

Efficacité des traitements anti-HER2
dans le cancer du sein métastatique
avec mutation activatrice d' *HER3*

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ESOPE study samples → Next Generation Sequencing @MSKCC

Frozen biopsy breast K & liver met

MSKCC

→ Microdissection & extraction ADN

→ SNP6

→ whole exome sequencing - Illumina HiSeq 2000 @ CGL

2 tumor samples (targeted mean depth : 250x)

Germline (100x)

Analysis of sequencing data (KYC Ng)

SNV called by Mutect & MutationSeq

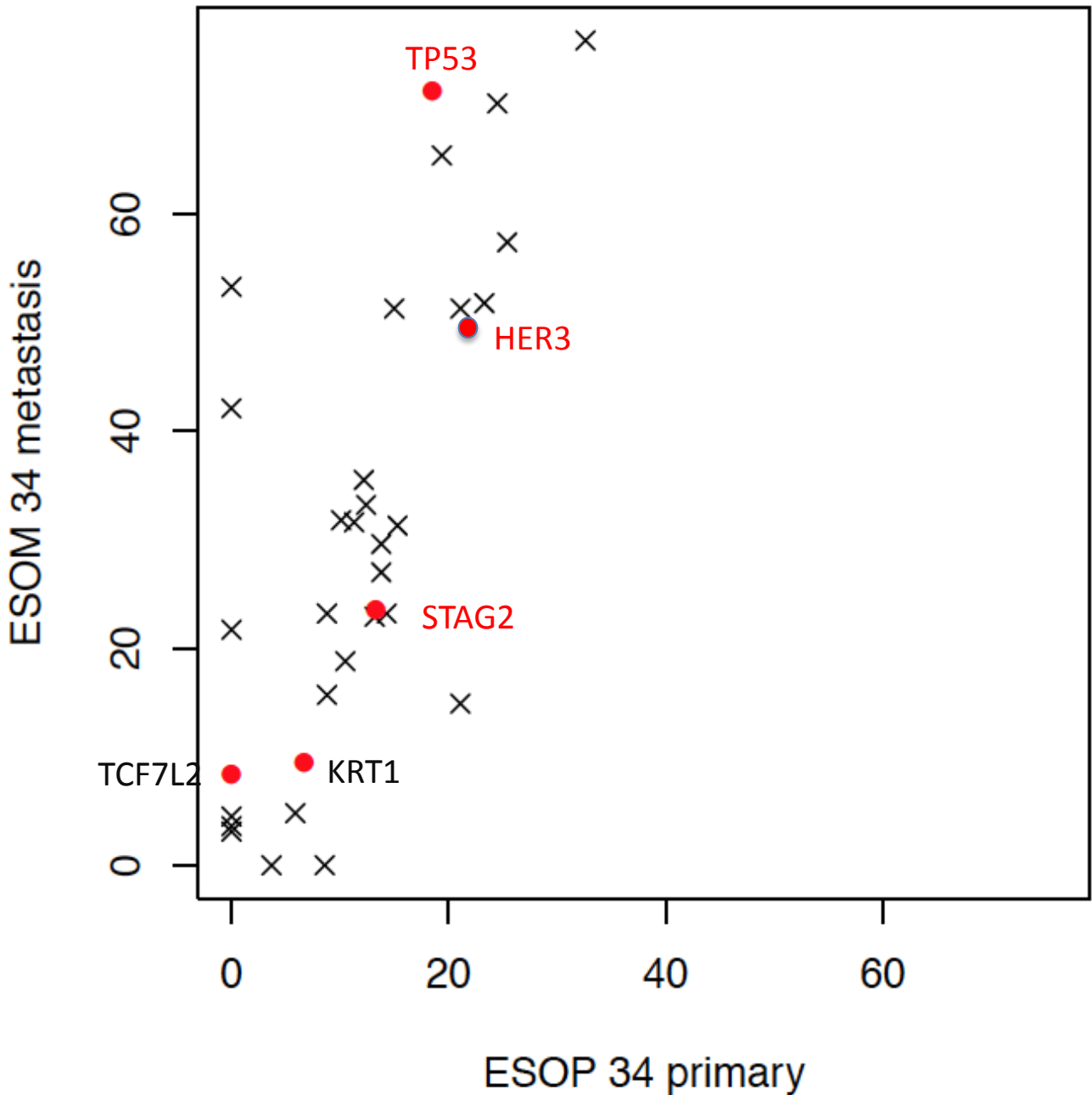
Indels called by GATK HaplotypeCaller

(Correction for cellularity & CNV determined by SNP6)

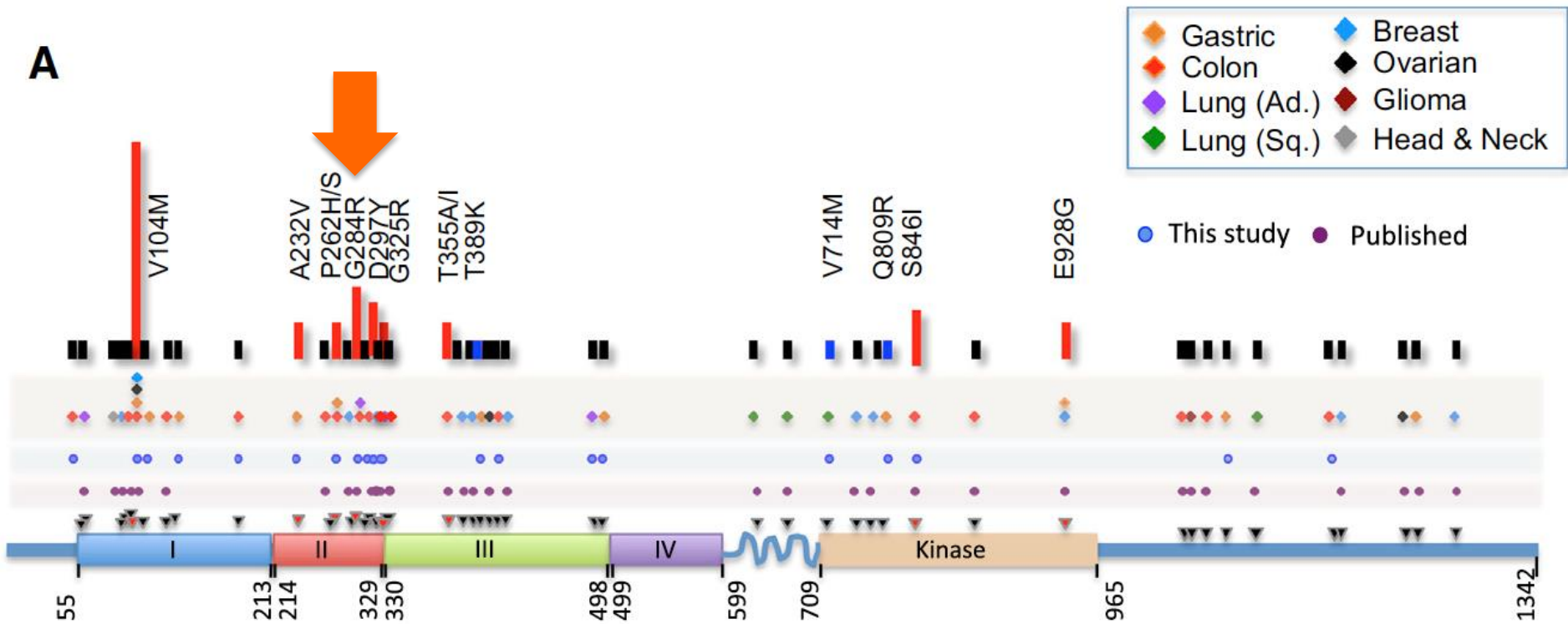
Couple #34

Depth / AF max
P 179x / 0.32
M 193x / 0.76
G 64x
35 mutations
PT only: 3
PT & Met: 26
Met only: 6

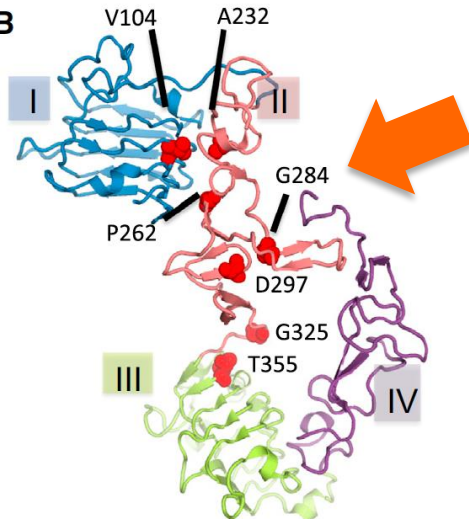
IDC-NST HR+ (low) HER2 neg



A



B



Extra-cellular domain

G284R in the domain I/II interface

Cancer Cell
Article



Oncogenic *ERBB3* Mutations in Human Cancers

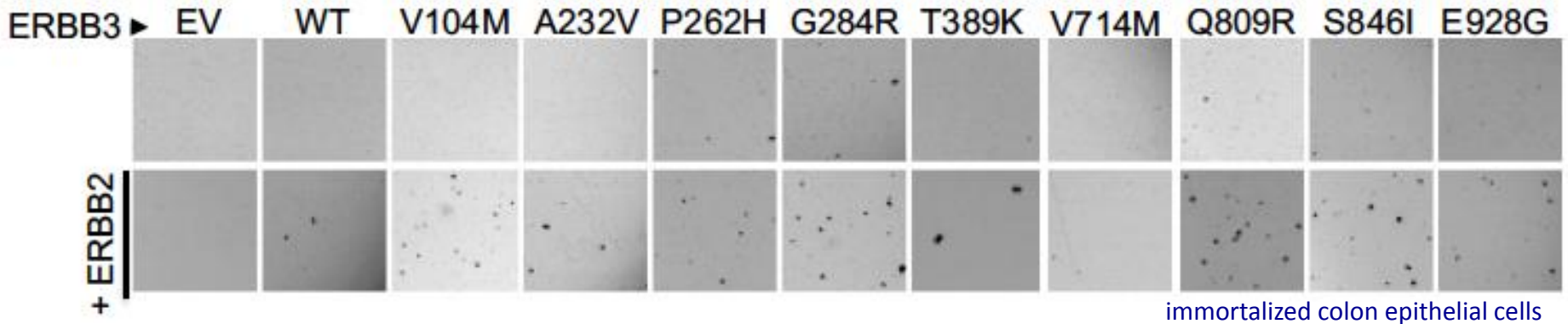
Bijay S. Jaiswal,¹ Noelyn M. Kijavin,¹ Eric W. Stawiski,^{1,9} Emily Chan,² Chaitali Parikh,¹ Steffen Durinck,^{1,9} Subhra Chaudhuri,¹ Kanan Pujara,¹ Joseph Guillory,¹ Kyle A. Edgar,³ Vasantharajan Janakiraman,¹ Rolf-Peter Scholz,¹⁰ Krista K. Bowman,^{4,7} Maria Lorenzo,⁸ Hong Li,⁸ Jiansheng Wu,⁸ Wenlin Yuan,¹ Brock A. Peters,¹ Zhengyan Kan,¹ Jeremy Stinson,¹ Michelle Mak,¹ Zora Modrusan,¹ Charles Eigenbrot,⁴ Ron Firestein,⁵ Howard M. Stern,⁵ Krishnaraj Rajalingam,¹⁰ Gabriele Schaefer,⁶ Mark A. Merchant,² Mark X. Sliwkowski,⁶ Frederic J. de Sauvage,¹ and Somasekar Seshagiri^{1,*}

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⁴Department of Structural Biology
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⁷Department of Protein Engineering
⁸Department of Protein Chemistry
⁹Department of Bioinformatics and Computational Biology

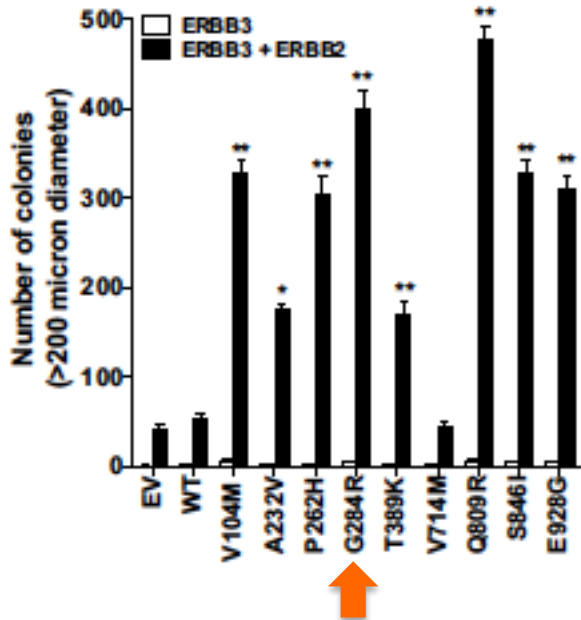
Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA

¹⁰Institute of Biochemistry II, Goethe University School of Medicine, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany

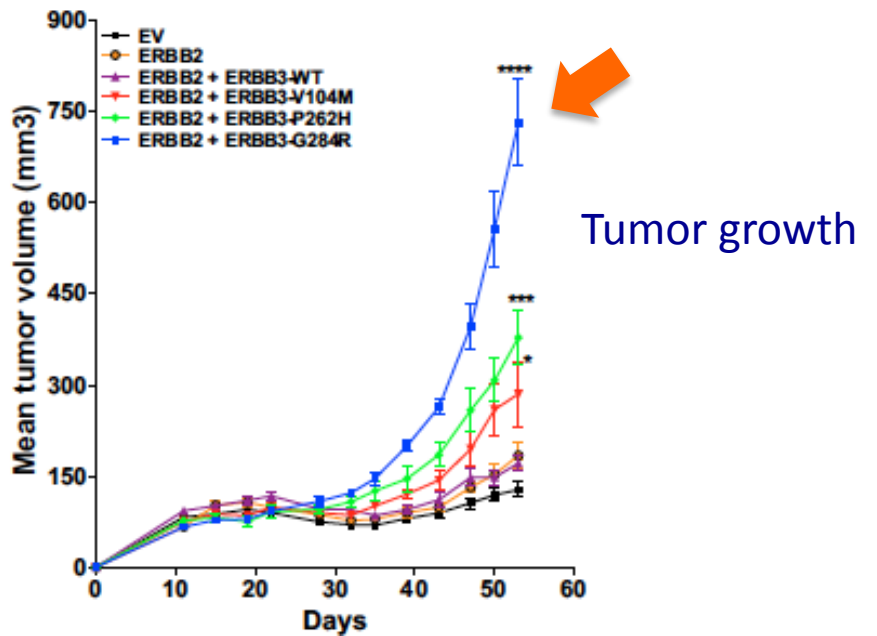
A HER2 co-expression required



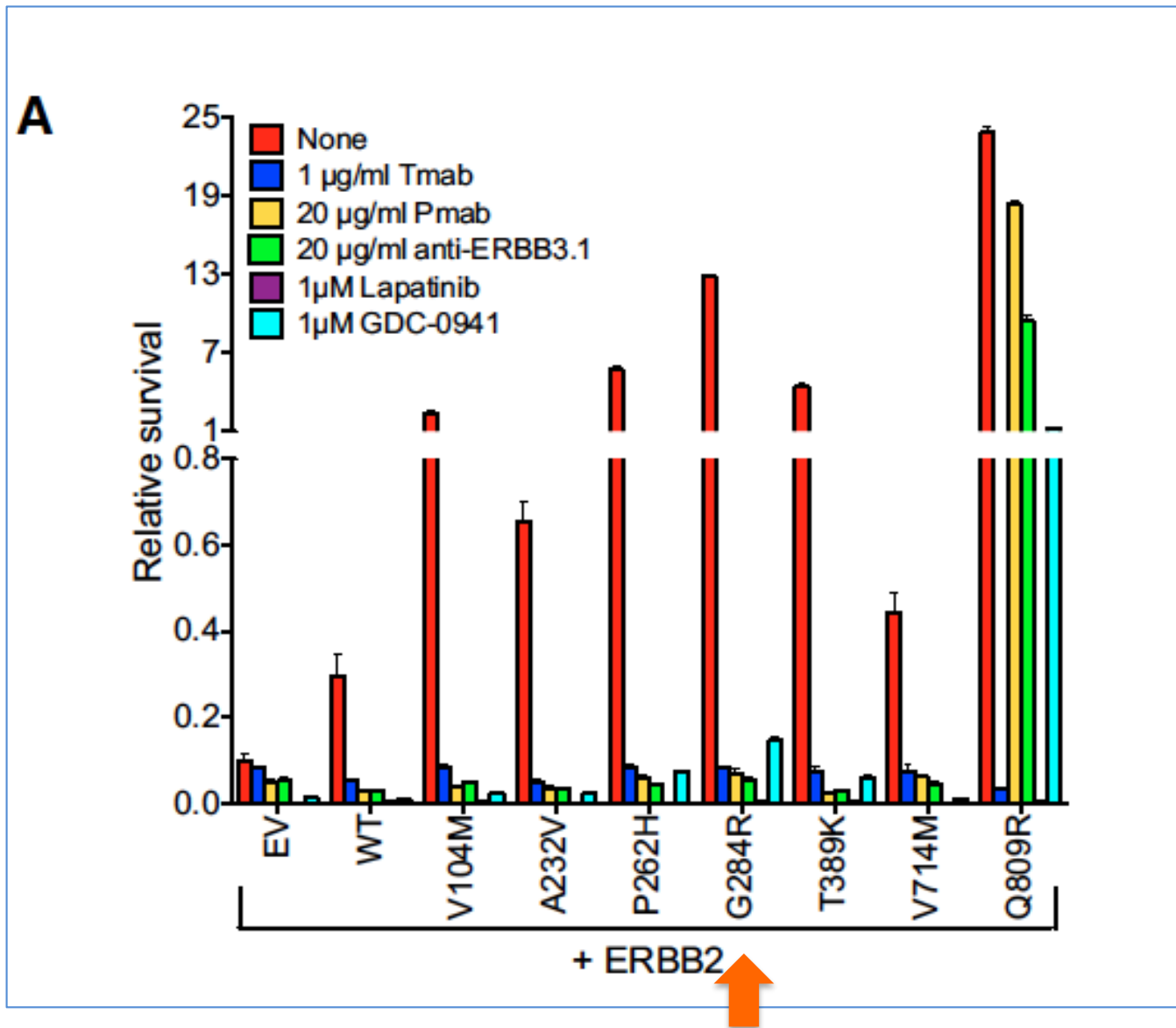
B



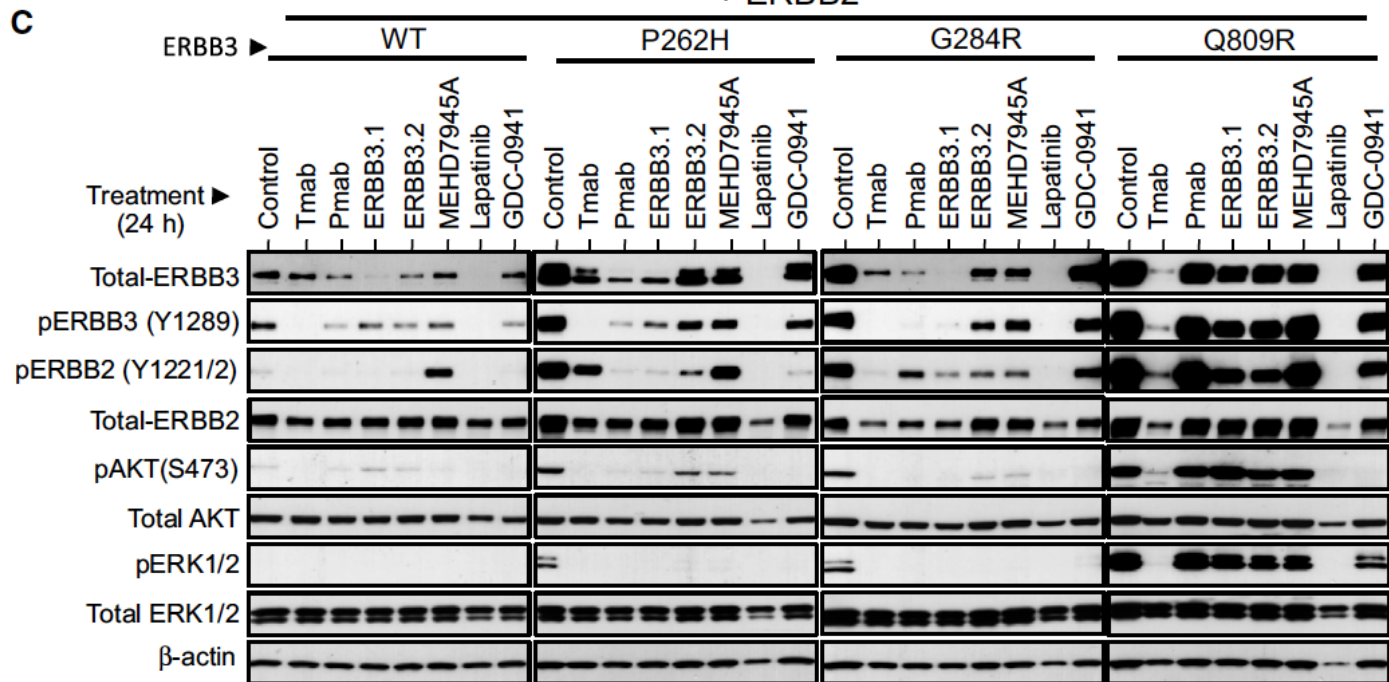
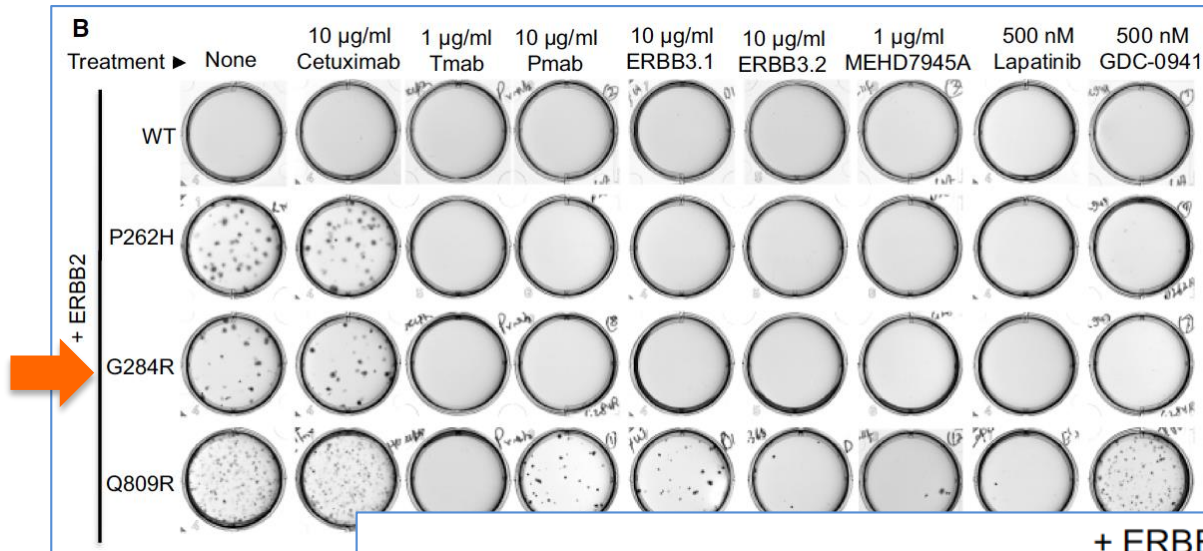
E



Sensitivity to anti-HER agents



Sensitivity to anti-HER agents



June 2012

March 2013

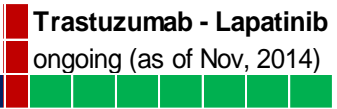
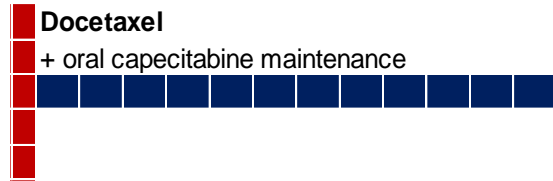
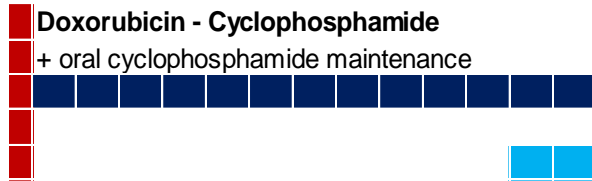
May 2013

April 2014

Initial diagnosis
cT3N1M1 breast cancer

Progressive disease (liver)

Progressive disease (liver)



Radiotherapy Mastectomy

Liver metastases resection
1st met.: 90% necrosis
2nd met.: 50% necrosis

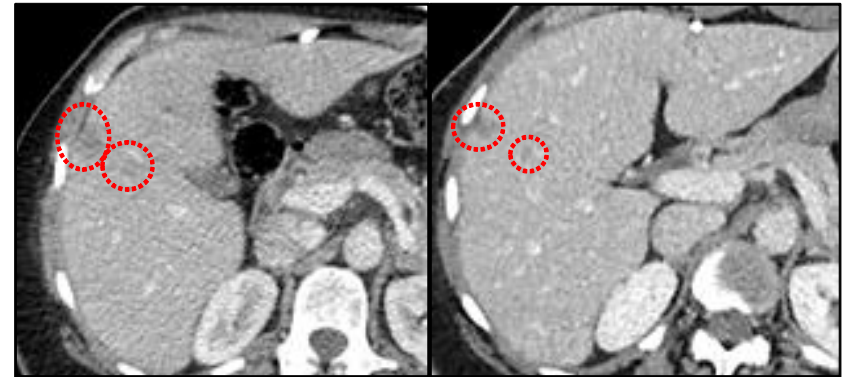
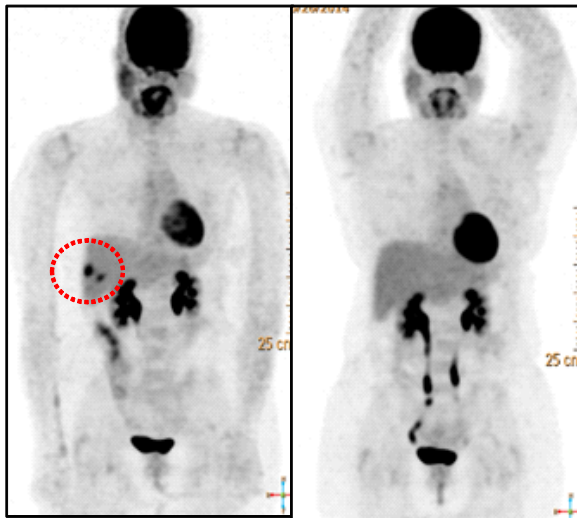
Primary tumor biopsies
Liver metastasis biopsies

Baseline

Day 15
Complete metabolic response

Baseline

Day 67
Partial Response



Response confirmed 1 month later

→ **1st in man - Proof of concept with no chemotherapy**

→ **Treatment to be continued**

pertuzumab more likely active than T-DM1 (?)

→ **HER3 activating mutations are rare in breast cancer**

1 case / 1000 TCGA

2% of colorectal and gastric cancers