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25/26 NOVEMBRE 2021



The **Liquid biopsy**  
Research Team

# News on Luminal-like MBC

## A Journey through Middle-earth

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# Conflict of Interest Disclosure Statement

■ Last updated on 26.11.2021

<b>What?</b>	<b>Who?</b>
<b>Stock and Other Ownership Interests:</b>	No Relationships to Disclose
<b>Honoraria:</b>	No Relationships to Disclose
<b>Consulting or Advisory Role:</b>	Eli Lilly, Novartis
<b>Expert Testimony</b>	No Relationships to Disclose
<b>Research Funding</b>	No Relationships to Disclose
<b>Patents, Royalties, Other Intellectual Property</b>	No Relationships to Disclose
<b>Travel Expenses</b>	Menarini Silicon Biosystems

# Our travel itinerary

■ Not all those who wander are lost



A

**No news is good news**

Updated OS data



**One does not simply walk into Mordor**

New biomarkers for an old question



B

**A Brave new world**

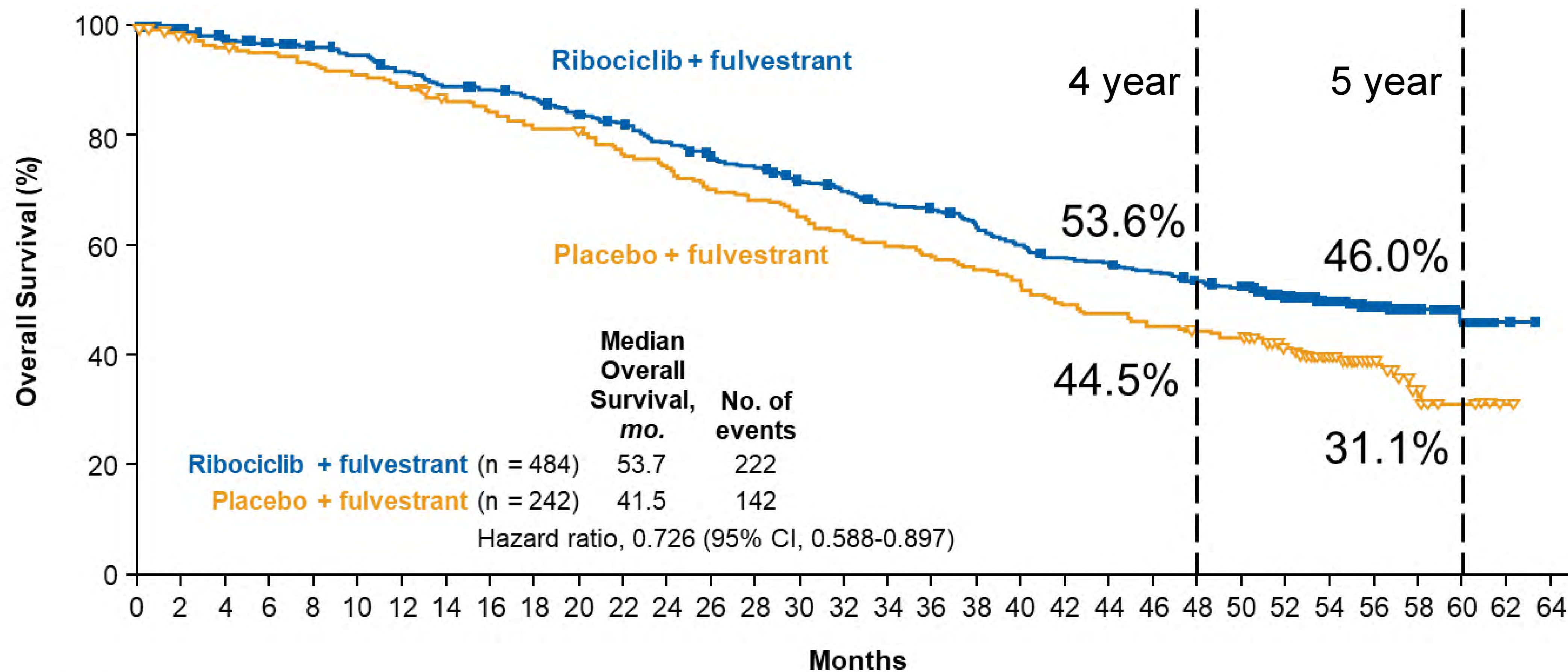


**No news is a good news**



# The MONALEESA-3 trial

■ Updated Overall Survival - median 56.3 months

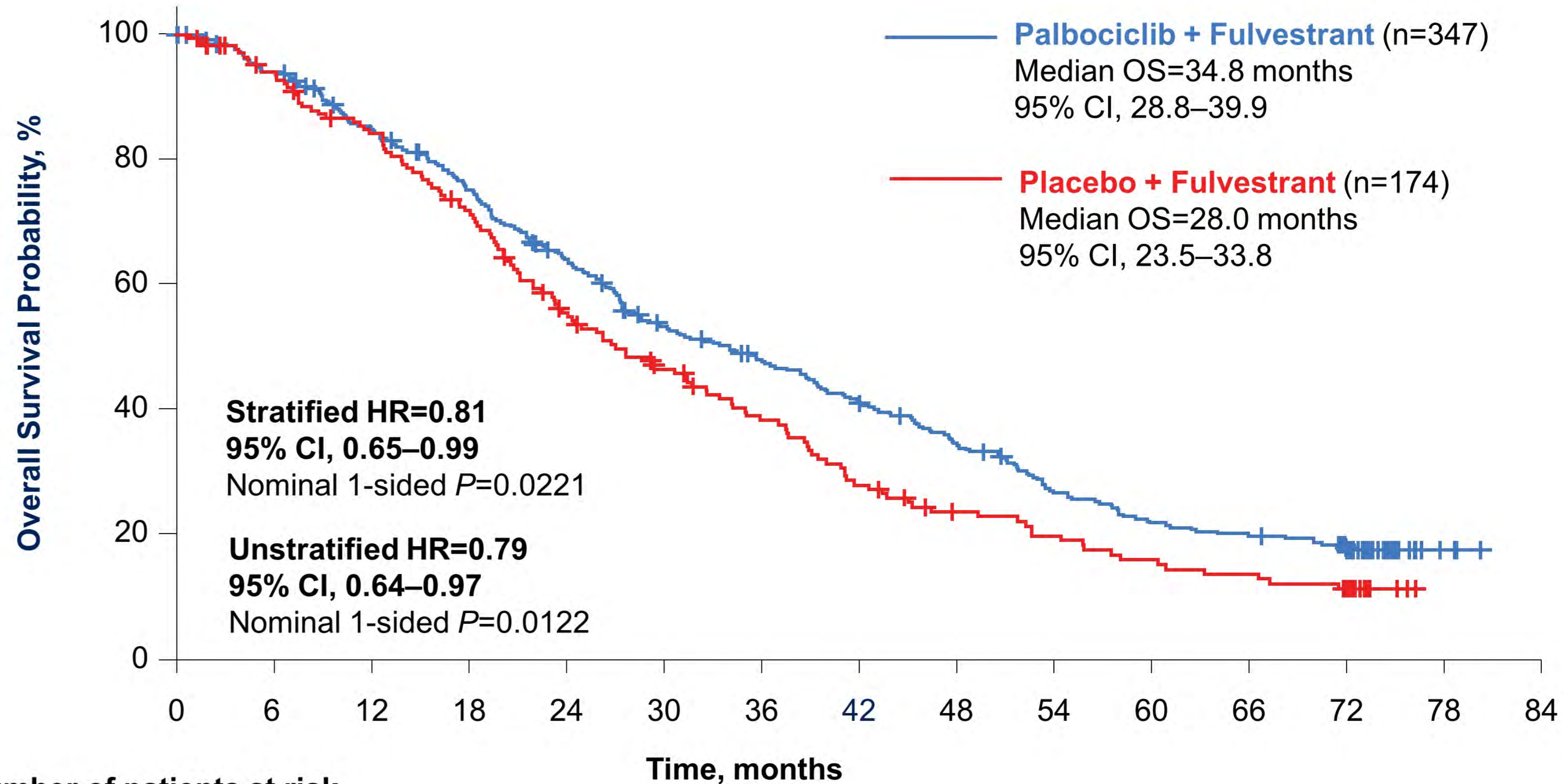


No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64
<b>Ribociclib + fulvestrant</b>	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	310	301	290	285	273	256	245	241	233	224	218	191	145	90	50	20	4	0
<b>Placebo + fulvestrant</b>	242	233	227	223	218	213	208	200	195	188	185	175	170	160	156	149	143	137	133	127	120	112	107	102	99	96	82	56	29	15	5	1	0



# The PALOMA3 trial

■ Updated Overall Survival - median 73.3 months



**Number of patients at risk**

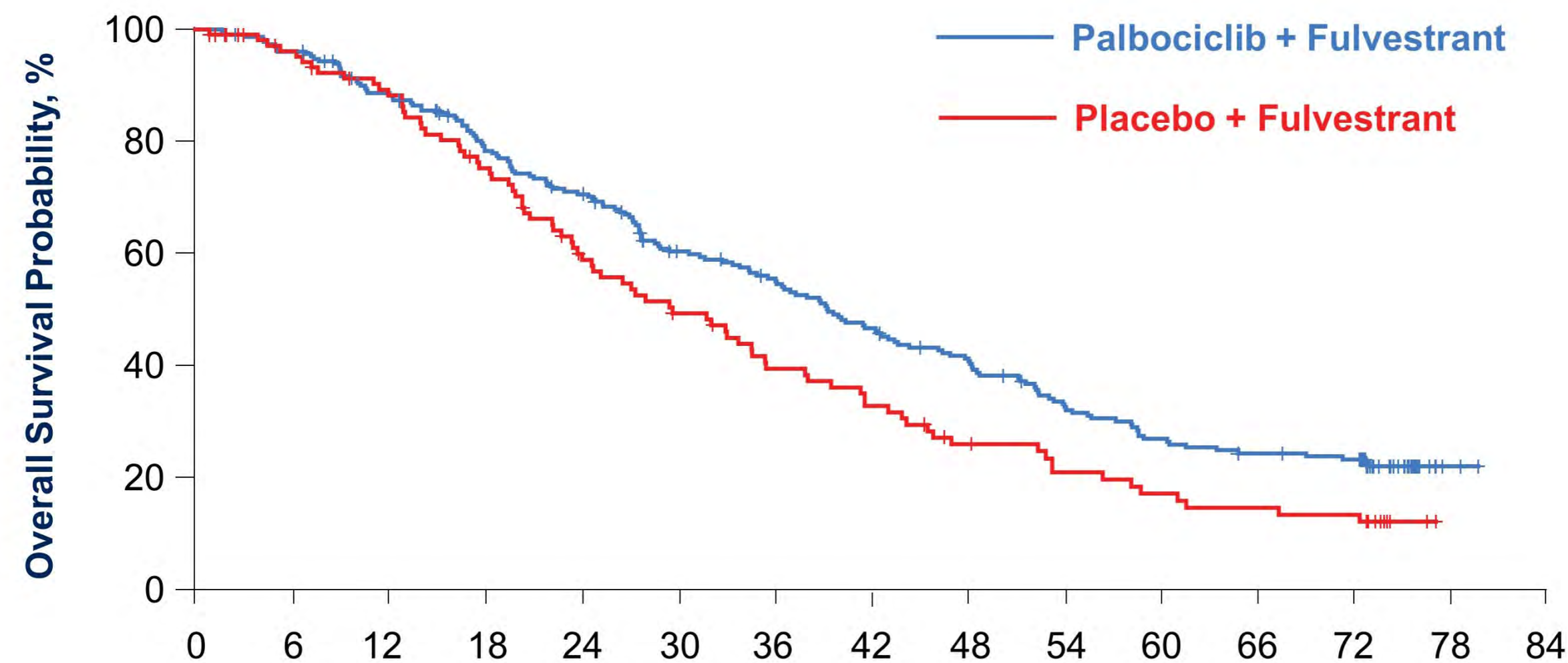
PAL+FUL	347	322	288	250	211	167	149	128	109	84	68	60	54	4	0
PBO+FUL	174	156	138	117	89	71	58	43	33	27	22	19	17	0	



# The PALOMA3 updated Overall Survival

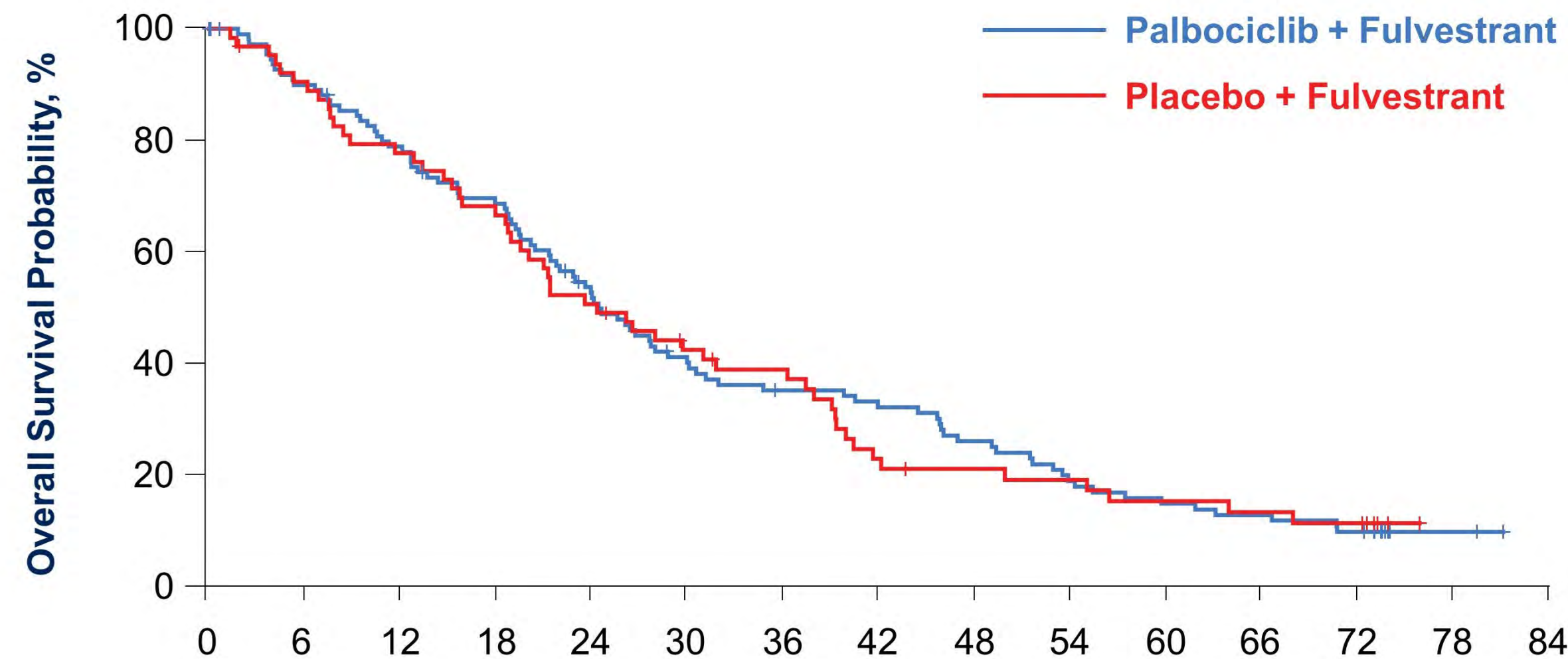
■ Prognosis according to previous chemotherapy

**No Prior Chemotherapy in ABC (66% of ITT)**



Number of patients at risk		Time, months														
		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
PAL+FUL	234	223	202	176	156	126	114	96	83	65	53	47	44	2	0	
PBO+FUL	110	99	89	75	57	46	36	30	22	17	14	12	11	0	0	

**Prior Chemotherapy in ABC (34% of ITT)**



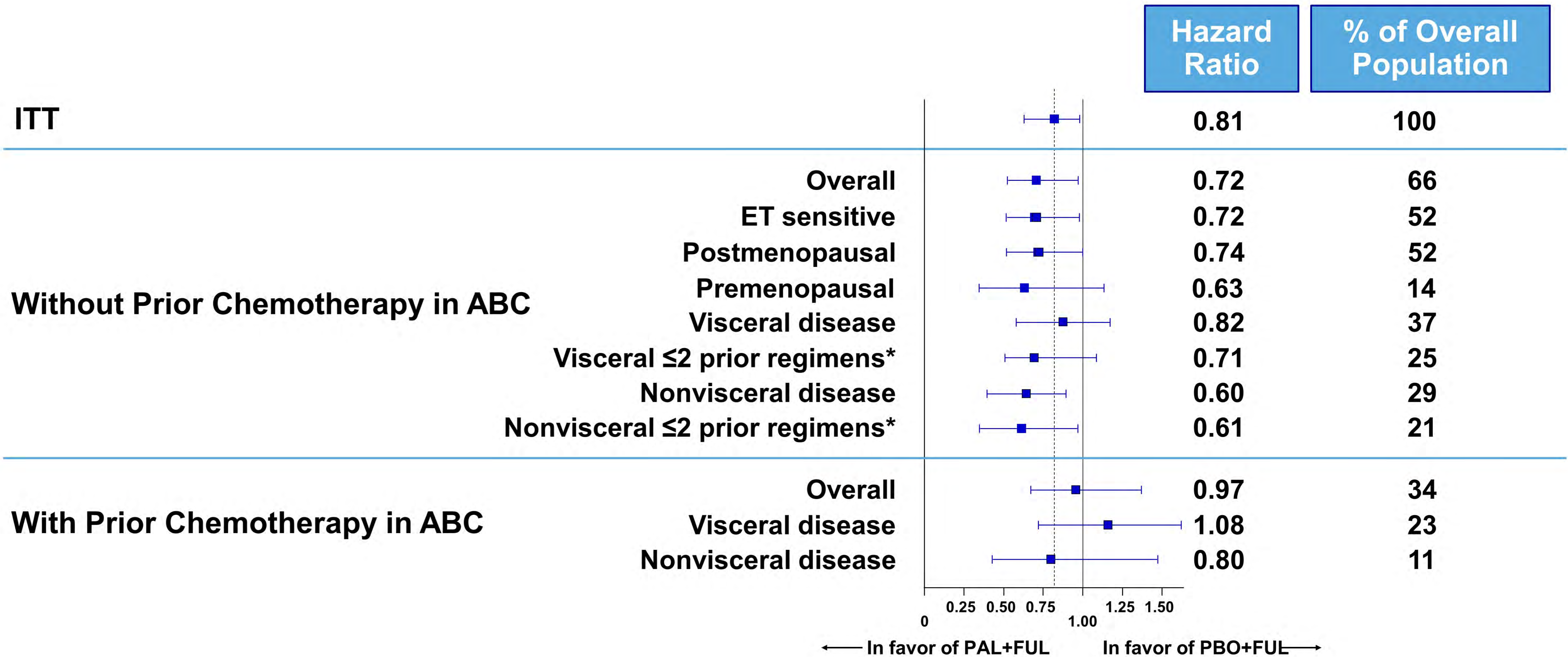
Number of patients at risk		Time, months														
		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
PAL+FUL	113	99	86	74	55	41	35	32	26	19	15	13	10	2	0	
PBO+FUL	64	57	49	42	32	25	22	13	11	10	8	7	6	0	0	

	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Palbociclib + Fulvestrant	Placebo + Fulvestrant
	<b>No Prior Chemotherapy</b>		<b>Prior Chemotherapy</b>	
Patients, n	234	110	113	64
Median OS (95% CI), mo	39.3 (34.5–44.4)	29.7 (23.8–35.5)	24.6 (21.3–30.0)	24.3 (18.9–36.3)
Hazard ratio (95% CI)	0.72 (0.55–0.94)		0.97 (0.69–1.36)	
Nominal P-Value	0.008		0.432	



# Prognosis according to previous chemotherapy

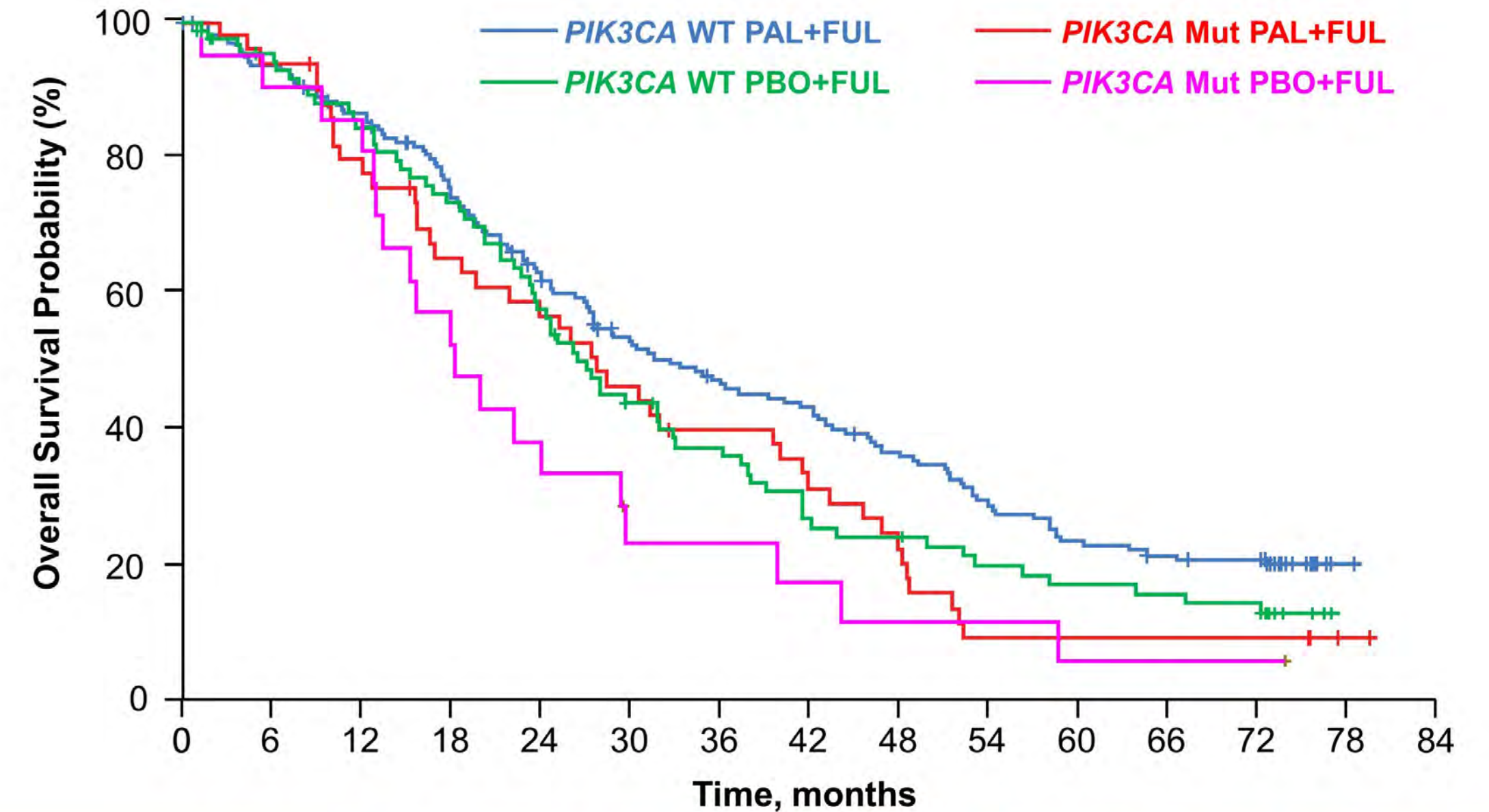
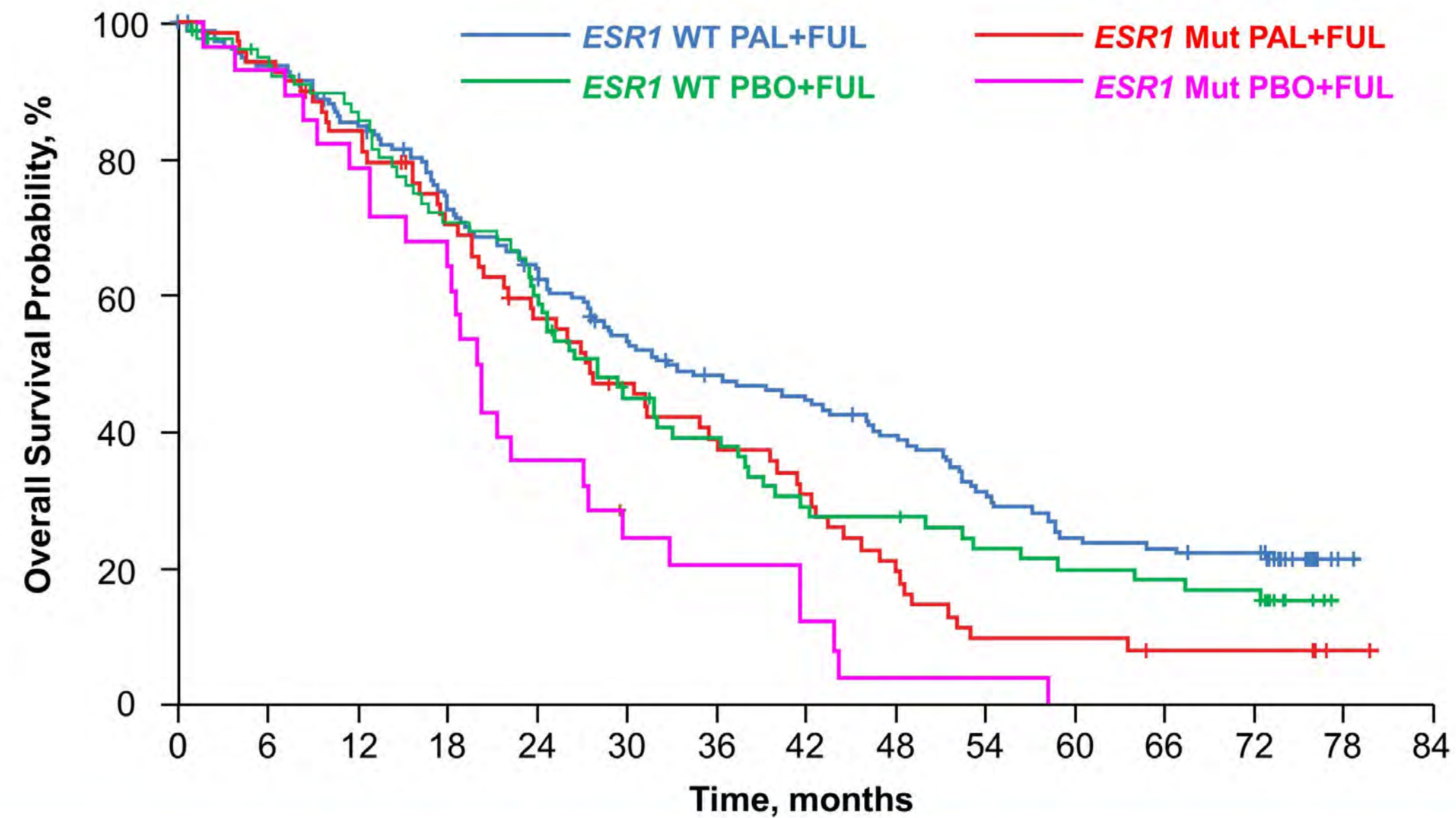
■ Subgroup analysis





# ET and ctDNA Biomarkers

■ Impact of *ESR1* and *PIK3CA* status on OS



	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Palbociclib + Fulvestrant	Placebo + Fulvestrant
	<b>No <i>ESR1</i> Mutation</b>		<b><i>ESR1</i> Mutation</b>	
Patients, n (%)	154 (69.1)	80 (74.1)	69 (30.9)	28 (25.9)
Median OS (95% CI), mo	32.8 (27.4–46.1)	28.0 (23.6–36.3)	27.7 (20.4–36.1)	20.2 (15.3–27.1)
Hazard ratio (95% CI)	0.81 (0.59–1.11)		0.59 (0.37–0.94)	

	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Palbociclib + Fulvestrant	Placebo + Fulvestrant
	<b>No <i>PIK3CA</i> Mutation</b>		<b><i>PIK3CA</i> Mutation</b>	
Patients, n (%)	173 (77.6)	87 (80.6)	50 (22.4)	21 (19.4)
Median OS (95% CI), mo	32.8 (27.2–42.3)	26.6 (23.4–33.0)	27.7 (16.9–40.1)	18.3 (12.9–29.5)
Hazard ratio (95% CI)	0.78 (0.58–1.04)		0.73 (0.42–1.25)	

OS benefit regardless of *ESR1* and *PIK3CA* status

The most prevalent *ESR1* mutations were D538G, Y537S and E380Q

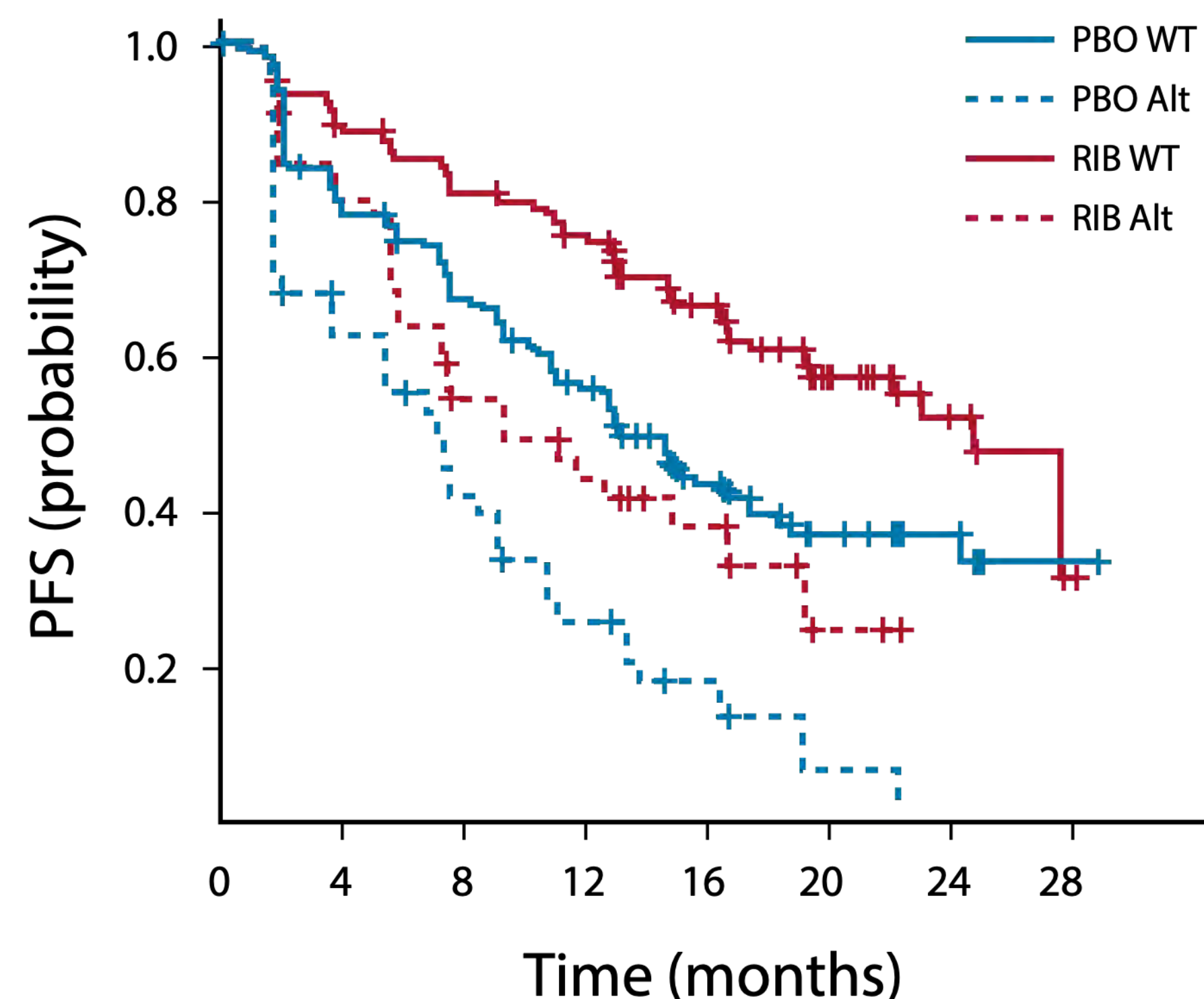
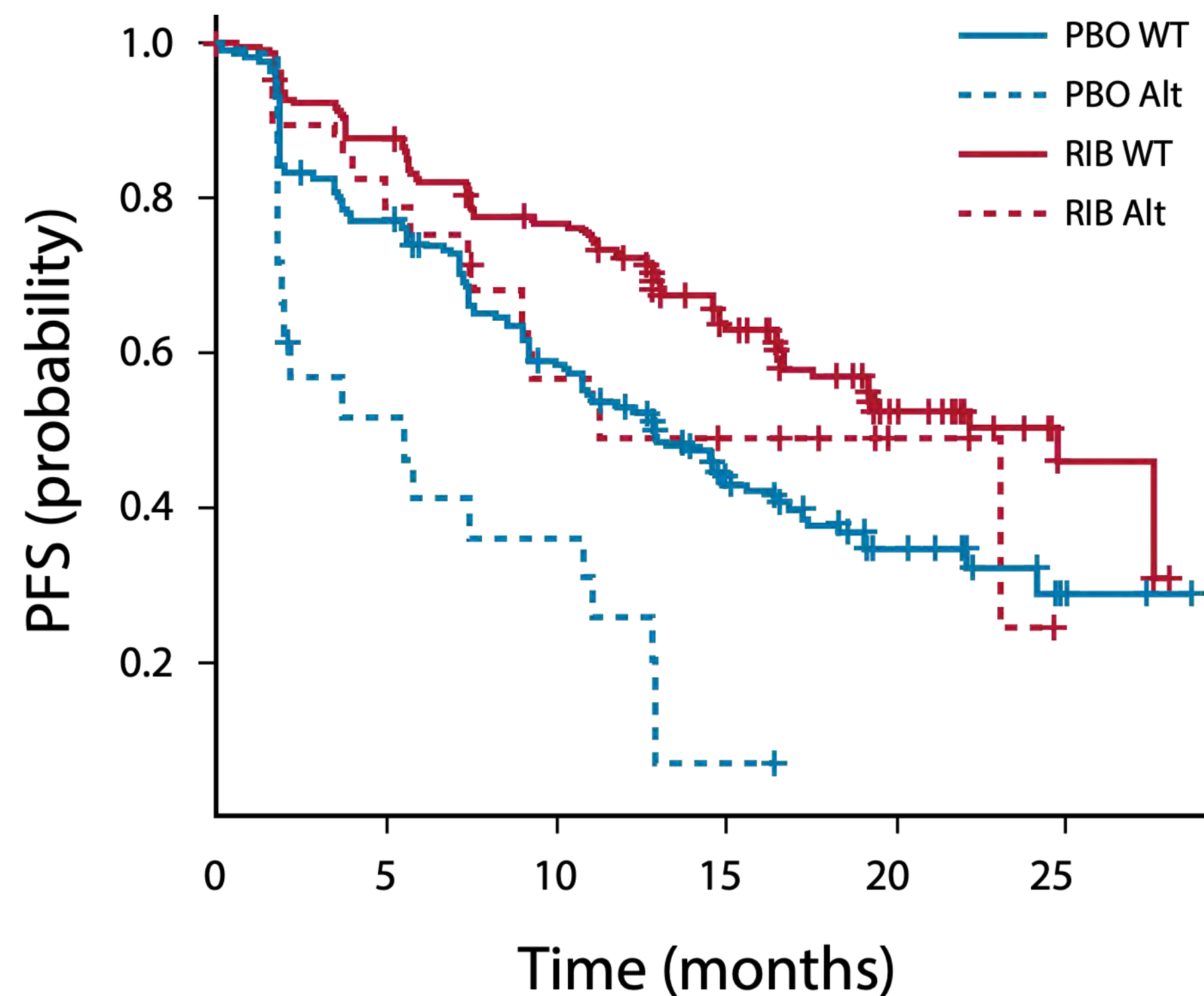


**But are there any really new biomarkers?**



# The translational side of MONALEESA-7

■ PFS by CCND1 and TP53 alteration status



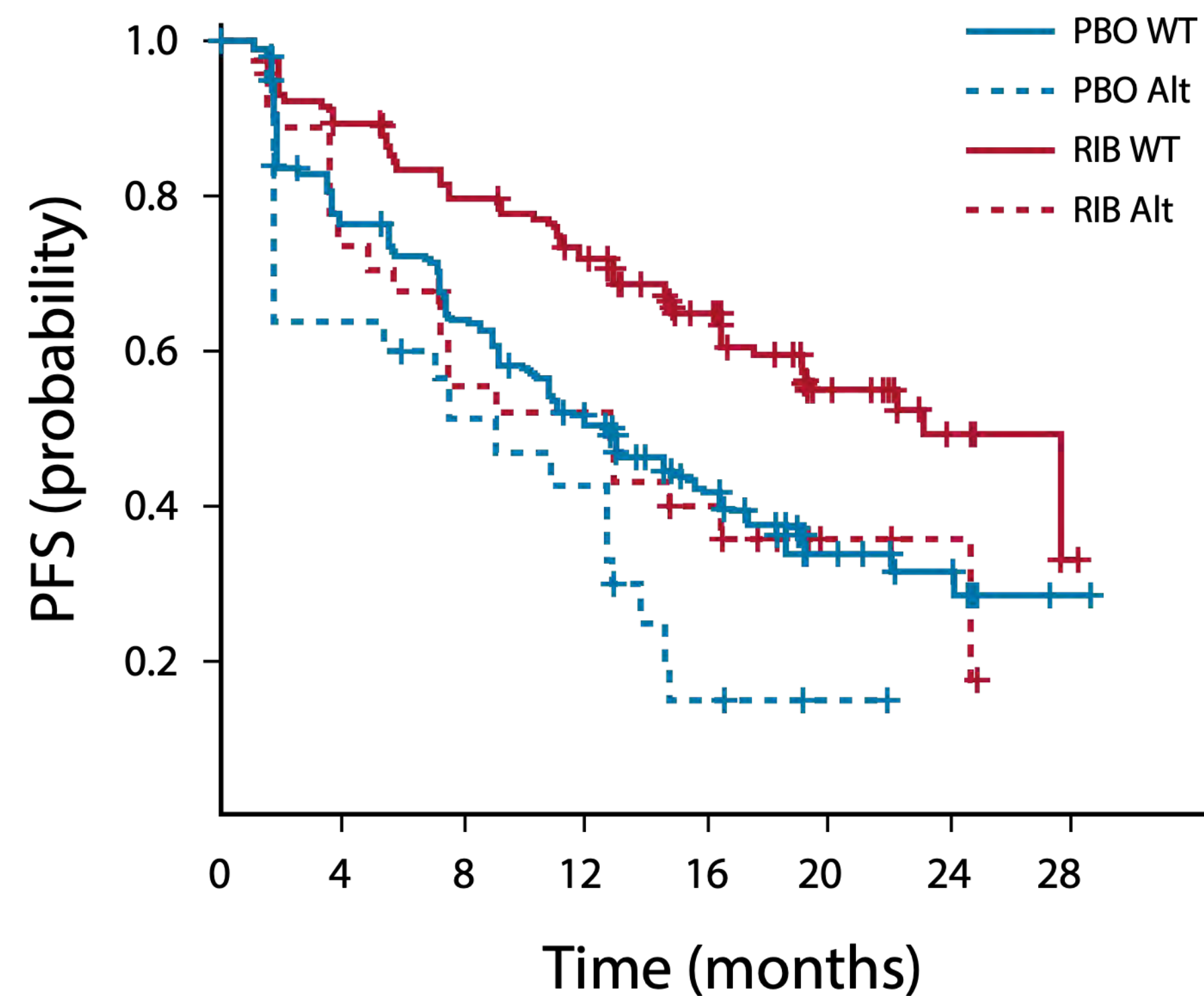
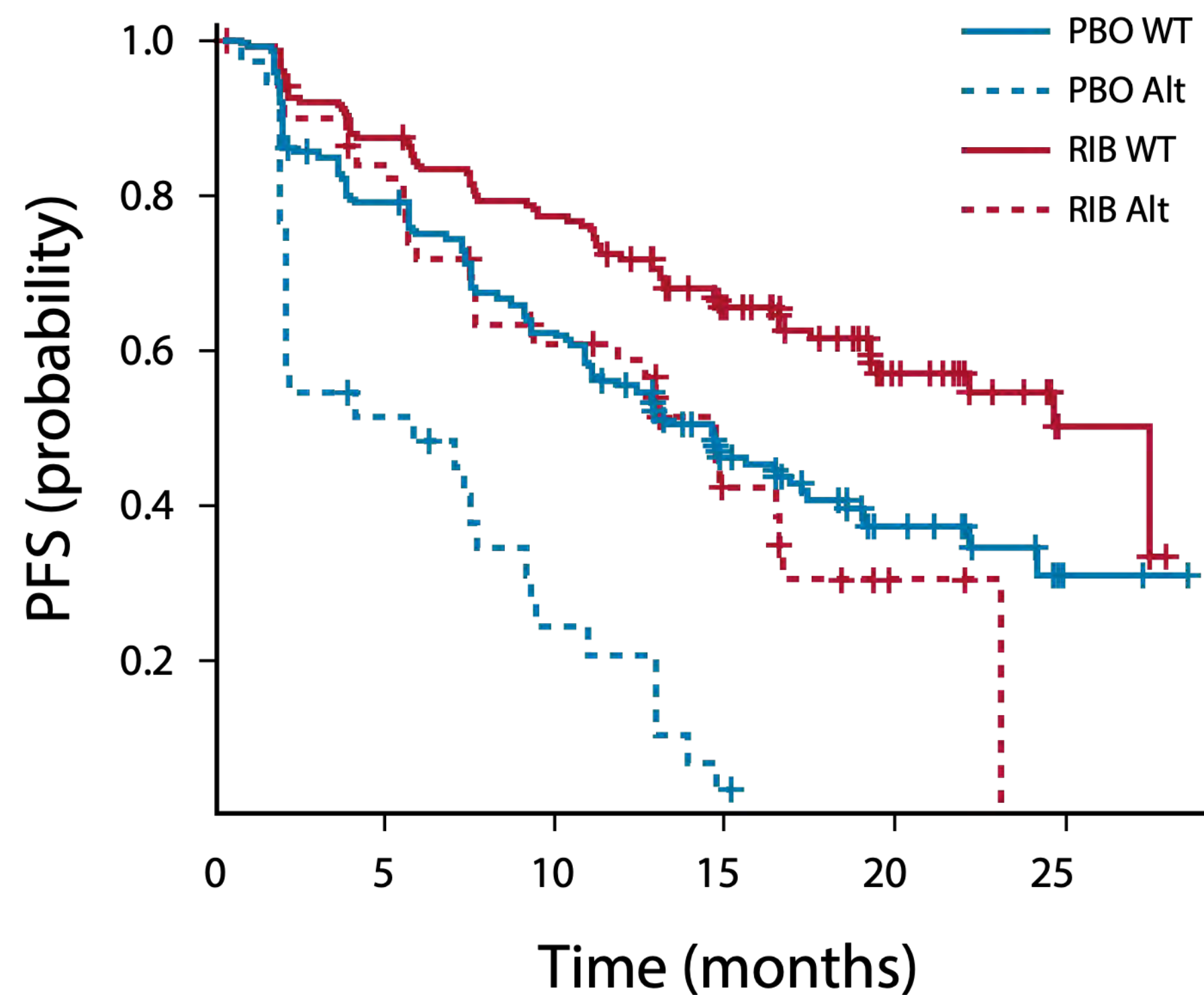
	No.	Events	PFS, Median (95% CI), months	HR (95% CI)
PBO WT	217	126	12.88 (10.78 to 15.01)	0.52 (0.39 to 0.68)
RIB WT	221	91	22.11 (16.62 to NA)	
PBO Alt	23	18	5.52 (1.87 to 11.04)	0.21 (0.08 to 0.54)
RIB Alt	28	15	11.27 (7.56 to NA)	

	No.	Events	PFS, Median (95% CI), months	HR (95% CI)
PBO WT	194	109	12.98 (11.04 to 16.53)	0.48 (0.36 to 0.65)
RIB WT	203	78	24.67 (19.35 to NA)	
PBO Alt	46	35	7.16 (3.68 to 9.13)	0.47 (0.27 to 0.82)
RIB Alt	46	28	9.23 (5.82 to 16.49)	



# The translational side of MONALEESA-7

■ PFS by RTK and Chr8p11.23 alteration status



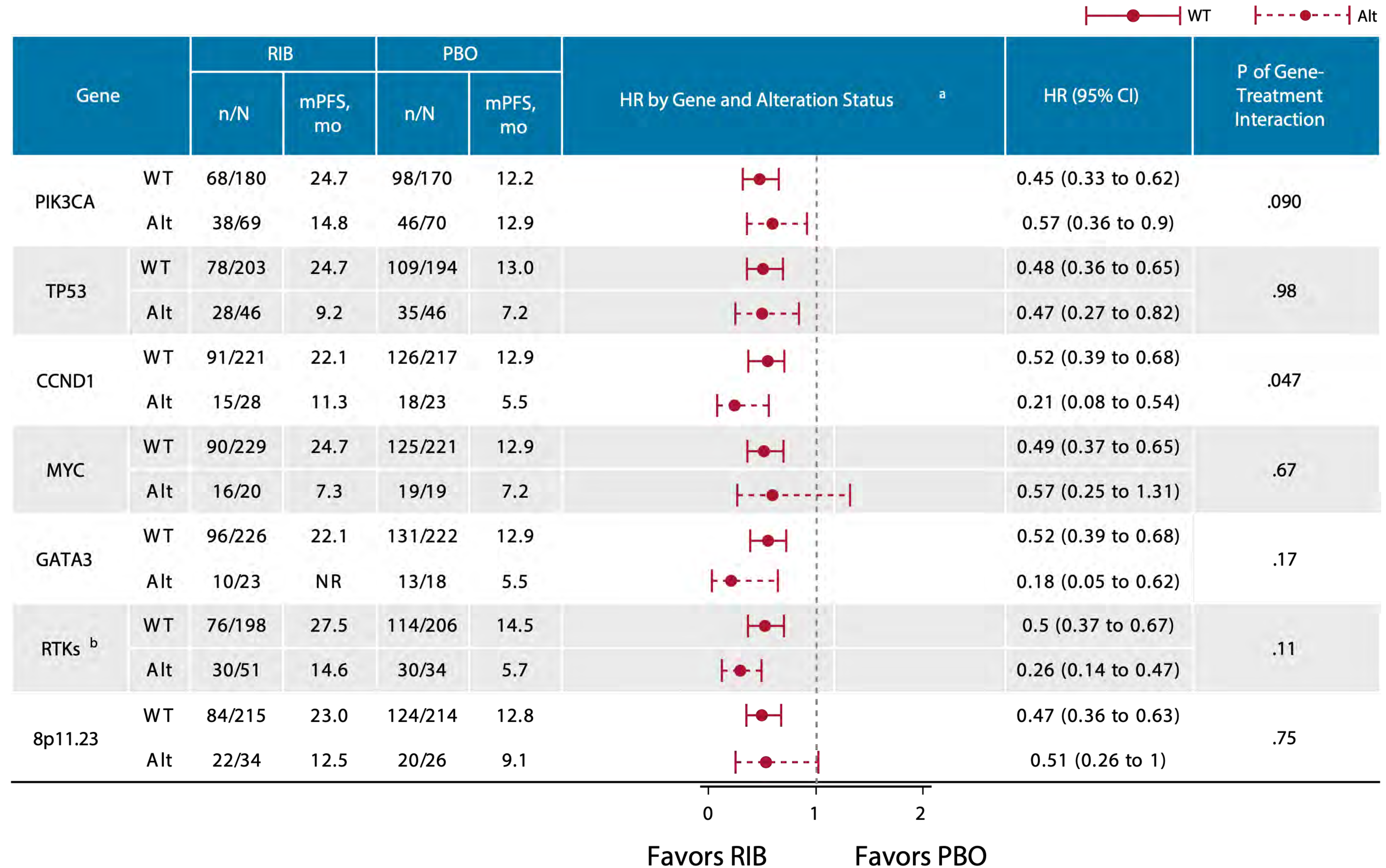
	No.	Events	PFS, Median (95% CI), months	HR (95% CI)
PBO WT	206	114	14.52 (11.04 to 16.89)	0.5 (0.37 to 0.67)
RIB WT	198	76	27.53 (19.35 to NA)	
PBO Alt	34	30	5.65 (1.87 to 9.03)	0.26 (0.14 to 0.47)
RIB Alt	51	30	14.55 (7.56 to 16.59)	

	No.	Events	PFS, Median (95% CI), months	HR (95% CI)
PBO WT	214	124	12.87 (10.38 to 15.61)	0.47 (0.36 to 0.63)
RIB WT	215	84	23.03 (19.12 to NA)	
PBO Alt	26	20	9.13 (1.87 to 12.88)	0.51 (0.26 to 1)
RIB Alt	34	22	12.52 (5.78 to 24.67)	



# The translational side of MONALEESA-7

## ■ PFS by genetic subgroup

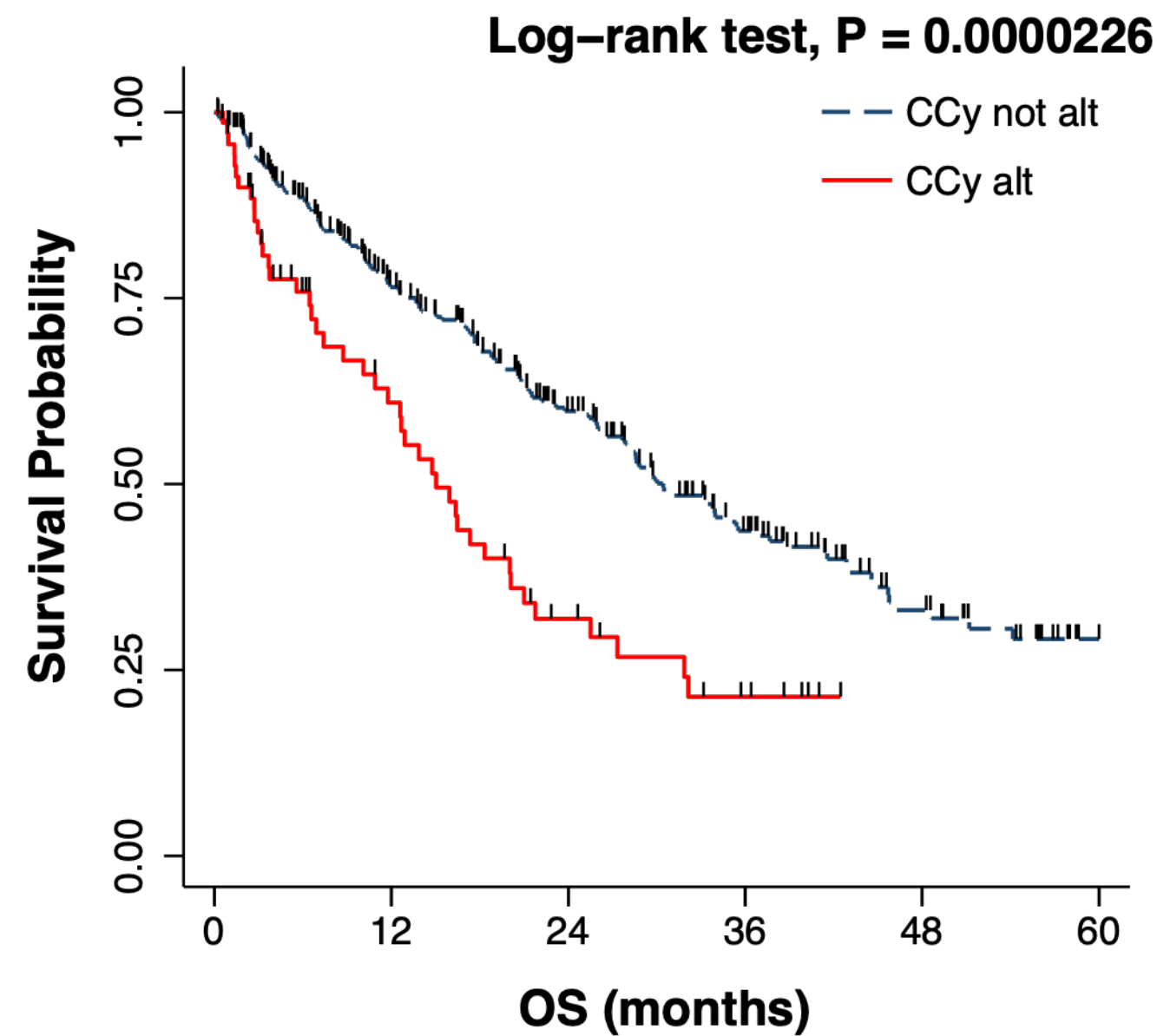




# ET resistance: One does not simply walk into Mordor

■ Classification based on oncogenic pathways can be promising

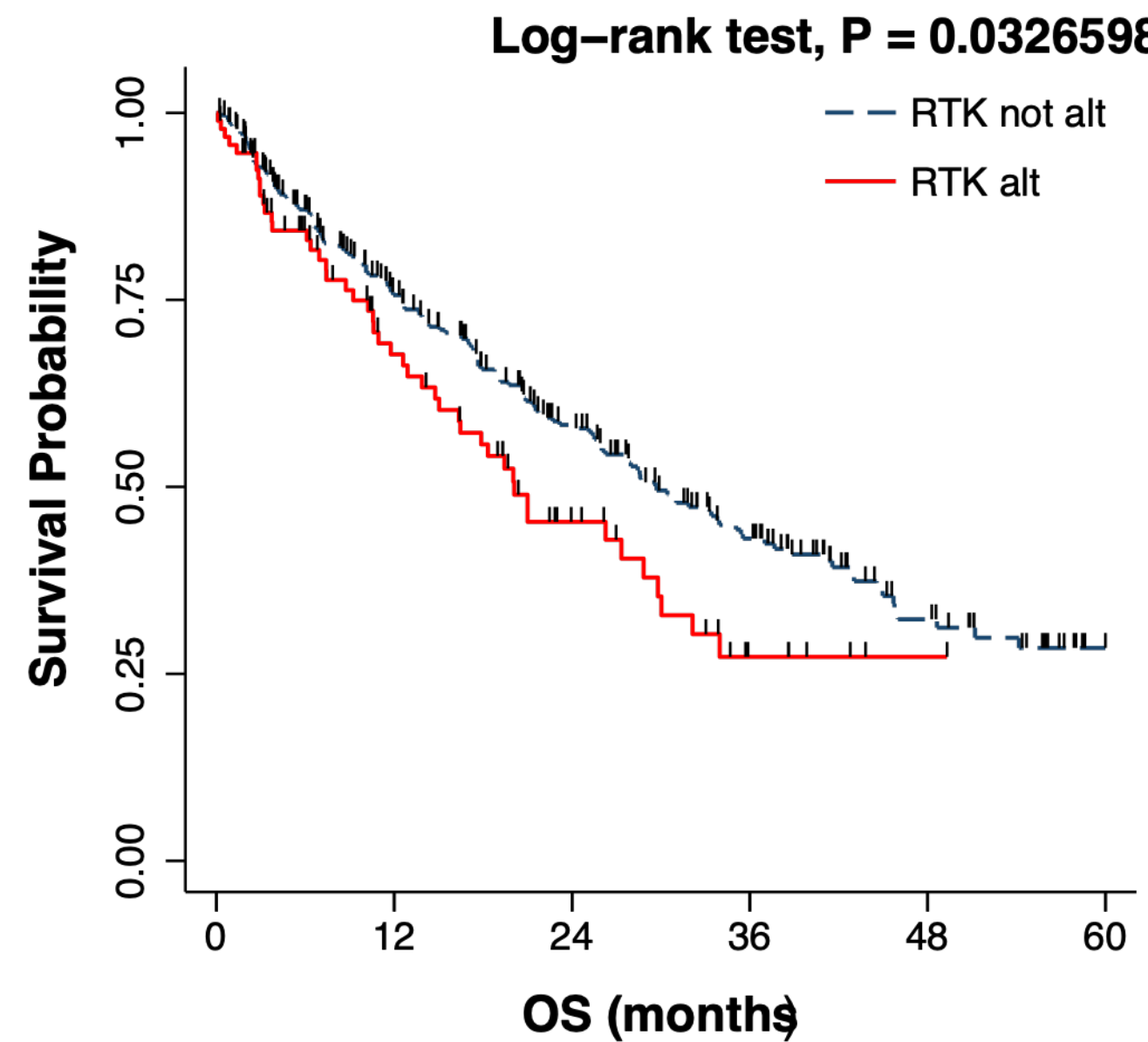
**A**



**Number at risk**

CCy not alt	349	214	129	71	32	8
CCy alt	71	32	14	6	0	0

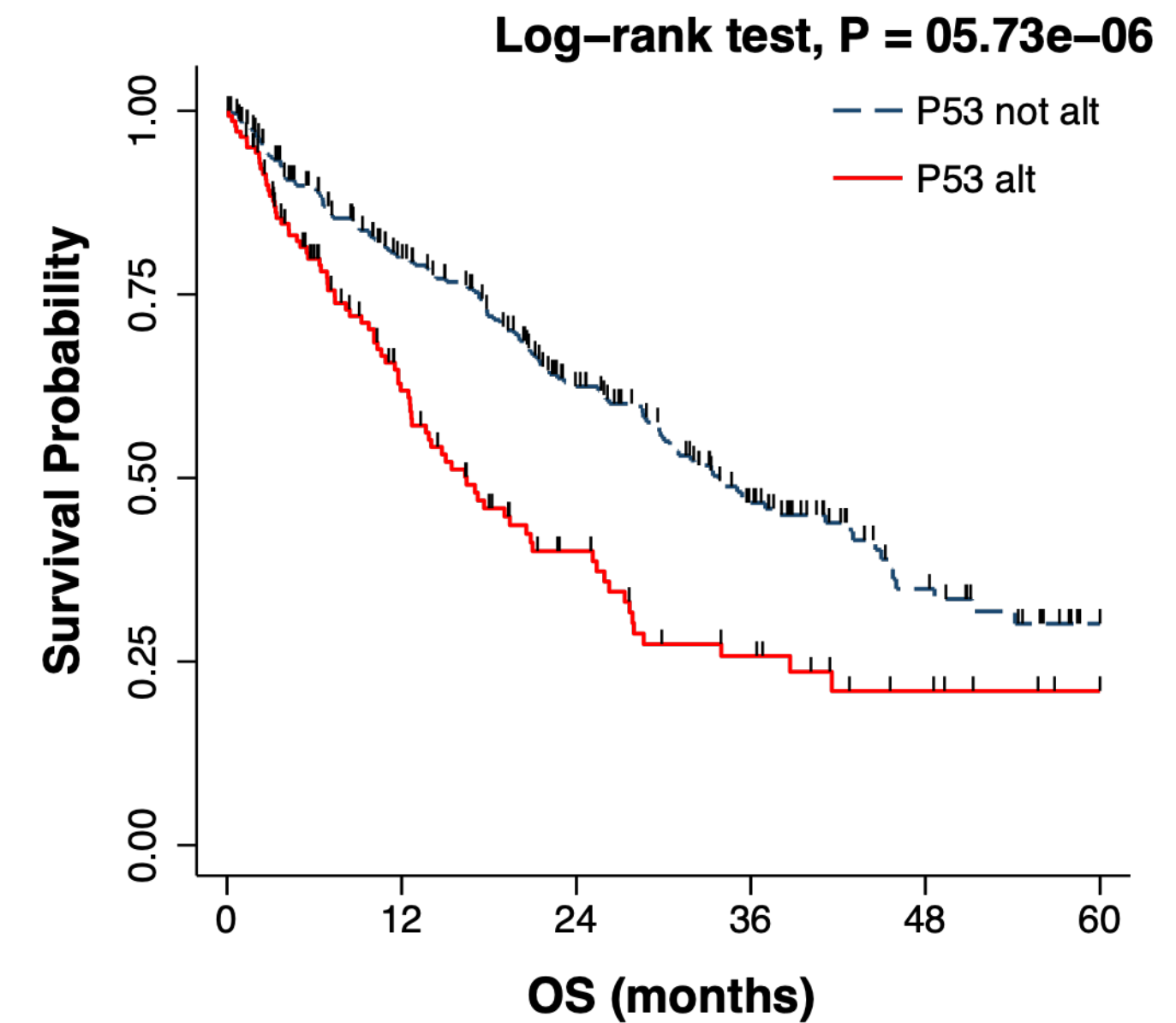
**B**



**Number at risk**

RTK not alt	326	200	122	71	31	8
RTK alt	94	46	21	6	1	0

**C**



**Number at risk**

P53 not alt	278	181	112	61	26	7
P53 alt	142	65	31	16	6	1



# ET resistance: One does not simply walk into Mordor

■ But *ESR1* codon variants have a differential biologic impact

	Odds Ratio	95% CI		P value
<b>ESR1 Y537</b>				
bone	10.91	1.38	86.40	0.024
liver	2.04	0.69	6.00	0.196
<b>ESR1 D538</b>				
bone	3.72	0.78	17.62	0.098
liver	3.77	1.11	12.76	0.033
lung	2.68	0.89	8.07	0.079
<b>ESR1 L536</b>				
liver	3.99	0.99	16.06	0.051
soft tissue	5.55	1.56	19.83	0.008
bone	6.35	0.76	52.94	0.087



**Not just mutations: transcriptomics biomarkers**

# Intrinsic Subtypes and Ribociclib

## ■ Predictive Value of Intrinsic Subtype on PFS by Treatment Arm

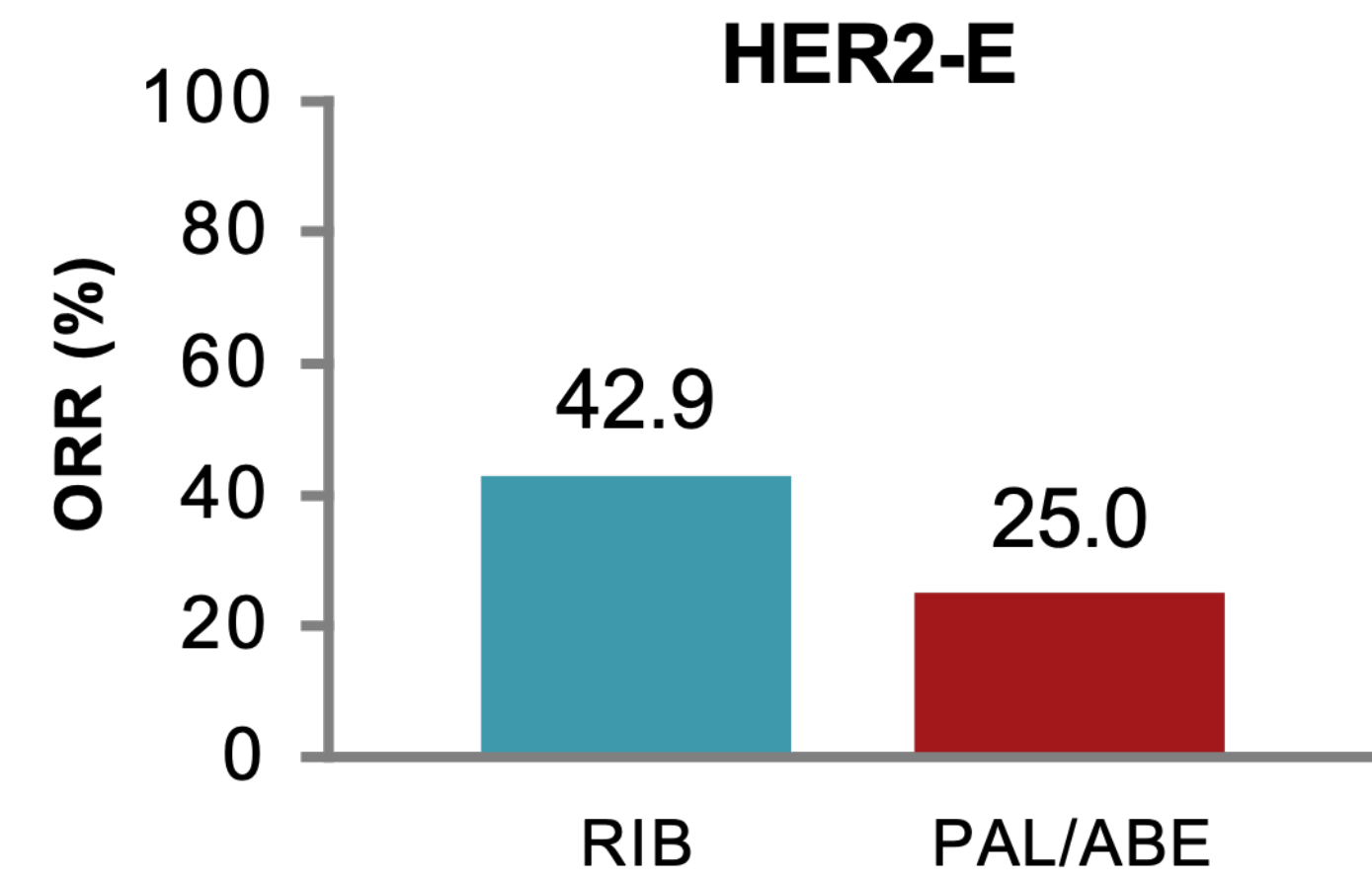
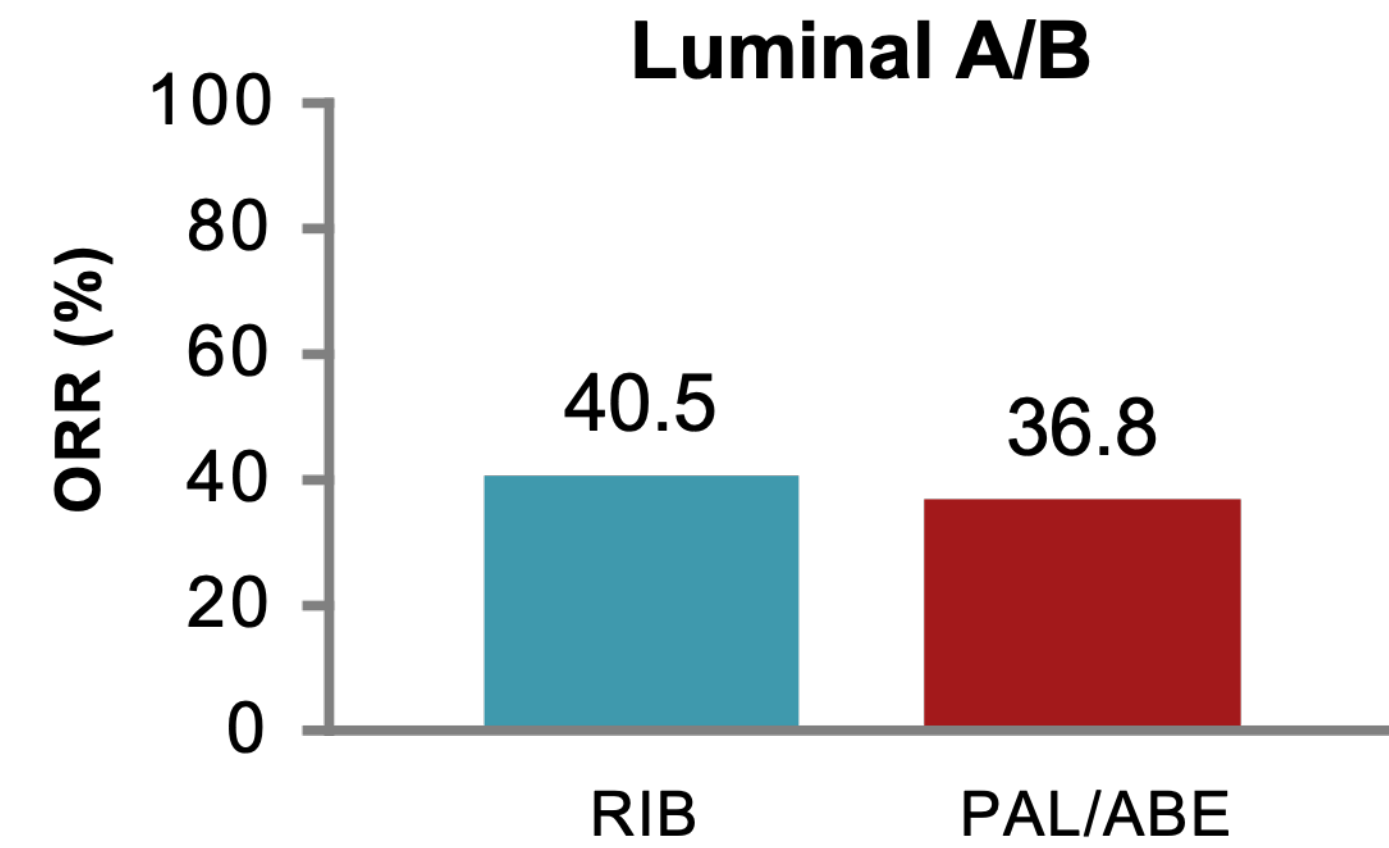
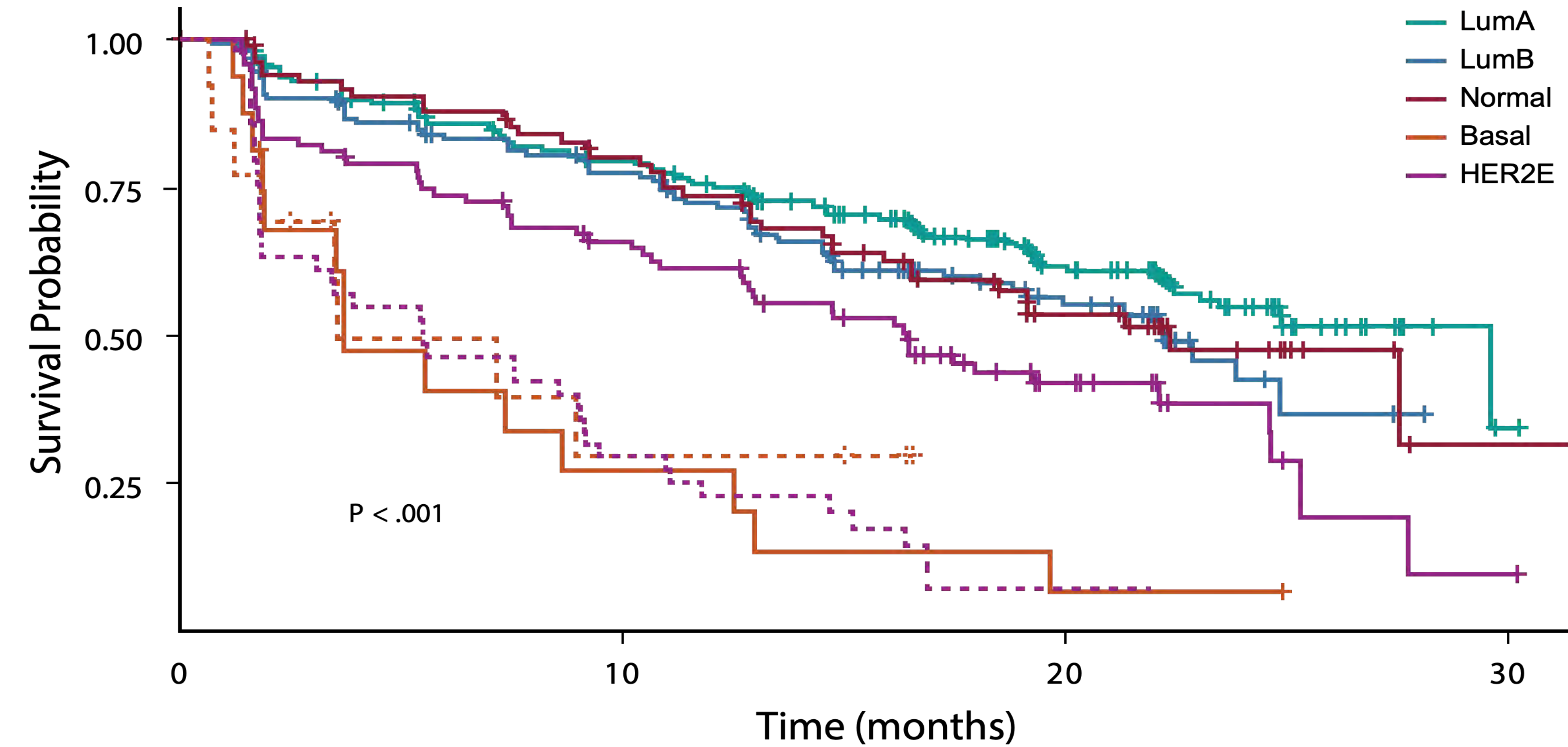
Subtype	Treatment Arm	Distribution, n (%)	Events, n (%)	Median PFS Estimate	Median PFS 95% CI	HR Estimate	HR 95% CI	P
LumA	PBO	222 (45)	110 (50)	19.48	15.61 to 24.80	0.63	0.49 to 0.83	.0007
	RIB	320 (48)	114 (36)	29.60	23.03 to NA			
LumB	PBO	124 (25)	89 (72)	12.85	10.84 to 14.82	0.52	0.38 to 0.72	, .0001
	RIB	154 (23)	66 (43)	22.21	18.79 to NA			
HER2E	PBO	52 (11)	41 (79)	5.52	3.12 to 9.17	0.39	0.25 to 0.60	, .0001
	RIB	95 (14)	56 (59)	16.39	12.71 to 24.6			
Basal-like	PBO	14 (3)	8 (57)	3.58	1.87 to NA	1.15	0.46 to 2.83	.77
	RIB	16 (2)	14 (88)	3.71	1.91 to 13			
Normal-like	PBO	76 (16)	53 (70)	11.10	7.39 to 16.56	0.47	0.30 to 0.72	, .001
	RIB	87 (13)	37 (43)	22.34	16.56 to NA			

Abbreviations: HER2E, human epidermal growth factor receptor 2–enriched; HR, hazard ratio; LumA, luminal A; LumB, luminal B; NA, not applicable; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.



# Intrinsic Subtypes and Ribociclib

■ PFS and ORR based on intrinsic subtype

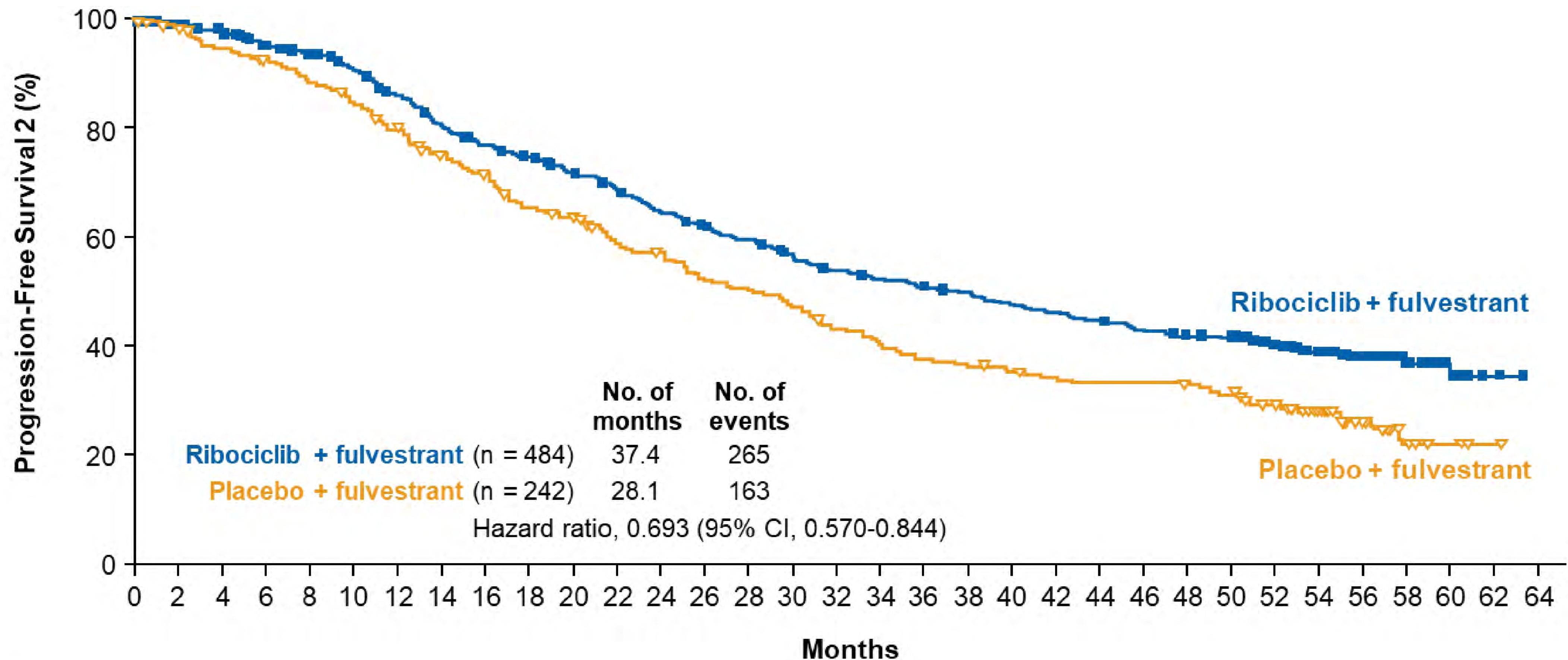


**What comes next?**



# What comes next?

■ Impact of Ribociclib on PFS2



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64
<b>Ribociclib + fulvestrant</b>	484	470	453	434	421	403	379	352	336	324	308	292	273	259	249	230	221	214	206	202	193	187	180	172	166	164	147	113	66	36	14	3	0
<b>Placebo + fulvestrant</b>	242	232	224	216	207	197	183	169	160	146	139	126	121	111	107	100	91	84	79	76	73	69	68	68	66	62	53	37	19	9	3	1	0

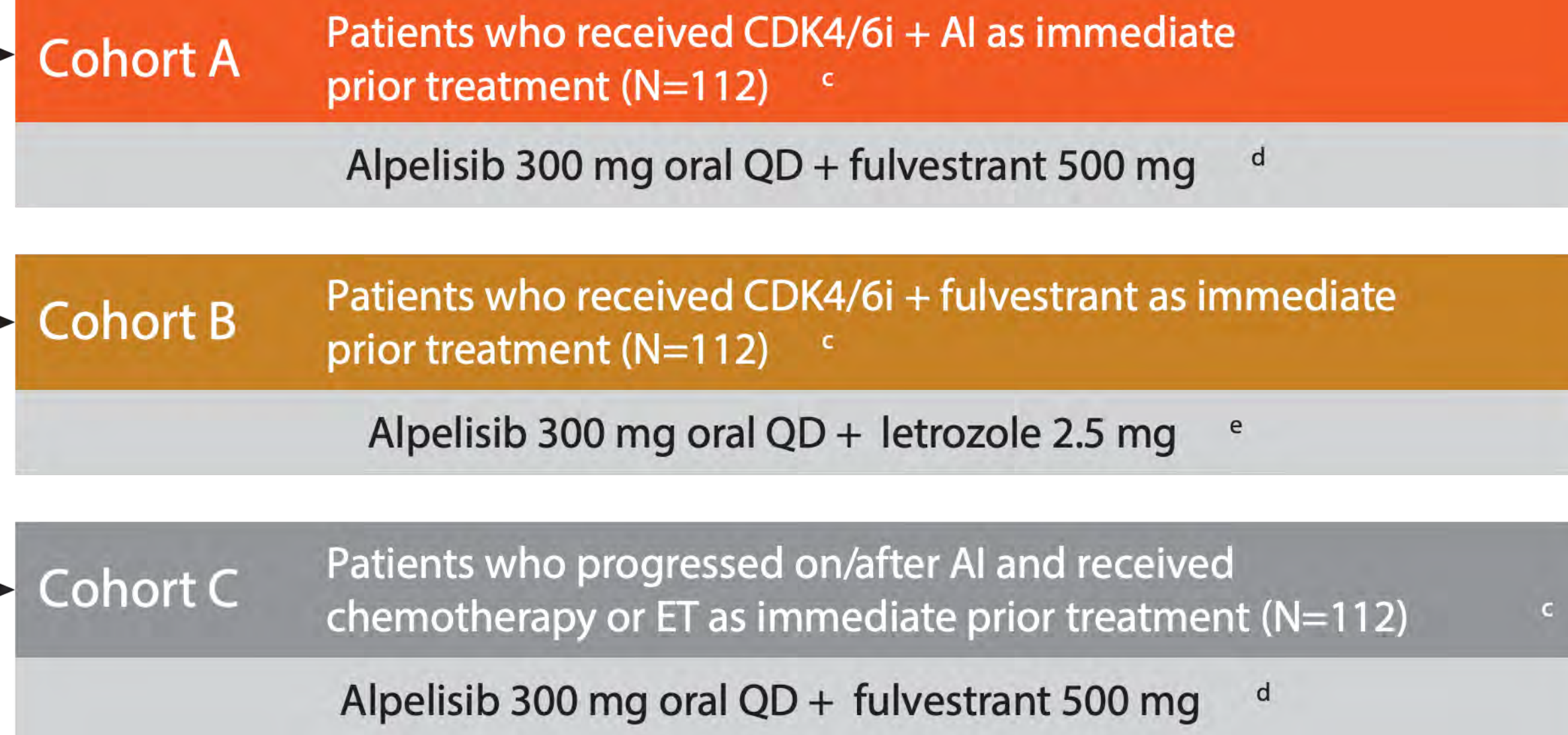


# Could the lack of benefit from CDK4/6i influence other ETs?

- An exploratory analysis of the BYLieve study

Men or pre-/postmenopausal women with HR+, HER2- ABC with a PIK3CA mutation

- PIK3CA mutation in tumor tissue or blood<sup>b</sup>



## Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort

Secondary endpoints include (assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

Cohort A: ALP + FUL	Event/N (%)	Stratified log-rank test		Cox model
		Median time (95% CI), months	P value	HR* (95% CI)
All patients	72/121 (59.5)	7.3 (5.55-8.34)	0.927	1.03 (0.64-1.64)
High (≥380 days)	34/60 (56.7)	8.0 (5.39-8.34)		
Low (<380 days)	37/60 (61.7)	7.0 (5.36-9.99)		

Cohort B: ALP + LET	Event/N (%)	Stratified log-rank test		Cox model
		Median time (95% CI), months	P value	HR* (95% CI)
All patients	87/115 (75.7)	5.7 (4.50-7.23)	0.400	1.20 (0.78-1.84)
High (≥305 days)	44/57 (77.2)	5.4 (3.58-7.26)		
Low (<305 days)	43/56 (76.8)	5.9 (3.71-8.31)		



# ERBB2, an intriguing plot twist?

■ Neratinib +/- Fulvestrant: part II of the MutHER

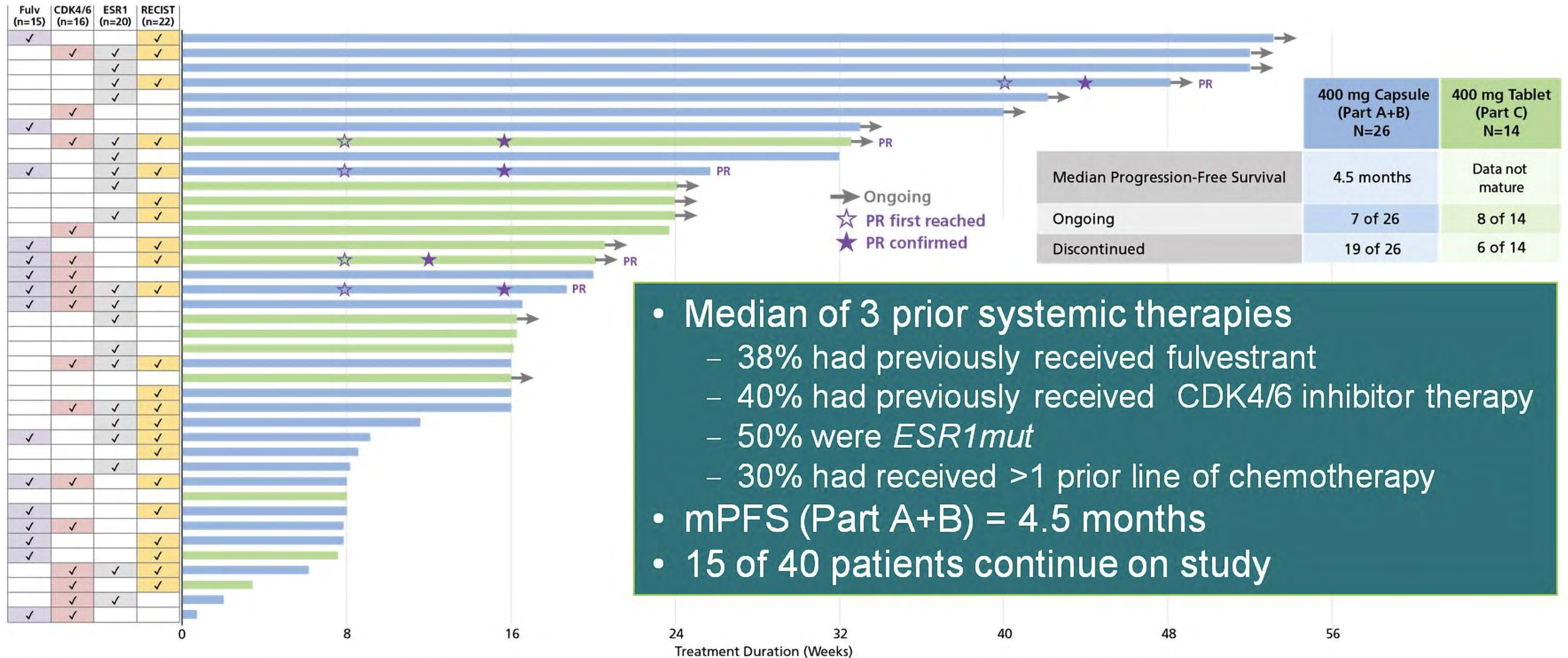
Cohort	FUL treated	FUL naïve	ER-
<b>Best Response</b>	n = 21	n = 10	n = 4
CR	1	0	0
PR	4	3	1
SD (≥ 24 wks)	3	0	0
SD (< 24 wks)	10	3	0
PD	3	4	3
<b>CBR</b>	8 of 20*, 40% (19~64%)	3 of 10, 30% (7~65%)	1 of 4, 25% (0.6~81%)
<b>mPFS</b>	24 (16~31) wks, (n = 24)	20 (8~NA) wks, (n = 11)	8.5 (8~NA) wks, (n = 5)

**Oral SERDs: the new gang in town**



# Oral SERDs: the new gang in town

## ■ Elacestrant phase I trial



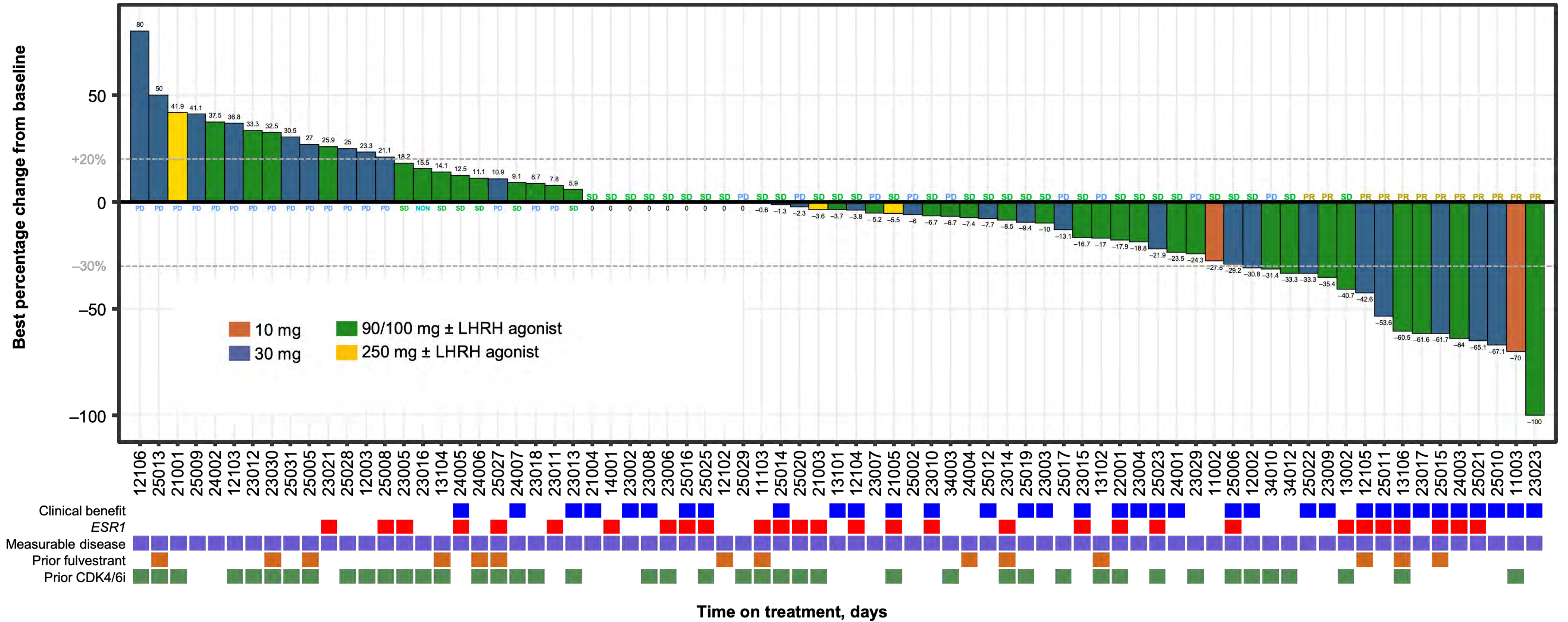
- Median of 3 prior systemic therapies
  - 38% had previously received fulvestrant
  - 40% had previously received CDK4/6 inhibitor therapy
  - 50% were *ESR1mut*
  - 30% had received >1 prior line of chemotherapy
- mPFS (Part A+B) = 4.5 months
- 15 of 40 patients continue on study

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



# Oral SERDs: the new gang in town

■ Giredestrant phase I trial





# Oral SERDs: the new gang in town

## Amcenestrant plus Palbociclib: AMEERA-1

### Antitumor activity in the response-evaluable population (N = 35)

	Response-evaluable population (Parts C + D; N = 35)
<b>Best Overall Response, n (%)</b>	
Complete Response (CR)	0 <sup>a</sup>
Partial Response (PR)	12 (34.3%)
Stable Disease (SD)	22 (62.9%)
Progressive Disease (PD)	1 (2.9%)
<b>Objective Response Rate<sup>b</sup>, n (%)</b> [90% CI] <sup>c</sup>	<b>12 (34.3%)</b> [21.1%, 49.6%]
<b>Clinical Benefit Rate<sup>d</sup>, n (%)</b> [90% CI] <sup>c</sup>	<b>26 (74.3%)</b> [59.4%, 85.9%]

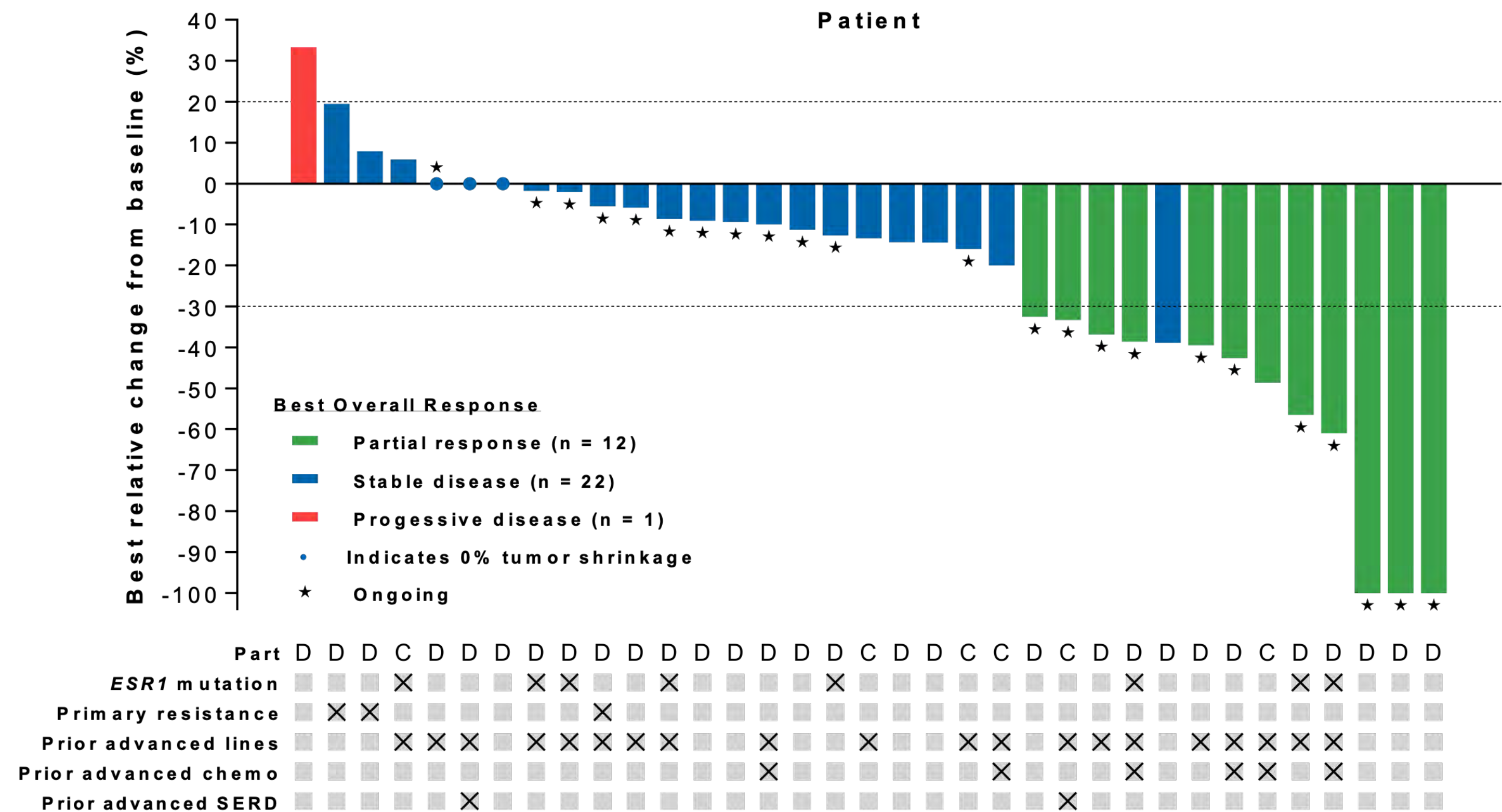
<sup>a</sup>CR was initially reported in 1 patient at a previous analysis but was revised to PR in the current analysis based on reassessment by the investigator;

<sup>b</sup>Confirmed CR or PR;

<sup>c</sup>Estimated by Clopper-Pearson method;

<sup>d</sup>CR, PR, or SD ≥24 weeks.

### Best relative change from baseline in target lesions and best overall response in patients in the response-evaluable population (N = 35)

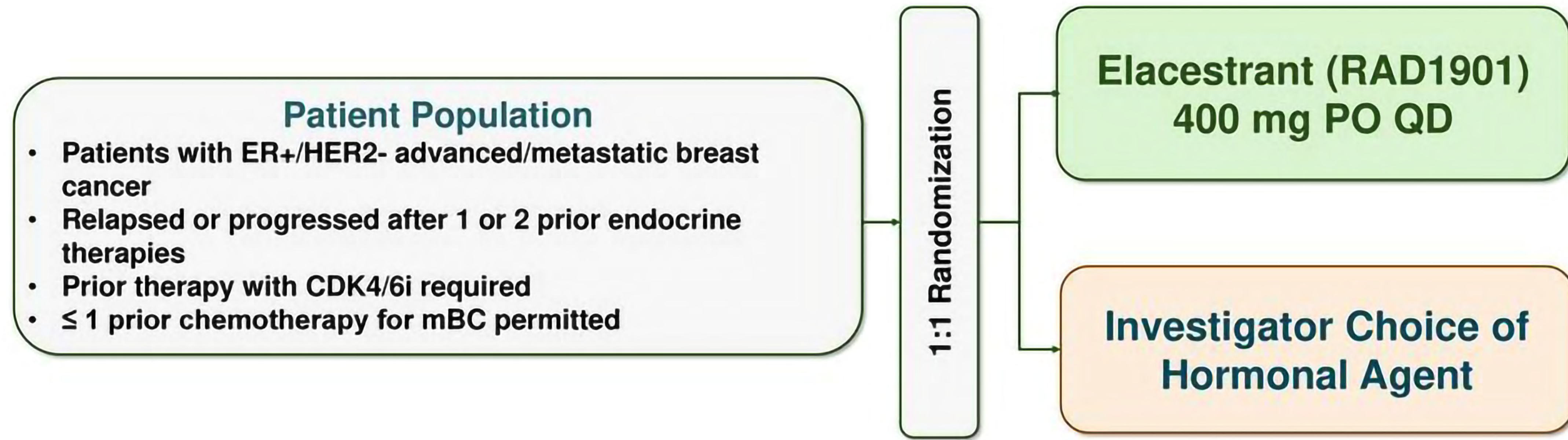


ORR was 34.3%, and the CBR was 74.3%; tumor shrinkage in 80% of patients



# Oral SERDs: 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



# Wrapping up

- Dawn of a new beginning in middle-earth

1

## **The CDK4/6i revolution has stably reshaped our clinical practice**

Data on overall survival are gradually adding up confirming the crucial role of CDK4/6i  
The benefit is equally distributed across all clinically relevant subgroups and established biomarkers

2

## **A brave new world is emerging and new strategies need to be designed in advance**

New drugs are being developed and will disrupt the current workflow, both in early and in late stage  
Sequencing strategies will become more and more crucial (e.g. beyond PD, combos)

3

## **ET resistance is not only a matter of changing targets, but rather a biology shift**

ESR1 mutations perturbate the transcriptome resulting in neomorphic properties  
ESR1 and PIK3CA are promising markers, but many others are coming (e.g. ERBB2, FGFR1, RTK)



# Thank you



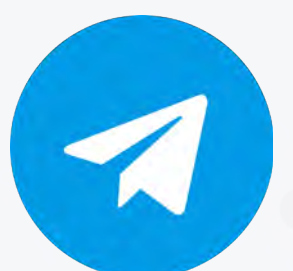
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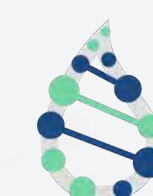
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Research Team

