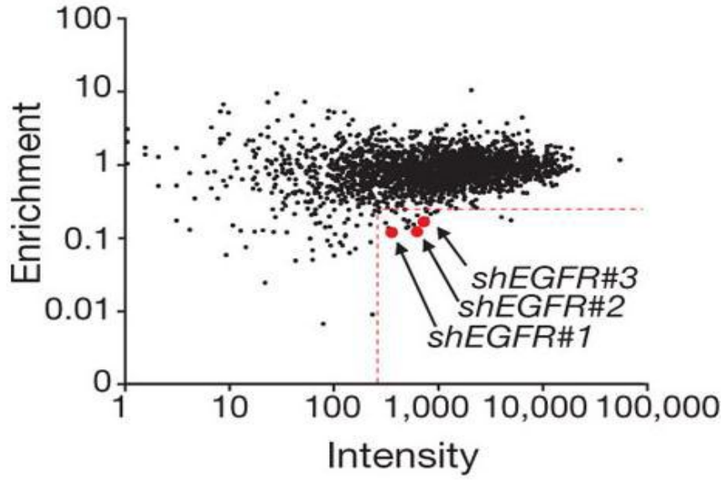

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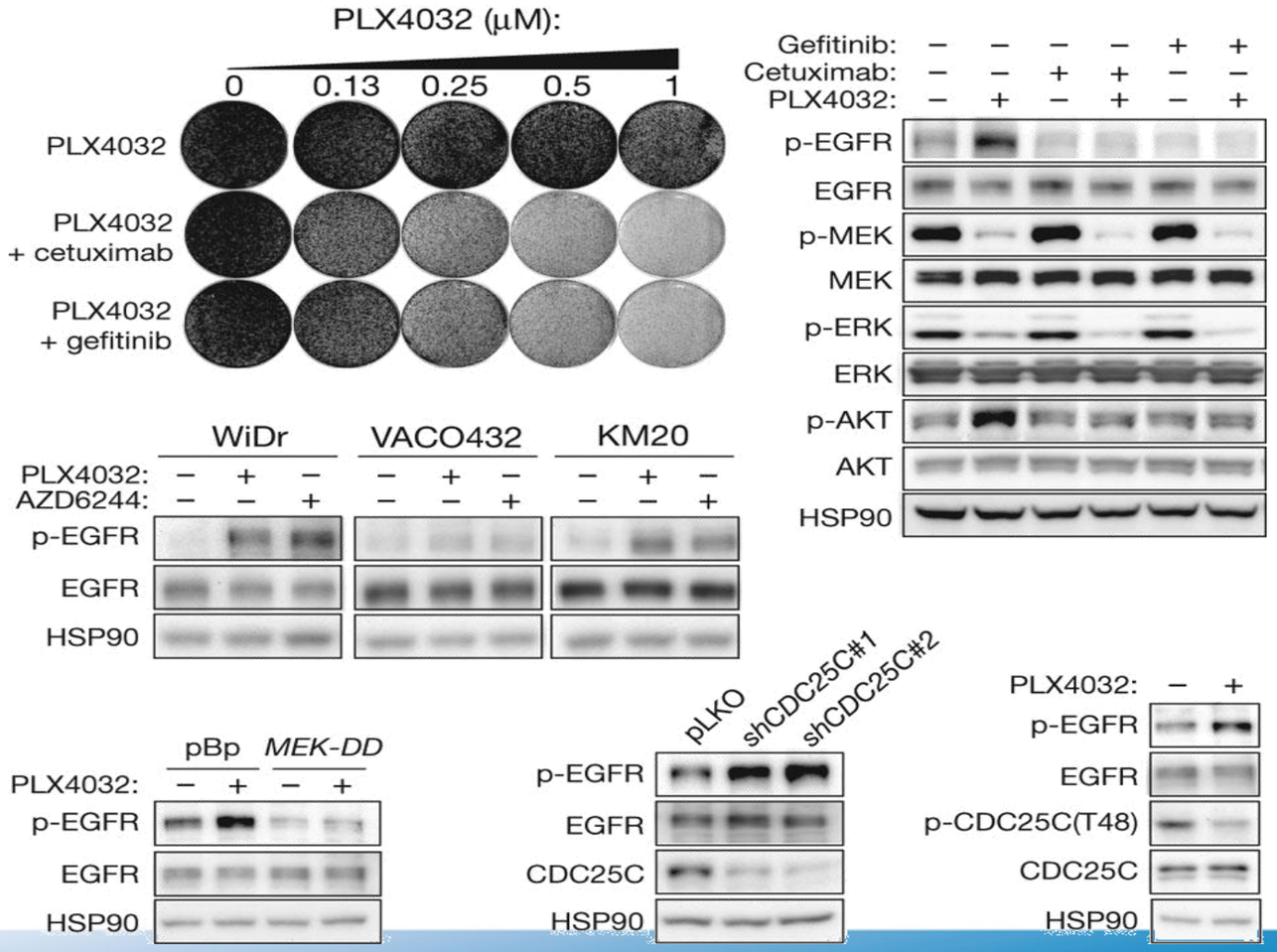

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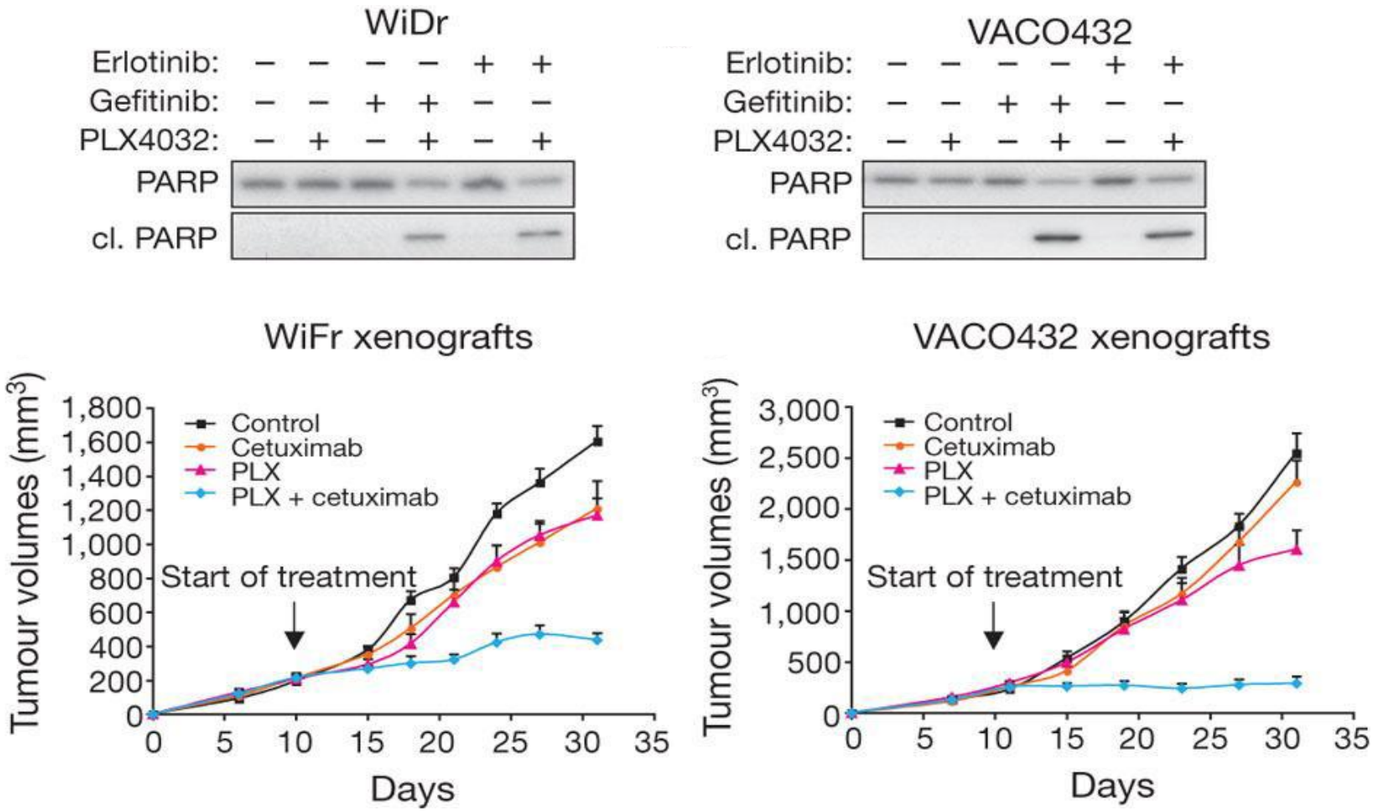

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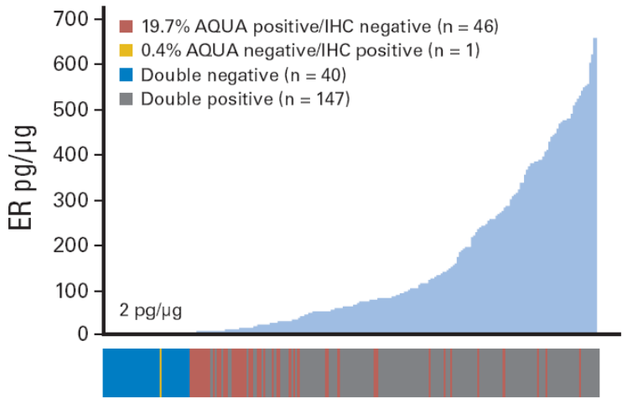
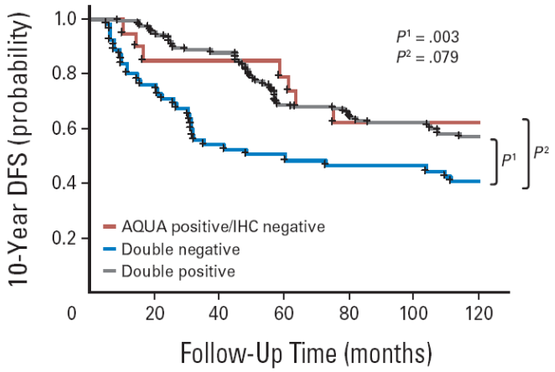
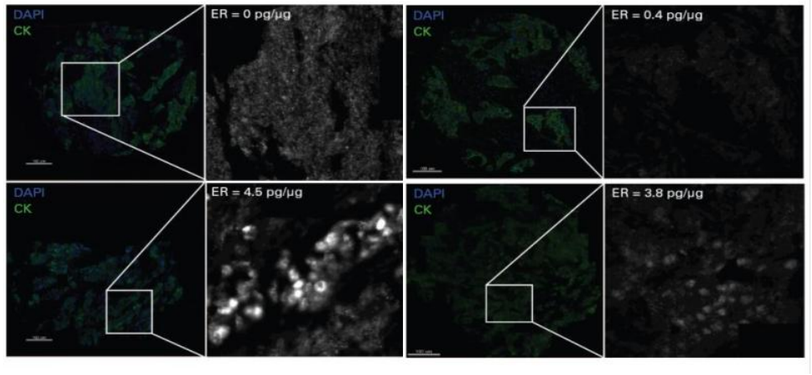
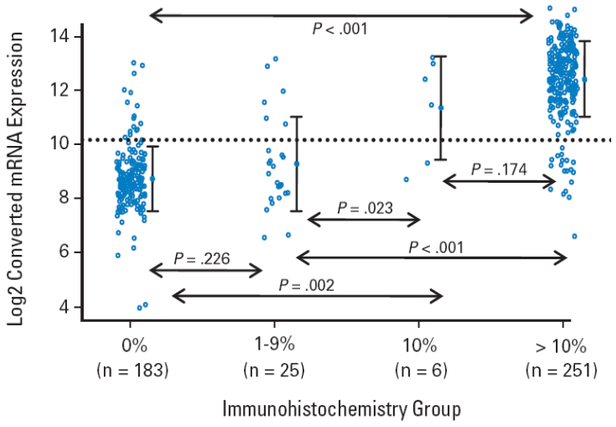
Estrogen receptor mRNA expression in breast cancer: correlation with response to tamoxifen

#691 Estrogen receptor mRNA level in breast cancer predicts response to tamoxifen. *J Bordeaux, H Cheng, A Welsh, B Haffty, D Lannin, X Wu, N Su, X Ma, Y Luo, D Rimm*

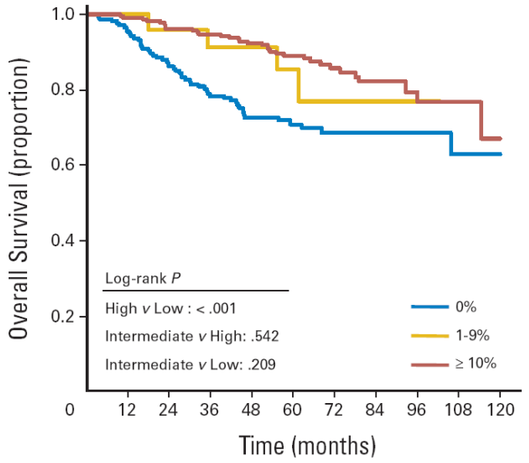




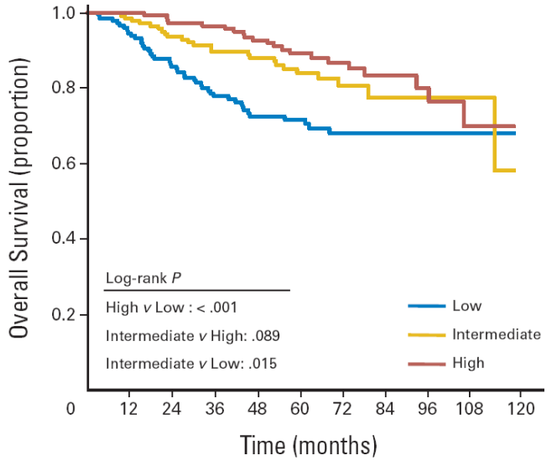




ER % expression (IHC)

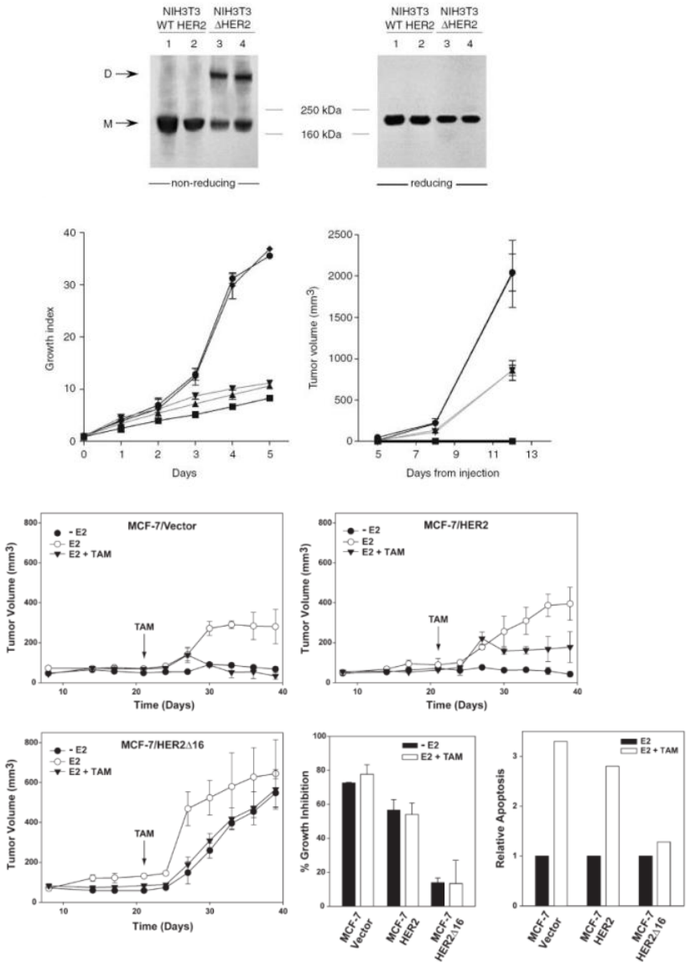


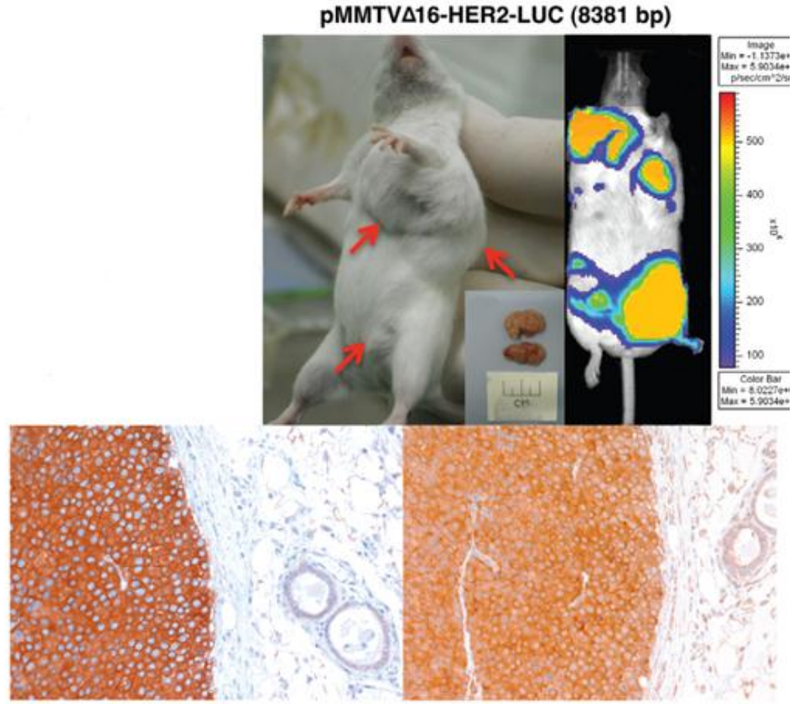
ERS mRNA expression

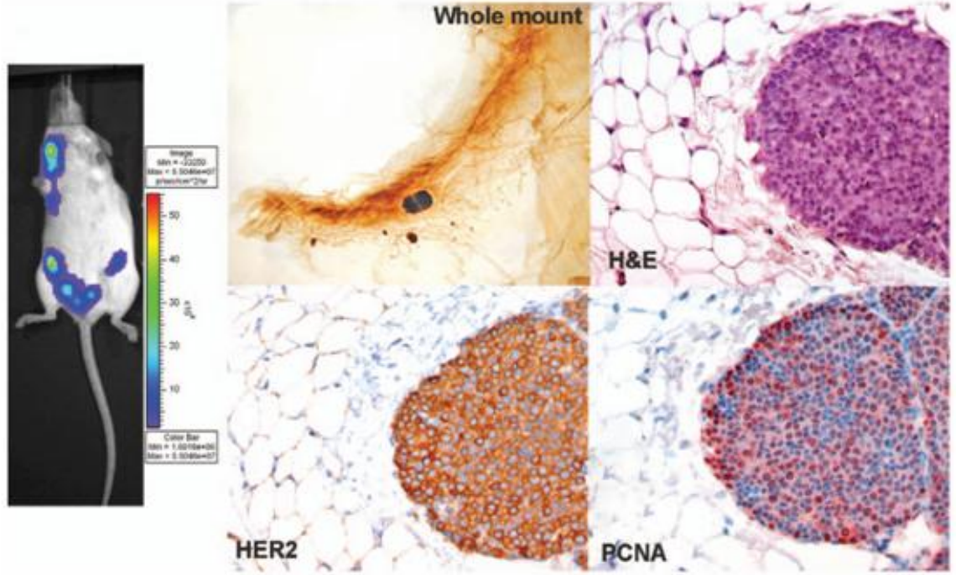


HER2 variants in breast cancer

#916 Role of delta16HER2 splice variant in HER2-driven tumor progression and response to targeted therapy. SM Pupa, L Castagnoli, GC Ghedini, R Zappasodi, V Ciravolo, G Marzano, G Santilli, A Amici, C Marchini, M Di Nicola, R Canese, E Iorio, M Iezzi, E Tagliabue



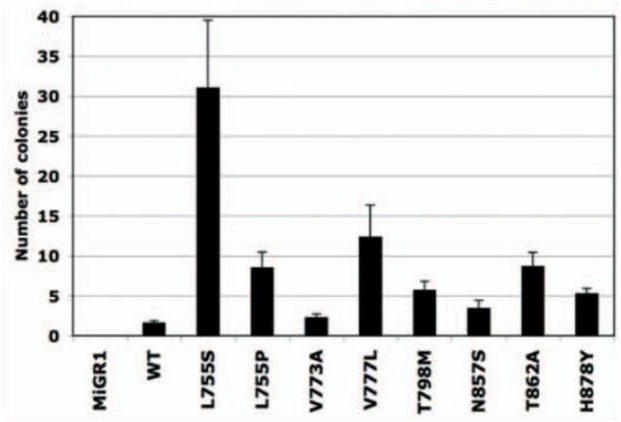


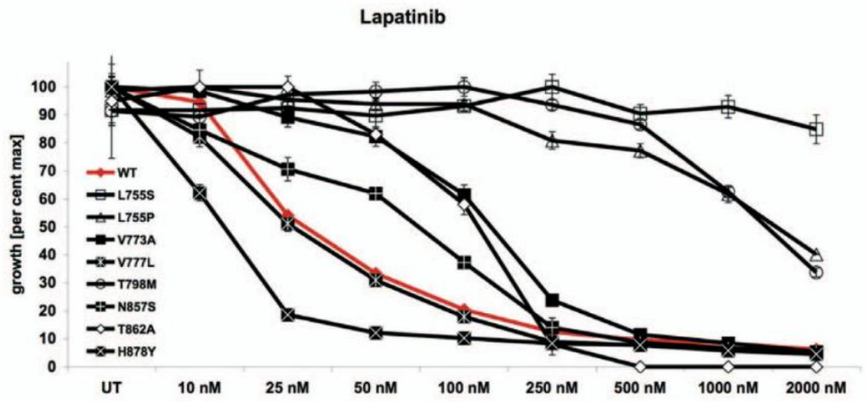


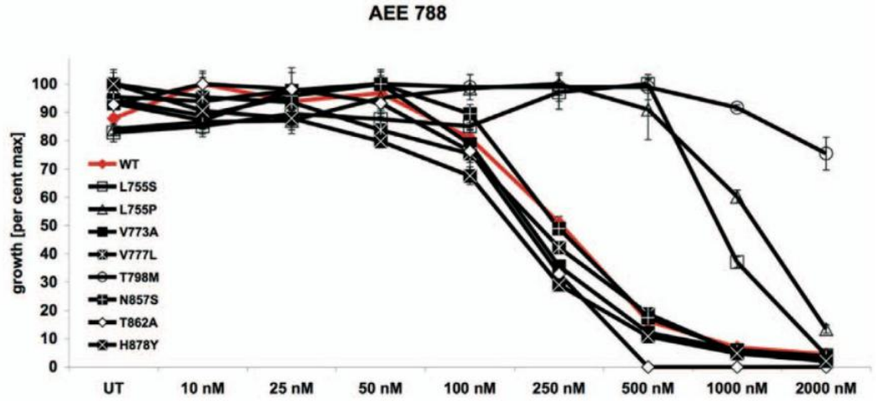
HER2 variants in breast cancer

#3 HER2 gene-amplified human breast cancer cells harboring a gatekeeper T768M mutation in HER2 overexpress EGFR ligands and are sensitive to dual therapeutic blockade of EGFR and HER2. *R Ghosh, A Narasanna, A Chakrabarty, JA Engelman, CL Arteaga*

ERBB2 mutation	Exon	Functional region	Cancer type	Lapatinib	AEE788
WT	NA	NA	Breast cancer	30	257
L755S	19	ATP binding region	Breast and gastric cancer	>2000	897
L755P	19	ATP binding region	NSCLC	1545	1216
V773A	20	ATP binding region	SCCHN	146	200
V777L	20	ATP binding region	Gastric, colon and lung	27	215
T798M	20	Gate keeper residue	NA	1433	>2000
N857S	21	Activation loop	Ovarian cancer	75	246
T862A	21	Activation loop	Primary gastric cancer	125	191
H878Y	21	Activation loop	Hepatocellular carcinoma	14	168

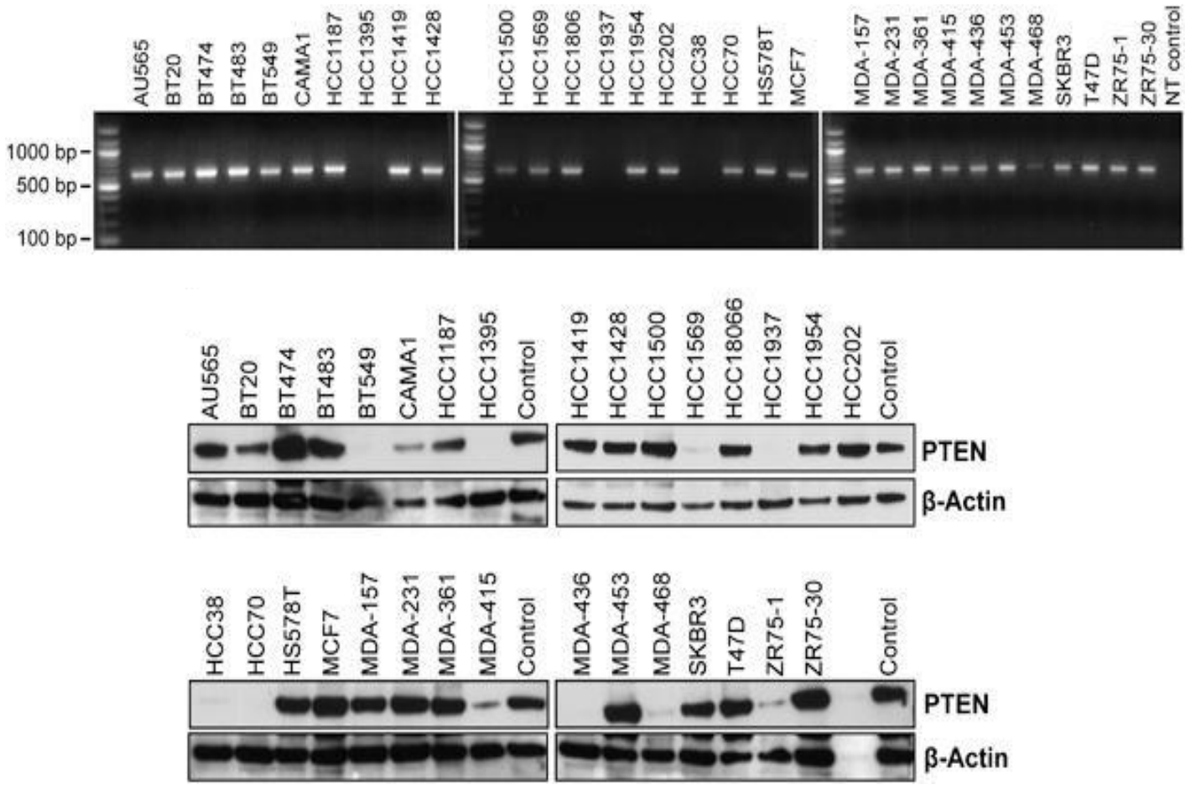


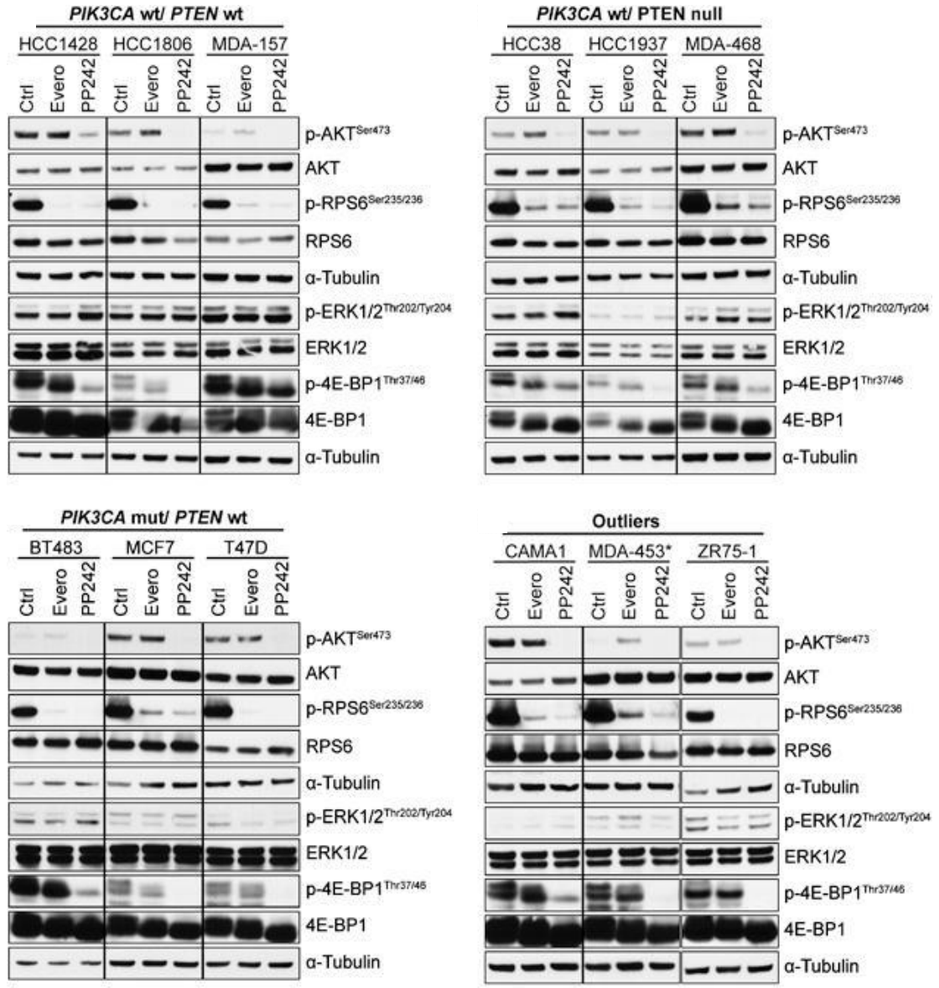




Predictive biomarkers for mTOR inhibitors

#4835 Genetic determinants of mTOR inhibitor response in breast and endometrial cancer. *B Weigelt, PH Warne, M Lambros, JS Reis-Filho, J Downward*





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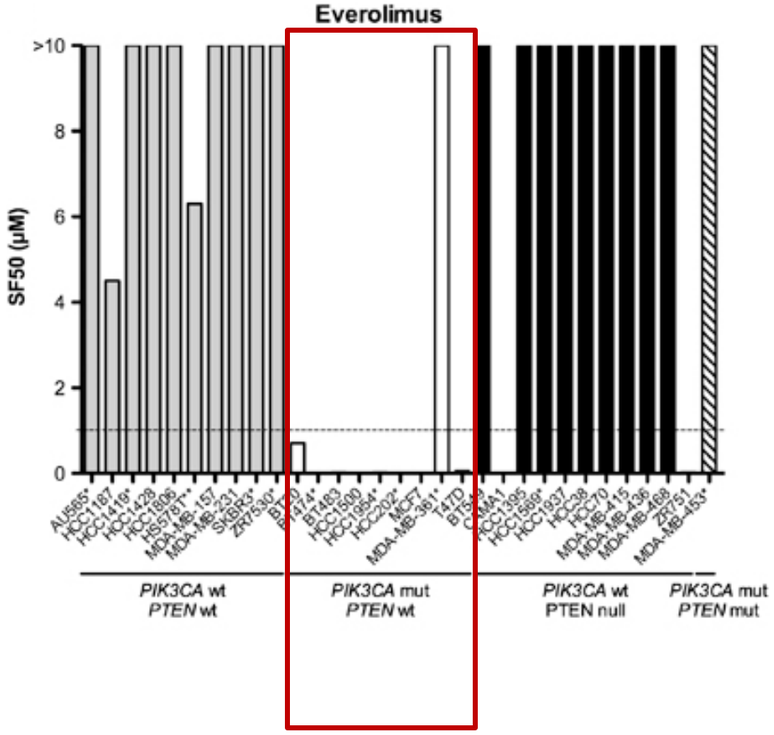
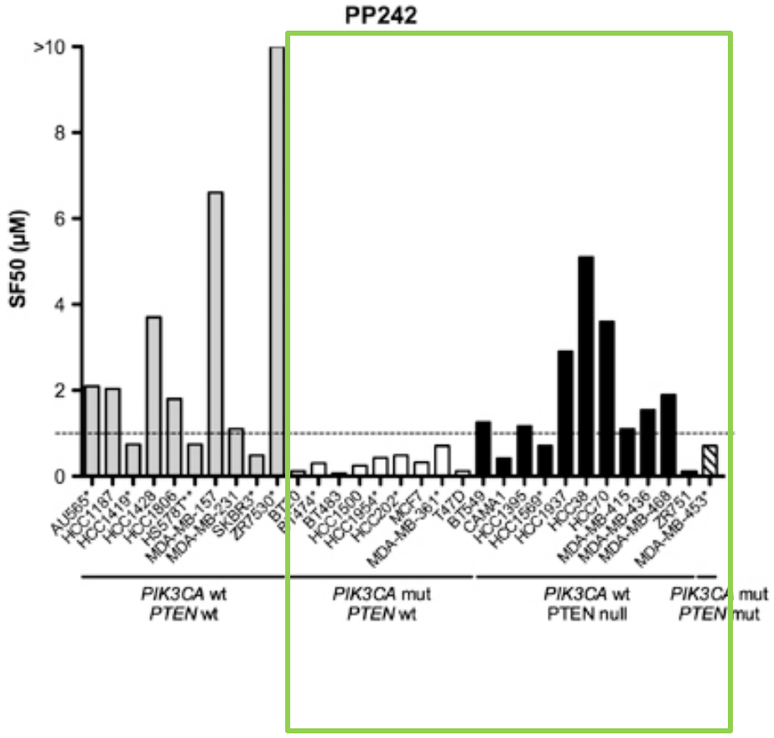
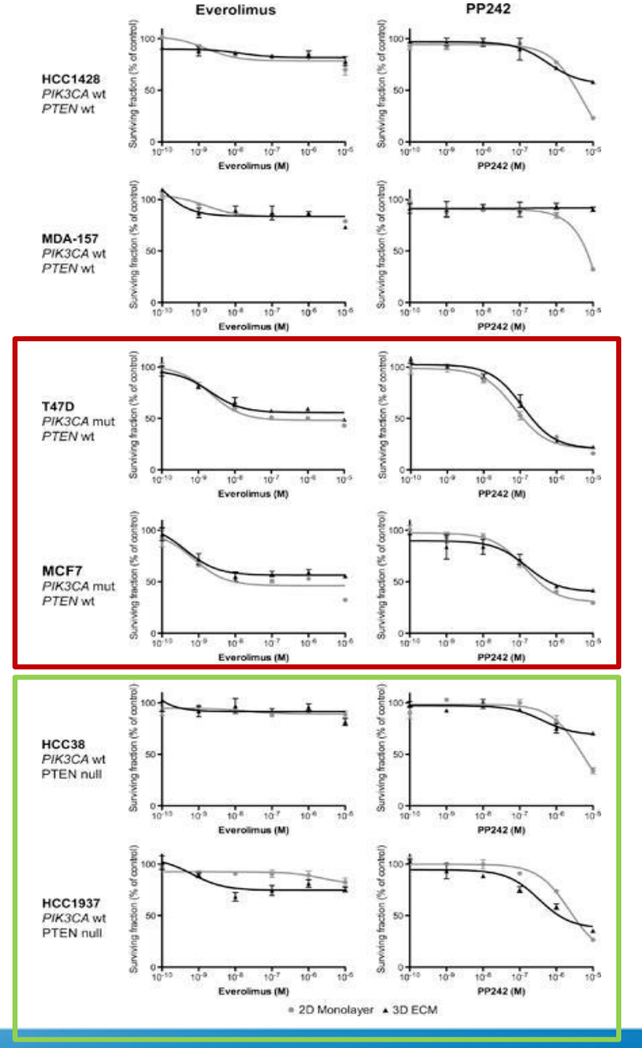
#4835 Genetic determinants of mTOR inhibitor response in breast and endometrial cancer. *B Weigelt, PH Warne, M Lambros, JS Reis-Filho, J Downward*





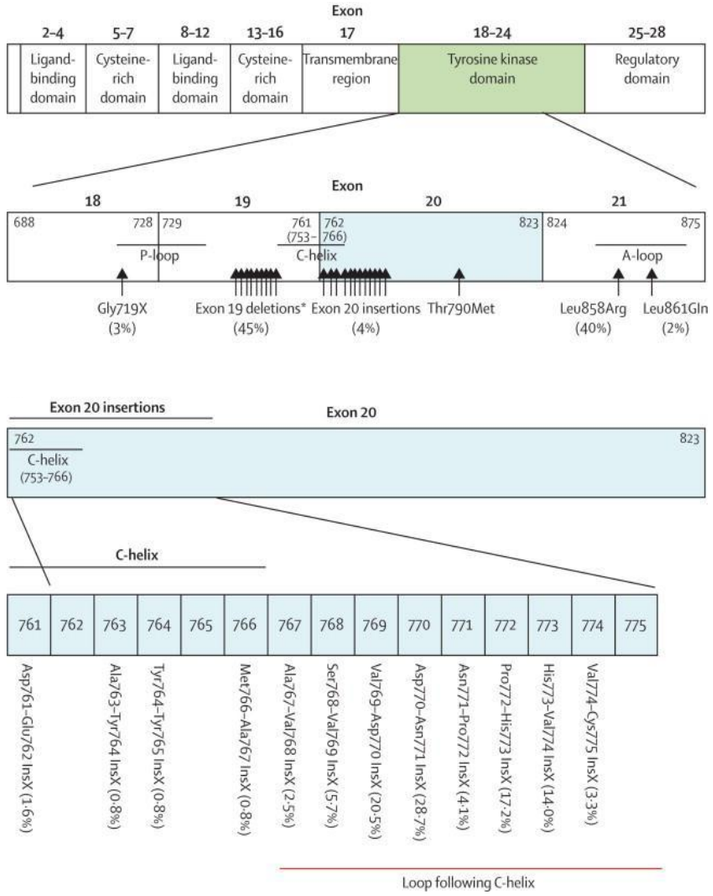


Guión de la presentación

- Avances en melanoma y BRAF
- Cáncer de mama: más allá de HER2
- NSCLC y EGFR
- Biología del cáncer: temas candentes

Predictive role of EGFR exon 20 mutations in NSCLC

#23 Sensitivity of EGFR exon 20 insertion mutations to EGFR inhibitors is determined by their location within the tyrosine kinase domain of EGFR. *H Yasuda, NJ Sng, WL Yeo, LL Figueiredo-Pontes, S Kobayashi, DB Costa.*



	EGFR mutation (number of mutations)	Number of patients (total=122)	Relative frequency (%)
762	Asp761_Glu762insGluAlaPheGln† (2)	2	1·6%
763	Ala763_Tyr764insPheGlnGluAla† (1)	1	0·8%
764	Tyr764-Val765insHisHis (1)	1	0·8%
765	-	..	..
766	Met766_Ala767insAlalle (1)	1	0·8%
767	Ala767_Val769dupAlaSerVal‡ (2), Ala767_Ser768insThrLeuAla (1)	3	2·5%
768	Ser768_Asp770dupSerValAsp§ (5), Ser768_Val769insValAlaSer (1), Ser768_Val769insAlaTrpThr (1)	7	5·7%
769	Val769_Asp770insAlaSerVal‡ (18), Val769_Asp770insGlyVal (1), Val769_Asp770insCysVal (1), Val769_Asp770insAspAsnVal (1), Val769_Asp770insGlySerVal (1), Val769_Asp770insGlyValVal (2), Val769_Asp770insMetAlaSerValAsp (1)	25	20·5%
770	Asp770_Asn771insSerValAsp§ (19), Asp770_Asn771insAsnProGly (1), Asp770_Asn771insAlaProTrp (1), Asp770_Asn771insAsp (1), Asp770_Asn771insAspGly (1), Asp770_Asn771insGly (5), Asp770_Asn771insGlyLeu (1), Asp770_Asn771insAsn (1), Asp770_Asn771insAsnProHis (1), Asp770_Asn771insSerValPro (1), Asp770_Asn771insSerValGln (1), Asp770_Asn771insMetAlaThrPro (1), delAsp770insGlyTyr (1)	35	28·7%
771	Asn771_Pro772insHis (1), Asn771_Pro772insAsn (1), Asn771_His773dupAsnProHis (1), delAsn771insGlyTyr (1), delAsn771insGlyPhe (1)	5	4·1%
772	Pro772_His773insProArg (11), Pro772_His773insTyrAsnPro (2), Pro772_His773insX (2), Pro772_His773insAspProHis (1), Pro772_His773insAspAsnPro (1), Pro772_His773insGlnVal (1), Pro772_His773insThrProHis (1), Pro772_His773insAsn (1), Pro772_His773insVal (1)	21	17·2%
773	His773_Val774insAsnProHis (6), His773_Val774insHis (3), His773_Val774insProHis (3), His773_Val774insGlyAsnProHis (2), His773_Val774dupHisVal (1), His773_Val774insGly (1), His773_Val774insGlyHis (1)	17	14%
774	Val774_Cys775insHisVal (4)	4	3·3%

	Best response to gefitinib or erlotinib		
	PR or prolonged SD	Total number of patients	% with PR or prolonged SD
Tyr764_Val765insHisHis	1 (patient had SD for 10 months)*	1	100%
Met766_Ala767insAlalle	1 (patient had SD for 10 months)†	1	100%
Ala767_Val769dupAlaSerVal	0	2	0%
Ser768_Asp770dupSerValAsp	1 (patient had PR for 24 months)‡	4	25%
Asp770_Asn771insAsp	0	1	0%
delAsn771insGlyTyr	0	1	0%
Pro772_His773insAsn	0	1	0%
Pro772_His773insVal	0	1	0%
Pro772_His773insTyrAsnPro§	0	1	0%
His773_Val774insGlyHis	0	1	0%
Exon 20 insertion (mutation type not reported)	0	4	0%
Exon 20 insertion (mutation type not reported)	0	1	0%
Exon 20 insertion (mutation type not reported)	0	1	0%
Total	3 (1 PR, 2 prolonged SD)	20	15% (PR 5%)

Guión de la presentación

- Avances en melanoma y BRAF
- Cáncer de mama: más allá de HER2
- NSCLC y EGFR
- Biología del cáncer: temas candentes

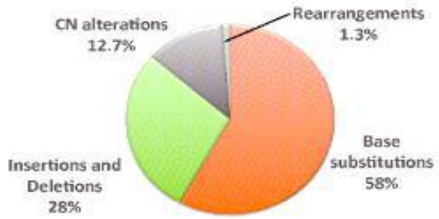
Comprehensive next-generation sequencing for clinically actionable mutations in FFPE cancer tissues

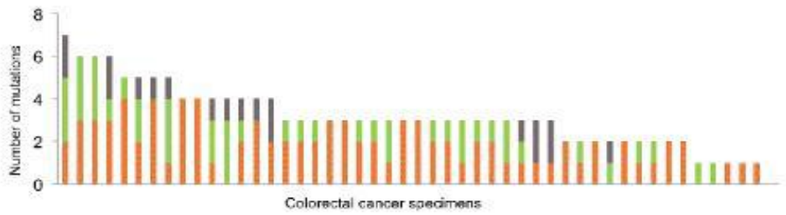
#3178 Can DNA from archived formalin-fixed paraffin embedded (FFPE) cancer tissues be used for somatic mutation analysis in next generation sequencing? *E Palescandolo, R Jones, A Raza, A Sunkavalli, PK Brastianos, M Ducar, C Go, C Roden, C Hatton, M Hanna, A Mills, R Adusumilli, P Kumar, ML Meyerson, HC William, L MacConaill, P Van Hummelen*

155 mutations found in 49 colorectal cancer specimens (of which 46 had previous *KRAS* testing)

KRAS testing in colorectal cancer: Concordance with reference lab

		FMI NGS Test	
	(N=46)	*KRAS* mutation positive	*KRAS* mutation negative
Reference Lab	*KRAS* mutation positive	12	
	KRAS mutation negative		34



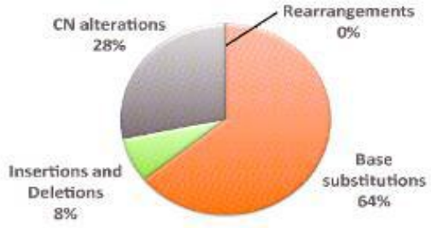


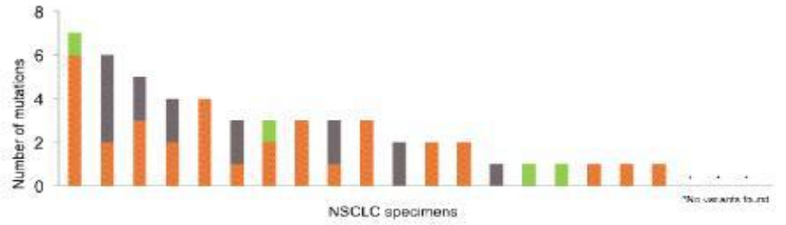
53 mutations found in 22 NSCLC specimens (of which 17 had previous *EGFR* testing)

EGFR testing in NSCLC: Concordance with 17 specimens tested by reference lab

		FMI NGS Test	
	(N=17)	*EGFR* mutation positive	*EGFR* mutation negative
Reference Lab	*EGFR* mutation positive	1*	
	EGFR mutation negative		16

*Rep. insertion in p.D770_N771insSVD in *EGFR* exon 20





Conclusions

- This study confirms the ability to perform NGS with the small amounts of tumor tissue present in routine FFPE cancer specimens with sensitivity and specificity suitable for clinical decision-making. An average coverage of ~200X and 100% concordance was achieved with reference laboratories' conventional single gene analysis for *BRAF*, *KRAS*, and *EGFR*.
- Comprehensive cancer genomic testing identifies many more mutations than traditional methods. A total of 214 driver mutations were identified of which only 37 (17.6%) could have been found using conventional "hot spot" analysis.
- More than 50% of the specimens analyzed in this study contained mutations that could be used to inform cancer treatment decisions.

Variant Summary 75 Samples

Tumor Type	# specimens	Somatic mutations (avg)	Other variants (avg)	Comprehensive molecular analysis identified numerous known and novel mutations
Colorectal	49	3.2	7	*TP53* (38), *APC* (32), *KRAS* (13), *BRAF* (6), *SMAD4* (5), *FBXW7* (4), *PIK3CA* (4), *CDH1* (3), *STK11* (3), *BRCA1* (2), *BRCA2* (2), *ERBB3* (2), *GNAS* (2), *ATM2* (1), *CDKN* (1), *ERBB2* (1), *MAP2K4* (1)
NSCLC	22	2.4	8	*KRAS* (10), *TP53* (6), *STK11* (3), *BRAF* (2), *MDM2* (2), *PIK3CA* (2), *ATM* (1), *CDK4* (1), *CDKN2A* (1), *CTNNB1* (1), *EGFR* (1), *NF1* (1)
Melanoma	4	1.5	4	*BRAF* (2), *TP53* (2), *CDKN2A* (1)
All Types	75	2.85	7.1	

Data were obtained for a total of 75 patient specimens. An average of 2.9 known somatic mutations or likely somatic mutations were seen with a low of 1.5 in the melanoma specimens to a high of 3.2 in colorectal specimens. The number of other likely somatic variants detected averaged 7 across all specimens with a low of 4 in the melanoma and a high of 8 in the NSCLC specimens.

Intratumor heterogenity and impact on biomarker detection

#5543 Hetmap: Evaluating tumor heterogeneity in immunohistochemistry-stained breast cancer tissue. *SJ Potts, N Landis, D Eberhard, SC Schmechel, D Young, JS Krueger, H Lange*

Consider a forest:

Each species of tree has a proportional abundance in a sample of that forest

A forest may be high in diversity

Or a forest may be high in evenness

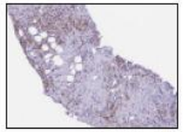
Deciduous trees

Tropical trees

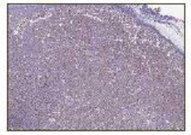
However, there is an important difference between *the types of trees* within a forest

Consider a breast biopsy:

Each type of cancer cell has a proportional abundance in a sample of that tissue section

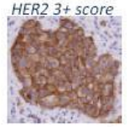


A region may be high in diversity

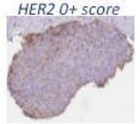


Or a region may be high in evenness

HER2 3+ score



HER2 0+ score



However, there is an important difference between *the types of cells* within a tissue

Variability

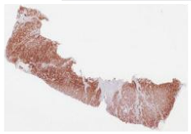
Tissue	Count	Number of sections sampled in a tissue	Number of tissues	Biological variability across a tissue section (average coefficient of variation)
Variation of different composite regions averaged across a single tissue section				
Human breast	HER2 (+3,+2,+1,0 scoring)	15-20 averaged as one composite region	180	17%
Human breast	ER percent positive cells	15-20 averaged as one composite region	180	11%
Human breast	PR percent positive cells	15-20 averaged as one composite region	180	33%

From *Drug Discovery Today* Volume 15, Numbers 21/22 November 2010 (Potts, Young, and Voeller)

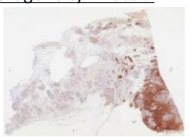
Table 1: Tissue cross-sections exhibit high levels of biological variability. The table shows typical coefficients of variation by sampling multiple small related sections across a large tissue section using a pathologist. CV values depend on the marker, and are high even when the companion diagnostic scoring rules are applied.

Heterogeneity

Tumor Level Heterogeneity: Het_{TUMOR}



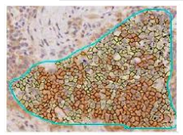
Low tumor heterogeneity



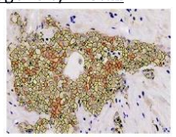
High tumor heterogeneity

Fig. 1: Tumor heterogeneity. Tumor level heterogeneity is the differential expression of a marker within the entire tumor section. The tumor on the left shows very strong HER2 staining, with low heterogeneity across the entire section. The tumor on the right has high HER2 staining in the lower right region, with variation in staining across the remainder of the tumor. Both regions received a summary +3 HER2 score according to ASCO/CAP scoring guidelines, despite clearly having differences in tumor profile.

Cell Level Heterogeneity: Het_{CELL}

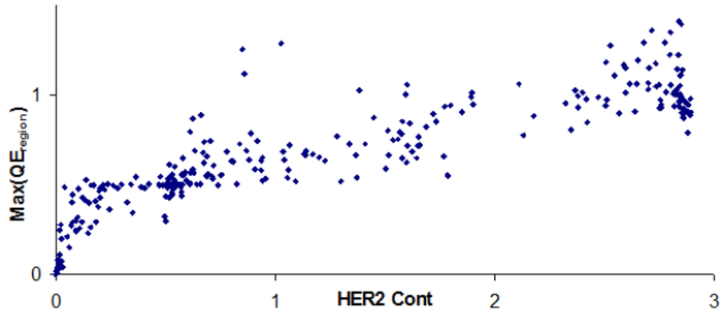


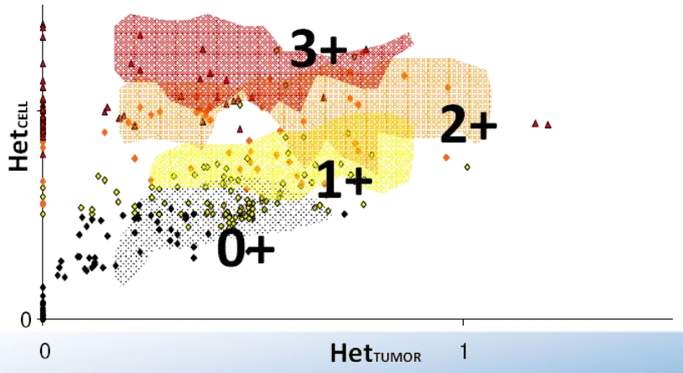
Low cell heterogeneity

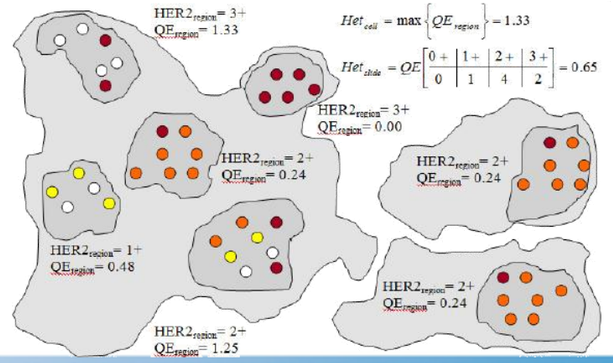


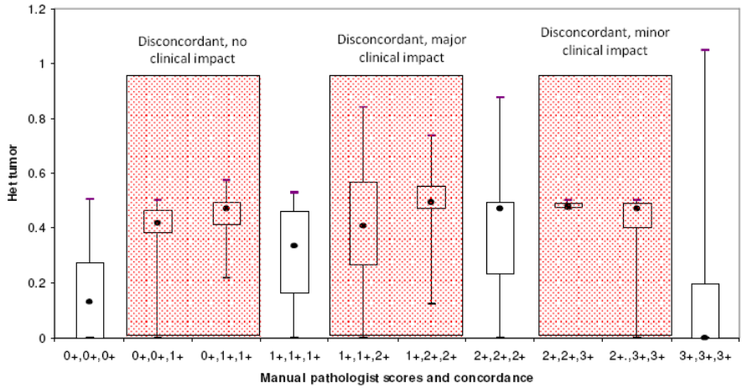
High cell heterogeneity

Figure 2: Cell Heterogeneity. Cell level heterogeneity is the differential expression of a marker from cell-to-cell in a region. The tumor on the left shows low cell-level heterogeneity in the lower right area of the region. The tumor on the right has high cell-level heterogeneity across the region. Both regions received a summary +3 HER2 score according to ASCO/CAP scoring guidelines, despite clearly having different population dynamics.



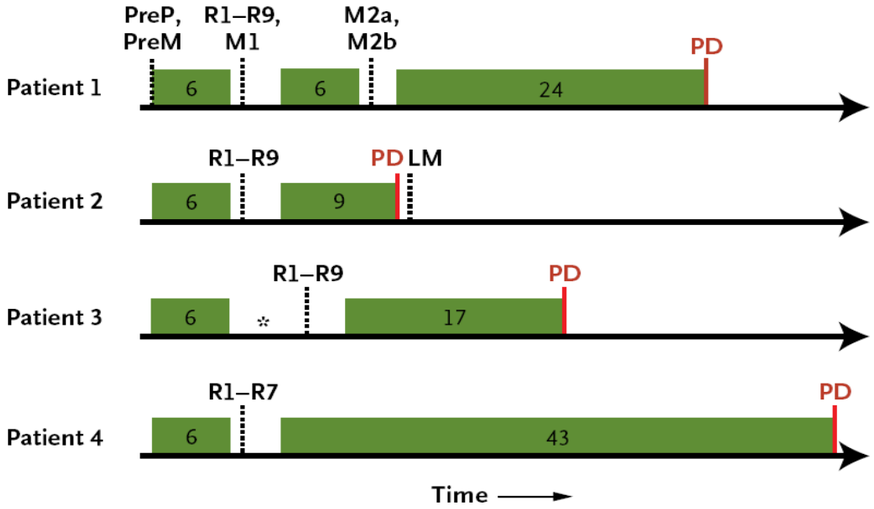


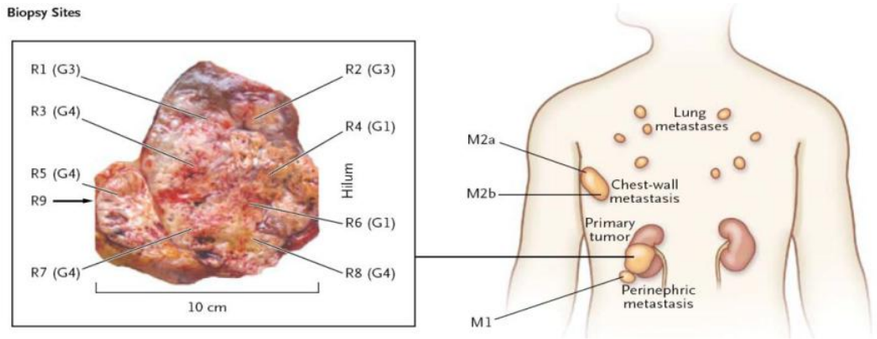


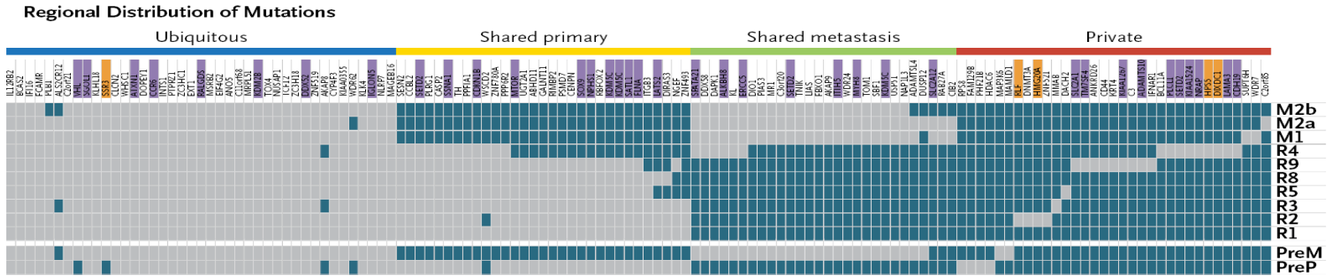


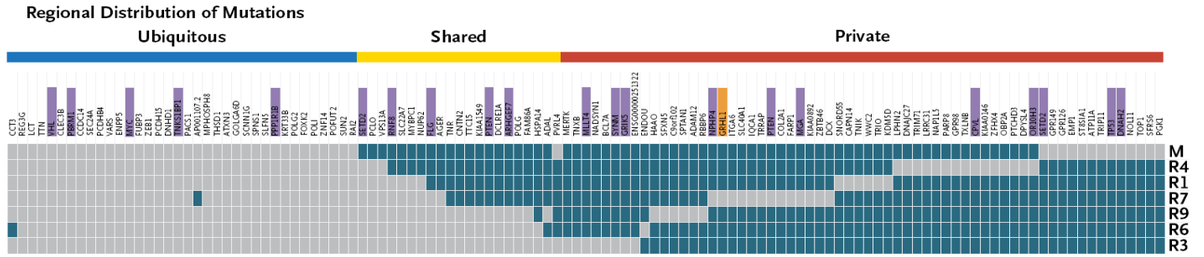
Intratumor heterogenity and impact on biomarker detection

#964 Intra-tumor heterogeneity and Darwinian selection revealed by multi-region exome sequencing of renal cell carcinomas. *M Gerlinger, A Rowan, S Horswell, J Larkin, D Endesfelder, E Gronroos, P Martinez, N Matthews, A Stewart, P Tarpey, I Varela, B Phillimore, S Begum, N McDonald, A Butler, D Jones, K Raine, C Latimer, C Santos, M Nohadani, A Eklund, B Spencer-Dene, G Clark, L Pickering, G Stamp, M Gore, Z Szallasi, J Downward, PA Futreal, C Swanton*









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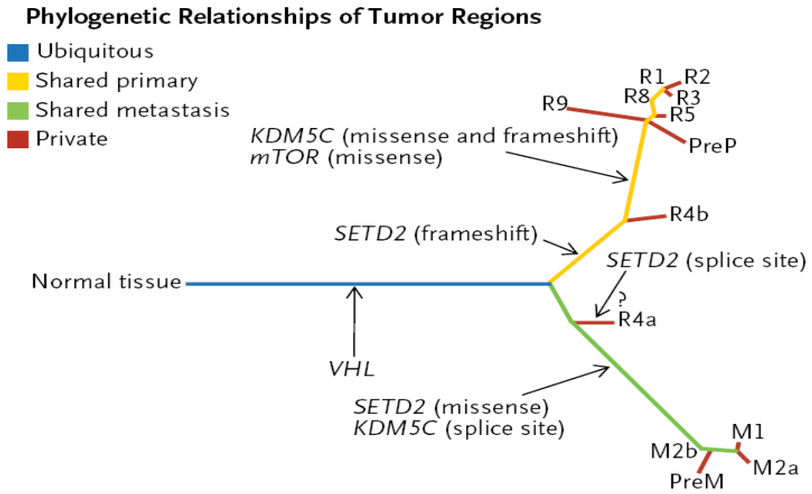

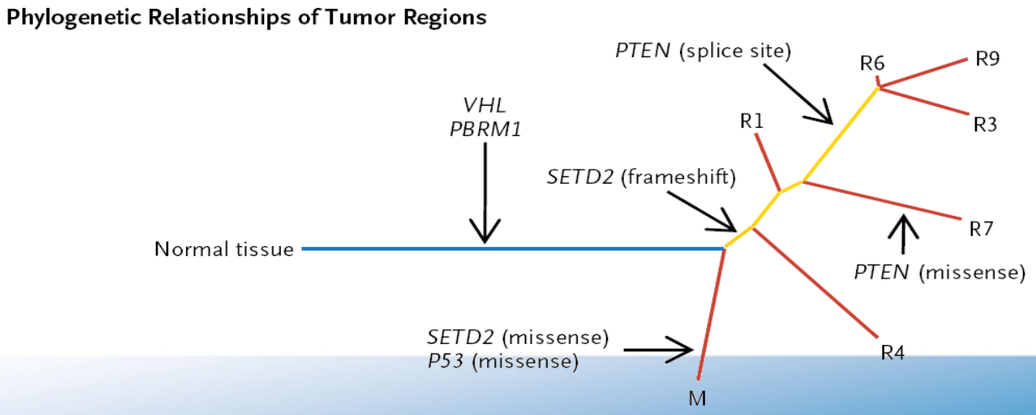

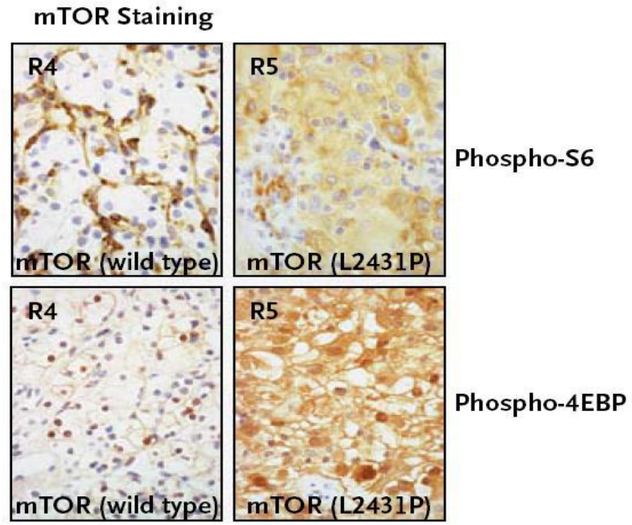

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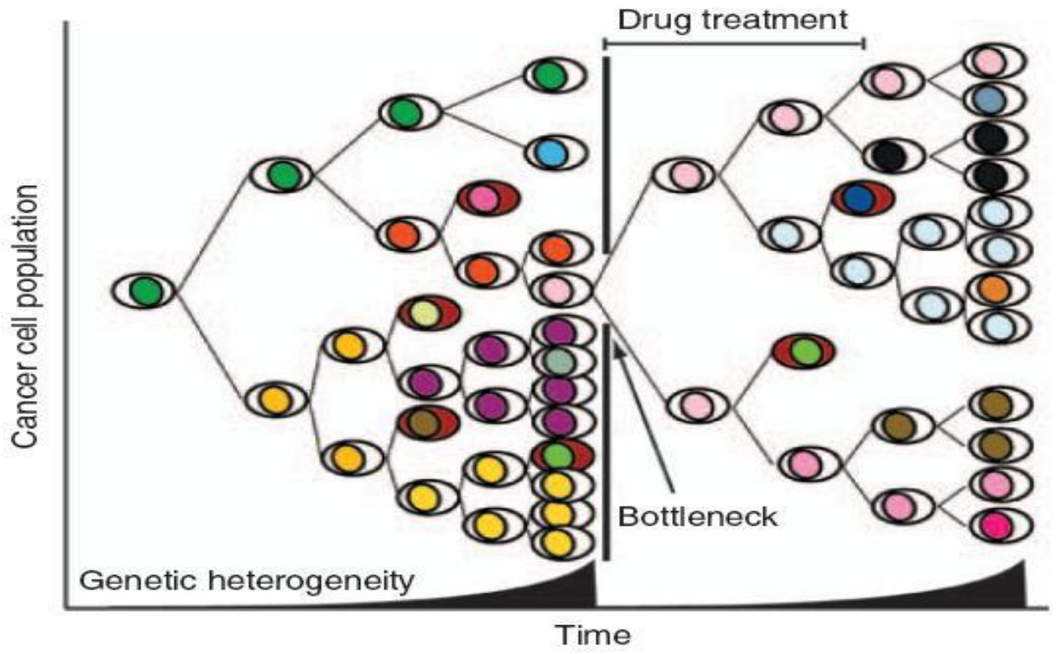

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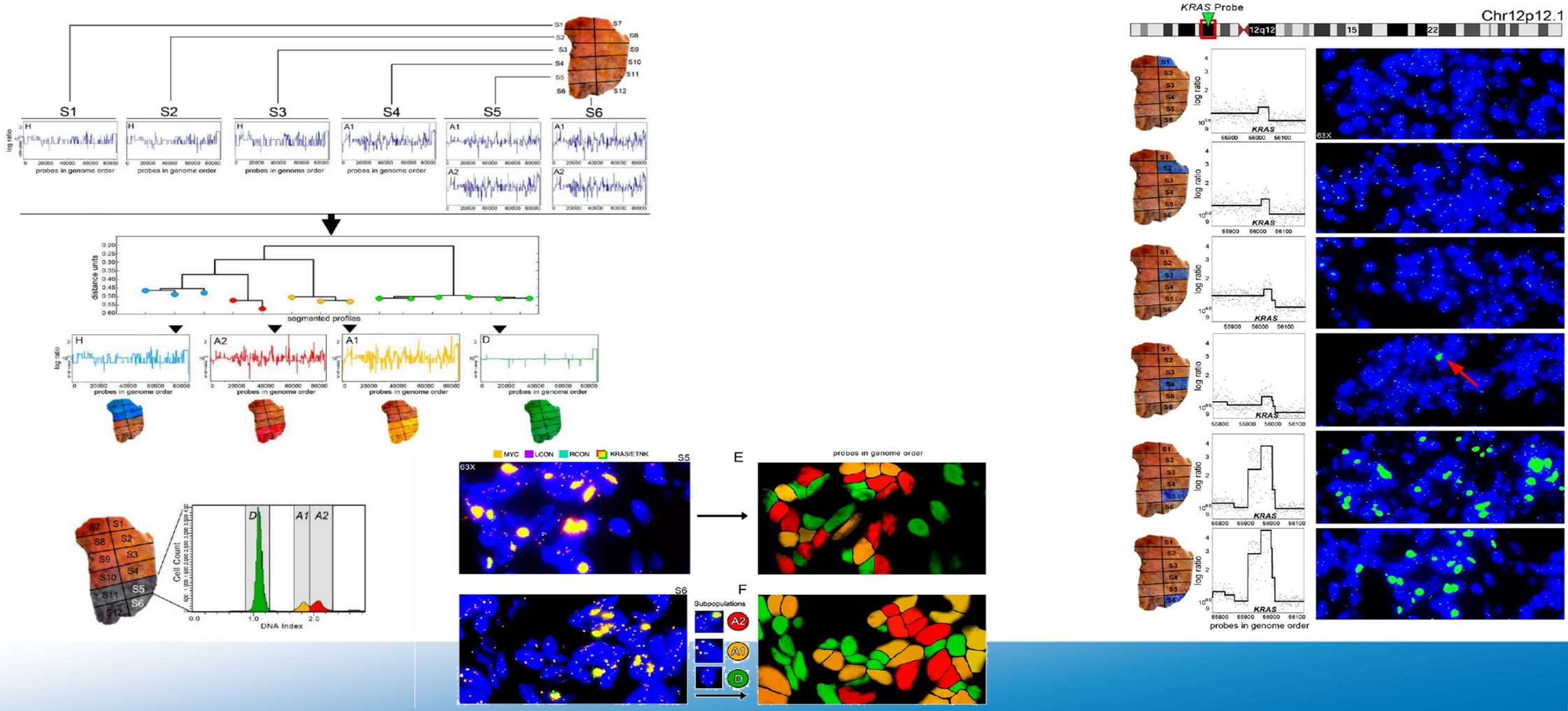
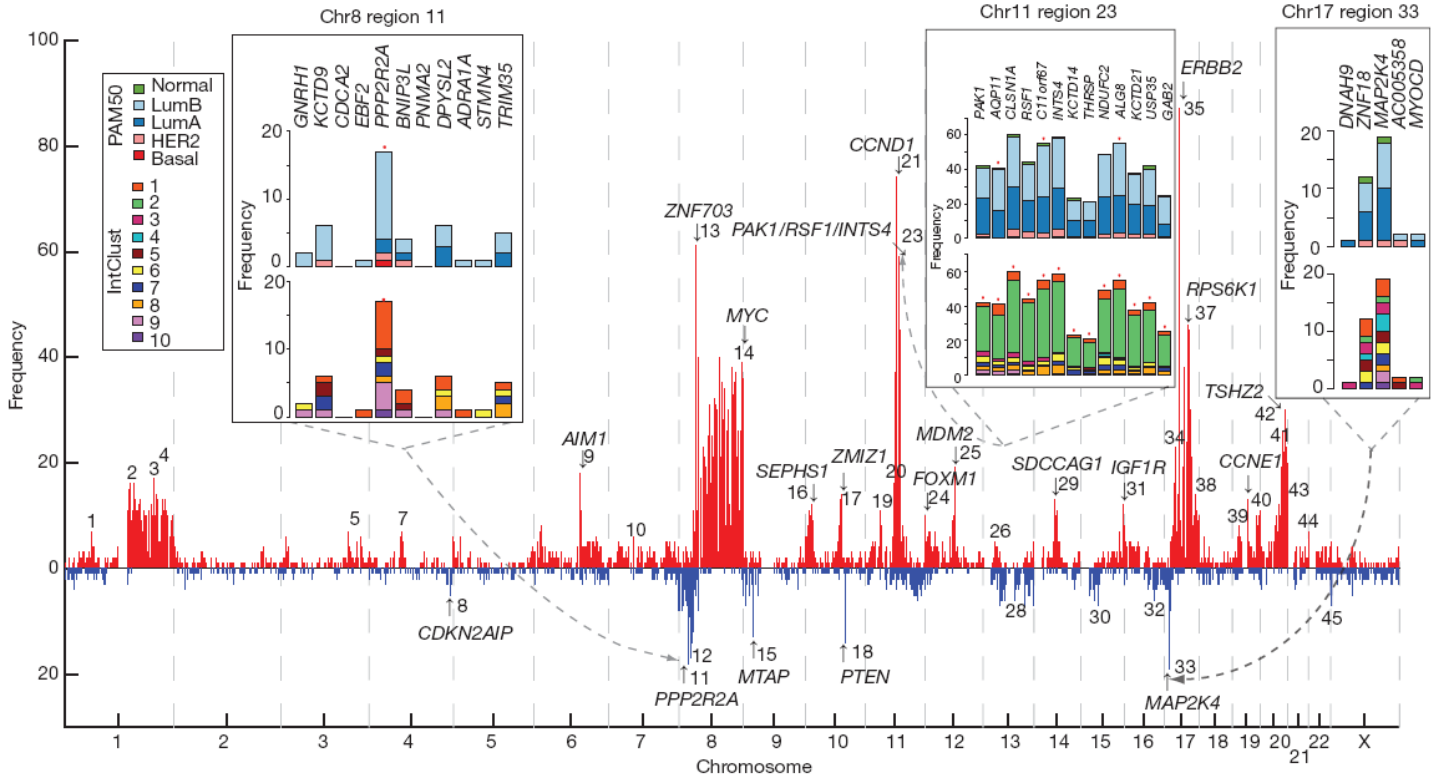


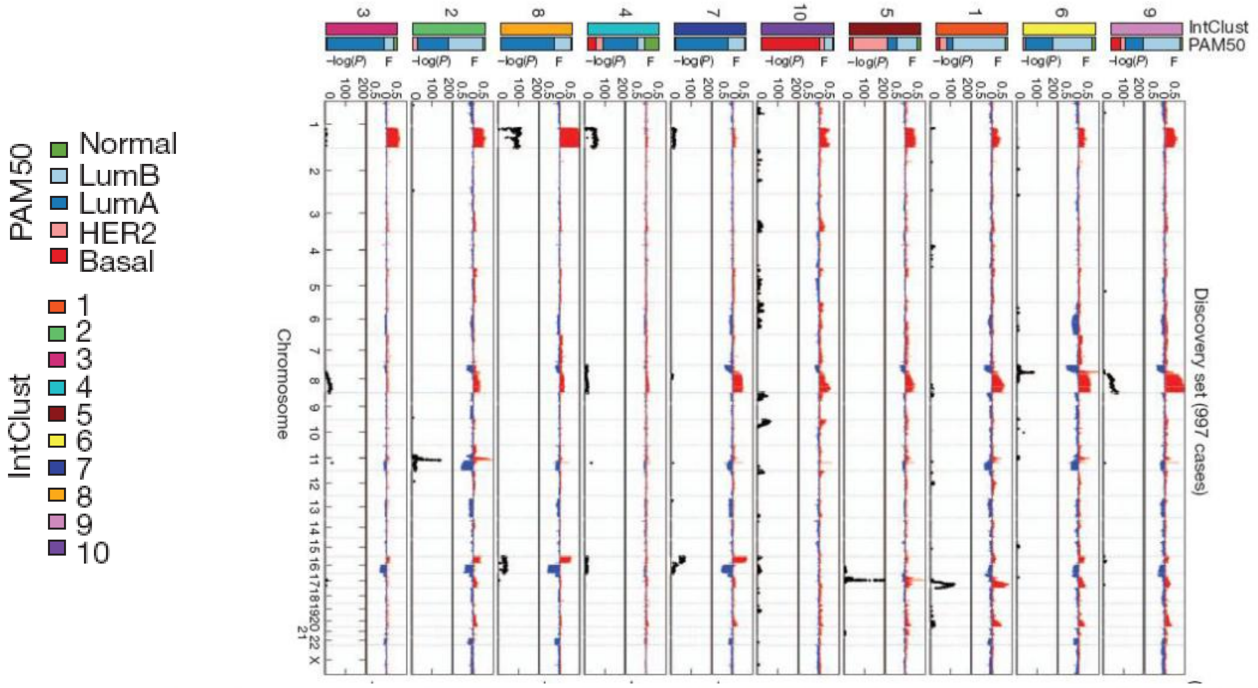
ARTICLE

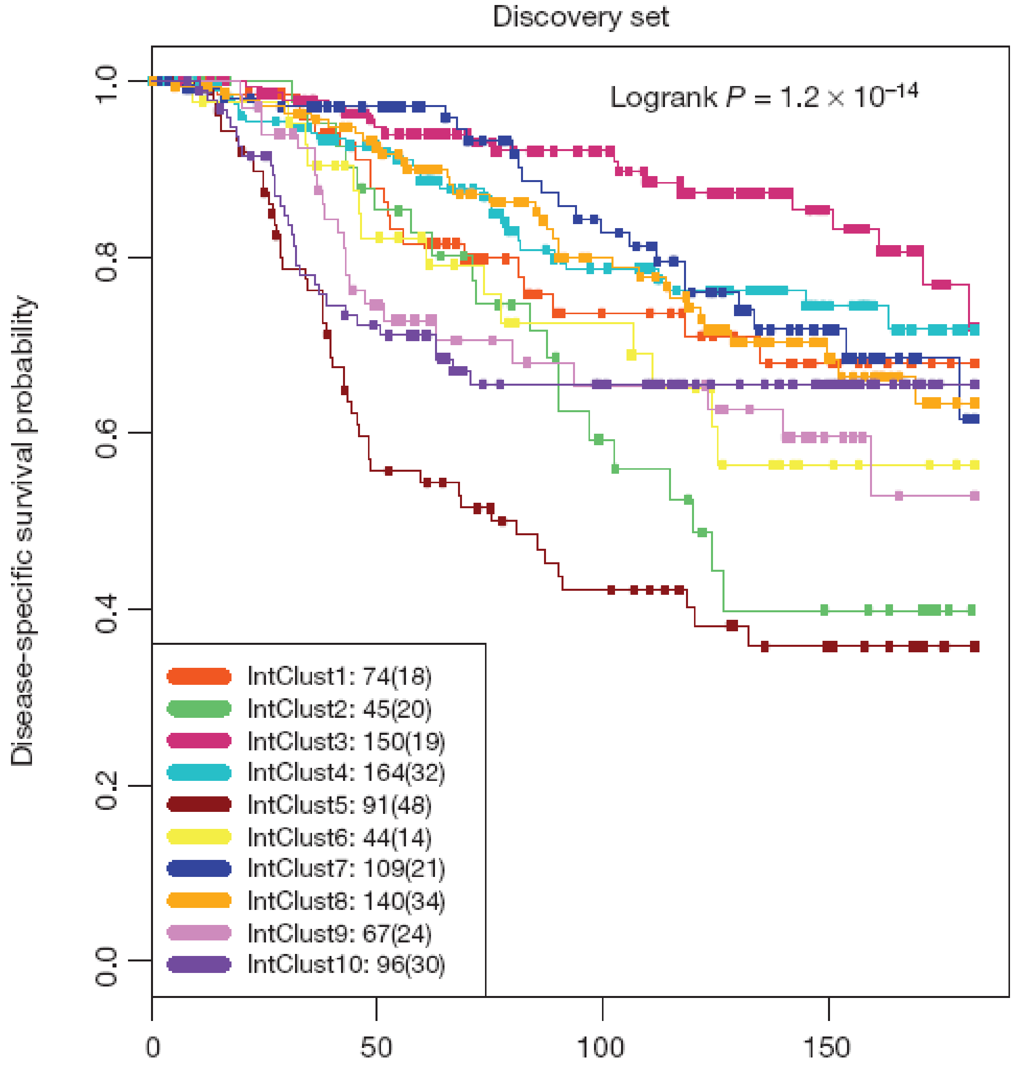
doi:10.1038/nature10983

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Christina Curtis[1,2]†*, Sohrab P. Shah[3,4]*, Suet-Feung Chin[1,2]*, Gulisa Turashvili[3,4]*, Oscar M. Rueda[1,2], Mark J. Dunning[2], Doug Speed[2,5]†, Andy G. Lynch[1,2], Shamith Samarajiwa[1,2], Yinyin Yuan[1,2], Stefan Gräf[1,2], Gavin Ha[3], Gholamreza Haffari[3], Ali Bashashati[3], Roslin Russell[2], Steven McKinney[3,4], METABRIC Group‡, Anita Langerød[6], Andrew Green[7], Elena Provenzano[8], Gordon Wishart[8], Sarah Pinder[9], Peter Watson[3,4,10], Florian Markowetz[1,2], Leigh Murphy[10], Ian Ellis[7], Arnie Purushotham[9,11], Anne-Lise Børresen-Dale[6,12], James D. Brenton[2,13], Simon Tavaré[1,2,5,14], Carlos Caldas[1,2,8,13] & Samuel Aparicio[3,4]







LETTER

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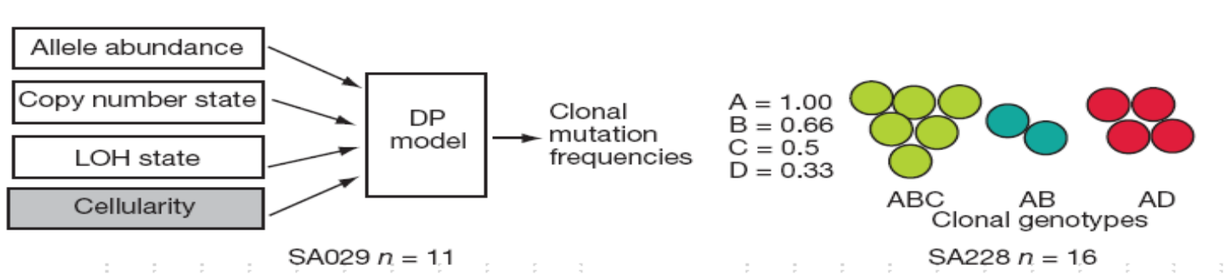
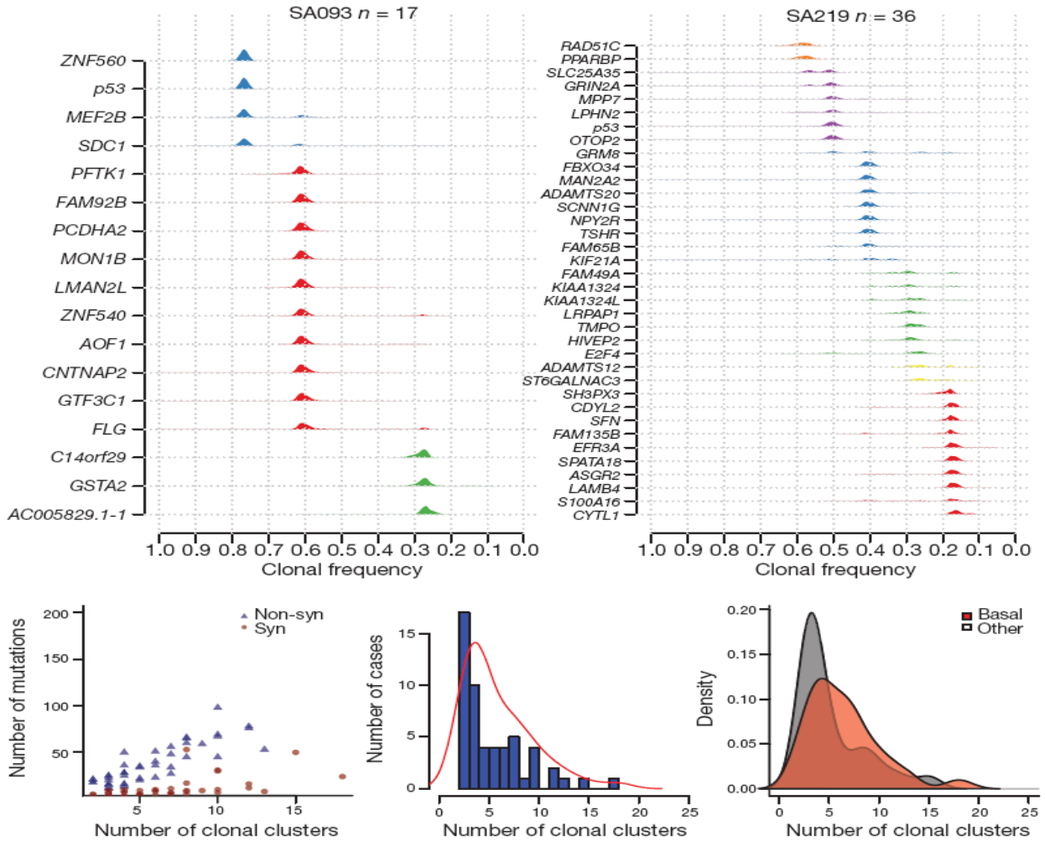
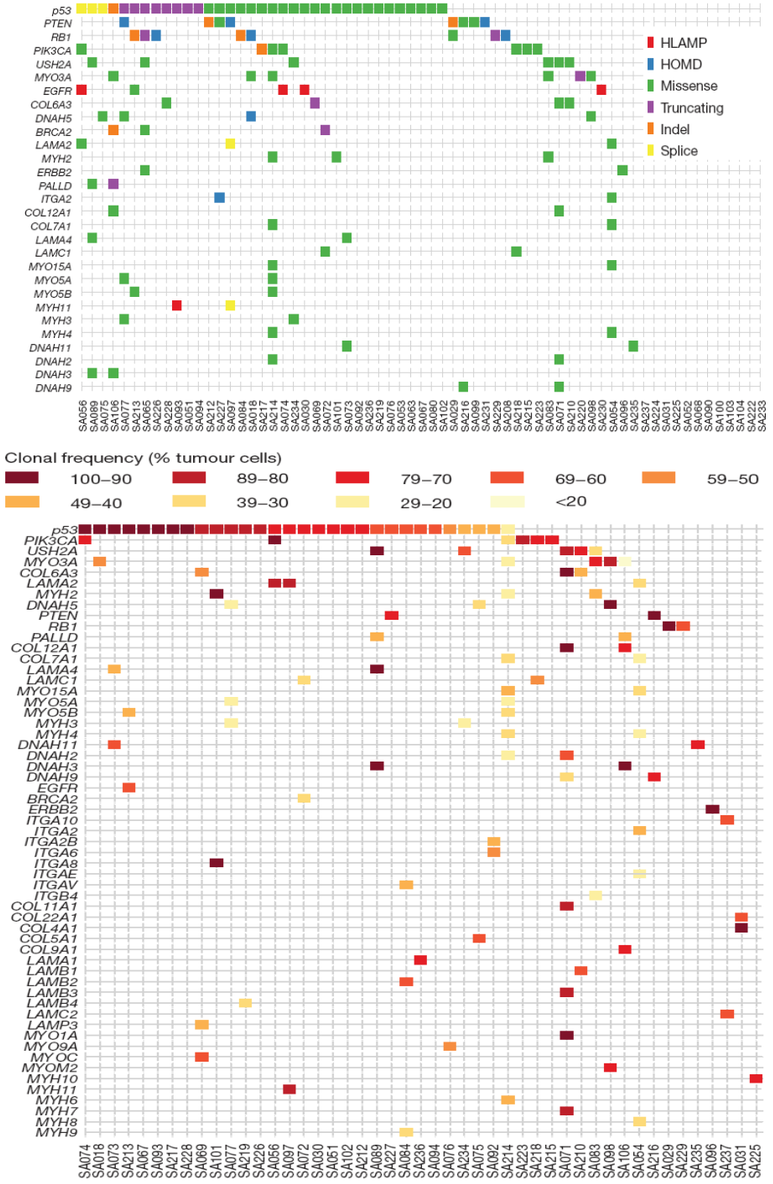
The clonal and mutational evolution spectrum of primary triple-negative breast cancers

Sohrab P. Shah[1,2], Andrew Roth[1,2]*, Rodrigo Goya[3]*, Arusha Oloumi[1,2]*, Gavin Ha[1,2]*, Yongjun Zhao[3]*, Gulisa Turashvili[1,2]*, Jiarui Ding[1,2]*, Kane Tse[3]*, Gholamreza Haffari[1,2]*, Ali Bashashati[1,2]*, Leah M. Prentice[1,2], Jaswinder Khattra[1,2], Angela Burleigh[1,2], Damian Yap[1,2], Virginie Bernard[4], Andrew McPherson[1,2], Karey Shumansky[1,2], Anamaria Crisan[1,2], Ryan Giuliany[1,2], Alireza Heravi-Moussavi[1,2], Jamie Rosner[1,2], Daniel Lai[1,2], Inanc Birol[3], Richard Varhol[3], Angela Tam[3], Noreen Dhalla[3], Thomas Zeng[3], Kevin Ma[3], Simon K. Chan[3], Malachi Griffith[3], Annie Moradian[3], S.-W. Grace Cheng[3], Gregg B. Morin[3,5], Peter Watson[1,6], Karen Gelmon[6], Stephen Chia[6], Suet-Feung Chin[7,8], Christina Curtis[7,8,9], Oscar M. Rueda[7,8], Paul D. Pharoah[7], Sambasivarao Damaraju[10], John Mackey[10], Kelly Hoon[11], Timothy Harkins[11], Vasisht Tadigotla[11], Mahvash Sigaroudinia[12], Philippe Gascard[12], Thea Tlsty[12], Joseph F. Costello[13], Irmtraud M. Meyer[5,14,15], Connie J. Eaves[16], Wyeth W. Wasserman[4,5], Steven Jones[3,5,17], David Huntsman[1,2,18], Martin Hirst[3,15,19], Carlos Caldas[7,8,20,21], Marco A. Marra[3,5] & Samuel Aparicio[1,2]


Allele abundance
Copy number state
LOH state
Cellularity
DP model
Clonal mutation frequencies
A = 1.00
B = 0.66
C = 0.5
D = 0.33
ABC
AB
AD
Clonal genotypes
SA029 n = 11
SA228 n = 16


SA093 n = 17
SA219 n = 36
ZNF560
p53
MEF2B
SDC1
PFTK1
FAM92B
PCDHA2
MON1B
LMAN2L
ZNF540
AOF1
CNTNAP2
GTF3C1
FLG
C14orf29
GSTA2
AC005829.1-1
RAD51C
PPARBP
SLC25A35
GRIN2A
MPP7
LPHN2
p53
OTOP2
GRM8
FBXO34
MAN2A2
ADAMTS20
SCNN1G
NPY2R
TSHR
FAM65B
KIF21A
FAM49A
KIAA1324
KIAA1324L
LRPAP1
TMPO
HIVEP2
E2F4
ADAMTS12
ST6GALNAC3
SH3PX3
CDYL2
SFN
FAM135B
EFR3A
SPATA18
ASGR2
LAMB4
S100A16
CYTL1
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Clonal frequency
Number of mutations
Non-syn
Syn
Number of clonal clusters
Number of cases
Density
Basal
Other


HLAMP
HOMD
Missense
Truncating
Indel
Splice
Clonal frequency (% tumour cells)
100–90
89–80
79–70
69–60
59–50
49–40
39–30
29–20
<20

Mensajes finales

- Emergen nuevos potenciales marcadores de sensibilidad a inhibidores de BRAF en melanoma
- La resistencia a los inhibidores de BRAF en cáncer colorectal se revierte combinando inhibidores de EGFR
- PI3K y PTEN, posibles marcadores de sensibilidad a los inhibidores de mTOR
- Importancia de las mutaciones/variantes de HER2 en la resistencia a los inhibidores de HER2
- Relevancia de la heterogeneidad tumoral