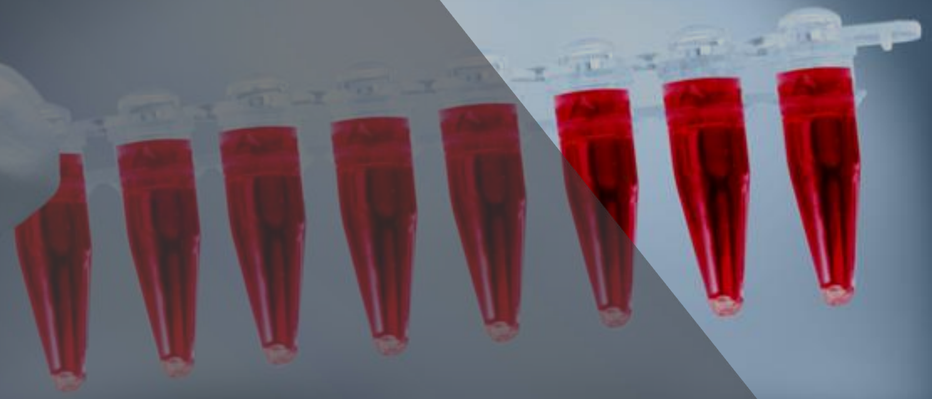
CRO AVIANO

UNIVERSITY OF UDINE
hic sunt futura

The **Liquid biopsy** Research Team



# **Liquid biopsy** and breast cancer

## Where are we now?

**Lorenzo Gerratana, MD**

**Department of Medical Oncology (OMP) - IRCCS CRO Aviano National Cancer Institute, Italy**

**Department of Medicine (DAME) - The University of Udine, Italy**

**Carcinoma Mammario Metastatico: Quali Novità? - Roma, 09.10.2023**

# Conflict of Interest Disclosure Statement

Last updated on 13.10.2023

**Stock and Other Ownership Interests:** None

**Honoraria:** None

**Consulting or Advisory Role:** AstraZeneca, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Incyte, Novartis, Pfizer, Merck Sharp & Dohme

**Expert Testimony:** None

**Research Funding:** Menarini Silicon Biosystems

**Patents, Royalties, Other Intellectual Property:** None

**Travel Expenses:** None

# The right tool for the right question

## Tissue vs liquid vs germline

### Tissue biopsy

Provides insights about a single portion of the tumor

Biomarker

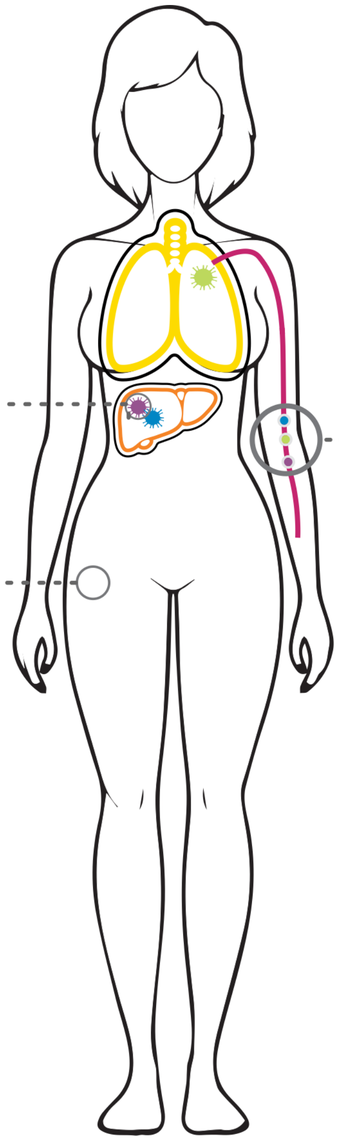
DNA is extracted from an FFPE tissue sample

### Germline

Provides insights about hereditary features

Biomarker

gDNA is generally extracted from leucocytes



### Liquid biopsy

Addresses tumor heterogeneity and sampling bias

Biomarker

Biomarker

Biomarker

Cell-free DNA is extracted from plasma

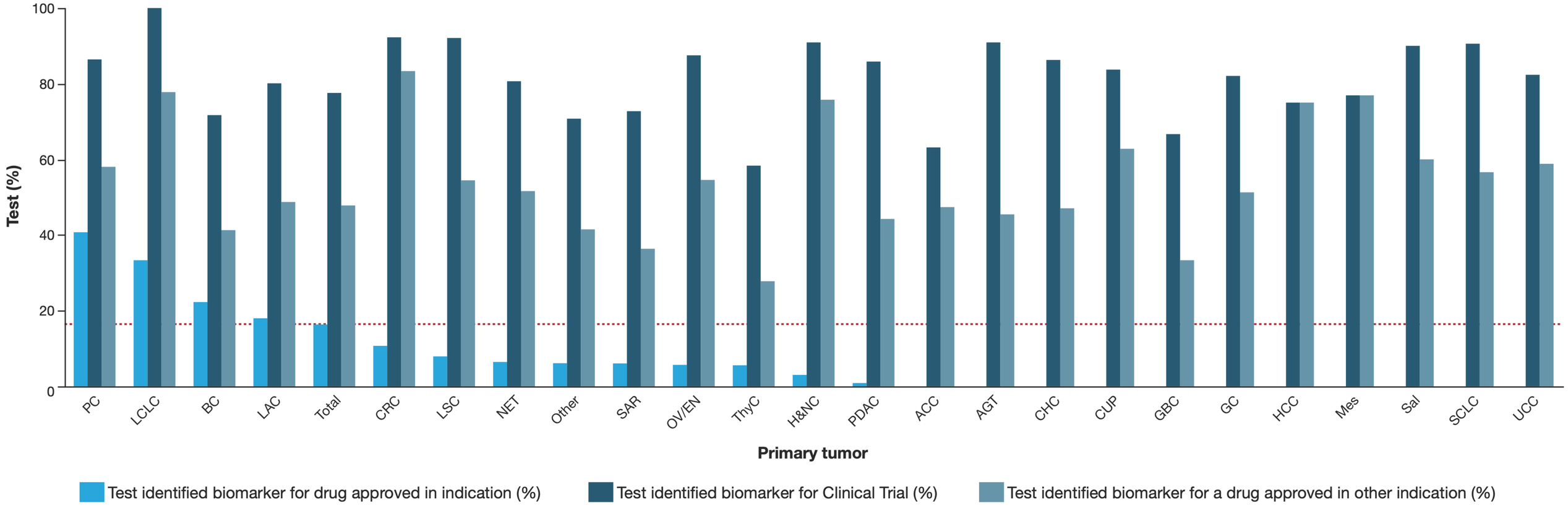
**Single baseline sample**
Target detection

**Longitudinal monitoring**
Treatment response/resistance
disease relapse/progression

Gerratana L, Davis AA, Shah AN, et al. *Curr Treat Options Oncol*, 2019; doi:10.1007/s11864-019-0667-9

# What do you see when you scale it up?

## Incidence of detectable alterations

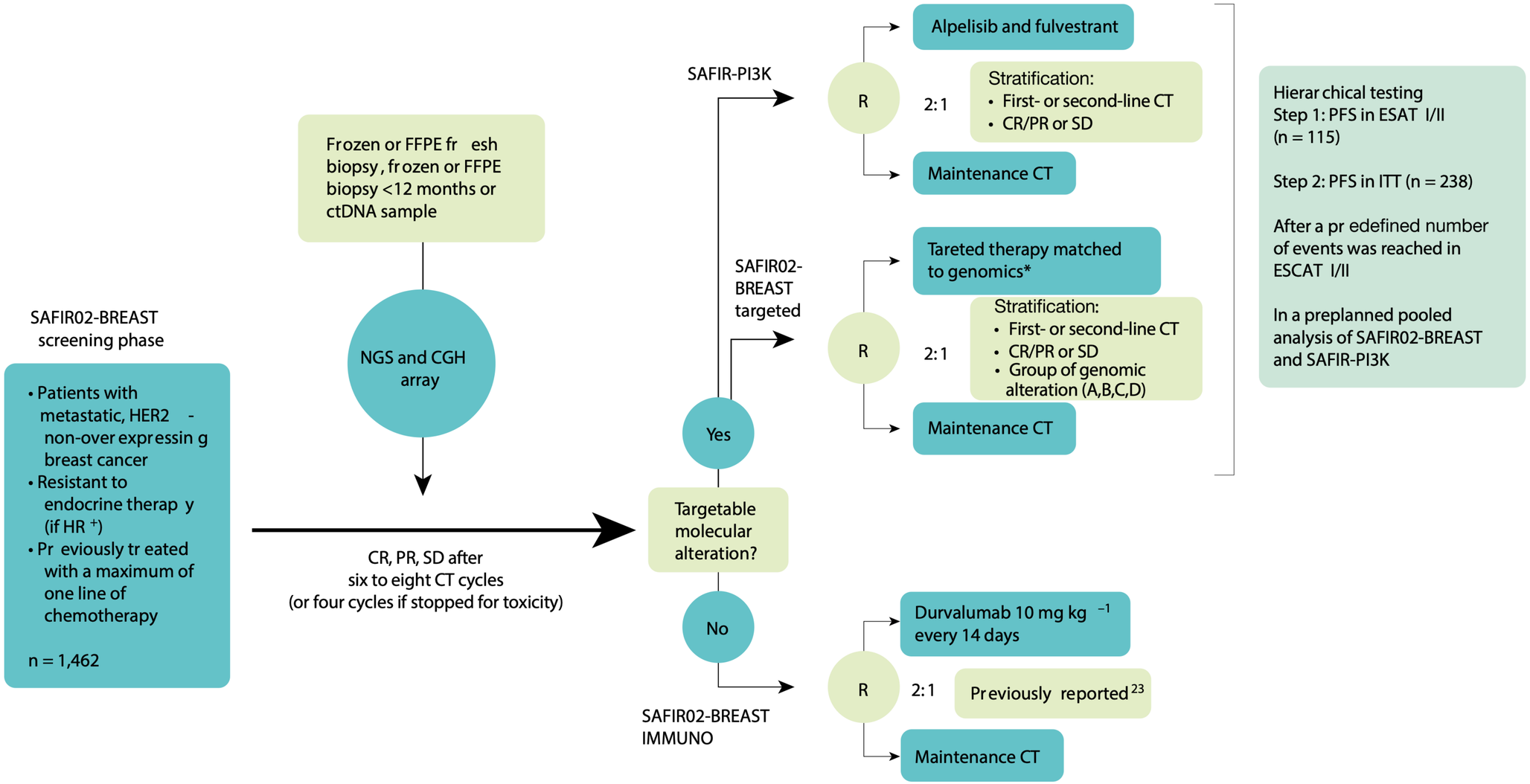



Gerratana L, Movarek M, Wehbe F, et al. *JCO Precis Oncol*, 2022; doi:10.1200/PO.21.00289

# What’s the role for ctDNA in MBC? **SAFIR02**

# Doesn’t SAFIR02 say another story?

## Genomics to select treatment for patients with metastatic breast cancer

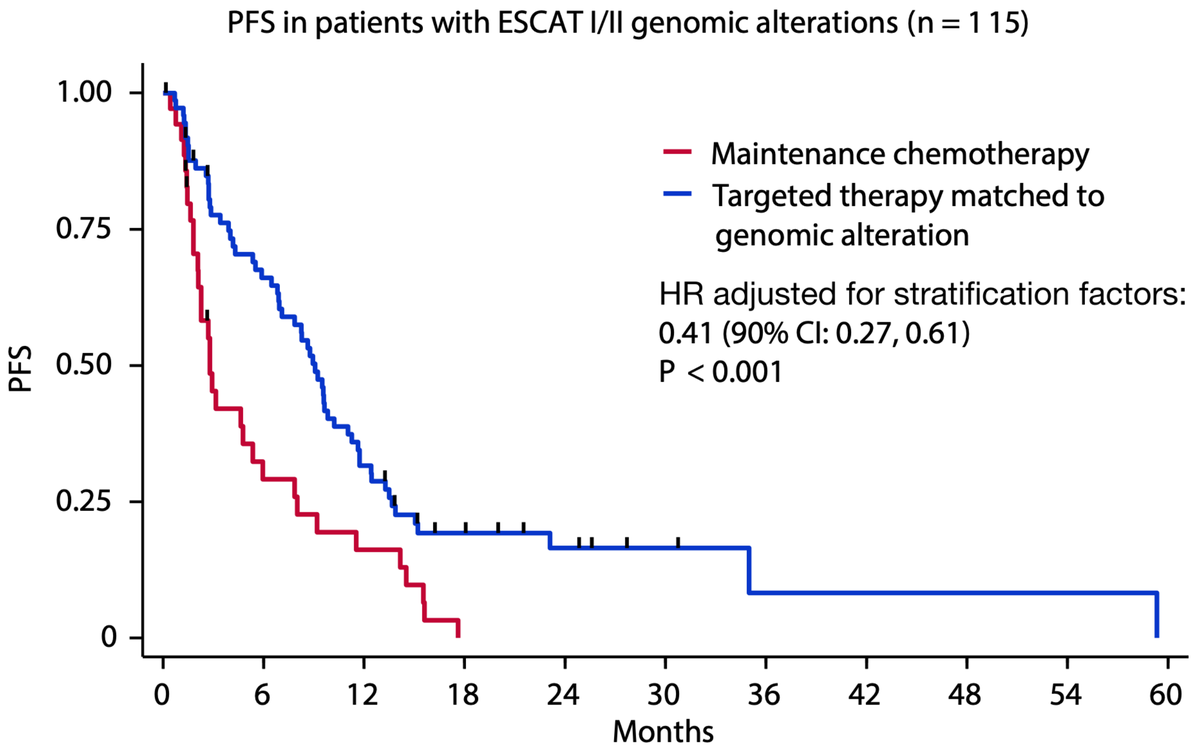


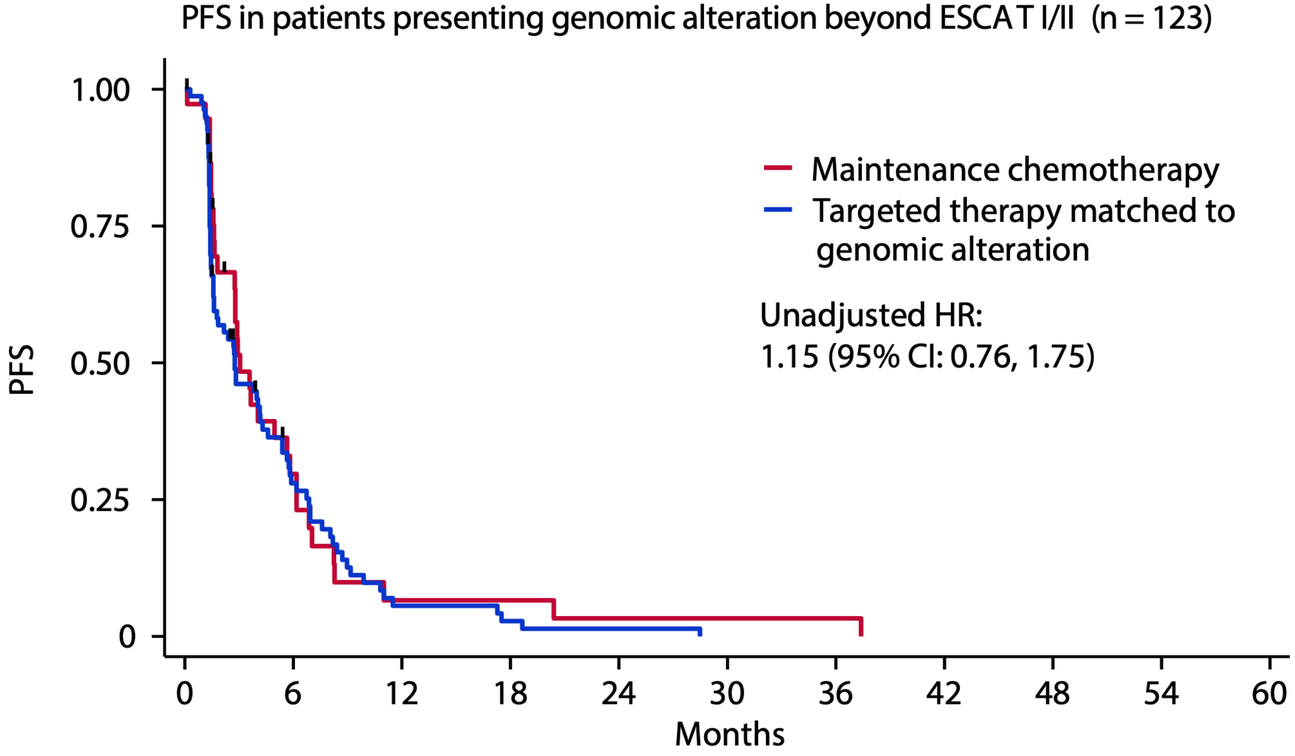

*olaparib, capivasertib, vistusertib, AZD8931, vandetanib, bicalutamide, AZD4547, selumetinib

Andre F, Filleron T, Kamal M, et al. *Nature*, 2022; doi:10.1038/s41586-022-05068-3

# Genomics to select treatment for patients with MBC

## PFS according to ESCAT classification



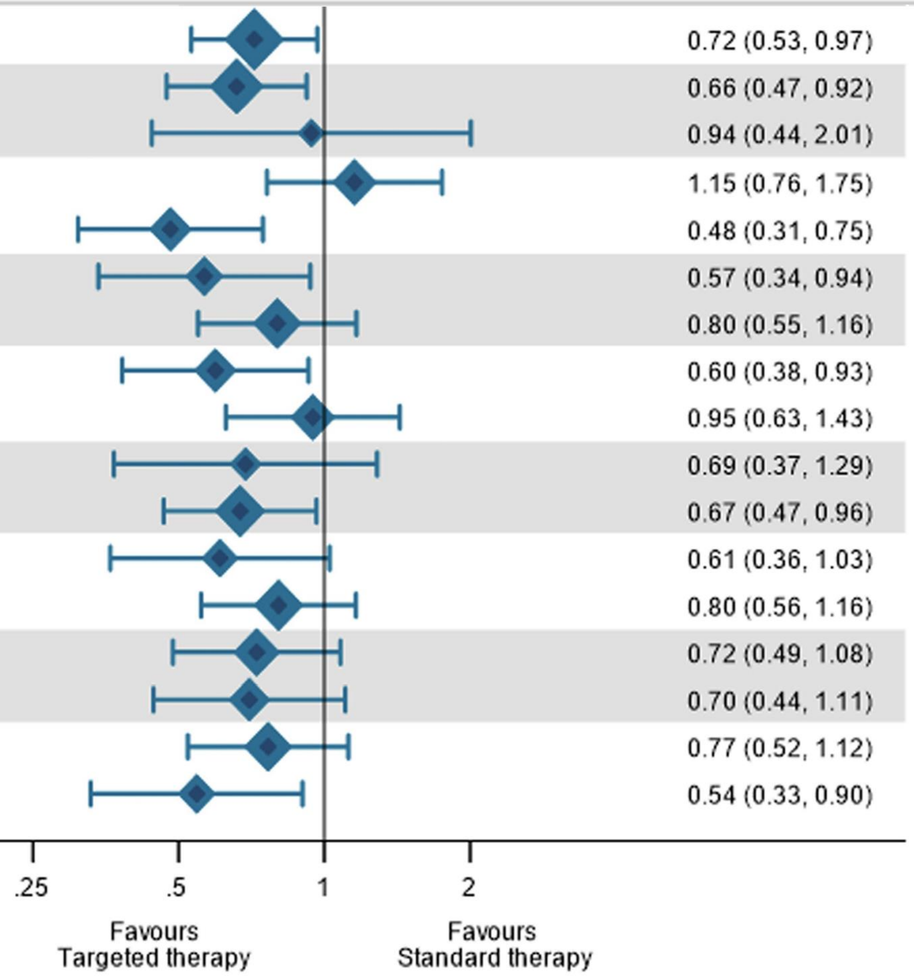




Andre F, Filleron T, Kamal M, et al. *Nature*, 2022; doi:10.1038/s41586-022-05068-3

# Genomics to select treatment for patients with MBC

## Subgroup analisys

| Subgroup | No. Evts / No. Pts | p-value Interaction | Unadjusted HR for PFS (90% CI) |
|---|---|---|---|
| All | 199 / 238 | | 0.72 (0.53, 0.97) |
| 1st Line | 166 / 201 | 0.210 | 0.66 (0.47, 0.92) |
| 2nd Line | 33 / 37 | | 0.94 (0.44, 2.01) |
| non-ESCAT I/II | 108 / 123 | 0.004 | 1.15 (0.76, 1.75) |
| ESCAT I/II | 91 / 115 | | 0.48 (0.31, 0.75) |
| Age < 50 years | 77 / 93 | 0.255 | 0.57 (0.34, 0.94) |
| Age ≥ 50 years | 122 / 145 | | 0.80 (0.55, 1.16) |
| Metastatic Sites < 3 | 93 / 120 | 0.093 | 0.60 (0.38, 0.93) |
| Metastatic Sites ≥ 3 | 106 / 118 | | 0.95 (0.63, 1.43) |
| TNBC | 44 / 51 | 0.903 | 0.69 (0.37, 1.29) |
| non-TNBC | 144 / 175 | | 0.67 (0.47, 0.96) |
| No Liver metastases | 68 / 84 | 0.341 | 0.61 (0.36, 1.03) |
| Liver metastases | 131 / 154 | | 0.80 (0.56, 1.16) |
| Delay metastatic to rando < 1y | 109 / 131 | 0.930 | 0.72 (0.49, 1.08) |
| Delay metastatic to rando ≥ 1y | 90 / 107 | | 0.70 (0.44, 1.11) |
| ECOG 0 at baseline | 119 / 144 | 0.209 | 0.77 (0.52, 1.12) |
| ECOG 1-2 at baseline | 79 / 91 | | 0.54 (0.33, 0.90) |




Andre F, Filleron T, Kamal M, et al. *Nature*, 2022; doi:10.1038/s41586-022-05068-3

Is this really **unexpected**?

# How to translate all of this to the clinic?

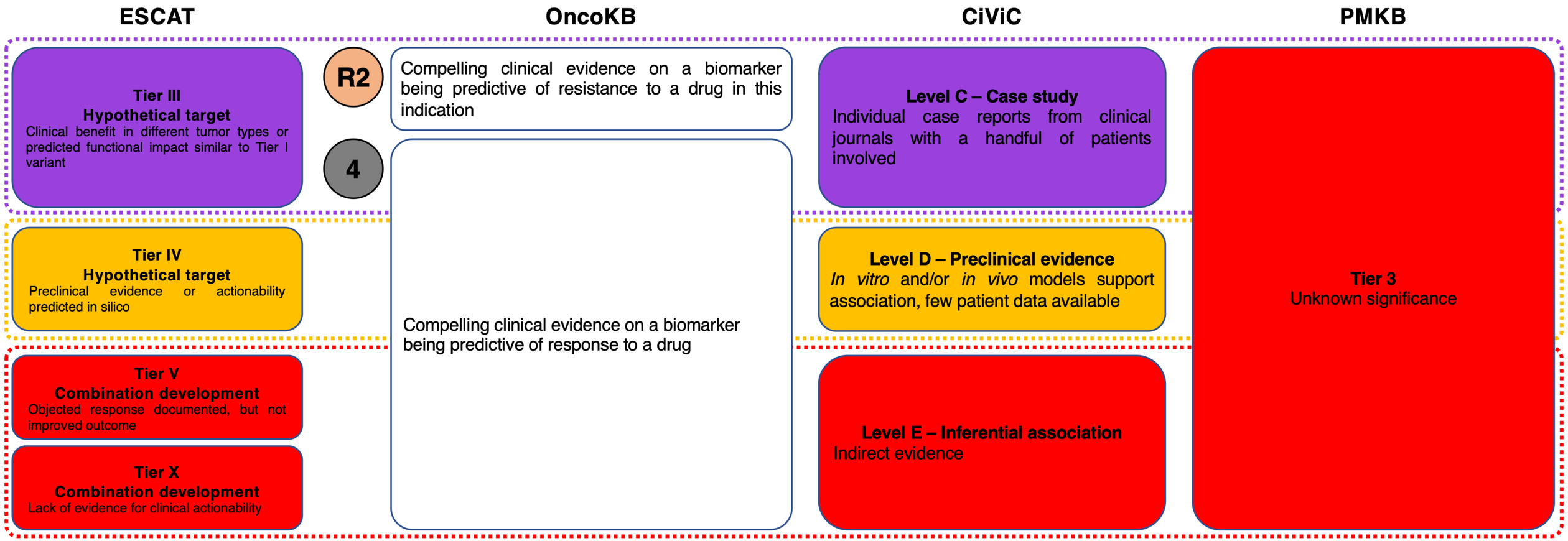
## The ESCAT classification

| ESCAT | OncoKB | | CiViC | PMKB |
|---|---|---|---|---|
| **Tier I**<br>**Ready for routine use** | 1 | FDA-recognized biomarker predictive of response to FDA-approved drug in this indication | **Level A – Validated association**<br>Proven or consensus association in human medicine, routine use in clinical practice or major clinical trials | **Tier 1**<br>Clinical utility demonstrated; actionable or clinically relevant variants with approved therapeutic indications and implications in specific tumors |
| | 2 | Standard of care biomarker predictive of response to FDA-approved drug in this indication | | |
| | R1 | Standard of care biomarker predictive of resistance to FDA-approved drug in this indication | | |
| **Tier II**<br>**Investigational therapeutic option** | 3A | Compelling clinical evidence on a biomarker being predictive of response to a drug in this indication | **Level B – Clinical evidence**<br>Clinical trial or other primary patient data support association; functional data may also be available | **Tier 2**<br>Clinical utility with potential diagnostic, prognostic or therapeutic implications in a specific tumor or with approved indications in other tumor types; novel variants in genes with known therapeutic implications |
| | 3B | Standard of care or investigational biomarker predictive of response to FDA-approved drug in other indication | | |

Pastò B, Buzzati G, Schettino C, in preparation

# How to translate all of this to the clinic?

## The ESCAT classification

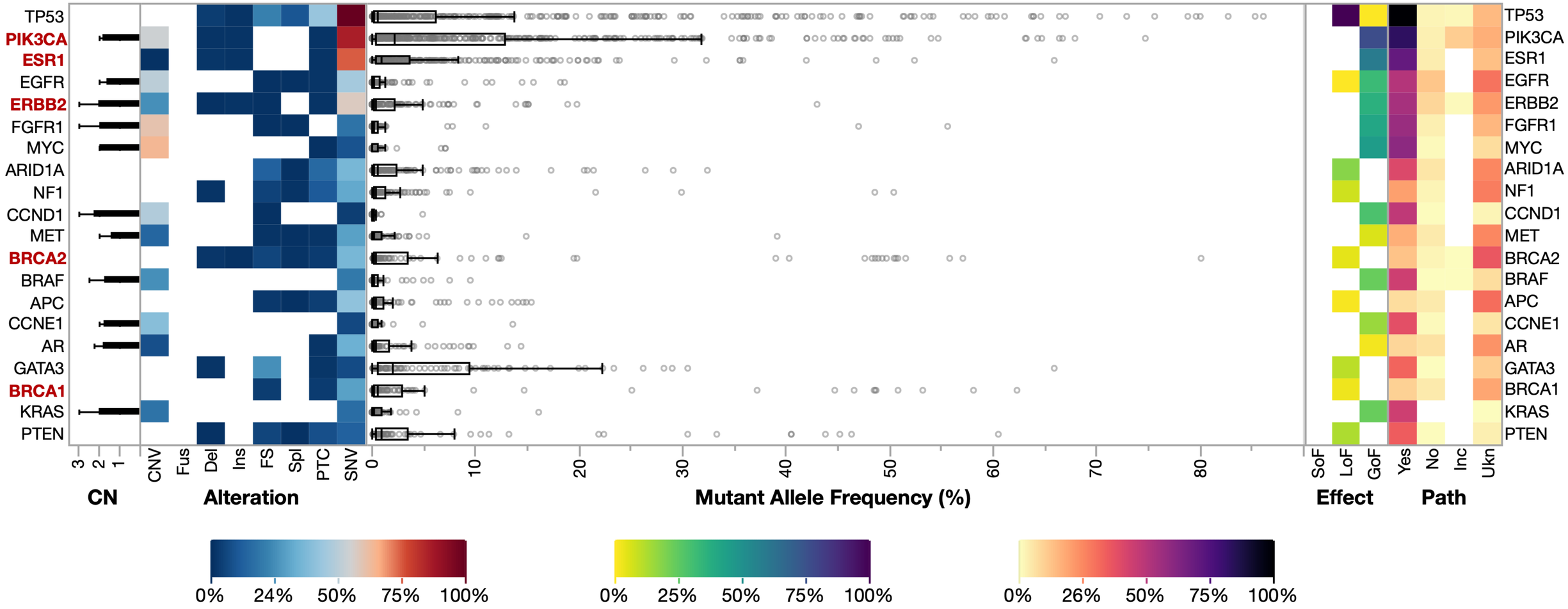



Pastò B, Buzzati G, Schettino C, in preparation

Do we have any ESCAT tier I/II in **breast cancer**?

# Do we have any ESCAT tier I/II in breast cancer?

Apparently all over the place

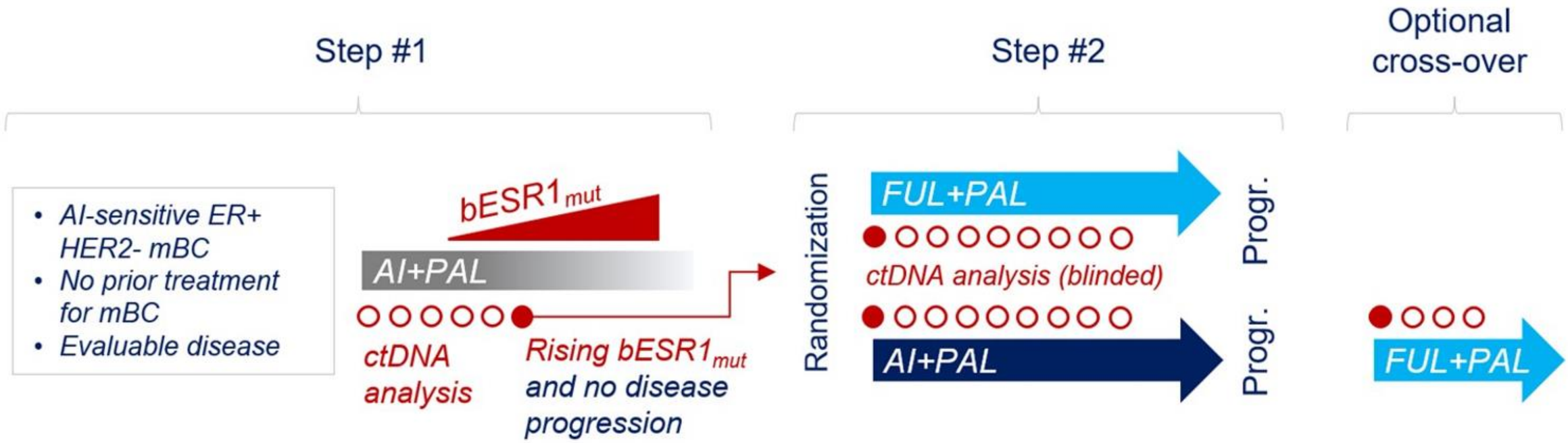



Gerratana L, Davis AA, Velimirovic M, et al. *JCO Precis Oncol*, 2023

*ESR1* between **resistance** and **monitoring**

# In the previous episode

## The PADA-1 design




## PADA-1

**Phase 3 trial to evaluate the utility of monitoring the onset of ESR1mut in cell-free DNA of patients receivi**

**Included pts had no prior therapy for MBC and no overt resistance to AI.**

Cabel L, Delaloge S, Hardy-Bessard A-C, et al. *J Clin Oncol*, 2023; doi:10.1200/JCO.2023.41.16_suppl.1002

# The PADA-1 design

## Updated PFS results - primary endpoint

**N= 1,017 pts enrolled in step #1**

**N= 283 pts with a rising *bESR1*$_{mut}$**

while the study was ongoing

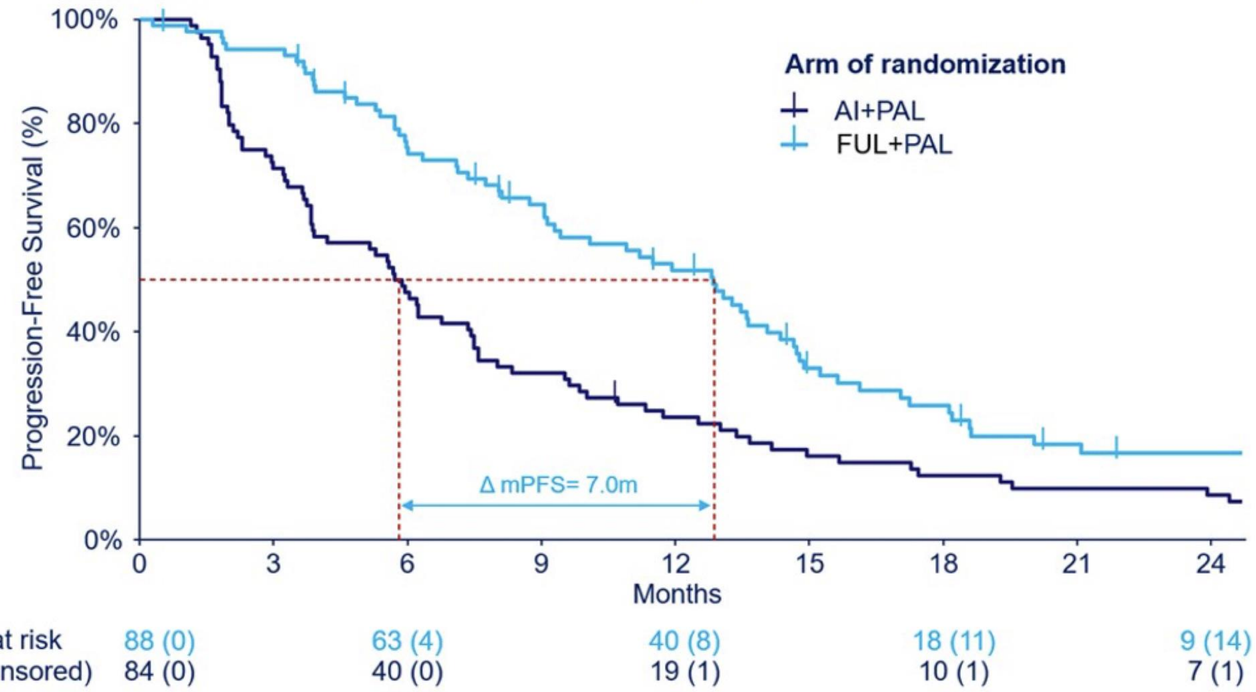
**N= 172 pts randomized**

- N= 88 pts allocated to FUL+PAL
- N= 84 pts allocated to AI+PAL

Data cut-off: June 21, 2022

Median FU from randomization: 28.2 months; N= 152 PFS events (89% maturity)

**Progression-Free Survival, from randomization**




**FUL+PAL mPFS: 12.8 months**, 95%CI [9.3;14.7]

**AI+PAL mPFS: 5.8 months**, 95%CI [3.9;7.5]

**PFS HR= 0.54 [0.38;0.75]**

**Optional cross-over (N=49 patients)**

mPFS: 3.5 months, 95%CI [2.4;5.4]

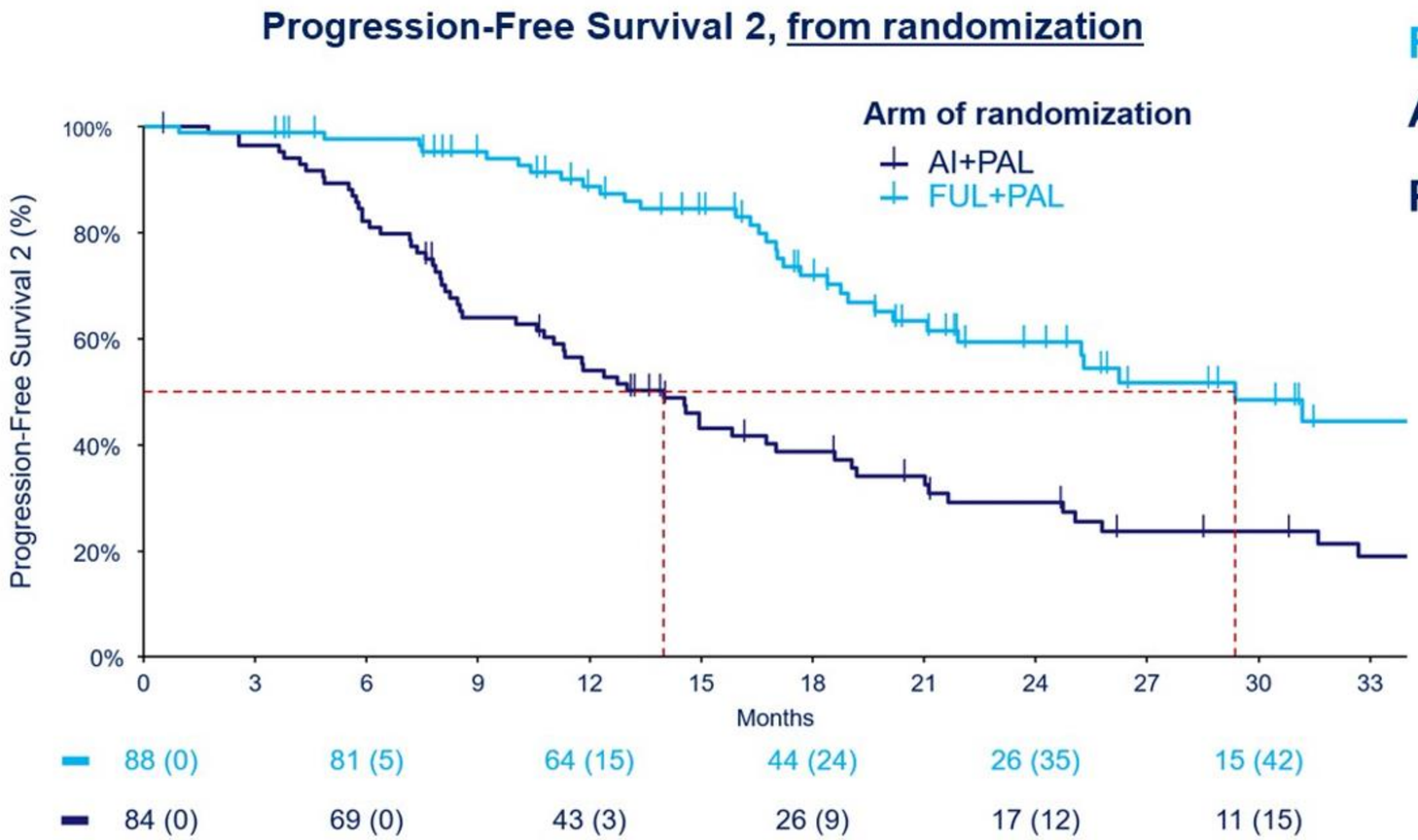
| **2021 analysis** [2] |
|---|
| N=134 events |
| 11.9 months |
| 5.7 months |
| 0.61 |
| 3.5 months |

Cabel L, Delaloge S, Hardy-Bessard A-C, et al. *J Clin Oncol*, 2023; doi:10.1200/JCO.2023.41.16_suppl.1002

# Are we really impressed?

## PFS2 results - secondary endpoint

Data cut-off: June 21, 2022 N= 93 PFS2 events (54% maturity) PFS2: time to 2nd progression or death in both arms




**FUL+PAL mPFS2: 29.4 months**, 95%CI [21.9;NR]

**AI+PAL mPFS2: 14.0 months**, 95%CI [11.0;18.6]

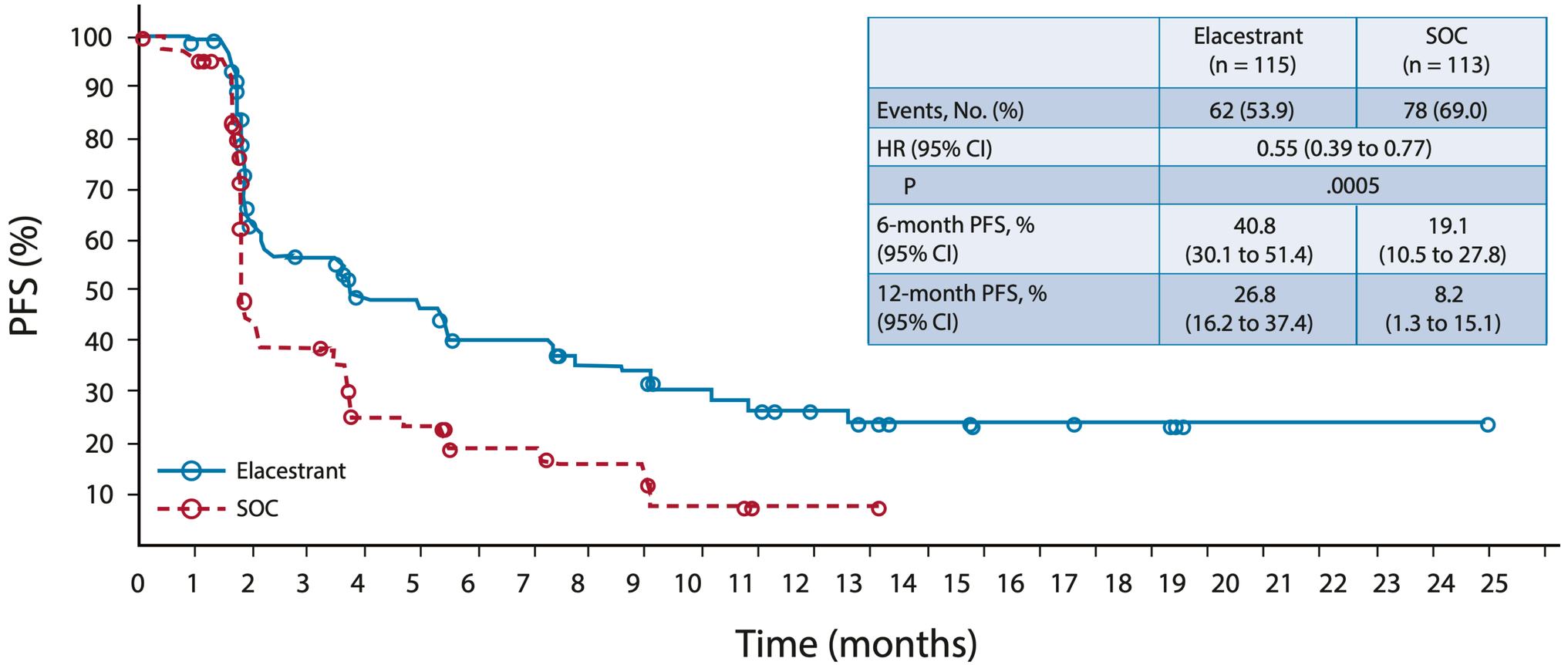
**PFS2 HR= 0.37 [0.24;0.56]**

Cabel L, Delaloge S, Hardy-Bessard A-C, et al. *J Clin Oncol*, 2023; doi:10.1200/JCO.2023.41.16_suppl.1002

# From resistance to selection: **a new life** for *ESR1*

# The Phase III trial EMERALD

## Progression Free Survival in the ESR1 mutated subgroup




| | Elacestrant (n = 115) | SOC (n = 113) |
|---|---|---|
| Events, No. (%) | 62 (53.9) | 78 (69.0) |
| HR (95% CI) | 0.55 (0.39 to 0.77) | |
| P | .0005 | |
| 6-month PFS, % (95% CI) | 40.8 (30.1 to 51.4) | 19.1 (10.5 to 27.8) |
| 12-month PFS, % (95% CI) | 26.8 (16.2 to 37.4) | 8.2 (1.3 to 15.1) |

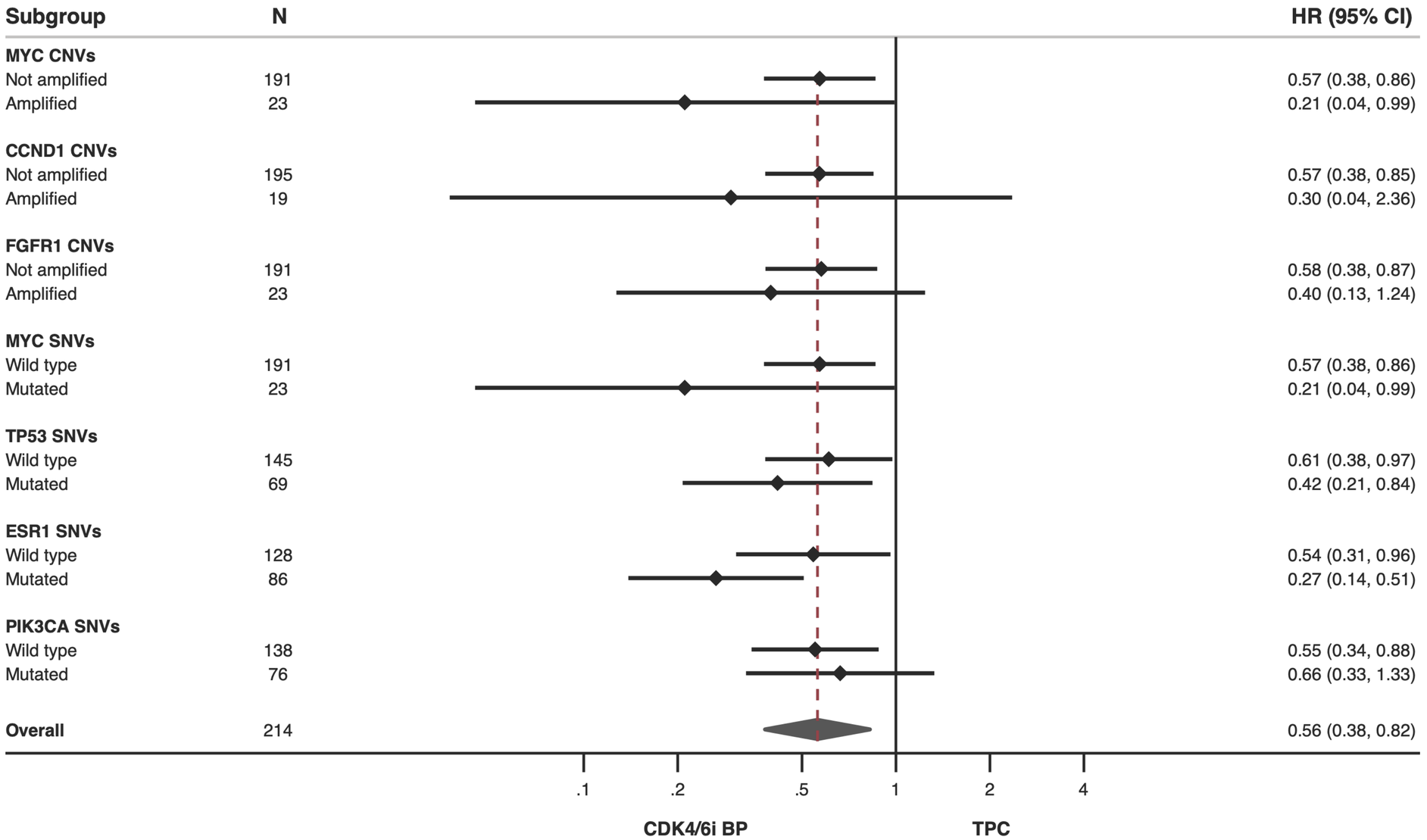
No. at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elacestrant | 115 | 105 | 54 | 46 | 35 | 33 | 26 | 26 | 21 | 20 | 16 | 14 | 11 | 9 | 7 | 5 | 5 | 4 | 4 | 1 | 1 | 1 | 1 | 1 | 0 |
| SOC | 113 | 99 | 39 | 34 | 19 | 18 | 12 | 12 | 9 | 9 | 4 | 1 | 1 | 1 | 0 | | | | | | | | | | |

Bidard FC, Kaklamani VG, Neven P, et al. *J Clin Oncol*, 2022; doi:10.1200/JCO.22.00338

# CDK4/6i BP: can liquid biopsy give us a hint?

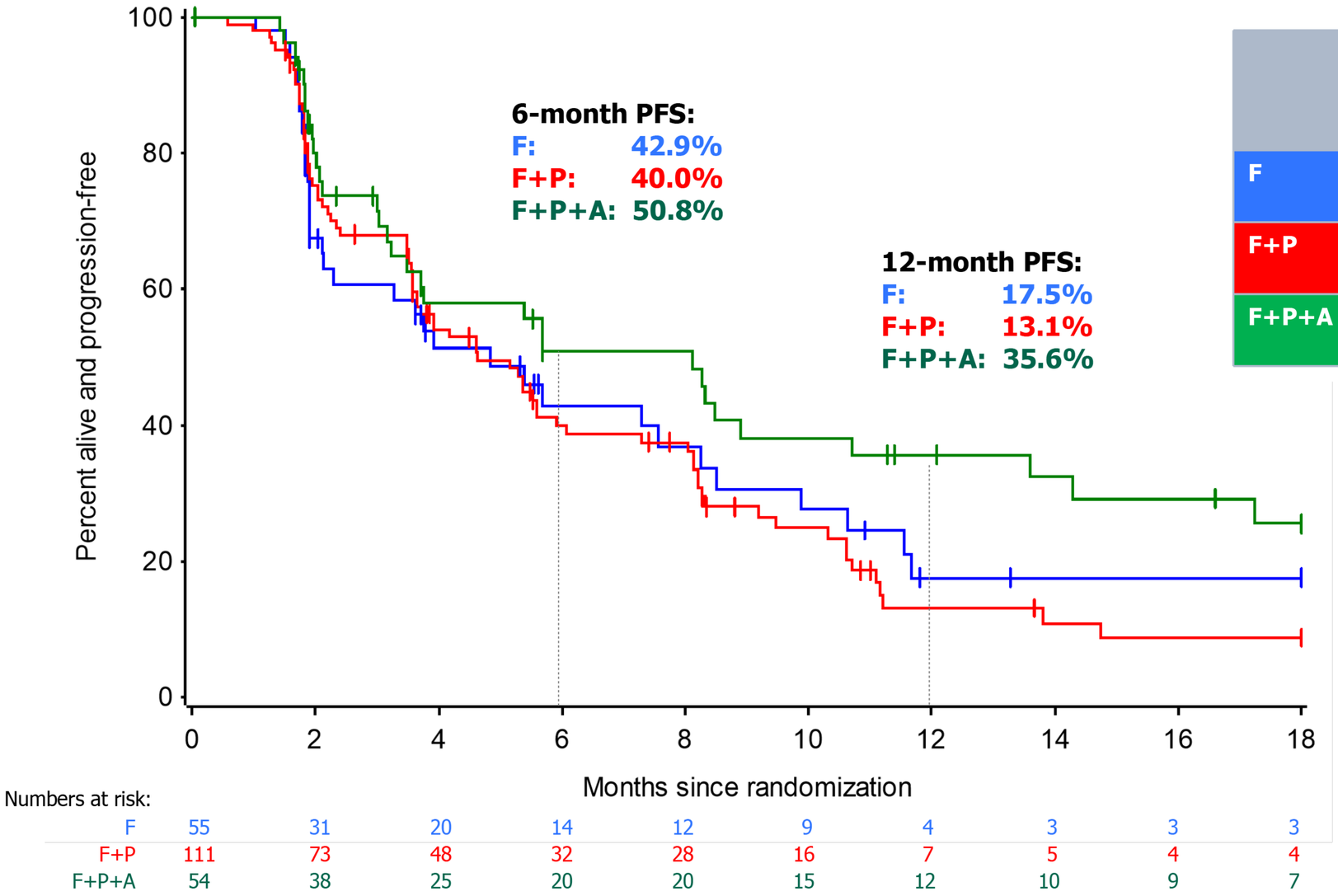
## CDK4/6i beyond progression: subgroup analysis, PFS




Gerratana L, Davis AA, Velimirovic M, et al. *JCO Precis Oncol*, 2023; doi:10. 1200/PO.22.00531

# CDK4/6i BP: can liquid biopsy give us a hint?

## The PACE study: all comers, PFS



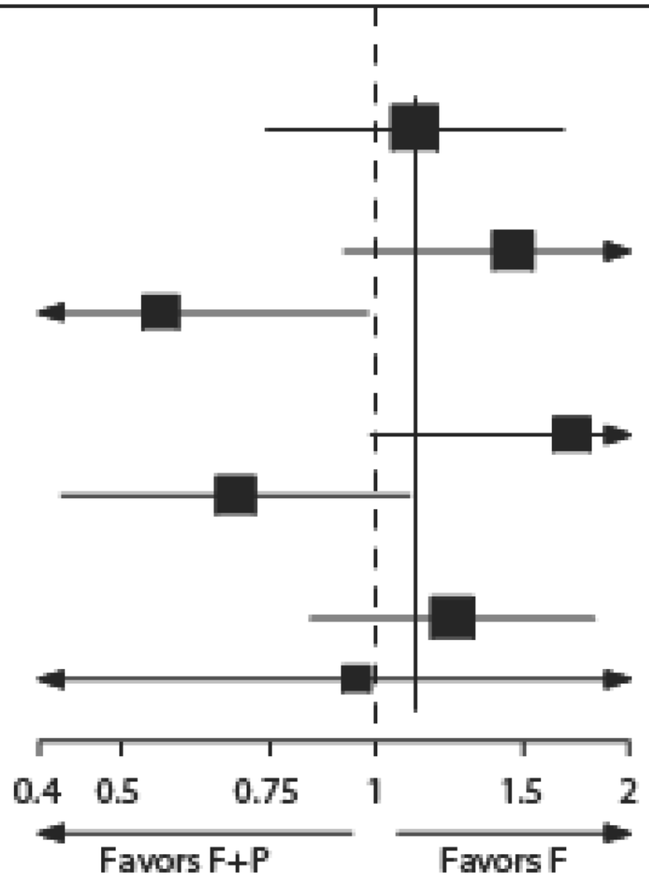

| | Pts | PFS Events | Median PFS, mo (90% CI) | HR vs F (90% CI) | P-value |
|---|---|---|---|---|---|
| F | 55 | 34 | **4.8** (2.1, 8.2) | -- | -- |
| F+P | 111 | 79 | **4.6** (3.6, 5.9) | 1.11 (0.74-1.66) | P=0.62 |
| F+P+A | 54 | 35 | **8.1** (3.2, 10.7) | 0.75 (0.47-1.20) | P=0.23 |

Mayer EL, Ren Y, Wagle N, et al. *Cancer Res*, 2023; doi:10.1158/1538-7445.SABCS22-GS3-06

# The PACE study

## Subgroup analysis according to PIK3CA, ESR1 and RB1 status

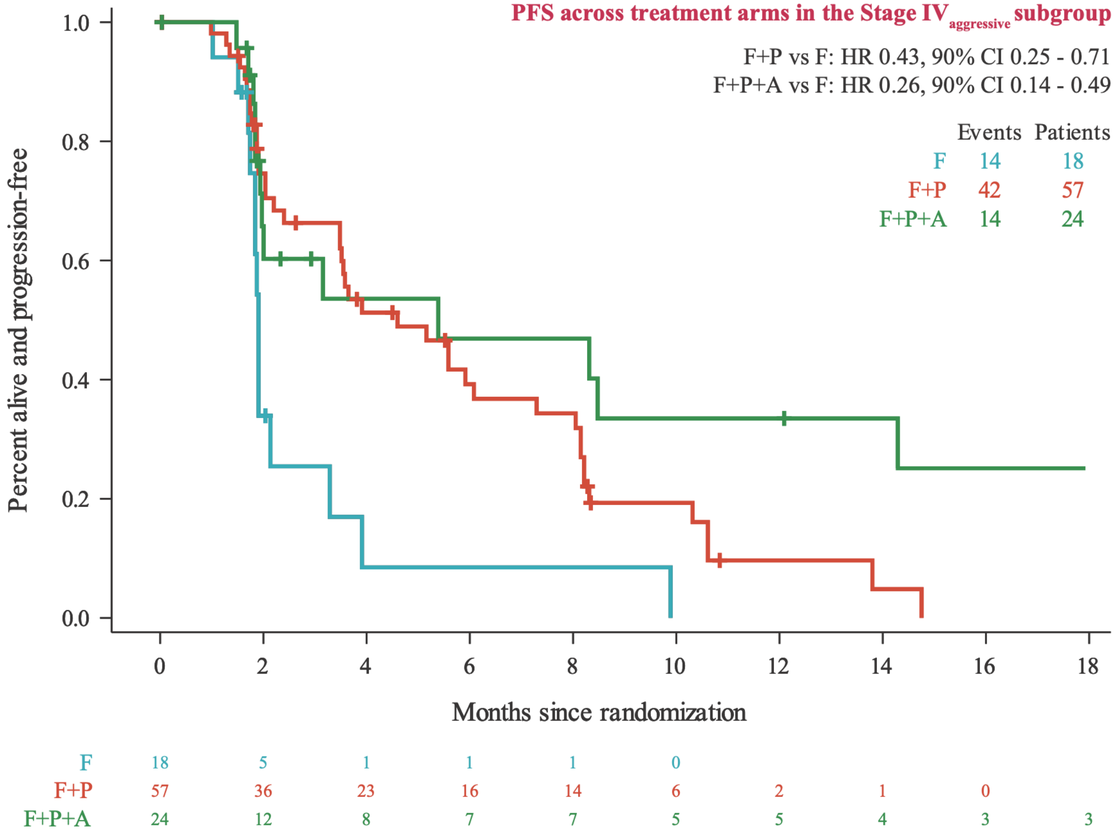
| Subgroup | F+P Events | F+P Patients | F Events | F Patients | Hazard Ratio (90% CI) |
|---|---|---|---|---|---|
| Progression-free survival | | | | | |
| All Patients | 79 | 111 | 34 | 55 | 1.11 (0.74-1.66) |
| Any PIK3CA mutation | | | | | |
| WT | 45 | 63 | 18 | 36 | 1.44 (0.91-2.29) |
| Mutation | 29 | 39 | 12 | 12 | 0.56 (0.32-0.99) |
| Any ESR1 mutation | | | | | |
| WT | 31 | 47 | 13 | 25 | 1.70 (0.99-2.95) |
| Mutation | 43 | 55 | 17 | 23 | 0.68 (0.42-1.09) |
| Any Rb1 mutation | | | | | |
| WT | 67 | 92 | 25 | 42 | 1.23 (0.83-1.81) |
| Mutation | 7 | 10 | 5 | 6 | 0.95 (0.36-2.49) |

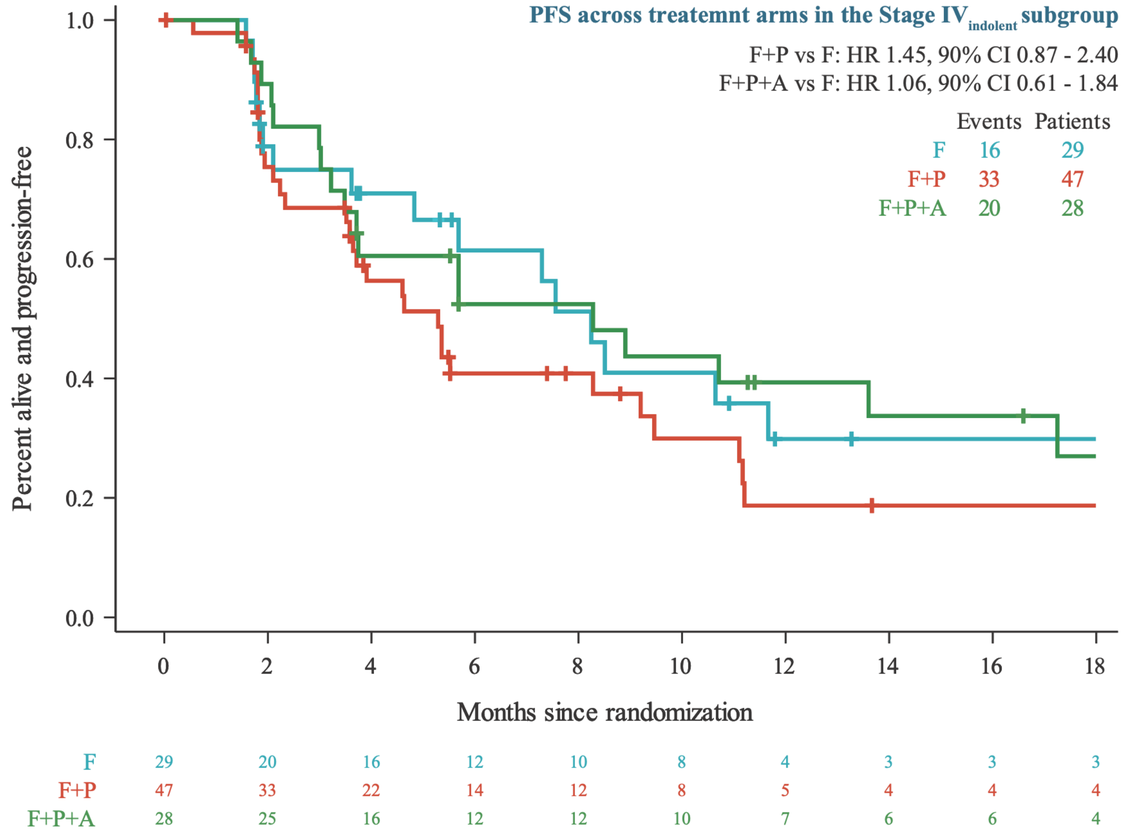



Mayer EL, Ren Y, Wagle N, et al. *Cancer Res*, 2023; doi:10.1158/1538-7445.SABCS22-GS3-06

# The PACE study

## Subgroup analysis according to CTCs staging

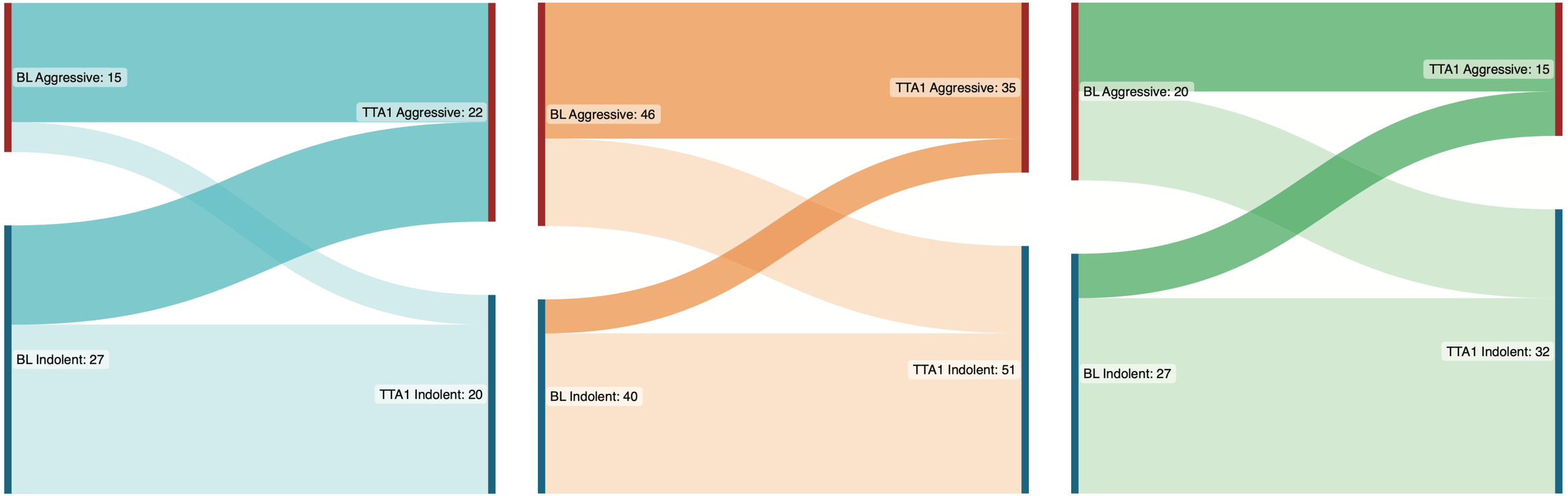



Gerratana L, Ren Y, Reduzzi C, et al. *J Clin Oncol*, 2023; doi:10.1200/JCO.2023.41.16_suppl.1059

# The PACE study

## CTCs dynamics across treatment arms

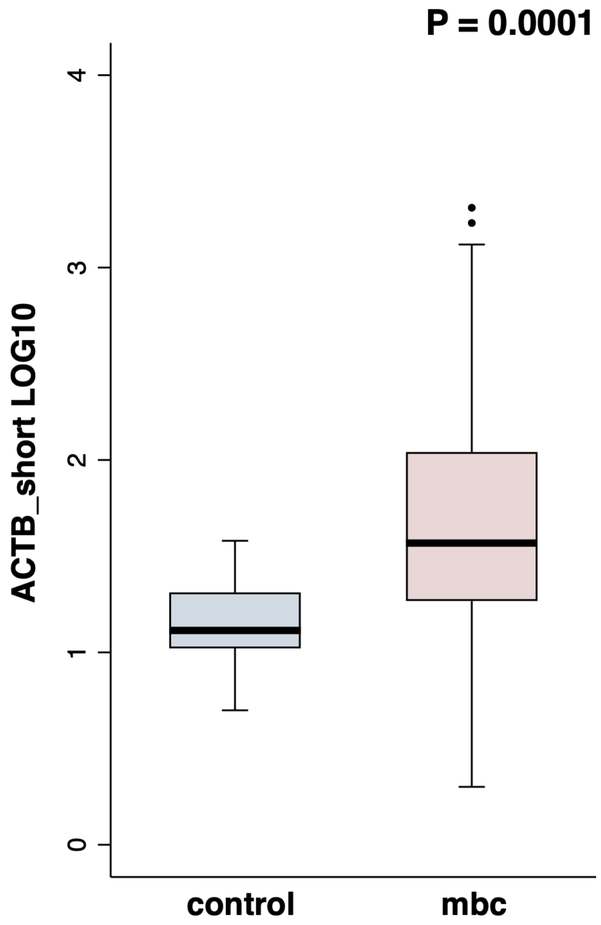


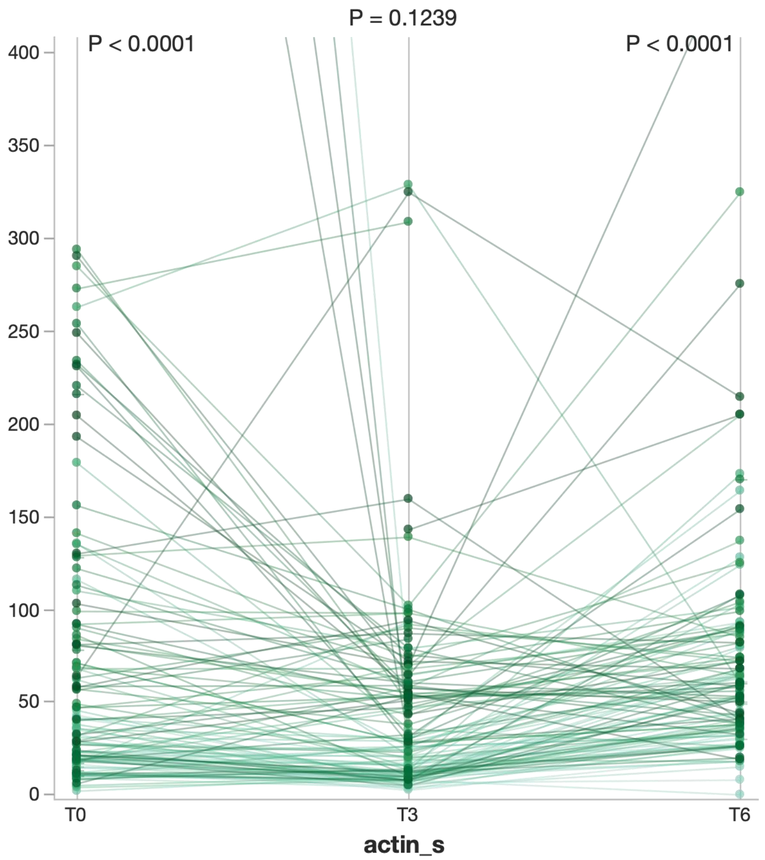

Gerratana L, Ren Y, Reduzzi C, et al. *J Clin Oncol*, 2023; doi:10.1200/JCO.2023.41.16_suppl.1059

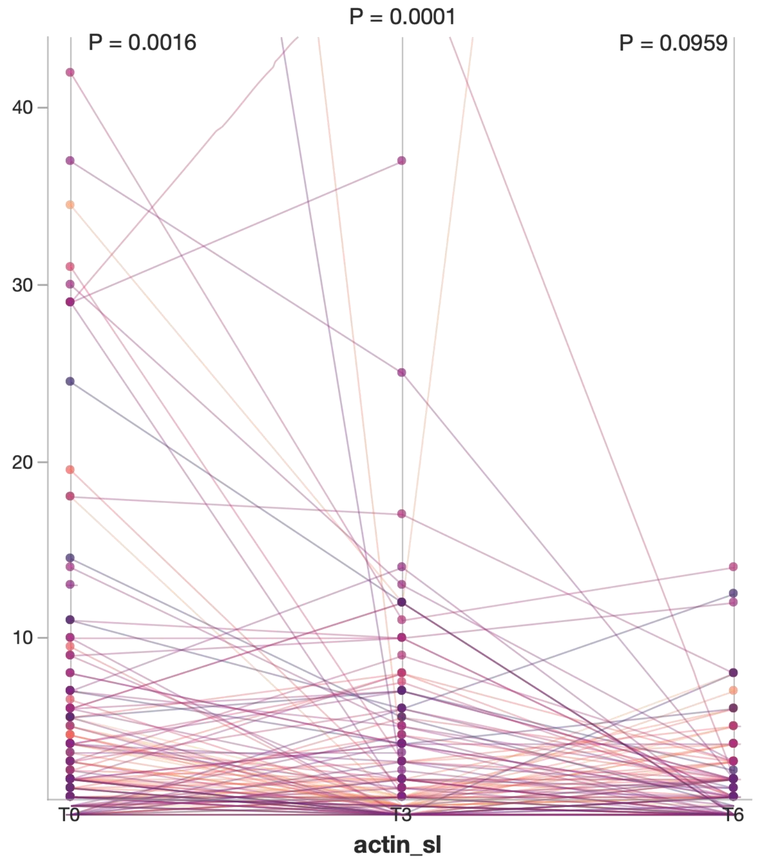
Fragmentomics: **following** the trail of crumbs

# Fragmentomics: following the trail of crumbs

## Metastatic breast cancer, a MAGNETIC ground proof



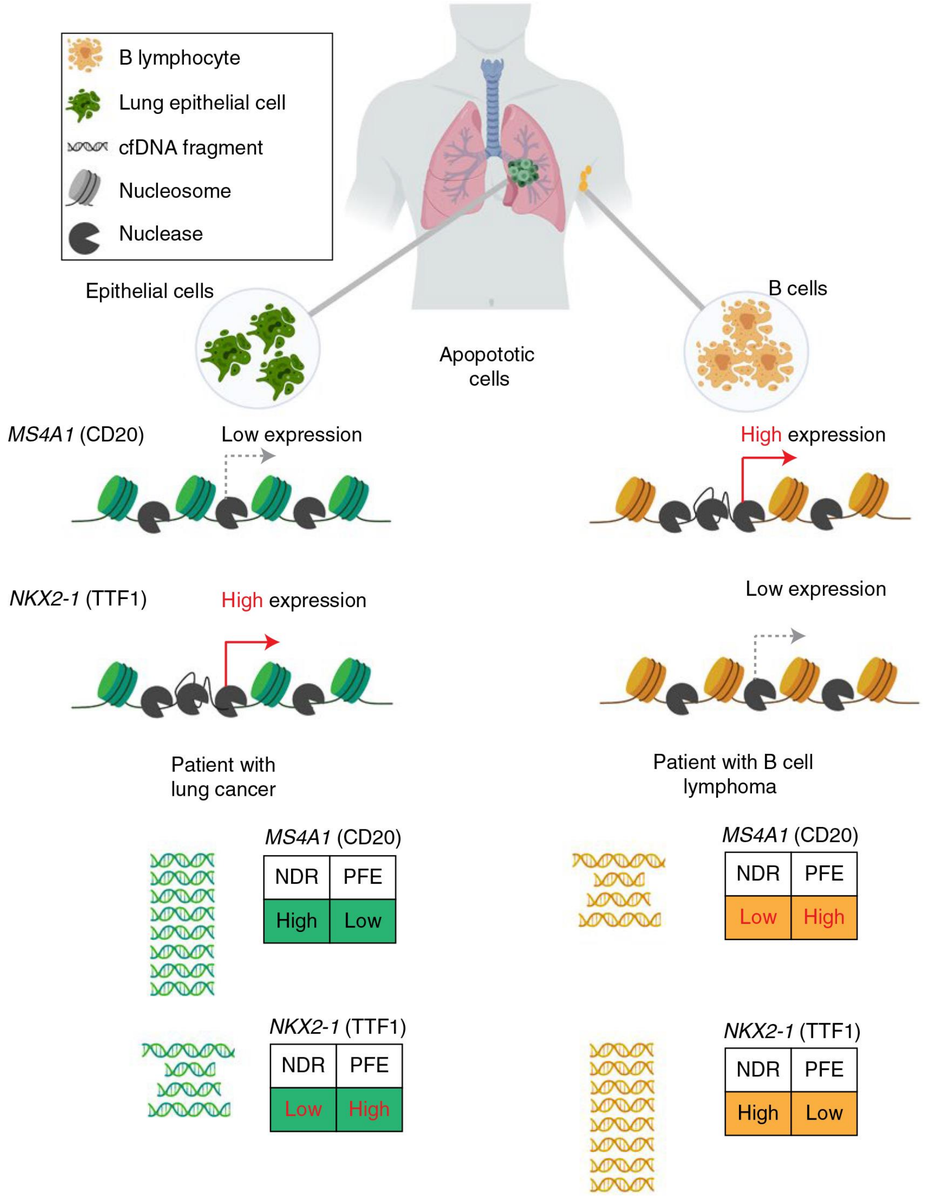



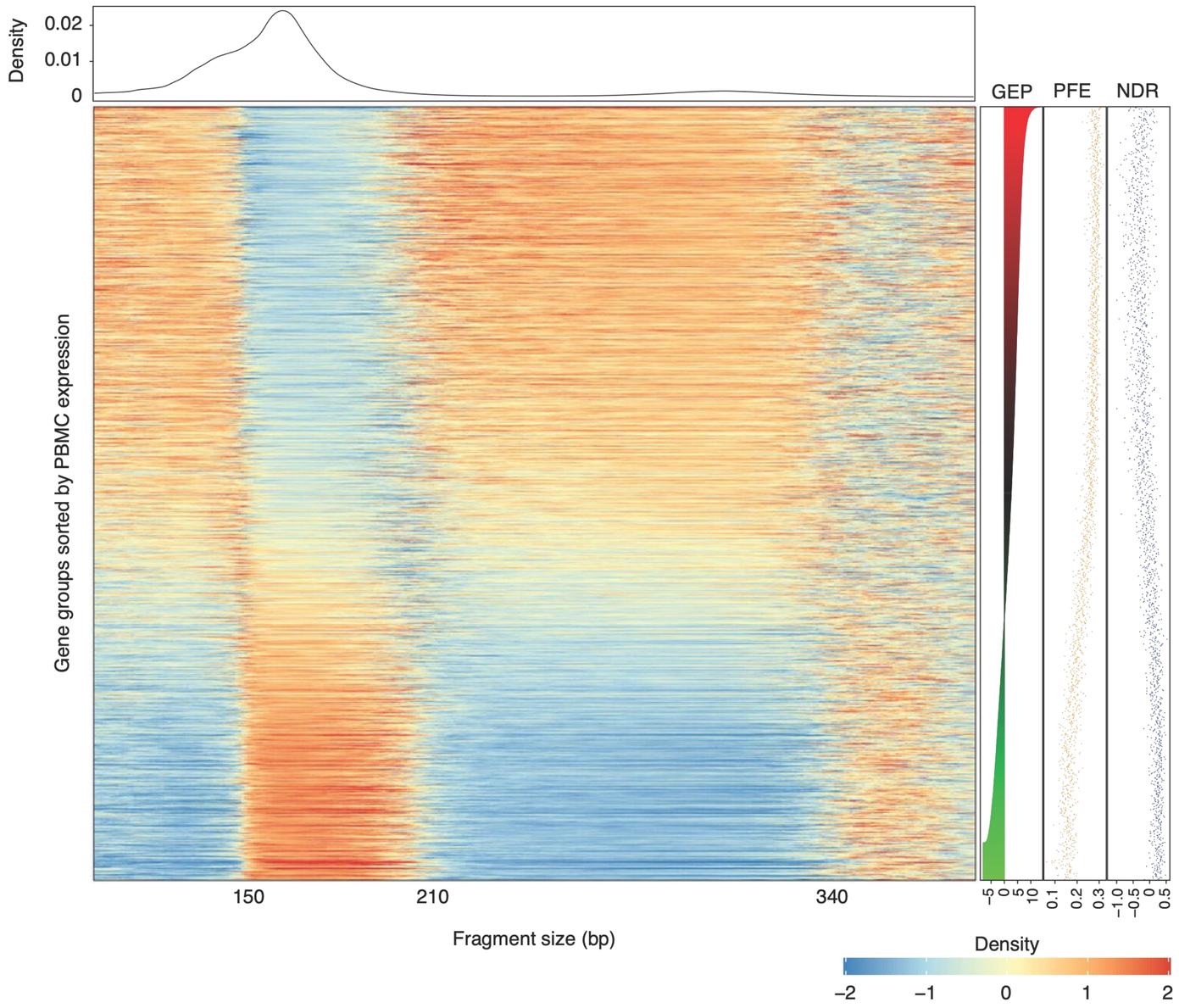




Franzoni A, Foffano L, Molteni E, et al. in submission

# An EPIC(seq) lighter leap

## Inferring gene expression from cell-free DNA fragmentation profiles




Esfahani MS, Hamilton EG, Mehrmohamadi M, et al. *Nat Biotechnol*, 2022; doi:10.1038/s41587-022-01222-4

# Wrapping up

Brace yourself, Winter Has Come

1

## Don’t miss the technology for the methodology

Expect a higher benefit with solid biomarkers

Breast Cancer has ESCAT I/II mutations that soon will be part of our algorithms

2

## Extended and targeted characterizations are different

Targeted panels will be recommended as new, mutation driven, drugs will be introduced in the clinic

Extended panels should be used in clinical trials only to select future ESCAT I/II mutations or MTBs

3

## The world as we know it will end up soon

Alternative resistance mechanisms are emerging as new agents are being introduced to the clinic

Such complexity can only be mastered with AI algorithms able to detect multi-feature patterns

Scan to **Link**

# Thank you


lorenzo.gerratana@uniud.it

@LGerratana

liquidbio.altervista.org

lorenzo.gerratana@cro.it

@LGerratana@med-mastodon.com

@gerratana


5 PER MILLE CRO

LILT
LEGA ITALIANA PER LA LOTTA CONTRO I TUMORI
prevenire è vivere

Ministero della Salute

GIM GRUPPO ITALIANO MAMMELLA

UNIVERSITY OF UDINE
hic sunt futura

The Liquid biopsy Research Team

CRO AVIANO

Cristofanilli CTC LAB