Intra-tumor heterogeneity defines subtypes of HER2+ breast cancer with clinical implication

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Radiumhospitalet

RADIUM HOSPITAL FOUNDATION

UiO : University of Oslo

HELSE SØR-ØST

STIFTELSEN KGJ

KREFTFORENINGEN

NFR

basis

SEVENTH FRAMEWORK PROGRAMME

EurocanPlatform

Disclosure Information

Board Member and consultant of Artic Pharma.
Holding a common grant from the Norwegian Research Council to explore on model systems new drugs inhibiting the glycolytic pathway.

Board Member and consultant of Biomolex.
Holding a common grant from the Norwegian Research Council to evaluate a kinome profiling tool to survey kinases and pathways in breast cancer

No financial interest in any of the Companies and will not discuss any of their products

Large inter-tumor heterogeneity in breast cancer

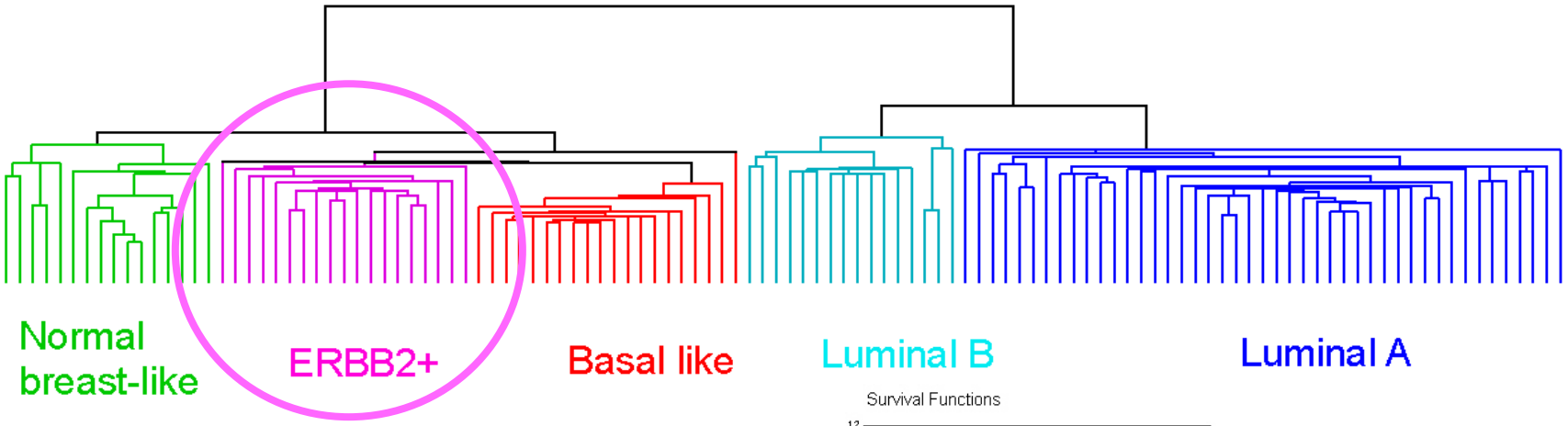
Perou, Sørlie et a 2000

5 molecular subtypes identified based on mRNA expression of tumors from Norwegian patients:

Intrinsic subtypes, based on 560 genes >>

A set of 50 genes identifies the subgroups; PAM50

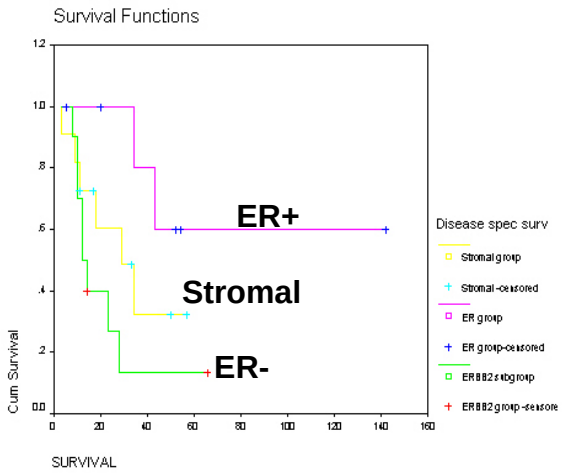
Different subgroups found in all datasets, have differences in:
Mutation spectrum, sequence alterations,
copy number aberrations, methylation, metabolism,
protein expression; >>biology



HER2 enriched tumors

- 15-20% of tumors
- At least three types

(ER -/+) with and without TP53 mut



METABRIC-Molecular Taxonomy of Breast cancer International Consortium

Generation of a robust molecular taxonomy of clinically annotated breast cancers

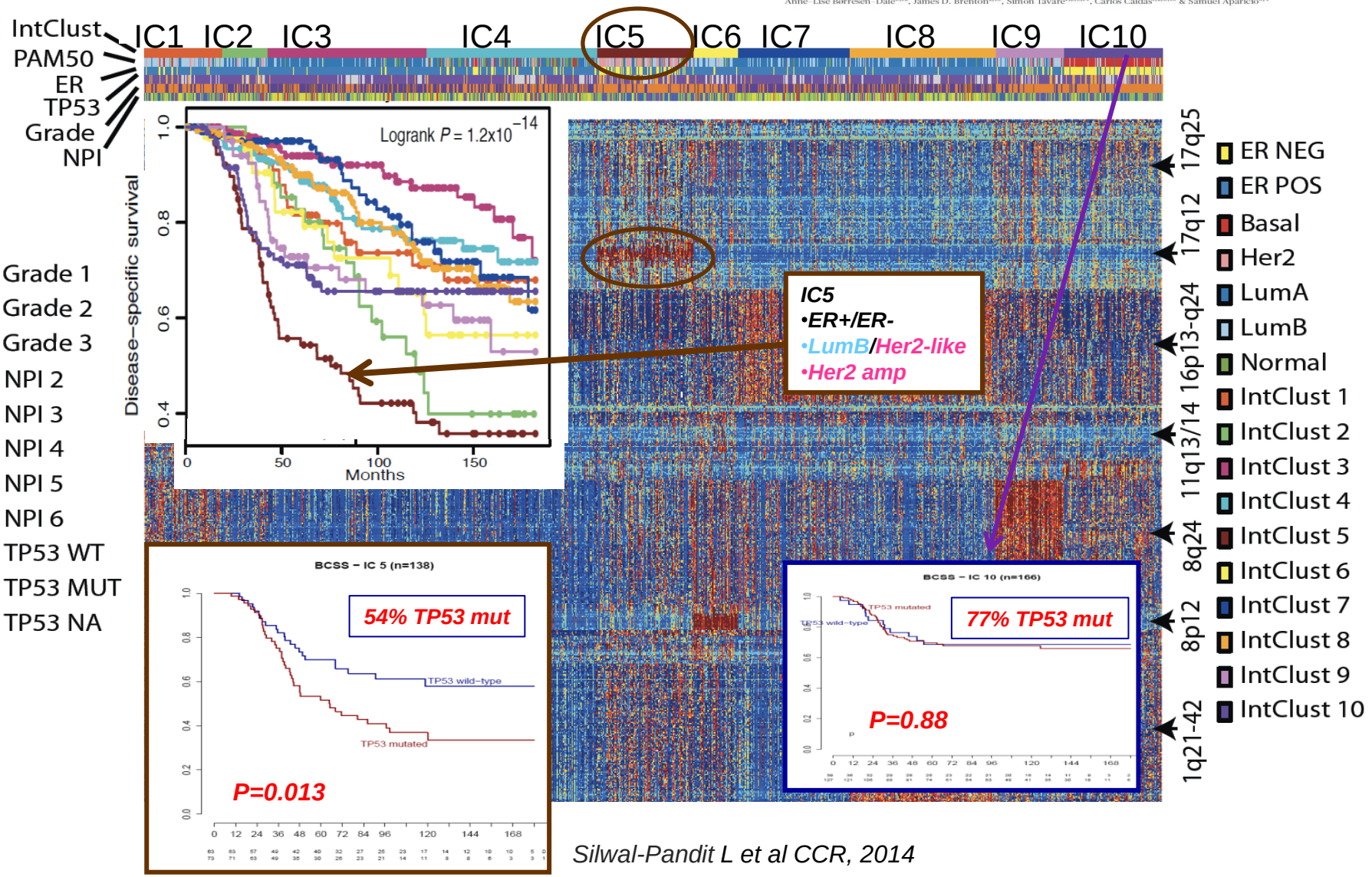
Anglo-Canadian collaboration

Carlos Caldas & Samuel Aparicio

ARTICLE nature 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-Feng 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]

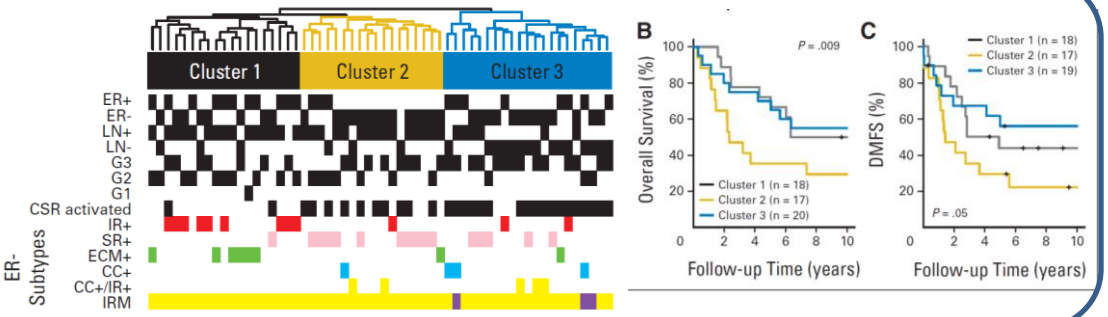


Silwal-Pandit L et al CCR, 2014

VOLUME 28 · NUMBER 11 · APRIL 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Identification of Subtypes in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer Reveals a Gene Signature Prognostic of Outcome

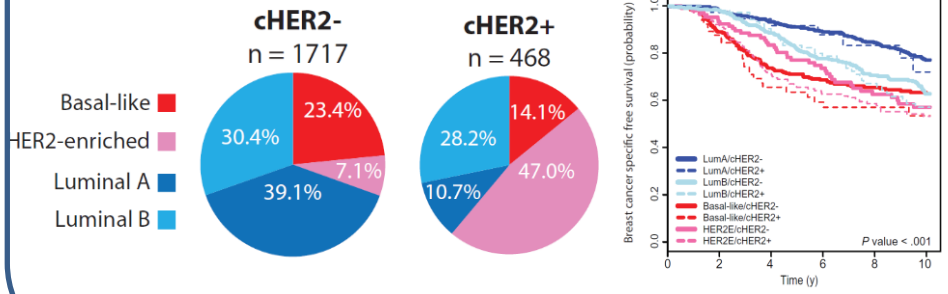
Johan Staaf, Markus Ringnér, Johan Vallon-Christersson, Göran Jönsson, Pär-Ola Bendahl, Karolina Holm, Adalgeir Arason, Haukur Gunnarsson, Cecilia Hegardt, Bjarni A. Agnarsson, Lena Luts, Dorthe Grabau, Mårten Fernö, Per-Olof Malmström, Oskar Th. Johannsson, Niklas Loman, Rosa B. Barkardottir, and Åke Borg



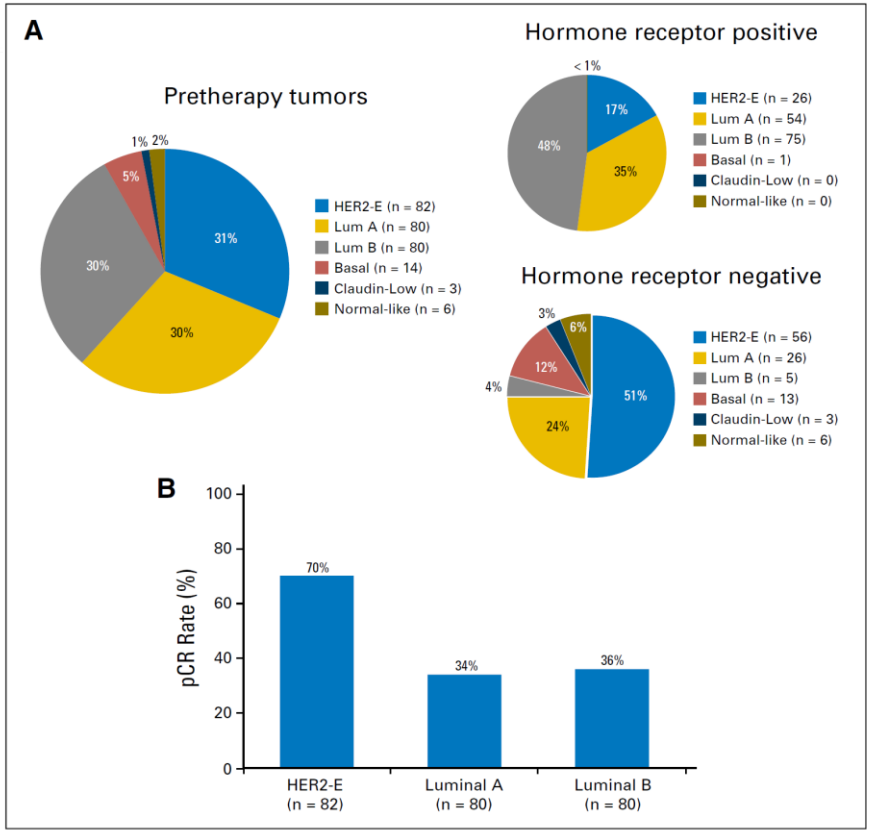
ARTICLE | JNCI 2014

Molecular Features and Survival Outcomes of the Intrinsic Subtypes Within HER2-Positive Breast Cancer

Aleix Prat, Lisa A. Carey, Barbara Adamo, Maria Vidal, Josep Tabernero, Javier Cortés, Joel S. Parker, Charles M. Perou, José Baselga



TCGA and METABRIC



VOLUME 34 · NUMBER 6 · FEBRUARY 20, 2016
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib

Lisa A. Carey, Donald A. Berry, Constance T. Cirrincione, William T. Barry, Brandelyn N. Pitcher, Lyndsay N. Harris, David W. Ollila, Ian E. Krop, Norah Lynn Henry, Douglas J. Weckstein, Carey K. Anders, Baljit Singh, Katherine A. Hoadley, Michael Iglesia, Maggie Chon U. Cheang, Charles M. Perou, Eric P. Winer, and Clifford A. Hudis

Author affiliations appear at the end of this article.

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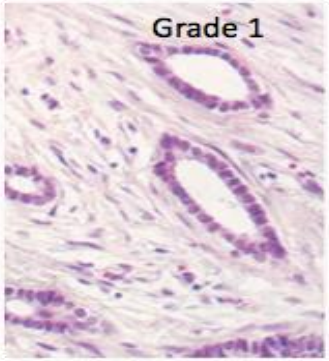
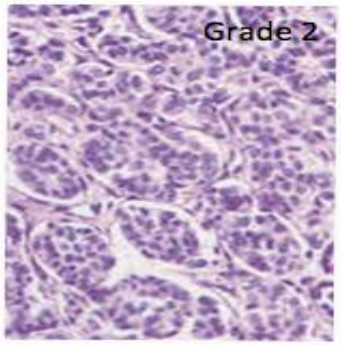
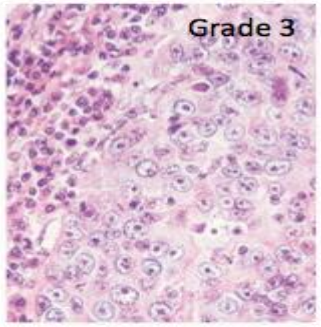
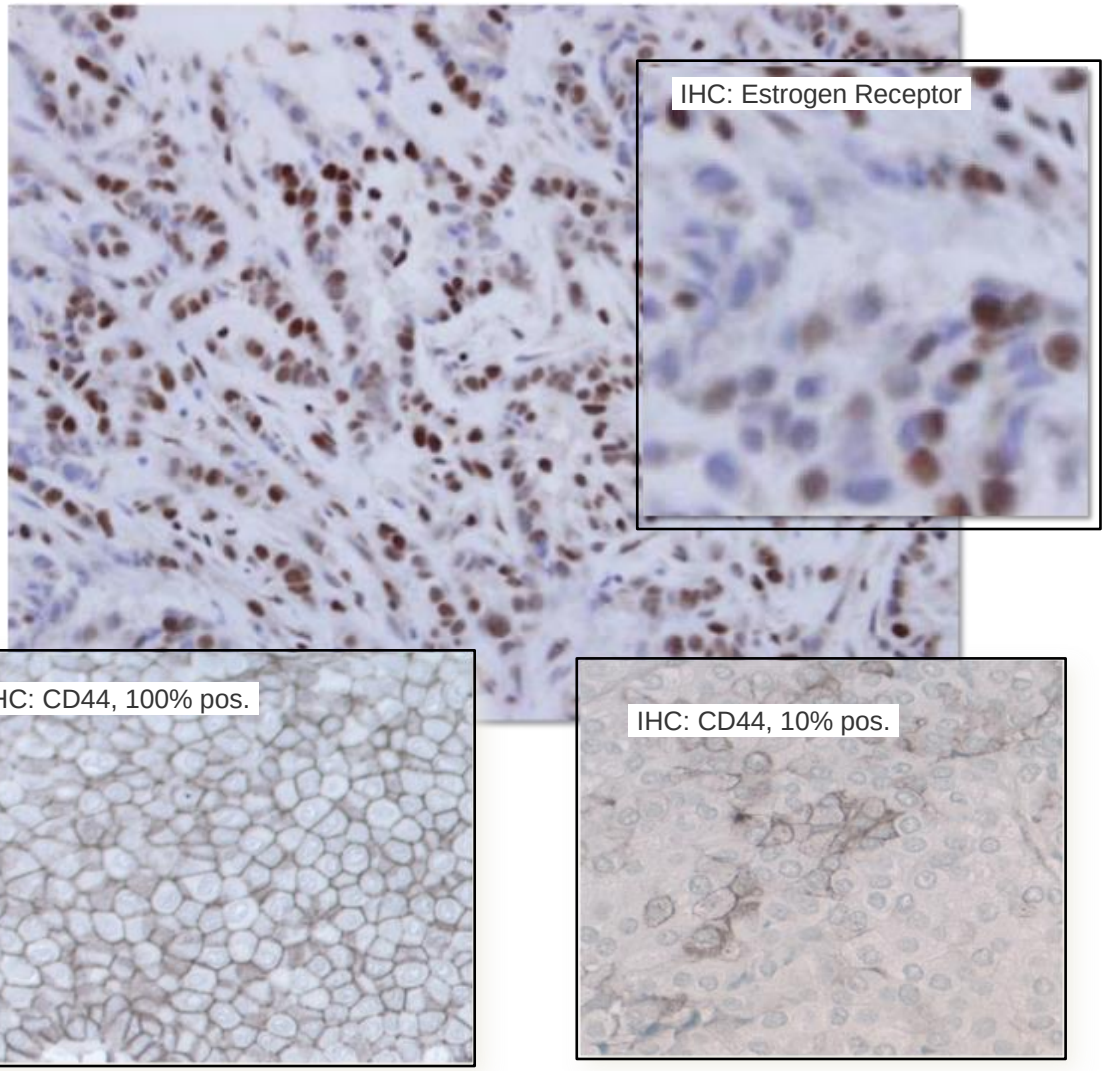
Inter-tumor heterogeneity







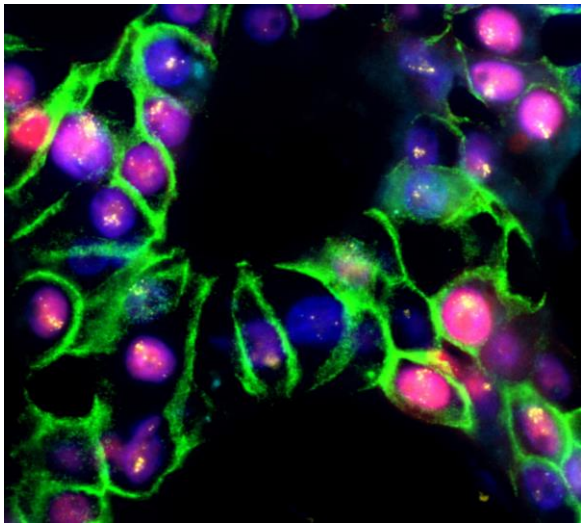
Intra-tumor heterogeneity



Intra tumor heterogeniety studied by *In situ* analyses and ImmunoFISH with patient specific markers

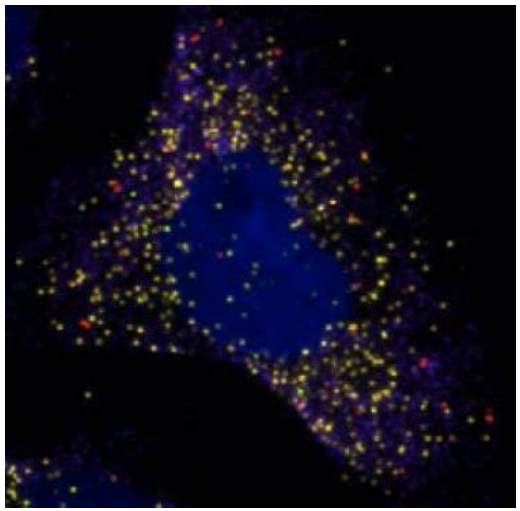
Hege G Russnes

Inga H Rye



DNA and protein in a breast tumor
4 um sections, FFPE tissue,
photographed in 21 levels,

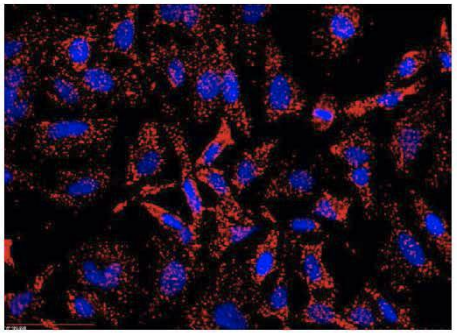
DAPI: Blue
HER2 gene: yellow
Cent17: light blue
HER2 protein: green
ER protein: red



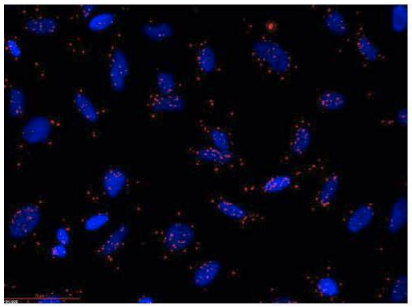
4 –plex mRNA Expression on a cell line
Affymetrix QuantiGene ViewRNA

ACTB: DarkBlue
PPIB: yellow
ERBB2: green
HPRT1: red

Let7a



miR-155

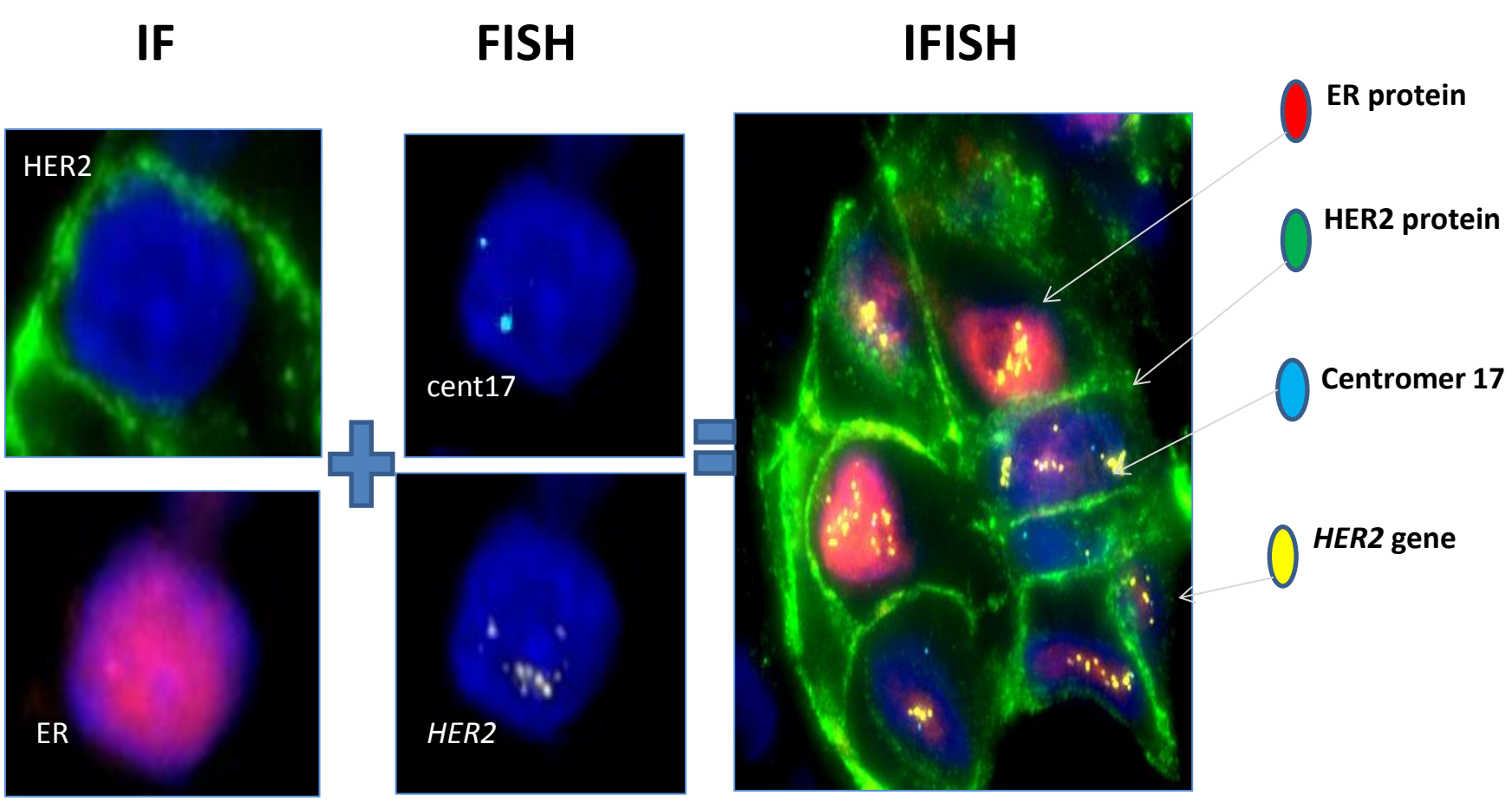


Micro RNA Expression
Affymetrix QuantiGene
View microRNA

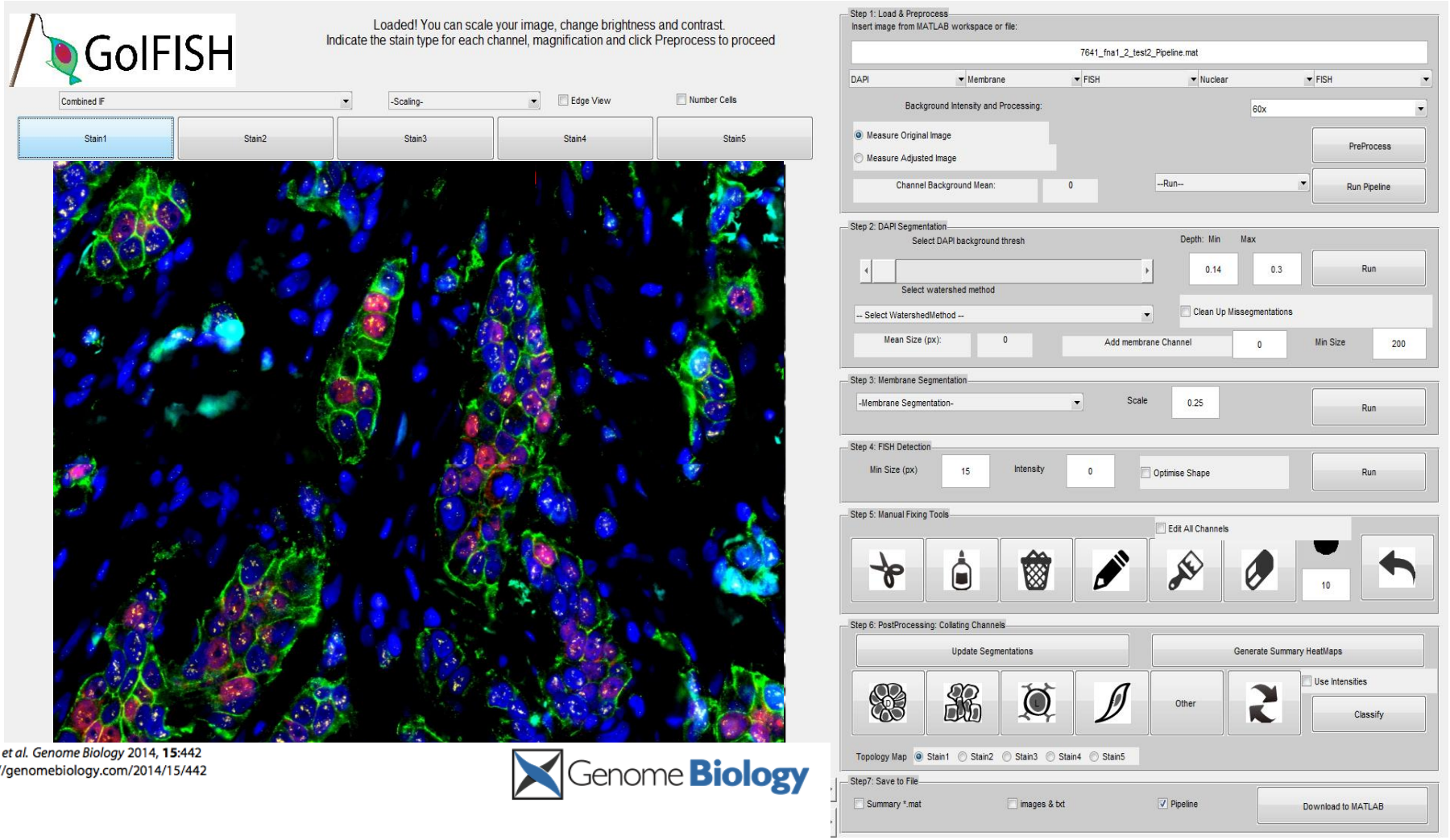
The RA-HER2 cohort

N=37

- Neo-adjuvant treated with taxan, FEC and Trastuzumab
- Biopsies (FFPE) at two time points + available metastates
  - Pre therapy (n=37)
  - Post therapy (n=25)
  - Metastatses (n=3)



Trinh, Rye et al. 2014



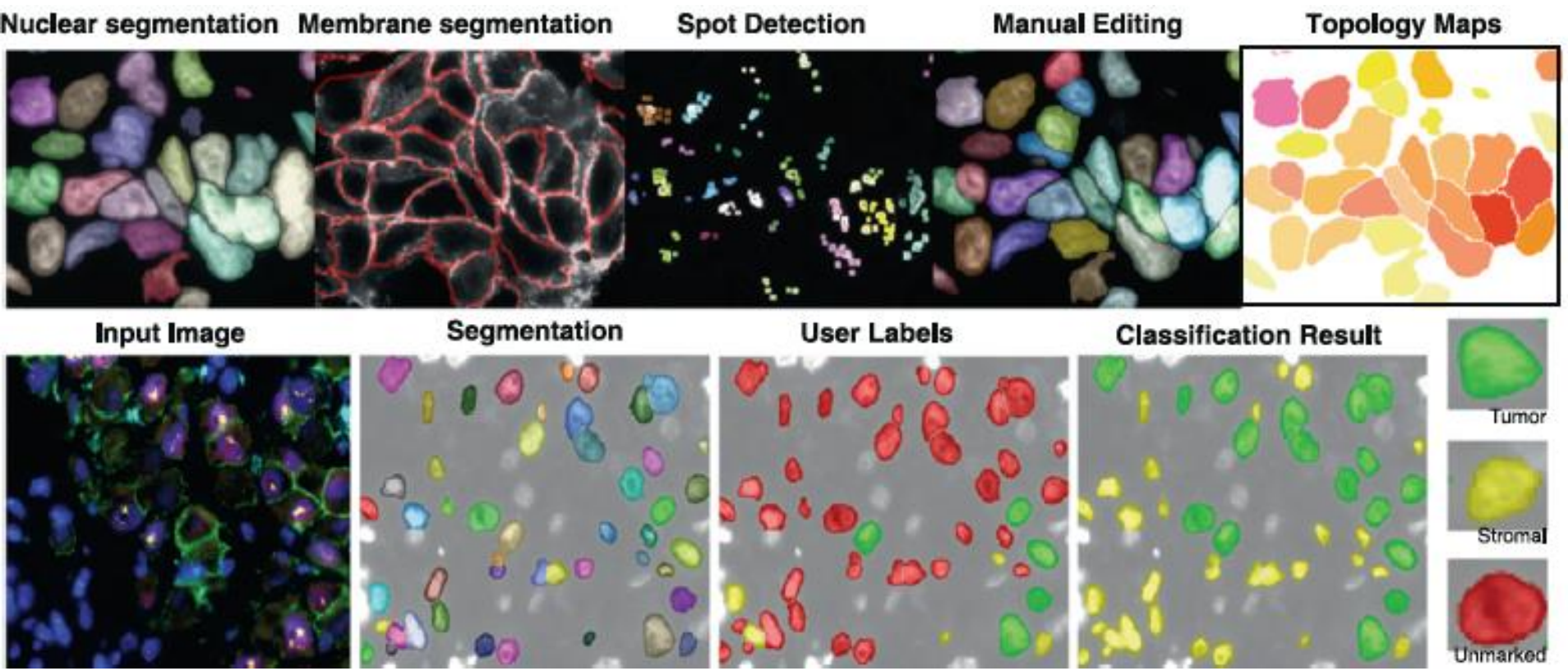
Trinh *et al. Genome Biology* 2014, **15**:442
http://genomebiology.com/2014/15/442

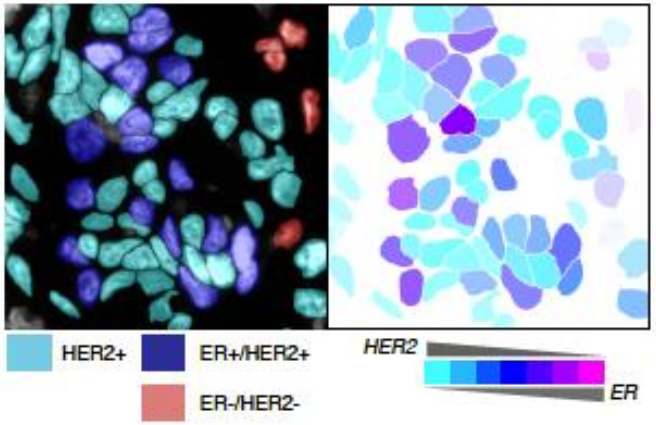
Genome Biology

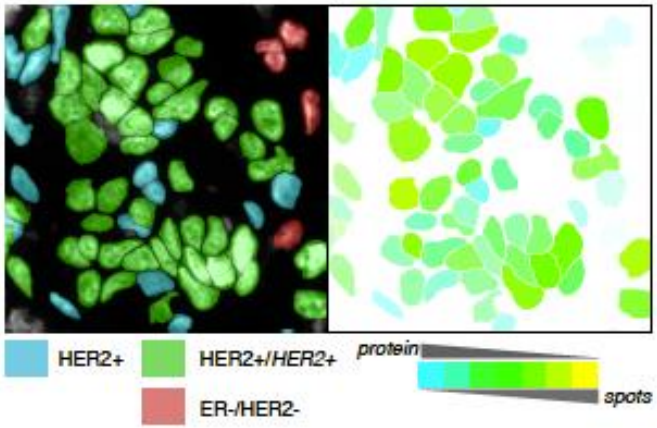
SOFTWARE **Open Access**

GoIFISH: a system for the quantification of single cell heterogeneity from IFISH images

Anne Trinh[1†], Inga H Rye[2,3†], Vanessa Almendro[4,5], Åslaug Helland[2,3,6], Hege G Russnes[2,3,7*] and Florian Markowetz[1*]



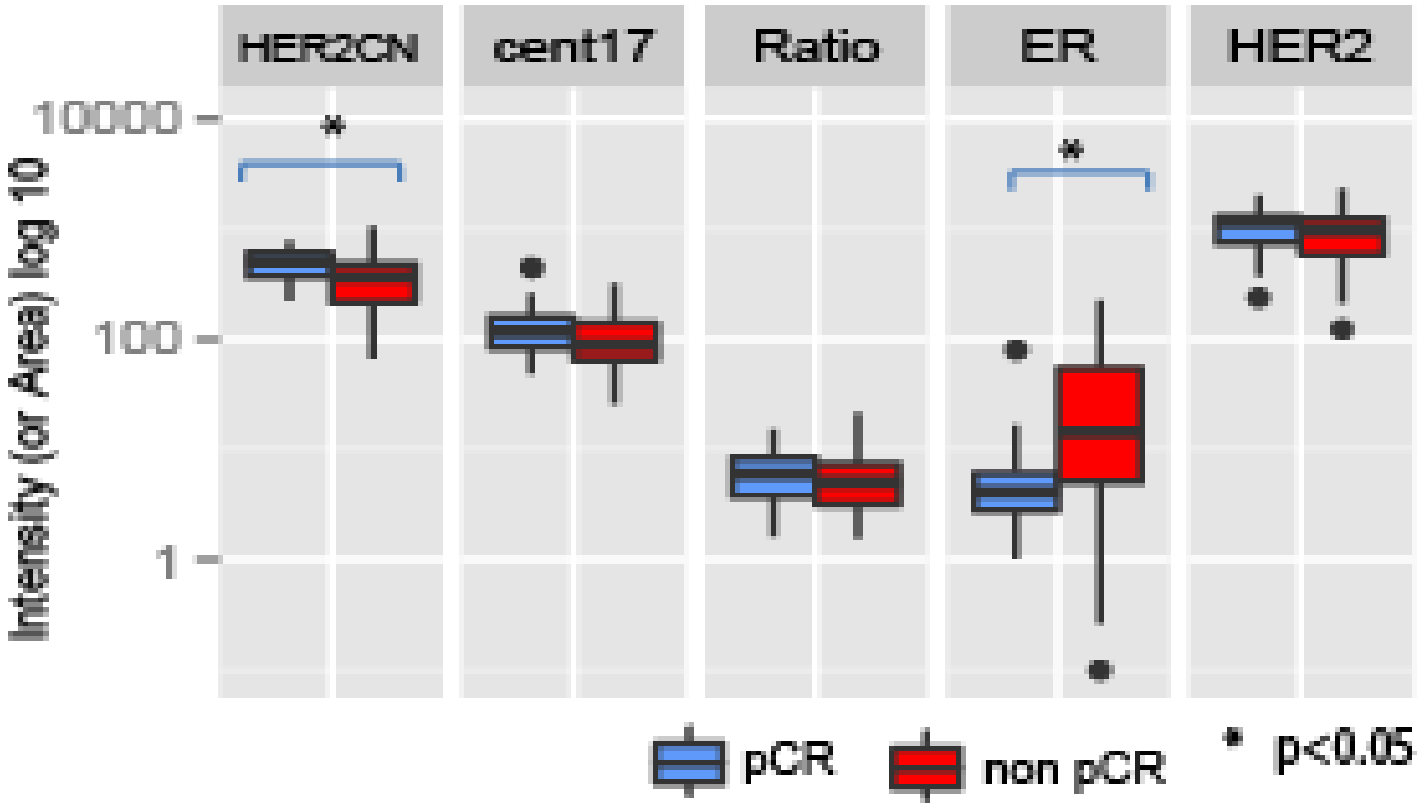




Trinh et al., Genome Biology 2014

http://sourceforge.net/projects/goifish/

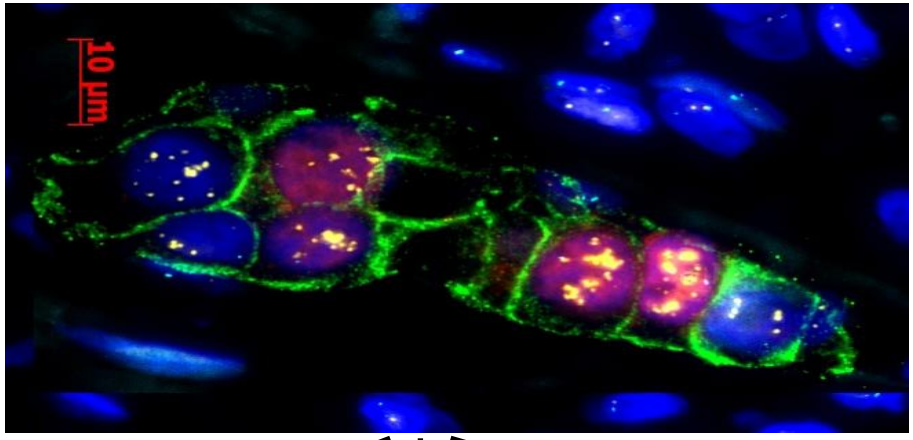
Comparing the pre samples (n=37), stratified by pCR (n=12)/non pCR (n=25) for the analyzed markers



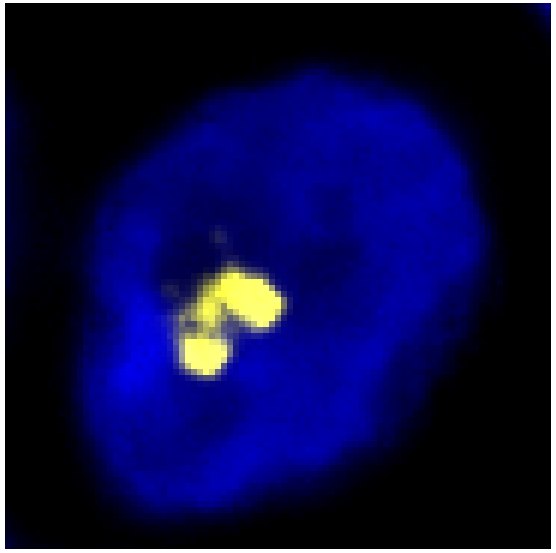
- Tumors with pCR have more cells with HER2 copy number gain
- Tumors with non pCR have more ER positive cells

Rye et al. unpublished

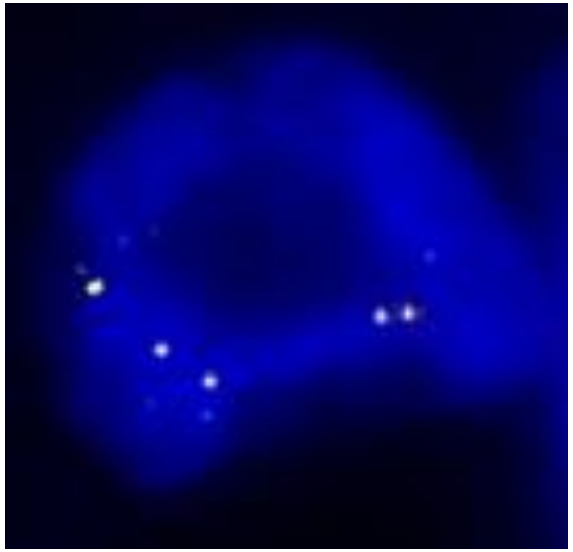
HER2 gene spatial organization within the nuclei differs between cells



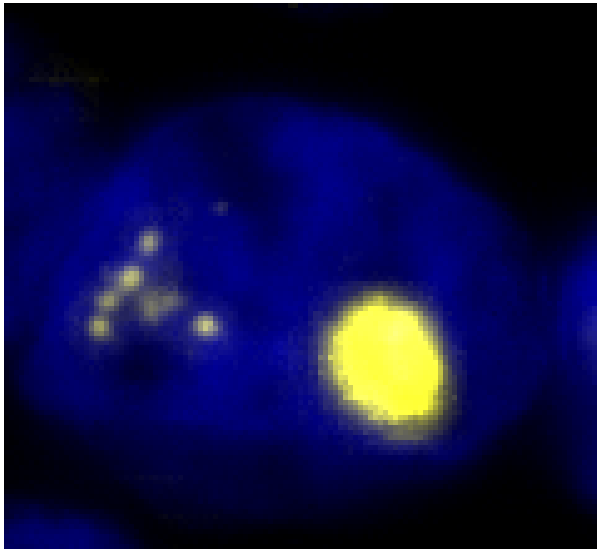
cluster



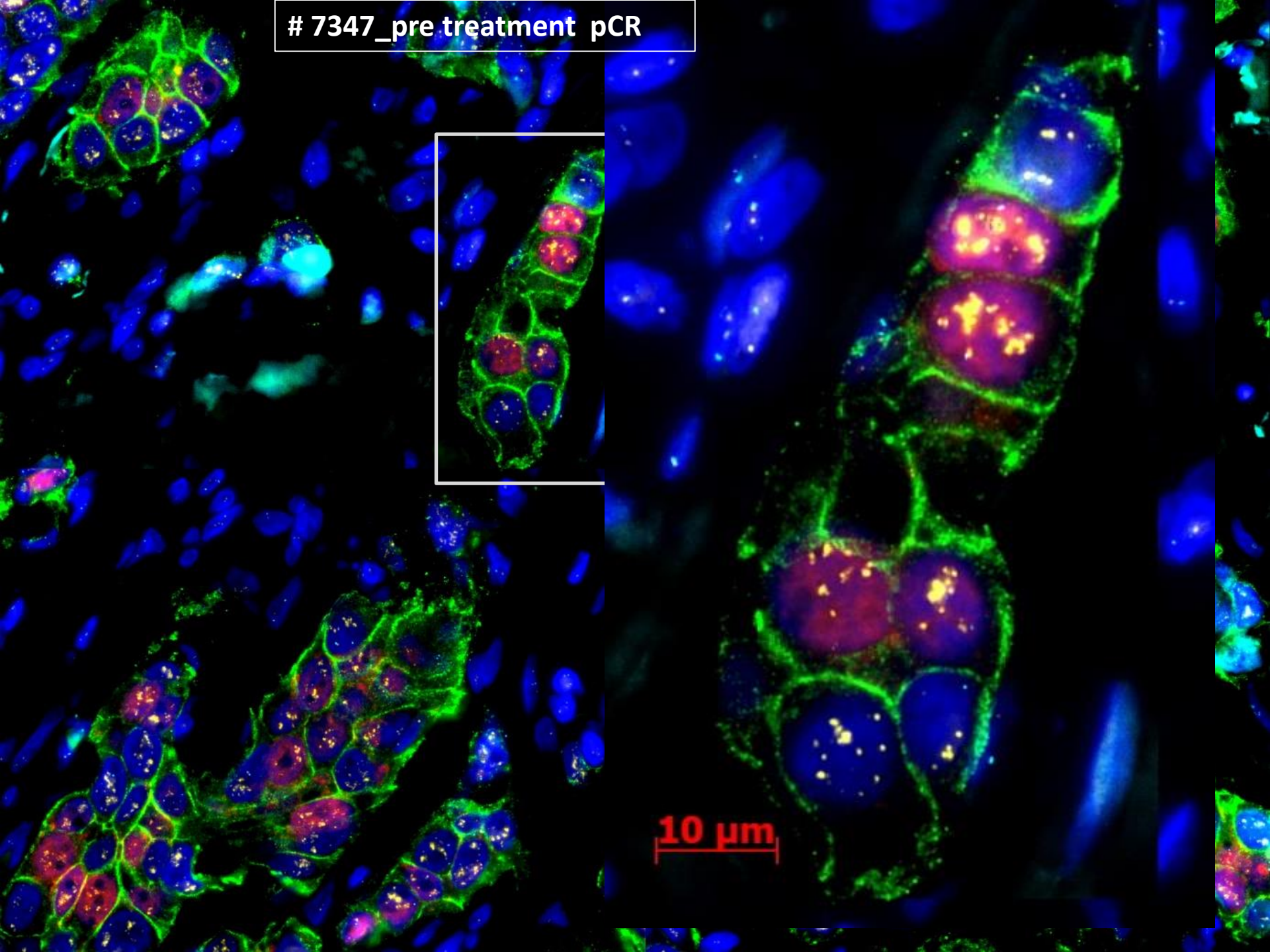
scatter

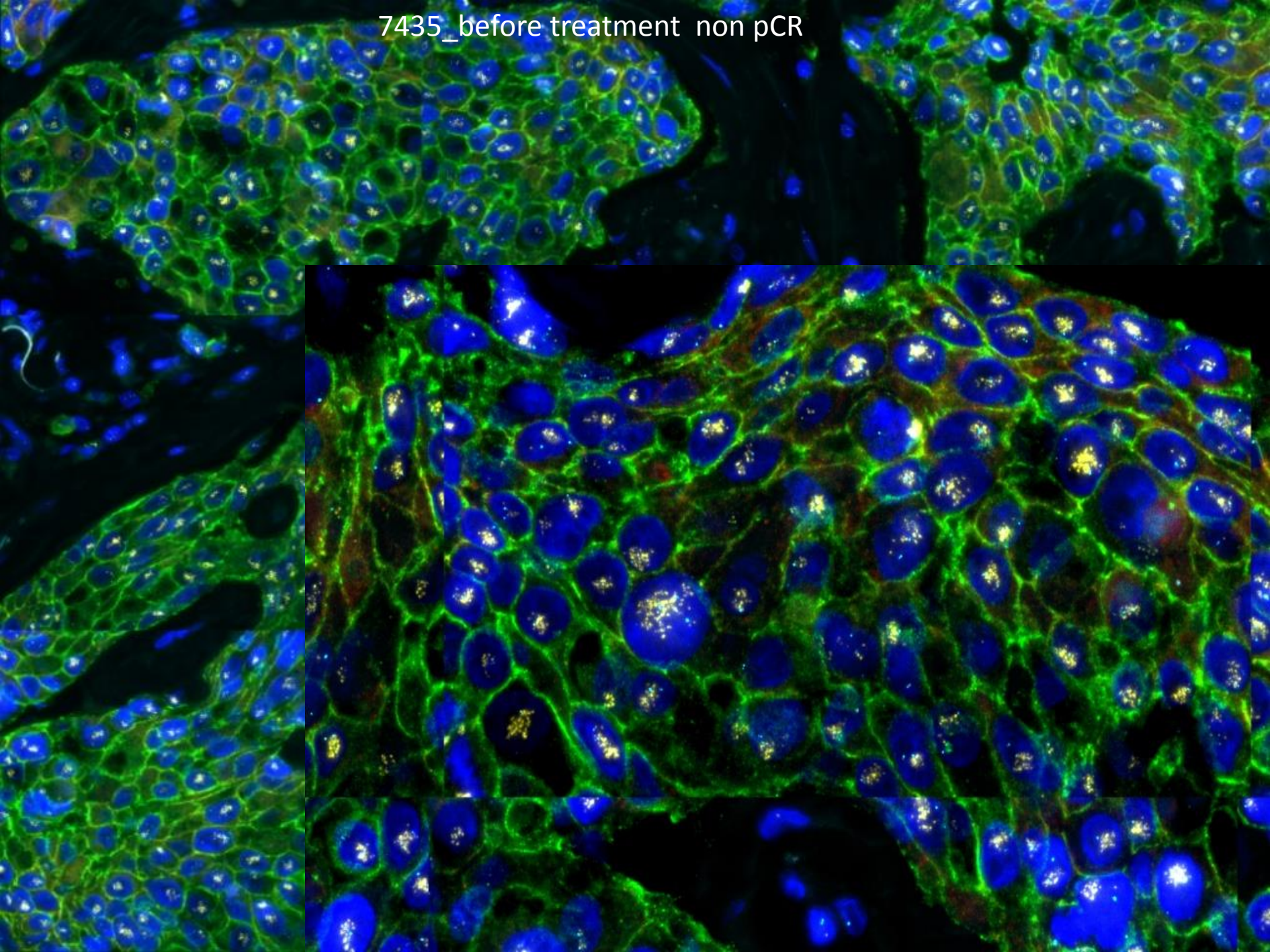


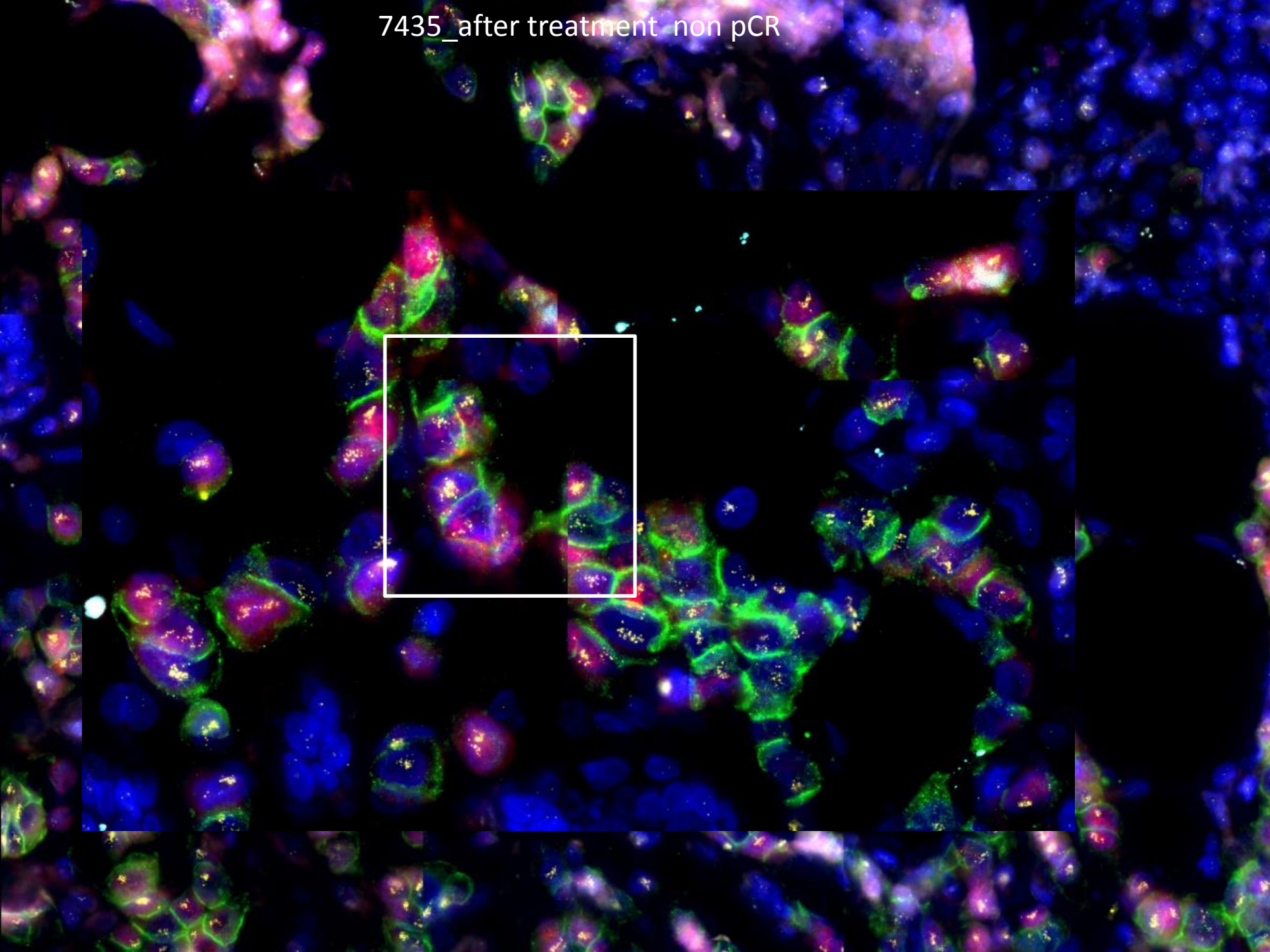
mix

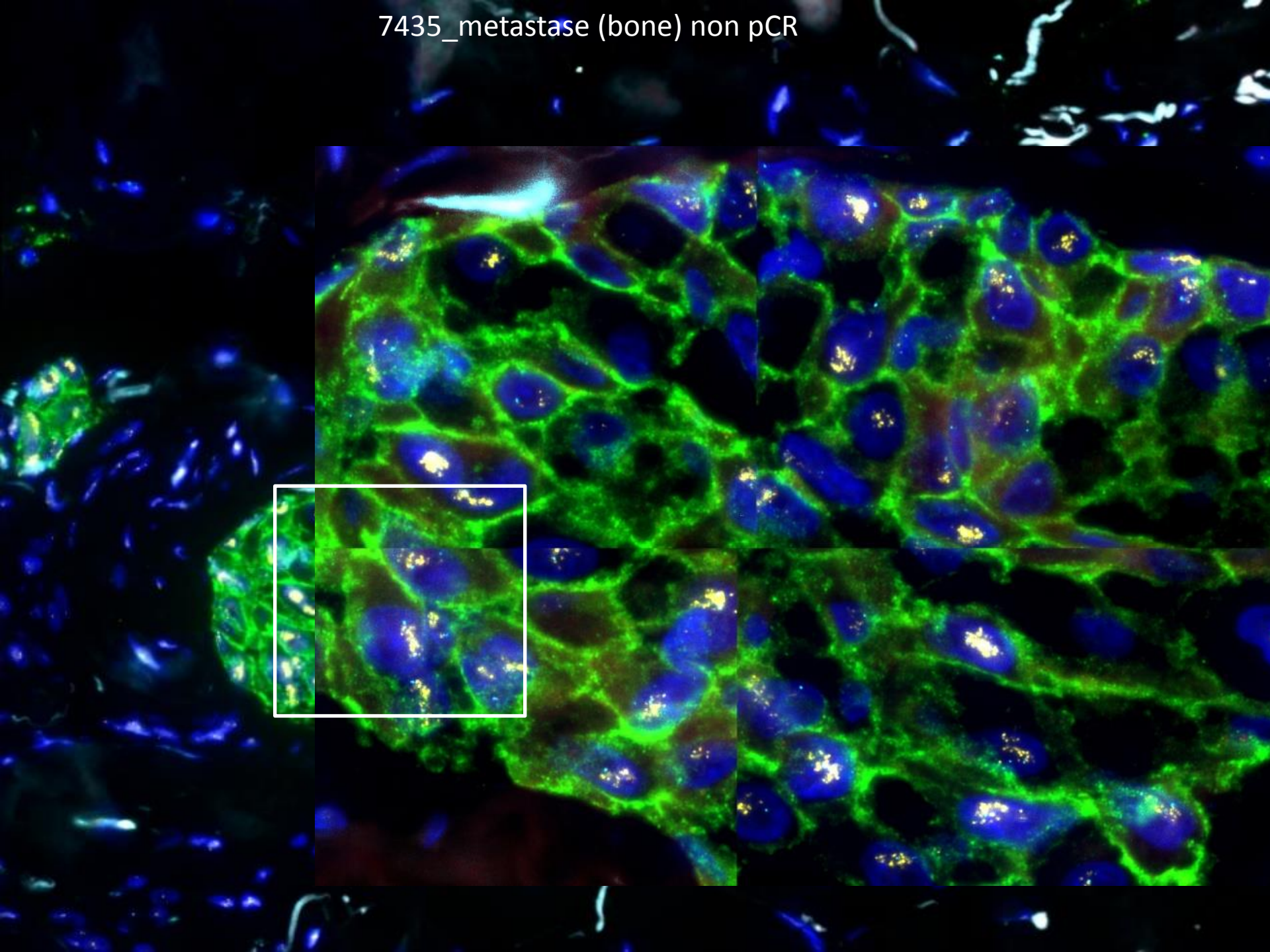


Rye et al. unpublished


7347_pre treatment pCR
10 µm

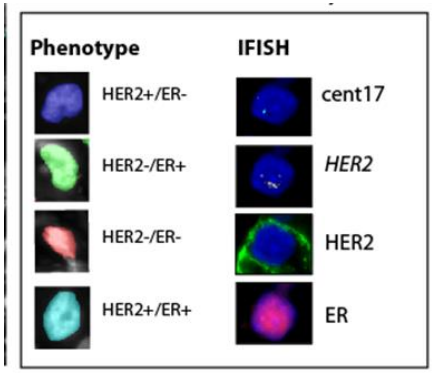

7435_before treatment non pCR

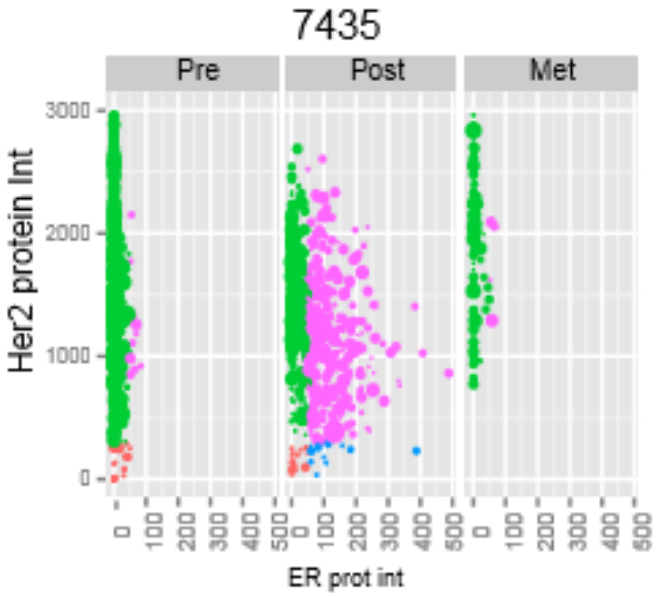

7435_after treatment_non pCR

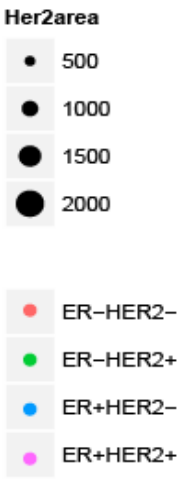

7435_metastase (bone) non pCR

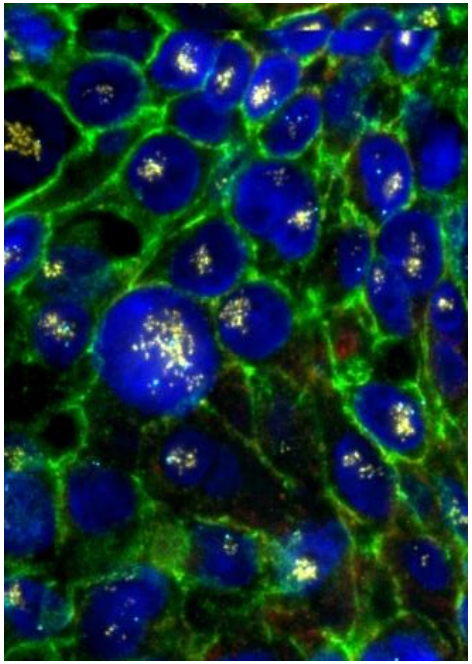
Observations:

- Copy number
- protein expression

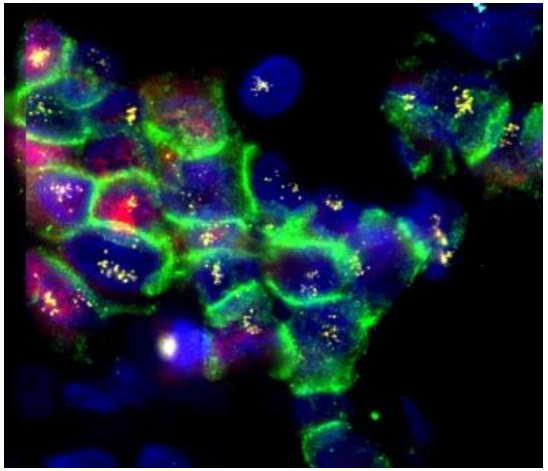




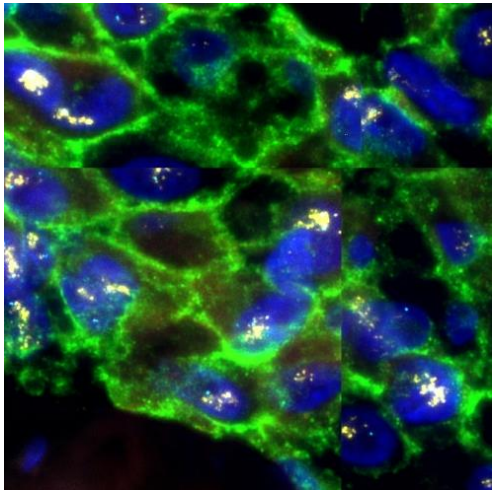




Pre treatment

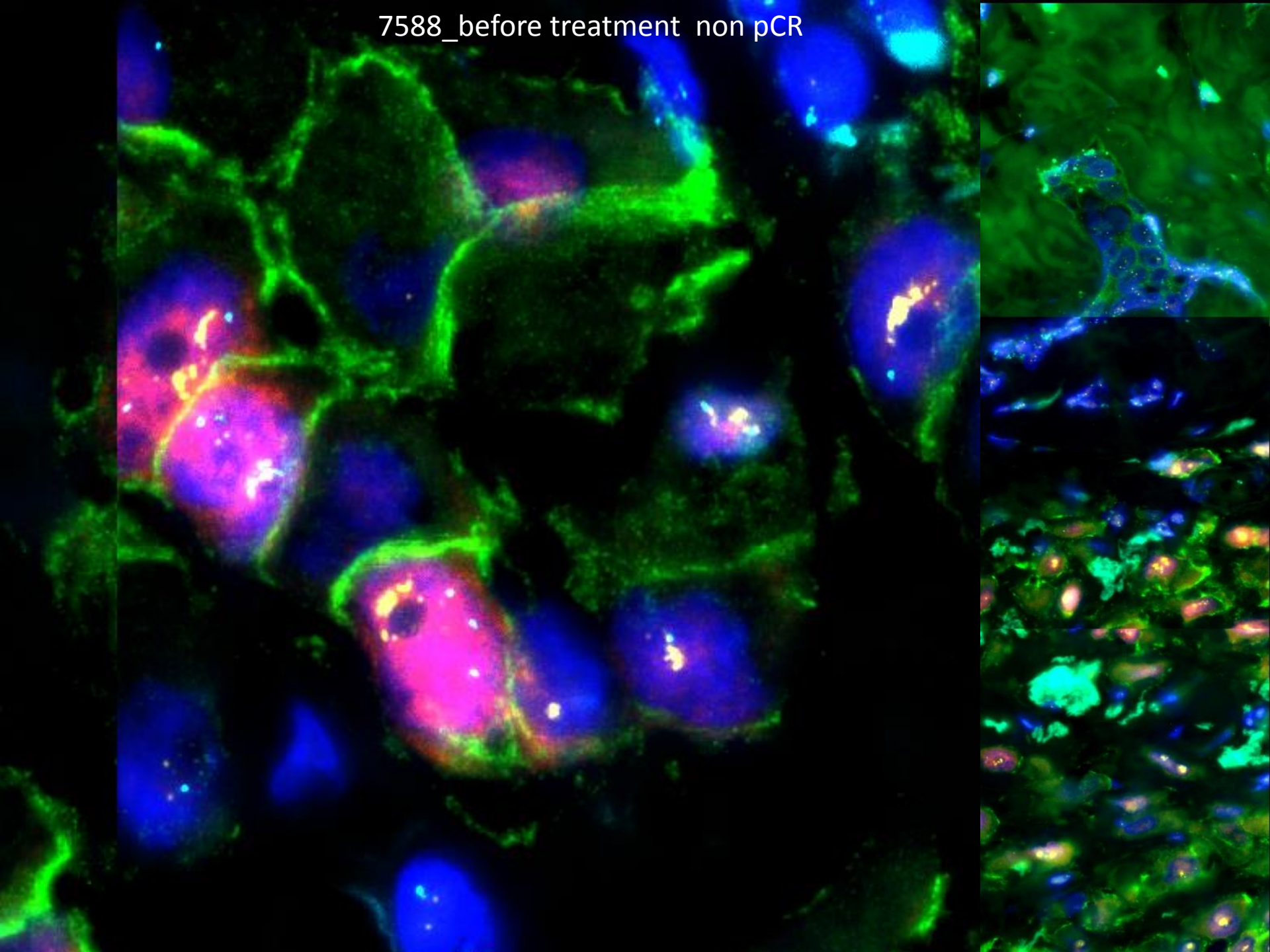


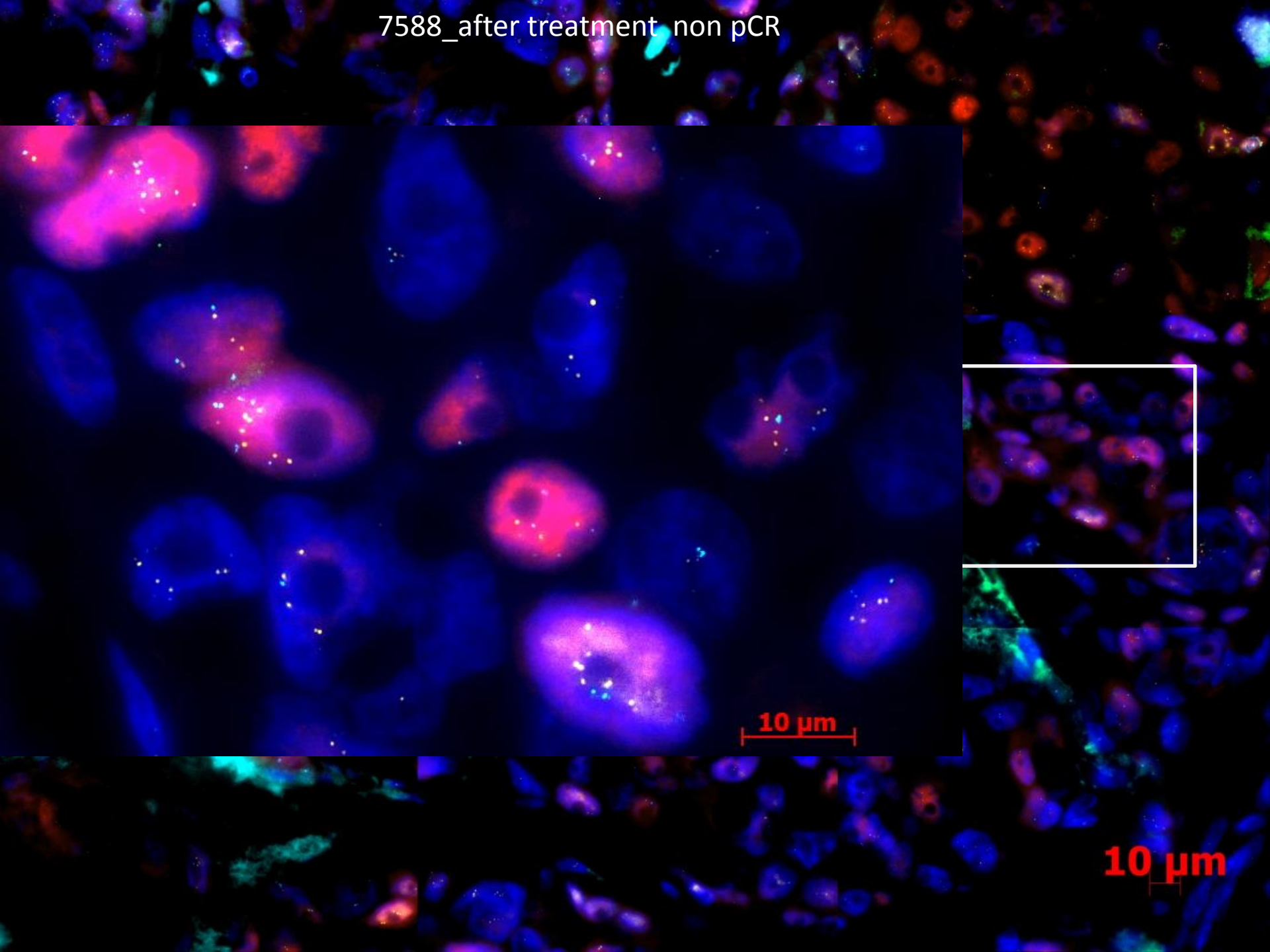
Post treatment



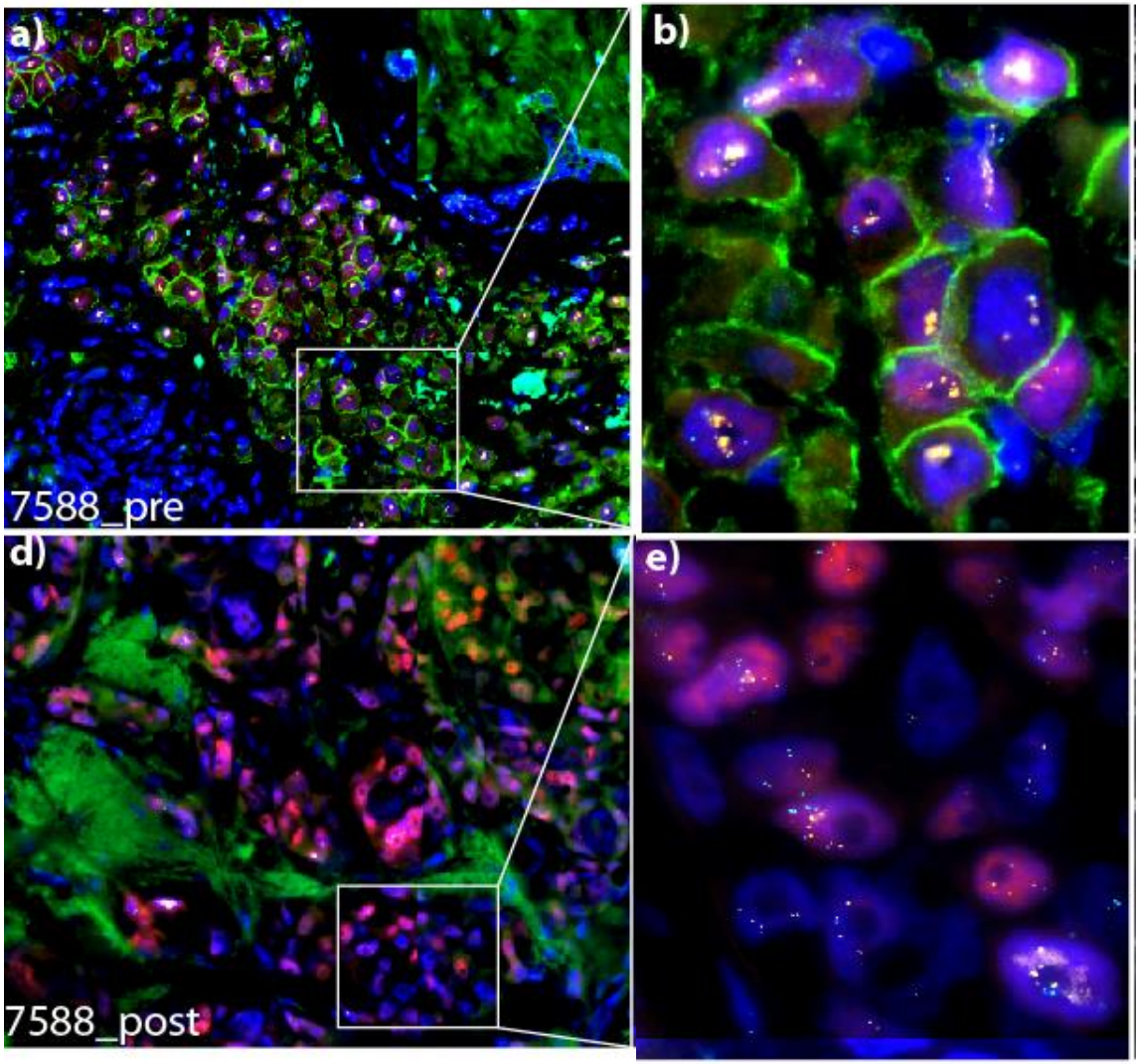
Metastase

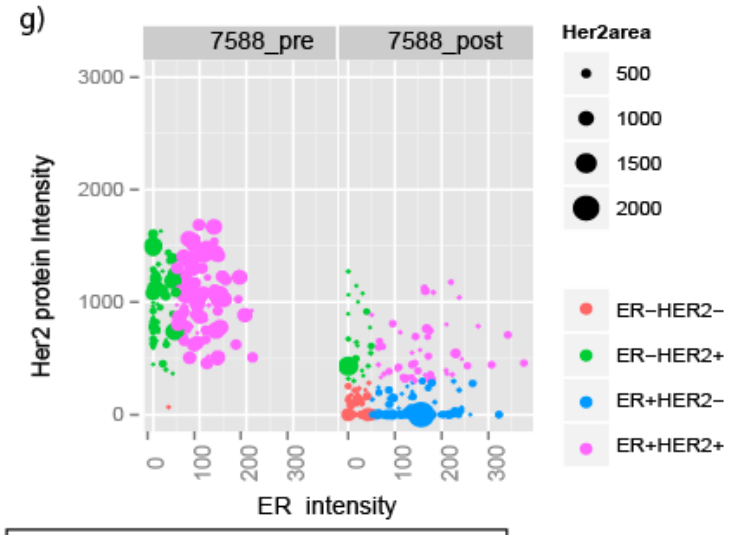
Rye et al. unpublished

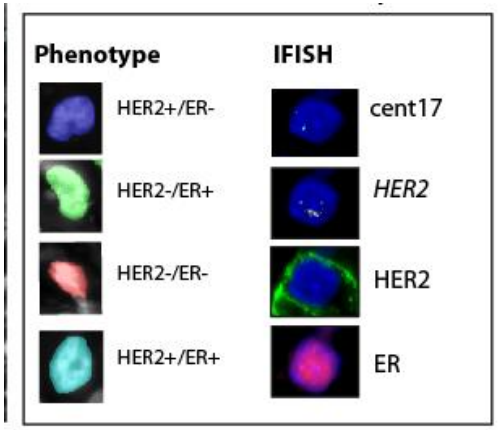

7588_before treatment non pCR


7588_after treatment_non pCR
10 µm
10 µm

Changes in Phenotypic Distribution During Treatment





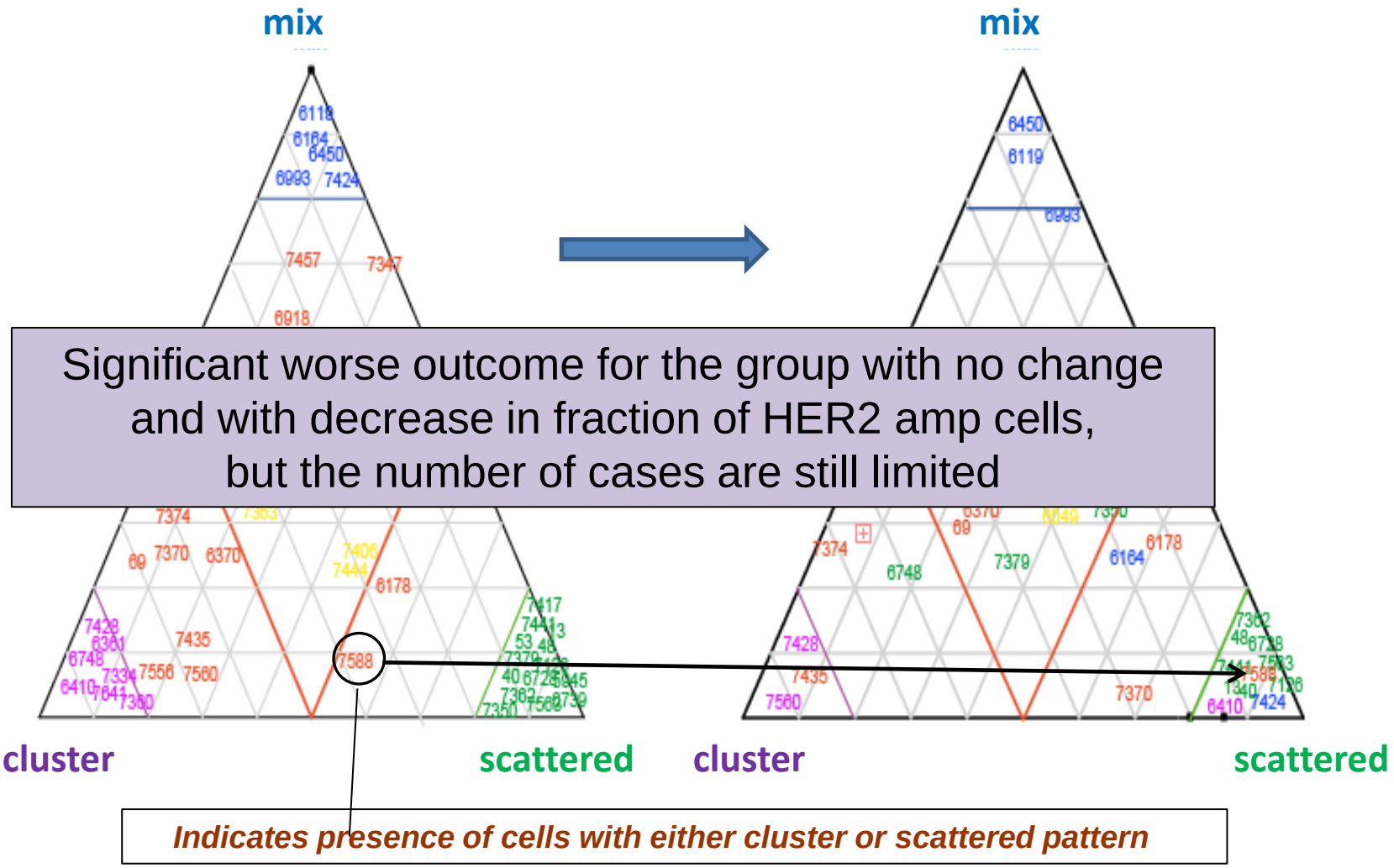


Rye et al. unpublished

HER2 gene spatial arrangment before and after treatment scored in 100 cells from each tumor

Before treatment

after treatment



Indicates presence of cells with either cluster or scattered pattern

Rye et al. unpublished

Department of Cancer Genetics

http://ous-research.no/genetics/

Oslo University Hospital
Norwegian Radium Hospital

Available positions:

The Institute for Cancer Research (ICR)

Division of Cancer, Surgery & Transplantation, Institute for Cancer Research - Oslo University Hospital

- **Head of Department of Cancer Genetics**

  Will be announced in the spring 2016

- **Sarcoma Research Group Lead Position**

  From Jan. 2017

  Will be announced in the summer 2016

http://ous-research.no/institute/

For additional information please contact The Head of ICR, Professor Gunnar Sæter at gunsae@rr-research.no, Tel +47 227 81 402 or mobile +47 970 31 845.

Personalized Cancer Care

18-20 May 2016, Holmenkollen Park Hotel, Oslo, Norway

Registration deadline April 1st, abstract deadline: March 14th.

See www.pccradiumhospital.org for more information

What have we achieved since 2012 in risk prediction, early diagnosis, progression, and therapy?

Opening keynote

Leroy Hood, Institute for Systems Biology, Seattle, USA

Genetic profiling of patients, prediction of risk and therapy response

Bruce Ponder, Cancer Research UK, Cambridge Research Inst, UK
Paul Pharoah, Strangeways Research Lab, Cambridge, UK

Molecular profiling of tumors and metastases

Elaine Mardis, The Genome Inst, Washington Uni, MO, USA
Zoltan Szallasi, Technical University of Denmark
Carlos Caldas, Cancer Research UK, Cambridge Research Inst, UK
Peter van Loo, Crick Center, London, UK
Charles M. Perou , UNC – Chapel Hill, NC, USA

Tumor-host microenvironment interaction and metabolism

Arnold Levine, Princeton University, USA
Larry Norton, Memorial Sloan-Kettering Cancer Center, NY, USA
Mina Bissell, Lawrence Berkley National Laboratory, CA, USA
Morag Park, McGill University, Montreal, Canada

Targeted therapy

Gordon Mills, MD Andersson Cancer Center, TX, USA
Rene Bernards, The Netherlands Cancer Institute, The Netherlands
Joe Gray, Oregon Health & Science University, OR, USA
Alberto Bardelli, University of Torino, Italy
Soldano Ferrone, Mass General Hosp, Harvard, MA, USA

Translation

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Impact of social and ethical issues on personalized medicine

Eva Winkler, NCT, Germany

Opening and closing remarks

Enrico Mihich
Hans-P. Huber
A.-L. Børresen-Dale
Kurt S. Zänker

Oslo University Hospital
UiO : University of Oslo
fritz bender stiftung
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EACR European Association for Cancer Research

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