



**UNIVERSITY  
OF UDINE**  
*hic sunt futura*

The **Liquid biopsy**  
Research Team

# News on PI3K-inhibition

## A bit of Sunshine after the Moonlight

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Carcinoma mammario: i traguardi raggiunti e le nuove sfide, 05.10.2019

# Conflict of Interest Disclosure Statement

----- Last updated on 05.10.2019

**Stock and Other Ownership Interests:**

No Relationships to Disclose

**Honoraria:**

No Relationships to Disclose

**Consulting or Advisory Role:**

Eli Lilly

**Expert Testimony**

No Relationships to Disclose

**Research Funding**

No Relationships to Disclose

**Patents, Royalties, Other Intellectual Property**

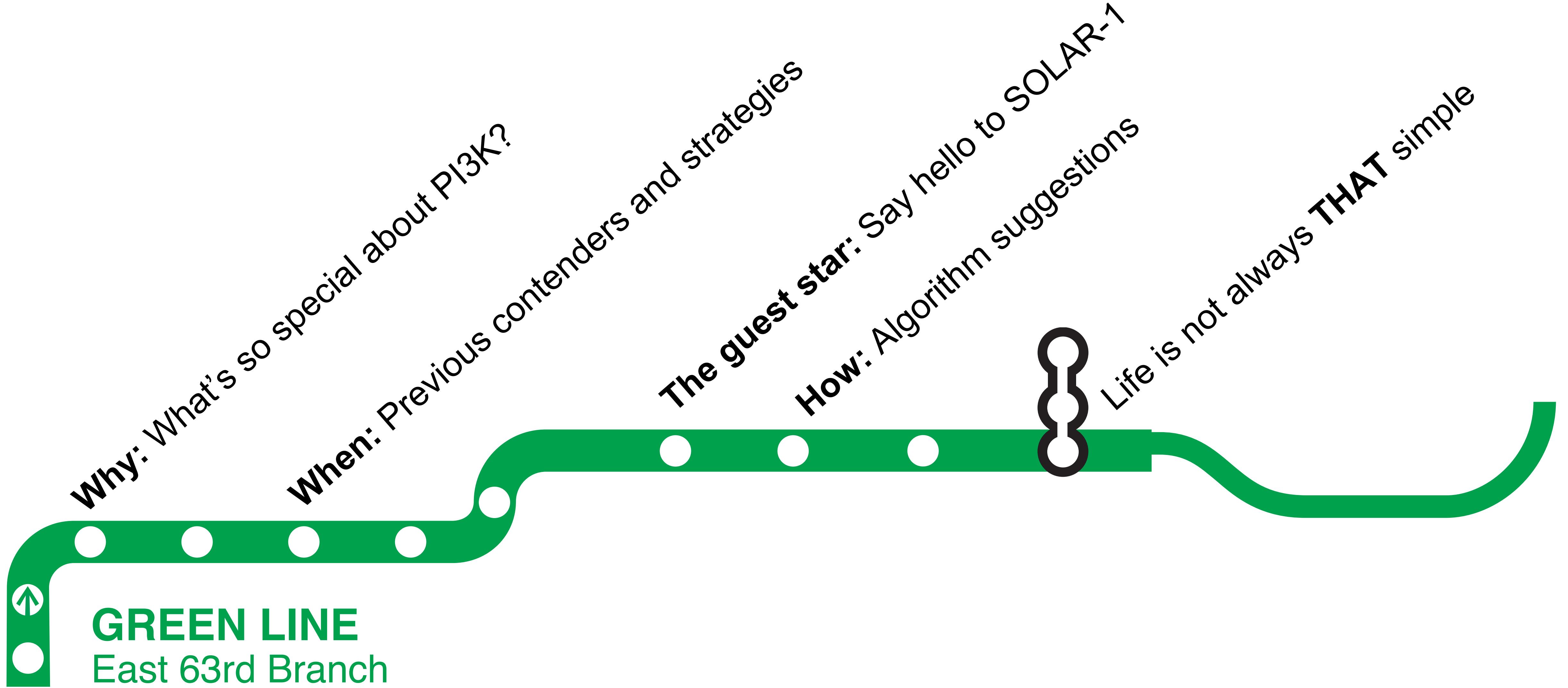
No Relationships to Disclose

**Travel Expenses**

Menarini Silicon Biosystems

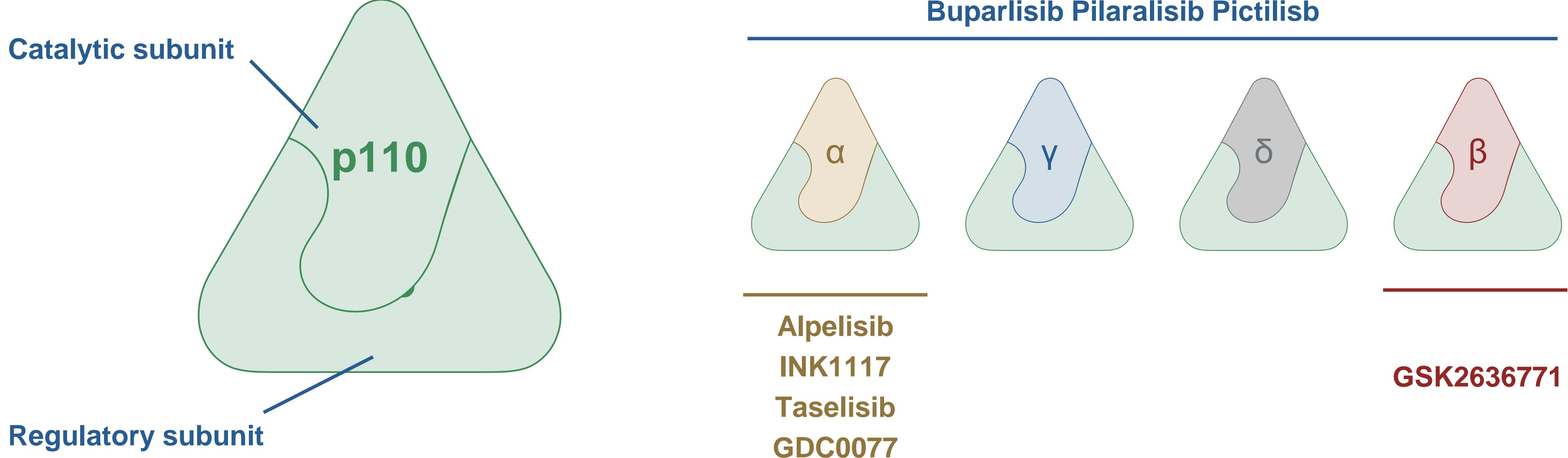
# Our itinerary

..... Stand clear the closing doors, please



# PI3K Class I isoforms

----- Meet the family



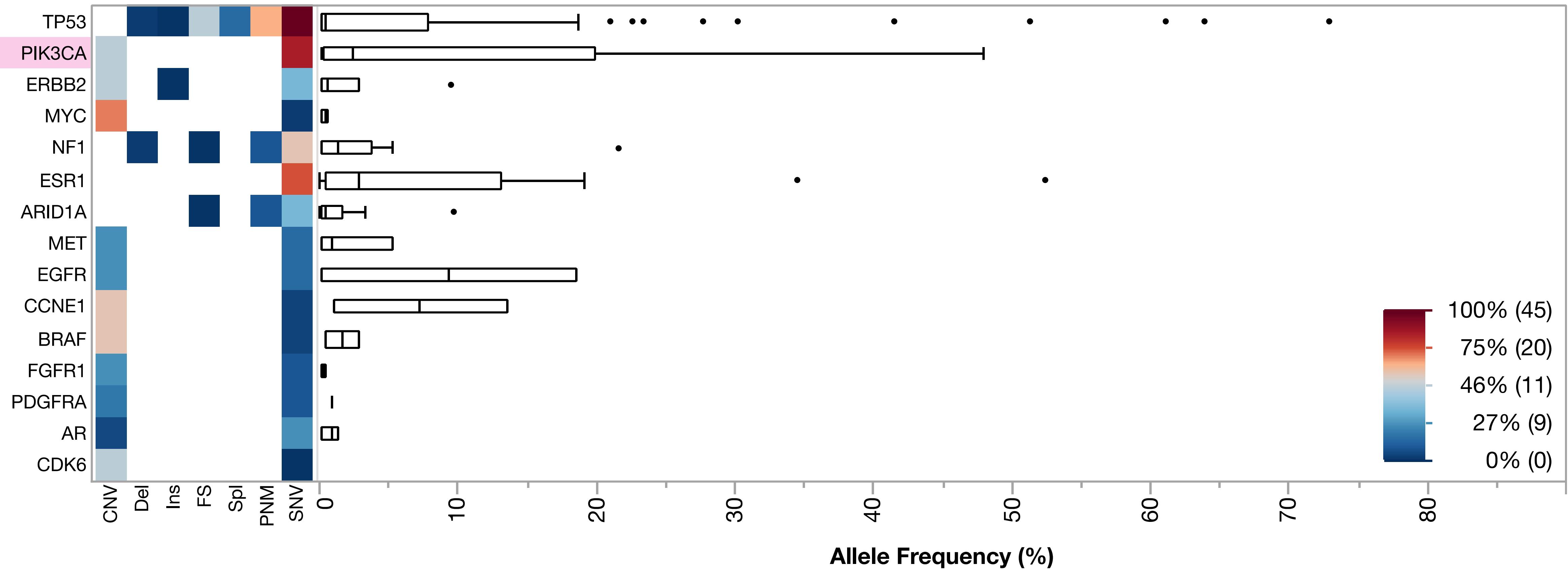
The alpha isoform is the dominant PI3K in breast cancer

First generation of PI3K inhibitors, are pan-inhibitors and burdened by high toxicities

**But what's so special about PI3K?**

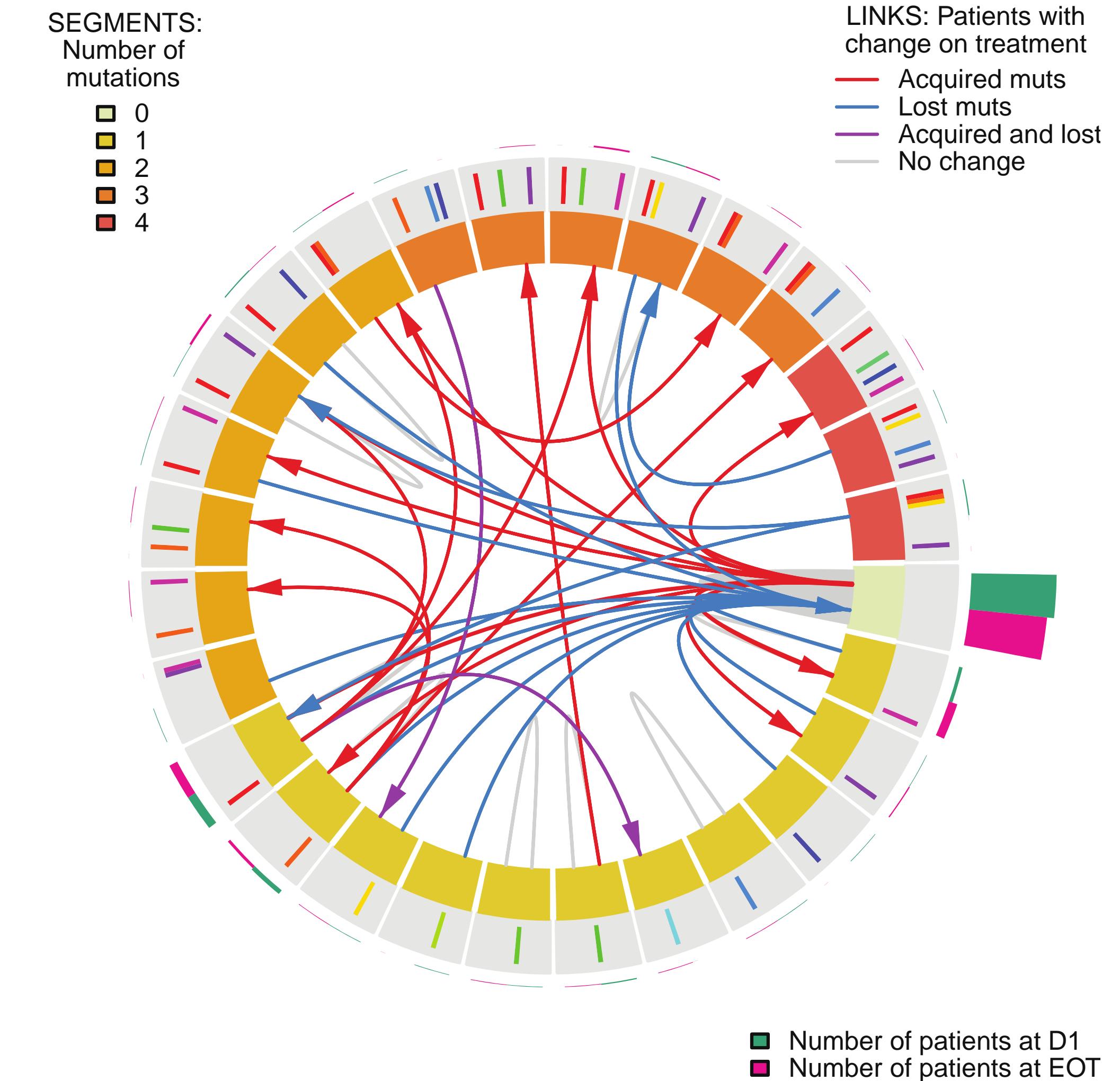
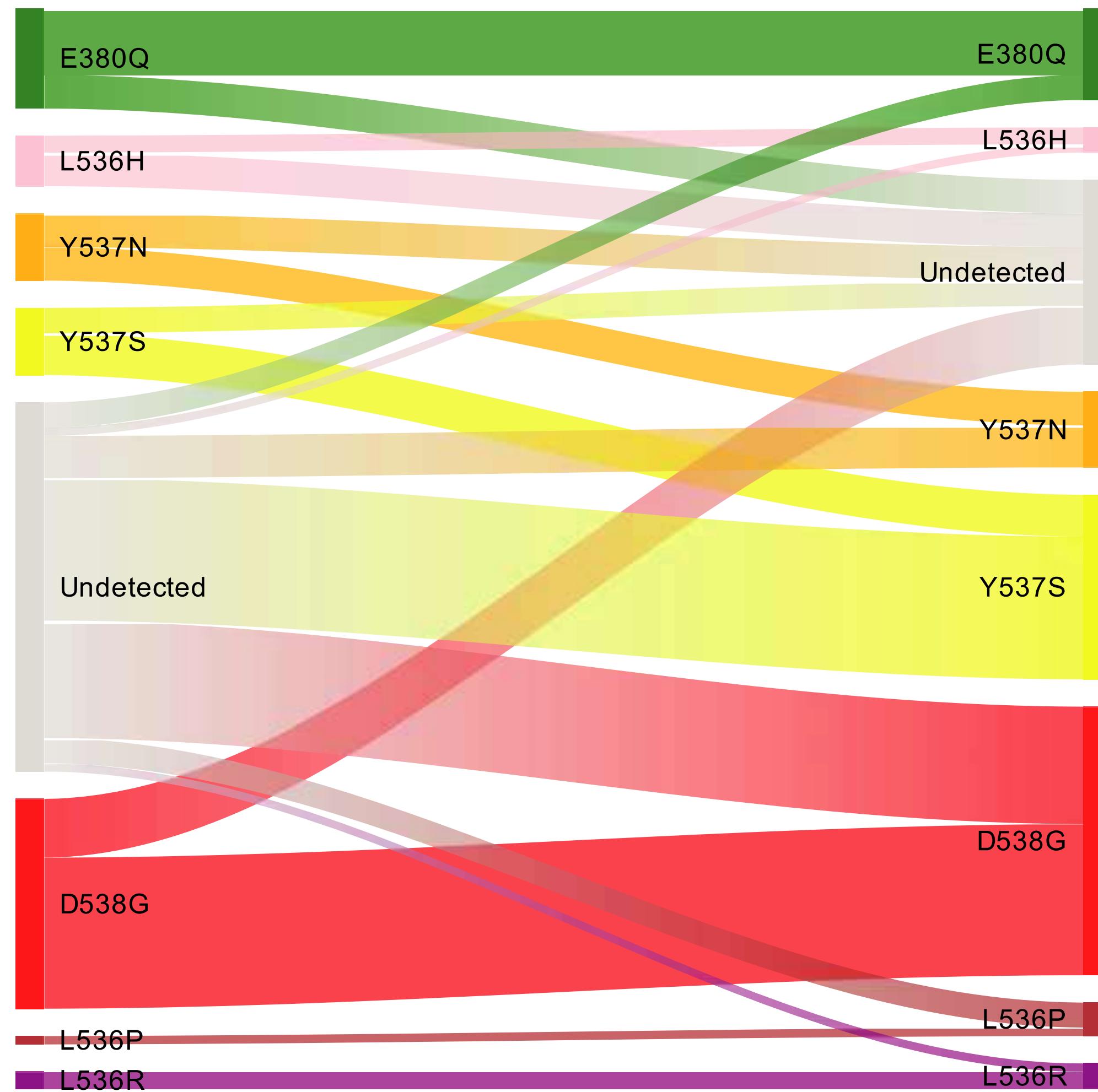
# Not just measuring, but also characterizing

----- Landscape plot on MBC



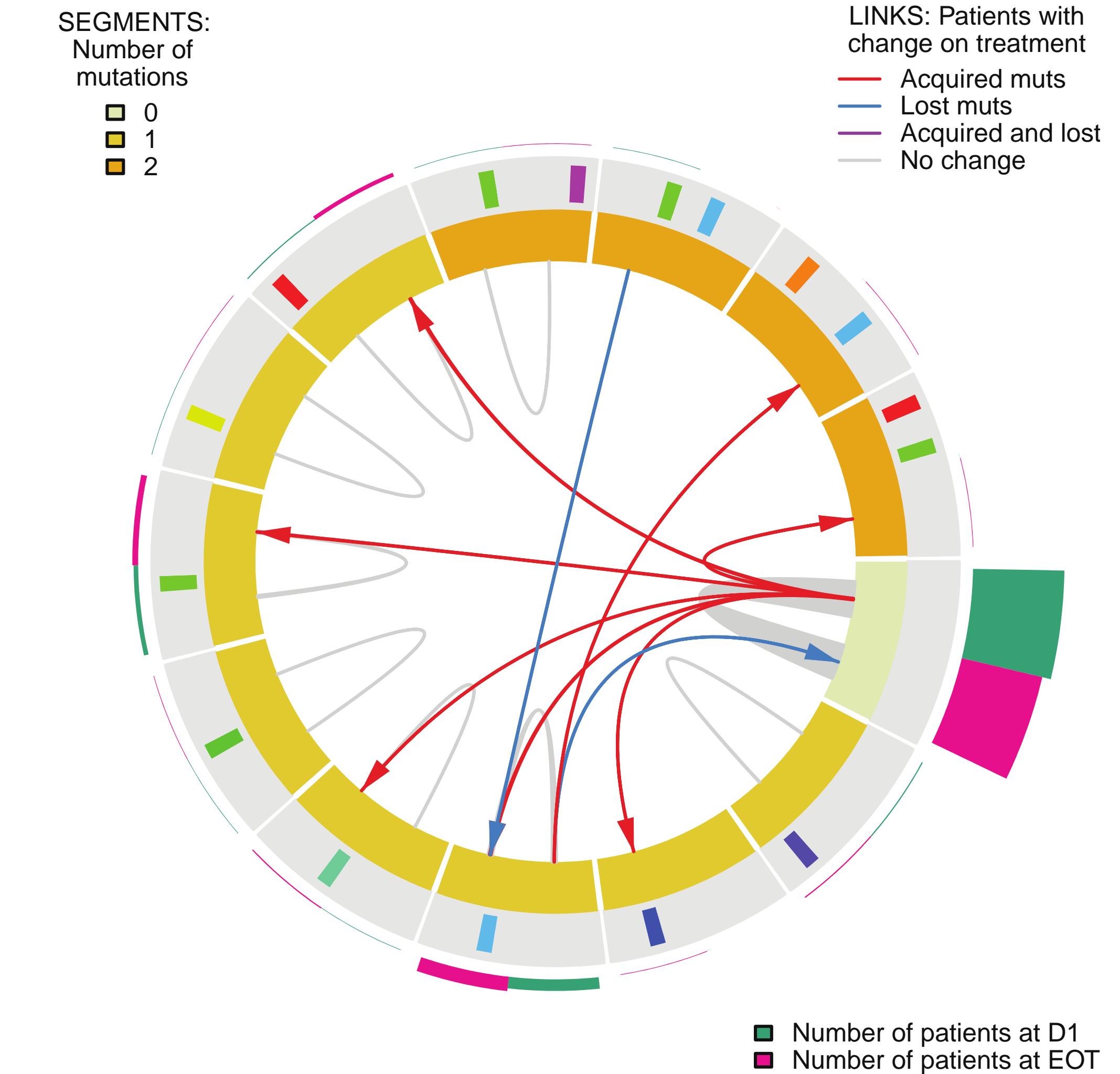
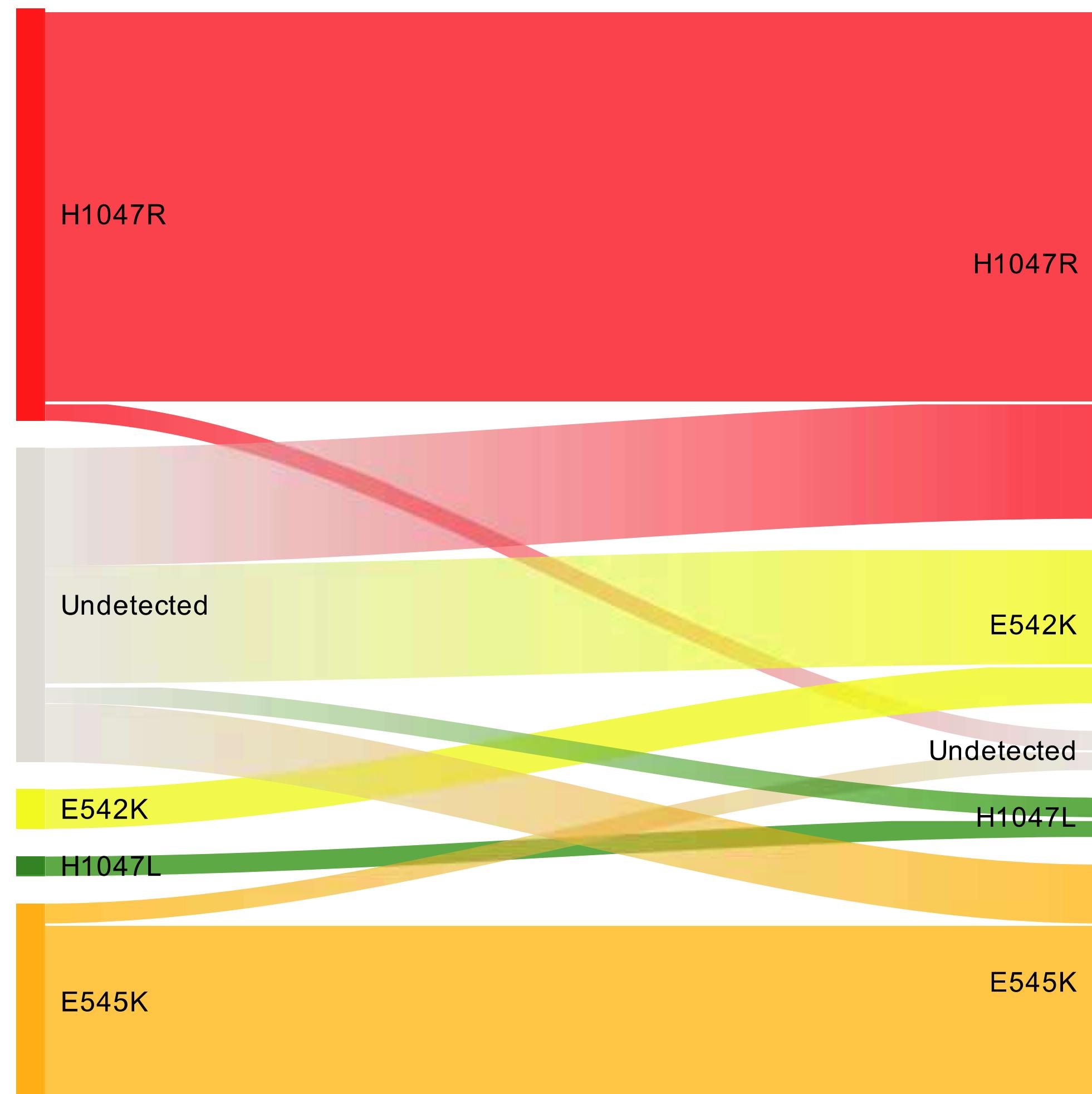
# Are all mutations made equal?

## ---- ESR1 - the whimsical one



# Are all mutations made equal?

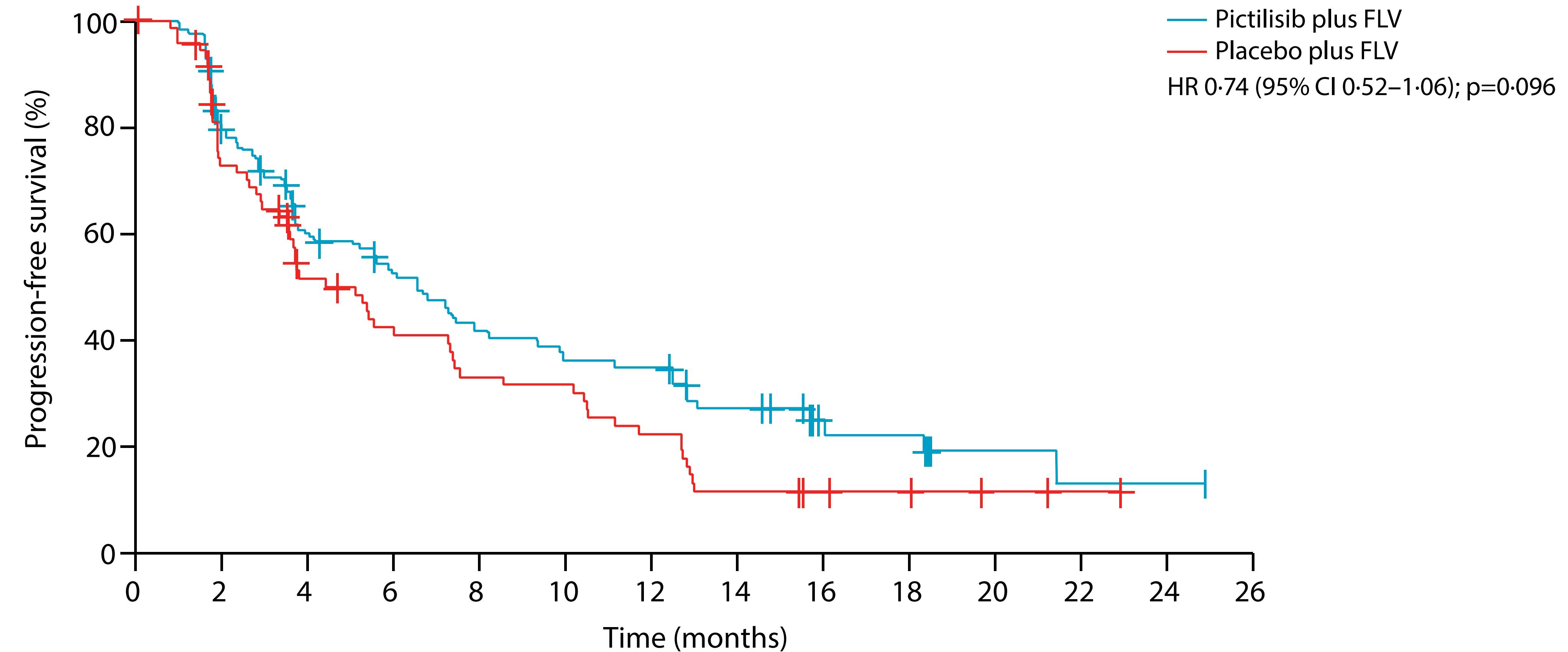
## PIK3CA - The reliable bet



# The previous attempts

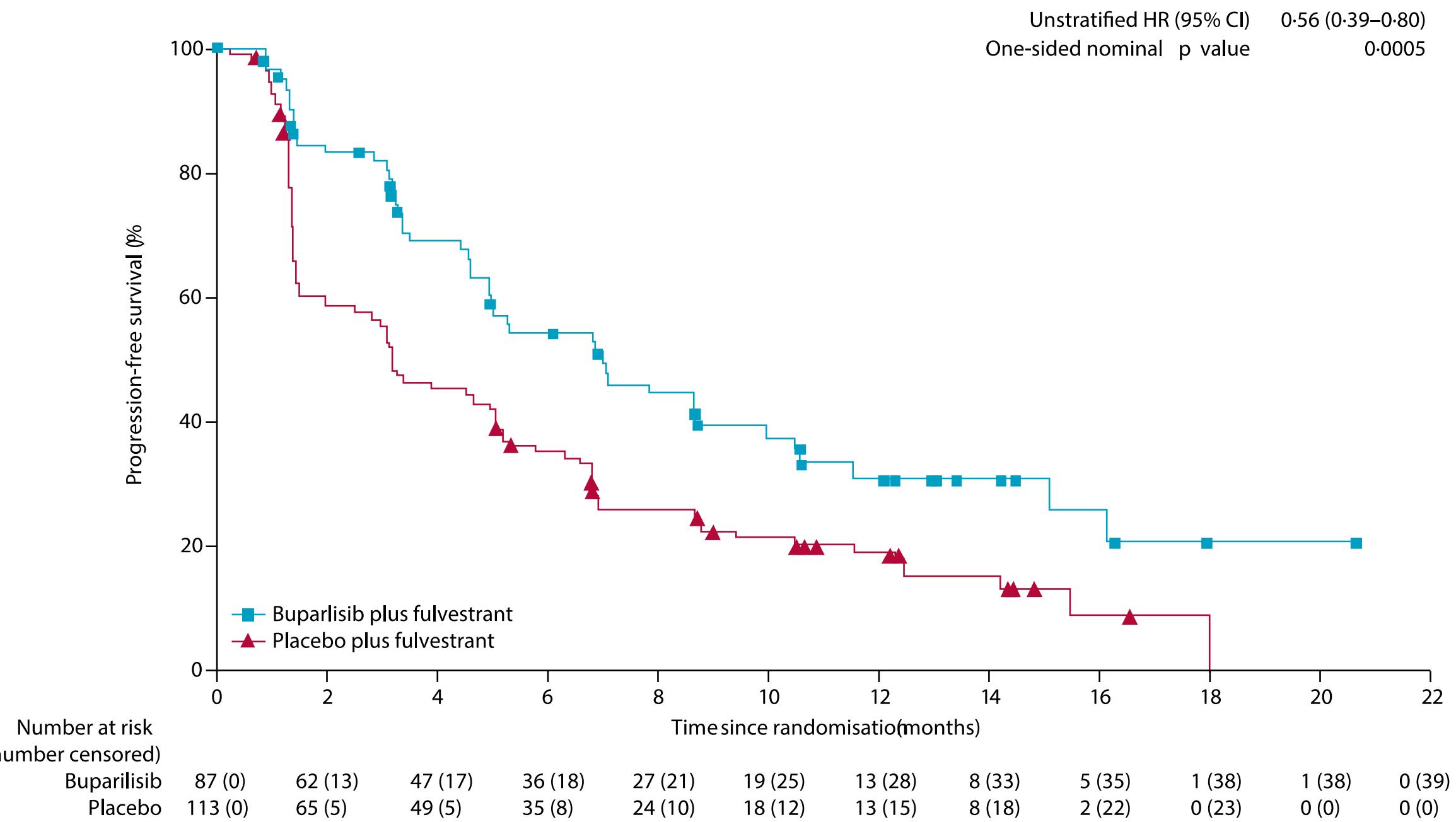
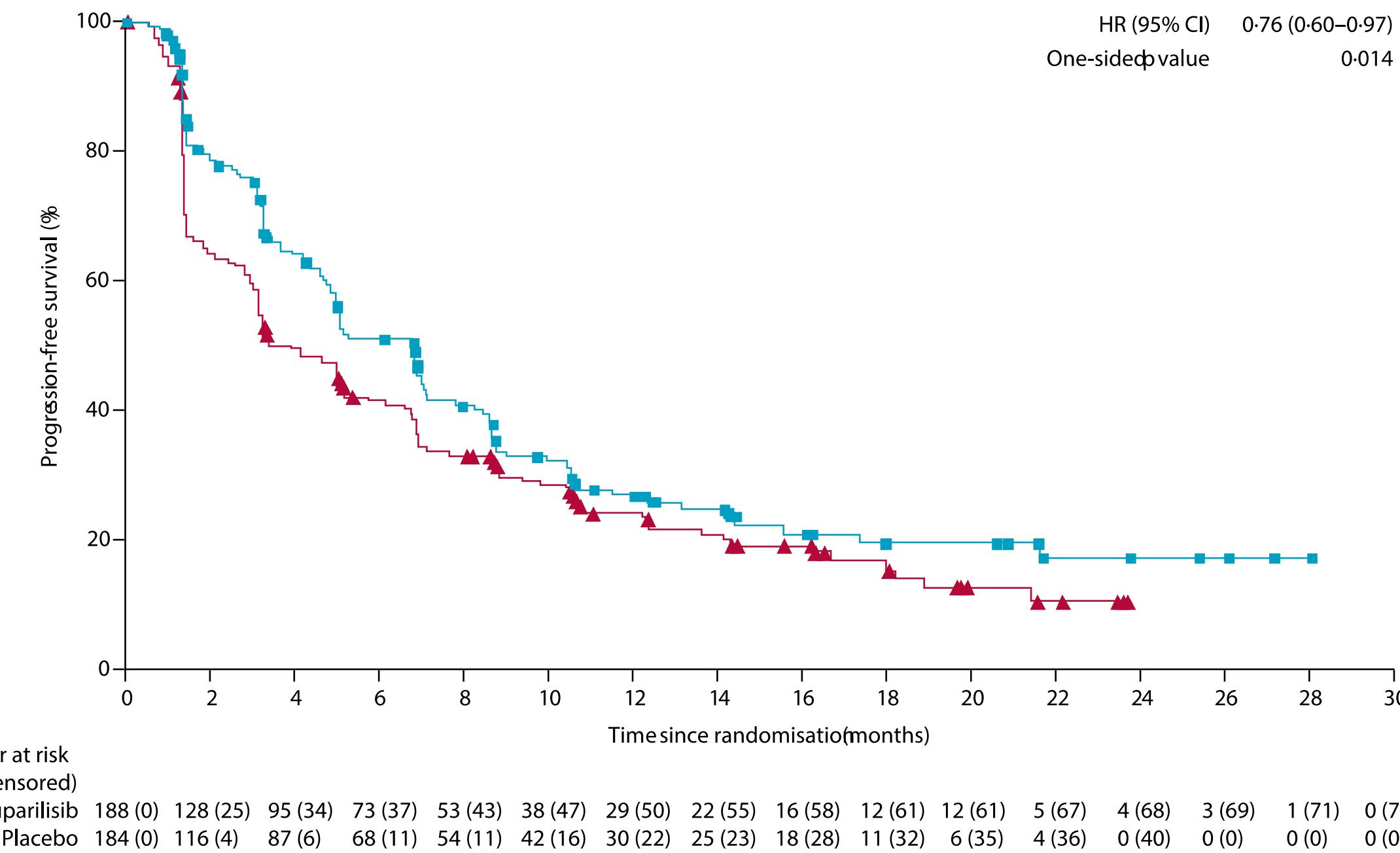
# The FERGI Trial

----- Progression Free Survival - Total population



# The moving target

## ----- The BELLE-2 trial

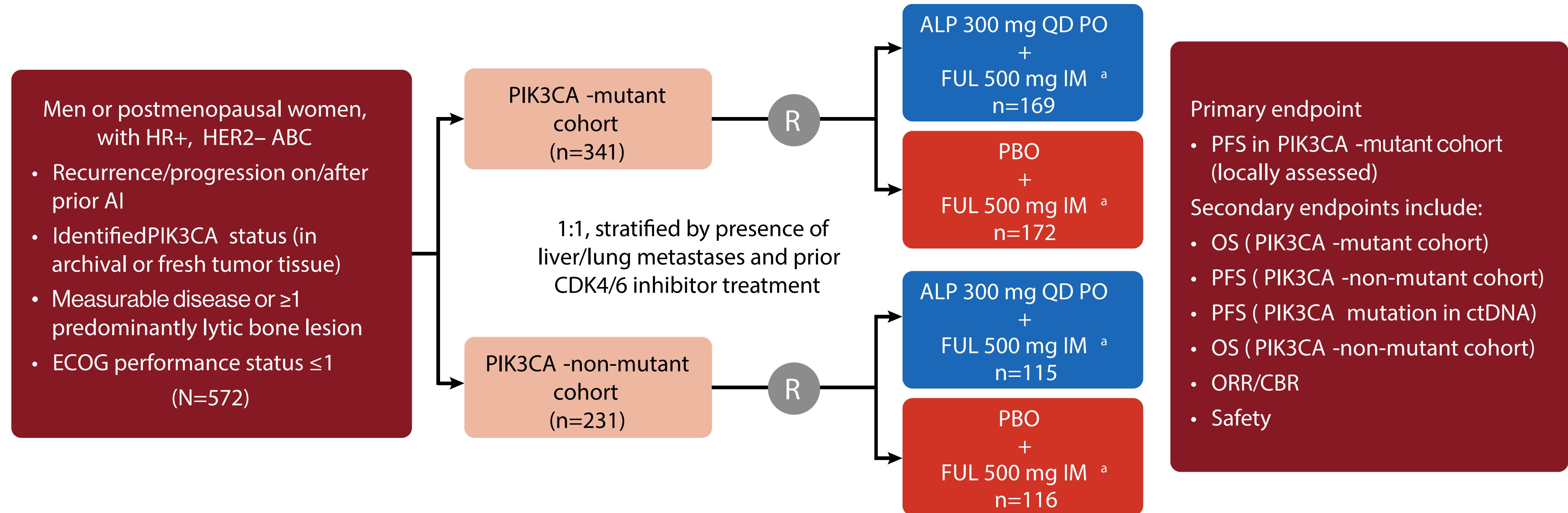


Among the ctDNA cohort, 200 had *PIK3CA* mutations. Median PFS was 7.0 months with the combination, vs 3.2 months with fulvestrant ( $P < 0.001$ ). With higher response rates (18.4% vs 3.5%) in this patient population. To the contrary, no benefit among patients with wild-type *PIK3CA* was observed

**Say hello to SOLAR-1**

# Welcome the guest star

## ---- The SOLAR-1 trial



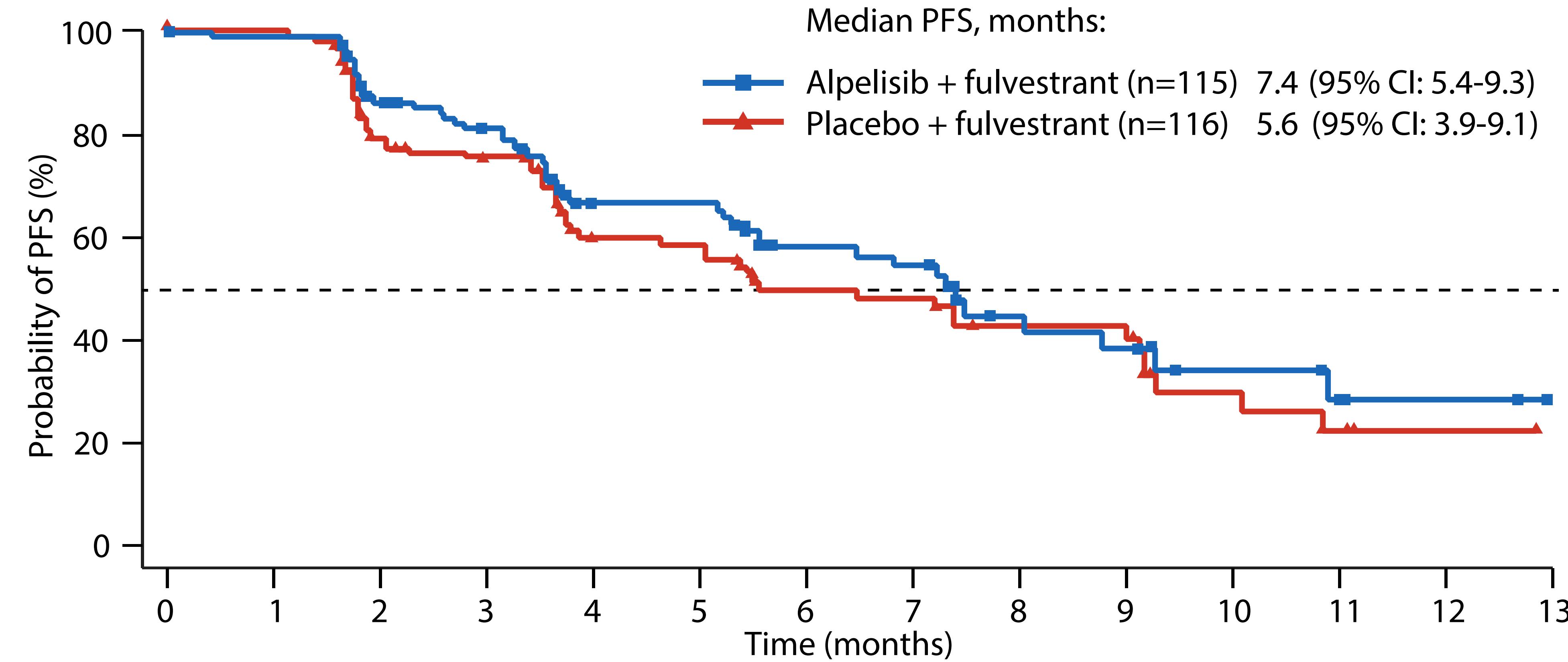
## SOLAR-1

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 with PIK3CA-Wild type Cancer

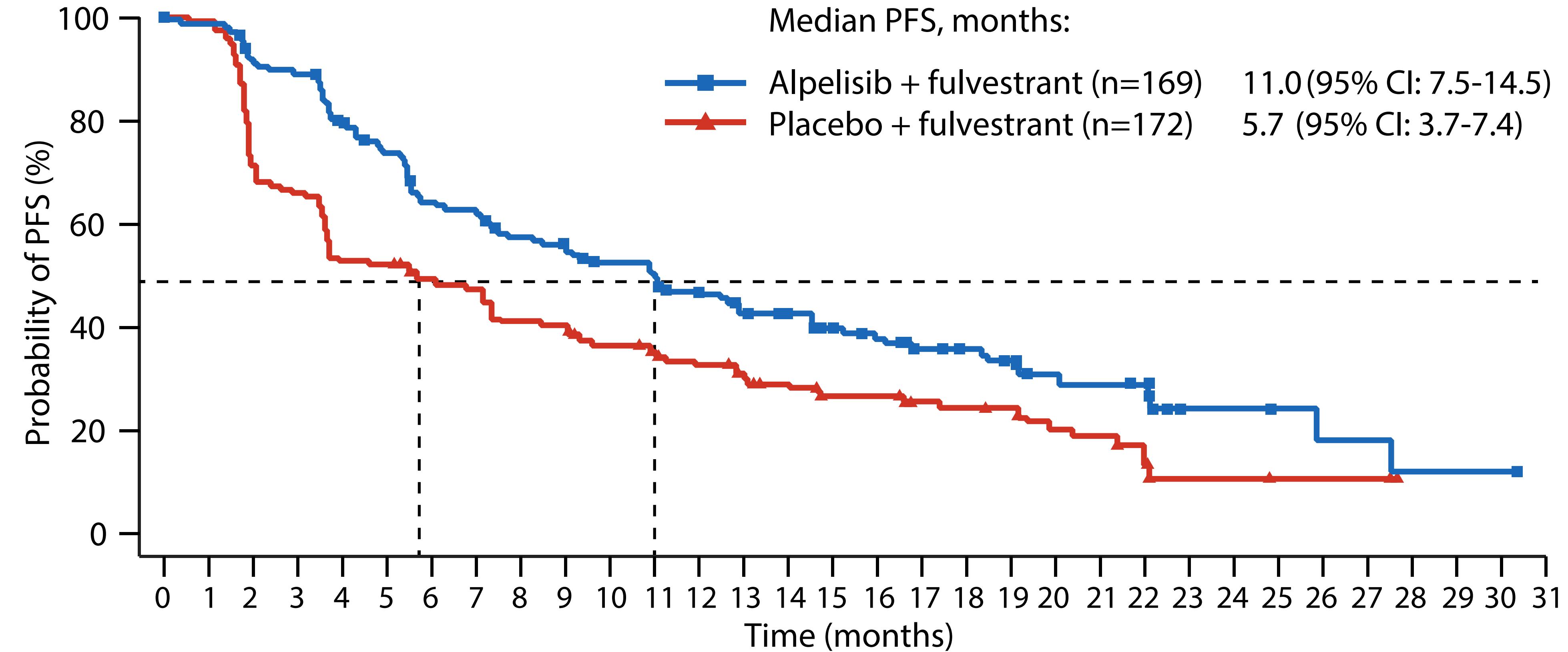


Number of patients still at risk

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	12	8	5	1	0

# The SOLAR-1 trial

## ---- Cohort with PIK3CA-Mutated Cancer

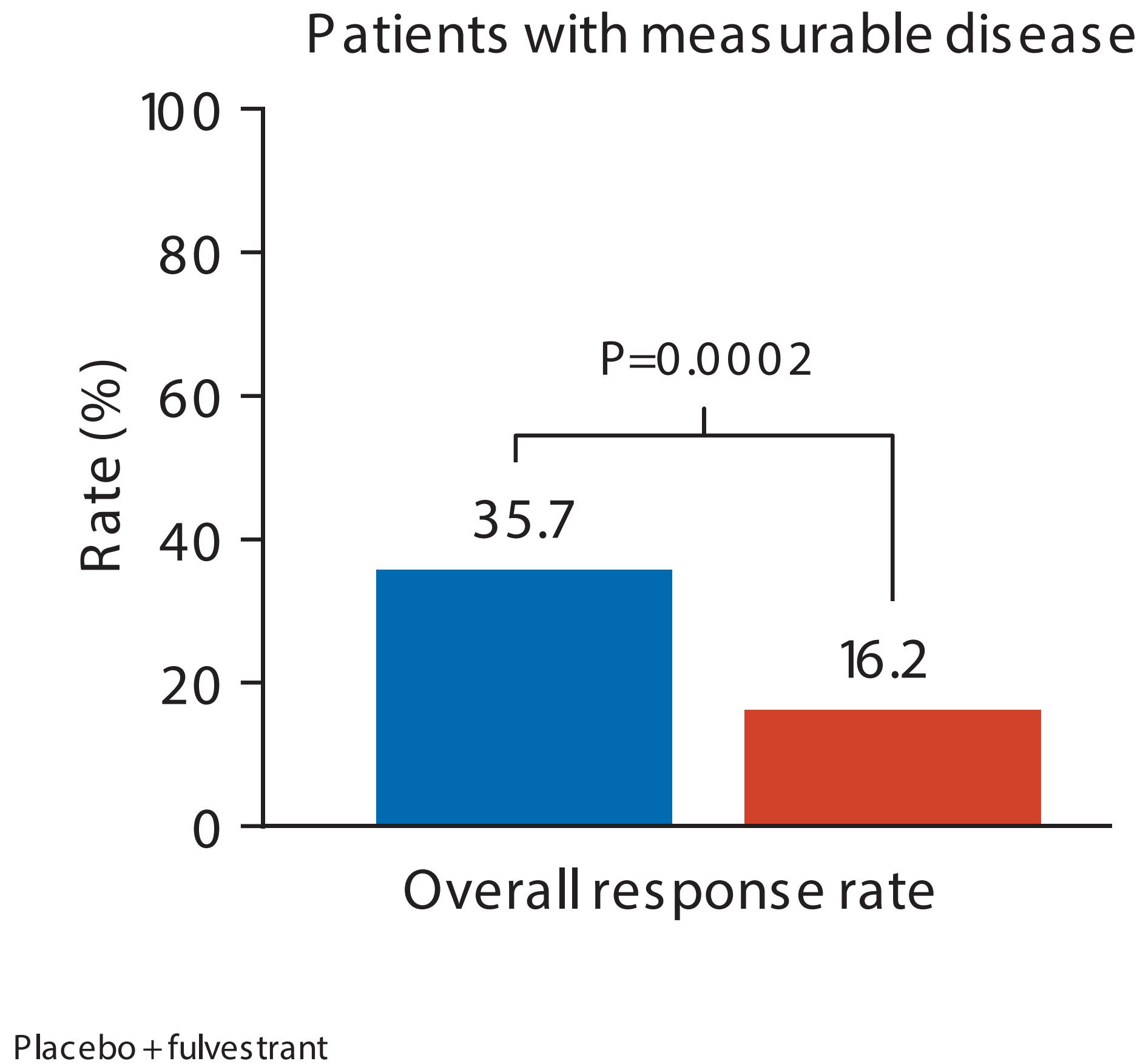
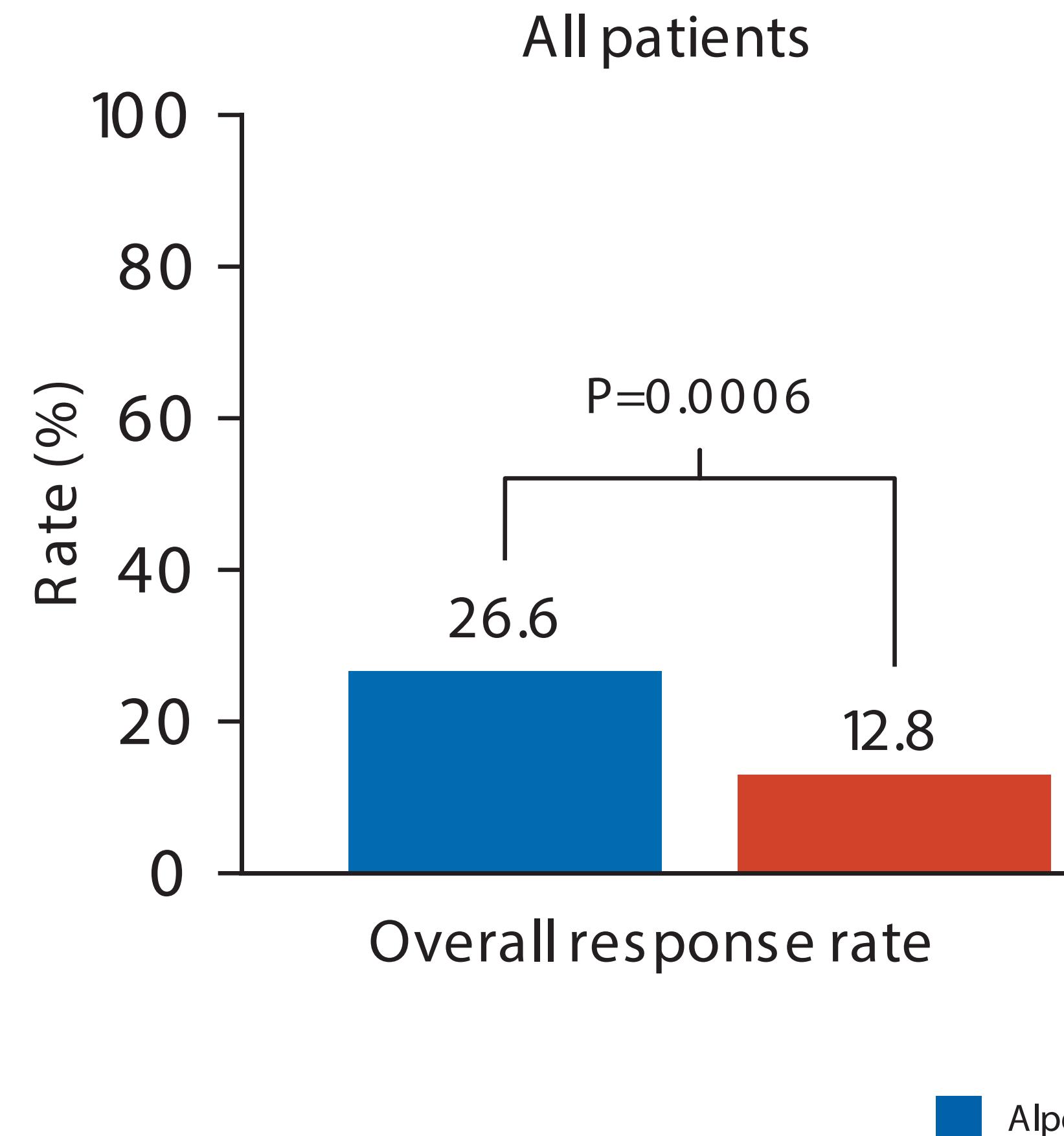


Number of patients still at risk

Alpelisib + fulvestrant	169	158	145	141	123	113	97	88	80	77	67	66	58	54	48	41	37	29	29	21	20	19	17	14	13	9	5	3	2	2	1	0	1	0	0
Placebo + fulvestrant	172	167	120	111	89	88	80	77	67	58	54	48	41	37	29	29	21	20	17	14	13	9	5	3	2	2	1	0	1	0	0	0			

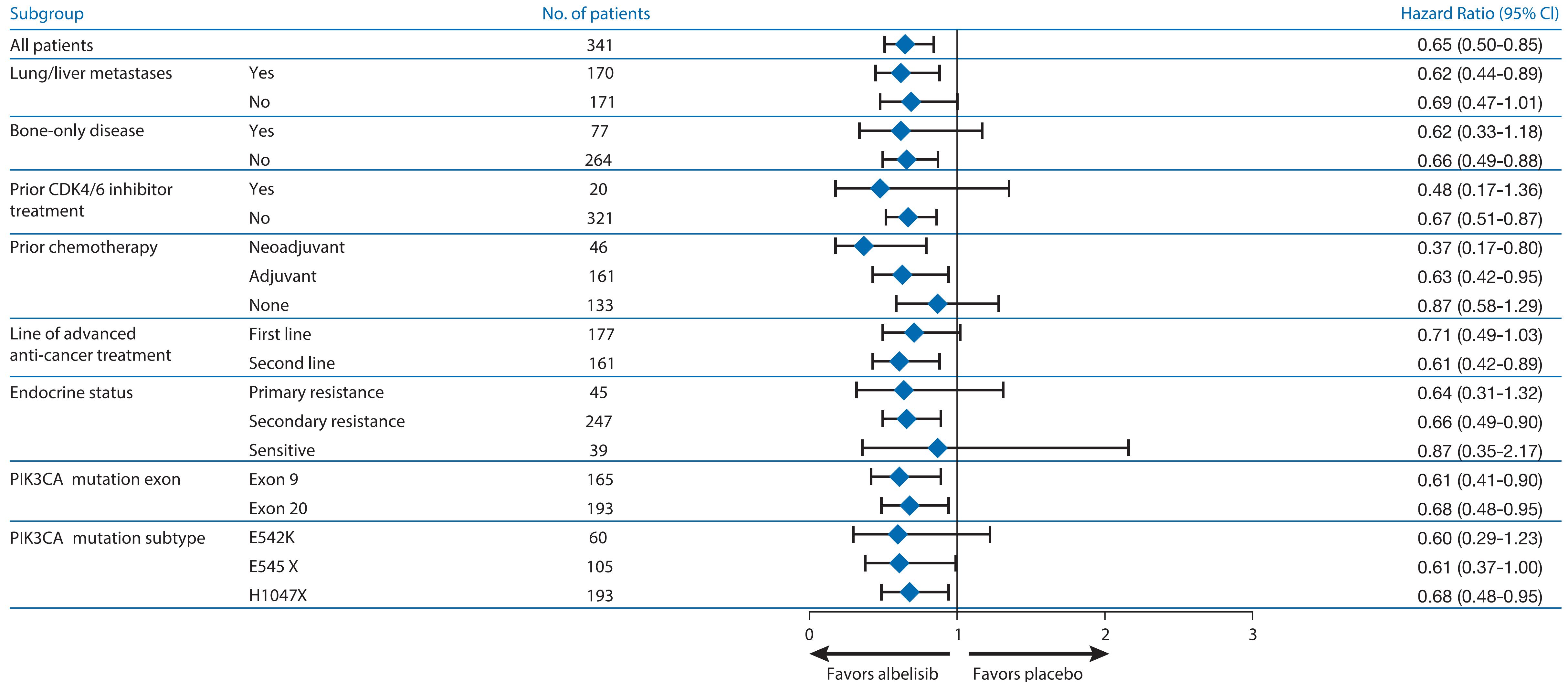
# The SOLAR-1 trial

• Cohort with PIK3CA-Mutated Cancer



# The SOLAR-1 trial

## •••• Cohort without PIK3CA-Mutated Cancer, subgroups



# The SOLAR-1 trial

## ----- Main adverse events

AEs ≥20% in either arm, %	Alpelisib + fulvestrant (N=284)			Placebo + fulvestrant (N=287)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

“

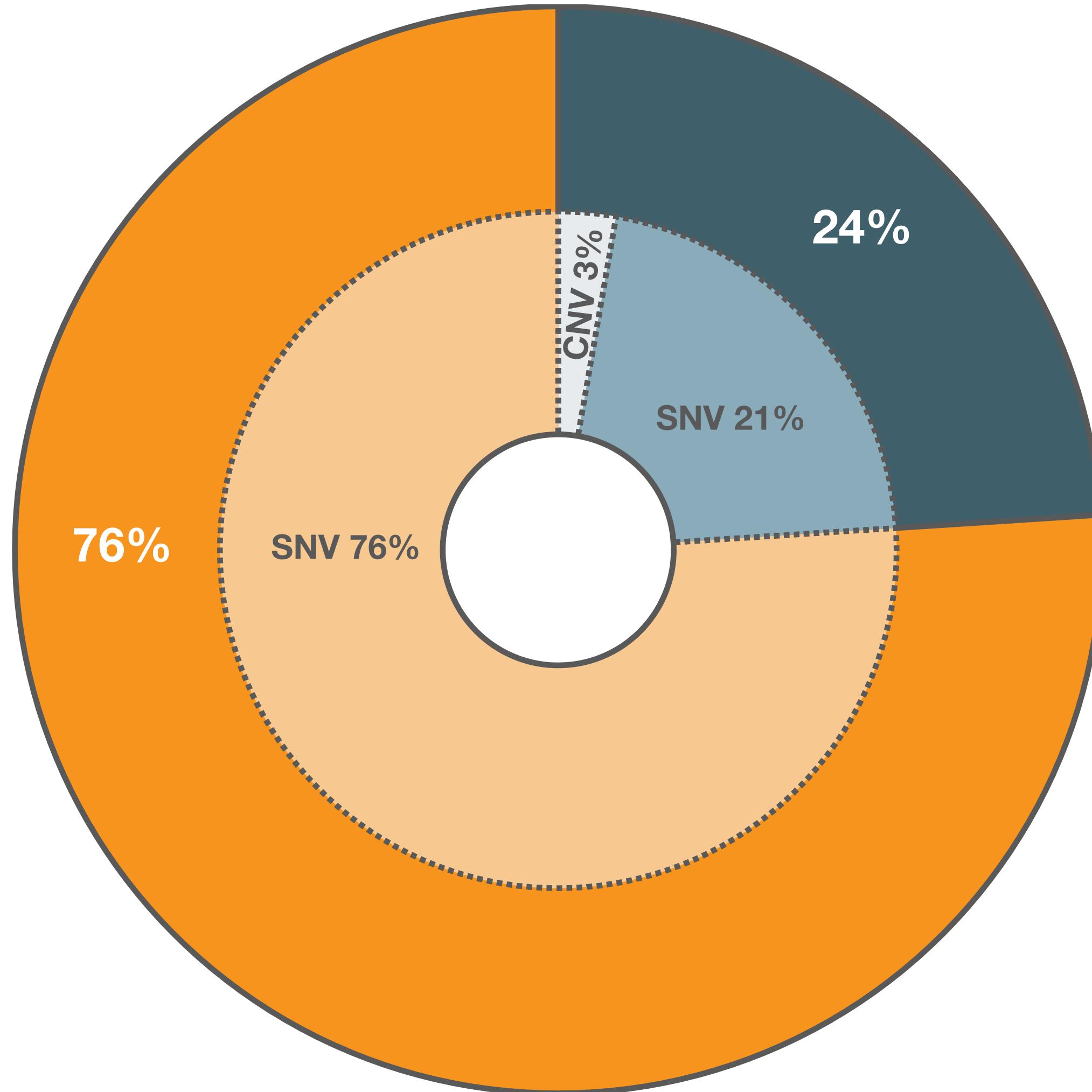
The FDA also approved the companion diagnostic test, therascreen PIK3CA RGQ PCR Kit, to detect the PIK3CA mutation in a tissue and/or a liquid biopsy. Patients who are negative by the therascreen test using the liquid biopsy should undergo tumor biopsy for PIK3CA mutation testing.

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**But the devil is in the details**

# Potential caveats of the Therascreen companion diagnostic

- Never make a companion equal to a brother (MBC Database, Tissue)



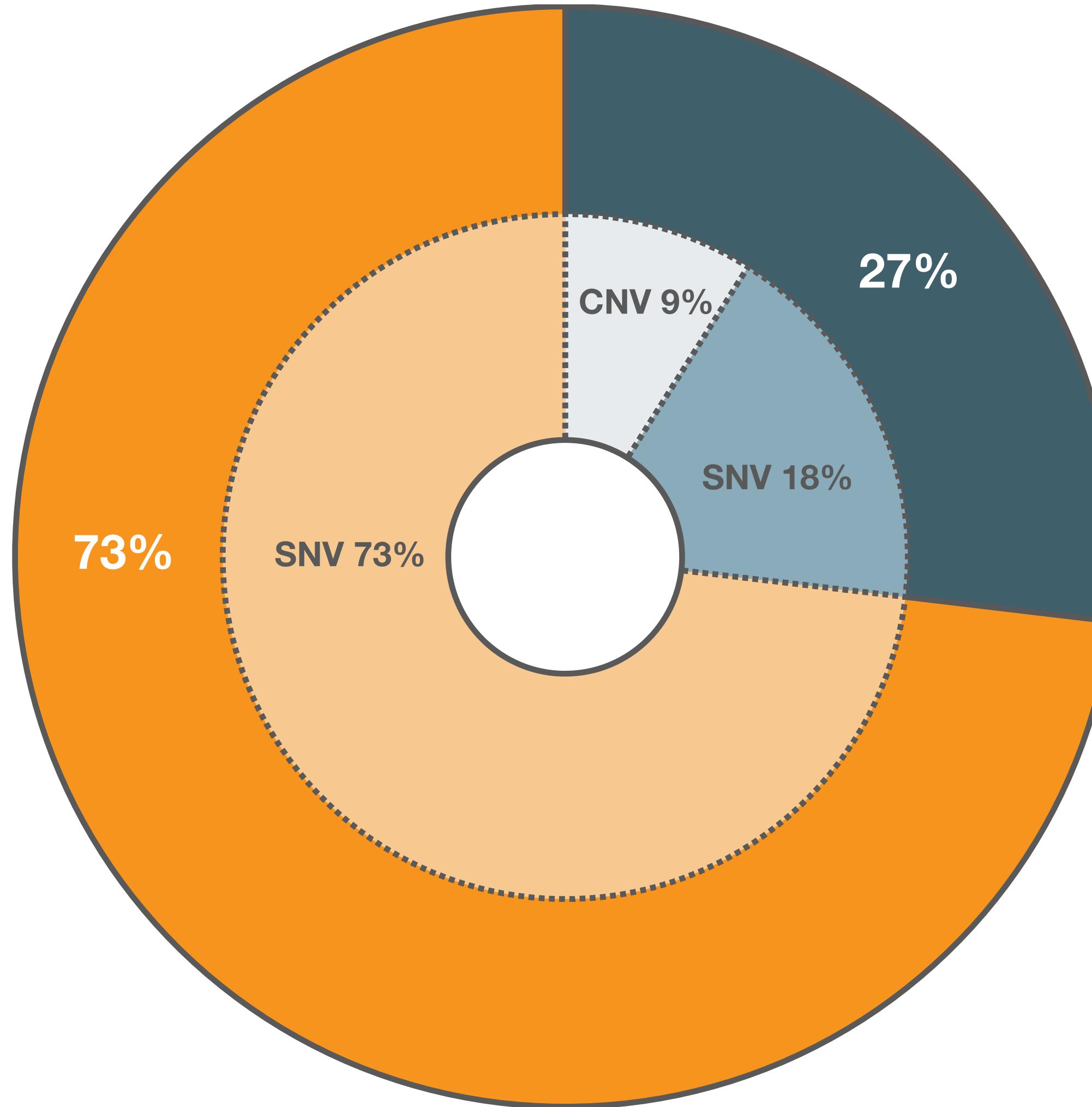
Exon	Mutation	Base change	LoD, % MAF
7	C420R	1258T>C	4.46 <sup>†</sup>
9	E542K	1624G>A	5.06 <sup>†‡</sup>
	E545A	1634A>C	1.82 <sup>†</sup>
	E545D	1635G>T	3.21 <sup>†</sup>
	E545G	1634A>G	1.94 <sup>†‡</sup>
	E545K	1633G>A	2.42 <sup>†‡</sup>
	Q546E	1636C>G	5.31 <sup>†</sup>
	Q546R	1637A>G	4.22 <sup>†</sup>
20	H1047L	3140A>T	2.37 <sup>†‡</sup>
	H1047R	3140A>G	1.98 <sup>†‡</sup>
	H1047Y	3139C>T	7.07 <sup>†</sup>

█ Detectable by therascreen

█ Not Detectable by therascreen

# Potential caveats of the Therascreen companion diagnostic

----- Never make a companion equal to a brother (TCGA, Tissue)



Exon	Mutation	Base change	LoD, % MAF
7	C420R	1258T>C	4.46 <sup>†</sup>
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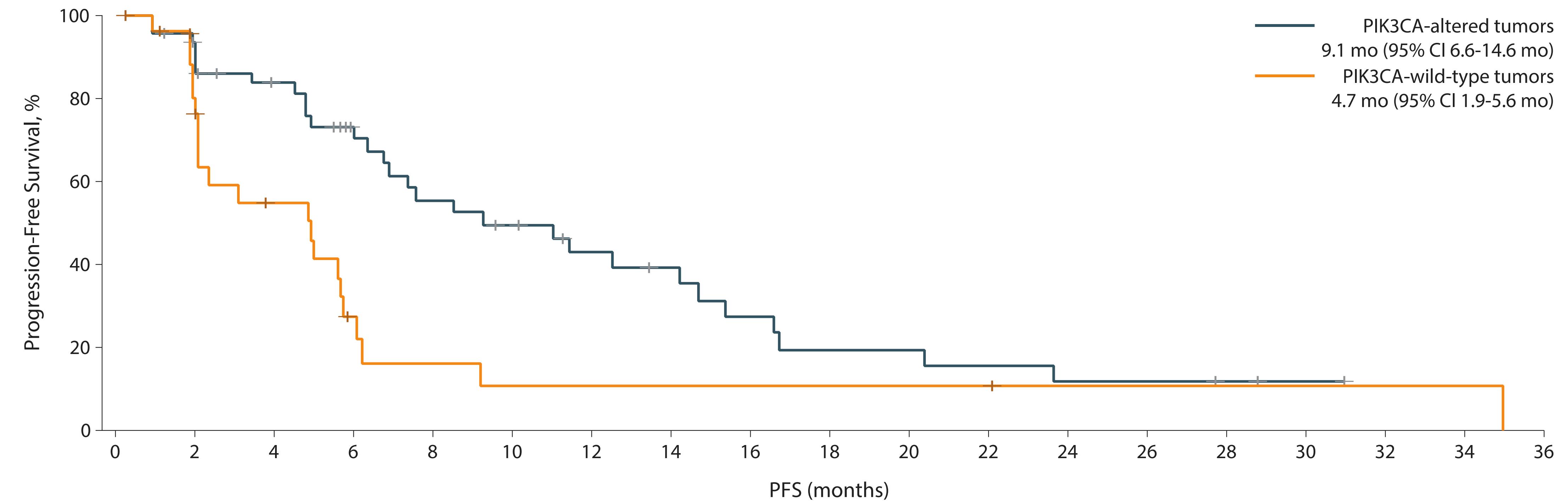
█ Detectable by therascreen

█ Not Detectable by therascreen

**But is it a **real** pitfall?**

# But is it a real pitfall?

Alpelisib Plus Fulvestrant in *PIK3CA*-Altered Luminal-like MBC

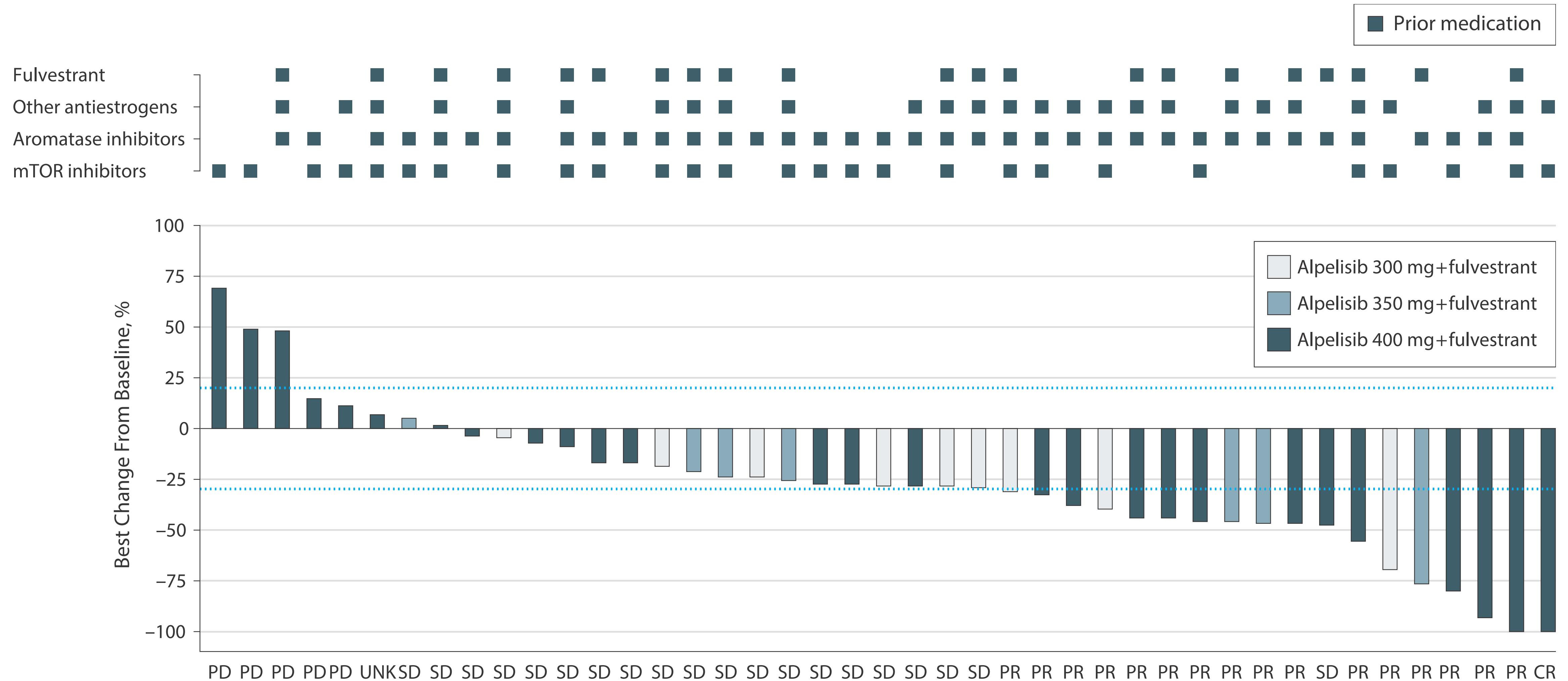


No. of patients at risk

PIK3CA-altered tumors	49	35	32	24	19	15	12	10	7	5	5	4	3	3	2	1	0
PIK3CA-wild-type tumors	32	15	12	4	3	2	2	2	2	2	1	1	1	1	1	1	0

# But is it a real pitfall?

## Alpelisib Plus Fulvestrant in *PIK3CA*-Altered Luminal-like MBC



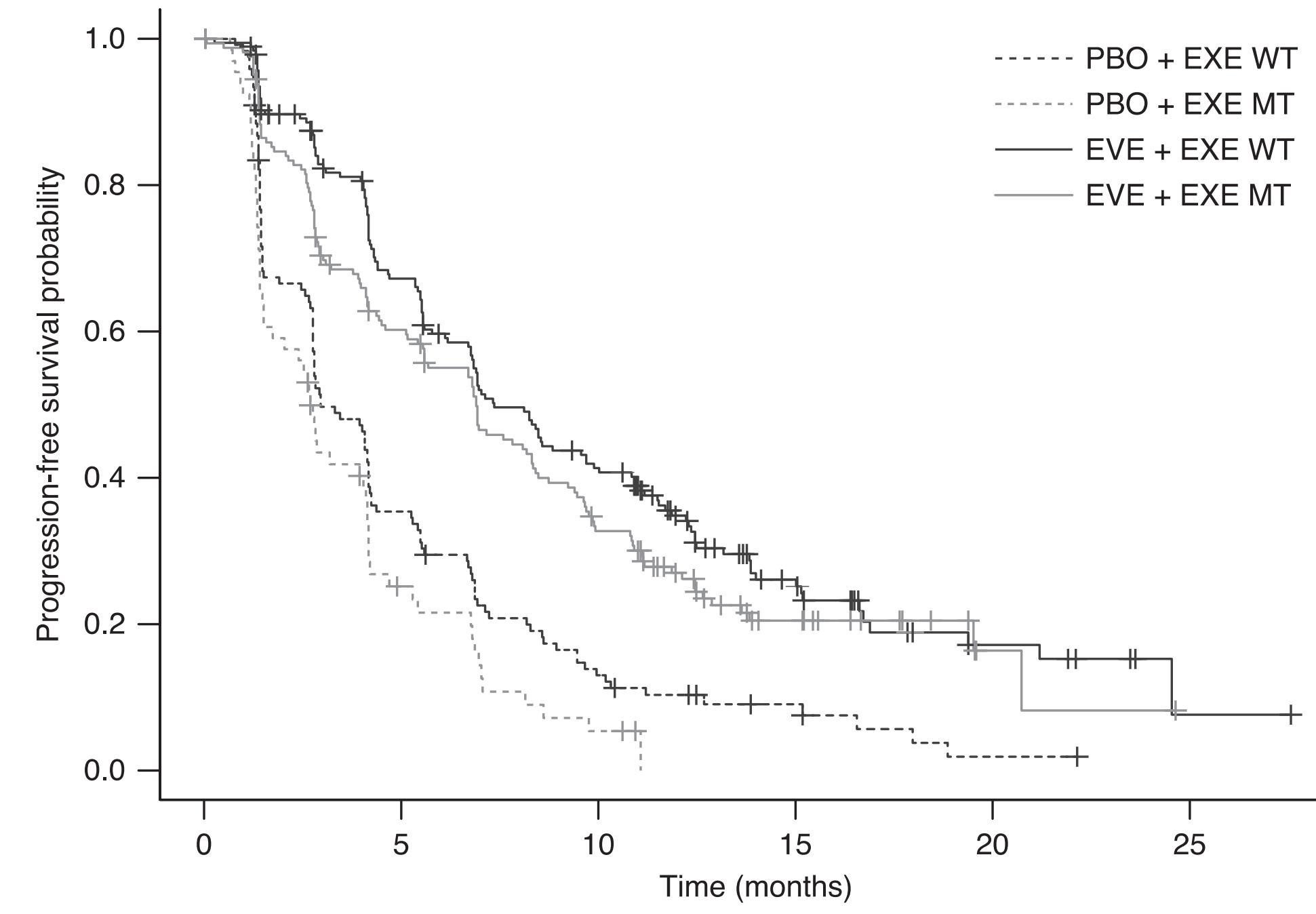
# The treatment algorithm

## ----- The therapeutic cascade

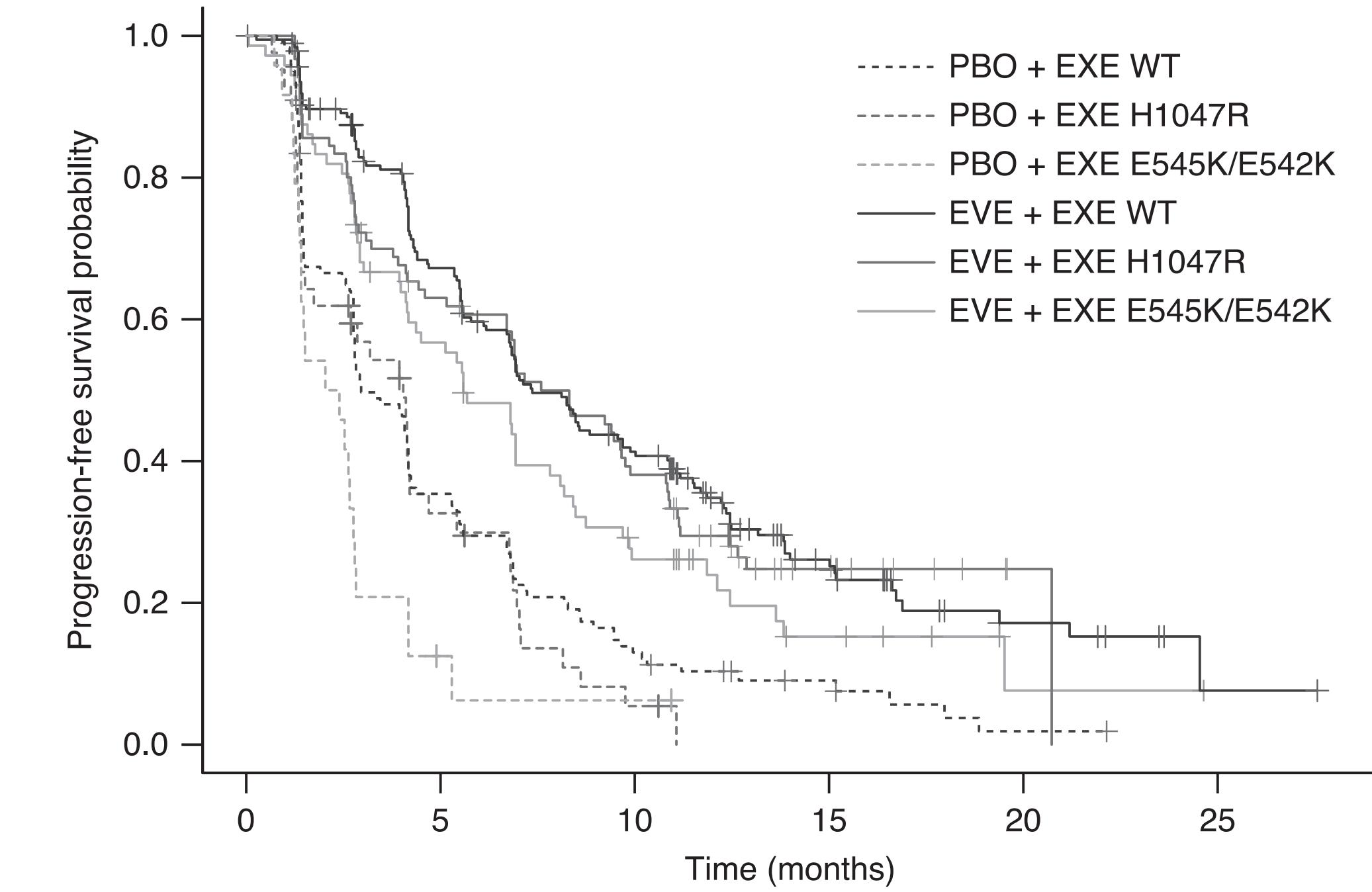
	Endocrine-Sensitive	Endocrine-Resistant
First-line	Letrozole + CDK 4/6i	Fulvestrant + CDK 4/6i
Second-line	Fulvestrant (+ Alpelisib)	Exemestane + Everolimus
Third-line	Oral SERDS?	Oral SERDS?

# Another bolero turn

## ----- The translational side of the trial - PIK3CA



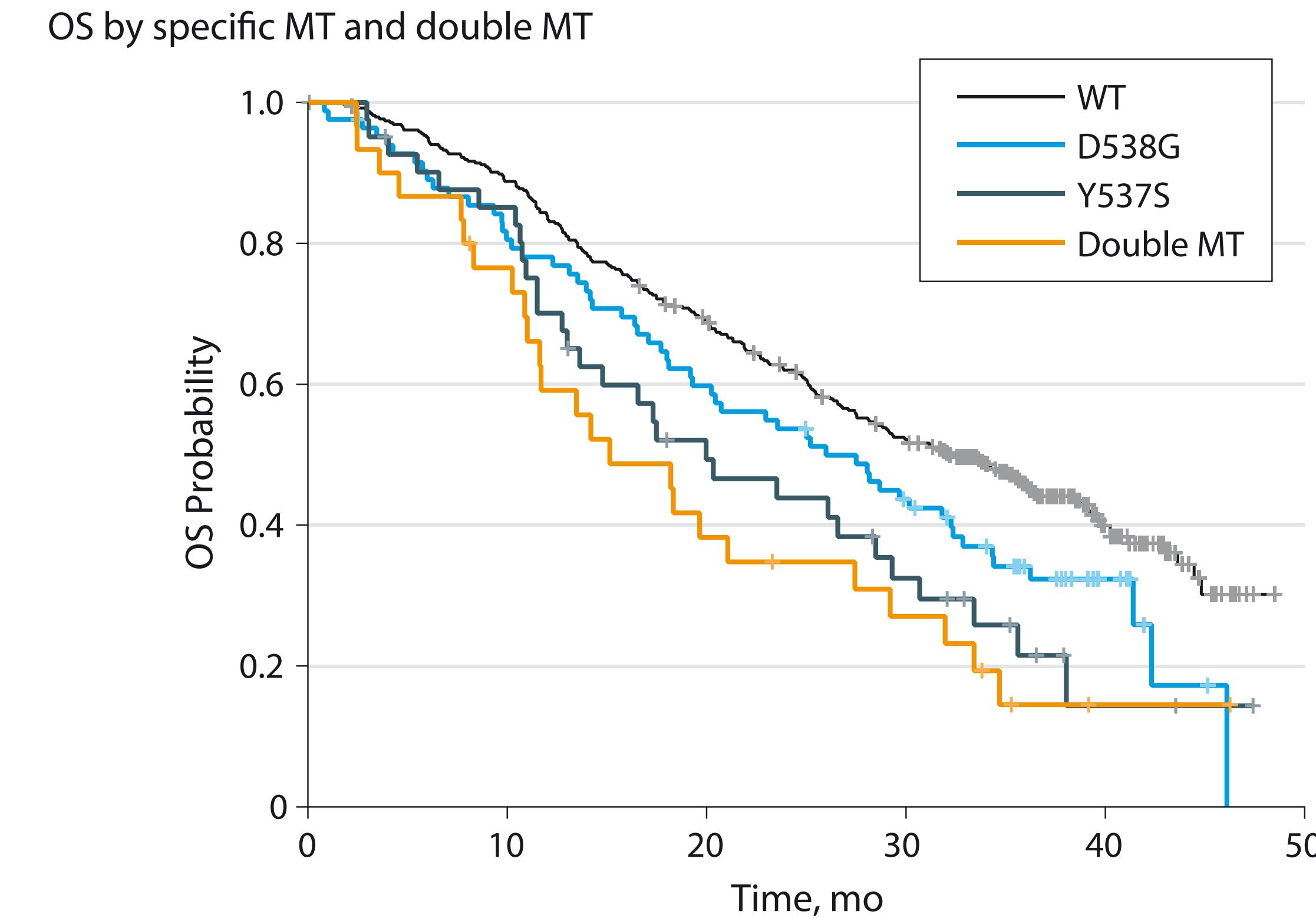
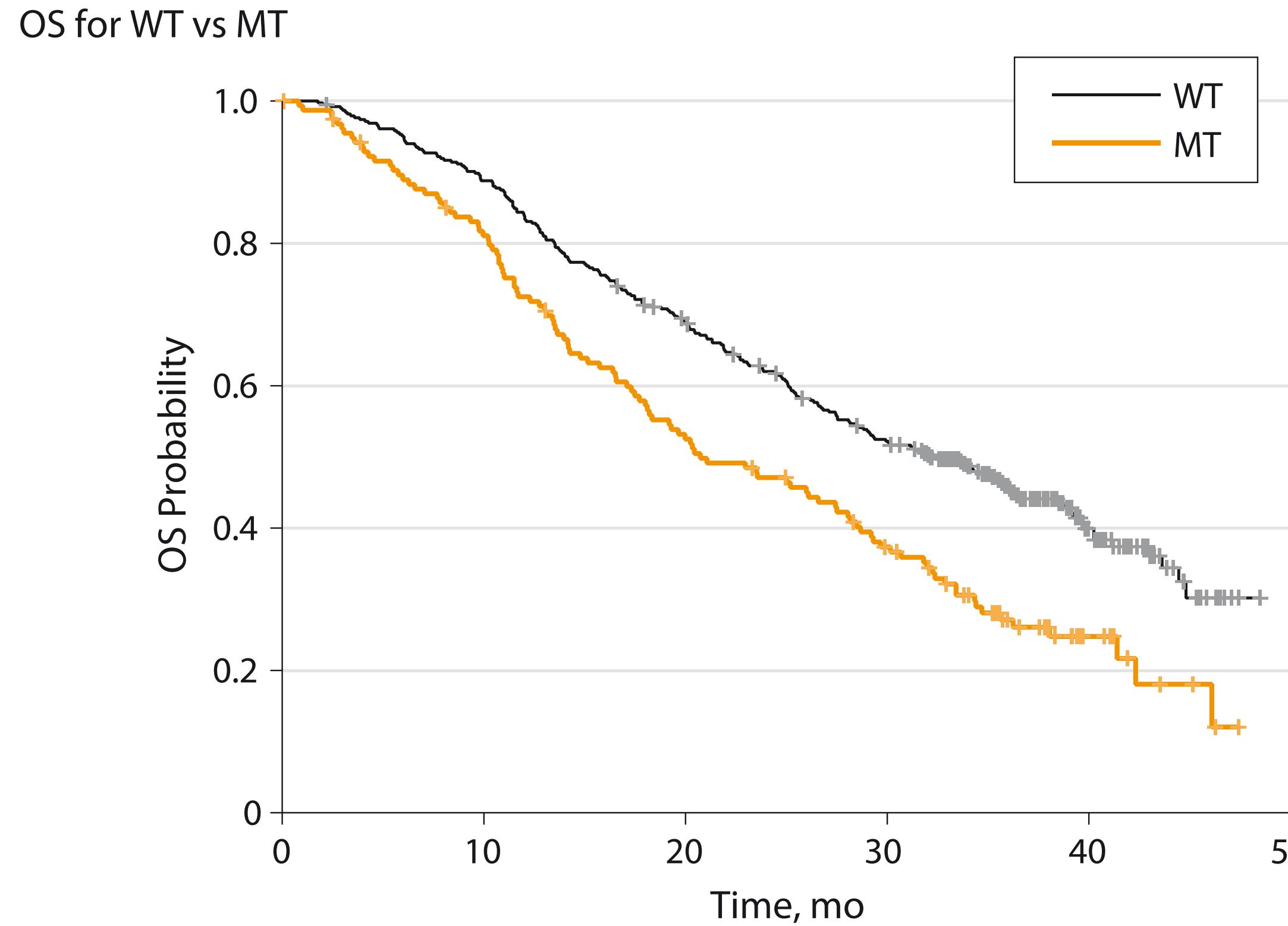
PBO + EXE WT	-----	124	42	15	6	1	
PBO + EXE MT	-----	69	14	3			
EVE + EXE WT	—	188	116	69	28	9	1
EVE + EXE MT	—	169	94	49	17	2	



PBO + EXE WT	-----	124	42	15	6	1	
PBO + EXE H1047R	-----	43	12	2			
PBO + EXE E545K/E542K	-----	26	2	1			
EVE + EXE WT	—	188	116	69	28	9	1
EVE + EXE H1047R	—	95	54	32	11	1	
EVE + EXE E545K/E542K	—	74	40	17	6	1	

# Another bolero turn

## ----- The translational side of the trial - ESR1



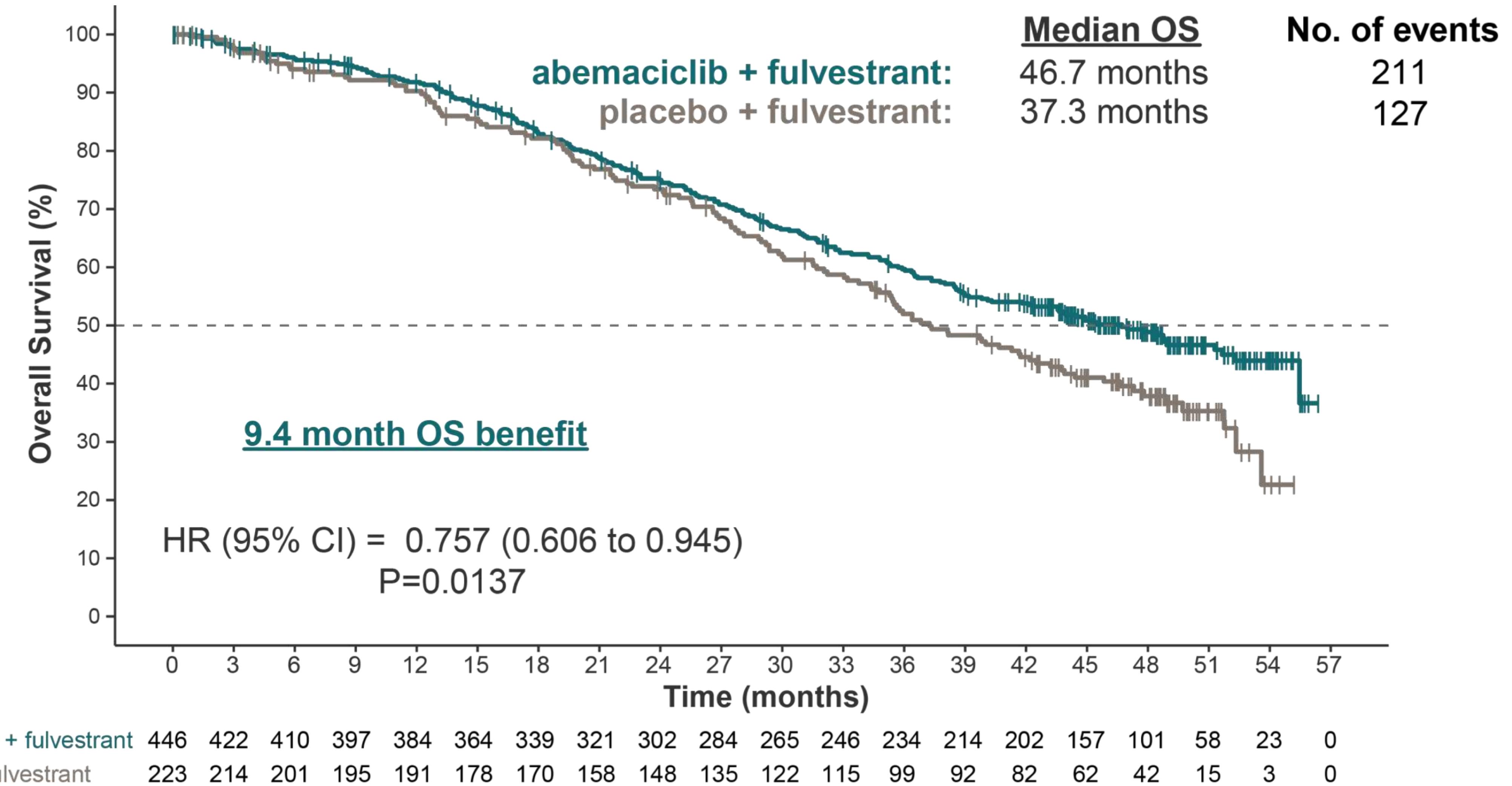
No. at risk	WT	MT
WT	385	156
MT	156	123

No. at risk	WT	D538G	Y537S	Double MT
WT	385	83	42	30
D538G	156	66	34	22
Y537S	123	49	18	11
Double MT	78	34	11	7
	52	22	7	1
	12	0	0	0
	0	0	0	0

**This issue will spread like wildfire**

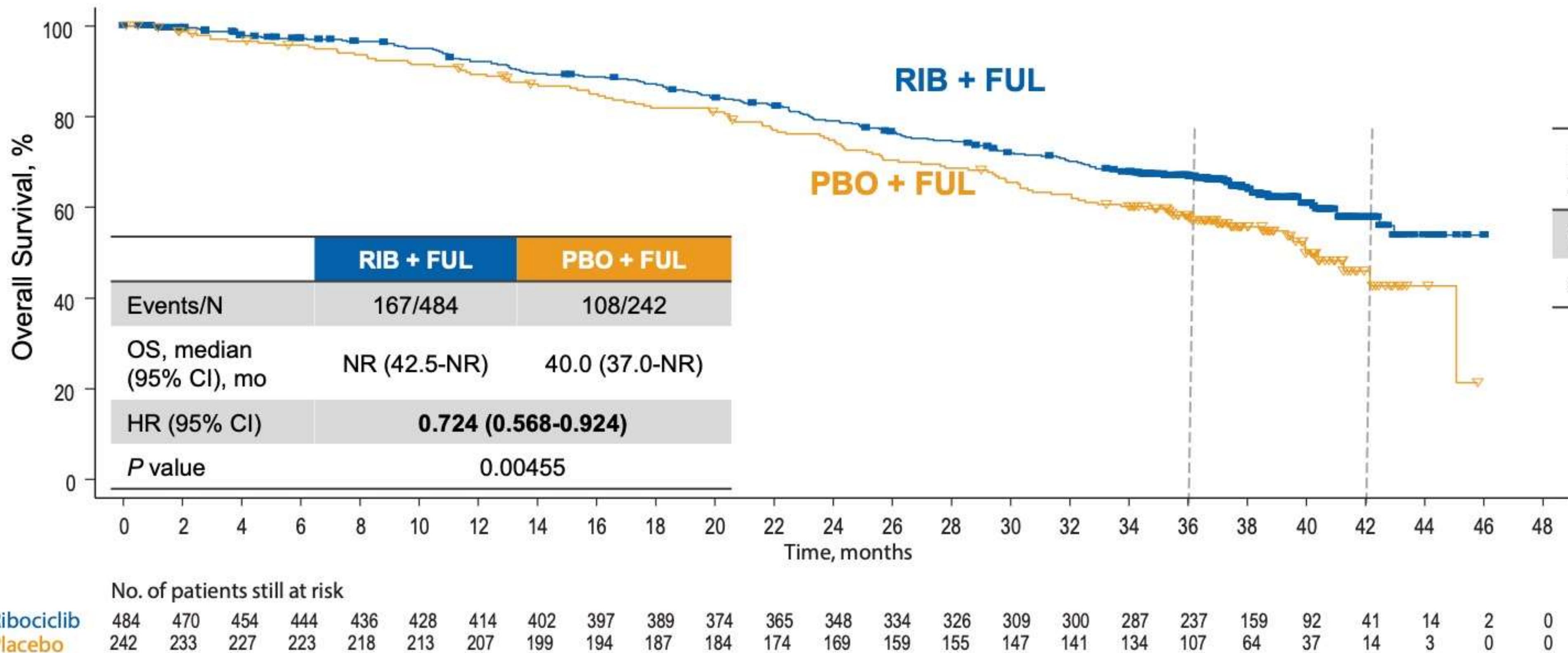
# Beware of dames and monarchs

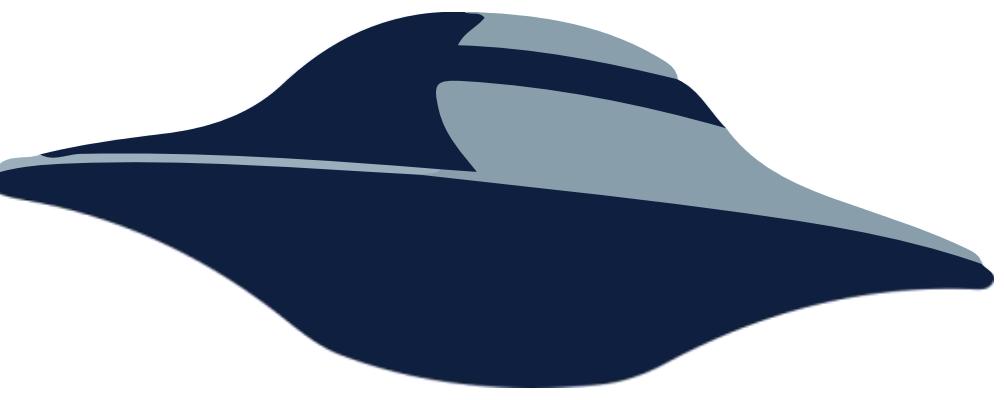
---- The MONARCH 2 Study



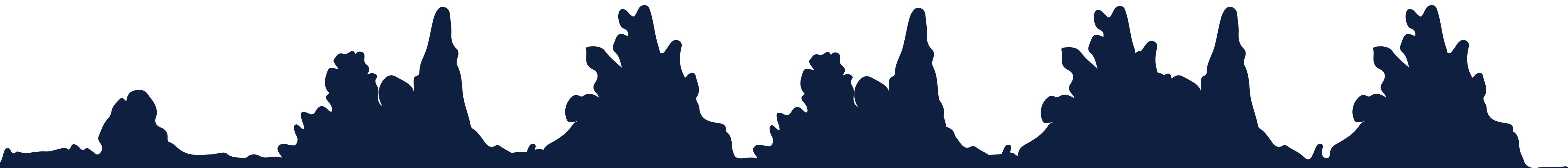
# Beware of dames and monarchs

## ----- The MONALEESA 3 Study



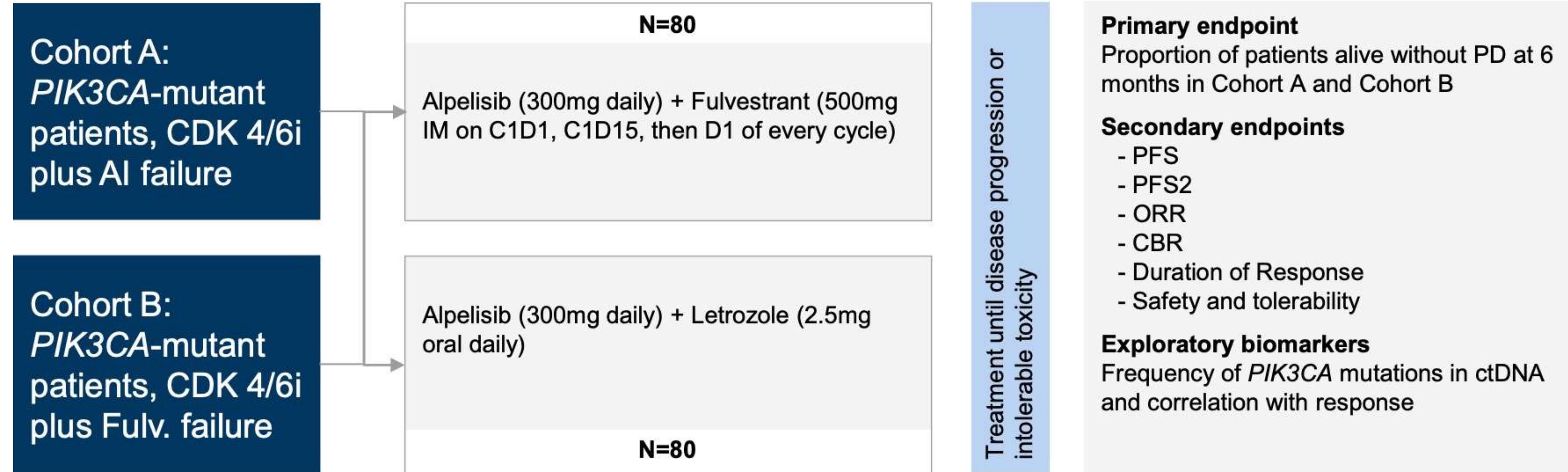


I want to **BYLieve**



# The BYLieve Study

## ----- Roommate Wanted



## BYLieve

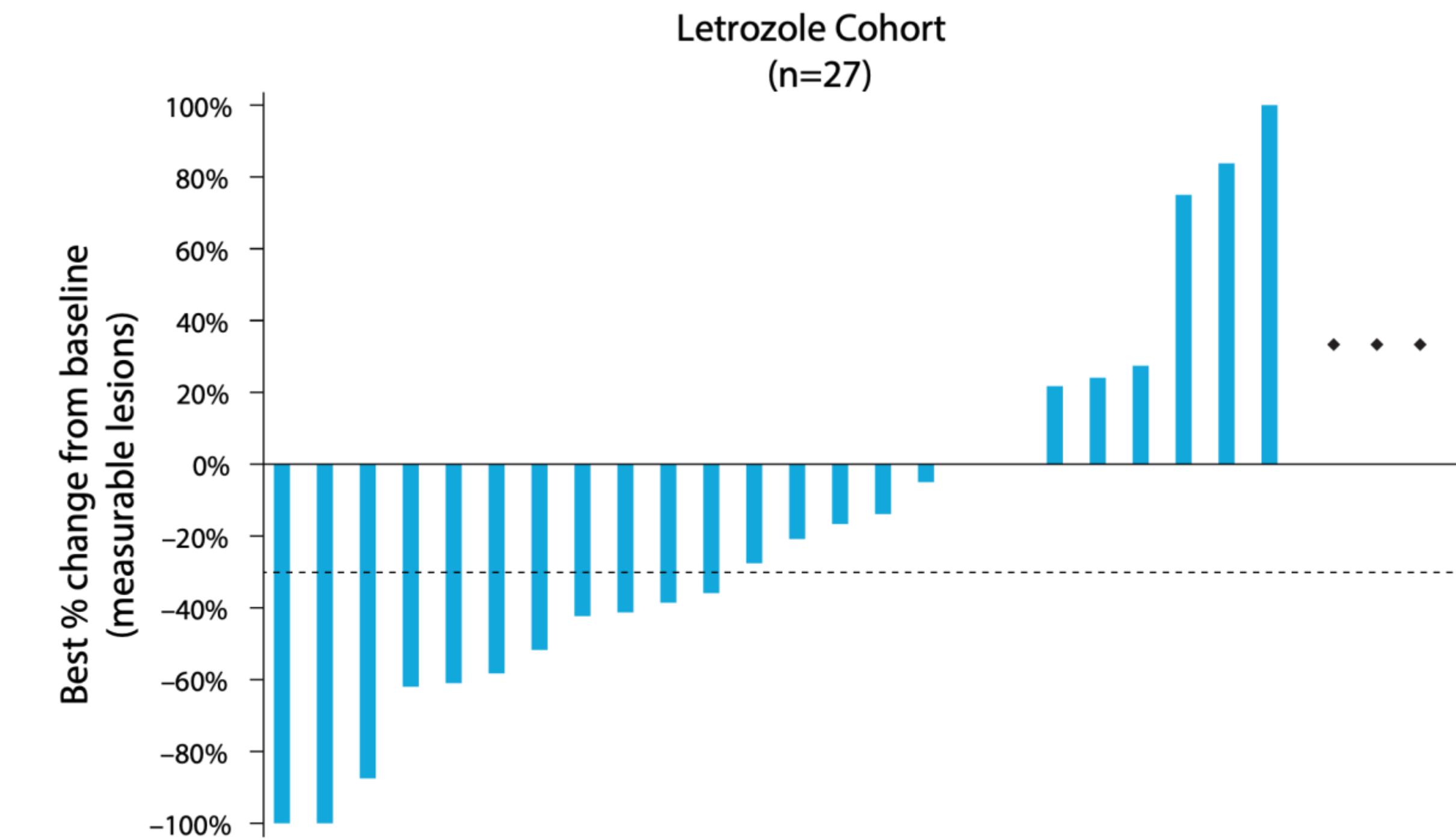
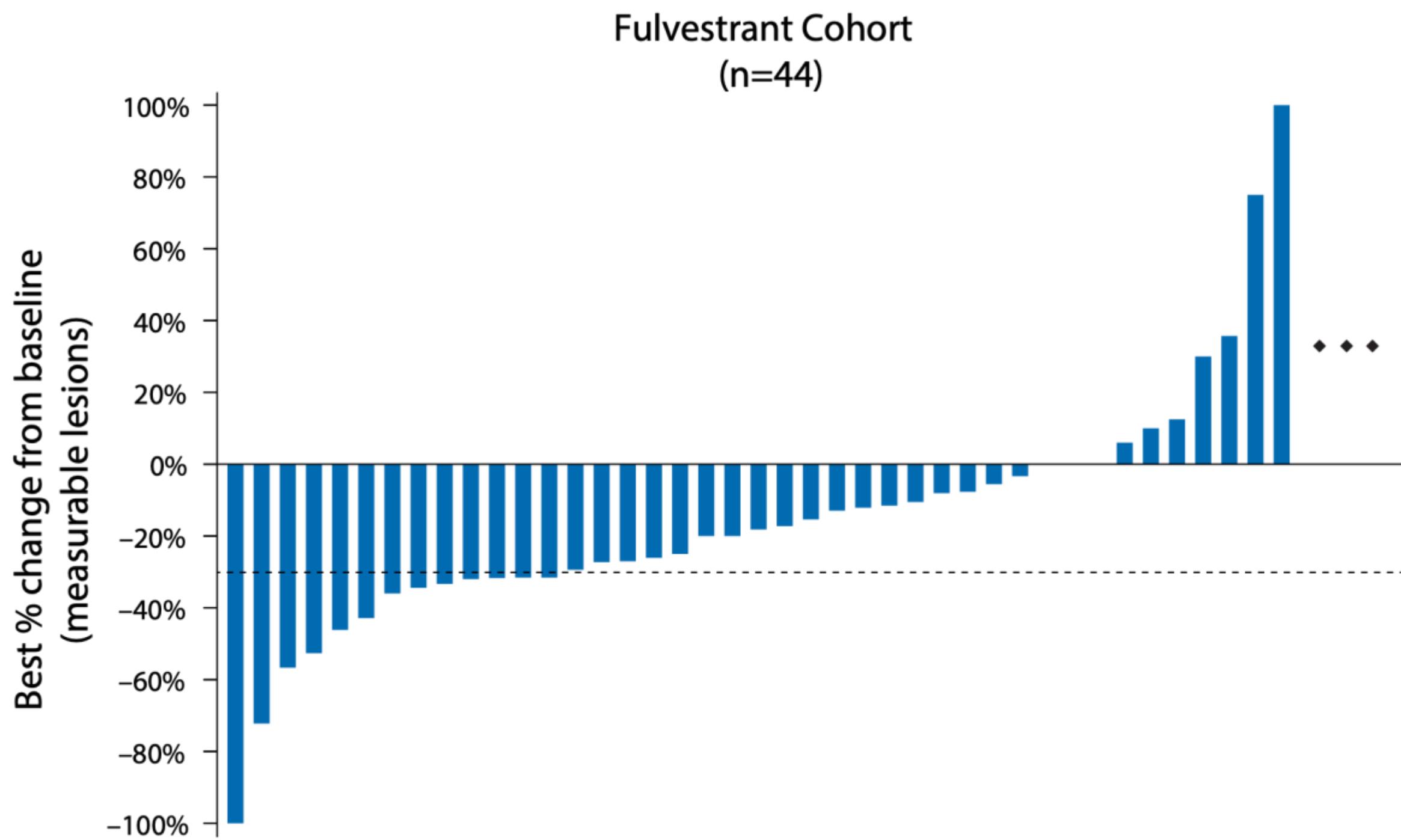
A phase 2, open-label, noncomparative study evaluating alpelisib plus ET (fulvestrant or letrozole).

HR+, HER2– ABC with *PIK3CA* mutation and previous CDK4/6i

Primary endpoint: proportion of progression free patients at 6 months in the 2 cohorts

# The BYLieve Study

## ----- Fulvestrant or letrozole?



Based on data from this planned interim analysis, alpelisib plus ET (fulvestrant or letrozole) is an efficacious treatment option for patients with HR+, HER2– ABC and a PIK3CA tumor mutation with progression on or after treatment with a CDK4/6 inhibitor plus ET

# The BYLieve Study

## Fulvestrant or letrozole - Adverse events

	Fulvestrant Cohort (n=64)		Letrozole Cohort (n=36)	
Adverse Events ≥20% in Either Cohort, n (%)	All	Grade ≥3	All	Grade ≥3
Any adverse event	63 (98.4)	44 (68.8)	36 (100.0)	24 (66.7)
Diarrhea	37 (57.8)	2 (3.1)	21 (58.3)	0
Hyperglycemia	35 (54.7)	16 (25.0)	26 (72.2)	10 (27.8)
Nausea	33 (51.6)	0	20 (55.6)	0
Decreased appetite	21 (32.8)	0	17 (47.2)	1 (2.8)
Stomatitis	19 (29.7)	1 (1.6)	13 (36.1)	0
Vomiting	19 (29.7)	1 (1.6)	7 (19.4)	0
Fatigue	16 (25.0)	0	7 (19.4)	0
Asthenia	13 (20.3)	1 (1.6)	10 (27.8)	1 (2.8)
Headache	13 (20.3)	1 (1.6)	10 (27.8)	2 (5.6)
Pyrexia	13 (20.3)	1 (1.6)	9 (25.0)	0
Rash <sup>a</sup>	13 (20.3)	5 (7.8)	9 (25.0)	2 (5.6)
Abdominal pain	13 (20.3)	2 (3.1)	8 (22.2)	1 (2.8)
Dysgeusia	10 (15.6)	0	8 (22.2)	0

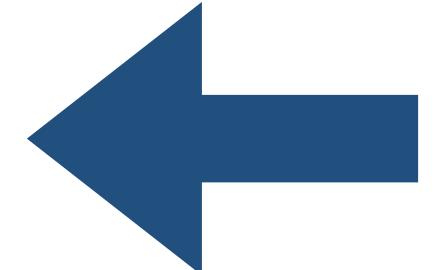
# Wrapping up

----- Today's science is tomorrow's medicine

**PI3K is an interesting target due to its high incidence and stability**

Although highly integrated, PI3K and mTOR are two distinct pathways

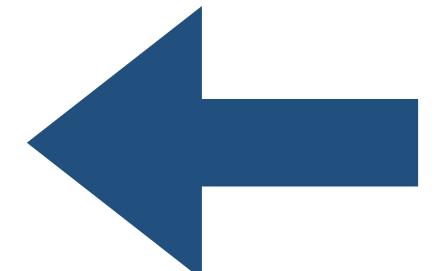
Aspecific PI3K inhibition is burdened by heavy side effects



**The SOLAR-1 implements a solid, biomarker-driven approach**

Clinically significant PFS benefit across all subgroups, hyperglycemia is the main AE

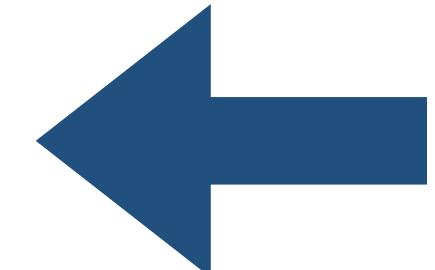
Clinicians need to be increasingly aware of sequencing tech's caveats and pitfalls



**The best is yet to come**

Other selective PI3K inhibitors are currently in development pipeline

The ET decisional algorithm needs to be deeply rethought in the future



# Thank you

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