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The Liquid biopsy Research Group

Carcinoma mammario metastatico: quali novità? - Roma, 11 ottobre 2024

Liquid biopsy and breast cancer

What is the evidence?

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The Liquid Biopsy Research Group (LBRG)

Precision Medicine Academic Consortium (PMAC)

Conflict of Interest Disclosure Statement

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Honoraria: None

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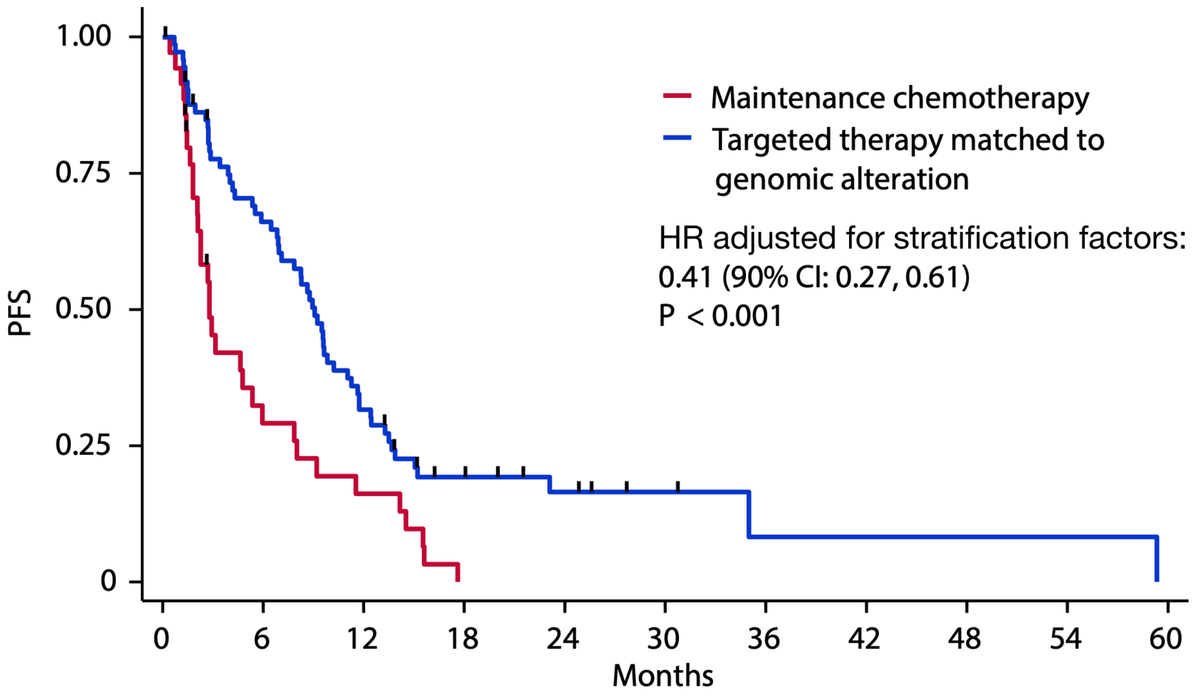
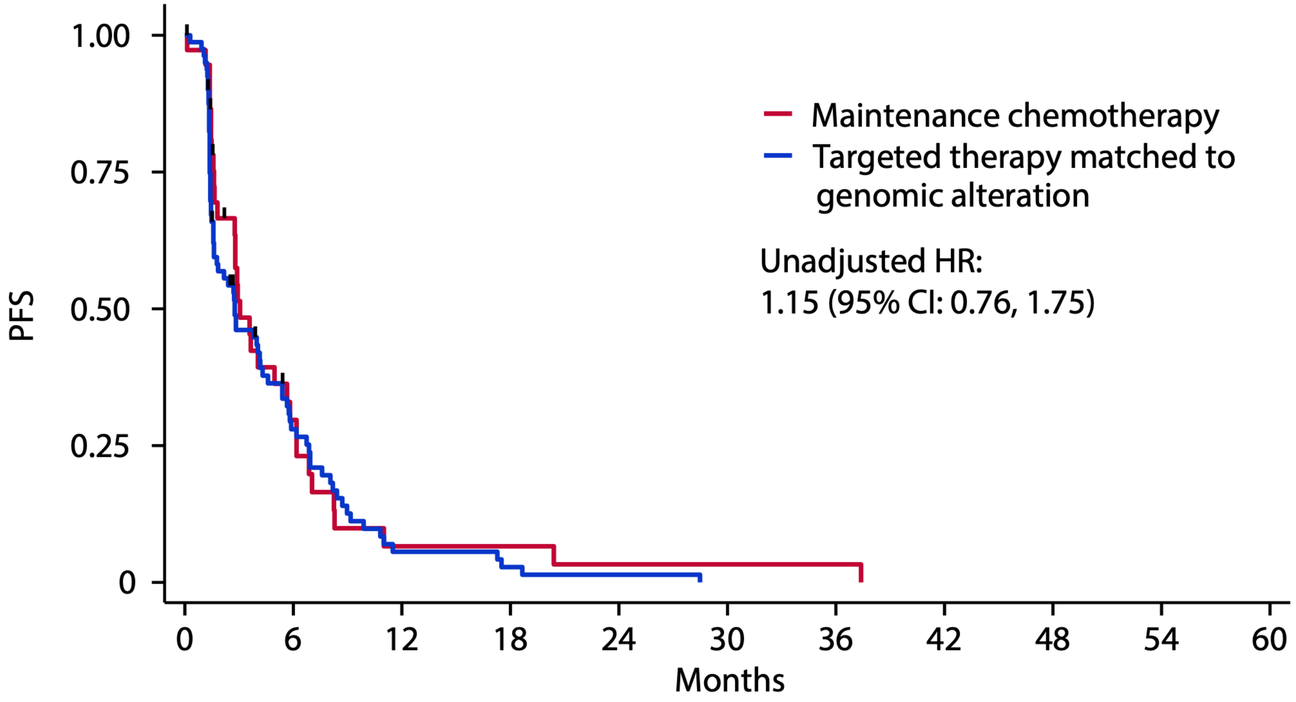
Travel Expenses: Menarini Stemline, Novartis

On the **last episode**

On the last episode

PFS according to ESCAT classification

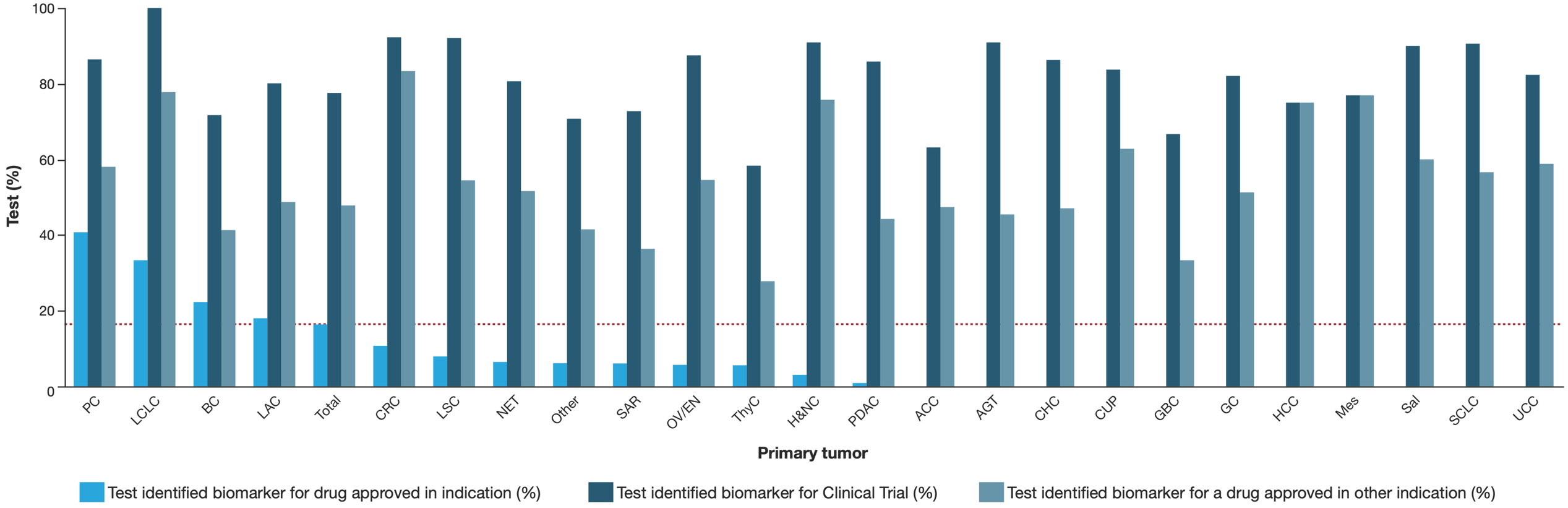




Andre F, Filleron T, Kamal M, et al. *Nature*, 2022; doi:10.1038/s41586-022-05068-3

On the last episode

Incidence of detectable alterations

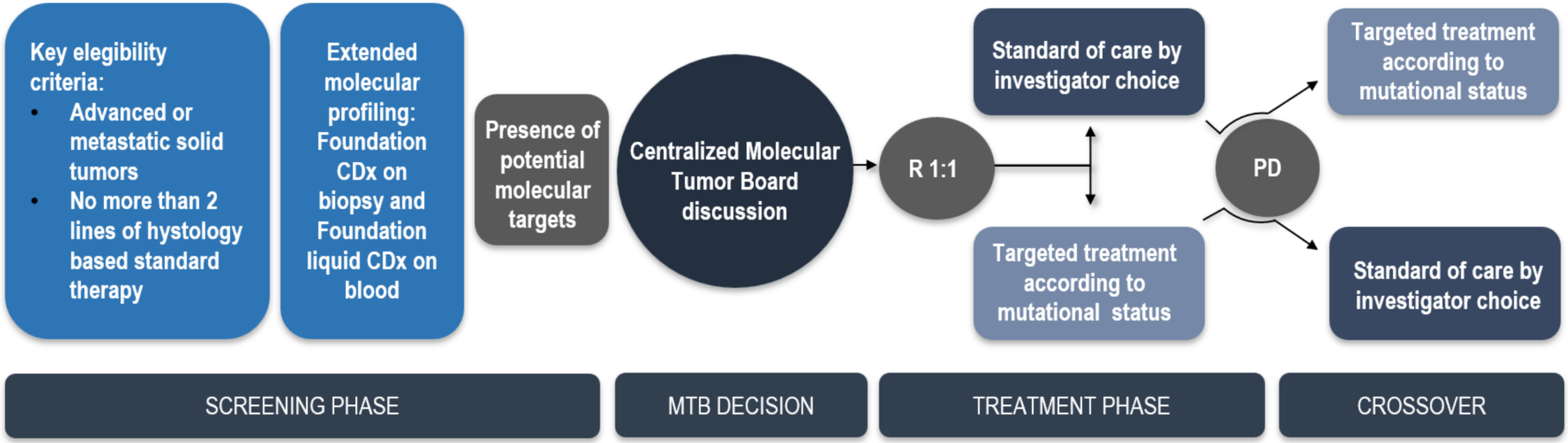


Gerratana L, Movarek M, Wehbe F, et al. *JCO Precis Oncol*, 2022; doi:10.1200/PO.21.00289

But it goes even **further**

But it goes even further

The Rome trial from histology to target



ROME (NCT04591431)

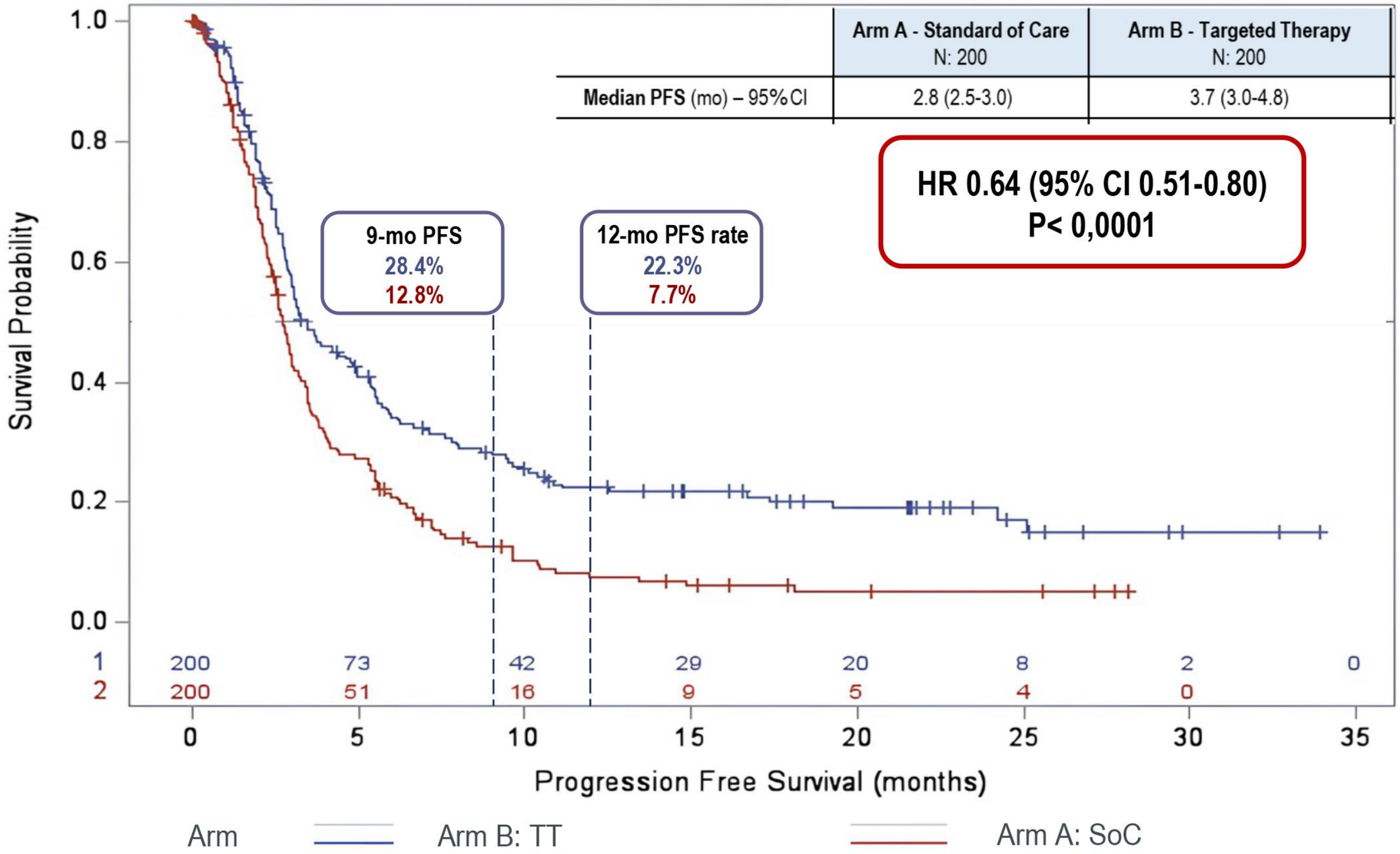
A Randomized, Multi-basket, Phase 2, Multicenter Trial. Following MTB discussion, pts bearing at least one targetable alteration were randomized 1:1 to TT at MTB choice or SoC at investigator choice

Primary Endpoint: ORR **Secondary Endpoint:** PFS, TTF, TTNT, safety profile ,OS

Botticelli A, Scagnoli S, Conte P, et al. Annals of Oncology, 2024; doi:10.1016/j.annonc.2024.08.2245

The Rome trial

Secondary endpoint: PFS in ITT population



Botticelli A, Scagnoli S, Conte P, et al. Annals of Oncology, 2024; doi:10.1016/j.annonc.2024.08.2245

Should we follow the *PIK3CA* north star?

INAVO120

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

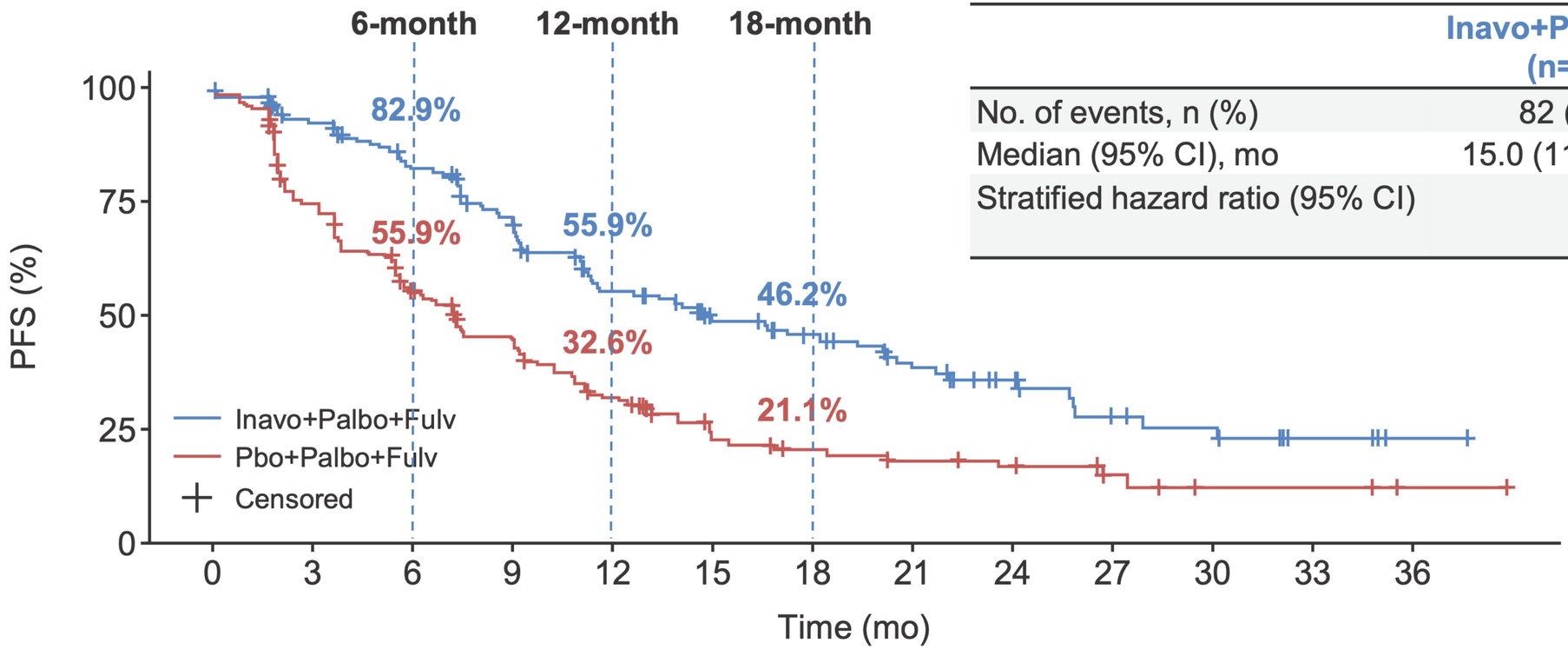
Primary endpoint (investigator-assessed PFS)

Key secondary endpoint (OS)

Jhaveri KL, Im SA, Saura C, et al. General Session 3; SABCS 2023

INAVO120

Primary endpoint: PFS (investigator-assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

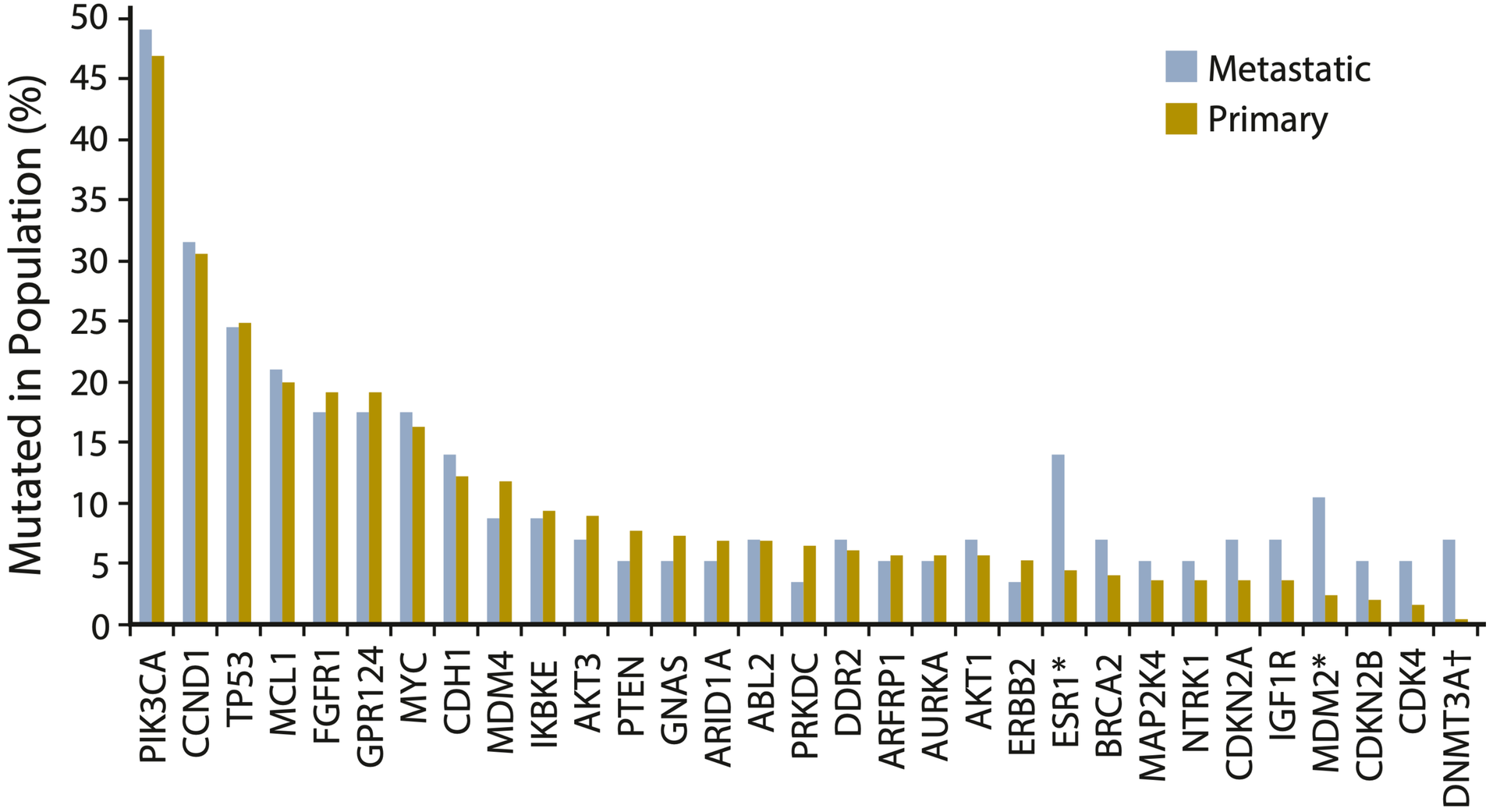
CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

When should we test? It **depends**

What’s the onset of these alterations?

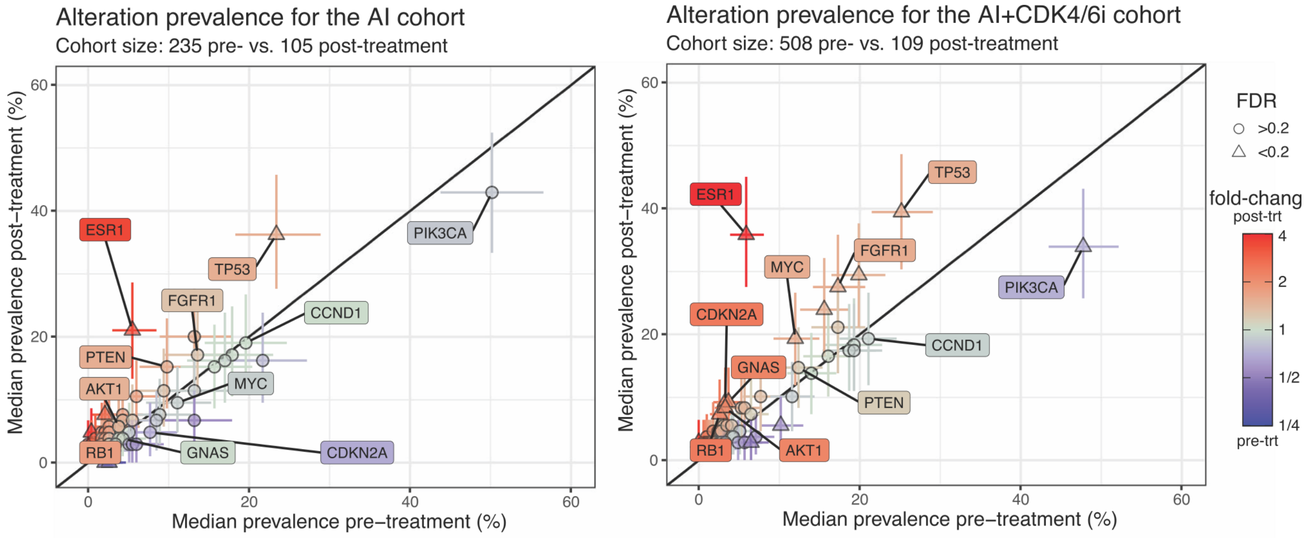
The translational side of the BOLERO trial

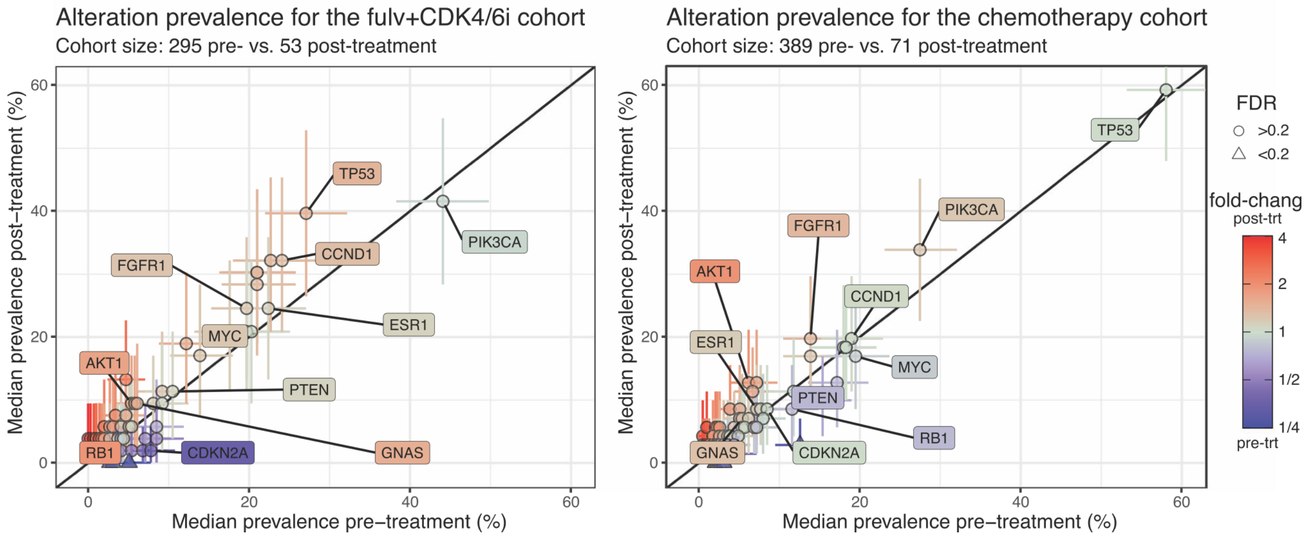


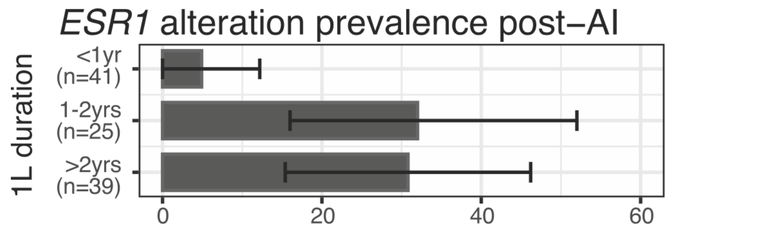
Hortobagyi GN, Chen D, Piccart M, et al. *J Clin Oncol*, 2016; doi:10.1200/JCO.2014.60.1971

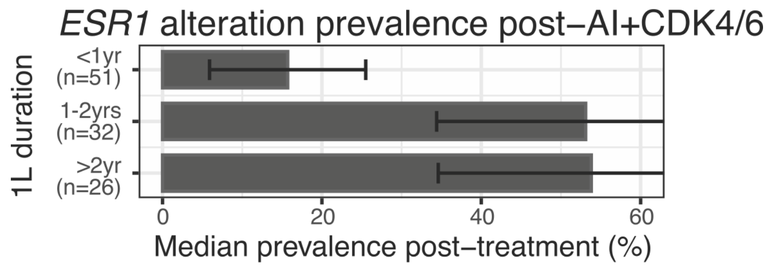
When should we test? It depends

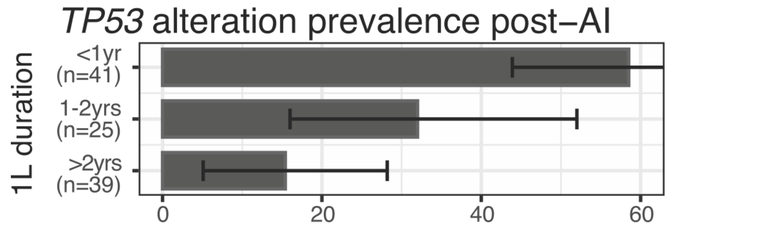
Does treatment impact on tumor evolution?

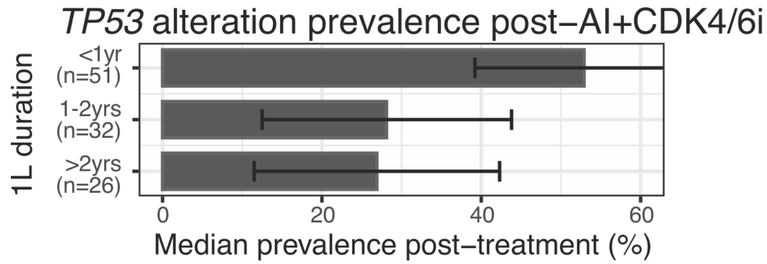








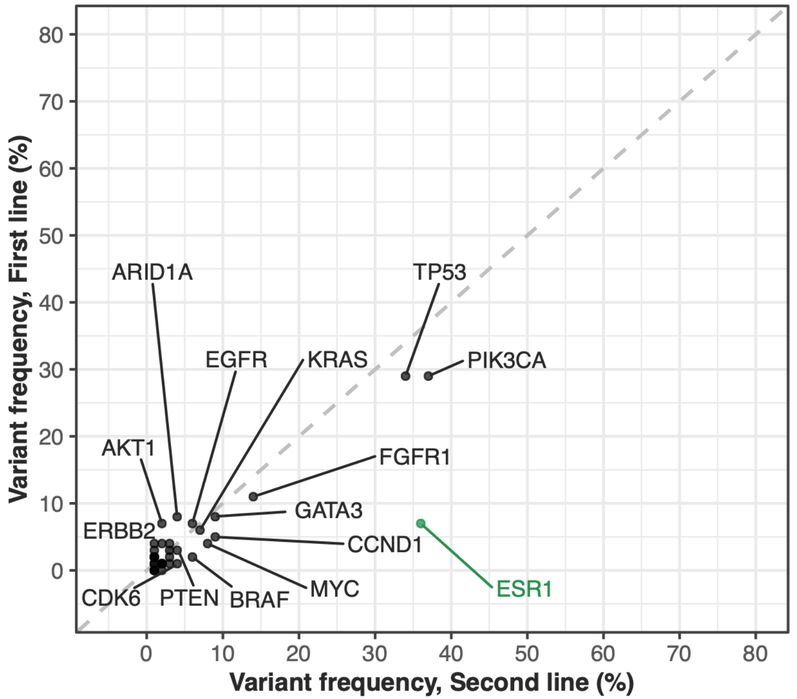


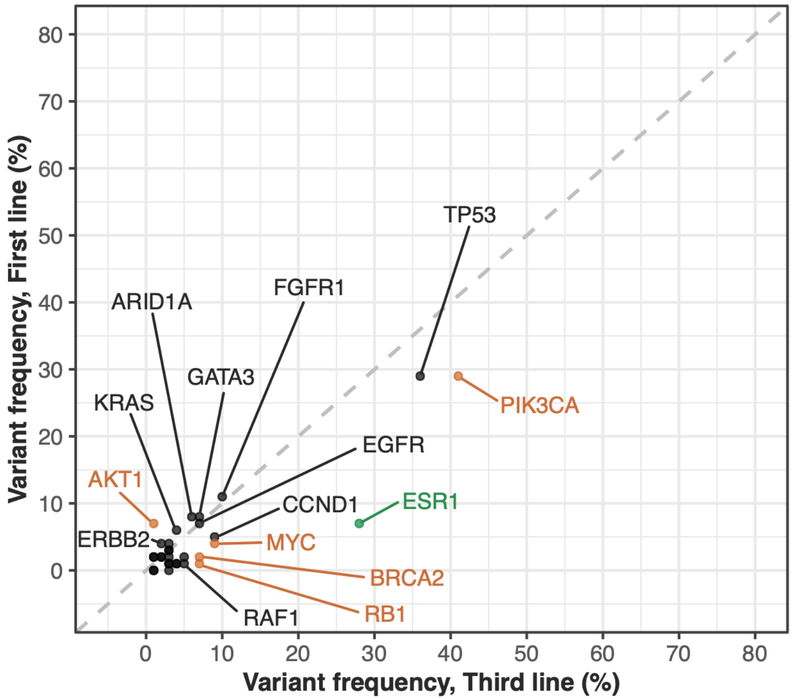


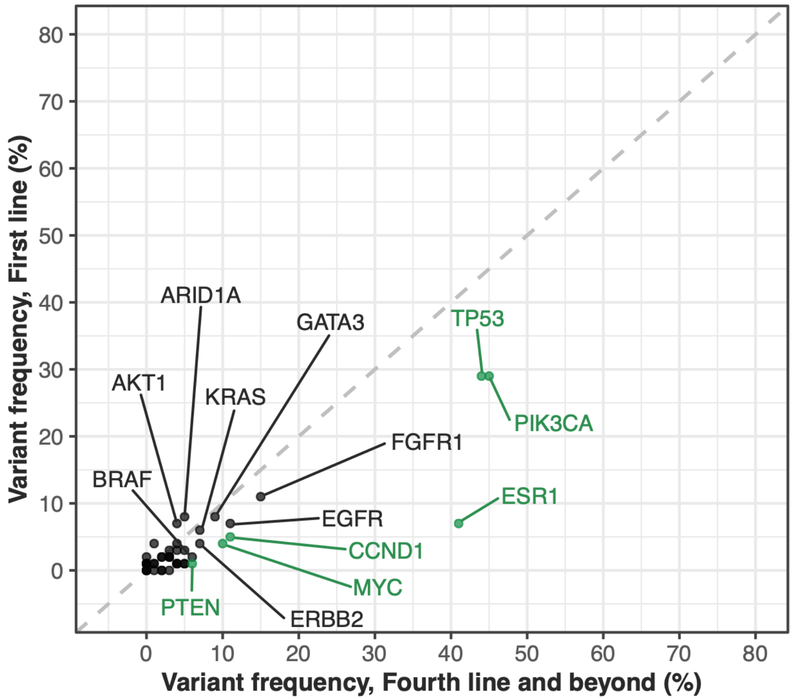
Chaudhary N, Chibly AM, Collier A, et al. *npj Breast Cancer*, 2024; doi:10.1038/s41523-024-00617-7

Does treatment impact on tumor evolution?

The PMAC real world biomarker database





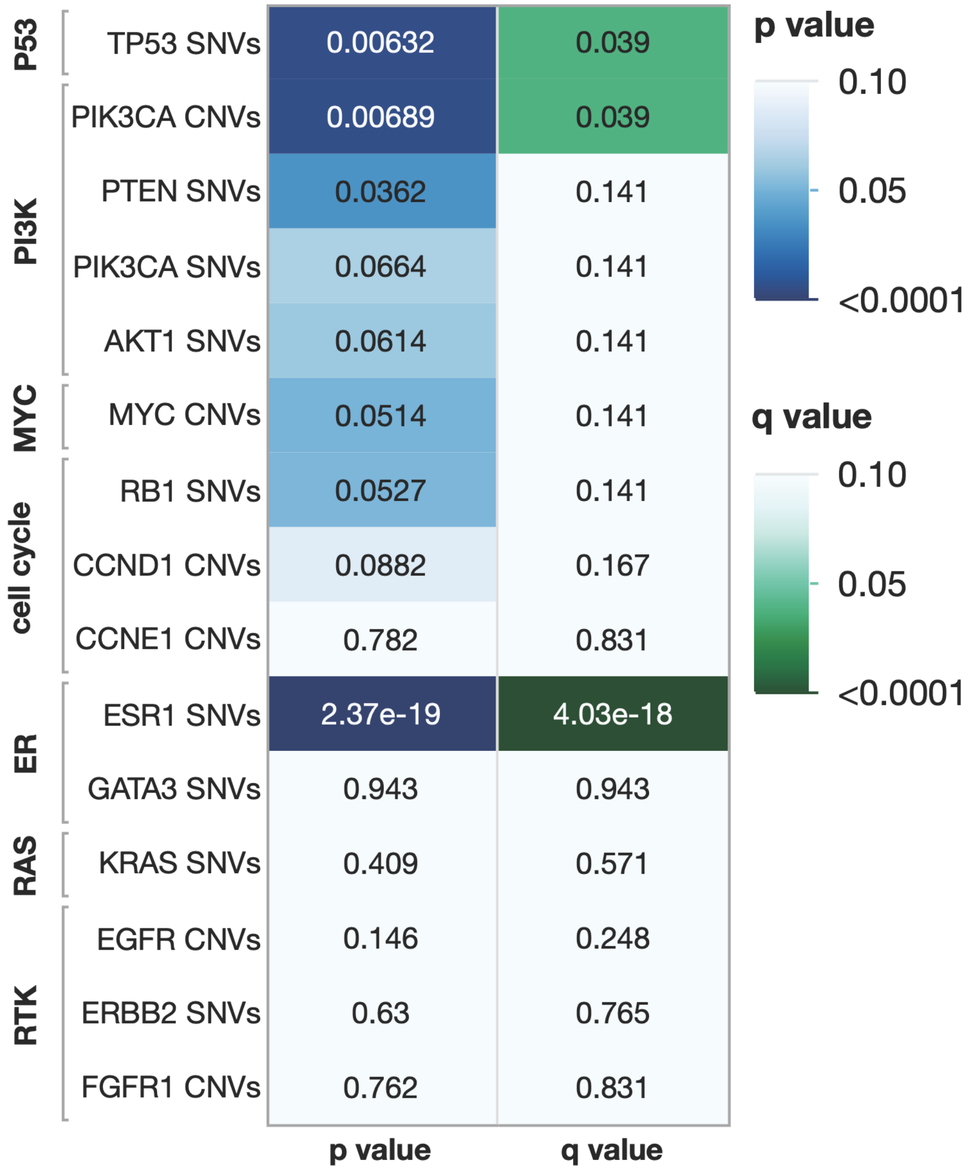


The study analyzed a retrospective cohort of 909 patients with ER pos, HER2 neg MBC within a large multi-center academic consortium

Gerratana L, Davis AA, Gaudio H, Dri A, Reduzzi C, et al. In preparation | Unpublished, do not post

Looking at the big picture: top detectable mutations

Genes significantly changing across lines and their predictors

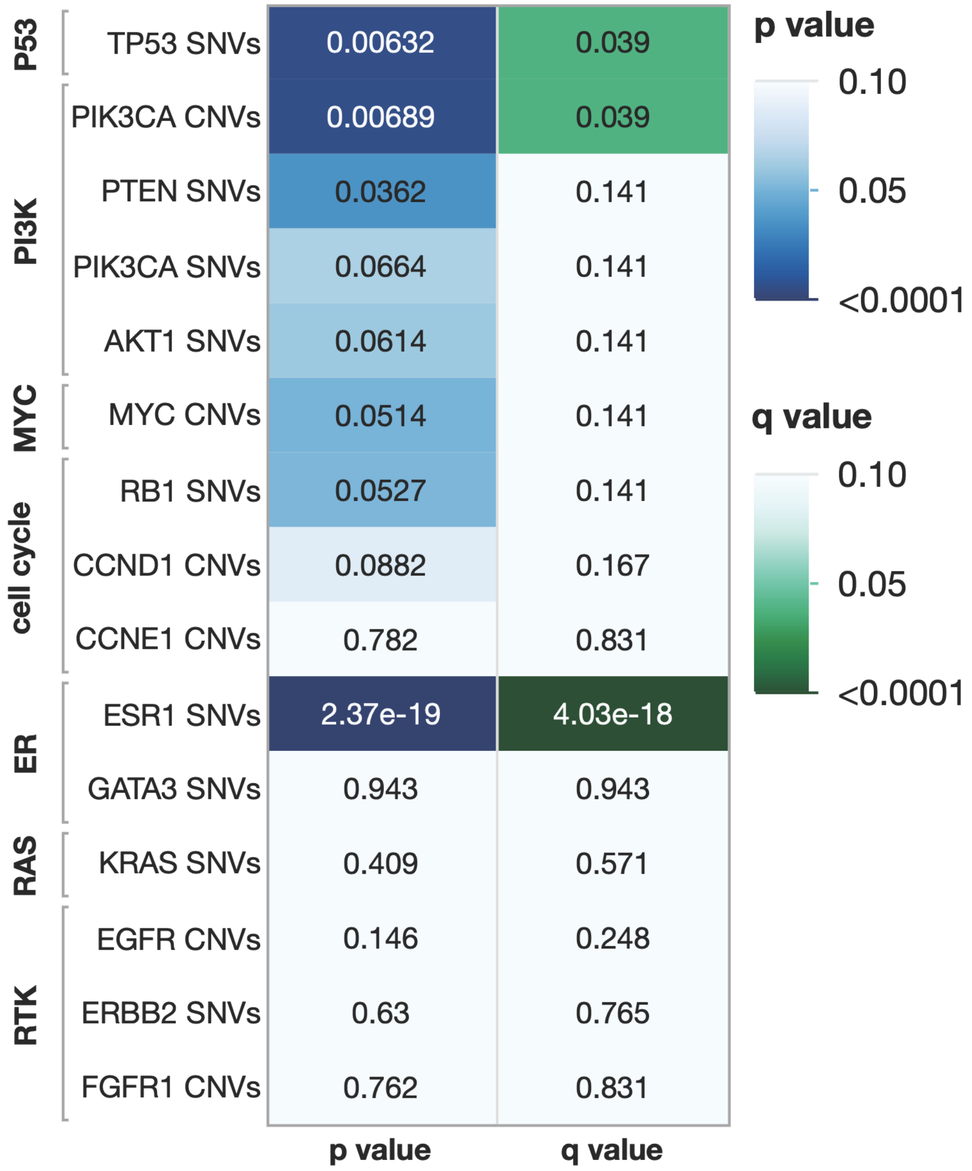


ESR1 SNVs	OR	P value
High MAF	2.12	< 0.001
Visceral involvement	1.23	0.320
bone involvement	3.08	< 0.001
Lines of therapy		
2	3.16	0.004
3	1.57	0.310
4	2.46	0.064
Previous CT	0.80	0.430
Previous ET	3.02	0.014
Previous CDK4/6i	1.75	0.022
Previous mTORi	1.22	0.451
Previous PI3Ki	1.75	0.129

Gerratana L, Davis AA, Gaudio H, Dri A, Reduzzi C, et al. In preparation | Unpublished, do not post

How stable are *PTEN* and *AKT1*?

Genes significantly changing across lines and their predictors

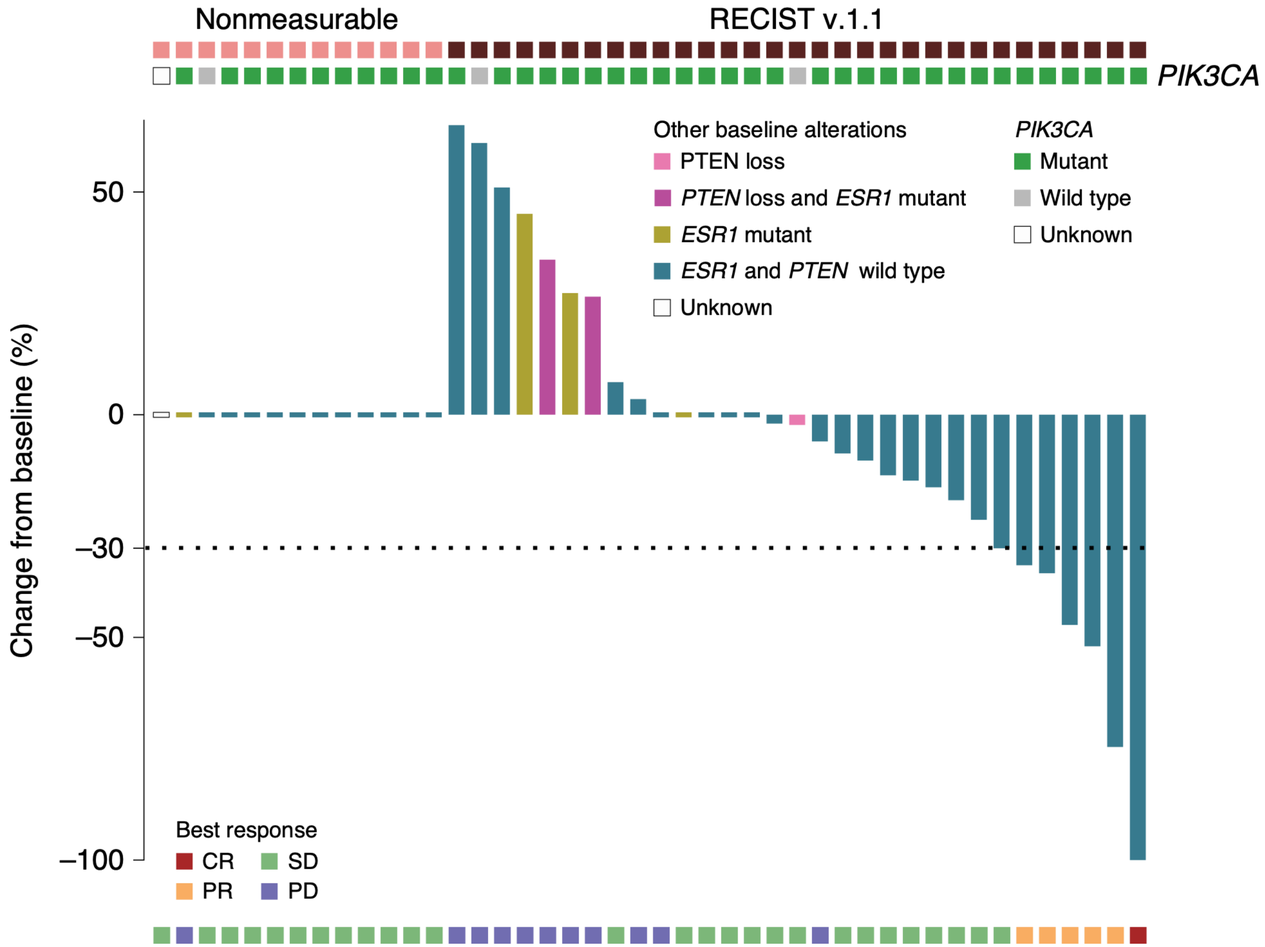


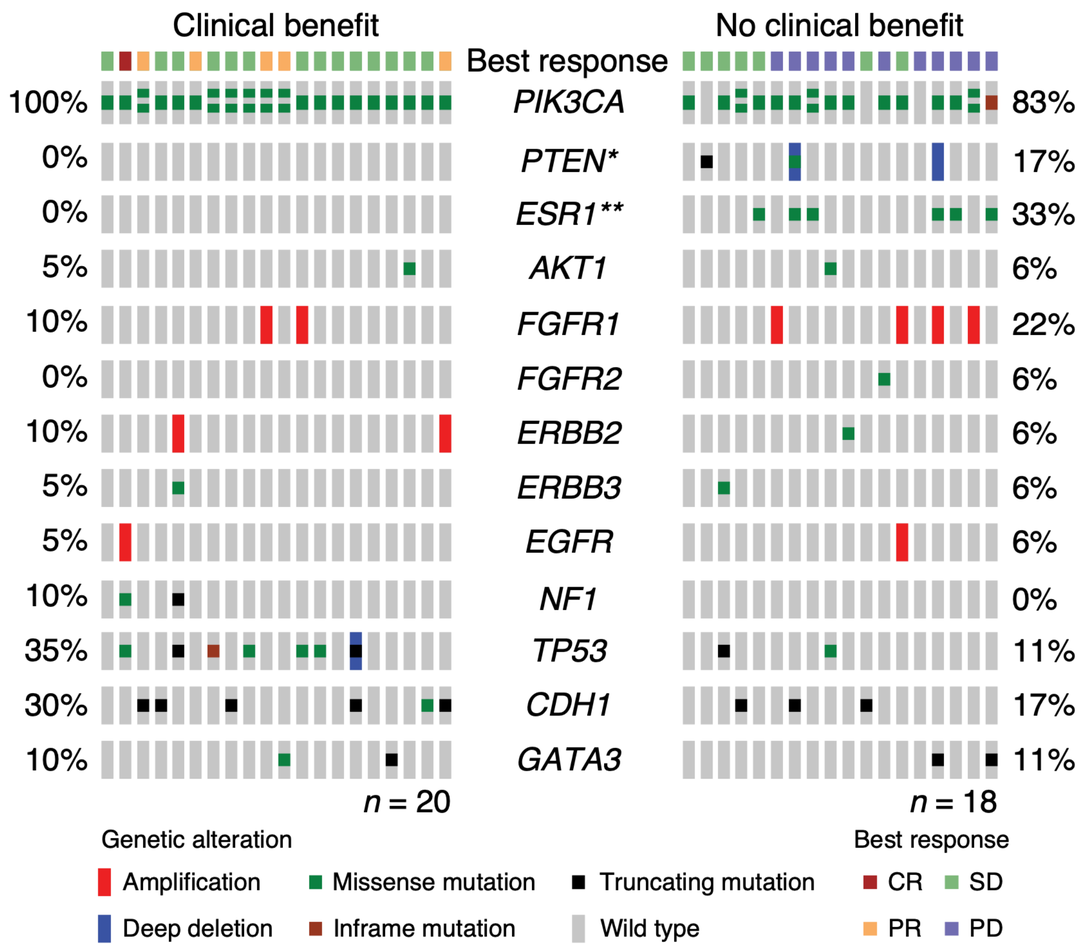
PTEN SNVs	OR	P value
High MAF	3.64	0.005
Histotype		
ILC	4.73	0.001
Lines of therapy		
2	2.10	0.357
3	1.85	0.506
4	2.55	0.244
Previous CDK4/6i	1.30	0.627
Previous PI3Ki	3.68	0.049

Gerratana L, Davis AA, Gaudio H, Dri A, Reduzzi C, et al. In preparation | Unpublished, do not post

How stable are *PTEN* and *AKT1*?

PTEN as a resistance factor

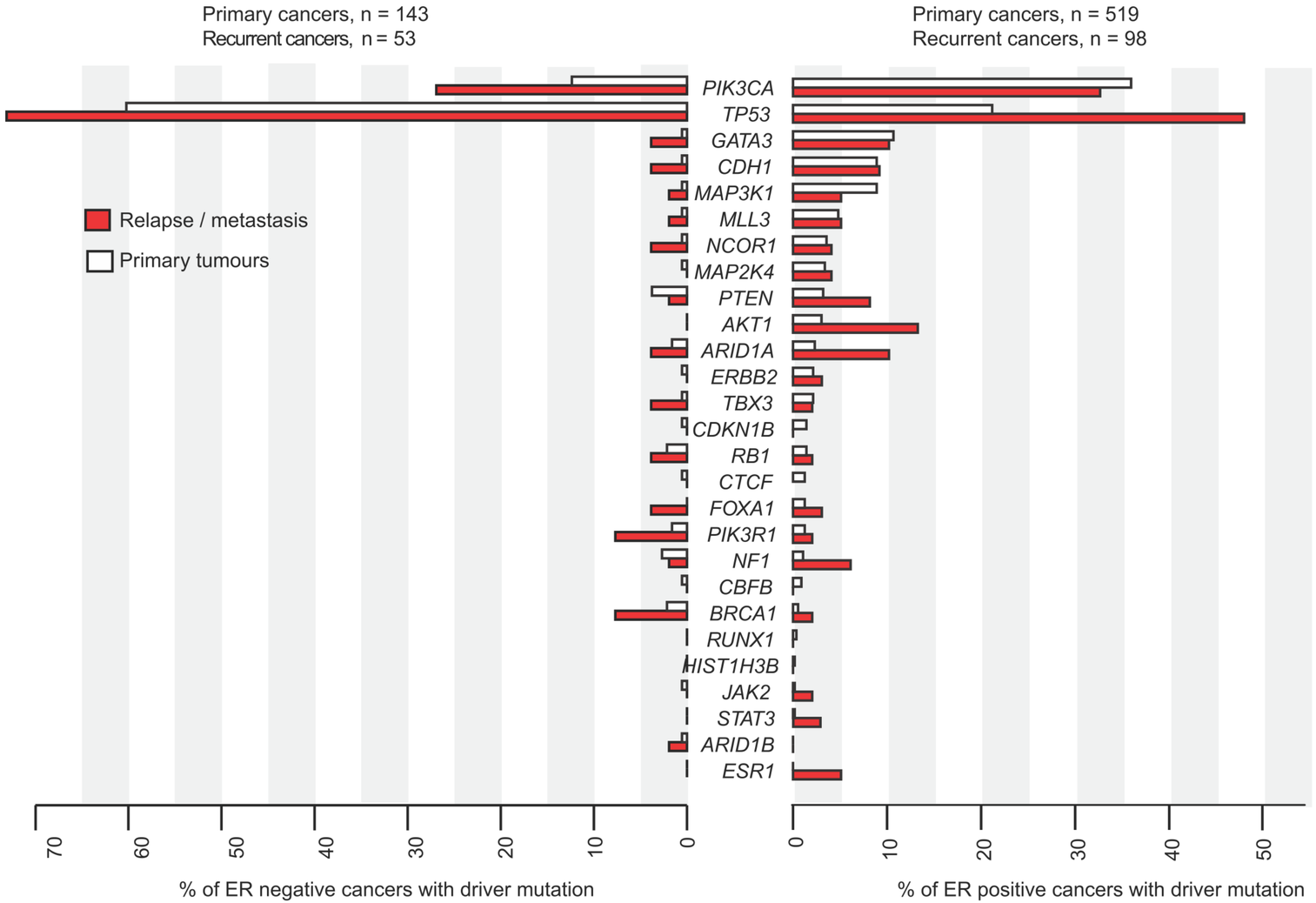


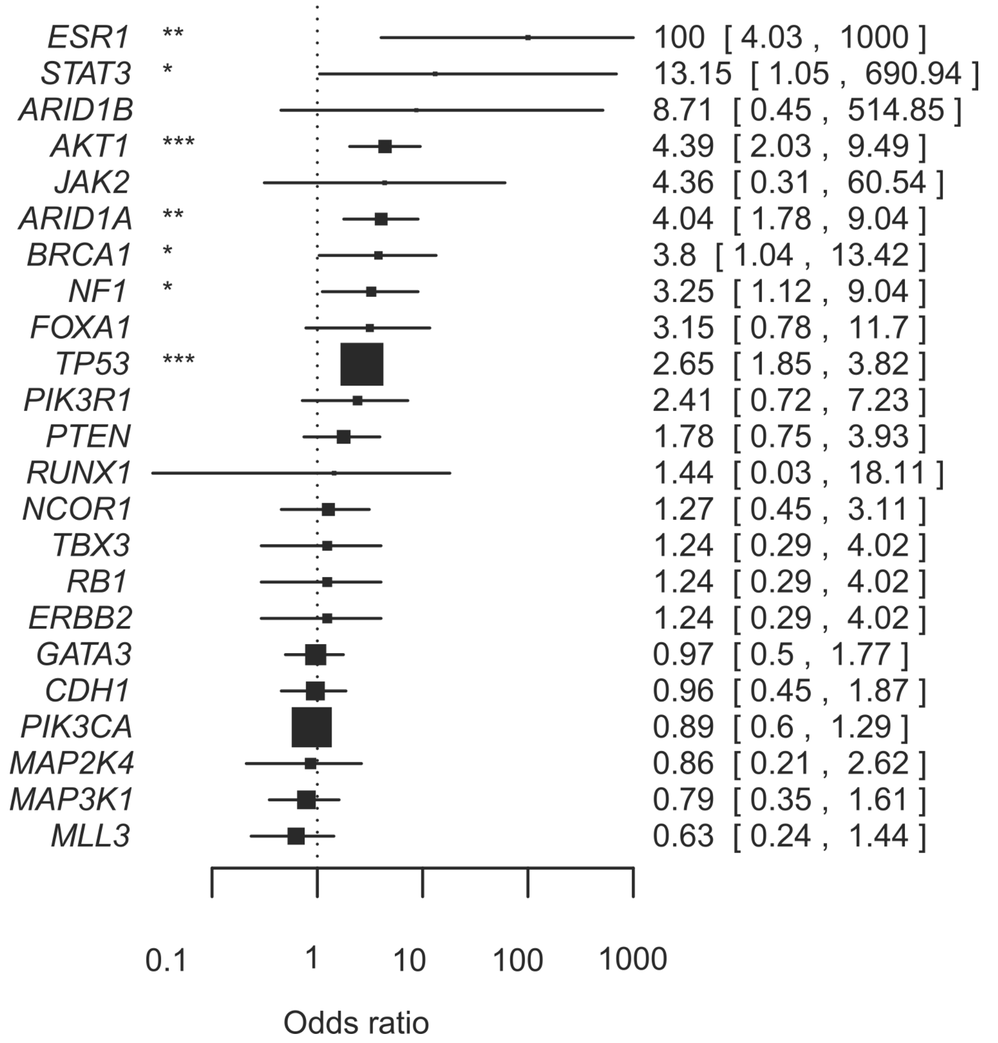


Razavi P, Dickler MN, Shah PD, et al. Nat Cancer, 2020; doi:10.1038/s43018-020-0047-1

How stable are *PTEN* and *AKT1*?

Driver Landscapes of 163 Recurrent and 705 Primary Breast Cancers





Yates LR, Knappskog S, Wedge D, et al. *Cancer Cell*, 2017; doi:10.1016/j.ccell.2017.07.005

Is there a **line-specific** mutational profile?

Let’s ask machine learning

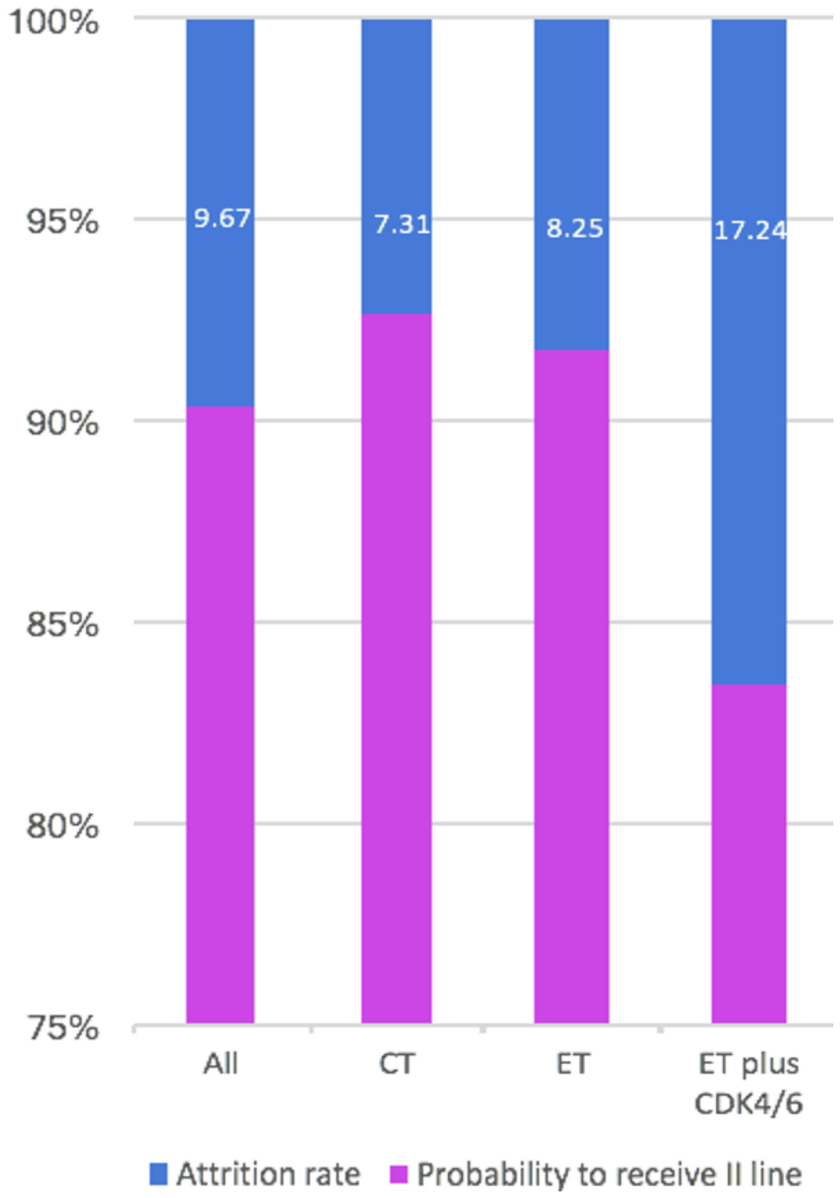
Top 5 gene alterations across the 3 best performing models

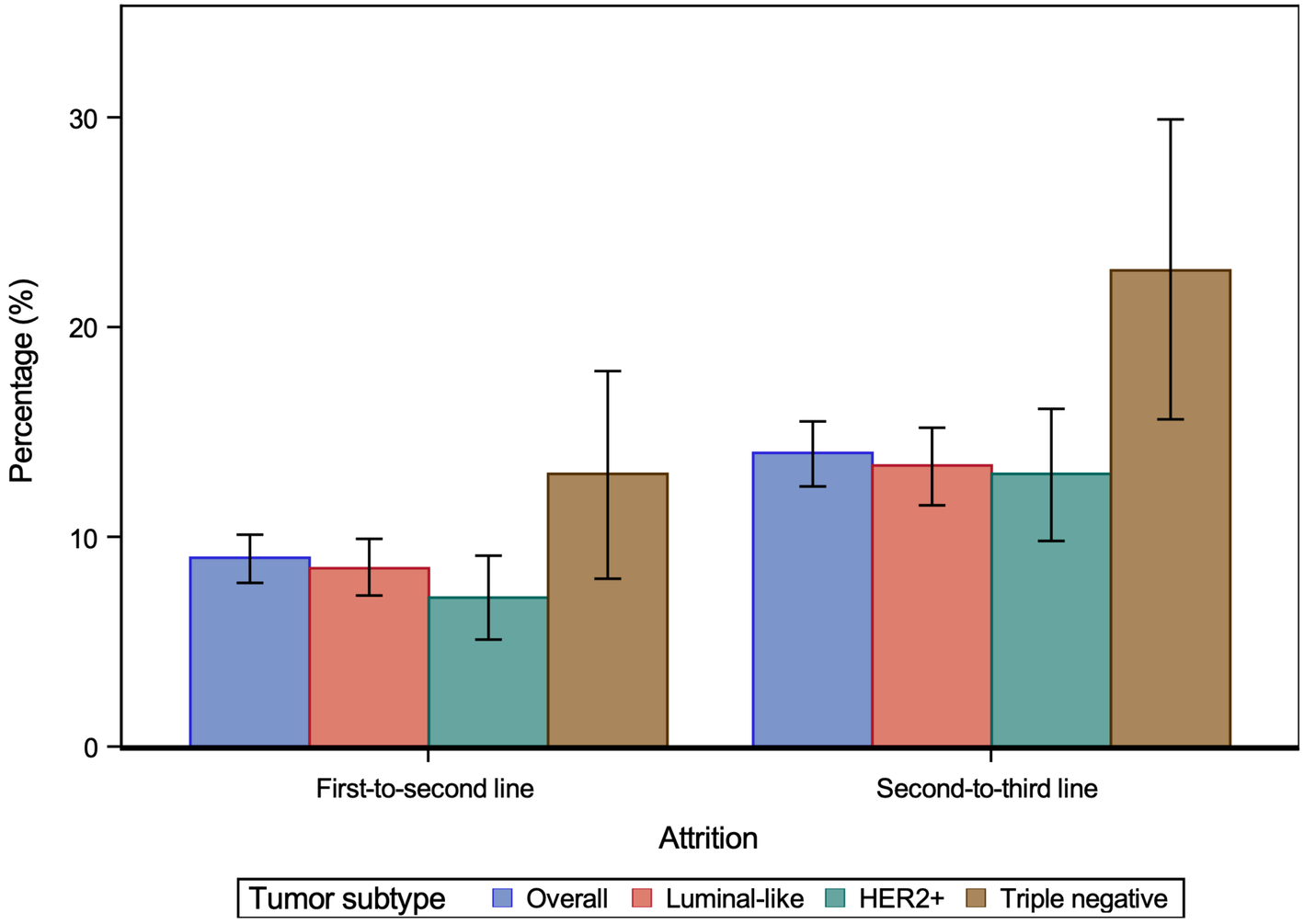
2nd Line (RFE + RF)		3rd Line (XGBoost)		≥4th Line (ANOVA + RF)	
Feature	**Importance**	**Feature**	**Importance**	**Feature**	**Importance**
ESR1 SNV	0.3856	ESR1 SNV	0.1647	ESR1 SNV	0.4437
CDH1 SNV	0.0703	AKT1 SNV	0.0800	TP53 SNV	0.1041
TP53 SNV	0.0534	CCND1 CNV	0.0708	PIK3CA SNV	0.0904
ERBB2 SNV	0.0424	ERBB2 SNV	0.0708	MYC CNV	0.0791
AKT1 SNV	0.0416	PTEN SNV	0.0705	PIK3CA CNV	0.0659

Timing is crucial

Why timing is crucial

Life is in 4D: resistance monitoring vs attrition rate

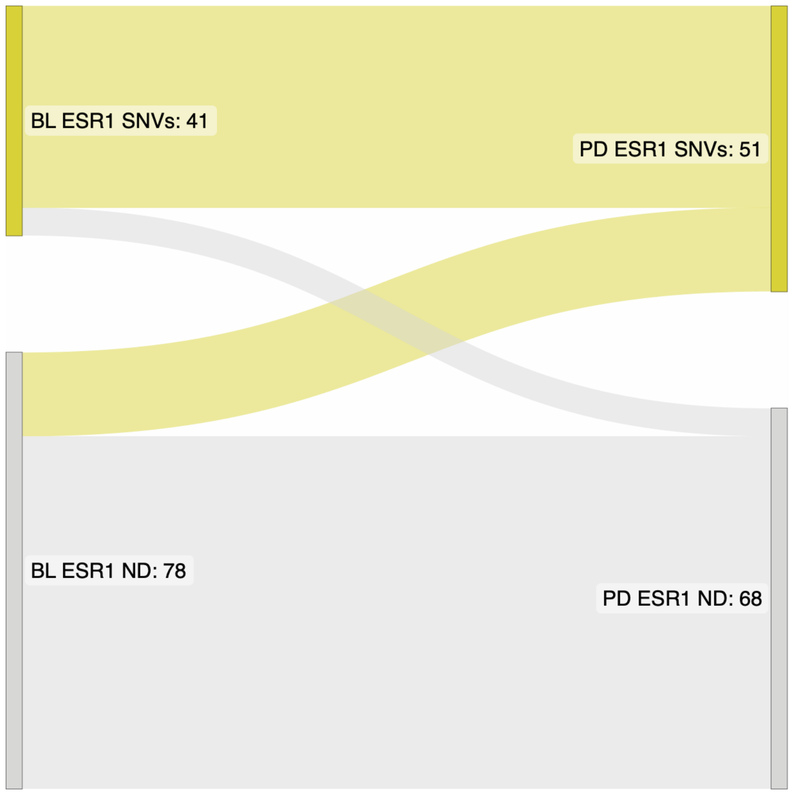


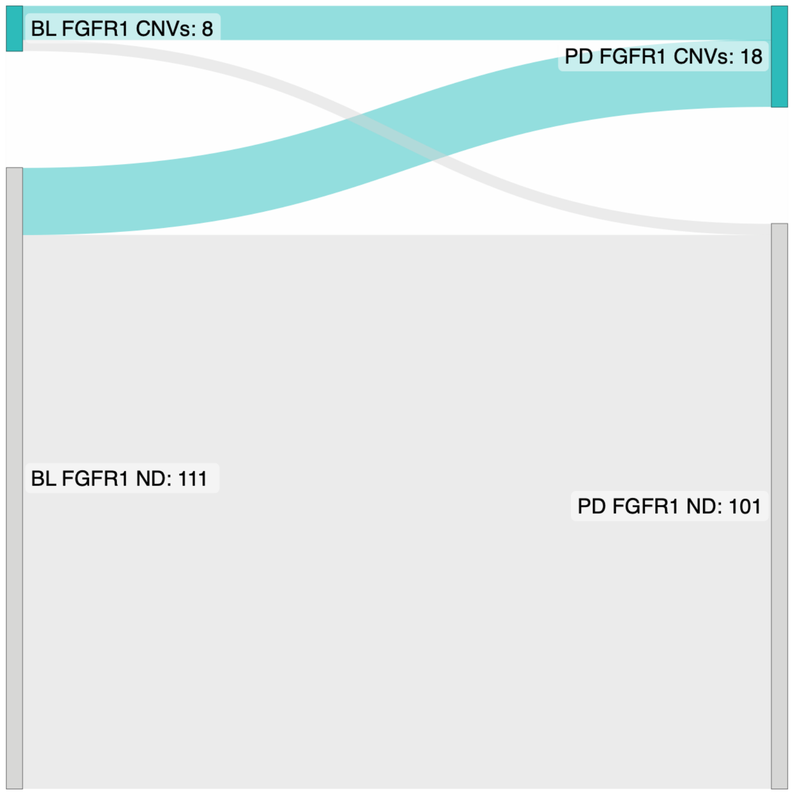


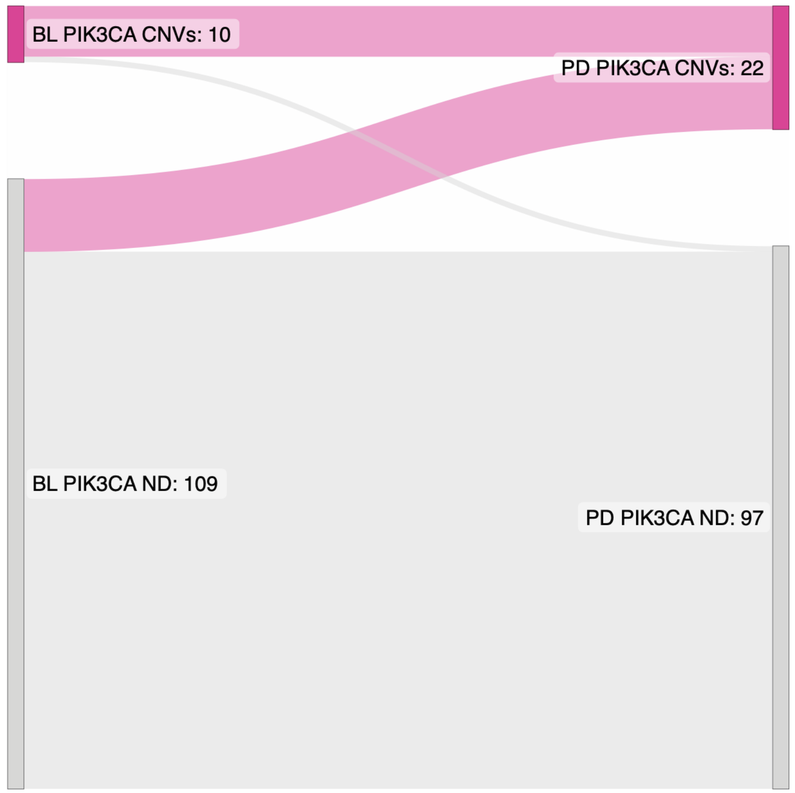
Basile D, Gerratana L, Corvaja C, et al. The Breast, 2021; doi:10.1016/j.breast.2021.02.015
Blondeaux E, Boni L, Chilà G, et al. Cancer Research, 2024; doi:10.1158/1538-7445.SABCS23-PO3-06-01

Why timing is crucial

Paired samples subgroup analysis



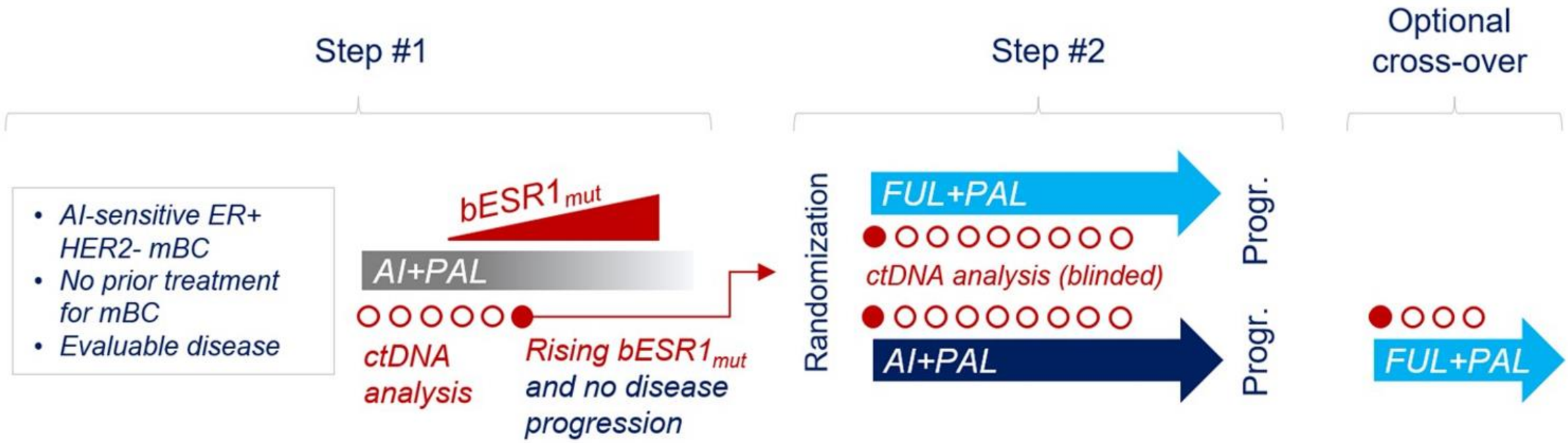




Gerratana L, Davis AA, Gaudio H, Dri A, Reduzzi C, et al. In preparation | Unpublished, do not post

Why timing is crucial

Dynamically test and decide: the PADA-1 study



PADA-1

Phase 3 trial to evaluate the utility of monitoring the onset of ESR1mut in cell-free DNA of patients receiving AI - Palbociclib in first line.

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

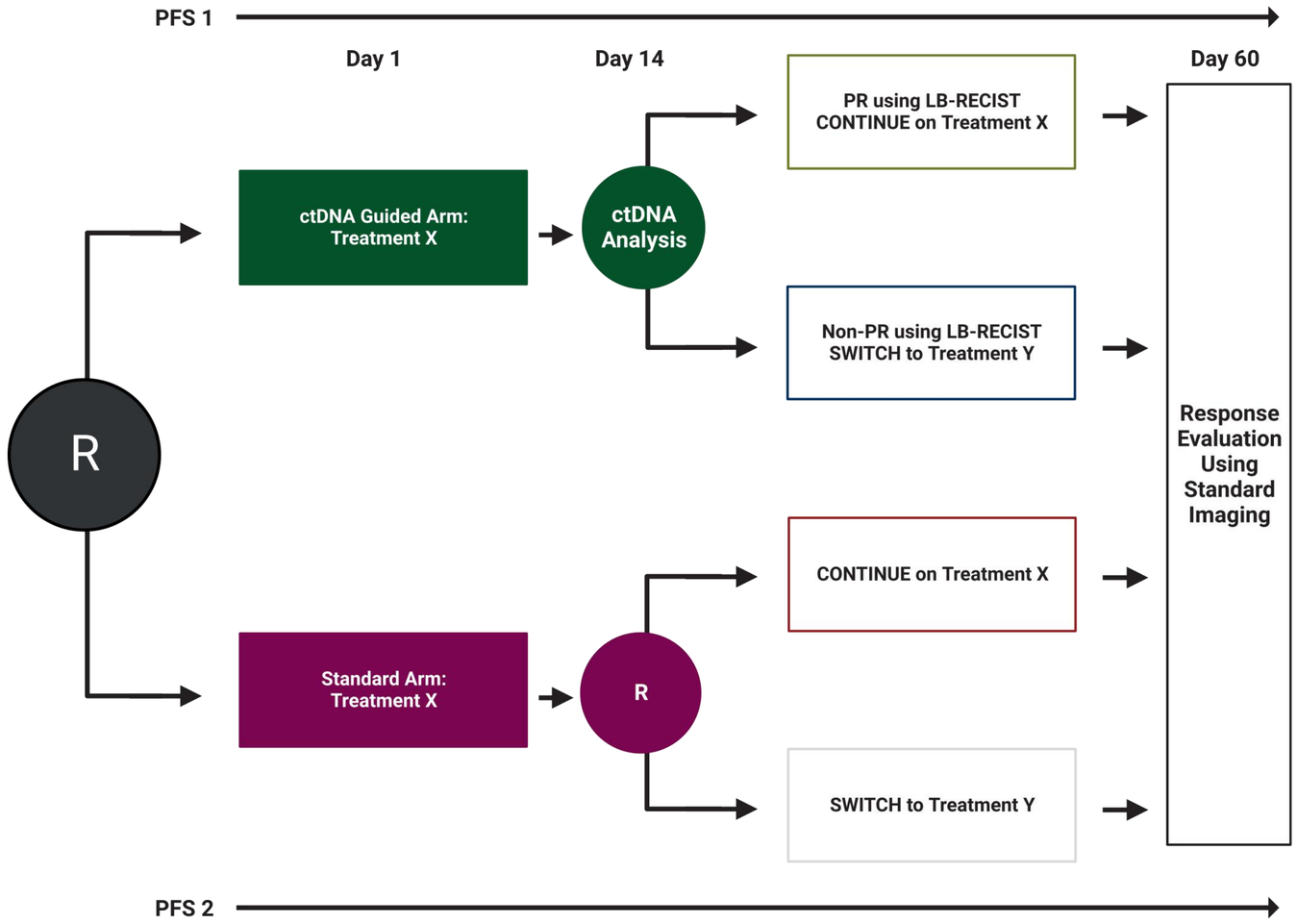
Cabel L, Delaloge S, Hardy-Bessard A-C, et al. JCO, 2023; doi:10.1200/JCO.2023.41.16_suppl.1002

But how much is **too much**?

But how much is too much?

One step in the right direction: LB-RECIST

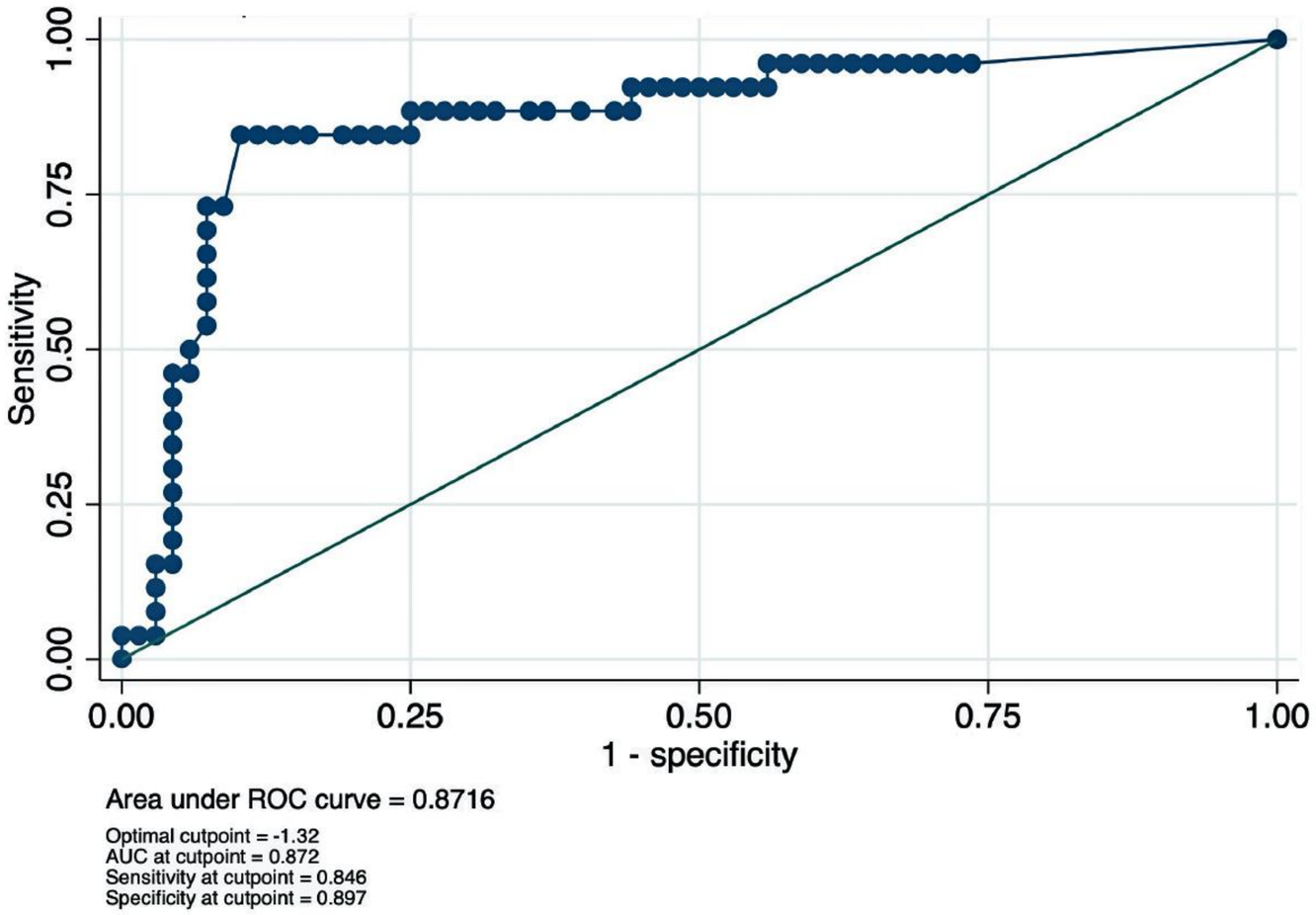
Criteria	Group	Definition
Qualitative response criteria	Group 1 (G1; D-D)	Patients with detectable ctDNA which remains detectable after therapy
	Group 2 (G2; D-U)	Patients with detectable ctDNA which becomes undetectable after therapy
	Group 3 (G3; U-D)	Patients with undetectable ctDNA which becomes detectable after therapy
	Group 4 (G4; U-U)	Patients with undetectable ctDNA which remains undetectable after therapy
Quantitative response criteria	ctDNA complete response (CCR)	ctDNA clearance after initial detectability
	ctDNA partial response (CPR)	Decrease of >10% in variant allele frequency
	ctDNA stable disease (CSD)	No increase or up to 10% increase or decrease in variant allele frequency
	ctDNA progressive disease (CPD)	Increase of >10% in variant allele frequency or *de novo* ctDNA detection
	ctDNA nonmeasurable disease (CND)	Undetectable ctDNA before and after treatment

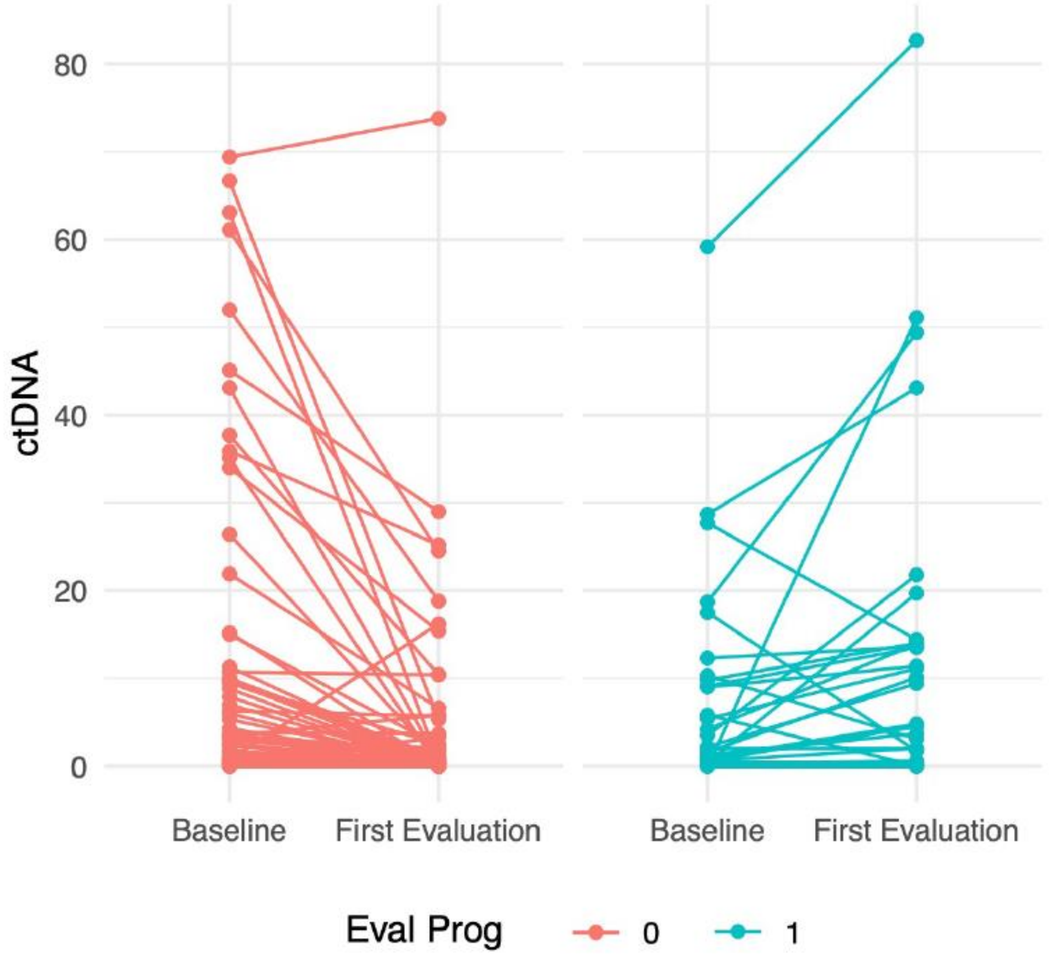


Gouda MA, Janku F, Wahida A, et al. Ann Oncol, 2024; doi:10.1016/j.annonc.2023.12.007

One step in the right direction?

Updated PFS results - primary endpoint

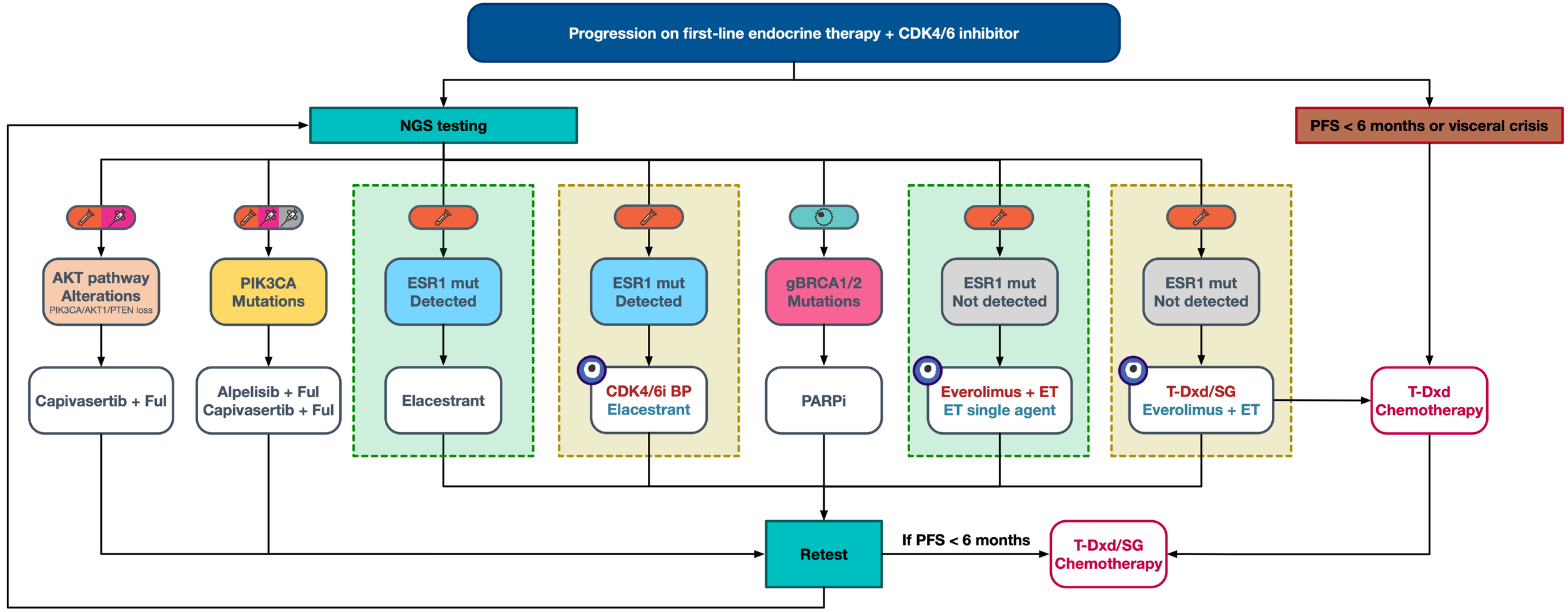




Foffano L, Davis AA, Reduzzi C, Podany E, Medford AJ, et al. In preparation | Unpublished, do not post

Why testing just once?

In a world of multiple options, you need multiple testing



Liquid biopsy | Updated tissue biopsy | Archival tissue biopsy | Germline | CTC enumeration

Stage $IV_{indolent}$ (<5 CTCs)

Stage $IV_{aggressive}$ (≥5 CTCs)

PFS1 ≤ 12 months

PFS1 > 12 months

Gerratana L, Davis AA, Gaudio H, Dri A, Reduzzi C, et al. In preparation | Unpublished, do not post

Wrapping up

What is the evidence?

1

Attention should be payed

NGS will be increasingly recommended as new, mutation driven, drugs will be introduced in the clinic
Extended panels should be used in clinical trials only or in Molecular Tumor Boards

2

Biology is ever-changing and its evolution is not neglected to a single line

Tissue biopsy can guarantee a higher DNA yield, but can't address spatial and temporal heterogeneity
Several gene alterations can be selected during treatments (e.g. *ESR1*, *PTEN*)

3

Liquid biopsy is not a one-shot diagnostic

Time is crucial, since attrition rate is an aspect we should consider
We should focus not just on targetable alterations but also on those that can assist treatment monitoring

Thank you

Scan to **Link**

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5 PER MILLE CRO

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

Ministero della Salute

GIM GRUPPO ITALIANO MAMMELLA

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The Liquid biopsy Research Group

CRO AVIANO

Cristofanilli CTC LAB