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hic sunt futura



The **Liquid biopsy**
Research Team

Sequenza del trattamento endocrino in HR positive MBC e possibile ruolo della biopsia liquida

Lorenzo Gerratana, MD

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

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

AIOM Giovani 2019, News in oncology

Conflict of Interest Disclosure Statement

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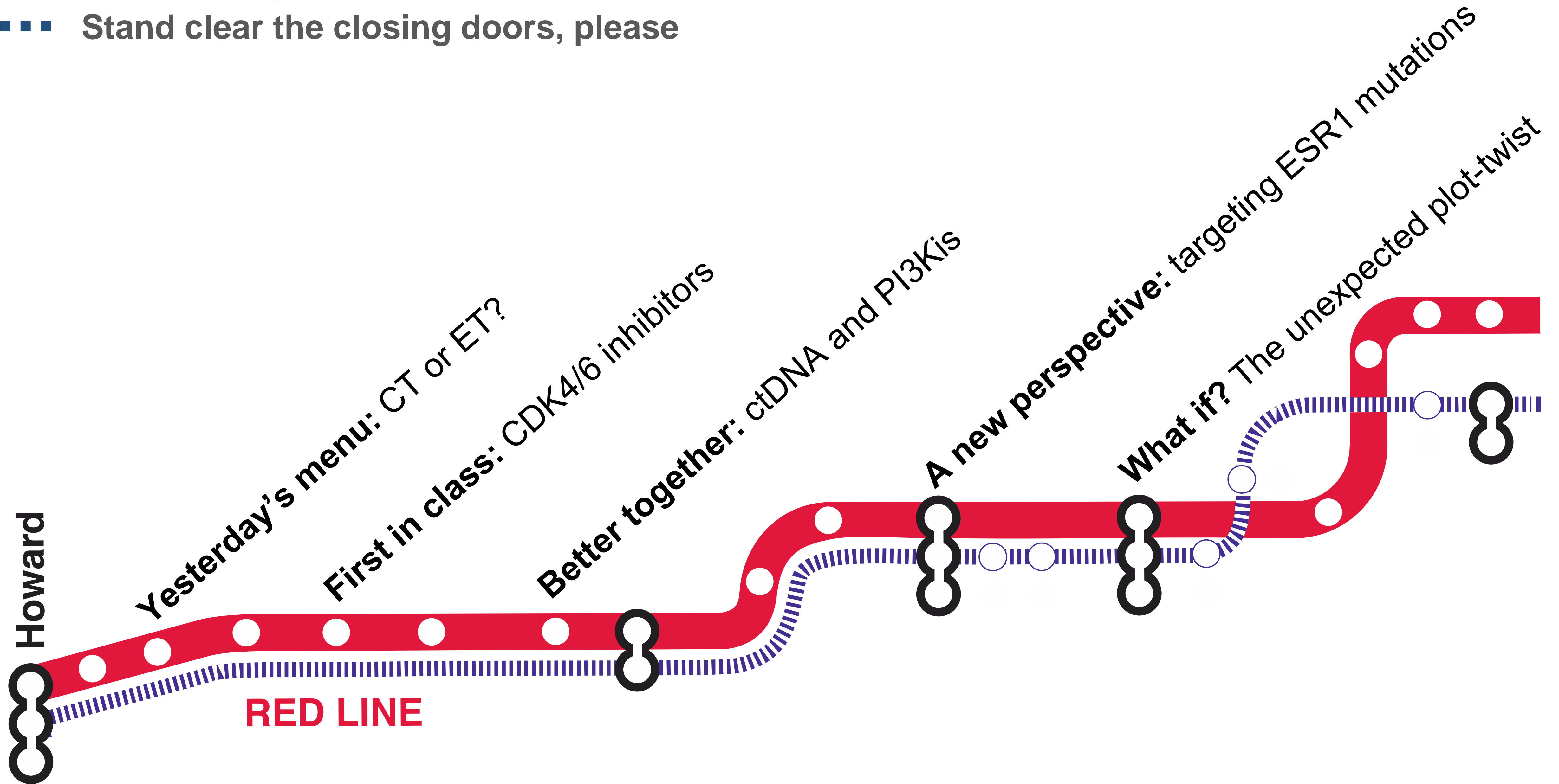
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Expert Testimony

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Our itinerary

■ ■ ■ ■ **Stand clear the closing doors, please**



Back to the past, with a translational twist

The STIC CTC trial

■ ■ ■ ■ Study design

1:1 randomization stratified on PS / center / disease-free interval



Clinician's choice

CTC count: blinded

→ **HT** (Clin._{low})

→ **CT** (Clin._{high})

CTC count (CellSearch®) ?

Clinician's choice: dismissed

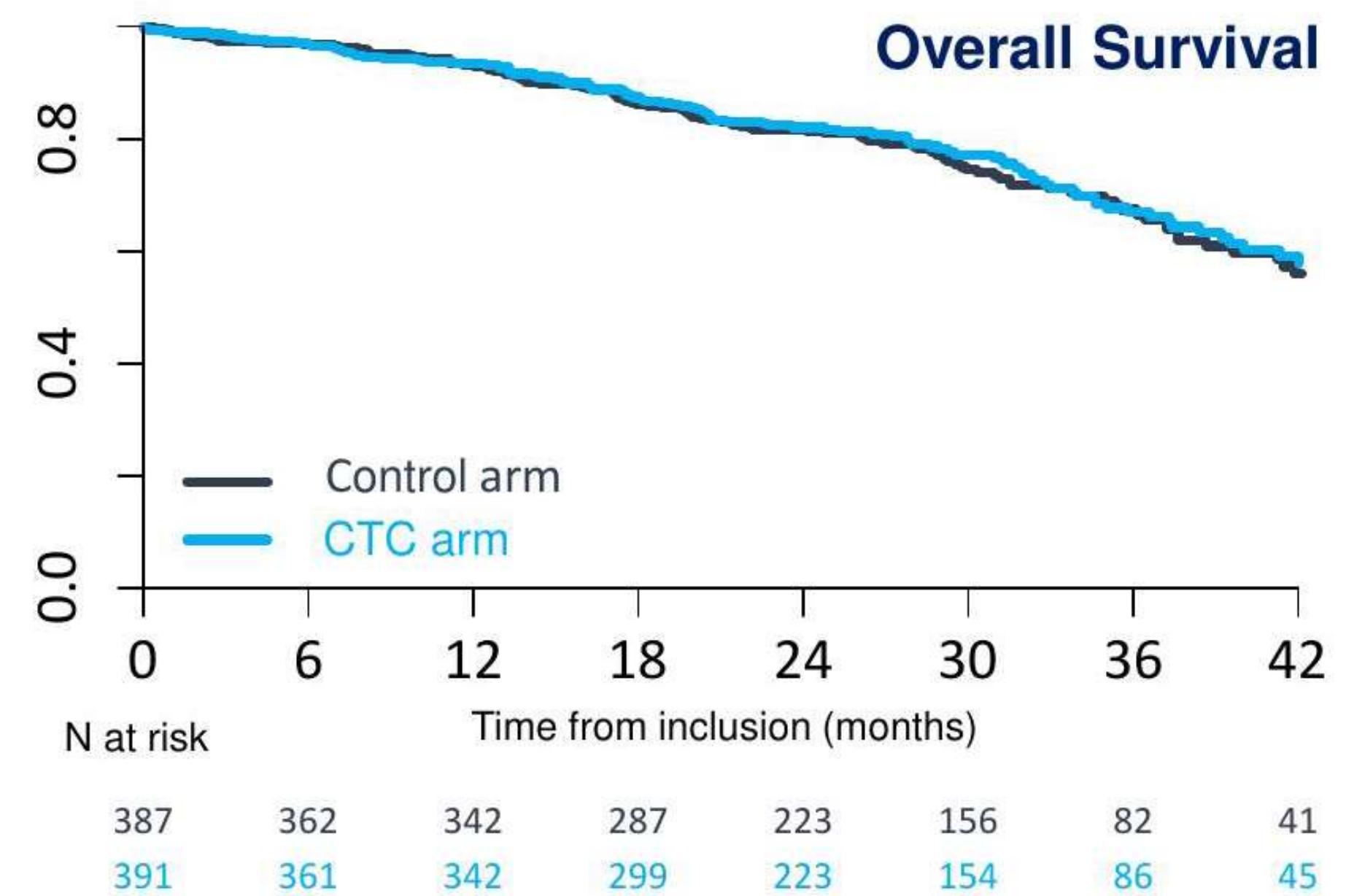
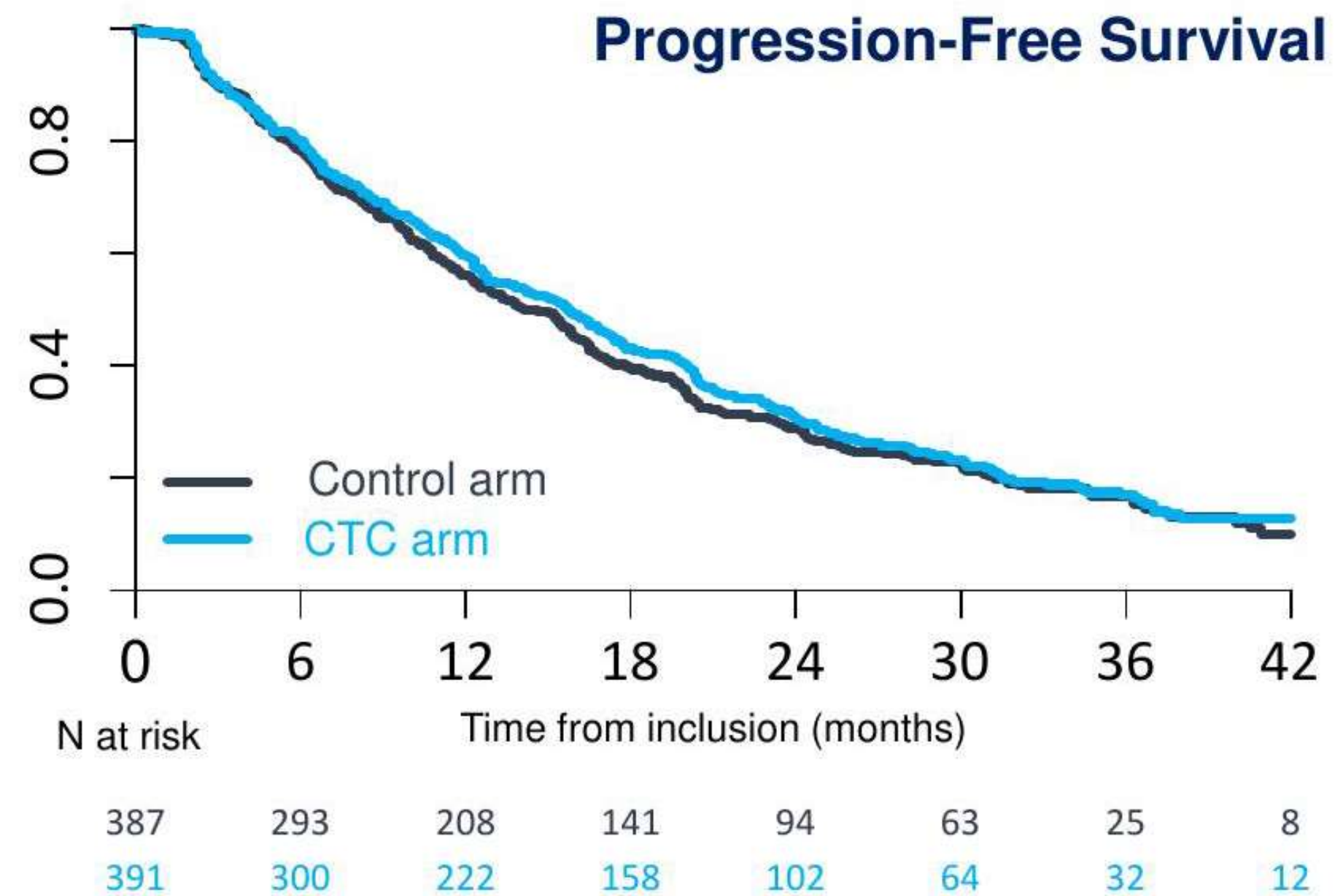
- <5 CTC /7.5mL → **HT** (CTC_{low})
- ≥ 5 CTC /7.5mL → **CT** (CTC_{high})

Primary endpoint: PFS non-inferiority between clinically-driven and CTC-driven arms

- pre-specified non-inferiority margin:1.25
- $\alpha=0.05$; $\beta=0.2$
- ➔ PFS events required: N= 498
- ➔ Patients to be included: N= 994, revised to N= 780

The STIC CTC trial

■ ■ ■ ■ Endpoints and population



Median PFS

CTC arm : 15.6 months [12.8-17.3]
Control arm : 14.0 months [12.2-16.0]

Primary objective met:

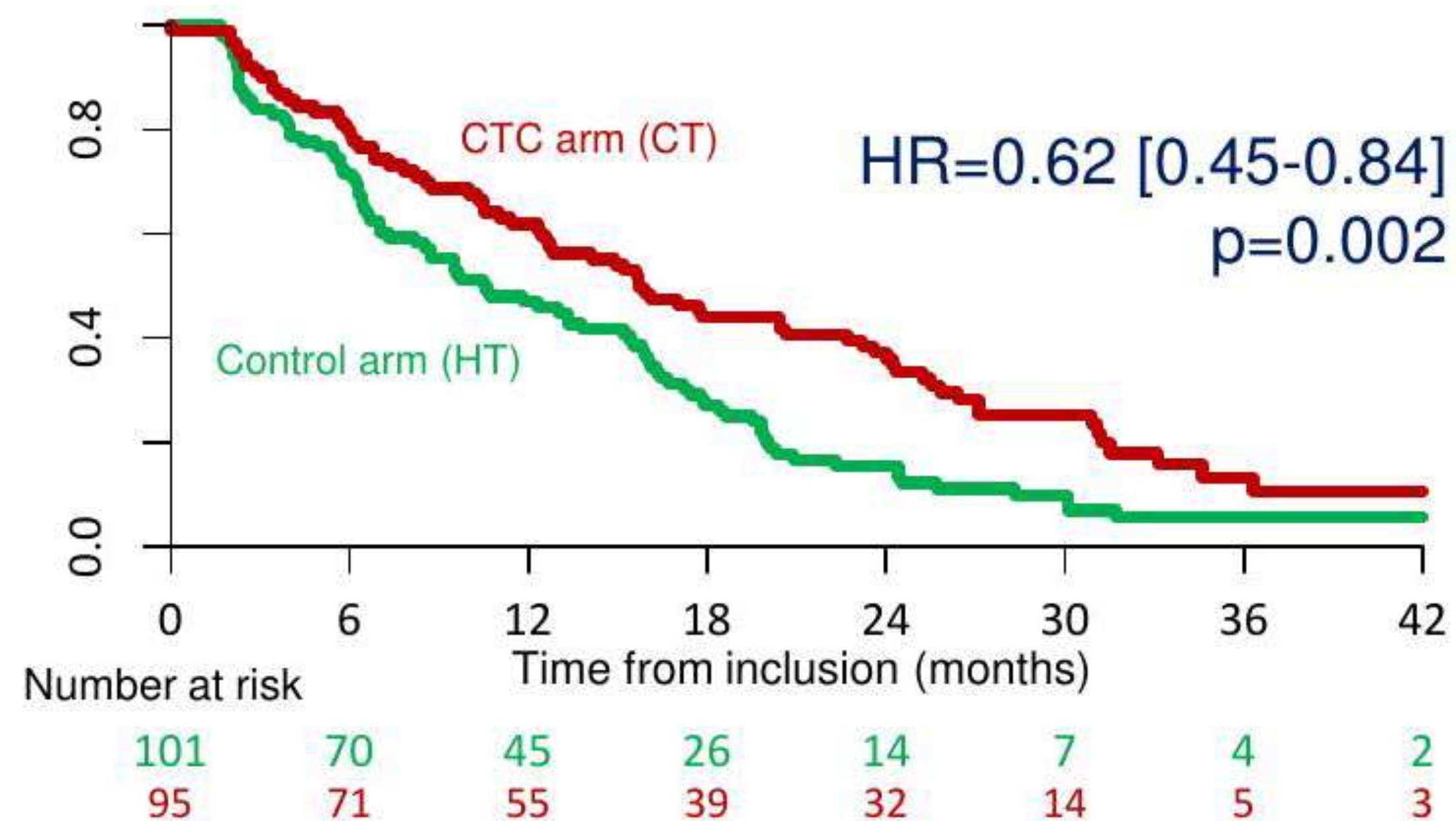
PFS HR=0.92, 90%CI[0.80-1.06]
No significant interaction with patient characteristics

OS rate at 24 months

82.1% [78.2-86.2]
81.4% [77.4-85.6]

The STIC CTC trial

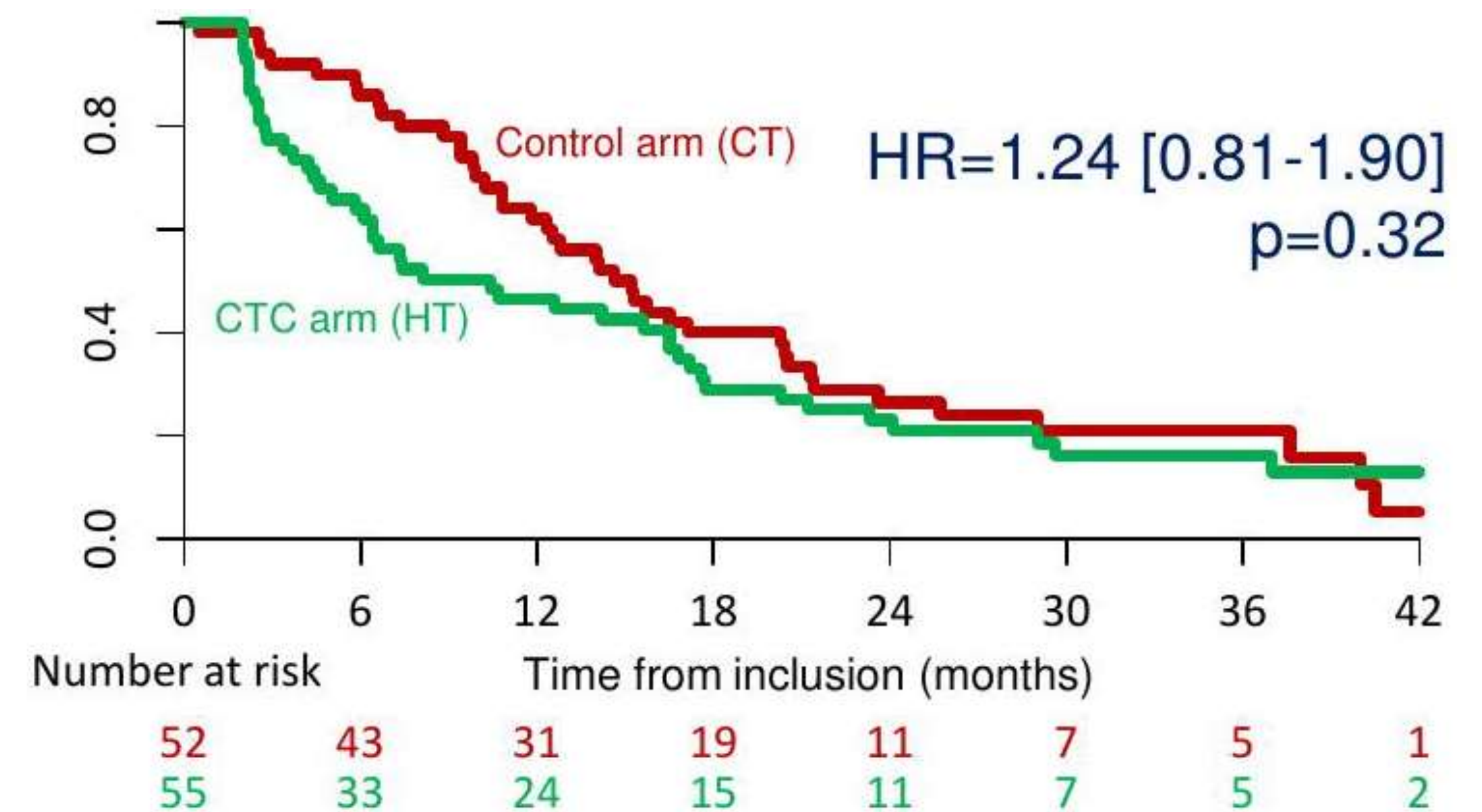
■ ■ ■ ■ Discordant group Clin^{low}/CTC^{high}



Median PFS

CTC arm (CT): 15.6 mo. [12.2-22.7]

Control arm (HT): 10.5 mo. [7.3-15.4]



Median PFS

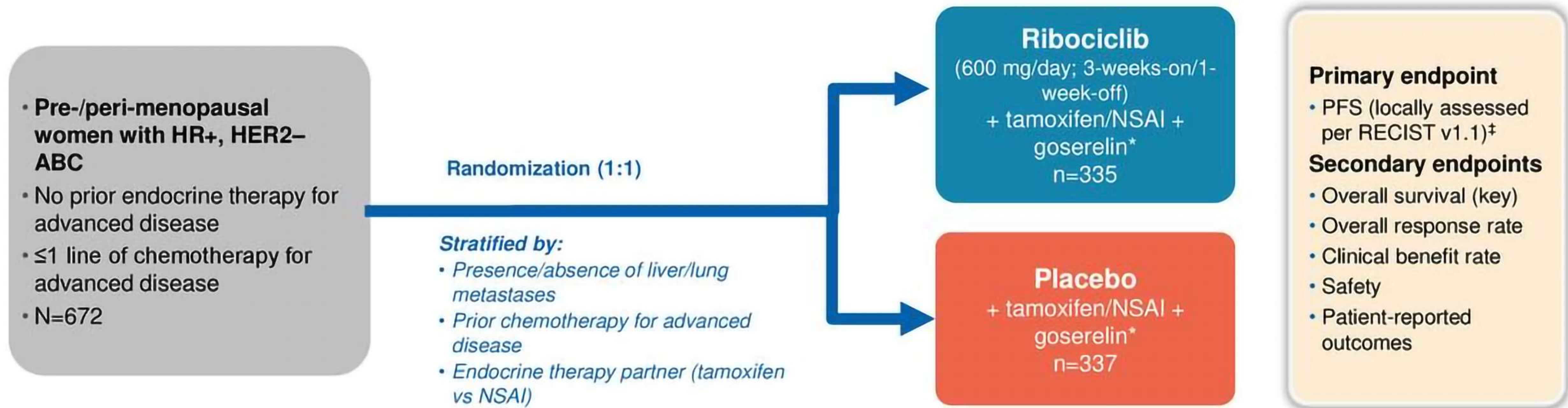
CTC arm (CT): 15.6 mo. [12.2-22.7]

Control arm (HT): 10.5 mo. [7.3-15.4]

It's 2019 again: the CDK 4/6 story

The CDK 4/6 story

■ ■ ■ The MONALEESA-7 trial



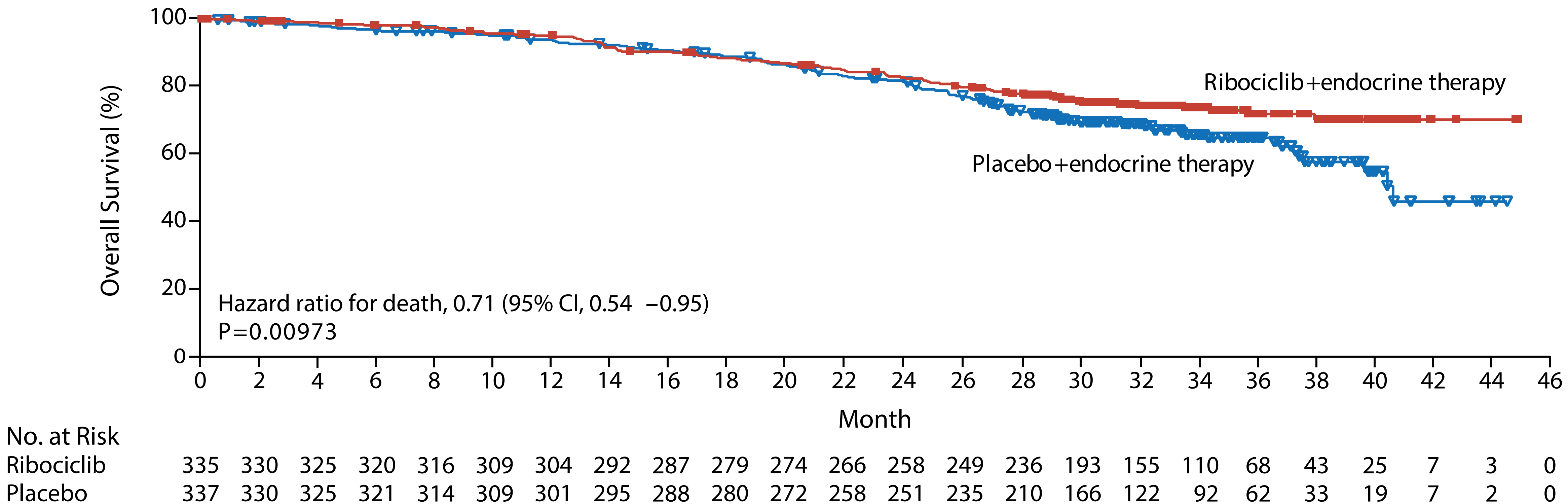
MONALEESA-7

Phase 3, randomized, double-blind, placebo-controlled trial. HR-positive, HER2-negative MBC Patients who had received previous treatment with an inhibitor of CDKs 4 and 6 were not eligible.

The primary endpoint was investigator-assessed PFS. OS was the key secondary endpoint,

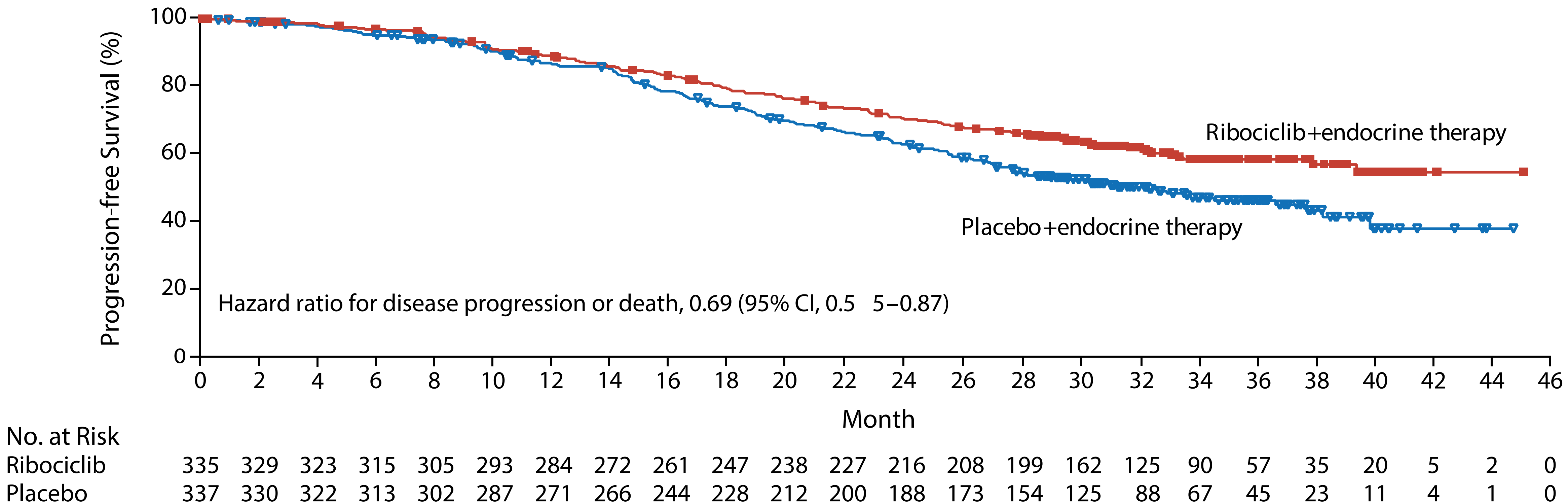
Overall Survival, at last

■ ■ ■ The MONALEESA-7 trial



What comes next?

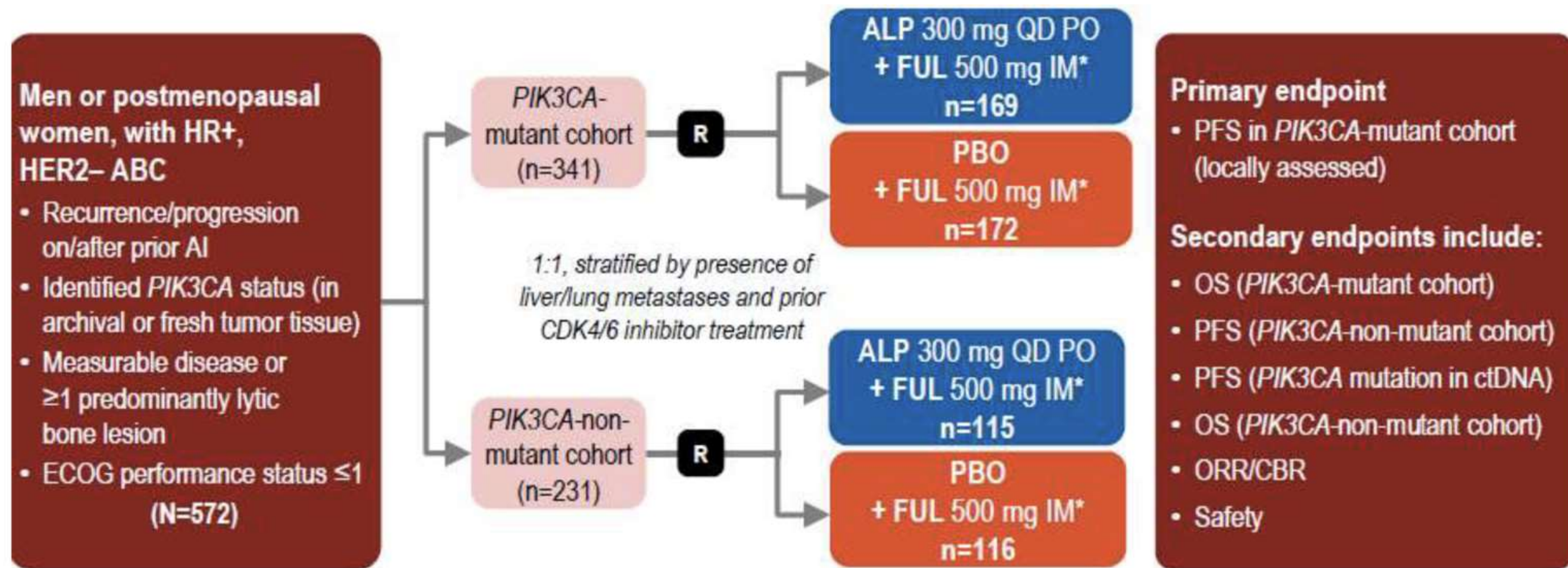
■ ■ ■ The MONALEESA-7 trial, PFS after CDK4/6 inhibition



And what about the PI3K saga?

What about PI3K?

■ ■ ■ ■ The SOLAR-1 trial



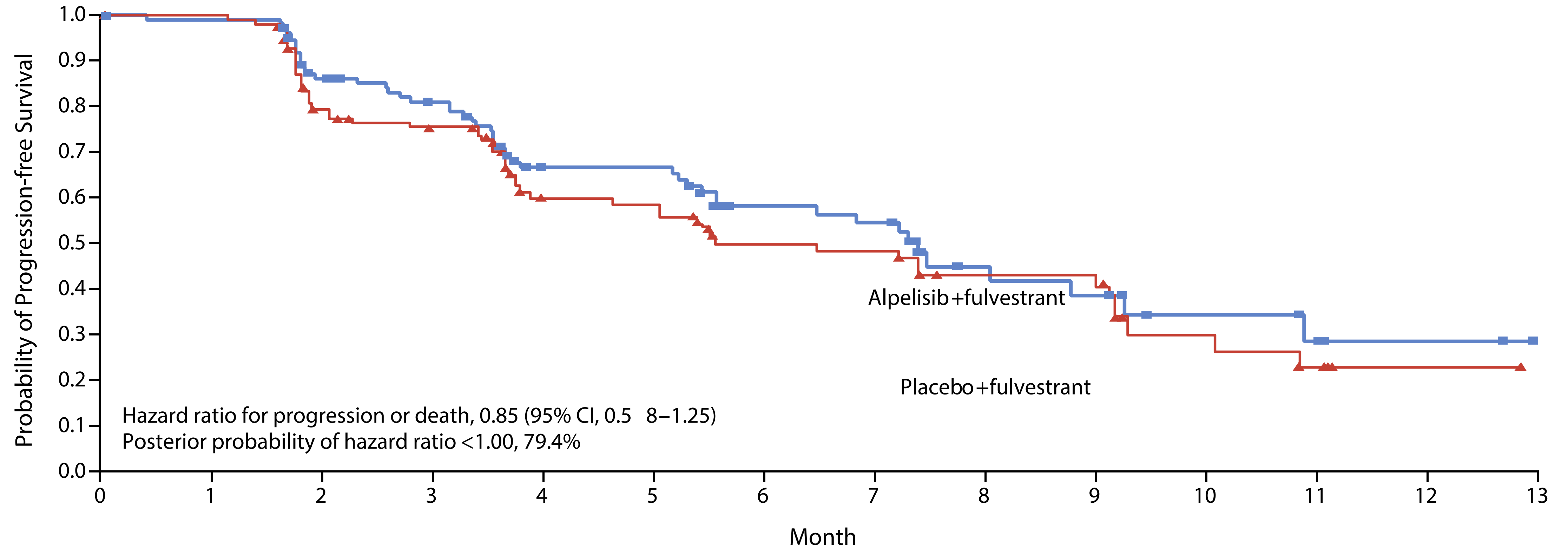
SOLAR-1

Phase III, randomized (1:1), double-blind study, 2 cohorts (*PIK3CA* mutation on tumor tissue) stratified by presence of liver and/or lung metastases, and prior CDK4/6 inhibitor treatment.

Primary endpoint: PFS. Secondary endpoints: OS, **PFS based on *PIK3CA* status in ctDNA**

The SOLAR-1 trial

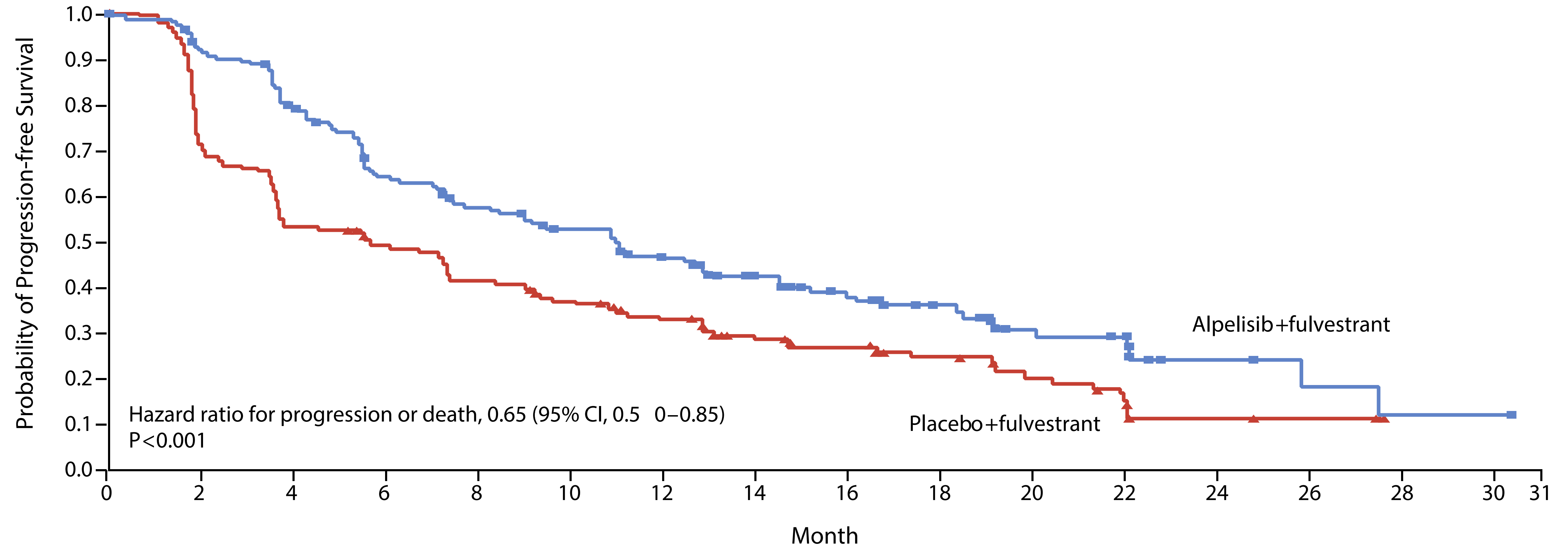
■ ■ ■ Cohort without PIK3CA-Mutated Cancer



No. at Risk																	
Alpelisib+fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0			
Placebo+fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0			

The SOLAR-1 trial

■ ■ ■ Cohort with PIK3CA-Mutated Cancer



No. at Risk		Month																
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0	
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0	

“

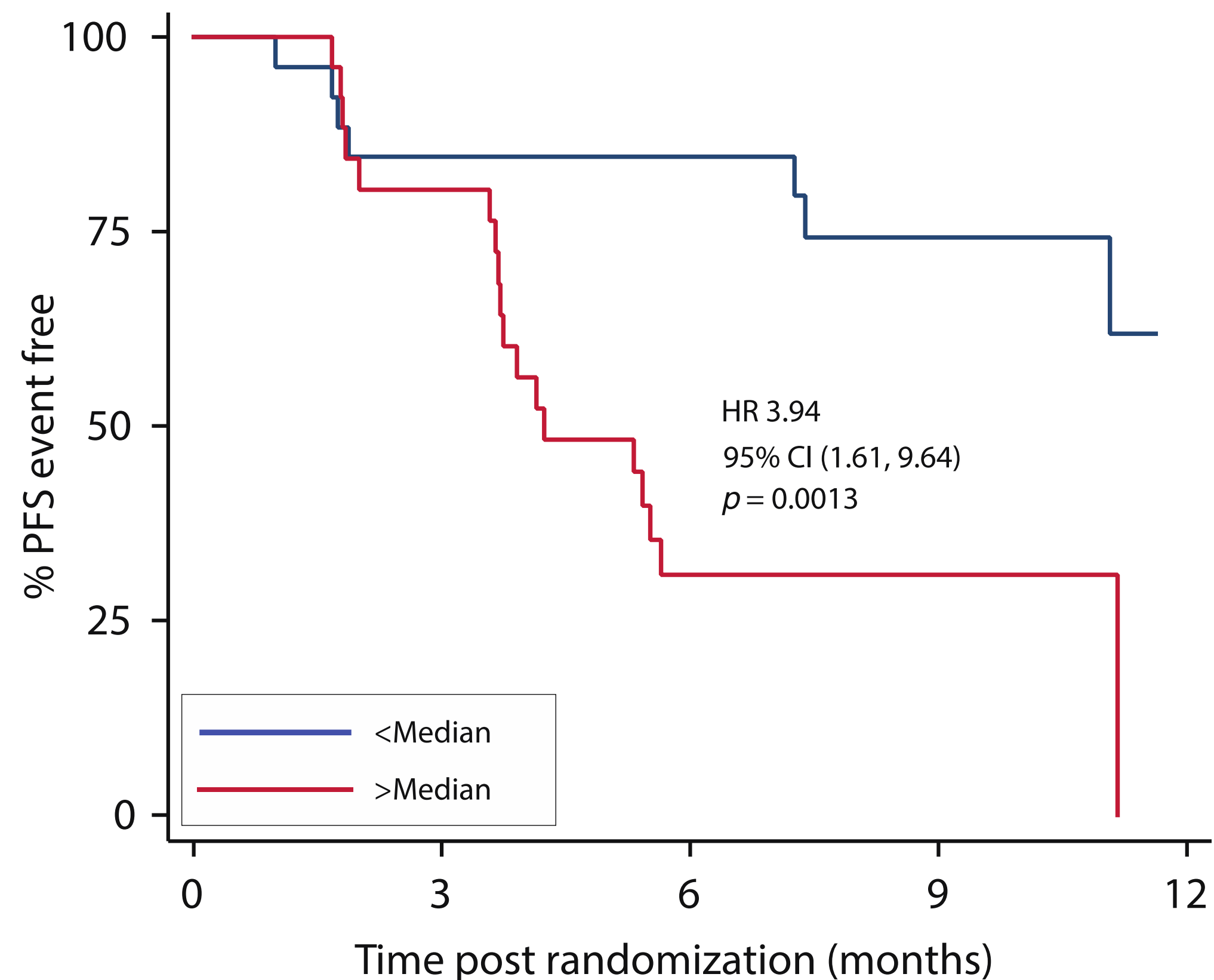
**The FDA also approved the companion diagnostic test, therascreen
PIK3CA RGQ PCR Kit, to detect the PIK3CA mutation in a tissue
and/or a liquid biopsy. Patients who are negative by the therascreen
test using the liquid biopsy should undergo tumor biopsy for
PIK3CA mutation testing.**

”

ESR1: the intriguing moving target

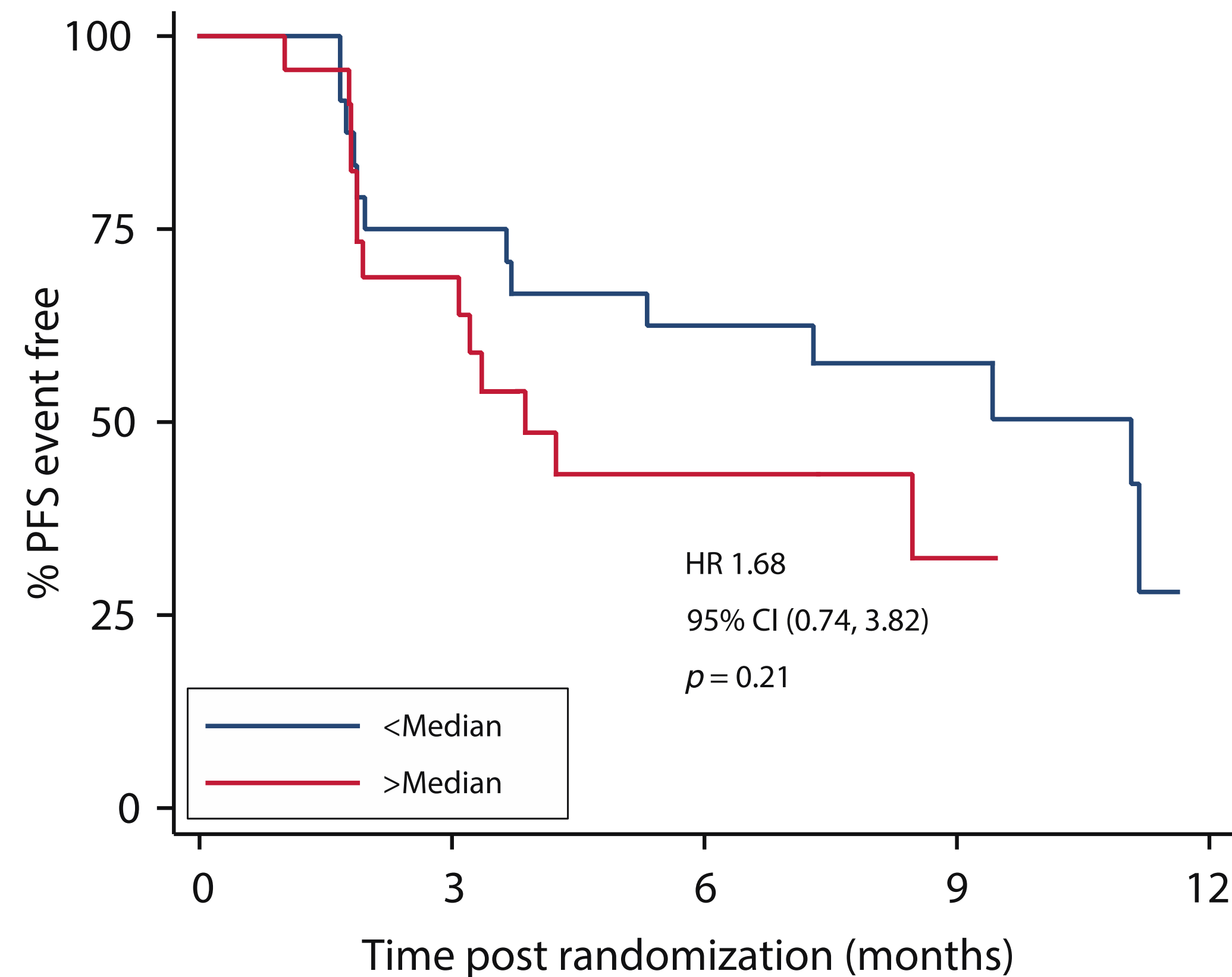
Are all mutations made equal?

PIK3CA vs ESR1 15-days dynamics



Number at risk (events)

<Median:	26	(4)	22	(0)	17	(2)	10	(1)	1
>Median:	26	(5)	20	(12)	7	(0)	4	(1)	0

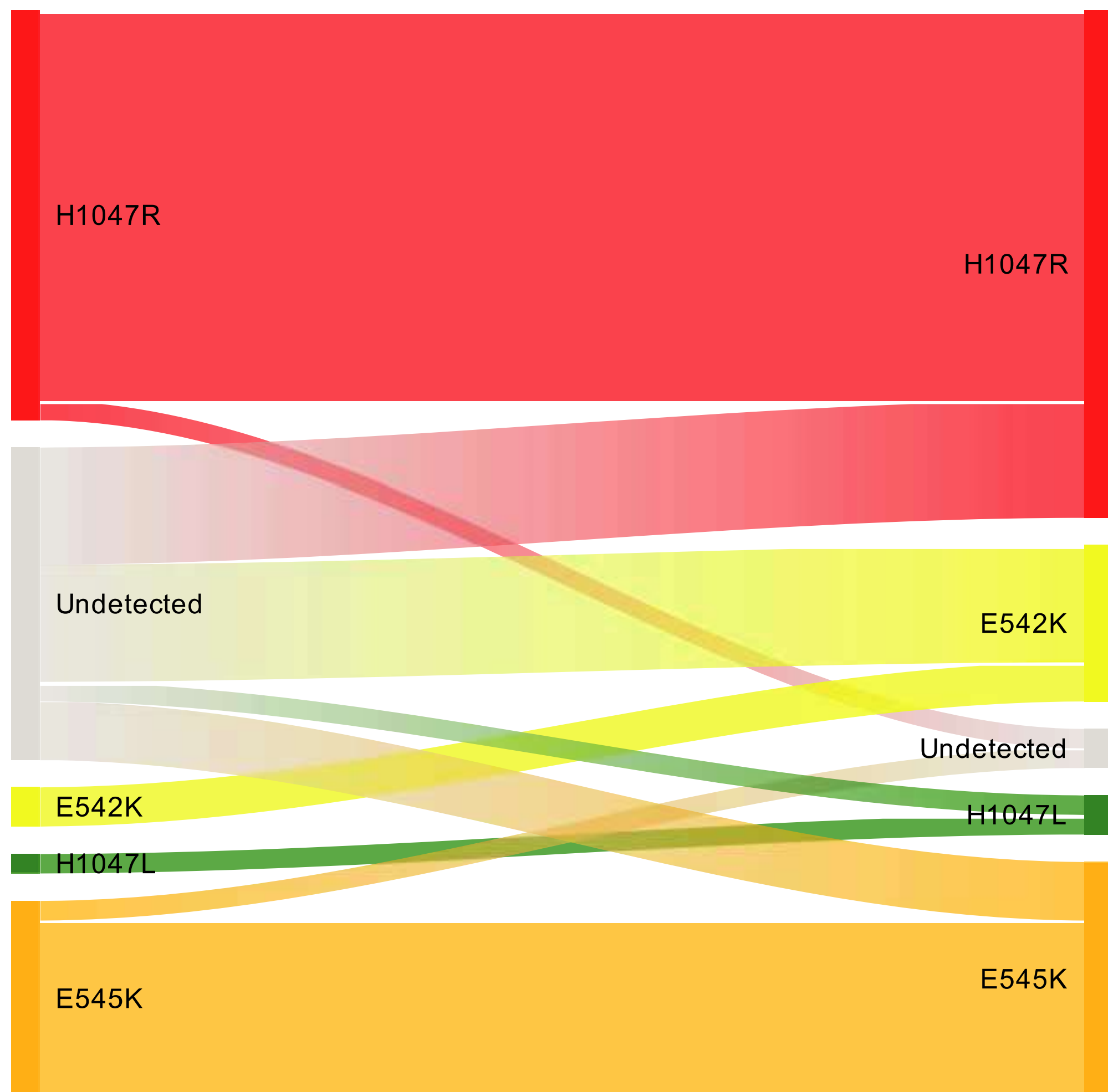


Number at risk (events)

<Median:	24	(6)	18	(3)	14	(1)	9	(3)	0
>Median:	23	(7)	14	(5)	6	(1)	3	(0)	0

Are all mutations made equal?

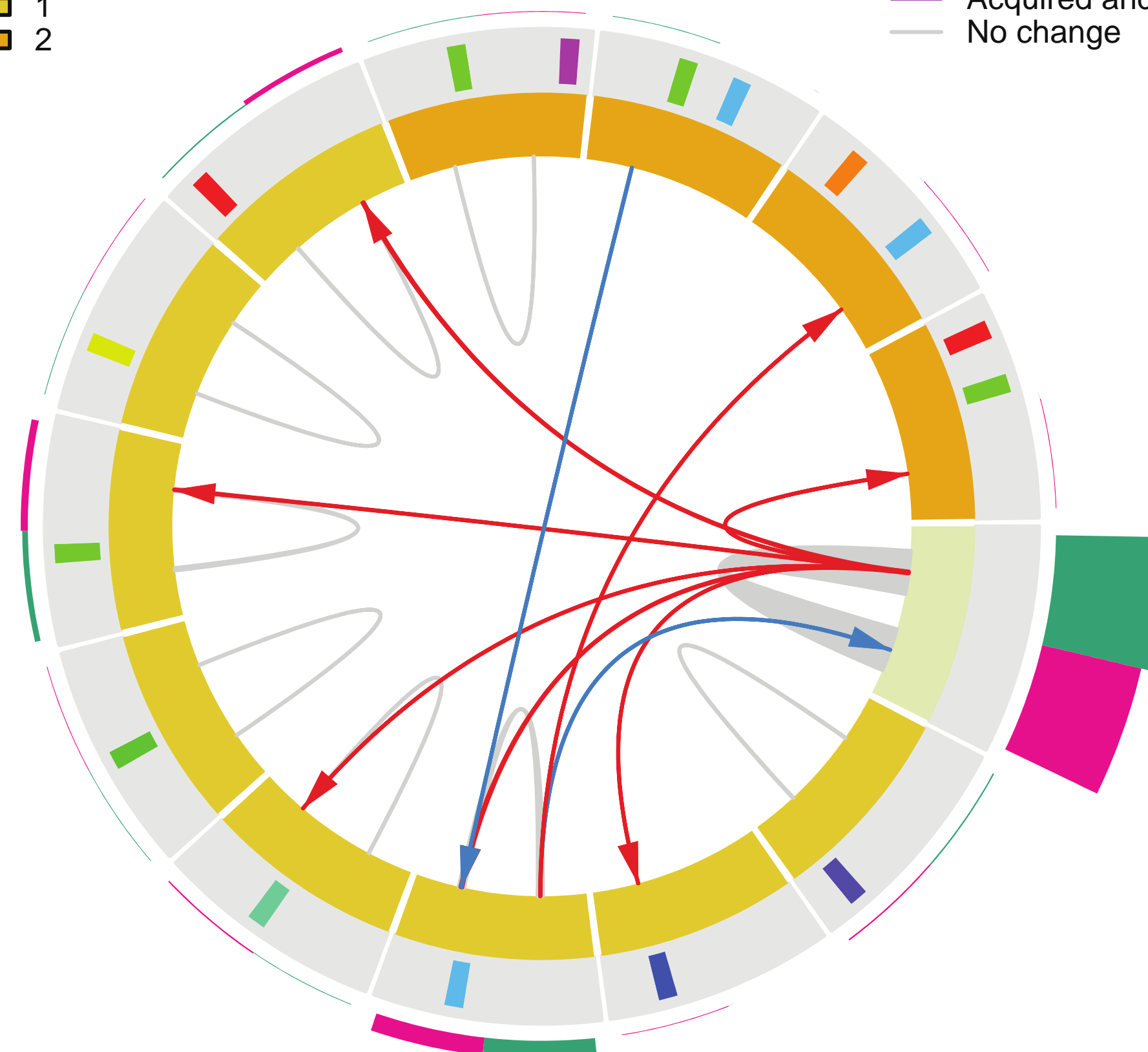
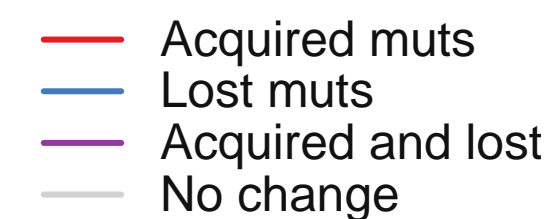
■■■■ PIK3CA - The reliable bet



SEGMENTS:
Number of
mutations



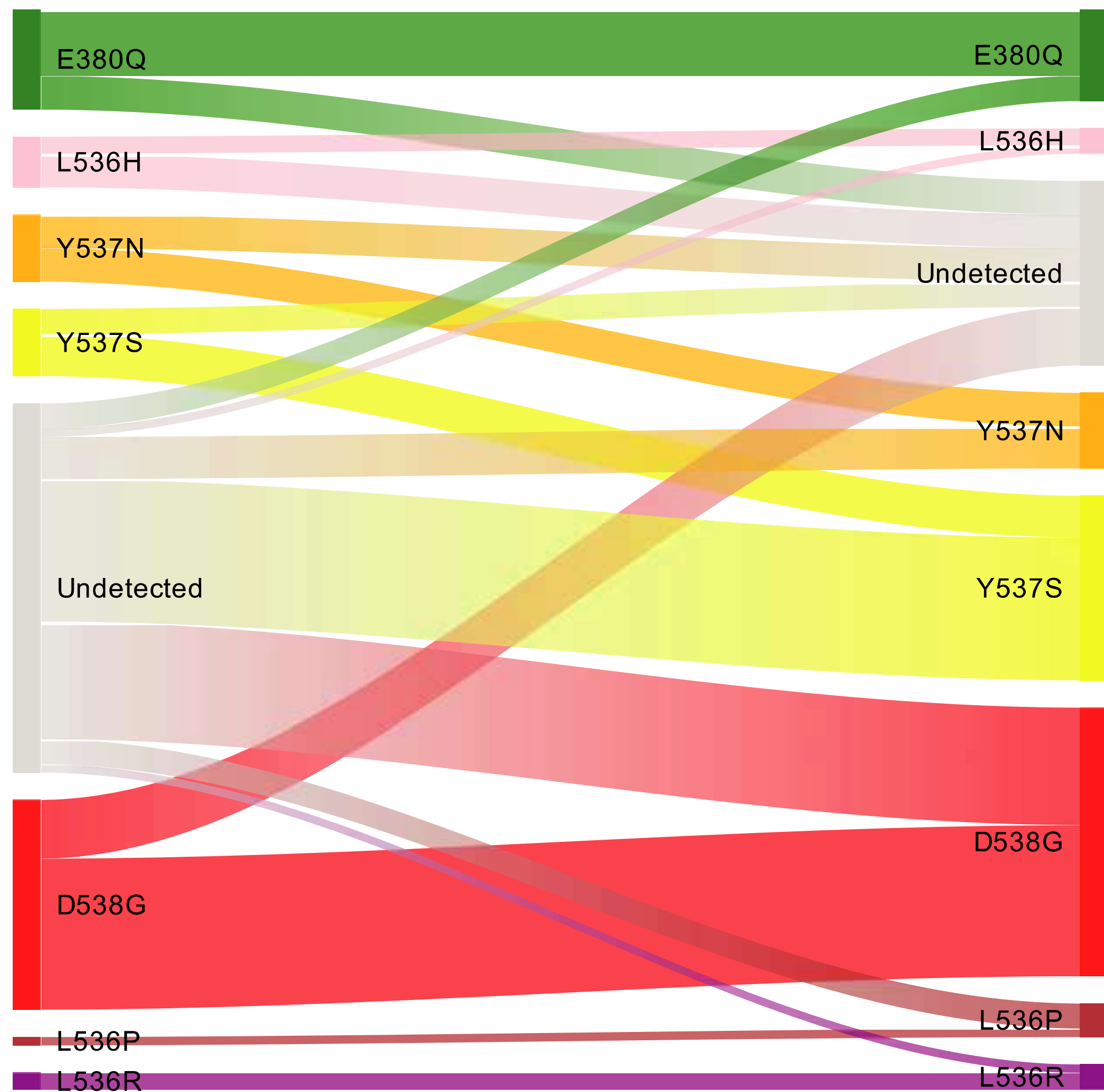
LINKS: Patients with
change on treatment



■ Number of patients at D1
■ Number of patients at EOT

Are all mutations made equal?

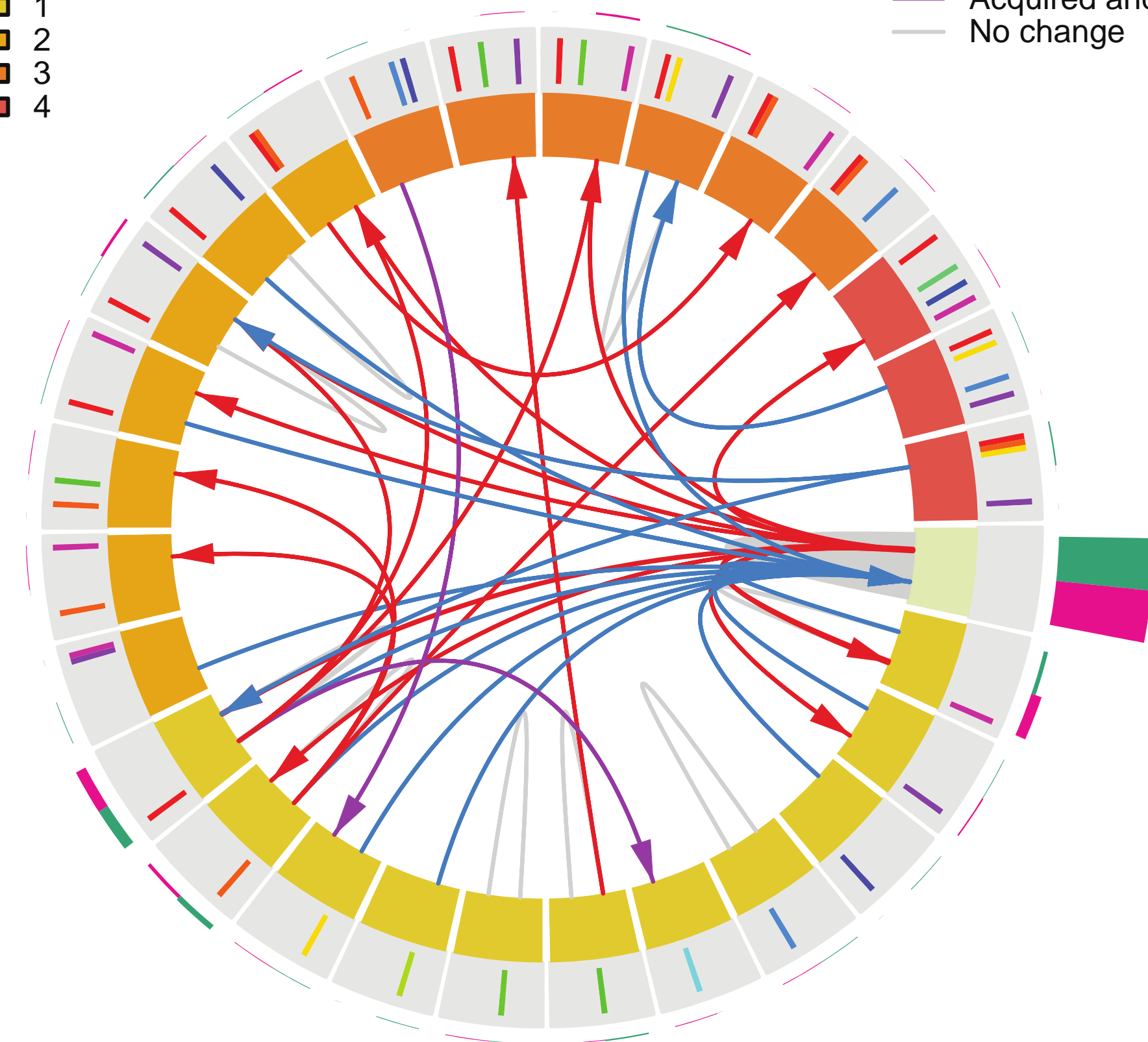
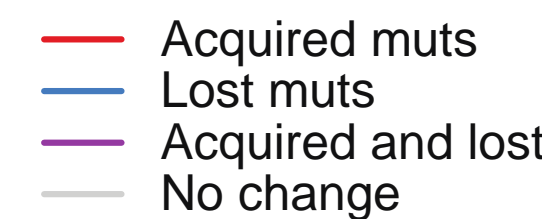
■■■■ ESR1 - the whimsical one



SEGMENTS:
Number of
mutations



LINKS: Patients with
change on treatment

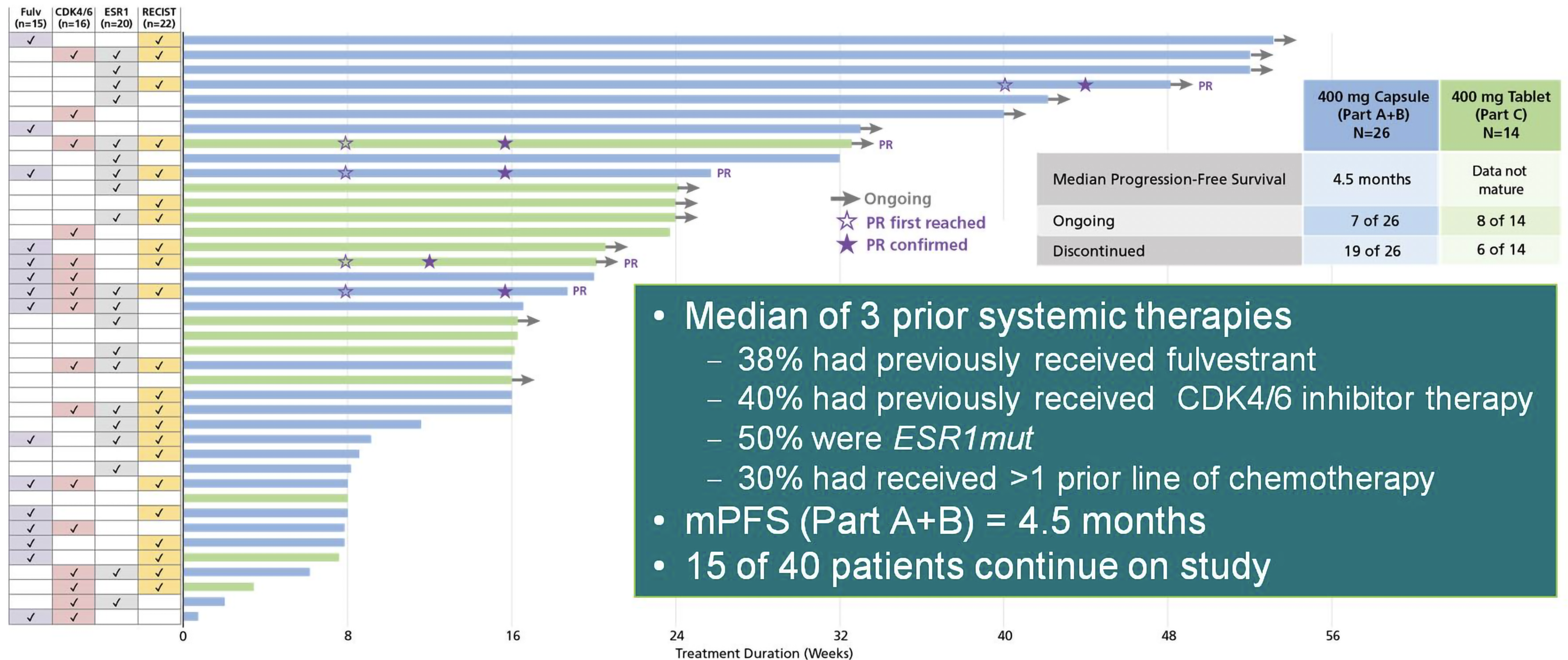


■ Number of patients at D1
■ Number of patients at EOT

Oral SERDs: the new gang in town

The new gang in town

■ ■ ■ ■ Elacestrant phase I trial

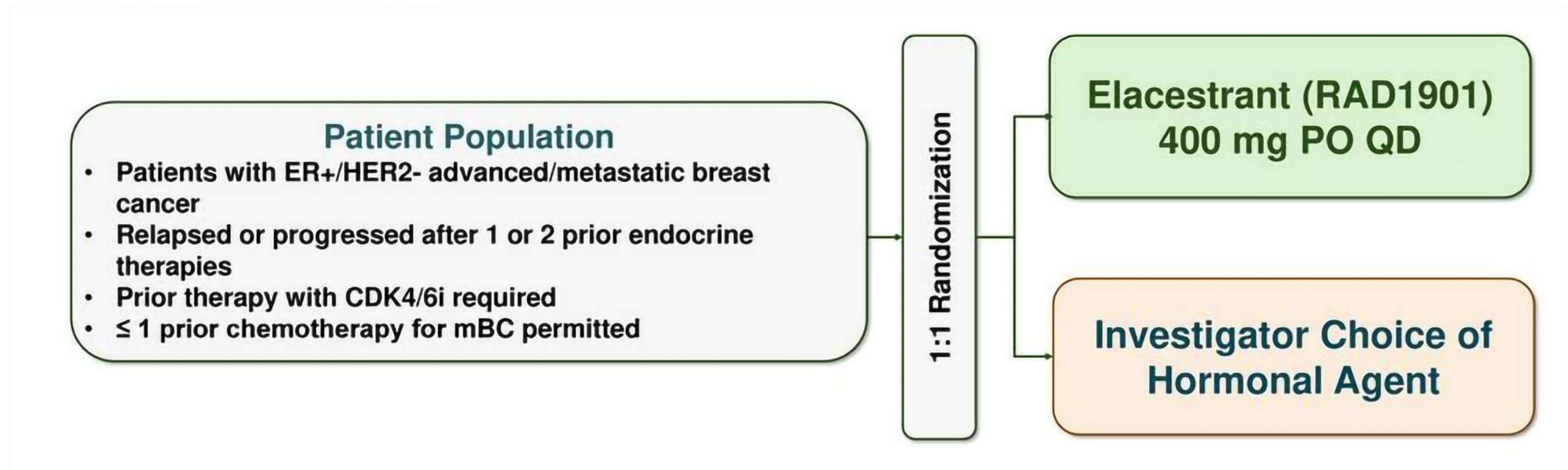


- Median of 3 prior systemic therapies
 - 38% had previously received fulvestrant
 - 40% had previously received CDK4/6 inhibitor therapy
 - 50% were *ESR1mut*
 - 30% had received >1 prior line of chemotherapy
- mPFS (Part A+B) = 4.5 months
- 15 of 40 patients continue on study

Fulv = prior fulvestrant treatment; CDK4/6 = prior CDK4/6 inhibitor treatment; ESR1 = ESR1 mutation detected at baseline; RECIST = patients with RECIST measurable disease.

The new gang in town

■ ■ ■ ■ The Phase III trial EMERALD



EMERALD

Randomized, open-label phase 3 trial for post-menopausal women or men with mBC.

Stratification factors include ESR1 mutation status (detected by ctDNA) and prior fulvestrant treatment

The primary endpoints are PFS by IRC, secondary endpoints include: OS, ORR and CBR

The treatment algorithm

■ ■ ■ ■ The therapeutic cascade

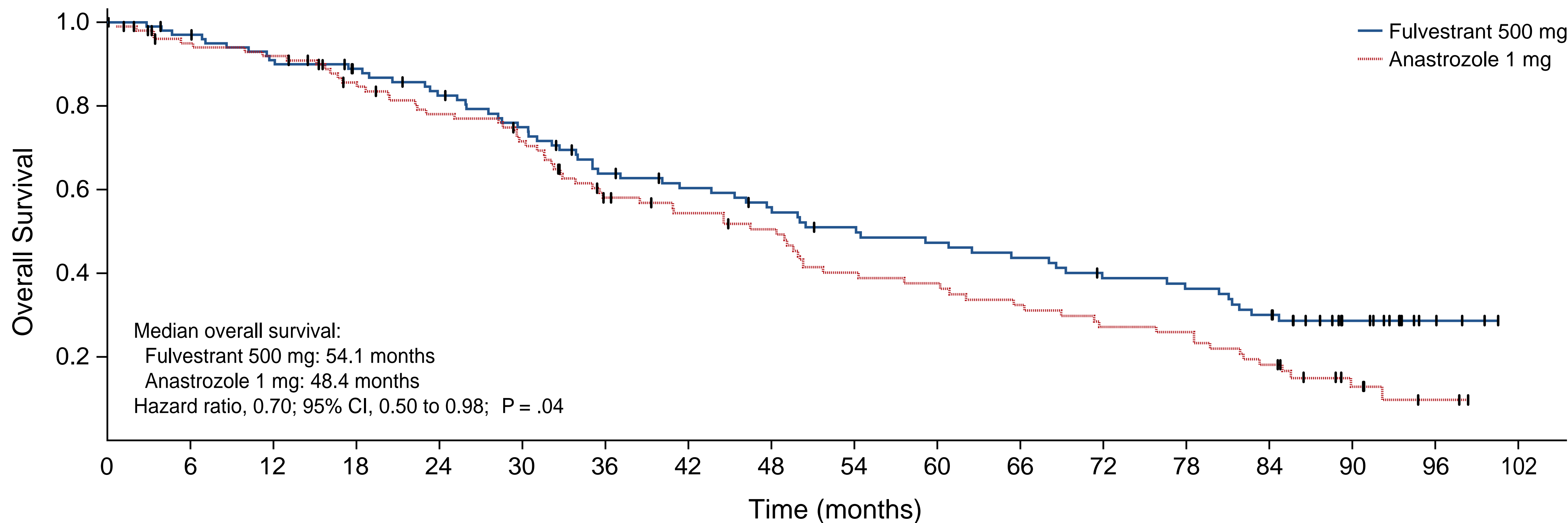
	Endocrine-Sensitive	Endocrine-Resistant
First-line	Letrozole + CDK 4/6i	Fulvestrant + CDK 4/6i
Second-line	Fulvestrant (+ Alpelisib)	Exemestane + Everolimus
Third-line	Oral SERDS?	Oral SERDS?

But are we sure about the concept?

Are we sure about the ET companion?

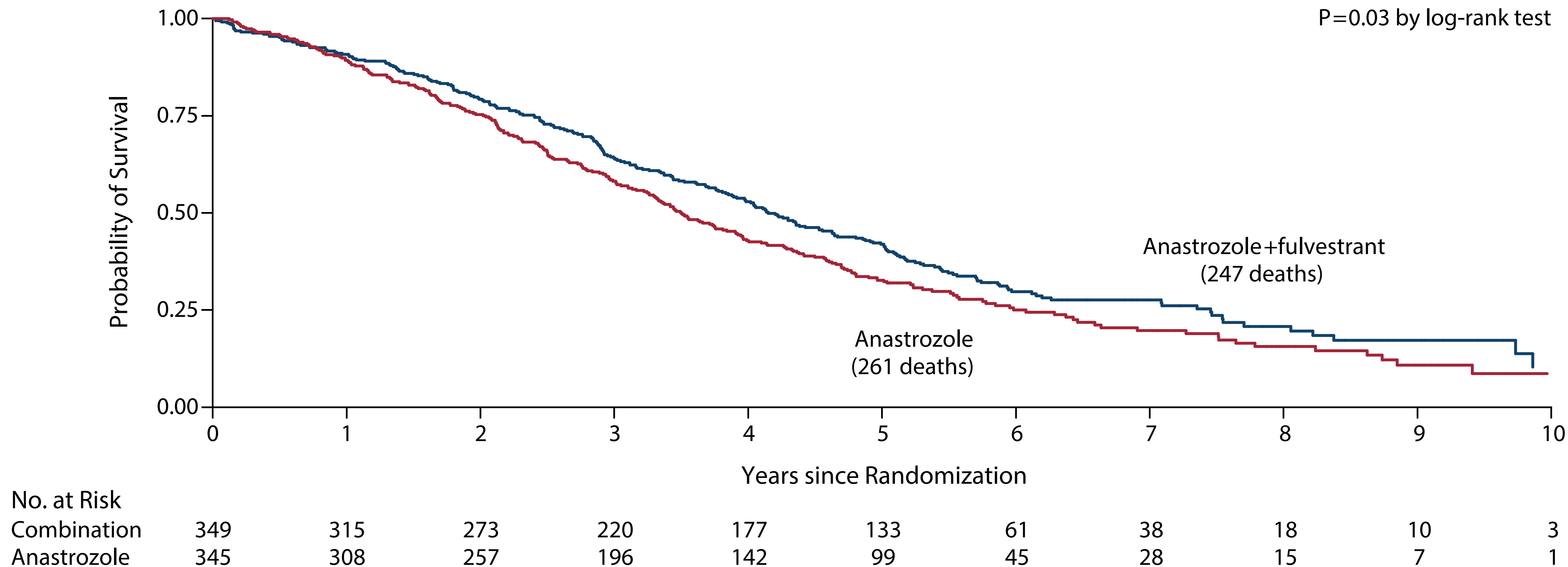
Are we sure about the ET companion?

■ ■ ■ Putting FALCONs and PALOMAs in the same cage



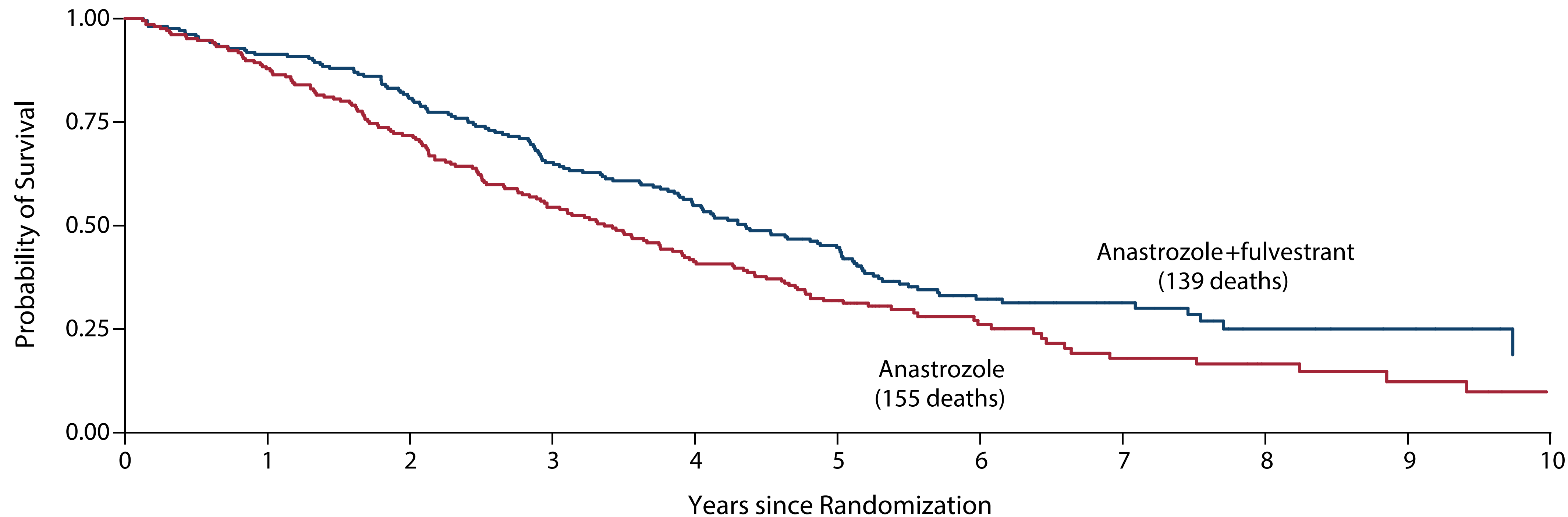
Are we sure about the ET companion?

■ ■ ■ The S0226 Trial - Total population



Are we sure about the ET companion?

■ ■ ■ The S0226 Trial - ET naïve



No. at Risk
Combination
Anastrozole

208	190	167	134	109	85	39	25	11	8	3
206	181	146	109	81	59	27	15	9	5	1

Are we *really* sure about the *biology*
behind the disease evolution?

If it has long ears, whiskers and a fur

■ ■ ■ ■ Think small: it's a cat



If it has long ears, whiskers and a fur

■ ■ ■ ■ When things start to get complicated: it's a bigger cat



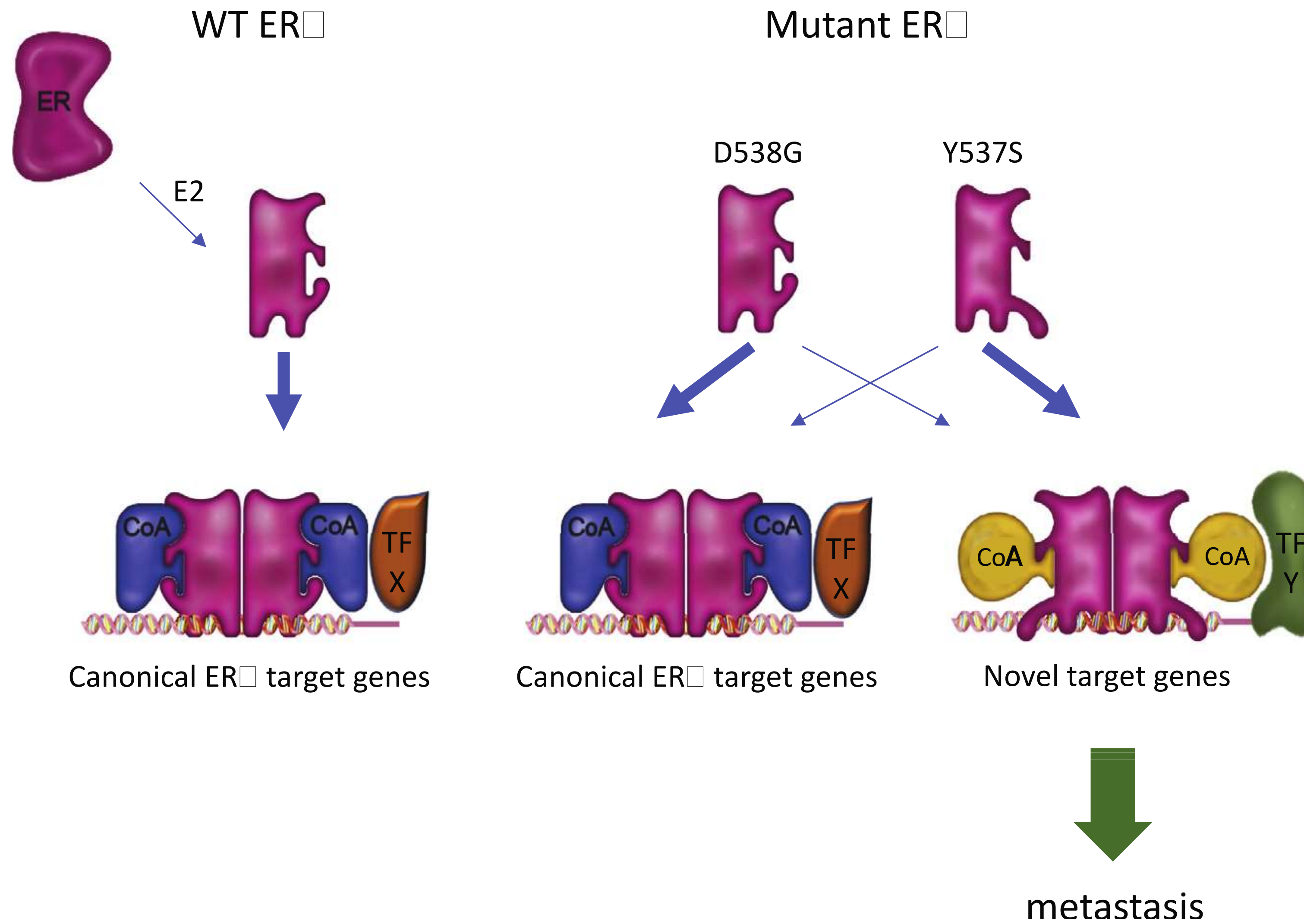
If it has long ears, whiskers and a fur

■ ■ ■ Or is it a Were-Rabbit?



The ESR1 domino effect

■ ■ ■ ■ ESR1 and neomorphic properties



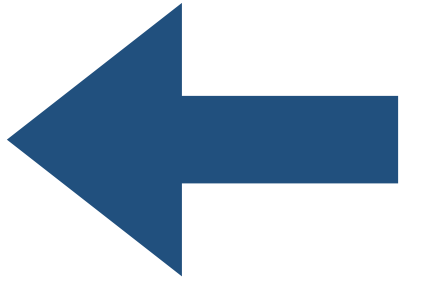
Wrapping up

■ ■ ■ ■ What can we bring back at home

Different, highly active ET-based options are becoming available

Sequencing strategies will become more and more crucial (e.g. beyond PD, combos)

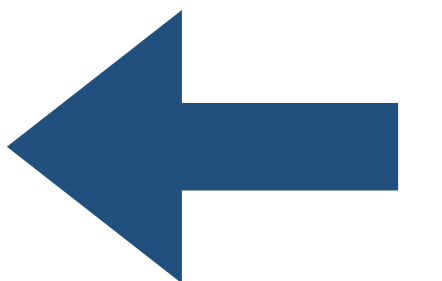
Biomarkers are greatly needed to correctly allocate different treatment options



HR positive breast cancer is spatially and temporally heterogeneous

ESR1 and PIK3CA are promising markers, but many others are coming (e.g. FGFR1)

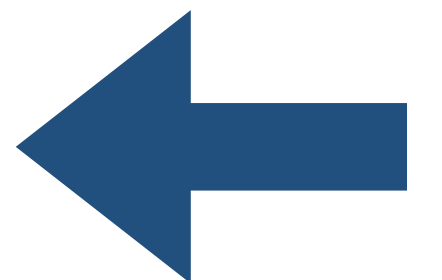
New clinical trials should embed biomarker discovery by design



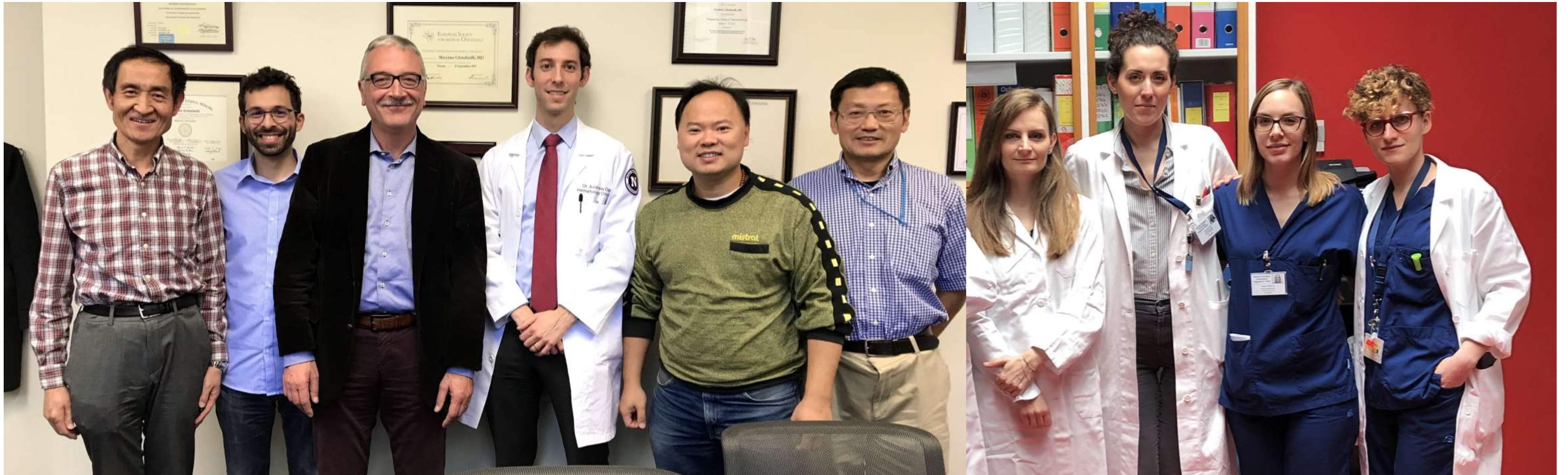
ET resistance is not only a matter of changing targets

ESR1 mutations perturbate the transcriptome resulting in neomorphic properties

ET resistant cancers have a different clinical behavior, requiring a tailored approach



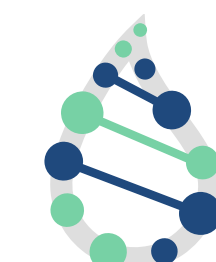
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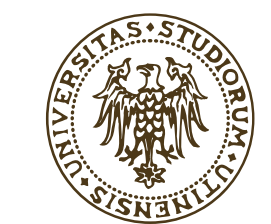


Acknowledgements

lorenzo.gerratana@uniud.it

@LGerratana

@LiquidBioTeam



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The icon for the Liquid Biopsy Research Team, featuring a stylized blue and green molecular structure.
The **Liquid biopsy**
Research Team



Ministero della Salute



The logo for LILT (Legg Italiana per la Lotta contro i Tumori), featuring a stylized red and grey figure.
LILT
LEGA ITALIANA PER LA LOTTA CONTRO I TUMORI
prevenire è vivere