ESMO Special Symposium

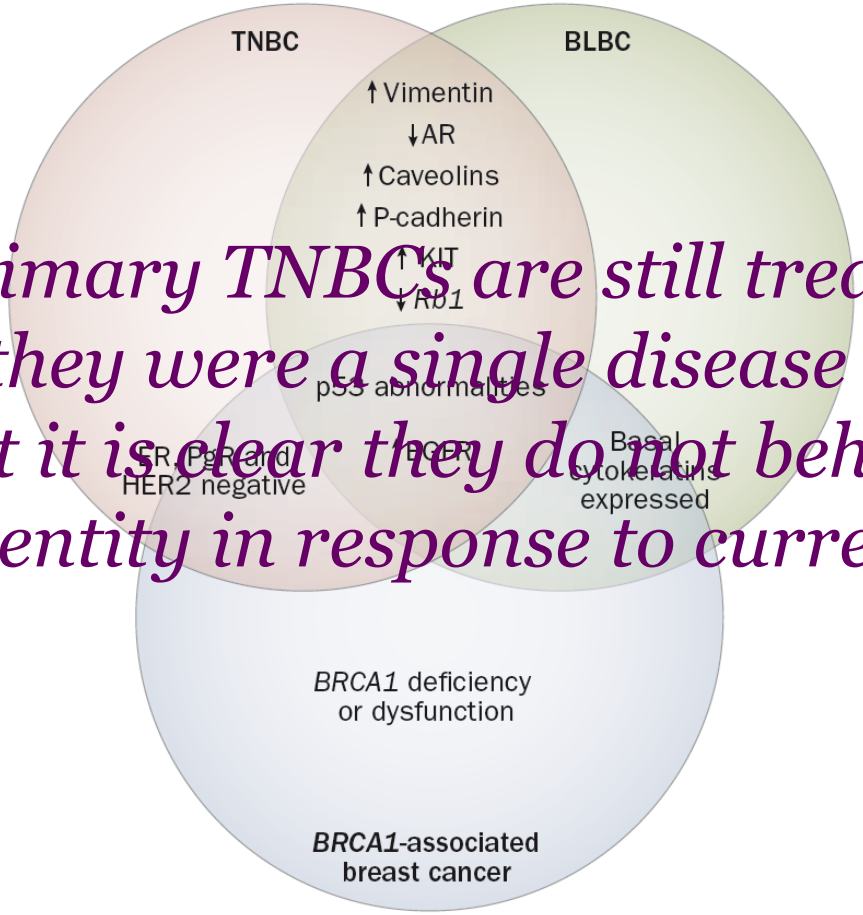
Conclusion

How to improve the outcome of Triple Negative Breast Cancer

Department of Medical Oncology
San Raffaele Scientific Institute
Milan - Italy

Luca Gianni

Triple Negative Breast Cancers



primary TNBCs are still treated as if they were a single disease entity, yet it is clear they do not behave as a single entity in response to current therapies

L. Carey et al, Nat Rev Clin Oncol 2010

ARTICLE

doi:10.1038/nature10983

A novel molecular stratification of breast cancer derived from the impact of somatic Copy Number Aberrations (CNAs) on the transcriptome

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

doi:10.1038/nature10933

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]

"... treatment-naïve TNBCs display a complete spectrum of mutational and clonal evolution...

...understanding the biology and therapeutic responses of patients with TNBC will require the determination of individual tumour clonal genotypes."

Nature 2012

Options and opportunities in TNBC

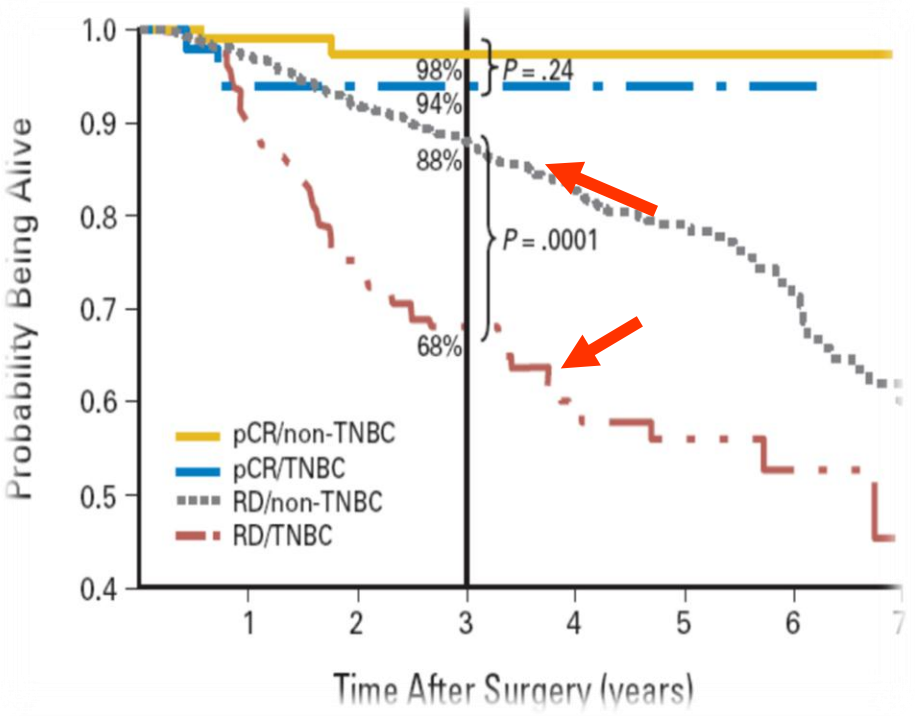
- New targets in cancer cells
- The role of stroma components
- New drugs
- Predictive markers
- ***Improved use of what we already have …***

MJ Lee et al, Cell 2012

Neoadjuvant treatment

Kaufmann M, et al. J Clin Oncol 2003;21:2600–8

Triple negative breast cancer and neoadjuvant chemotherapy – can we increase pCR rates?



Strong prognostic value of pCR

Liedtke *et al. JCO* 26:1275, 2008

Cell

Sequential Application of Anticancer Drugs Enhances Cell Death by Rewiring Apoptotic Signaling Networks

Michael J. Lee,[1,2] Albert S. Ye,[2,3] Alexandra K. Gardino,[1,2] Anne Margriet Heijink,[1] Peter K. Sorger,[2,4] Gavin MacBeath,[2,4] and Michael B. Yaffe[1,2,*]

- *Efficacy of combination treatments depends on drug order and timing*
- *Rewiring of signaling networks by drugs can provide therapeutic benefit*
- *Sustained EGFR inhibition sensitizes TNBC cells to DNA damage*
- *EGFR activity, but not EGFR expression, is a marker of response to this treatment*

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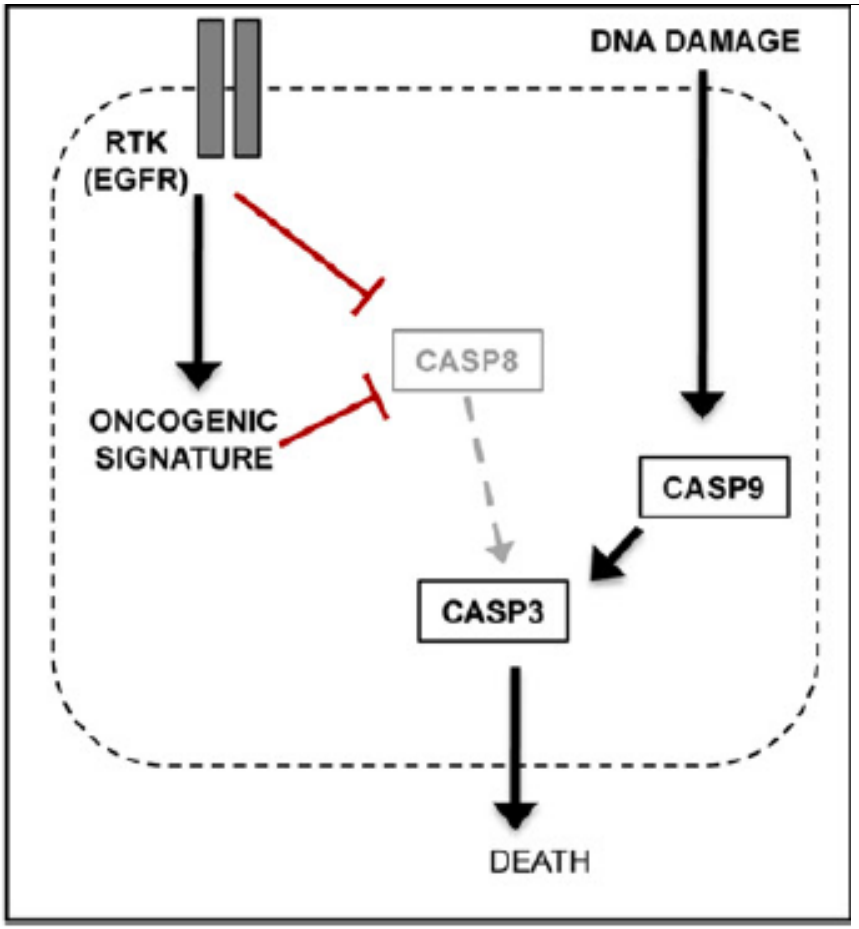
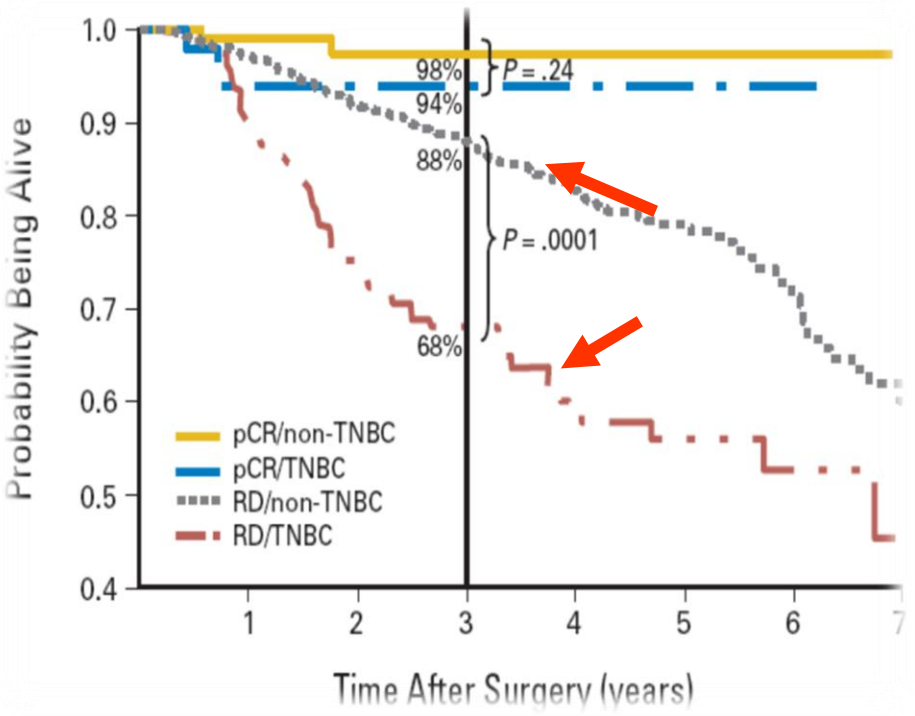
Staggered treatment with RTKi & DNA-damaging chemotherapy



MJ Lee et al, Cell 2012

Triple negative breast cancer and neoadjuvant chemotherapy – can we predict pCR ?



Strong prognostic value of pCR

Liedtke *et al. JCO* 26:1275, 2008

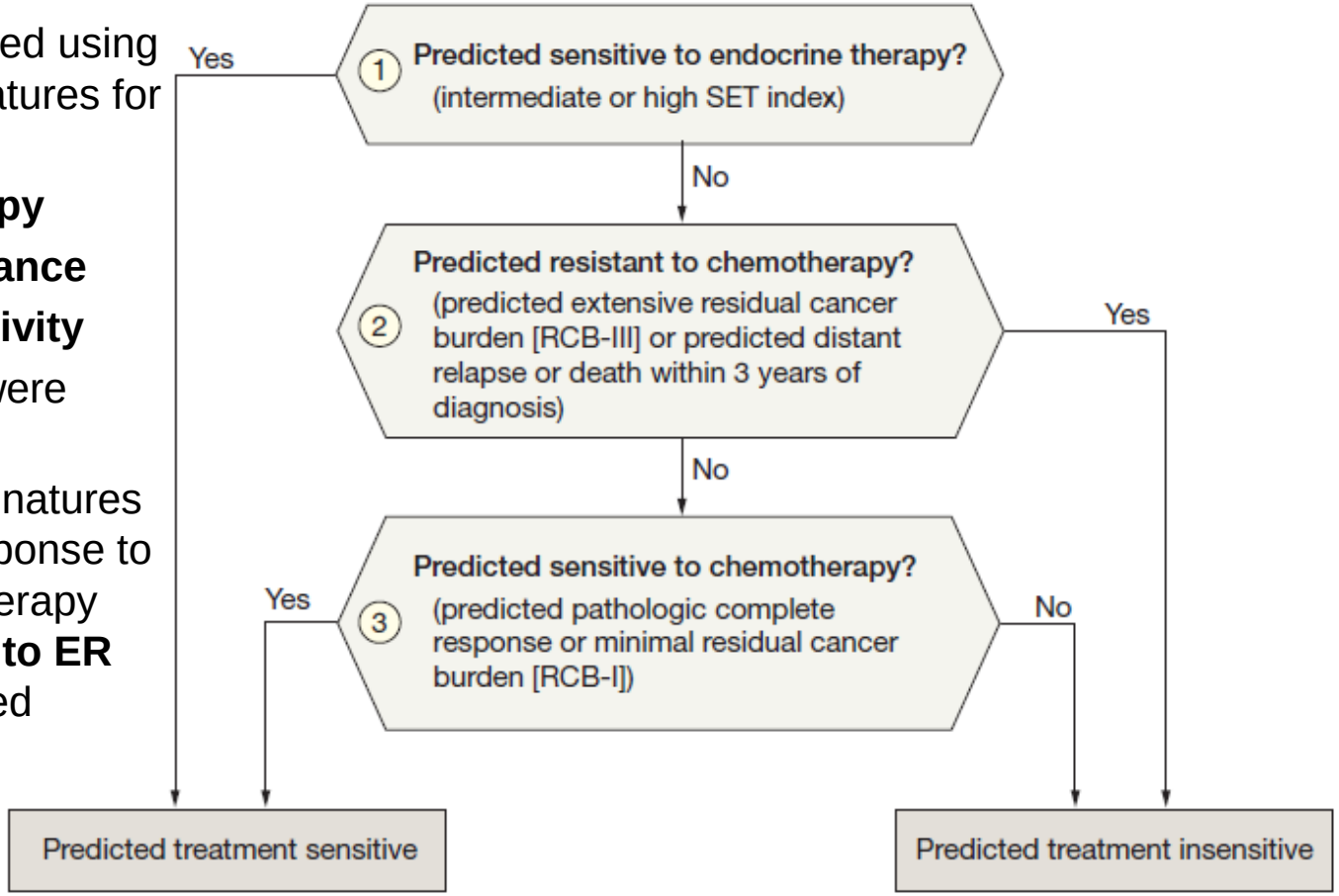
Decision algorithm used in genomic test to predict “clinical benefit”

Sensitivity was predicted using a combination of signatures for

- **(1) sensitivity to endocrine therapy**
- **(2) chemoresistance**
- **(3) chemosensitivity**

Only **HER2- tumors** were included

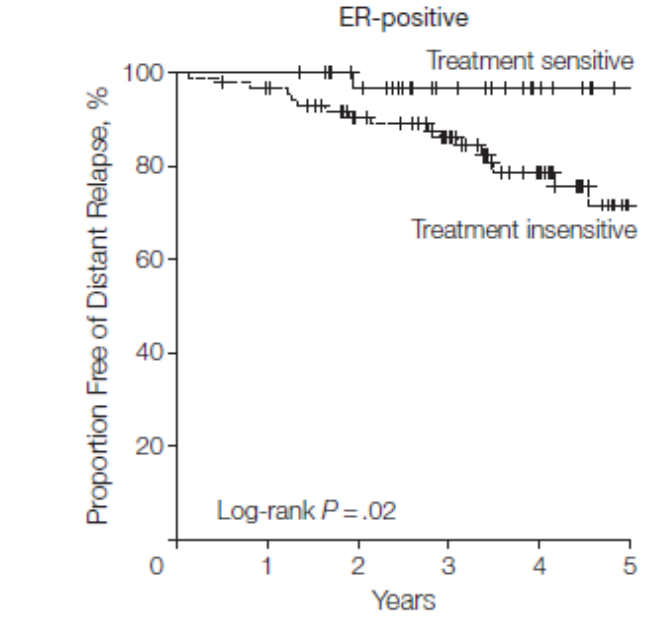
Different predictive signatures for resistance and response to preoperative chemotherapy (**stratified according to ER status**) were developed

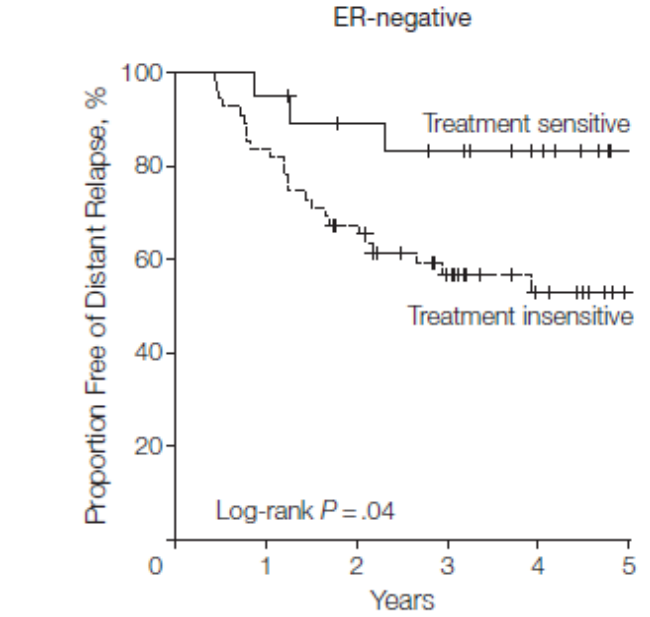


Hatzis C JAMA 2011

Prediction of “sensitivity” holds in in a validation cohort

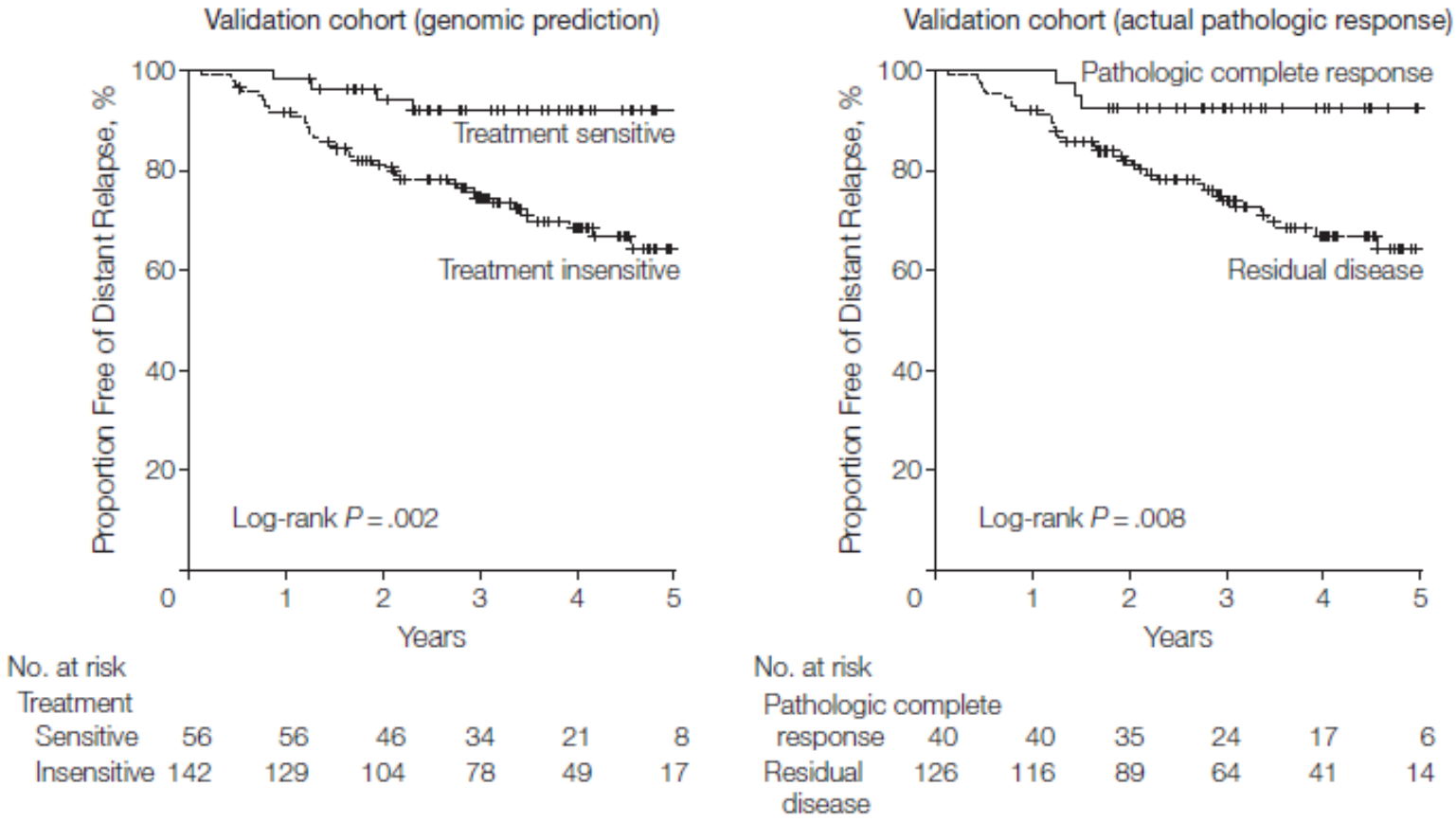
- Patients predicted as “treatment sensitive” according to the algorithm had better DRFS in both ER+ and ER- tumors





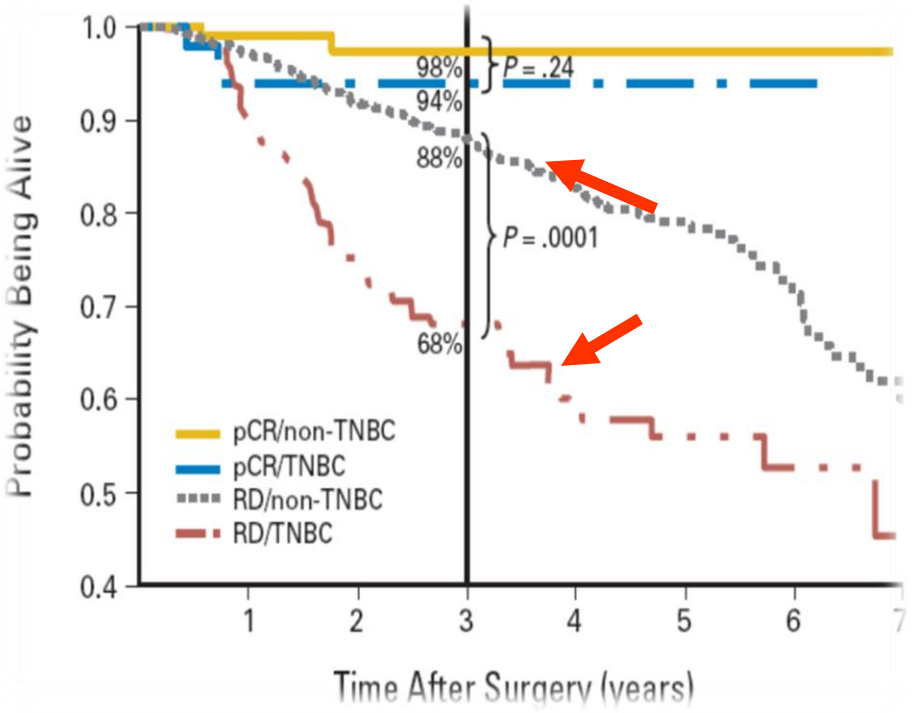
Hatzis C JAMA 2011

Outocome of patients predicted as “sensitive” is as good as for patients achieving pCR



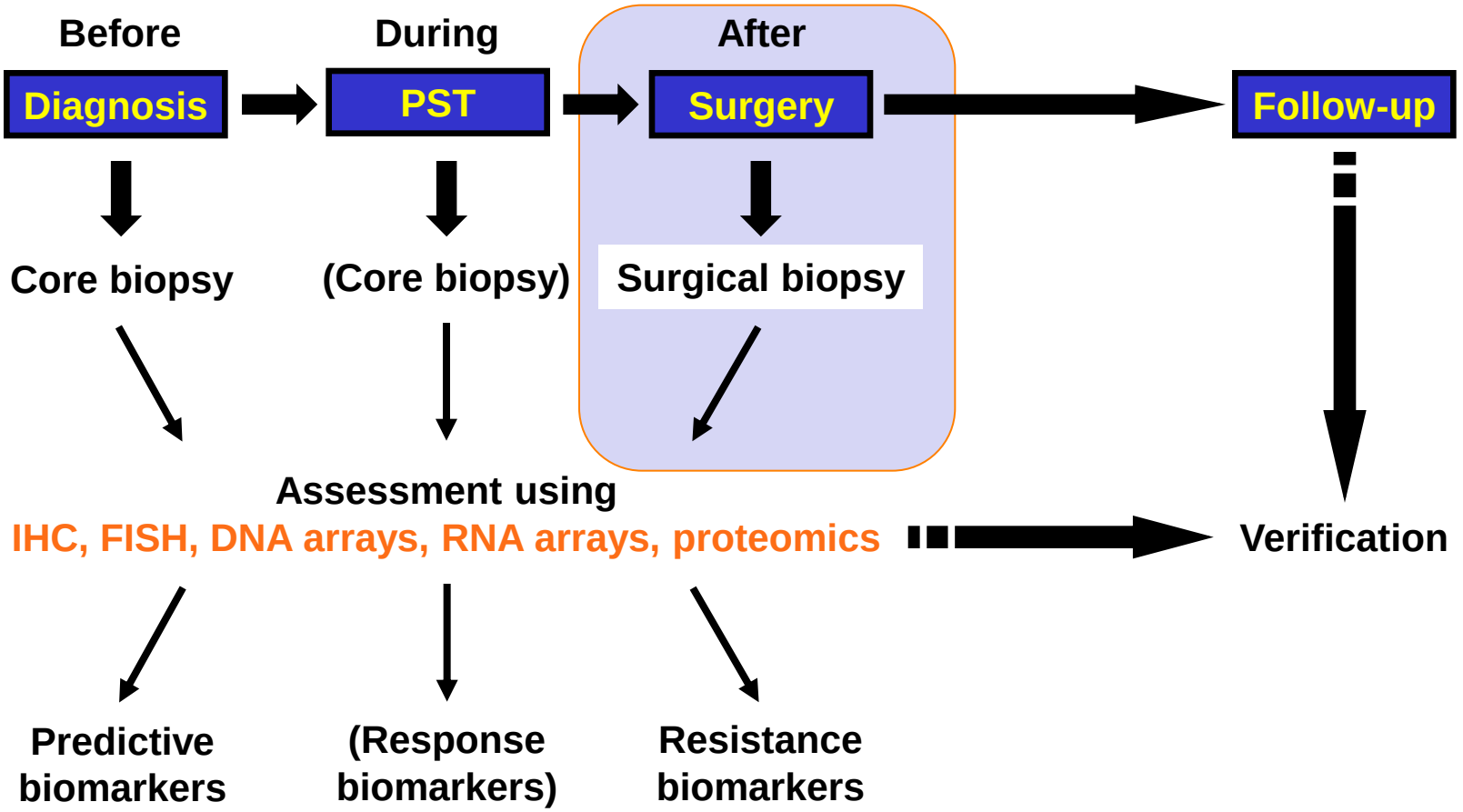
Hatzis C JAMA 2011

Triple negative breast cancer and neoadjuvant chemotherapy – the residual tumor



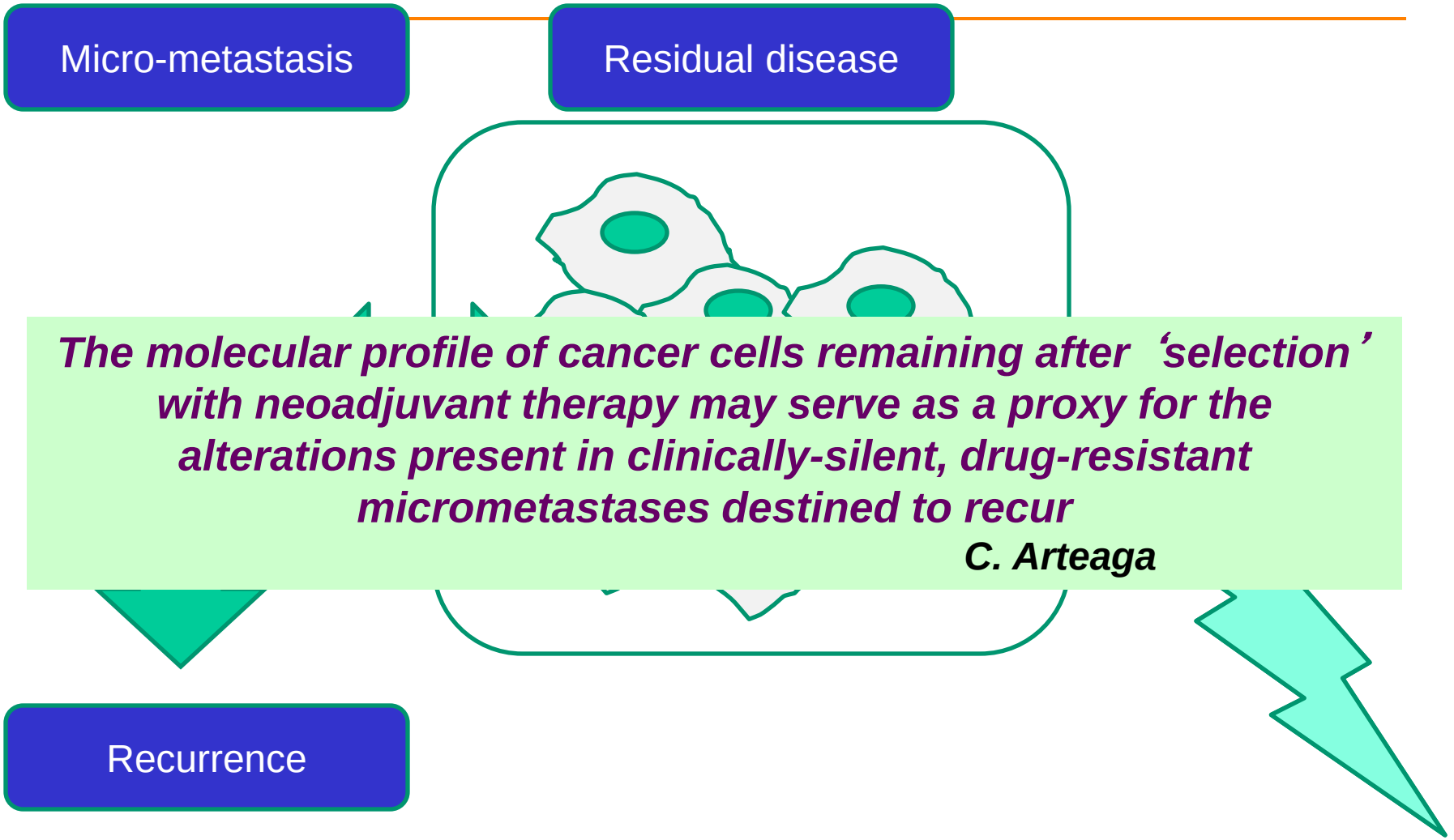
Liedtke *et al. JCO* 26:1275, 2008

Neoadjuvant treatment as ideal tool to study therapeutic failure



Kaufmann M, et al. J Clin Oncol 2003;21:2600–8

Residual disease after neoadjuvant therapy = micro-metastasis



The molecular profile of cancer cells remaining after 'selection' with neoadjuvant therapy may serve as a proxy for the alterations present in clinically-silent, drug-resistant micrometastases destined to recur

C. Arteaga

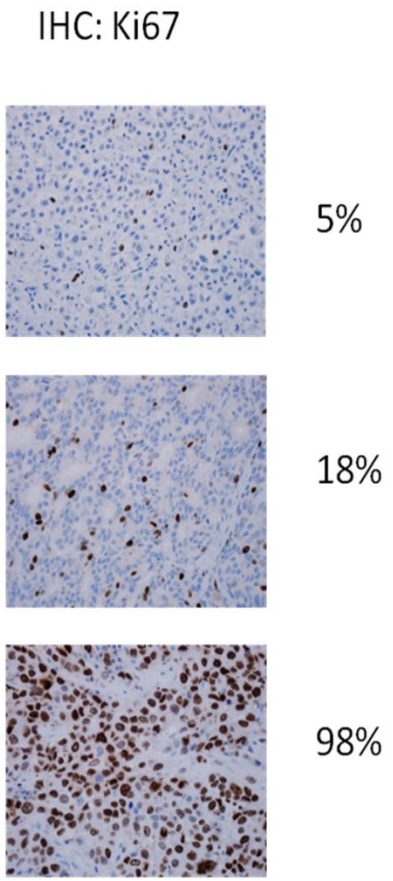
nature medicine

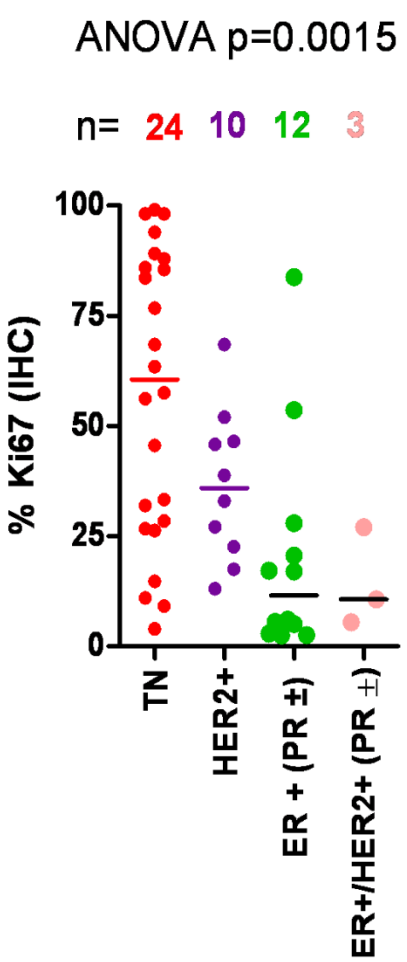
Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance

Justin M Balko[1], Rebecca S Cook[2,3], David B Vaught[2], María G Kuba[4], Todd W Miller[2,3], Neil E Bhola[1], Melinda E Sanders[3,4], Nara M Granja-Ingram[4], J Joshua Smith[5], Ingrid M Meszoely[3,5], Janine Salter[6,7], Mitch Dowsett[6,7], Katherine Stemke-Hale[8], Ana M González-Angulo[8,9], Gordon B Mills[8], Joseph A Pinto[10], Henry L Gómez[11] & Carlos L Arteaga[1–3]

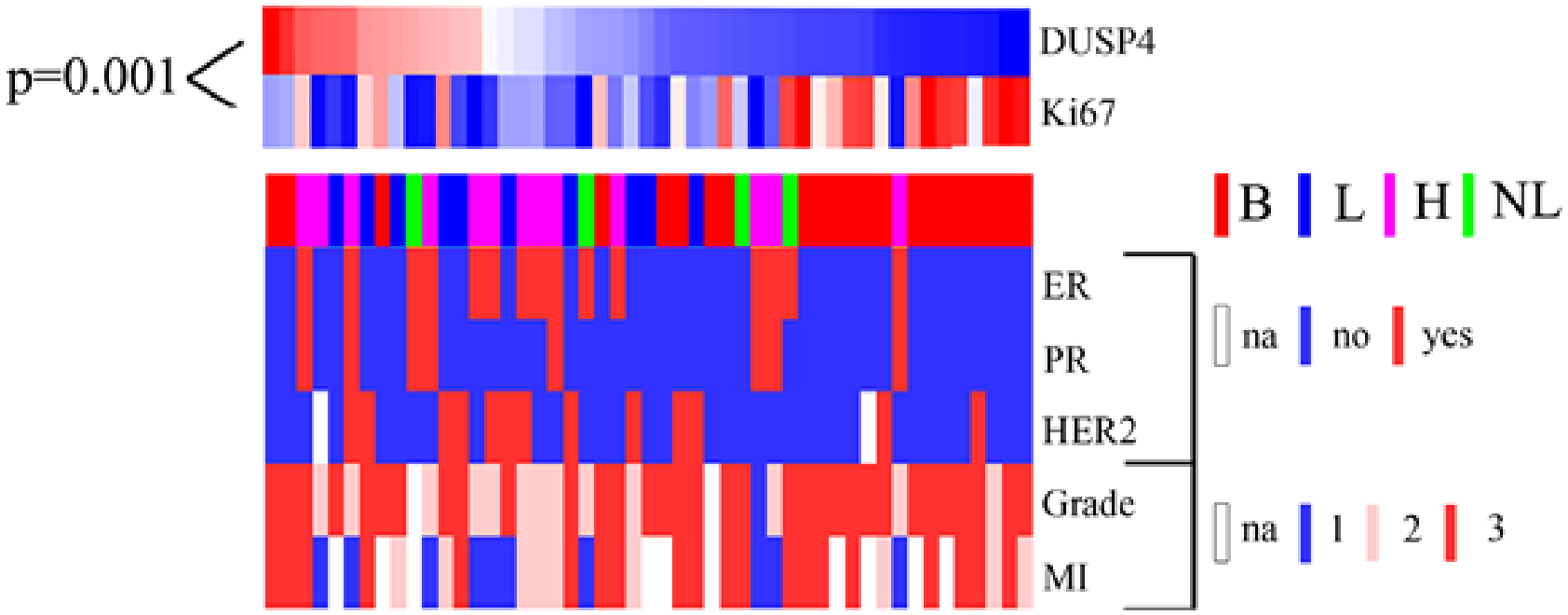
Post-neoadjuvant chemotherapy (NAC) and clinical subtype

- Ki67 IHC performed in 49 residual breast tumors after NAC
- Post-NAC Ki67 ***differed significantly*** among clinical subtypes



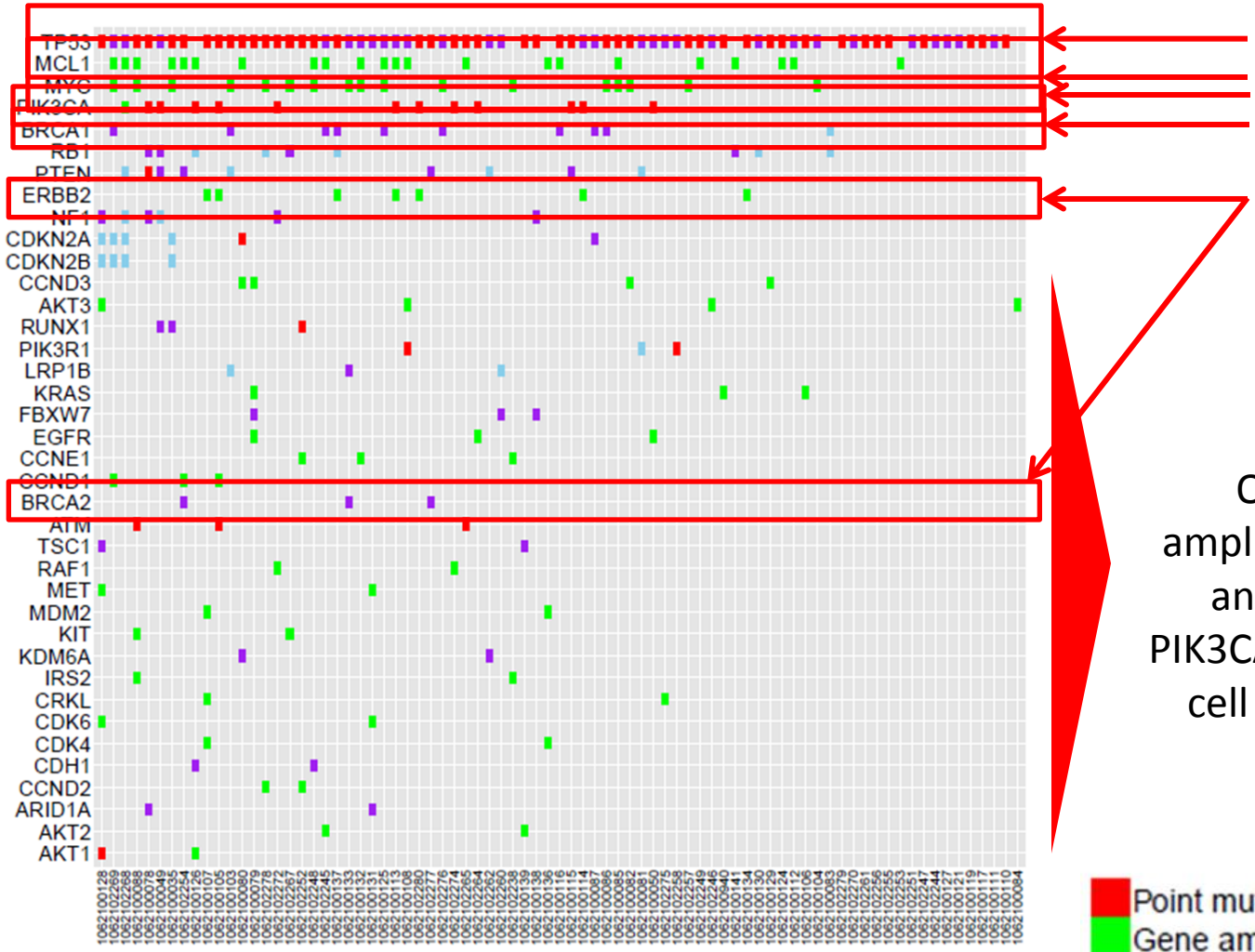


High Ki67 and basal-like gene expression in residual tumors after NAC correlate with loss of DUSP4 MAPK phosphatase



Balko *et al. Nat Med* , 2012

Diverse oncogenic alterations in TNBCs after neoadjuvant chemotherapy



TP53 is universally lost

High rates of MYC and MCL1 amplifications

PIK3CA mutations overlap BRCA1/2 DNA repair with HER2 gains aberrations

Other diverse amplifications in RTKs and members of PIK3CA/AKT, MAPK and cell cycle pathways

Point mutation
Gene amplification
Gene deletion
Truncation

n=81

Balko and Arteaga, Unpublished

Conclusion

- Heterogeneity is the challenging hallmark of TNBC
- Continuous progress in the understanding the molecular pathology of TNBC is leading to identification of new drugs (RTKs, intracellular signaling, immunotherapy…)
- The neoadjuvant approach
  - is an ideal tool to test new ideas and hypotheses (triage….)
  - has great promise for allowing individual tailoring of treatments
  - allows for the early characterization of disease destined to relapse and for the identification of new treatments for metastases