# Integration of molecular analysis in the management of metastatic breast cancer

Dr Nicholas Turner

ESMO 2014

# Disclosure slide

- Advisory Board – Genomic health, Pfizer

# Outline

- Genetic analysis of metastatic breast cancer
- Prognostication in metastatic breast cancer
- Prediction of sensitivity to treatment

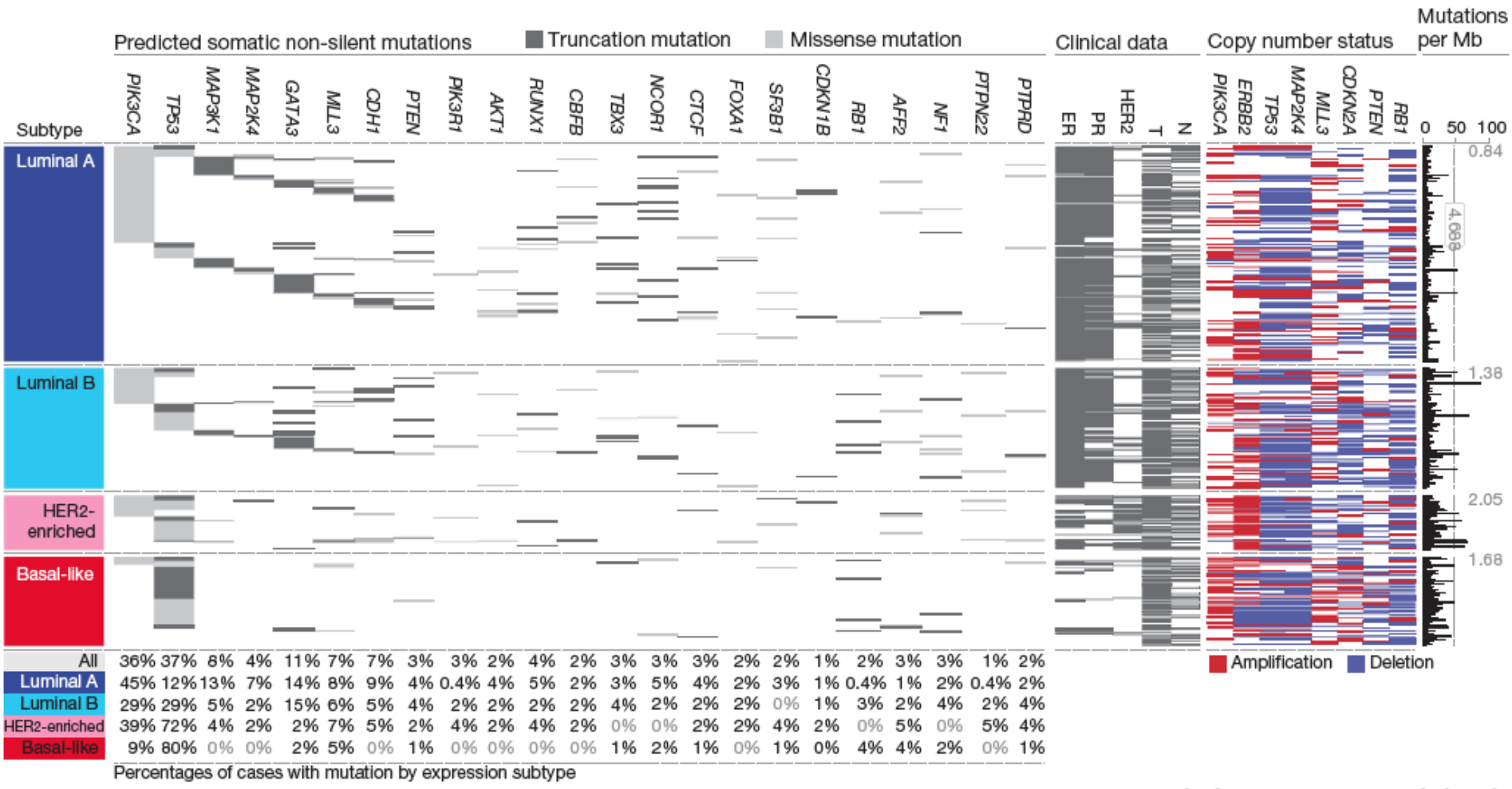
ARTICLE

doi:10.1038/nature11412

# Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

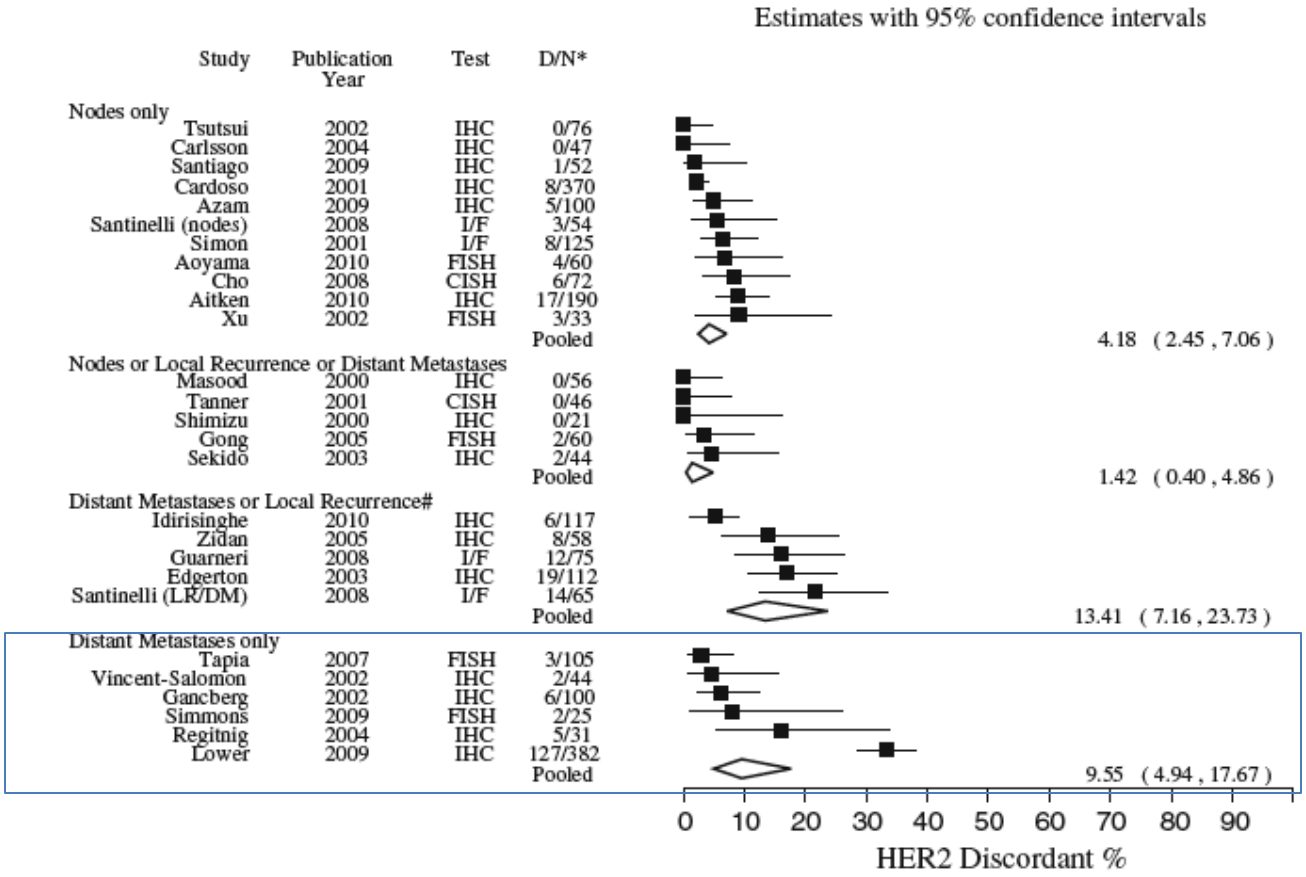
# Diverse mutations of breast cancer subtypes




TCGA Nature 2012

# Why do we need genetic analysis of recurrent breast cancer?

# HER2 amplification - discordance with primary




Houssami et al BCRT 2011

**Clinical Cancer Research**

**Diagnostic Evaluation of HER-2 as a Molecular Target: An Assessment of Accuracy and Reproducibility of Laboratory Testing in Large, Prospective, Randomized Clinical Trials**

Michael F. Press, Guido Sauter, Leslie Bernstein, et al.

*Clin Cancer Res* 2005;11:6598-6607.

2500 cancers from BCIRG studies

Central re-testing of *HER2* by FISH

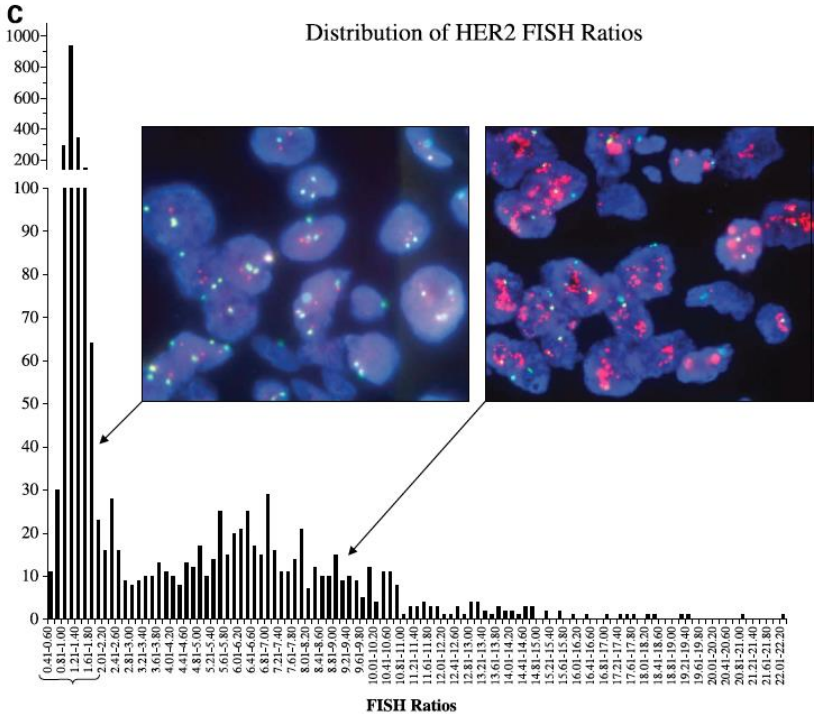
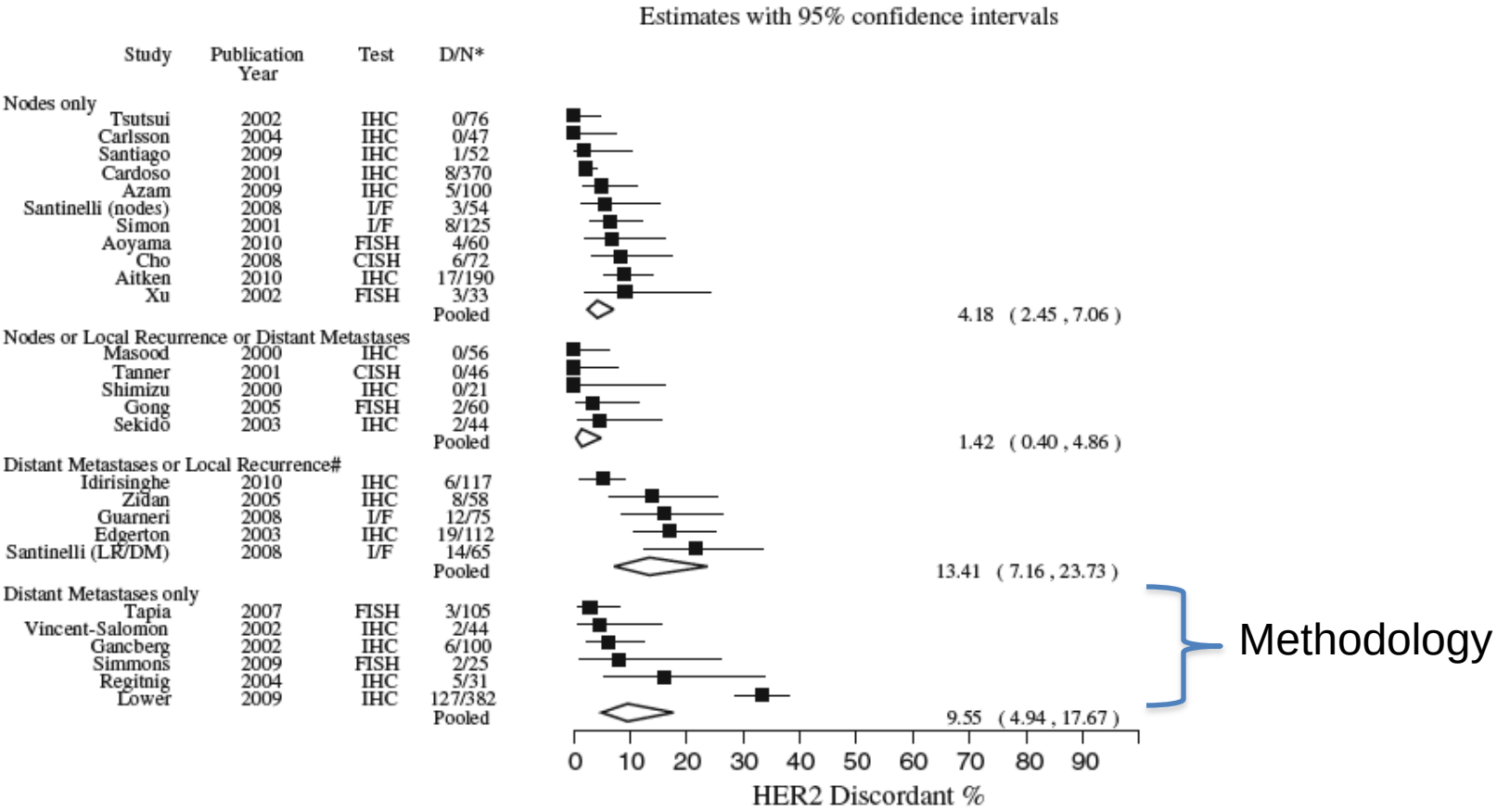



**Table 2.** DAKO HercepTest immunohistochemical assay results from outside laboratories compared with FISH assay results from the BCIRG central laboratories

| | Outside laboratory immunohistochemistry scores (0-3+) | | | | |
|---|---|---|---|---|---|
| | 0 | 1+ | 2+ | 3+ | Total |
| FISH negative (%) | 296 (96.4) | 142 (94.7) | 103 (83.1) | 57 (21.8) | 598 (71.0) |
| FISH positive (%) | 11 (3.6) | 8 (5.3) | 21 (16.9) | 204 (78.2) | 244 (29.0) |
| Total (%) | 307 (100) | 150 (100) | 124 (100) | 261 (100) | 842 (100) |

# HER2 - Discordance with primary breast cancer




HER2 discordant in ~5% of metastatic breast cancer compared to primary breast cancer

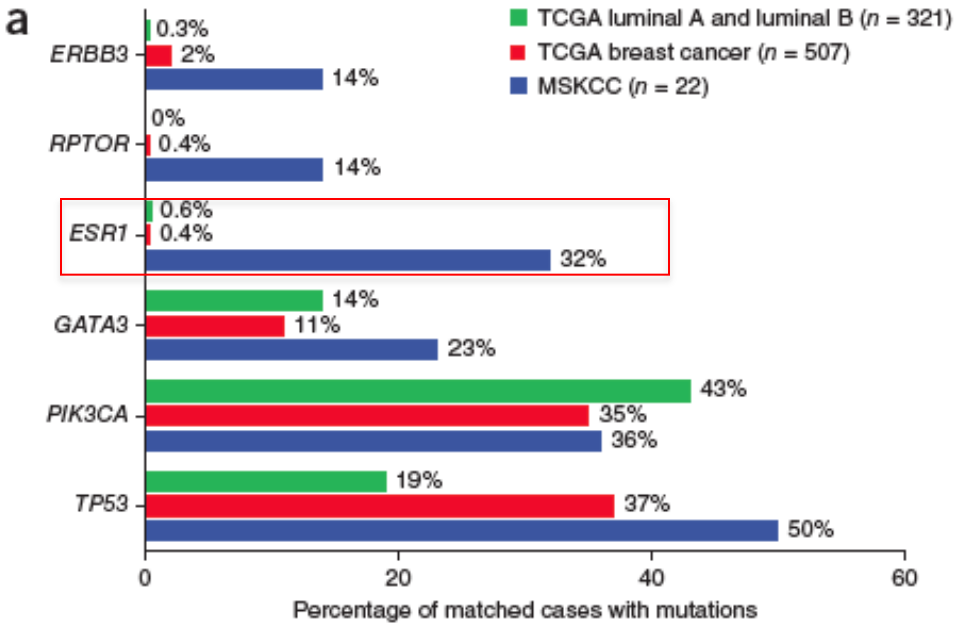
Standard of care to repeat biopsy on recurrence where feasible

# Genetic events are acquired in metastatic breast cancer

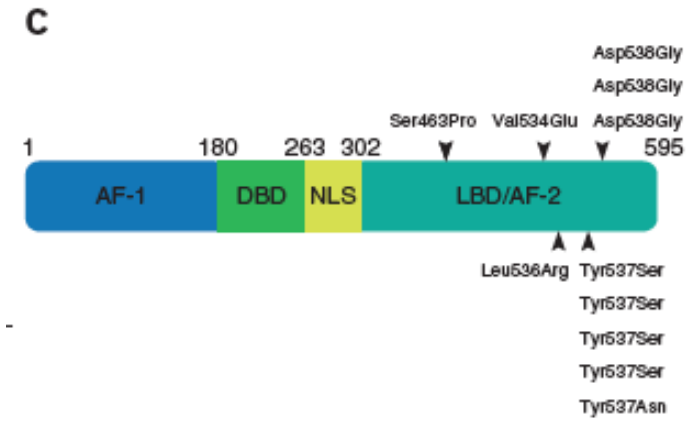
nature genetics

*ESR1* ligand-binding domain mutations in hormone-resistant breast cancer

Weiyi Toy[1], Yang Shen[2], Helen Won[1], Bradley Green[3], Rita A Sakr[4], Marie Will[5], Zhiqiang Li[1], Kinisha Gala[1], Sean Fanning[3], Tari A King[4], Clifford Hudis[5,6], David Chen[7], Tetiana Taran[7], Gabriel Hortobagyi[8], Geoffrey Greene[3], Michael Berger[1,9], José Baselga[1,5] & Sarat Chandarlapaty[1,5,6]

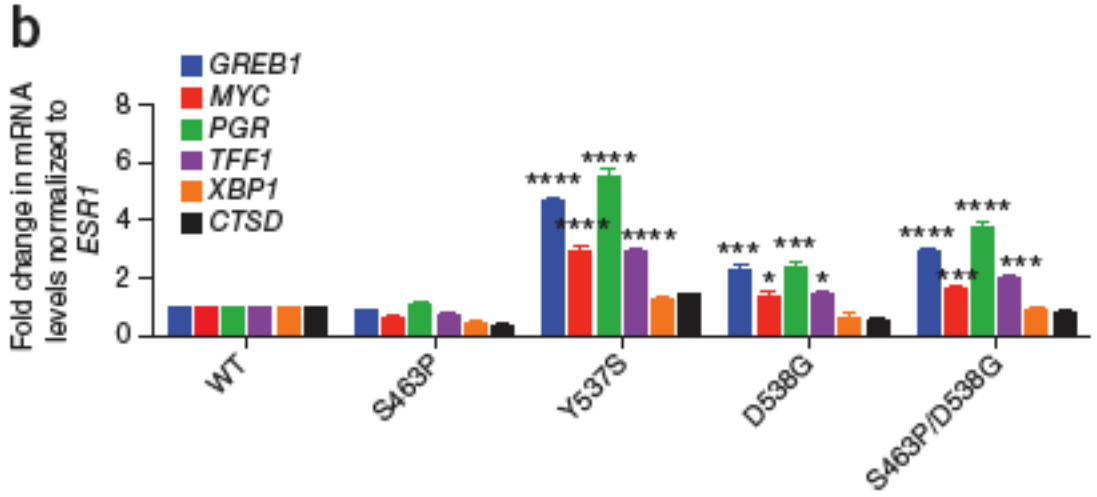



*ESR1* mutations occur in 20% of endocrine resistant ER positive breast cancer

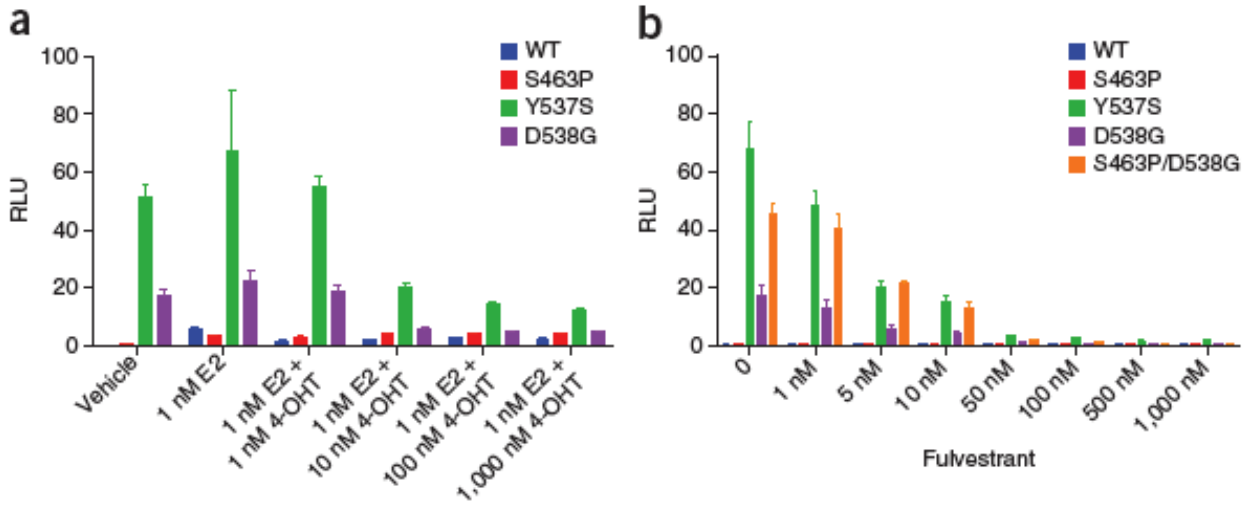



Toy *et al* Nat Genetics 2013

# *ESR1* mutations active the estrogen Receptor




Mutations in ligand binding domain activate ER signaling

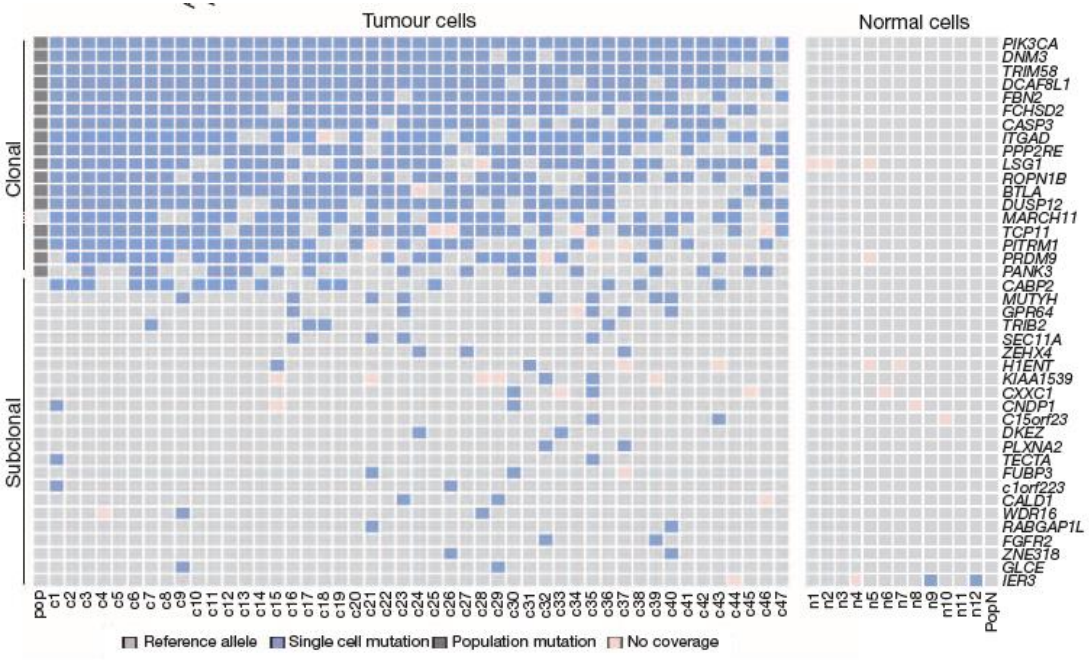



Cause resistance to Ais

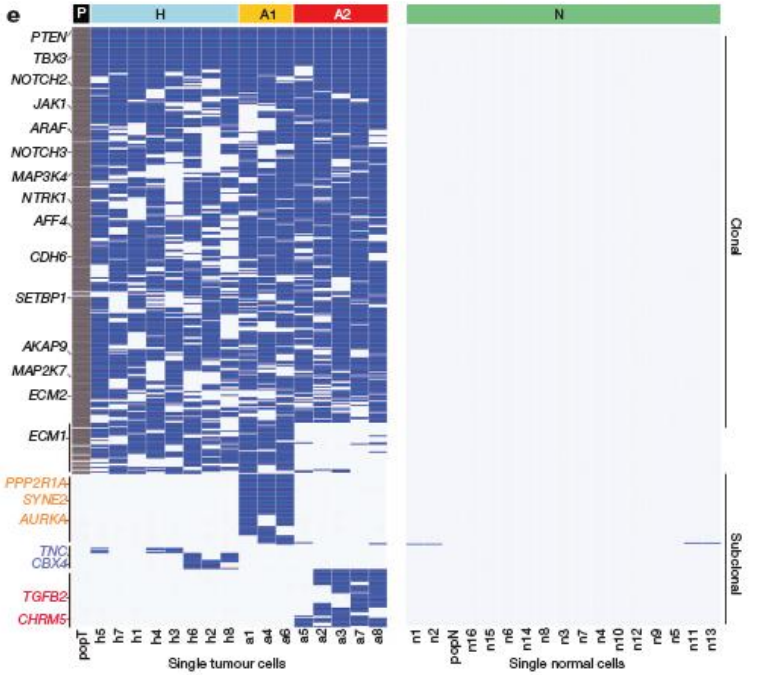
Potentially sensitive to SERDs

# Single cell sequencing in primary breast cancer

ER positive BC

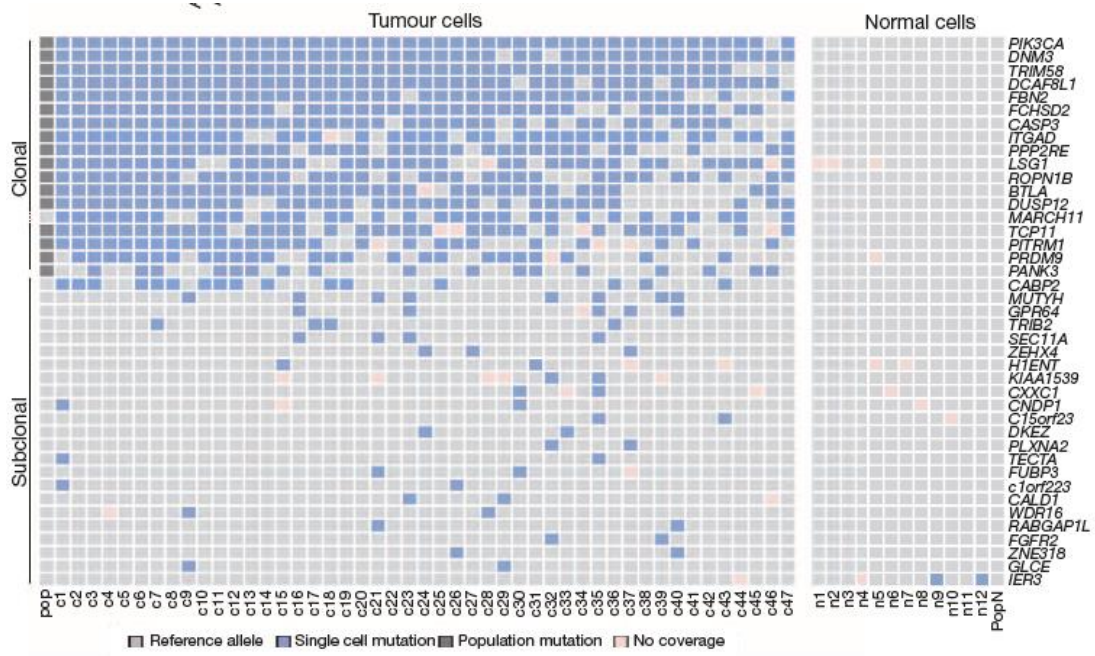



TNBC




Wand et al Nature 2014

# Genetic heterogeneity and drug resistance




Genetic heterogeneity as the engine of targeted therapy resistance


Turner et al Lancet Oncol 2012

# Whole exome sequencing (WES) of HER2+ metastatic breast cancer from patients with or without prior trastuzumab exposure: A correlative analysis of TBCRC003

Nikhil Wagle, Nancy U. Lin, Andrea L. Richardson, Ignaty Leshchiner, Ingrid A. Mayer, Andres Forero-Torres, Timothy J. Hobday, Elizabeth Claire Dees, Rita Nanda, Mothaffar F. Rimawi, Hao Guo, William T. Barry, Antonio C. Wolff, Stacey B. Gabriel, Levi A. Garraway, Eric P. Winer, and Ian E. Krop

on behalf of the Translational Breast Cancer Research Consortium

2014 ASCO Annual Meeting

Breast Cancer - Her2/ER - Poster Highlights Session

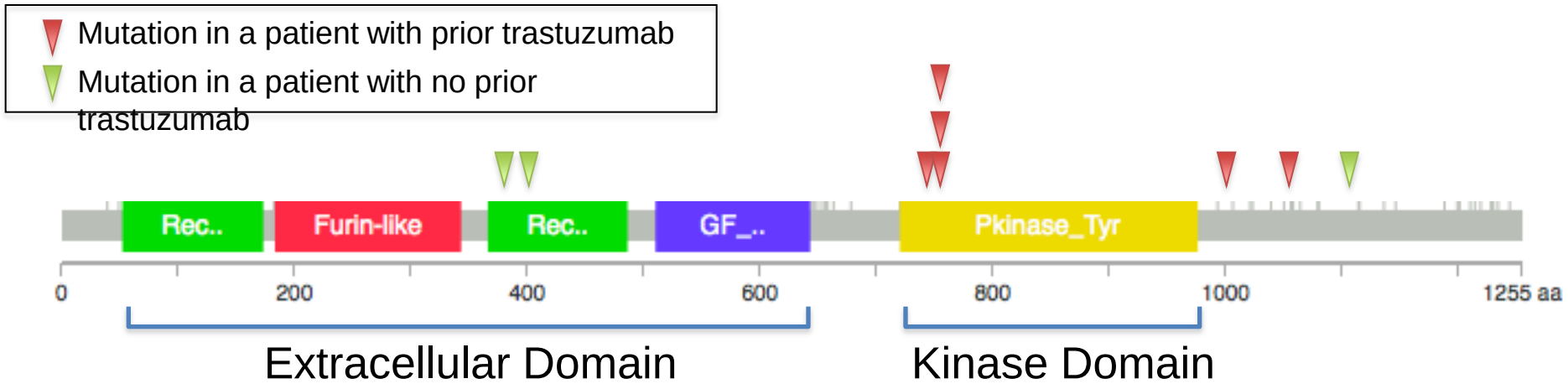
tbcrc Translational Breast Cancer Research Consortium

DANA-FARBER CANCER INSTITUTE

BWH BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

BROAD INSTITUTE

# Somatic HER2 Mutations in Pts Who Received Prior Trastuzumab




- HER2 mutations have previously been identified in ~2% of HER2- cancers and <1% of primary HER2+ cancers (CBio portal)
- ***In 3/40 patients who had received prior trastuzumab (8%), we identified a HER2 L755S kinase mutation.***
- HER2 L755S results in resistance to lapatinib and sensitivity to irreversible inhibitors (e.g. neratinib)[1]
- 5 additional patients, 3 of whom received prior trastuzumab, had uncharacterized mutations in HER2 at low allelic fractions, including a novel kinase domain mutation D742N in a patient with prior trastuzumab.
- Functional characterization of novel HER2 mutations is currently underway

[1]Kancha et al, PLOS One, 2011; Bose et al, Cancer Discovery,

# How do we sample the genetics of metastatic breast caner?

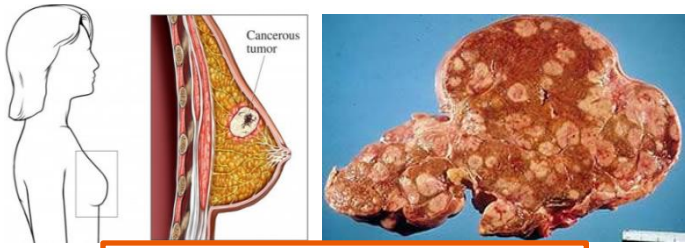
# ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNICANCER SAFIR-01)

**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

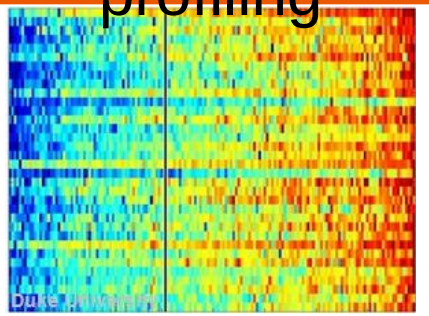
Andre *et al* Lancet Oncol 2014

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

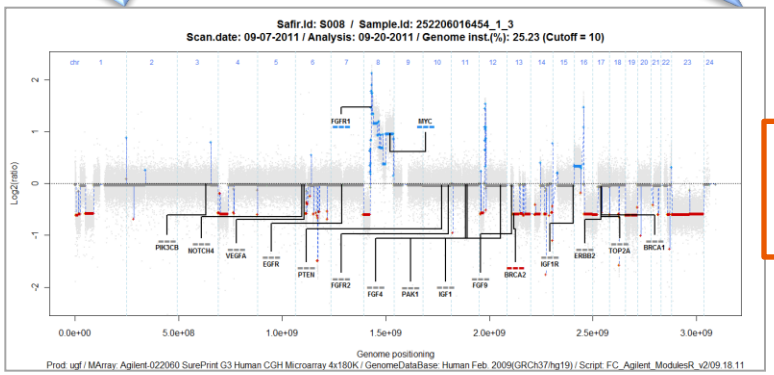



Biopsy metastases

Whole genome profiling

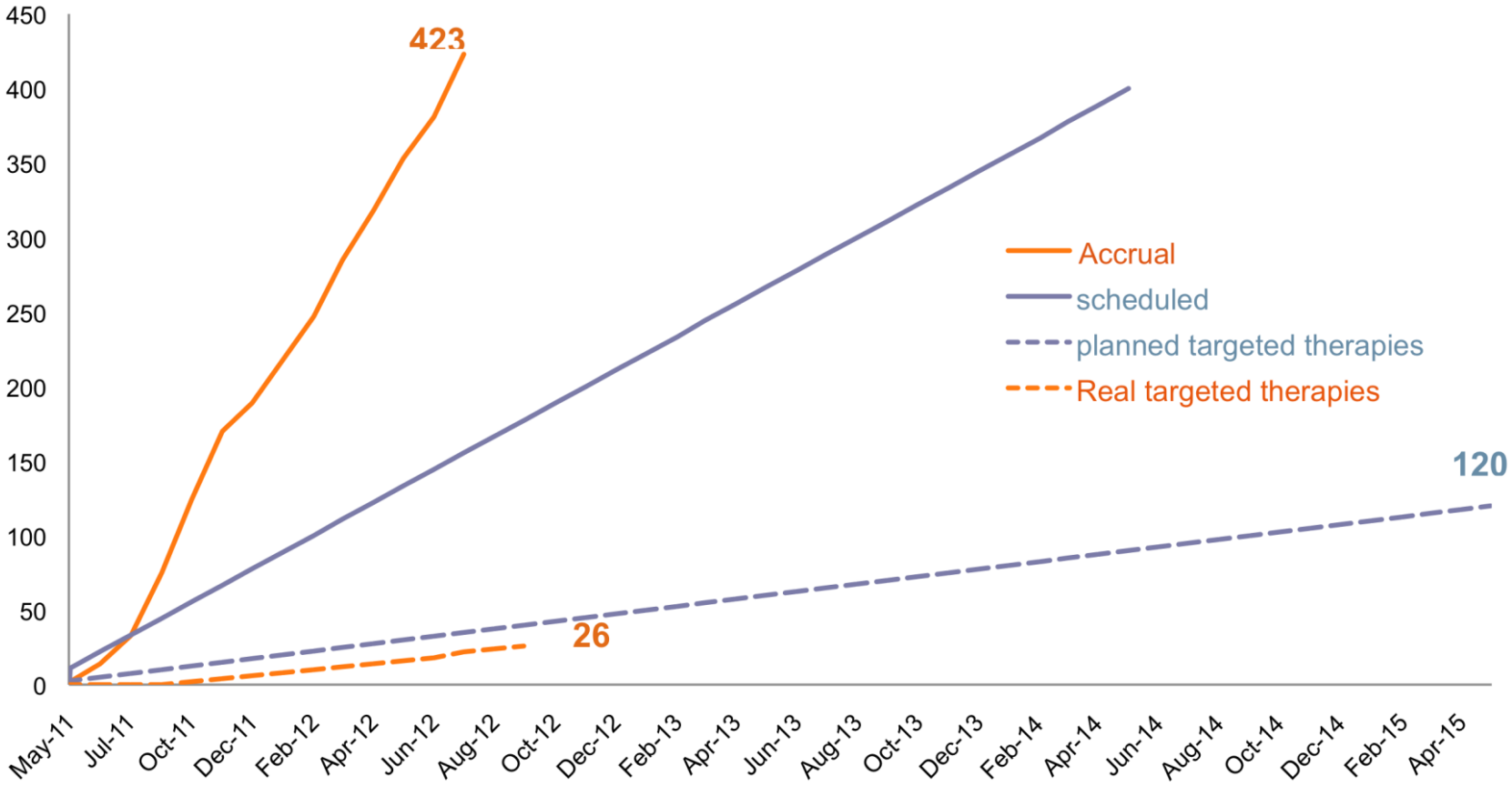


Identification of the Genomic Alteration

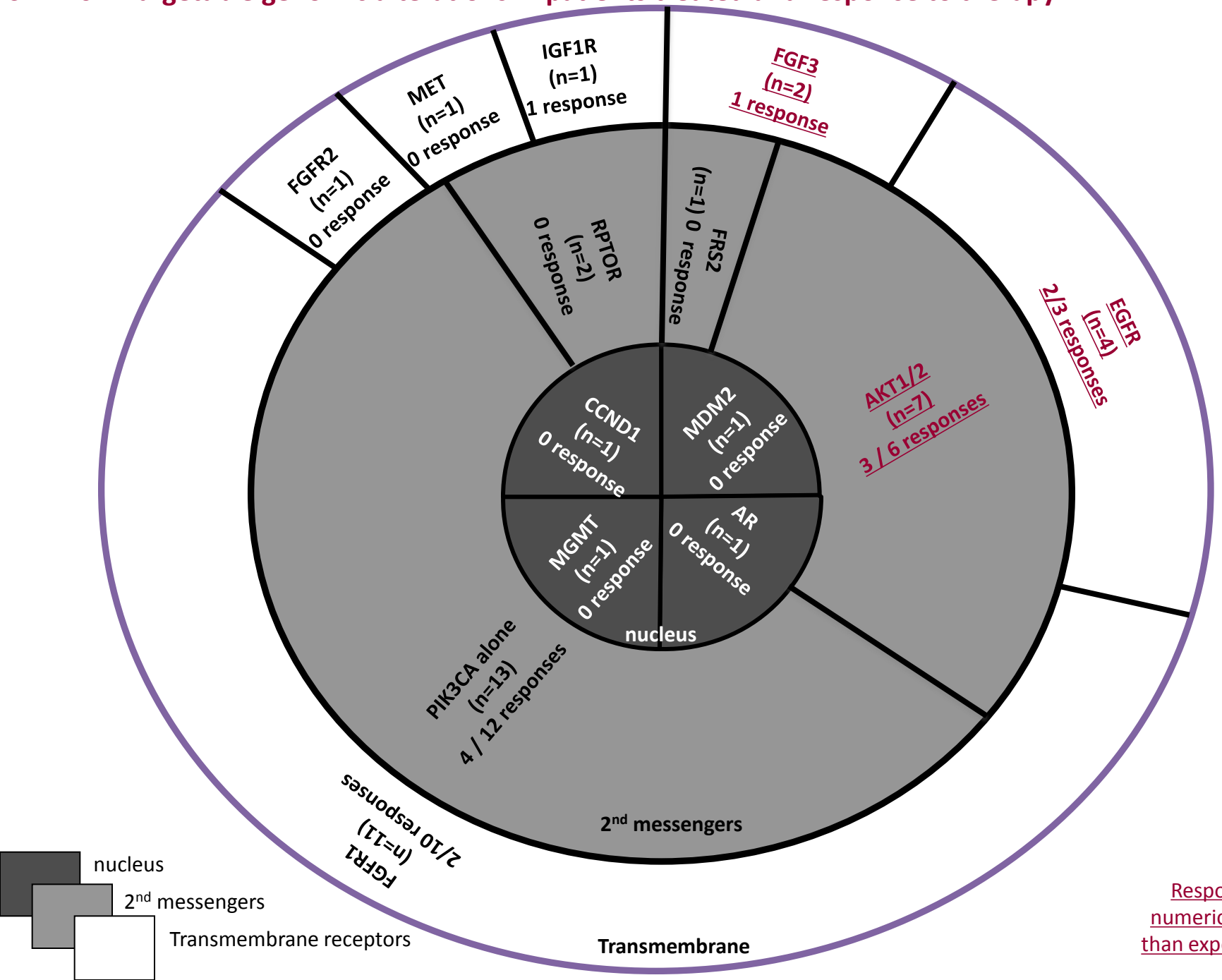



Targeted therapy according to the genomic profile

# SAFIR01 Accrual

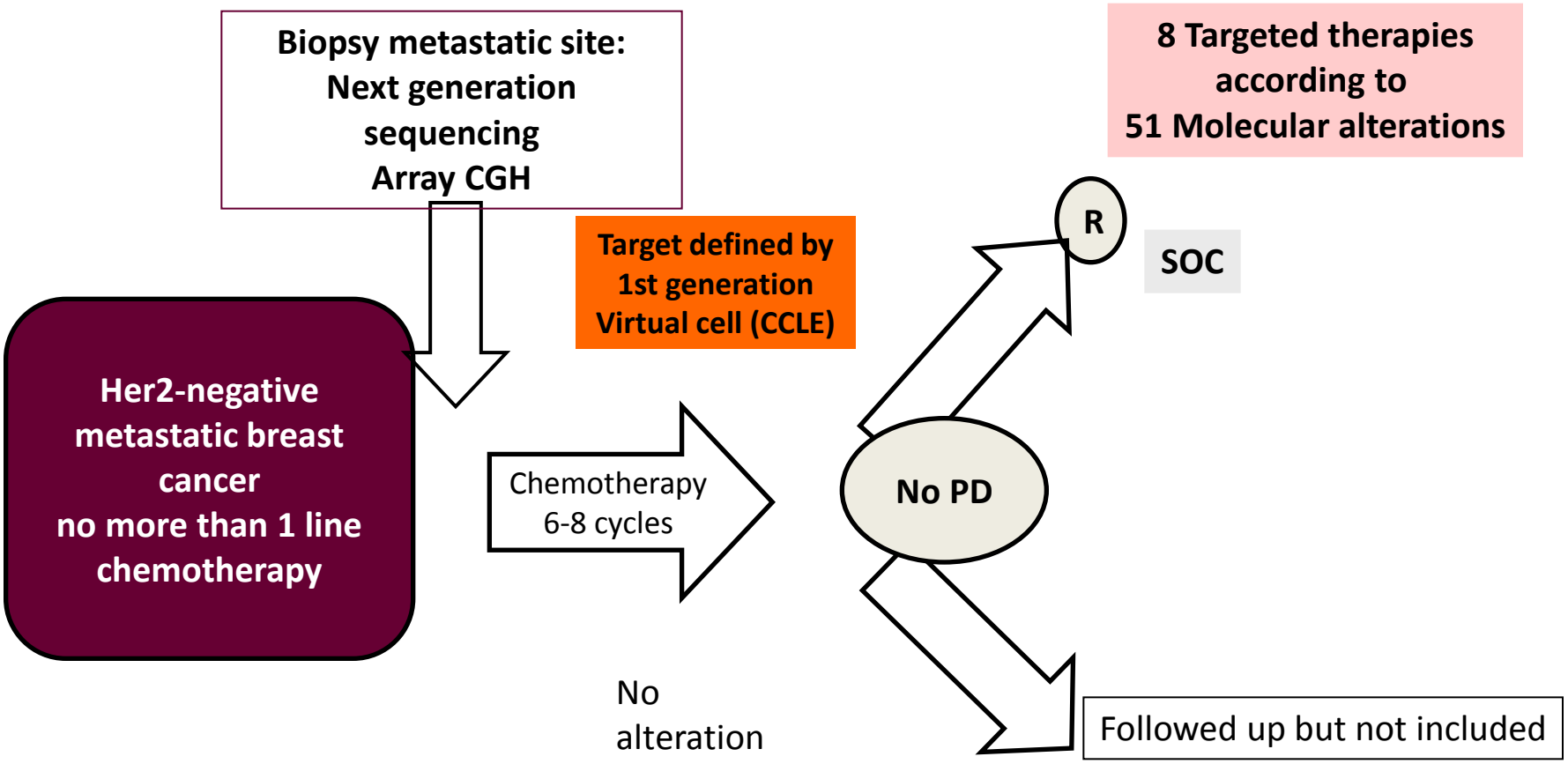


# SAFIR01: Targetable genomic alterations in patients treated and response to therapy




Response rate numerically higher than expected (30%)

# Personalized medicine trial - SAFIR02 trial



BIG
Breast International Group

AURORA
Metastatic Breast Cancer - molecular aberrations

Newly diagnosed or 1st Line MBC Patients

N=1,300

Screening Failure n=300

'Actionable' Mutation(s) (n~300)

'Non-Actionable' Mutations (n~700)

Downstream Targeted Clinical Trials as first or second line

Standard of Care

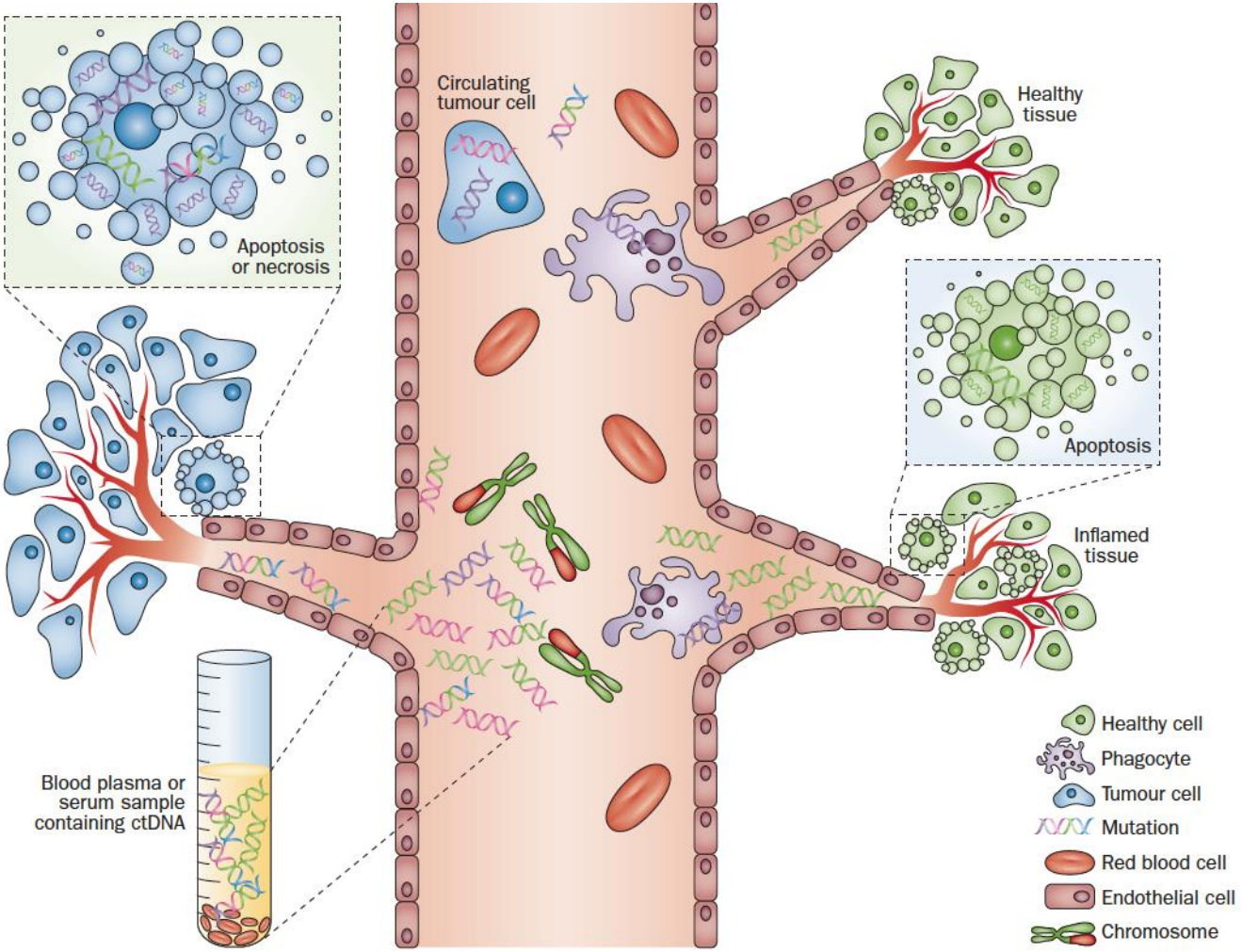
Clinical Outliers (Exceptional Responders and Rapid Progressors) to be subjected to WES

....

How do we sample the genetics of metastatic breast caner?

Non-invasive detection

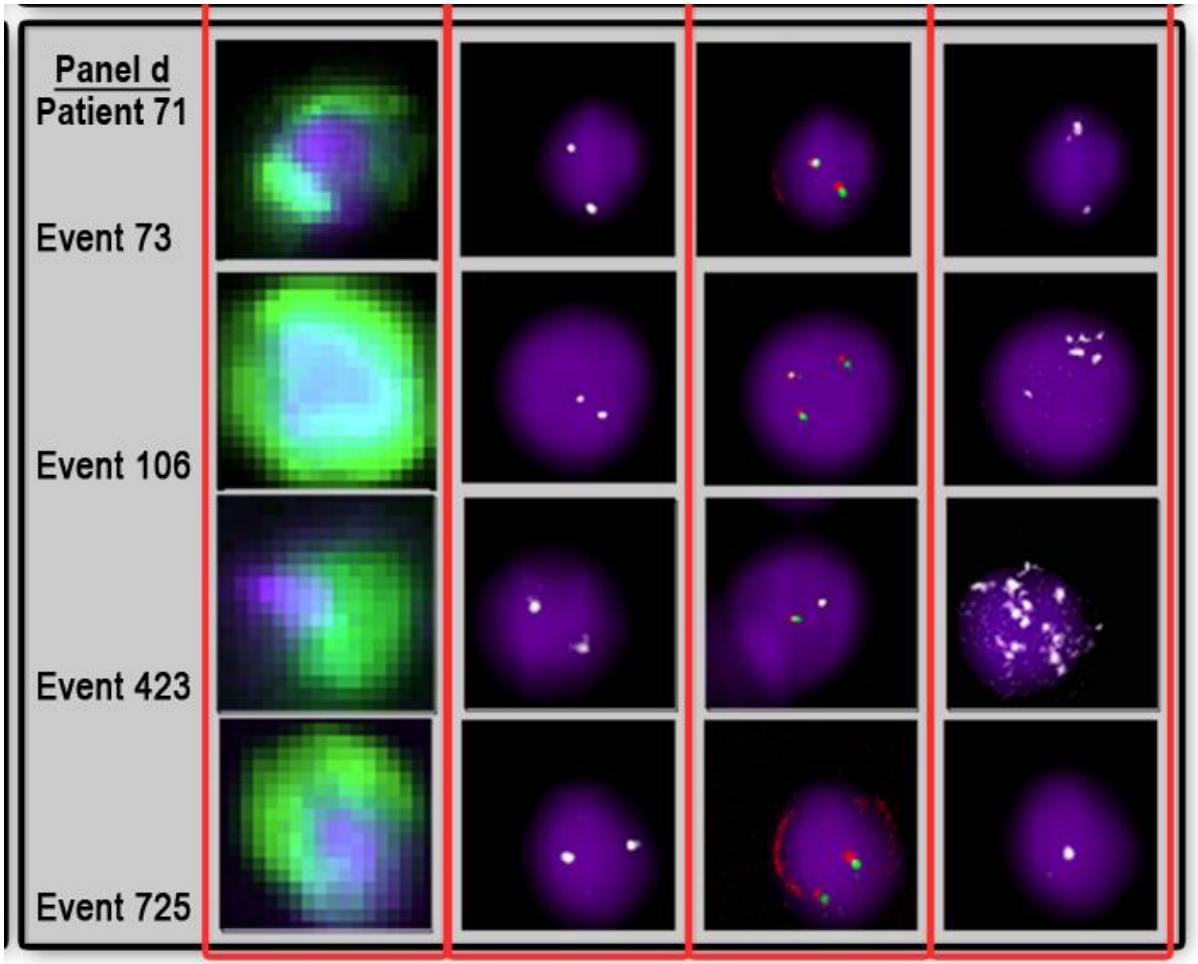
# Non-invasive interrogation of cancer genetics




Crowley et al Nat Rev Clin Oncol 2013

# Androgen receptor amplification in CTC

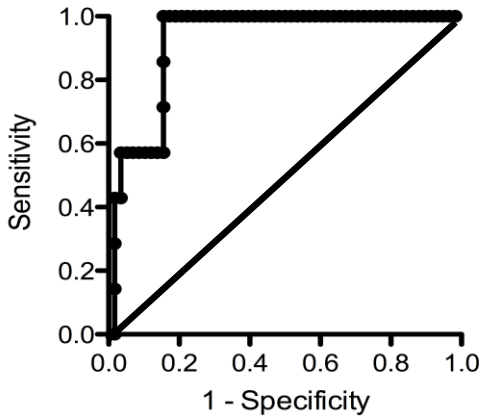
*AR* FISH




*Attard et al, Cancer Res 2009*

# HER2 status in plasma DNA – independent validation set

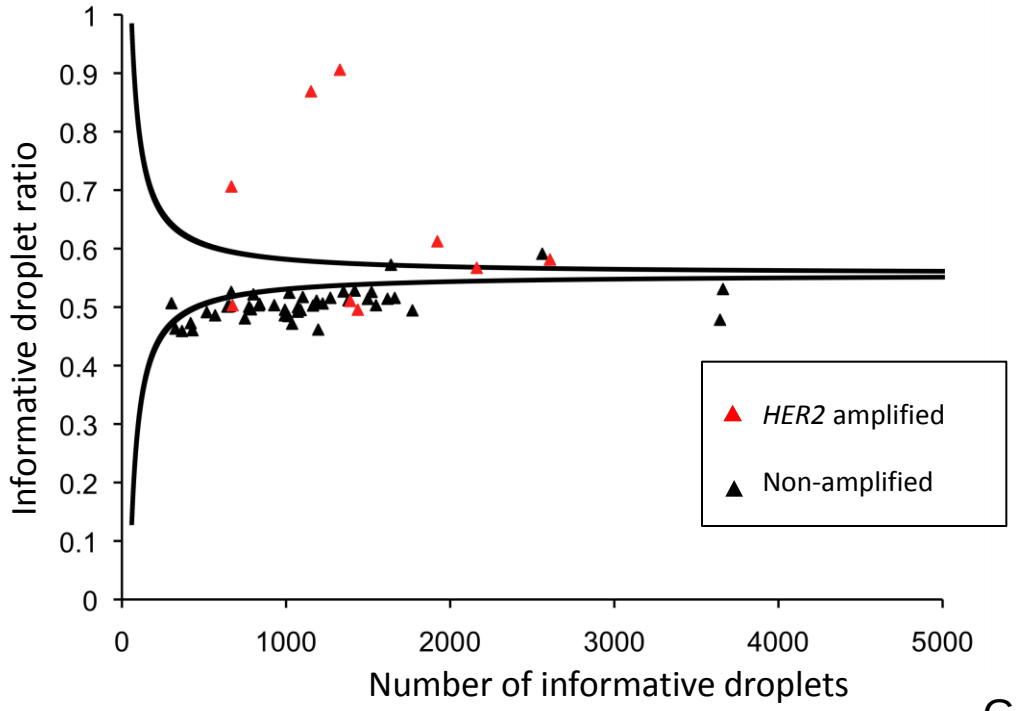
A




C

| Plasma DNA Digital PCR | Tumour HER2 status: Amp | Tumour HER2 status: Non-Amp |
|---|---|---|
| +ve | 7 | 3 |
| -ve | 4 | 44 |

B




Sensitivity 64%

Specificity 94%

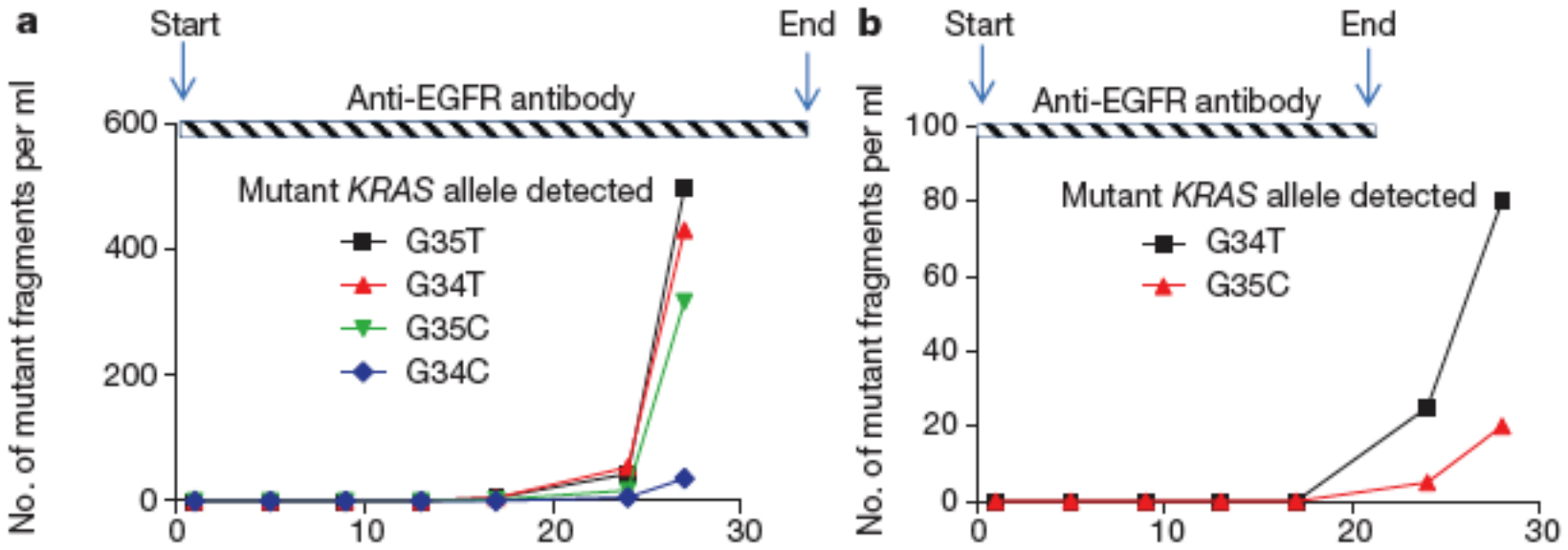
PPV 70%

NPV 92%

Gevensleben et al *Clin Cancer Res* 2013

# Detection of resistance mutations in plasma

Metastatic colon cancer on cetuxumab



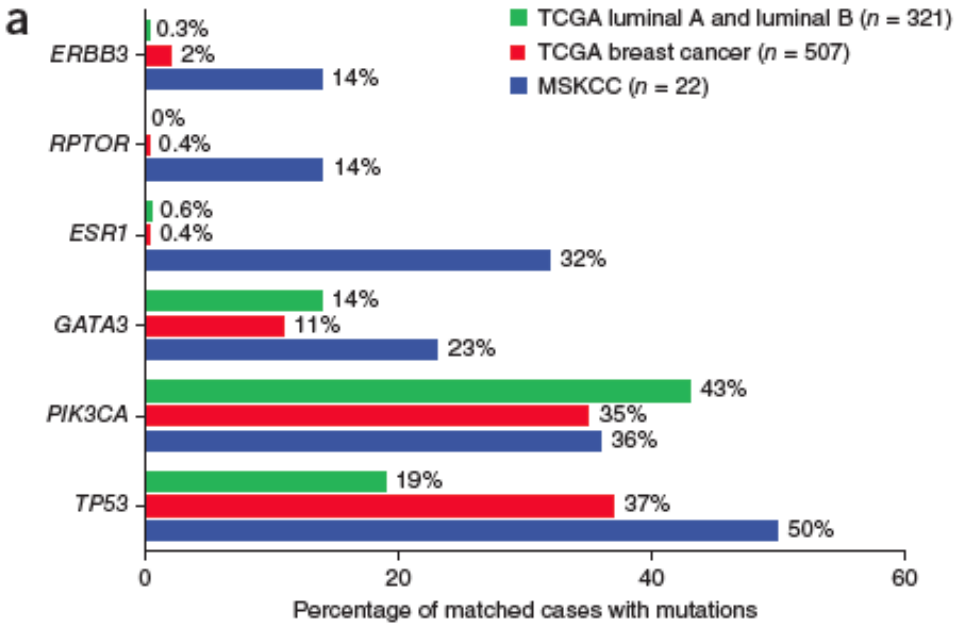

Diaz et al Nature 2012

# Genetic events are acquired in metastatic breast cancer

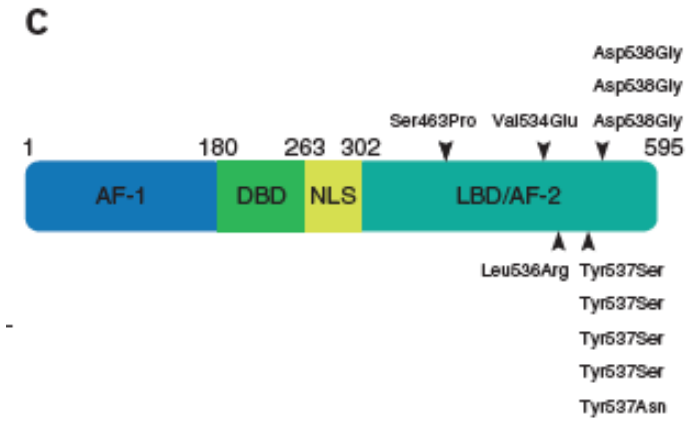
nature genetics

*ESR1* ligand-binding domain mutations in hormone-resistant breast cancer

Weiyi Toy[1], Yang Shen[2], Helen Won[1], Bradley Green[3], Rita A Sakr[4], Marie Will[5], Zhiqiang Li[1], Kinisha Gala[1], Sean Fanning[3], Tari A King[4], Clifford Hudis[5,6], David Chen[7], Tetiana Taran[7], Gabriel Hortobagyi[8], Geoffrey Greene[3], Michael Berger[1,9], José Baselga[1,5] & Sarat Chandarlapaty[1,5,6]




*ESR1* mutations occur in 20% of endocrine resistant ER positive breast cancer




Nat Genetics 2013

# Prognostication in metastatic breast cancer

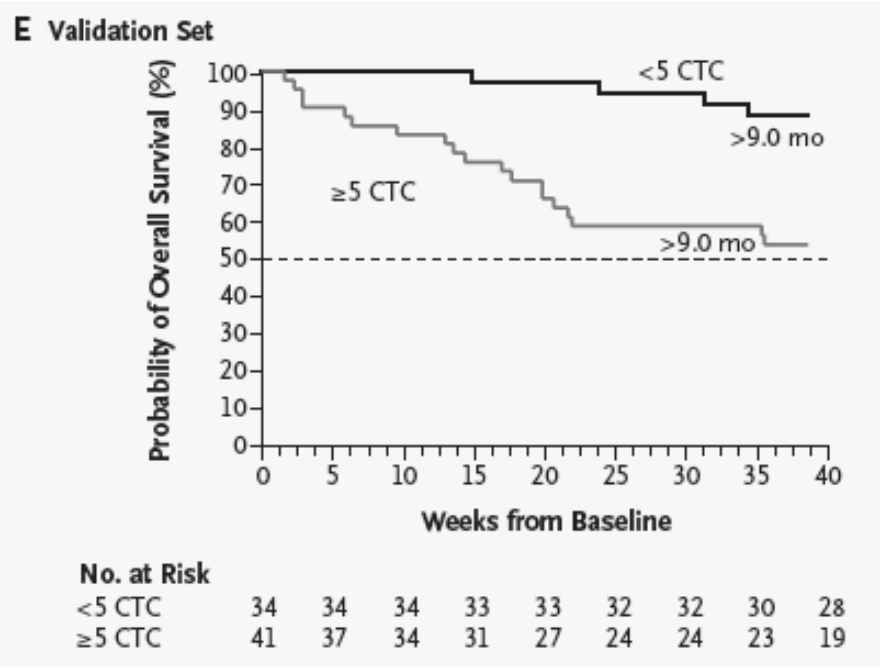
Tumour bulk surrogates

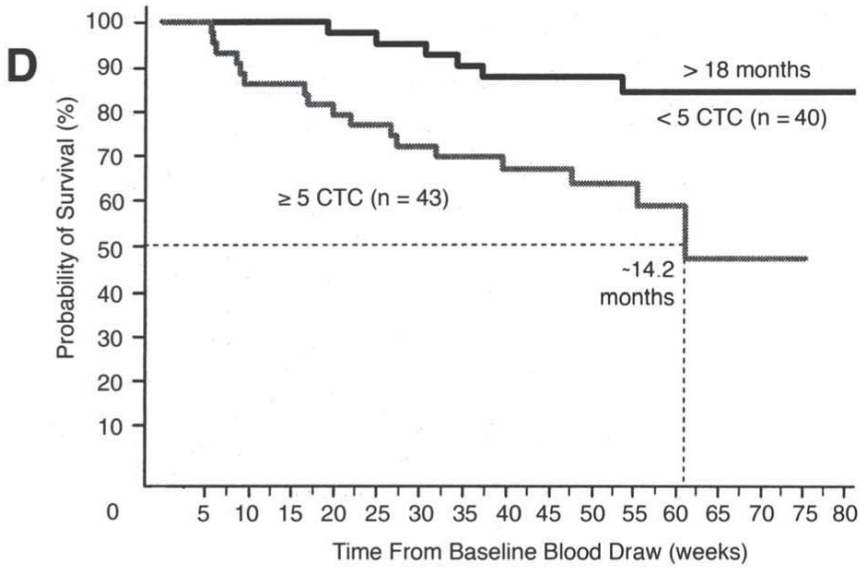
Tumour biology

# Tumour bulk surrogates – circulating tumour cells

Any line therapy

First line

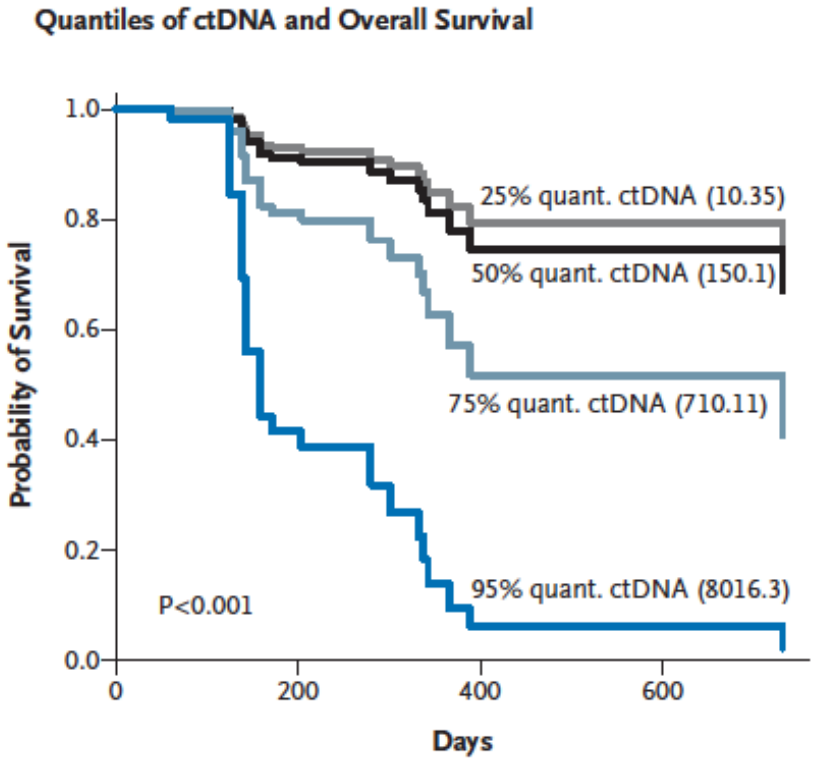



Cristofani et al NEJM 2004

Cristofani et al JCO 2005

# Tumour bulk surrogates – circulating tumour DNA

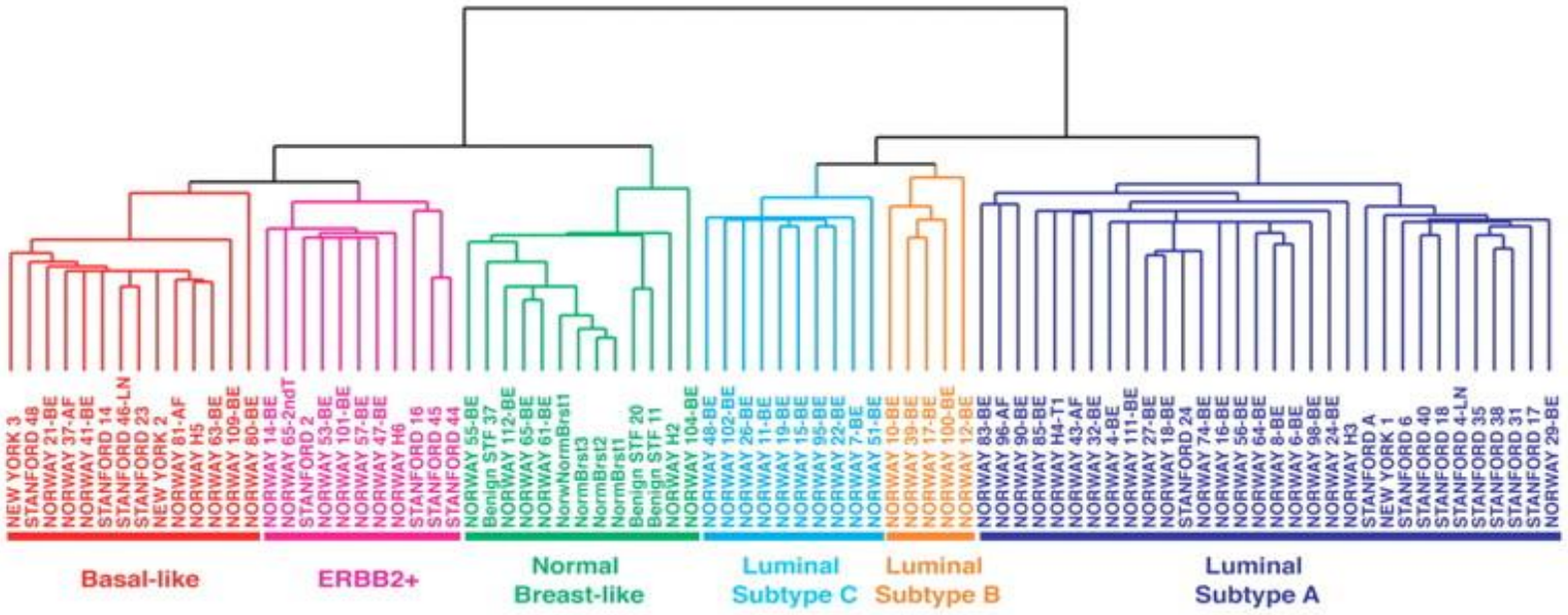



Level of circulating tumour DNA is prognostic

Dawson et al NEJM 2013

# Tumour Biology

# Breast cancer subtypes – ER positive subtypes




| Luminal B | Luminal A |
|---|---|
| Low ER | High ER |
| High | Low |
| Proliferation | Proliferation |

# 21 gene recurrence score - Oncotype DX

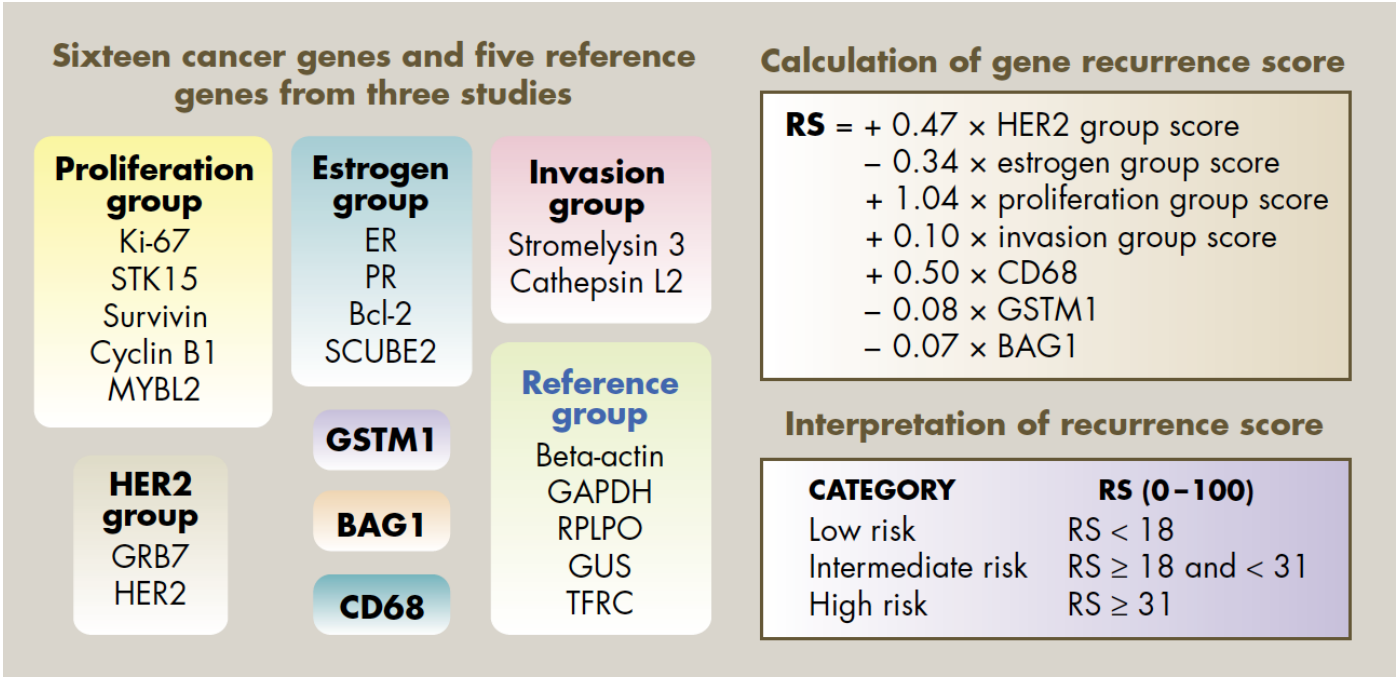
Formalin fixed tumour sections

↓

RNA extraction

↓

RT-PCR to assess gene expression

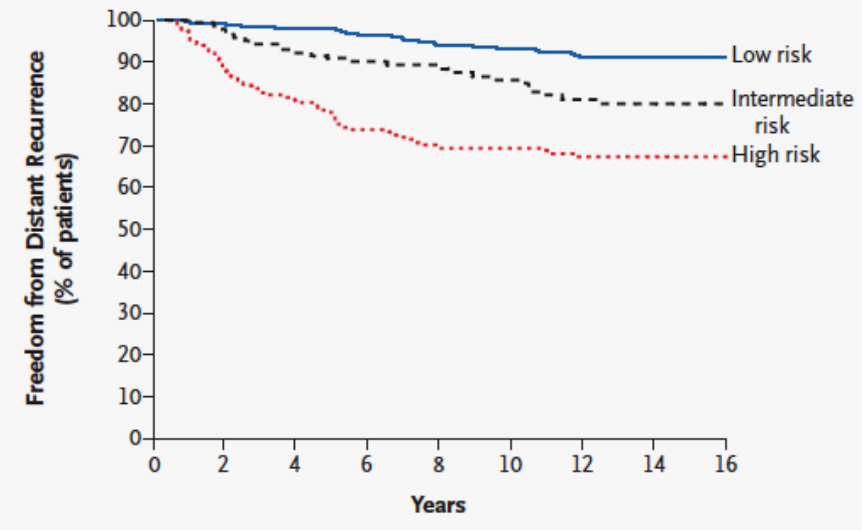


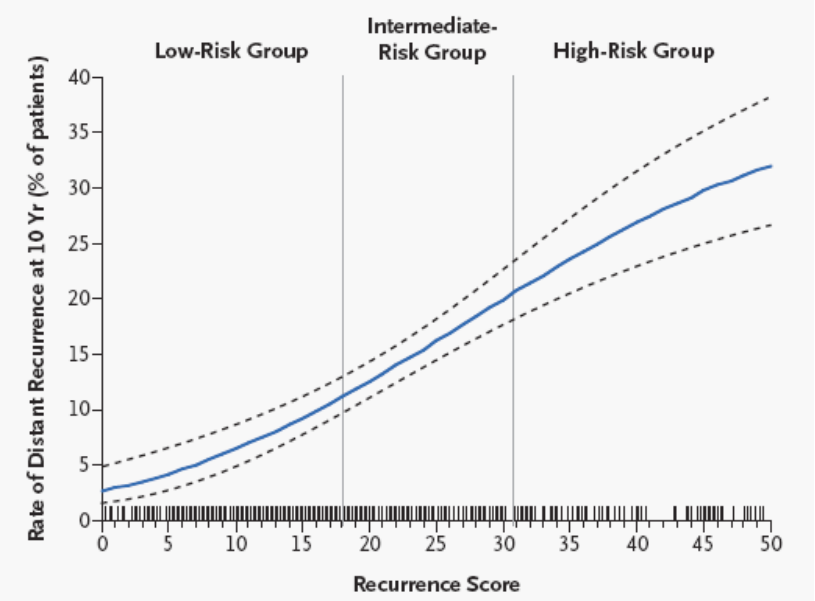
# NSABP B14 - Recurrence Score predicts recurrence

675 women treated with tamoxifen only

All ER positive, node negative

| Risk Category | Percentage of Patients | Rate of Distant Recurrence at 10 Yr (95% CI)† |
|---|---|---|
| | | *percent* |
| Low | 51 | 6.8 (4.0–9.6) |
| Intermediate | 22 | 14.3 (8.3–20.3) |
| High | 27 | 30.5 (23.6–37.4)‡ |




Paik et al NEJM 2004

# Prognostic impact of 21-gene Recurrence Score® in patients presenting with Stage IV breast cancer

King TA, Lyman JP, Gonen M, Voci A, deBrot M, Boafo C, Sing AP, Hwang ES, Alvarado M, Liu M, Boughey JC, Jacobs L, Krontiras H, McGuire K, Meszoely IM, Van Poznak C, Babiera G, Norton L, Morrow M, Hudis C

**Translational Breast Cancer Research Consortium**

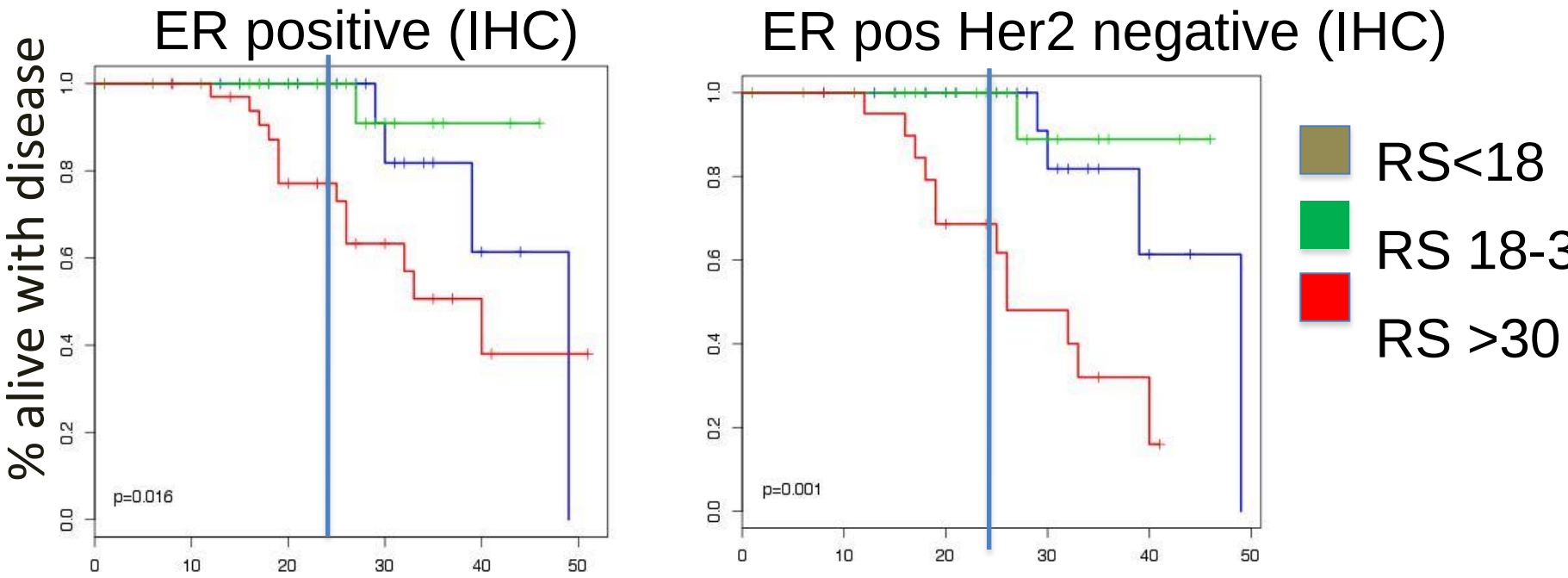
**TBCRC 013**

# Samples and Statistical Analyses

- 110 pts (86%) with pre-treatment primary tumor samples suitable for 21-gene Recurrence Score® analysis

- Clinical variables, time to first progression (TTP) and 2yr overall survival (OS) were correlated with 21-gene Recurrence Score® using log-rank, Kaplan-Meier and Cox regression
  - All patients (any ER, Her2)
  - ER positive (IHC)
  - ER positive Her 2 negative (IHC, FISH)

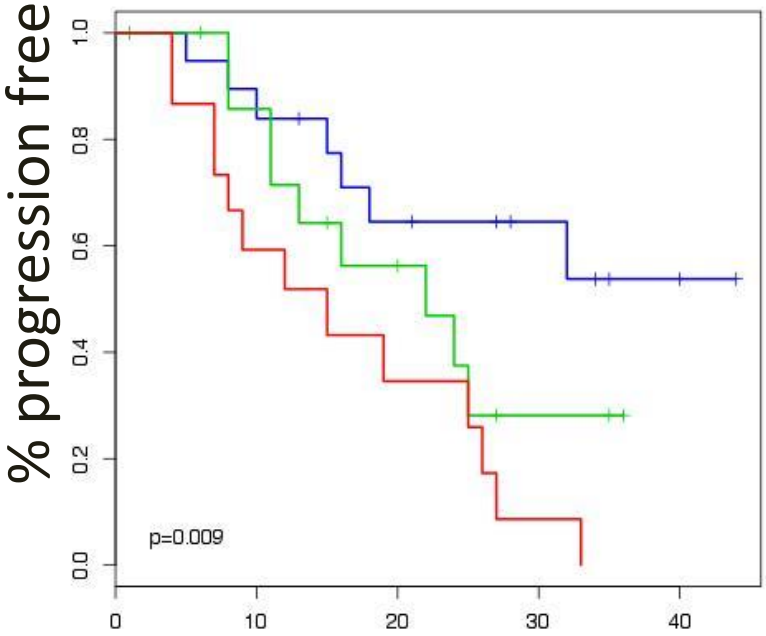
# 2yr Overall Survival by Risk Group



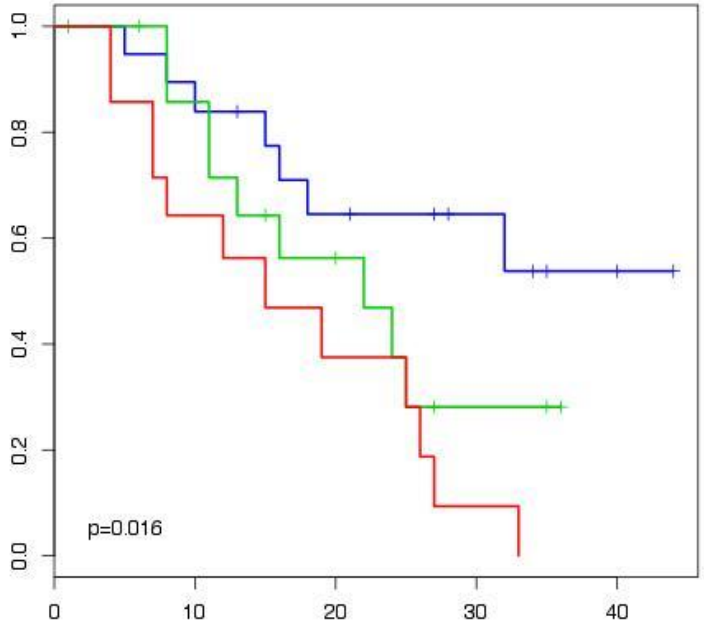

| **2 yr OS, %** | RS<18 | RS18-30 | RS>30 | Log rank, p |
|---|---|---|---|---|
| | | | | |
| All pts (n=102) | 100 (78-100) | 100 (78-100) | 80 (69-93) | 0.049 |
| ER+ (n=86) | 100 (78-100) | 100 (78-100) | 77 (64-94) | 0.016 |
| ER+HER2- (n=70) | 100 (78-100) | 100 (75-100) | 69 (51-93) | 0.001 |

# ER+ pts treated with 1st line endocrine tx
# High RS shorter TTP

ER positive (IHC)




ER pos Her 2 neg



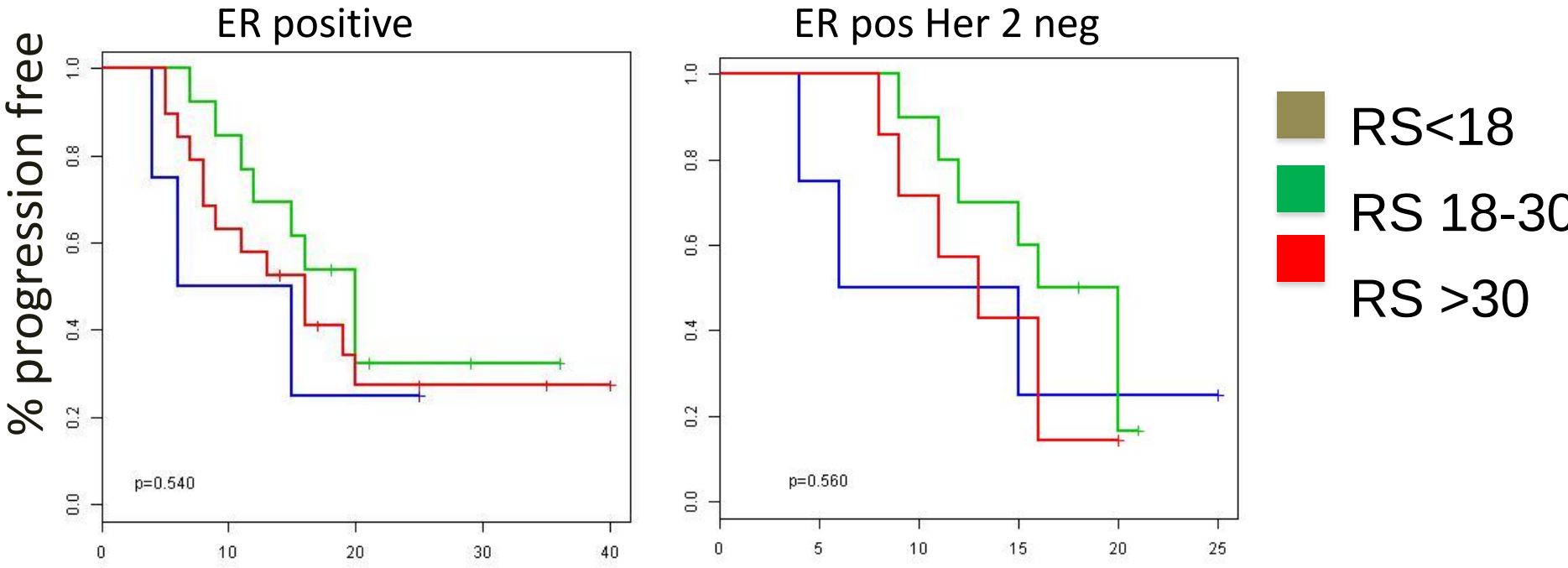

RS<18

RS 18-3

RS >30

| Median TTP, mos | RS<18 | RS18-30 | RS>30 | Log rank, p |
|---|---|---|---|---|
| | | | | |
| ER+ (n=50) | NR (18-NR) | 22 (13-NR) | 15 (8-NR) | 0.009 |
| ER+HER2- (n=49) | NR (18-NR) | 22 (13-NR) | 15 (8-NR) | 0.016 |

# ER+ pts treated with 1st line chemotherapy
# No difference by RS




| Median TTP, mos | RS<18 | RS18-30 | RS>30 | Log rank, p |
|---|---|---|---|---|
| | | | | |
| ER+ (n=36) | 10.5 (4-NR) | 20 (12-NR) | 16 (9-NR) | 0.54 |
| ER+HER2- (n=21) | 10.5 (4-NR) | 18 (12-NR) | 13 (9-NR) | 0.56 |

Is prognostication important?

Abstract CT101

# Final Results of a Randomized Phase 2 Study of Palbociclib (PD 0332991) a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (PALOMA-1/TRIO-18)

RS Finn,[1] JP Crown,[2] I Lang,[3] K Boer,[4] IM Bondarenko,[5] SO Kulyk,[6] J Ettl,[7] R Patel,[8] T Pinter,[9] M Schmidt,[10] Y Shparyk,[11] AR Thummala,[12] NL Voytko,[13] X Huang,[14] ST Kim,[14] S Randolph,[14] DJ Slamon[1]

*[1]University of California Los Angeles, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]Orszagos Onkologiai Intezet, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]University Hospital Mainz, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Henderson, NV, USA; [13]Kyiv City Clinical Oncology Center, Ukraine; [14]Pfizer Oncology, San Diego, CA, USA*

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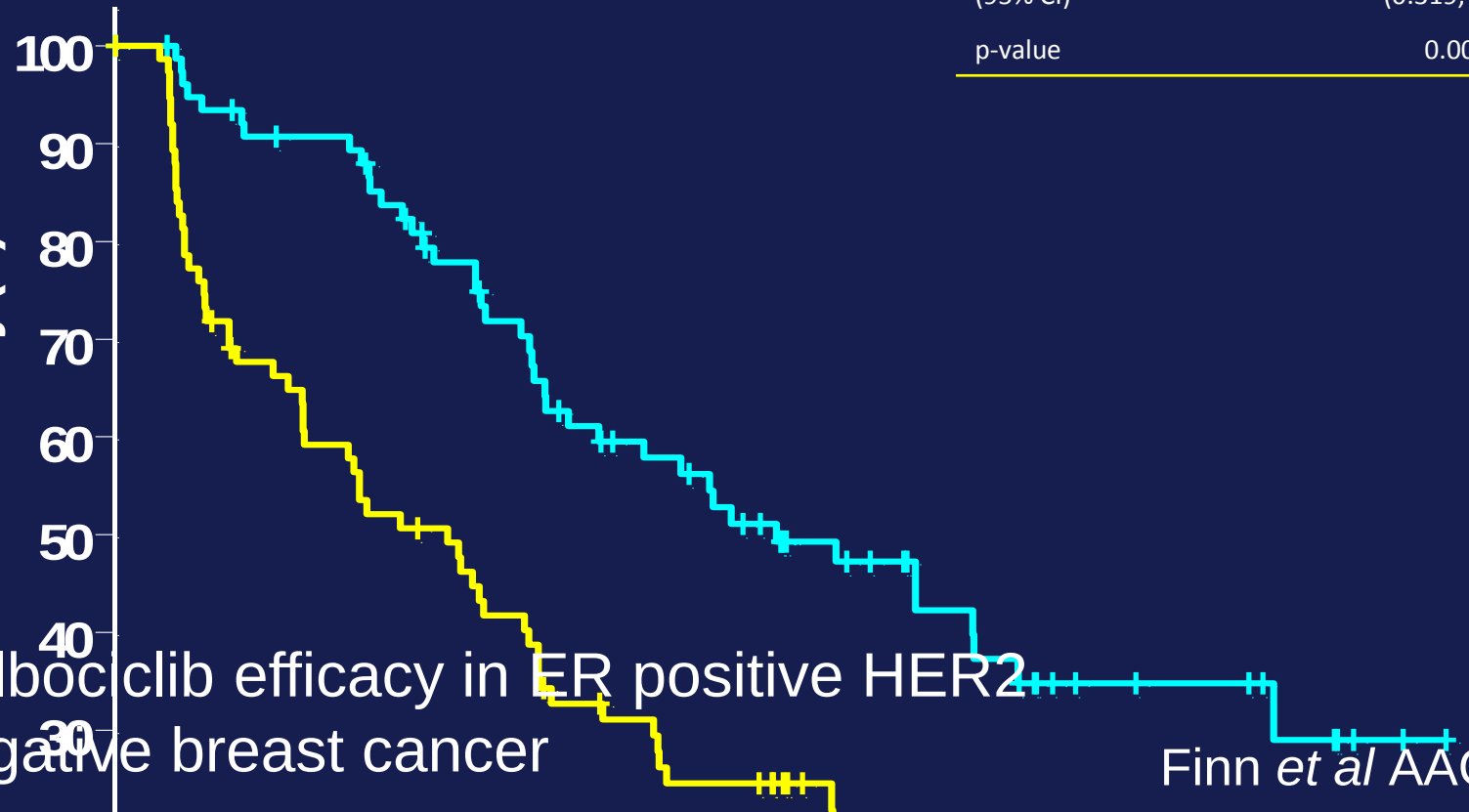
# Progression-Free Survival (ITT)

| | *PAL + LET (N=84)* | *LET (N=81)* |
|---|---|---|
| Number of Events (%) | 41 (49) | 59 (73) |
| Median PFS, months (95% CI) | 20.2 (13.8, 27.5) | 10.2 (5.7, 12.6) |
| Hazard Ratio (95% CI) | 0.488 (0.319, 0.748) | |
| p-value | 0.0004 | |




Palbociclib efficacy in ER positive HER2 negative breast cancer

Finn *et al* AACR 2014

# Prognostication is first line metastatic breast cancer

Who will do well on endocrine therapy alone?

# Prognostication is first line metastatic breast cancer

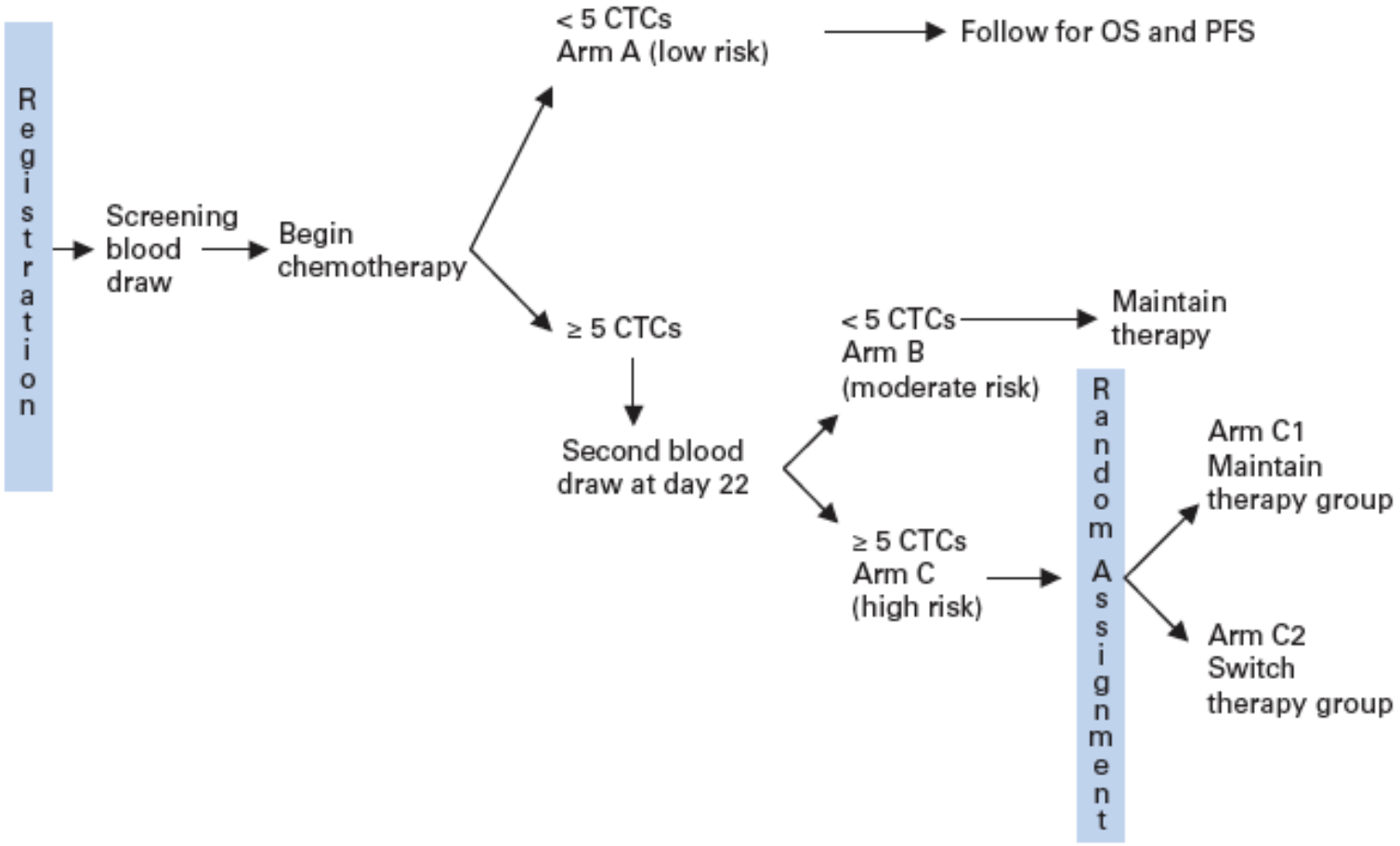
Who will do well on endocrine therapy alone?

| Low risk | High risk |
| --- | --- |
| Endocrine niave | Relapse on prior endocrine |
| Low CTC/ctDNA | High CTC/ctDNA |
| Luminal A biology | Luminal B biology |
| Undetectable *ESR1* mutation | Detectable *ESR1* mutation |

Studies required to demonstrate clinical utility

# Prediction of response

# Does failure to suppress CTCs indicate resistance?

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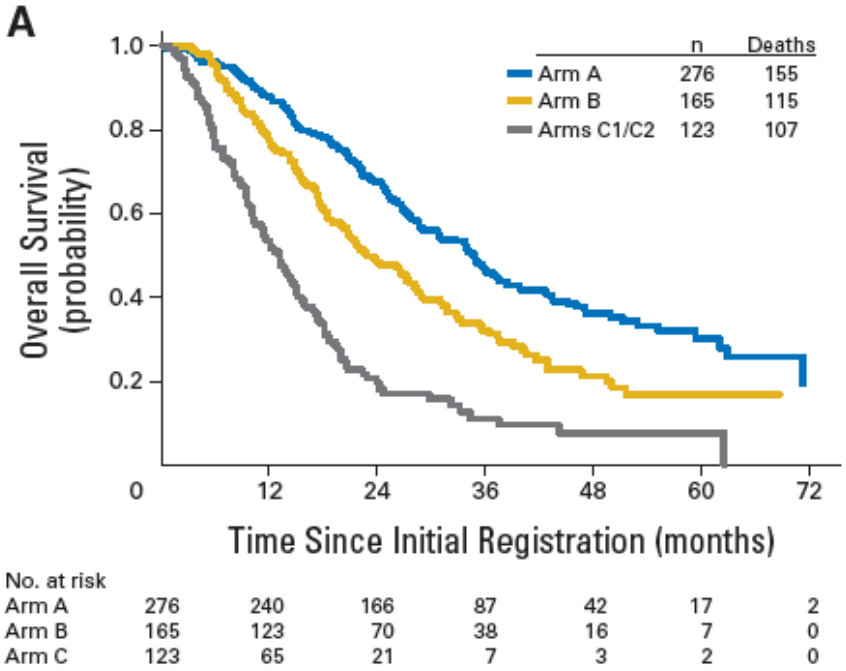
# Does failure to suppress CTCs indicate resistance?

Failure to suppress CTCs poor prognosis




Why is the study negative - inability to identify those resistant to chemo

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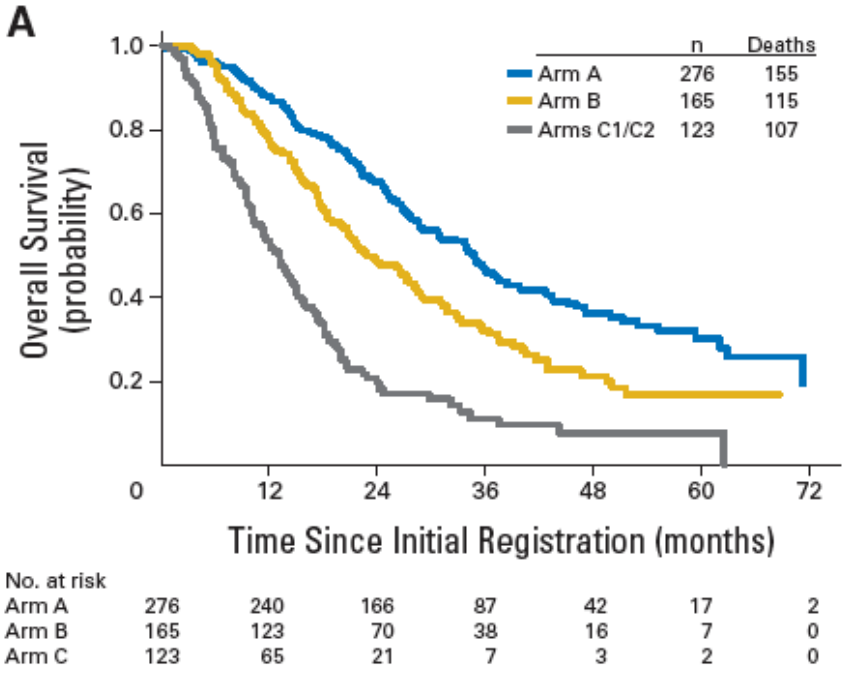
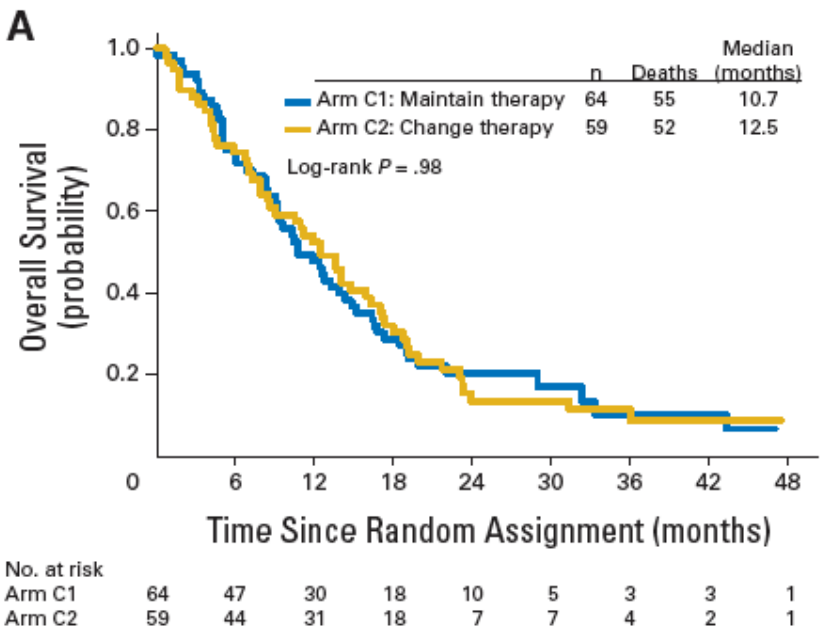
# Does failure to suppress CTCs indicate resistance?

Failure to suppress CTCs poor prognosis




Changing chemotherapy makes no difference




Why is the study negative

- inability to identify those resistant to chemo?
- cross-resistance to changed therapy?

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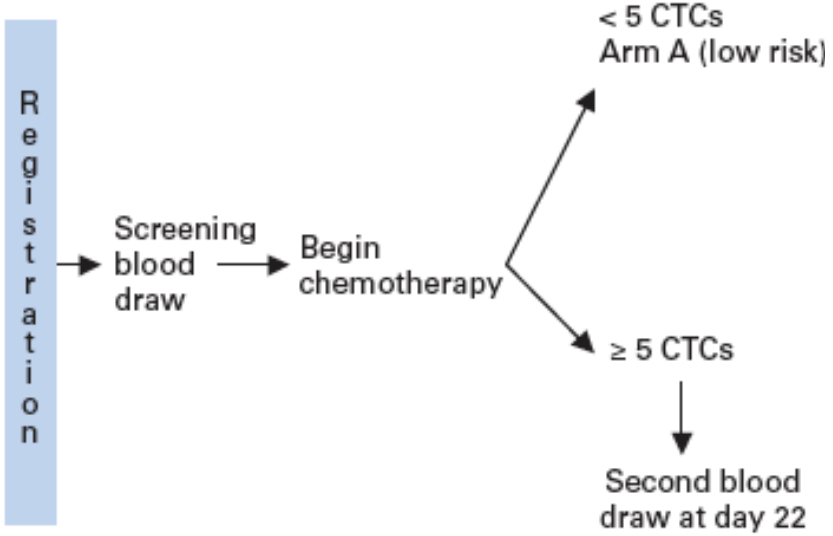
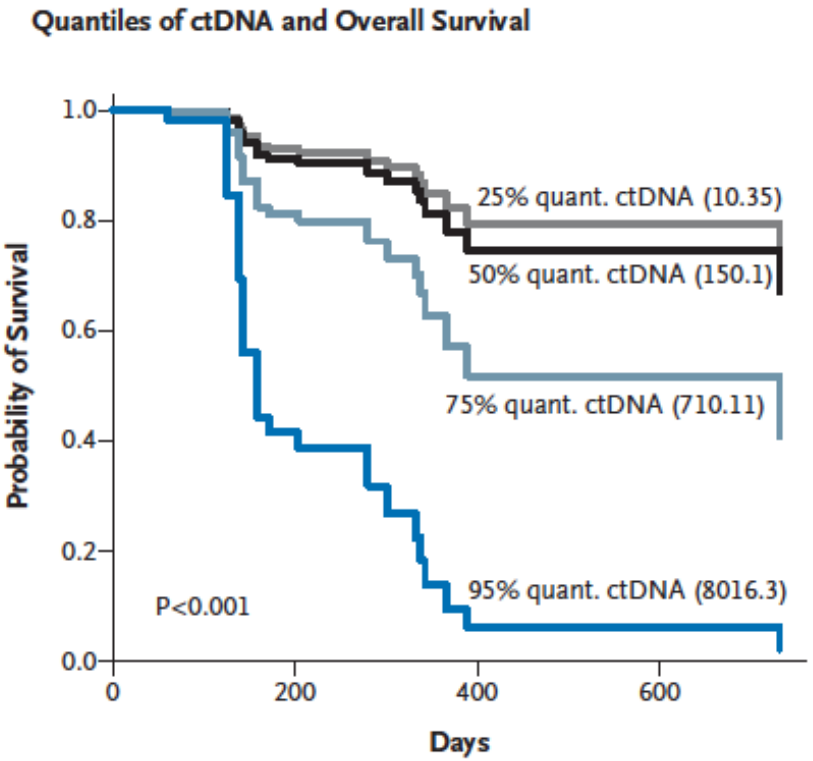
# Does ctDNA provide the dynamic range to improve on this?



# Molecular analysis in metastatic breast cancer

- Repeat *HER2* (and ER) testing of metachronous metastatic disease has become a standard

- Genetic analysis via biopsy or ctDNA for research now

  - Will become standard in the future

- Molecular analysis for prognostication or prediction

  - Promising research tools
  - Clinical utility unproven