CRO AVIANO

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DMED
DIPARTIMENTO DI MEDICINA

The **Liquid biopsy** Research Group

bjclub breast Journal club
L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

HR positive **HER2** negative

Highlights in the metastatic setting

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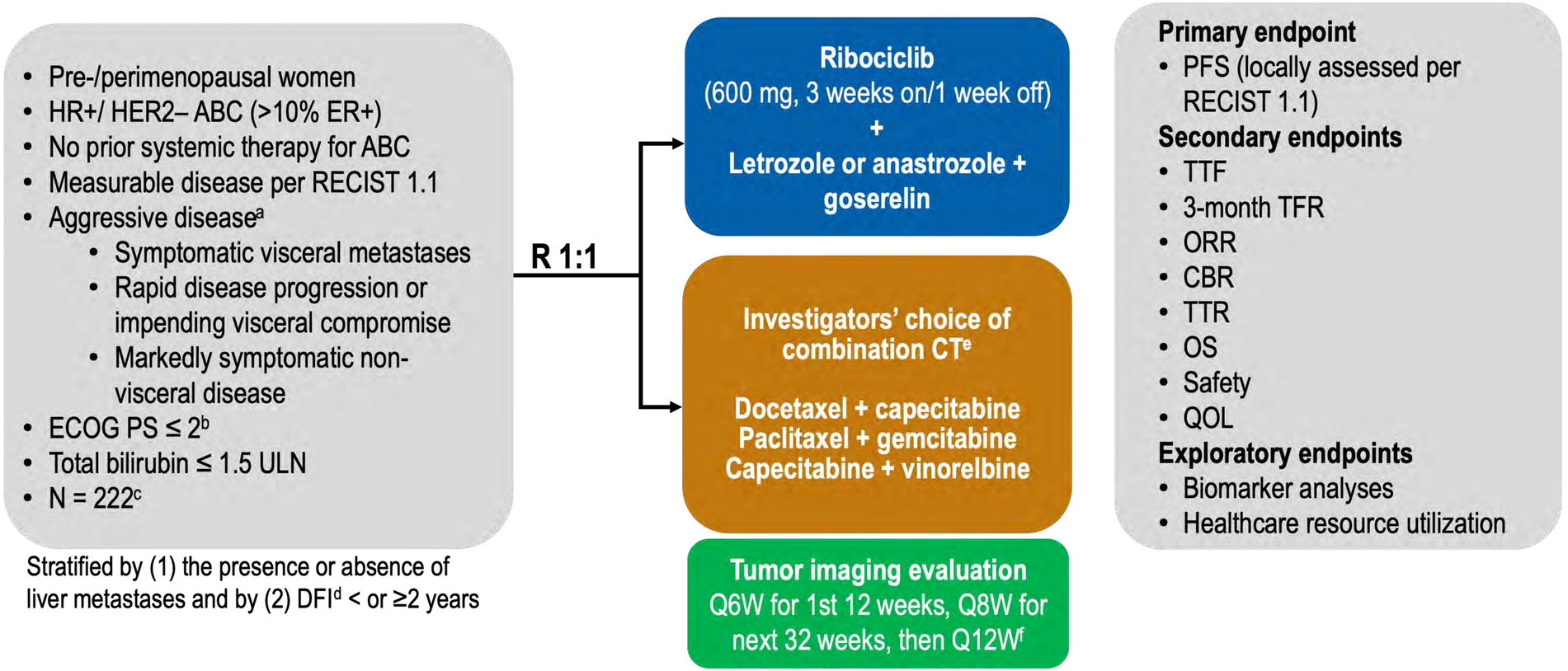
First line: the calm before the storm

Are CDK4/6i fitting for and aggressive disease?

The RIGHT Choice study



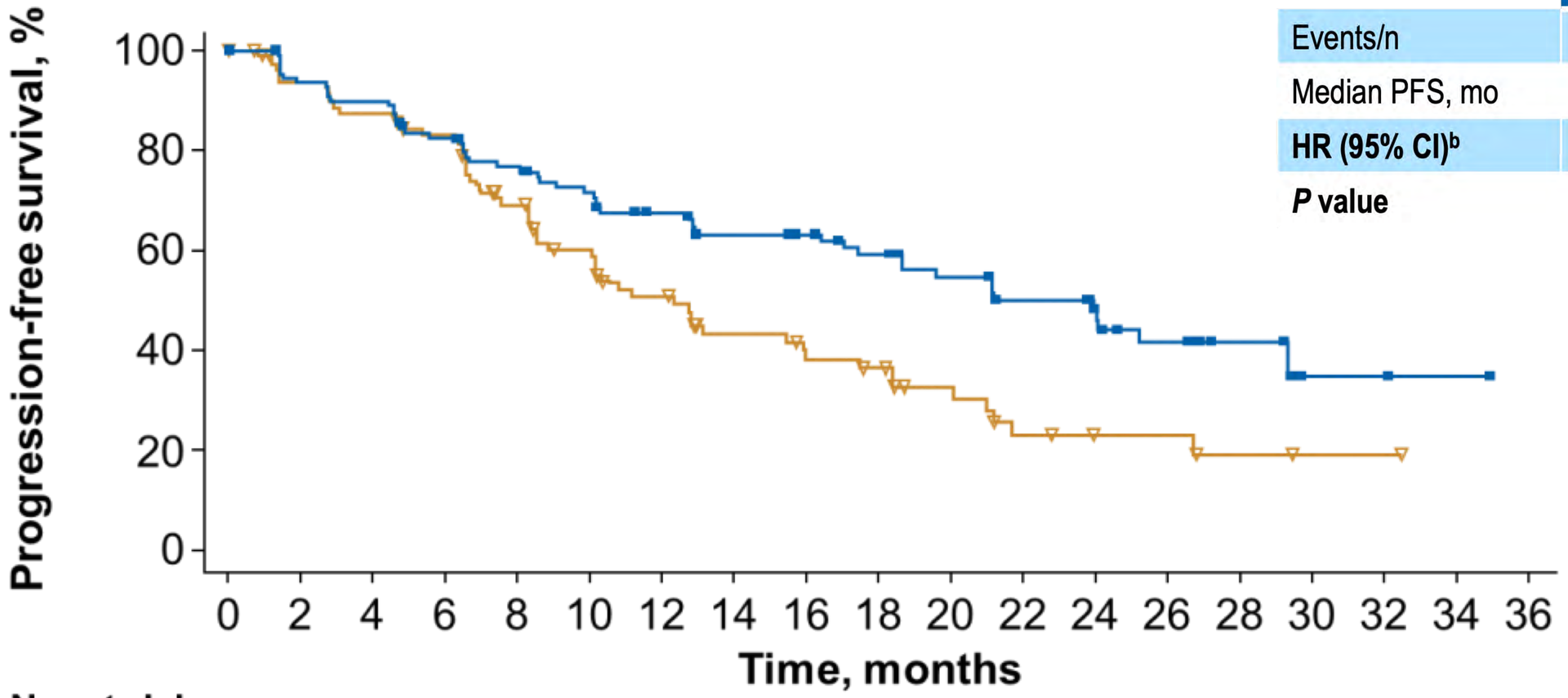
RIGHT Choice

Phase II randomized 1:1 trial of premenopausal patients with aggressive HR+/HER2− advanced breast cancer treated with CDK4/6i + endocrine therapy vs PCT (docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine).

Lu Y, Bin Mohd Mahidin EI, Azim H, SABCS 2022

The RIGHT Choice study

Progression Free Survival



	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

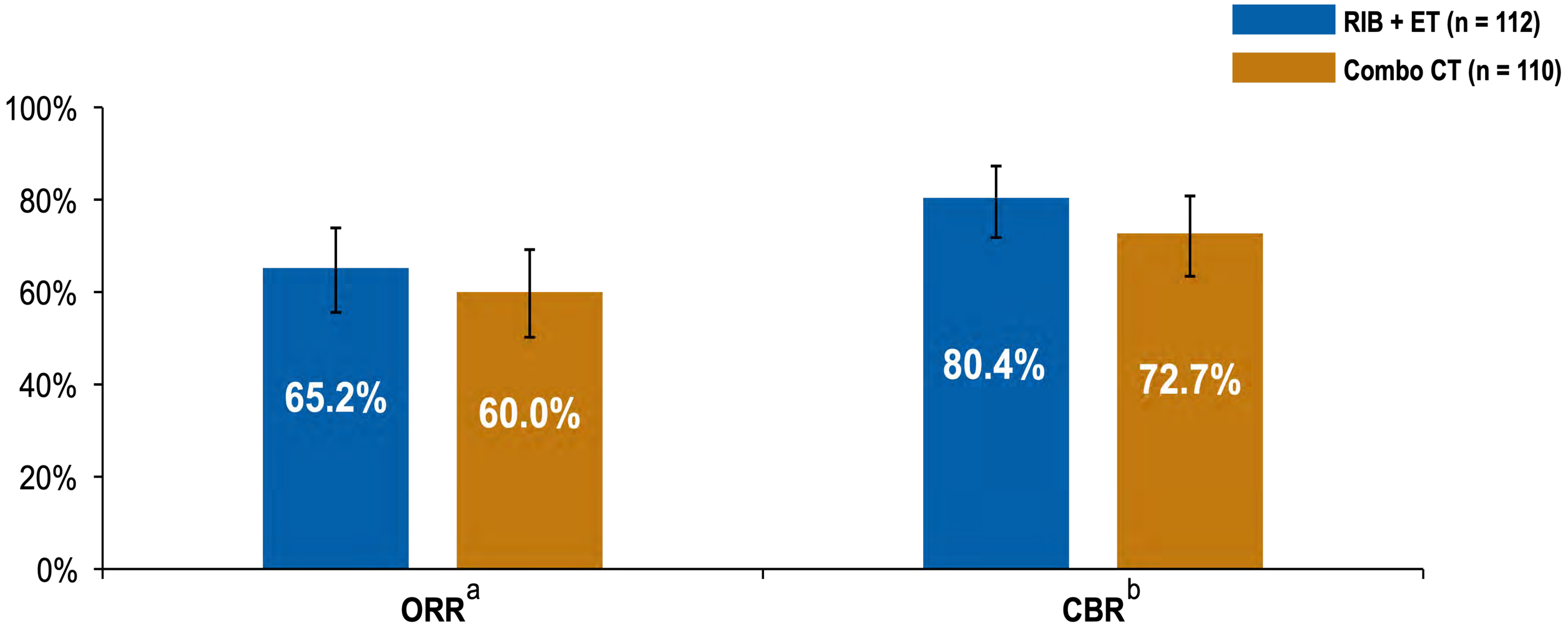
No. at risk

RIB + ET	112	103	99	88	78	70	63	56	50	45	36	30	24	18	7	2	2	1	0
Combination CT	110	90	84	75	56	46	37	26	22	20	14	9	6	6	3	1	1	0	0

Lu Y, Bin Mohd Mahidin EI, Azim H, SABCS 2022

The RIGHT Choice study

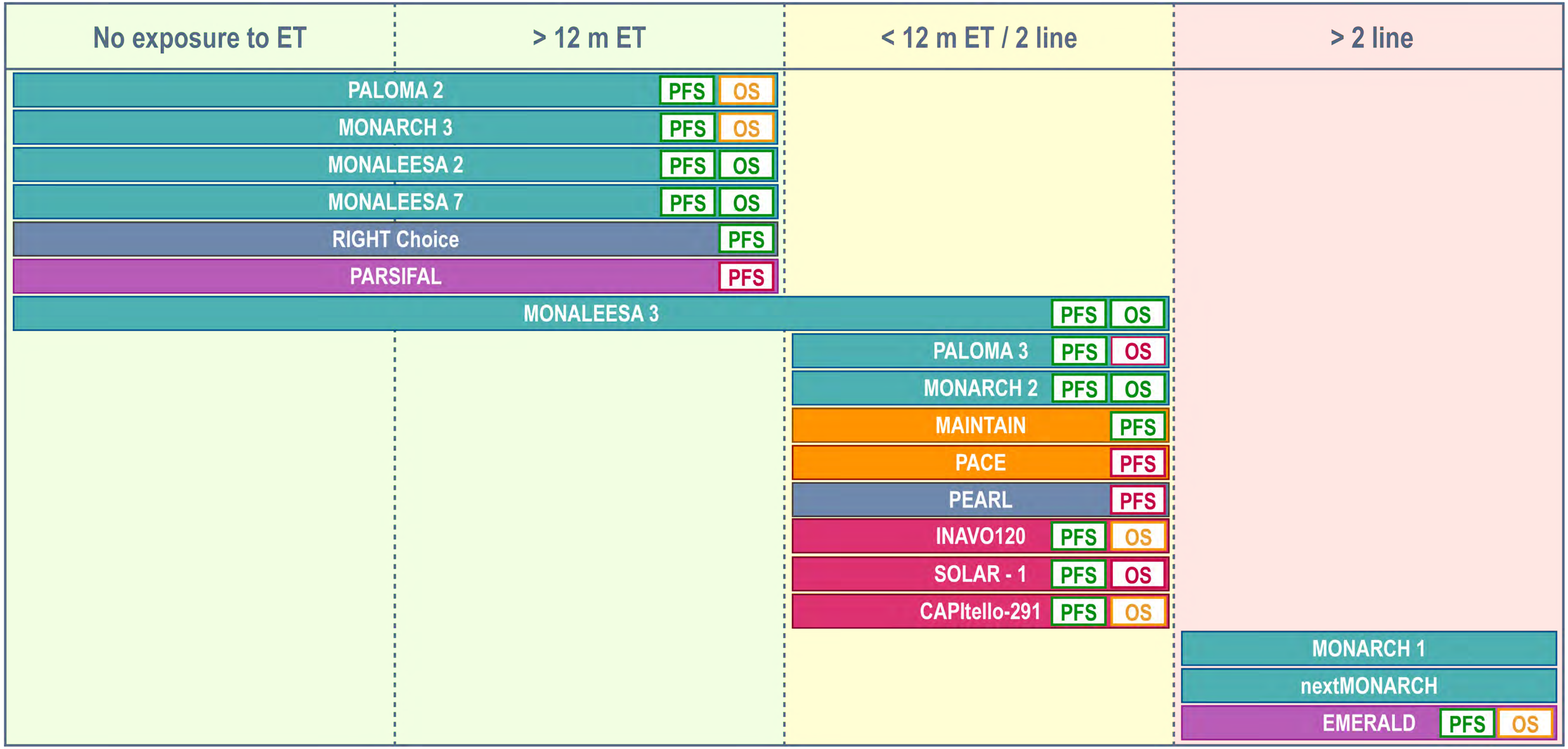
Overall Response Rate and Clinical Benefit Rate



Lu Y, Bin Mohd Mahidin EI, Azim H, SABCS 2022

How can we support our choices?

The treatment Gantt chart



From doublet to **triplet**?

The last minute presentation

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

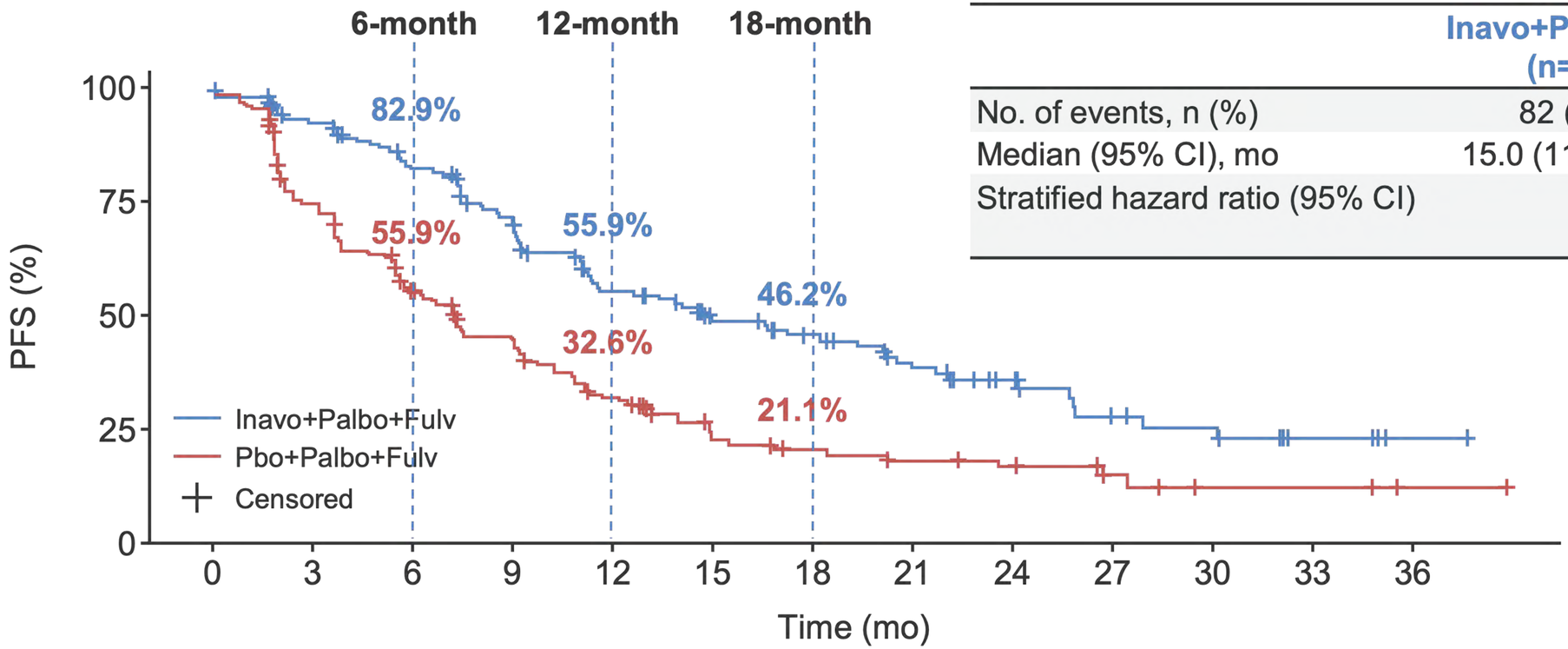
Primary endpoint (investigator-assessed PFS)

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

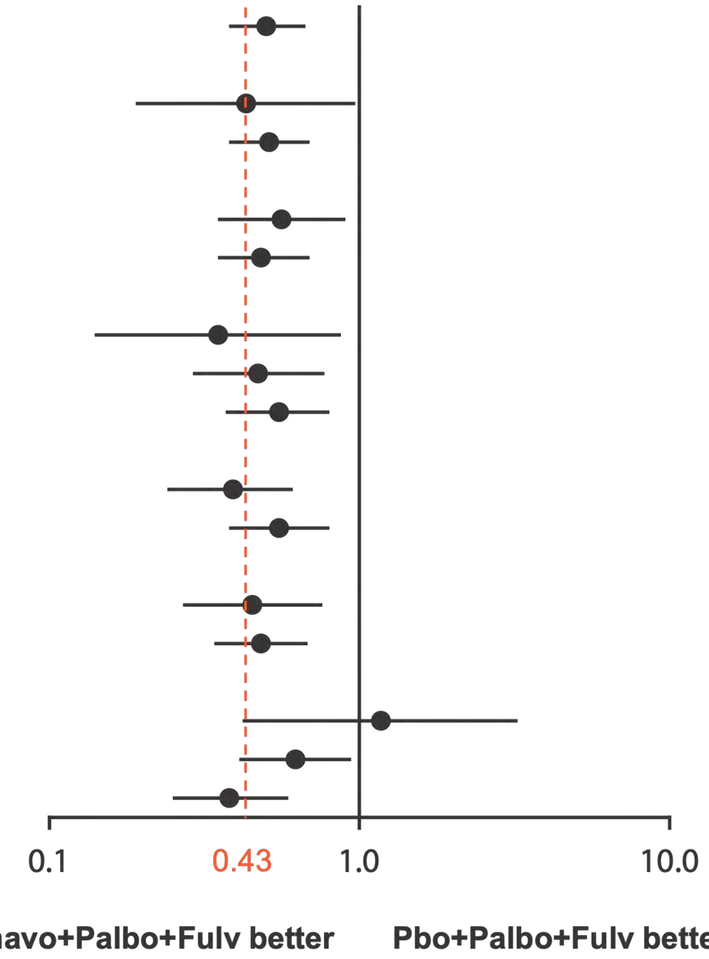
CCOD: 29th September 2023

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

INAVO120

Progression Free Survival - key subgroups

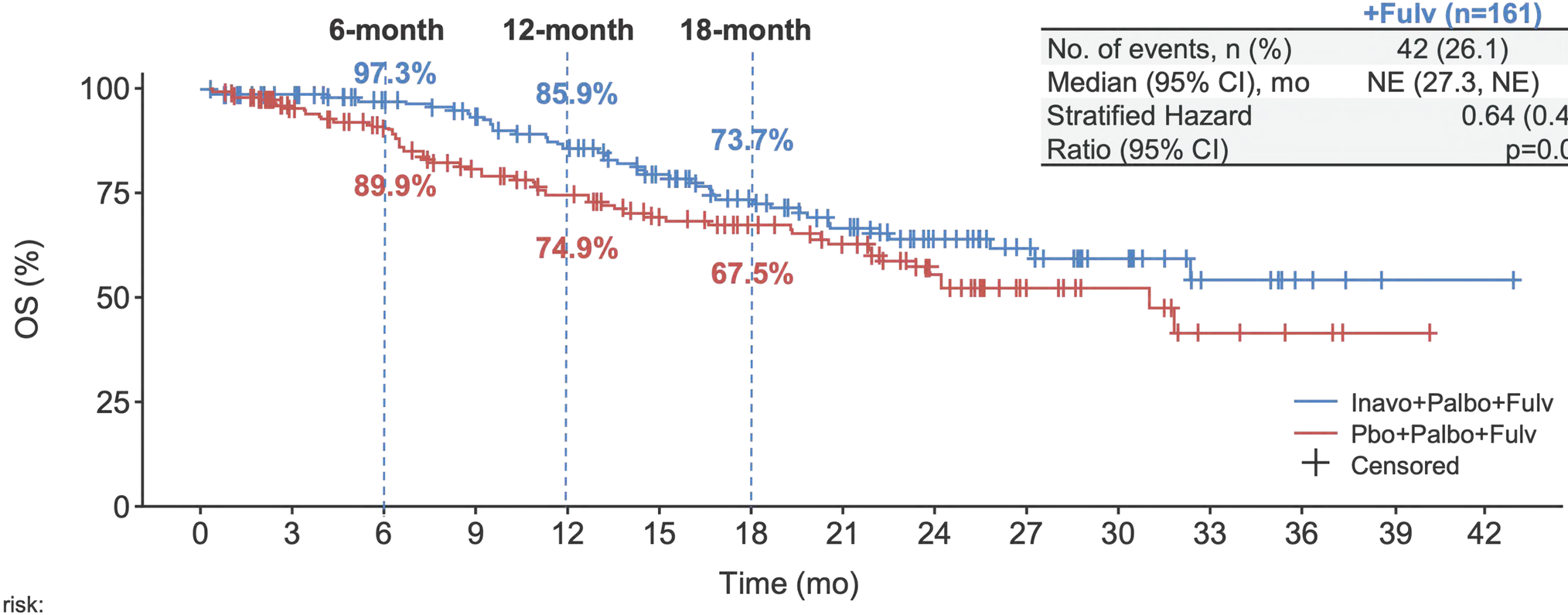
	Inavo+Palbo+Fulv n	Pbo+Palbo+Fulv n	Hazard ratio (95% CI)
All patients	161	164	0.50* (0.38, 0.67)
Visceral disease			
No	29	36	0.43 (0.19, 0.97)
Yes	132	128	0.51 (0.38, 0.69)
Liver metastasis at enrollment			
No	84	73	0.56 (0.35, 0.90)
Yes	77	91	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment			
1	21	32	0.35 (0.14, 0.87)
2	59	46	0.47 (0.29, 0.77)
≥3	81	86	0.55 (0.37, 0.80)
Endocrine resistance			
Primary	53	58	0.39 (0.24, 0.61)
Secondary	108	105	0.55 (0.38, 0.80)
HR status			
ER+/PgR-	45	45	0.45 (0.27, 0.76)
ER+/PgR+	113	113	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy			
Aromatase inhibitor and tamoxifen	18	19	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	71	0.62 (0.41, 0.94)
Tamoxifen only	82	73	0.38 (0.25, 0.59)



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

INAVO120

Key secondary endpoint: Overall survival (interim analysis)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

Can we bring INAVO120 to the clinic?

Is the triplet really more toxic?

Patients with key AEs,↑ %	INAVO120[1] Palbocilib + fulvestrant Control arm (n = 162)		INAVO120[1] Inavo + Palbociclib+ Fulvestrant (N=162)		SOLAR-1[2] Alpelisib + fulvestrant (n = 284)		CAPitello-291[3] Capivasertib + fulvestrant (n = 355)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperglycemia#	9	0	59	6	64	33	16	2
Diarrhea	16	0	48	4	58	7	72	9
Rash	17	0	25	0	54	20	38	12
Stomatitis*	27	0	51	6	25	3	15	2
Nausea	17	0	28	1	45	3	35	1
AEs leading to study treatment discontinuation	1	N/A	7	N/A	25	N/A	13	N/A

Cross-trial comparisons should be interpreted with caution due to **differences in patient populations and AE reporting.** SOLAR-1, for example, had a significant learning curve.

Adapted from Rugo H . General Session 3; SABCS 2023

The whole paradigm is **shifting**

The whole paradigm is shifting

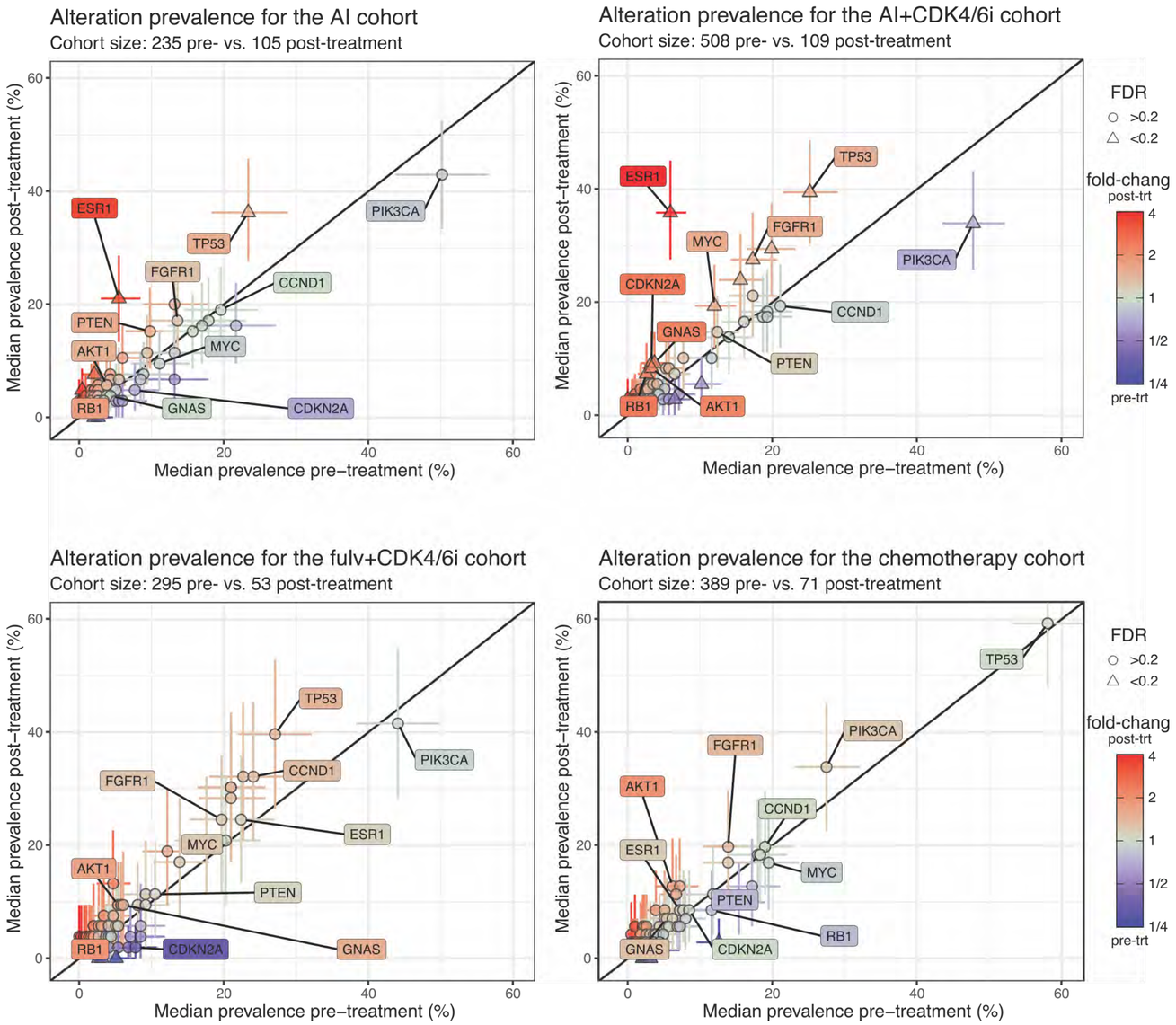
How this translates to the clinical practice

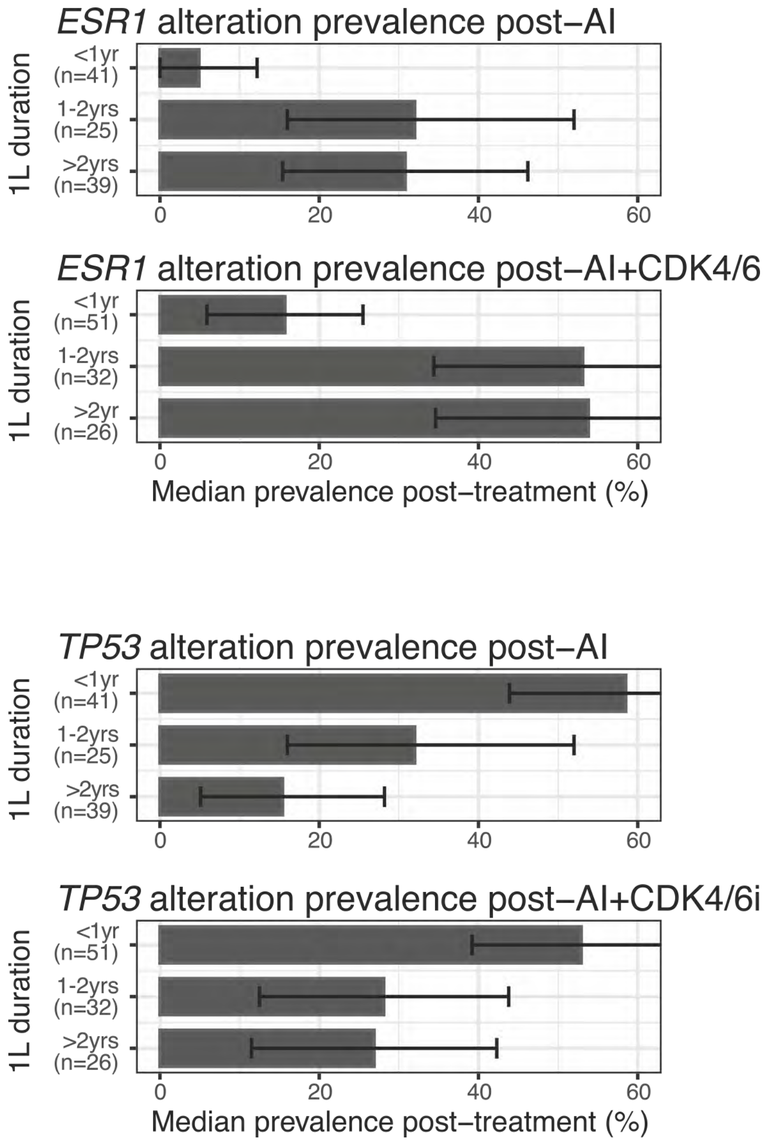
AJCC	TN (M0)	NATALEE	MonarchE	Difference
IIA	T0 N1	11	only if G3 or Ki-67 ≥ 20% 11	0
	T1 N1	170	only if G3 or Ki-67 ≥ 20% 59	111
	T2 N0	only if G3 or G2 with Ki-67 ≥ 20% or high genomic risk 154		154
IIB	T2 N1	199	only if G3 or Ki-67 ≥ 20% 87	112
	T3 N0	29		29
IIIA	T0 N2	2	1	1
	T1 N2	20	19	1
	T2 N2	46	43	3
	T3 N1	32	29	3
	T3 N2	13	13	0
IIIB	T4 N0	6		6
	T4 N1	16	only if tumor size ≥ 5 cm or Ki-67 ≥ 20% 6	10
	T4 N2	11	11	0
IIIC	Any TN3	38	37	1
	total	747/ 1738 (42.9%)	316/ 1738 (18.1%)	430

Schäffler H, Mergel F, Pfister K, et al. *Int J Mol Sci*, 2023; doi:10.3390/ijms242216366

Two biologically distinct populations

The boiling variants' pot



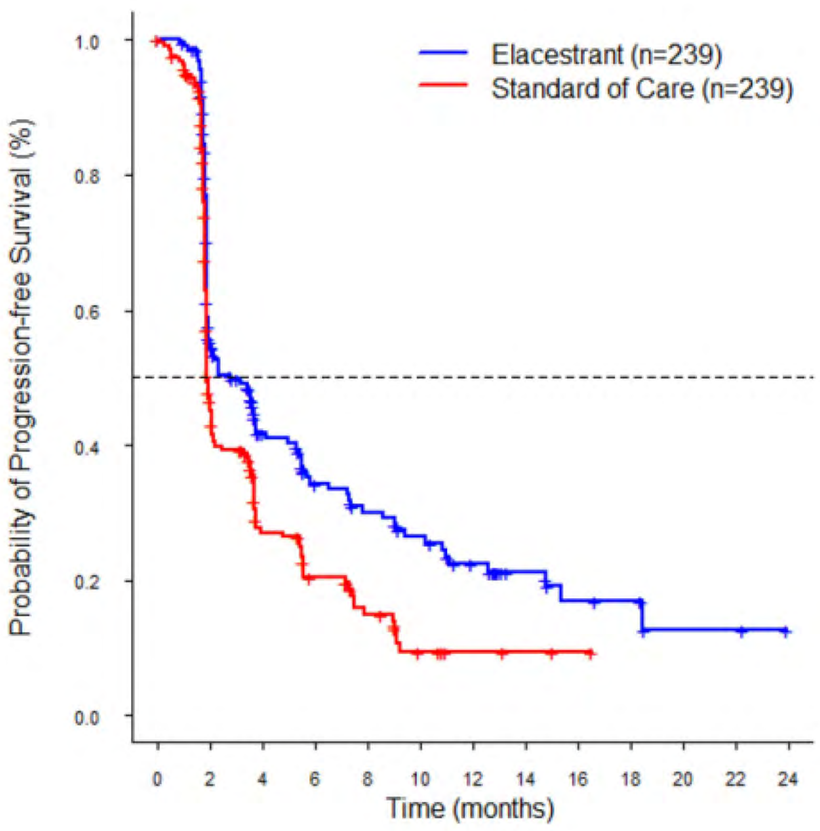


Chaudhary N, Chibly AM, Collier A, et al. *npj Breast Cancer*, 2024; doi:10.1038/s41523-024-00617-7

But what comes **after the first line**?

The Phase III trial EMERALD

What FDA saw: PFS Kaplan Meiers



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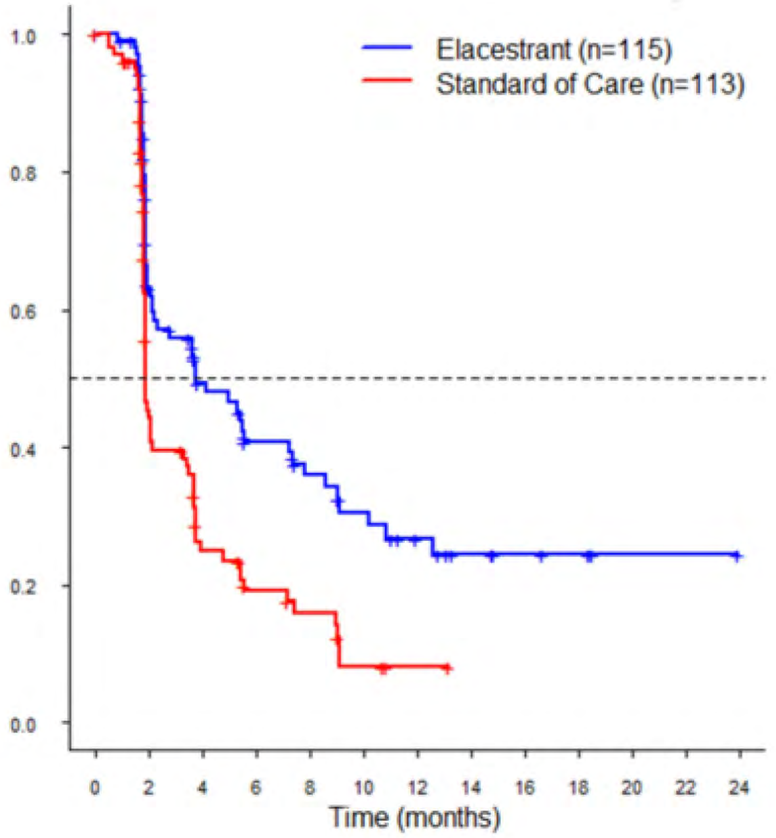
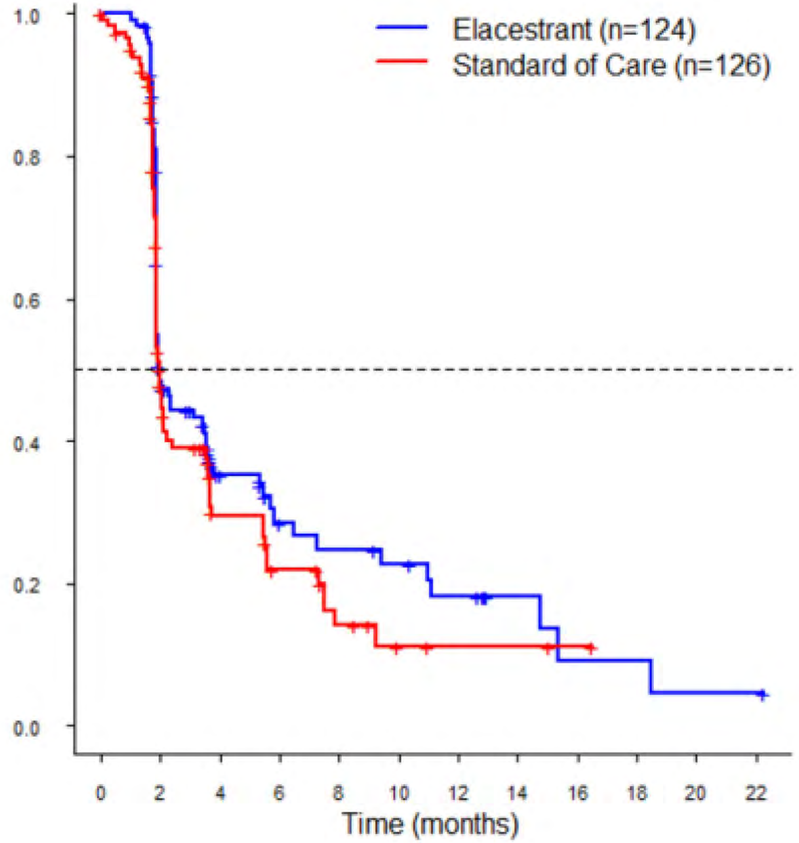


ESR1 mut - detected



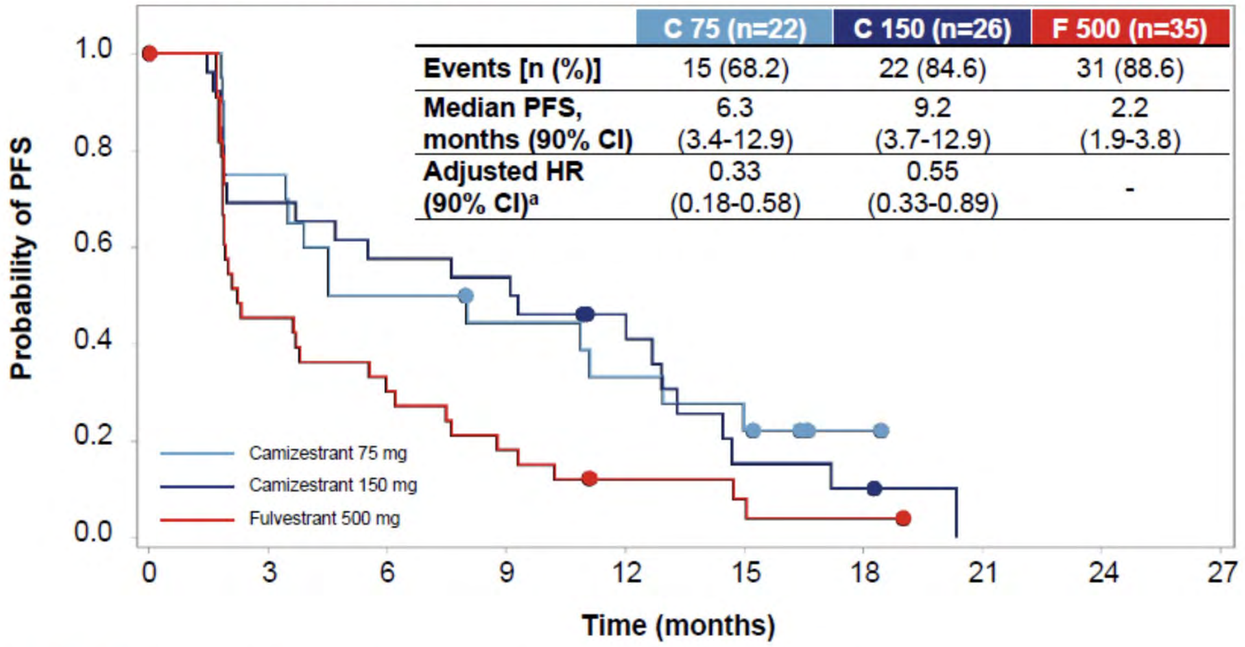
ESR1 mut - not detected

SERENA2 trial

PFS according to *ESR1* status

*ESR1*m detectable at baseline

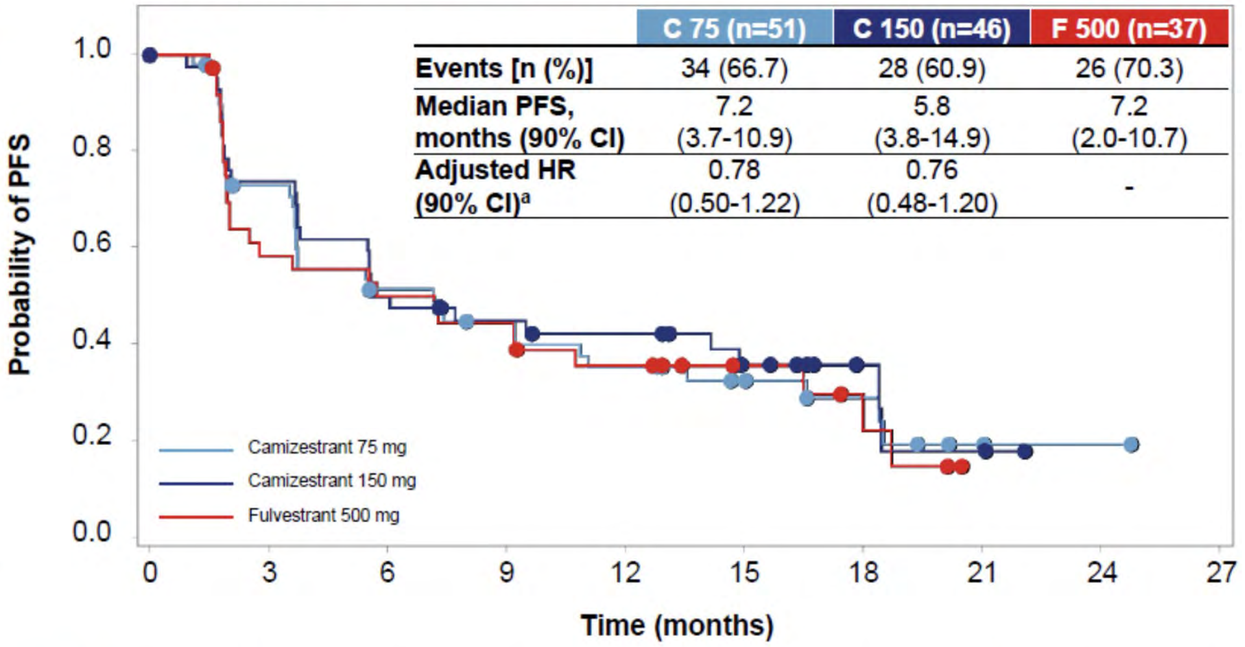
	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-



C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline

	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-



C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Oliveira M, Pominchuck D, Nowecki Z, et al. *Cancer Res*, 2023; doi:10.1158/1538-7445.SABCS22-GS3-02

Striking at the center: AKTi

CAPItello-291 trial

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

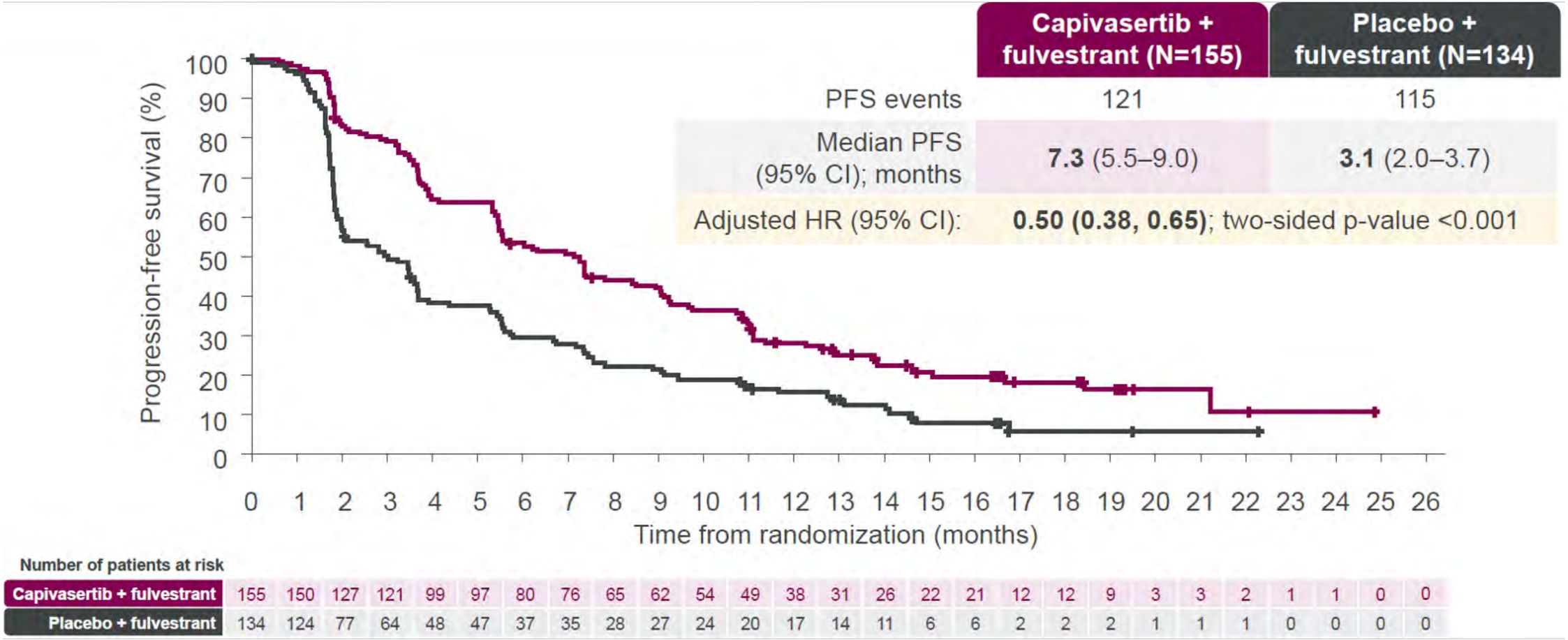
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Turner N, Oliveira M, Howell SJ, et al. *Cancer Res*, 2023; doi:10.1158/1538-7445.SABCS22-GS3-04

CAPItello-291 trial

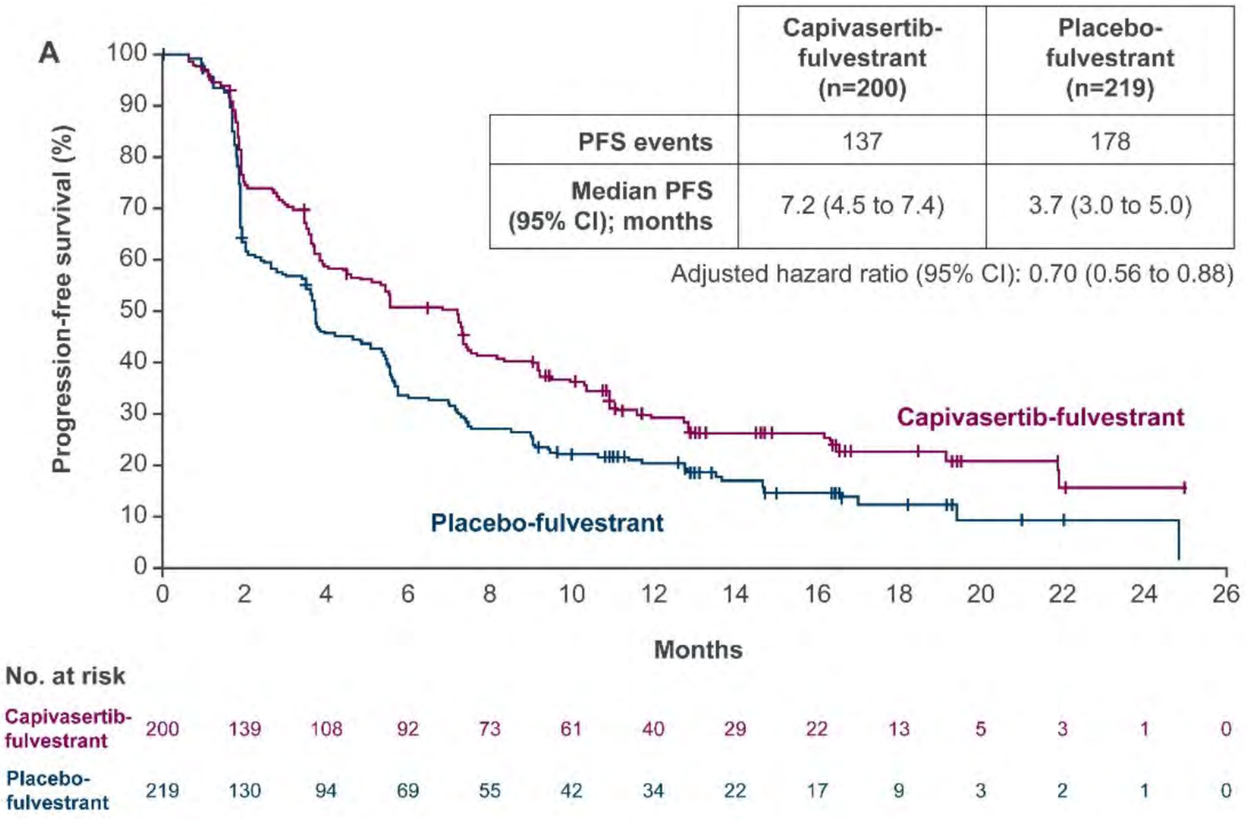
PFS in the AKT pathway altered population



Turner N, Oliveira M, Howell SJ, et al. *Cancer Res*, 2023; doi:10.1158/1538-7445.SABCS22-GS3-04

CAPItello-291 trial

Just because you don't know something, it doesn't mean it's irrelevant

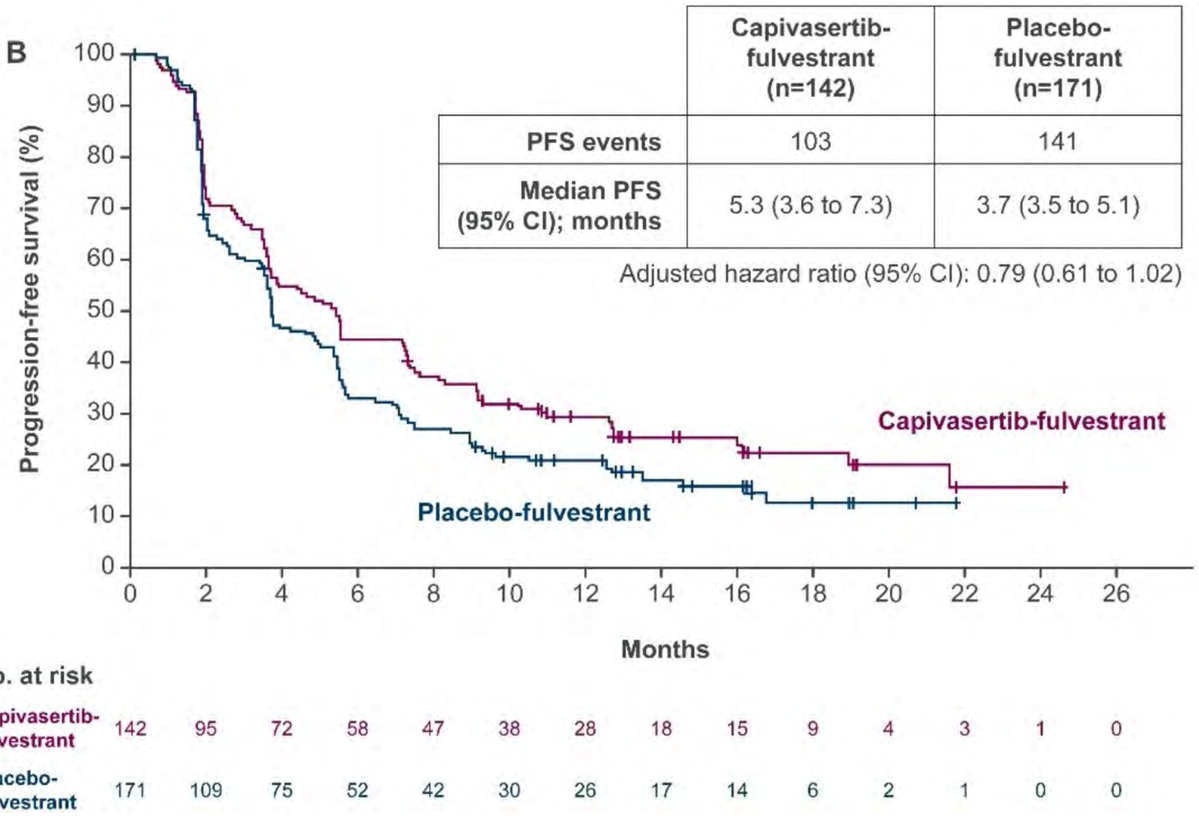


	Capivasertib-fulvestrant (n=200)	Placebo-fulvestrant (n=219)
PFS events	137	178
Median PFS (95% CI); months	7.2 (4.5 to 7.4)	3.7 (3.0 to 5.0)

Adjusted hazard ratio (95% CI): 0.70 (0.56 to 0.88)

No. at risk

Capivasertib-fulvestrant	200	139	108	92	73	61	40	29	22	13	5	3	1	0
Placebo-fulvestrant	219	130	94	69	55	42	34	22	17	9	3	2	1	0



	Capivasertib-fulvestrant (n=142)	Placebo-fulvestrant (n=171)
PFS events	103	141
Median PFS (95% CI); months	5.3 (3.6 to 7.3)	3.7 (3.5 to 5.1)

Adjusted hazard ratio (95% CI): 0.79 (0.61 to 1.02)

No. at risk

Capivasertib-fulvestrant	142	95	72	58	47	38	28	18	15	9	4	3	1	0
Placebo-fulvestrant	171	109	75	52	42	30	26	17	14	6	2	1	0	0

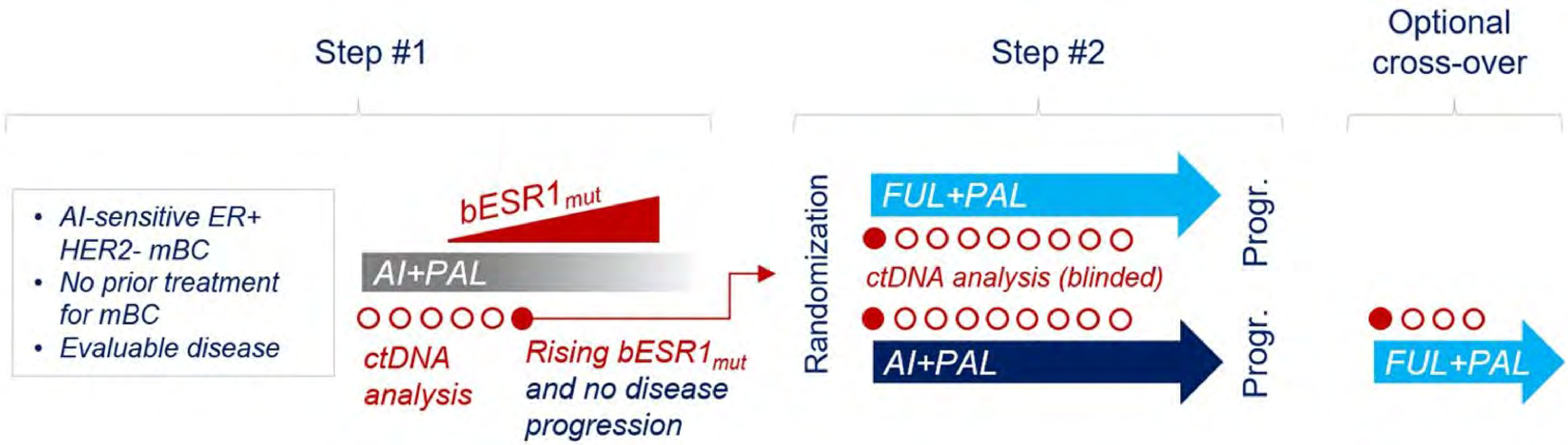
PFS in A) patients with AKT pathway non-altered tumors **including unknown NGS result** (per protocol) and B) patients with AKT pathway non-altered tumors **excluding unknown NGS result**

Turner NC, Oliveira M, Howell SJ, et al. *N Engl J Med*, 2023; doi:10.1056/NEJMoa2214131

But when should we **test & switch**?

But when should we test & switch?

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.

L Cabel, S Delaloge, AC Hardy-Bessard, et al ASCO 2023

The PADA-1 Study

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

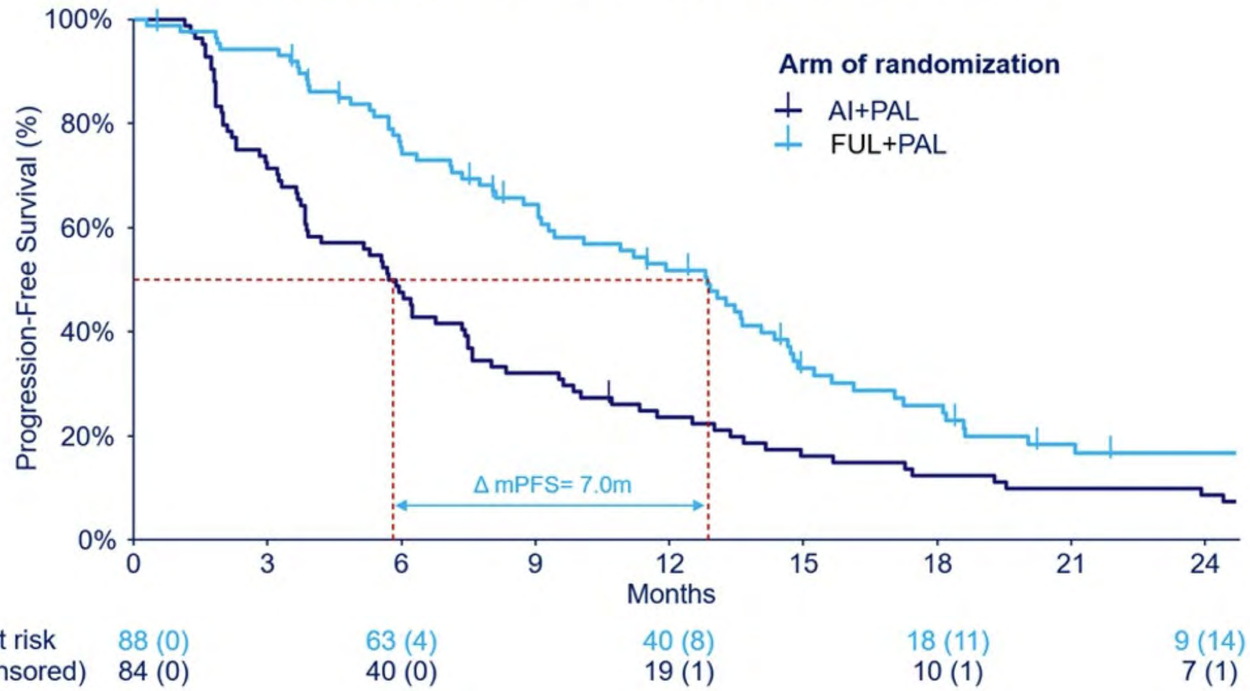
N= 172 pts randomized

- 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)

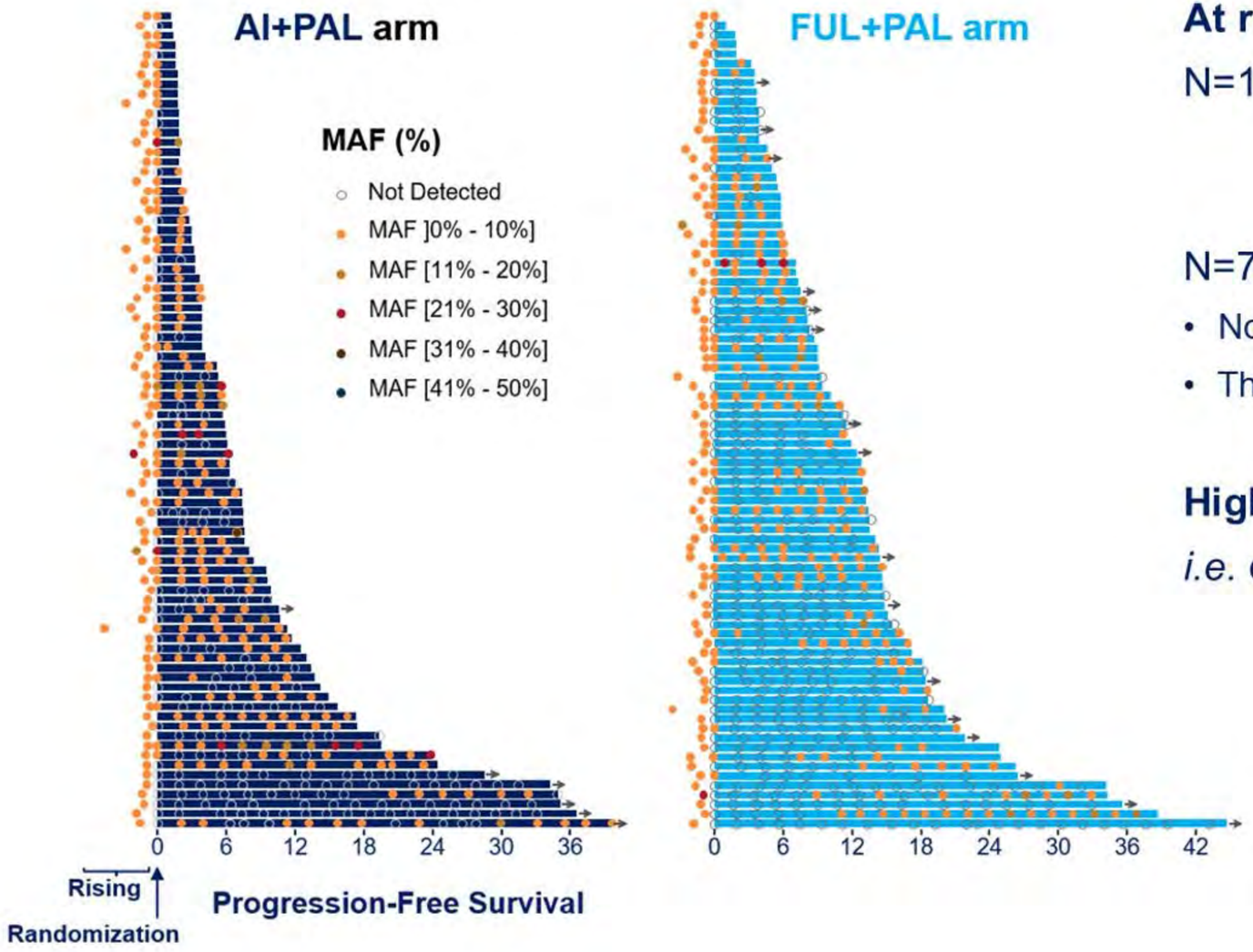
mPFS: 3.5 months, 95%CI [2.4;5.4]

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

L Cabel, S Delaloge, AC Hardy-Bessard, et al ASCO 2023

But does kinetics mean something?

bESR1 mut kinetics from randomization



At randomization

N=161 pts had a 2nd ctDNA result available

(AI+PAL was continued until randomization)

N=75/161 (46.6%) had no *bESR1*$_{mut}$ detected

- No difference between arms
- These patients globally had lower levels of rising *bESR1*$_{mut}$ (p=0.01)

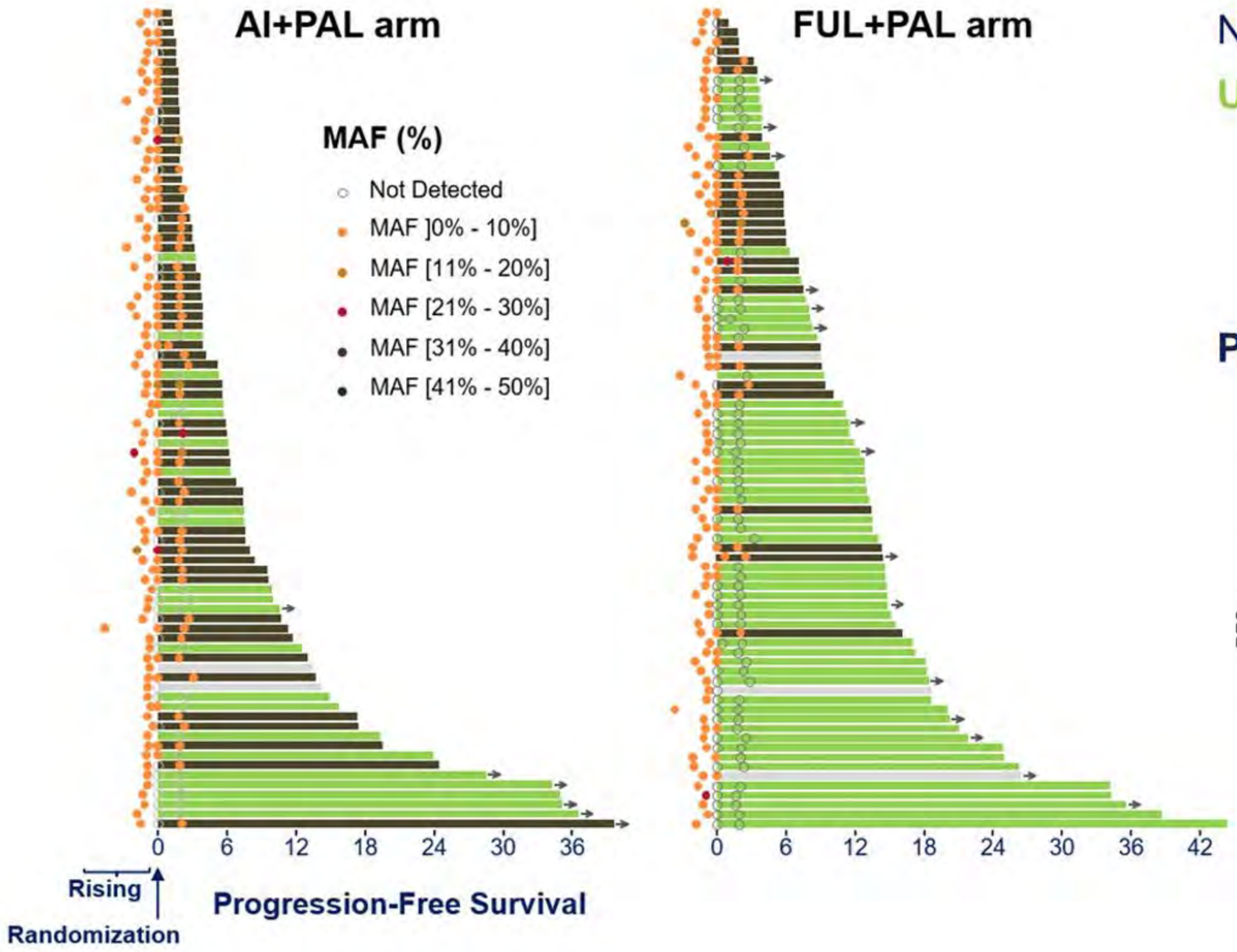
Highlight the specific context of 'rising' mutations

i.e. detection made at the limit of sensitivity of the ctDNA assay

L Cabel, S Delaloge, AC Hardy-Bessard, et al ASCO 2023

But does kinetics mean something?

bESR1 mut after 2 months on therapy



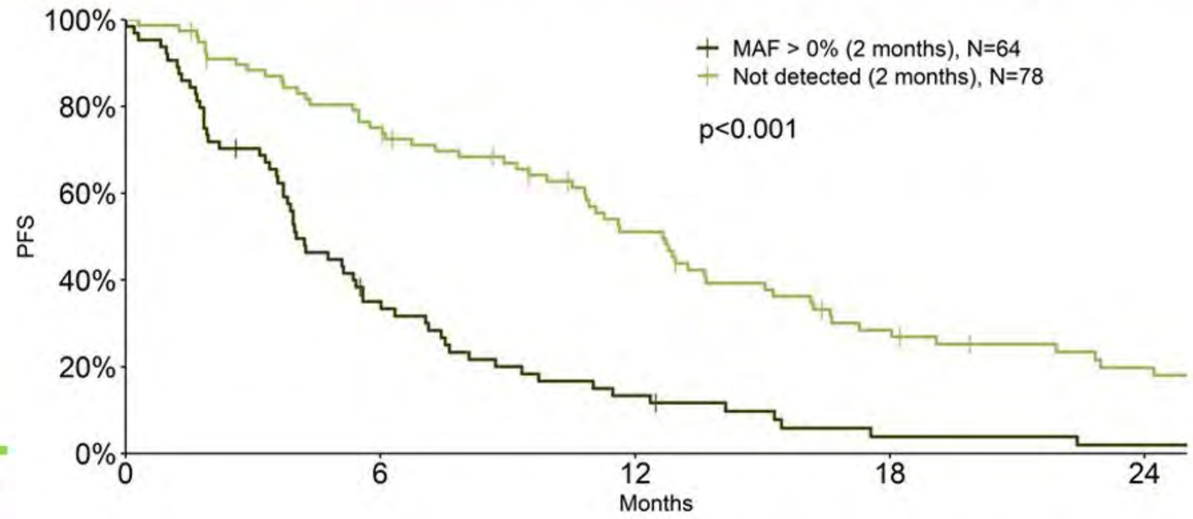
N=163 pts with ctDNA results available at 2 months

Undetectability rate:

FUL+PAL: N=58/85 68.2% [58.3%;78.1%]

AI+PAL: N=25/78 32.1% [21.7%;42.4%]

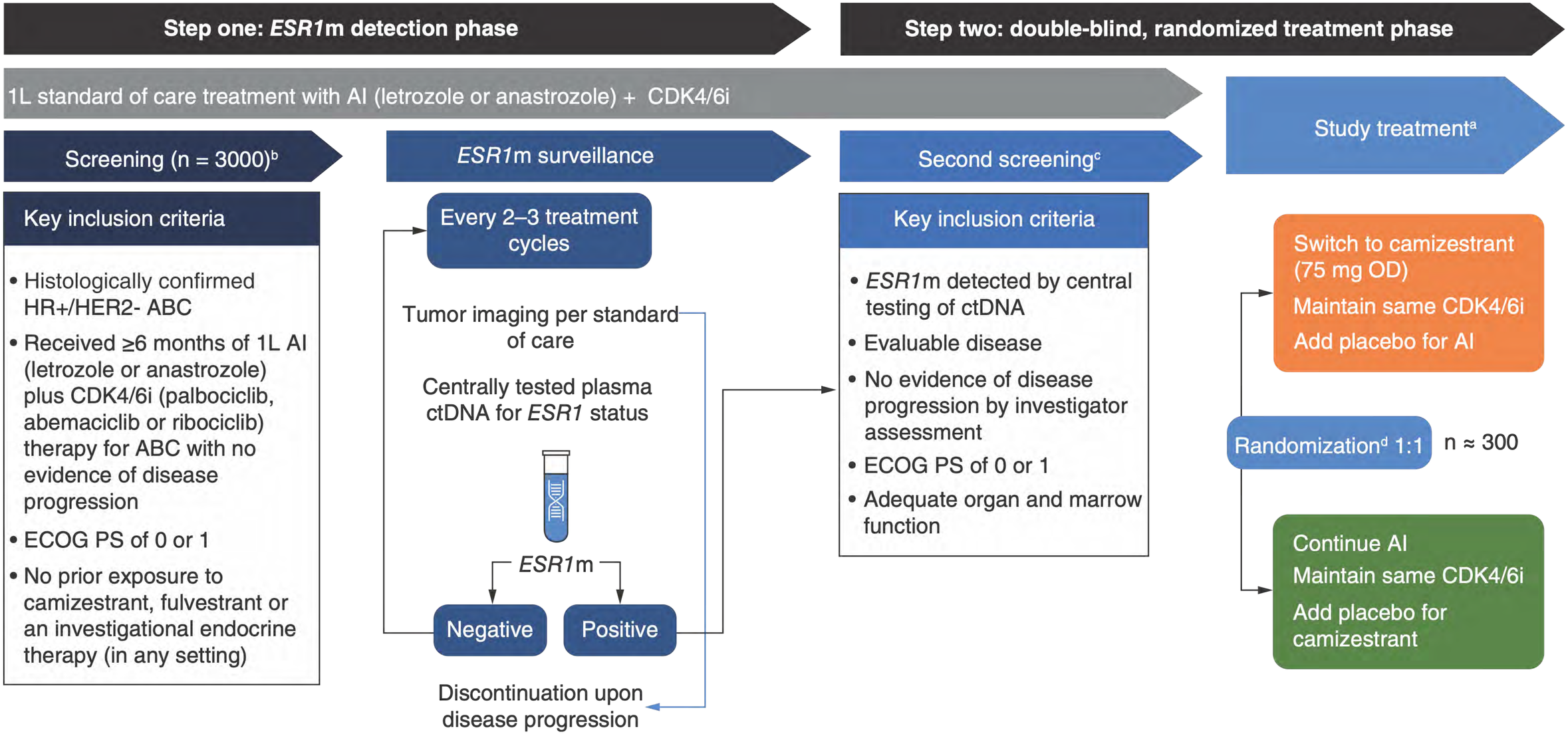
PFS by mutation status at 2 months (landmark analysis)



L Cabel, S Delaloge, AC Hardy-Bessard, et al ASCO 2023

Can we leverage the new oral SERDs?

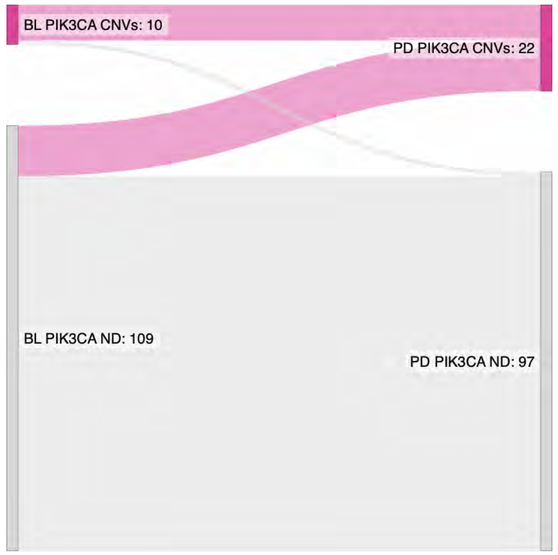
SERENA-6: a phase III switching trial

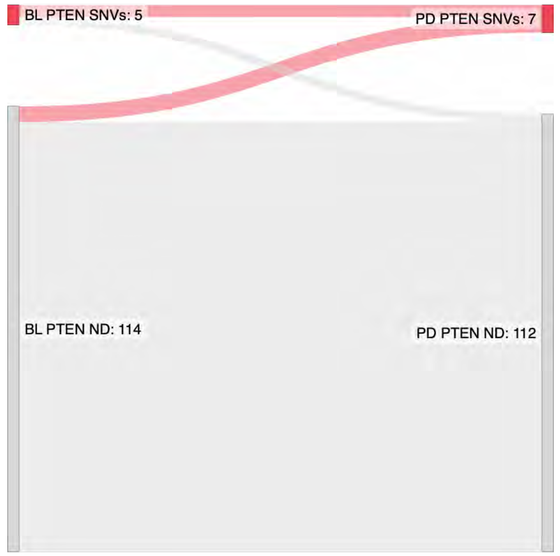


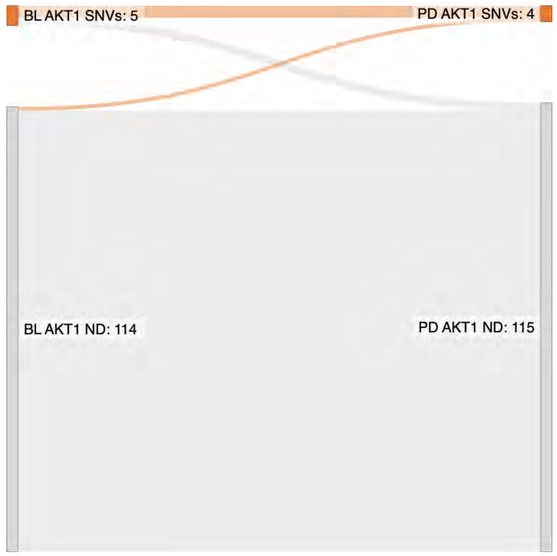
Turner N, Huang-Bartlett C, Kalinsky K, et al. *Futur Oncol*, 2023; doi:10.2217/fon-2022-1196

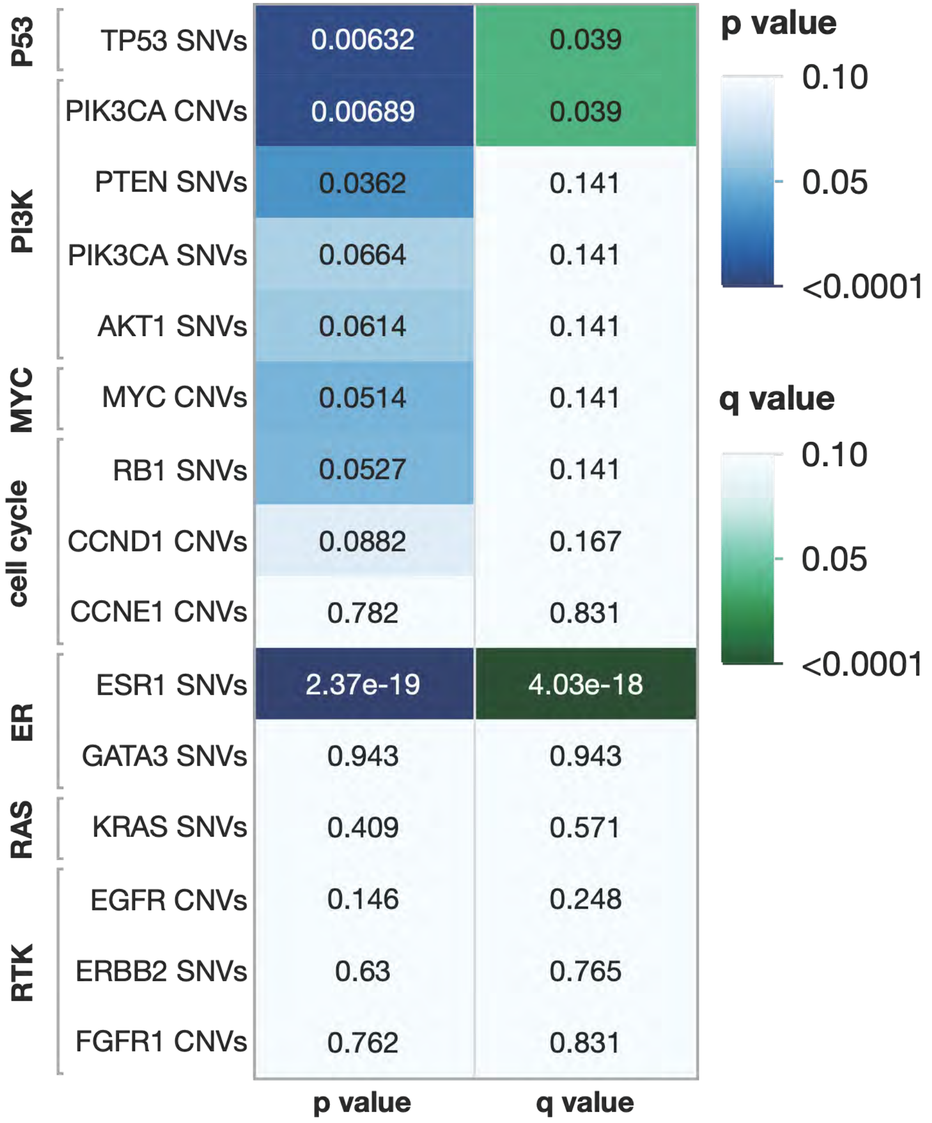
But when should we test & switch?

Putting together all available evidence









Gerratana L, Davis AA, Dri A, Reduzzi C, et al. In preparation

Wrapping up

From translational to daily clinical practice

1

Resistance biomarkers are pivotal for treatment sequencing in early and advanced BC

- Beyond progression regimens may become useful both as first and second line treatments
- Future data with CDK4/6i switch will be crucial (e.g. EMBER3, ELAINE3)

2

ET resistance is not only a matter of changing targets

- For example, ESR1 mutations perturbate the transcriptome resulting in neomorphic proprieties
- Composite biomarkers are, therefore, needed to capture the emergent swarm resistance

3

Algorithm for molecular testing and treatment switching is still unclear

- ESR1 mutations are heterogeneous and significantly change across lines, warranting retesting
- dynamics for PTEN and AKT1 alterations is still unclear, warranting ctDNA and updated tissue biopsy

Thank you

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

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