

# A Randomized, Multicenter, Open-label, Phase II Trial to Evaluate Palbociclib in Combination with Fulvestrant or Letrozole in Endocrine-sensitive Patients with Estrogen Receptor (ER)[+]/HER2[-] Metastatic Breast Cancer: PARSIFAL trial

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# Background

- The CDK4/6 inhibitor palbociclib in combination with letrozole has become a standard treatment for patients with endocrine-sensitive<sup>1</sup> metastatic breast cancer (MBC) (PALOMA-1 and PALOMA-2 trials).<sup>2,3</sup>
- For endocrine-resistant<sup>1</sup> patients, the combination of a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) with the anti-estrogen fulvestrant has provided consistent overall survival gains (PALOMA-3, MONALEESA-3, and MONARCH-2 trials).<sup>4-6</sup>
- In patients with endocrine-naïve MBC, a progression-free survival (PFS) superiority has been shown for fulvestrant over anastrozole (FALCON trial).<sup>7</sup>
- PARSIFAL trial wanted to explore the optimal endocrine agent to combine with palbociclib in the first-line endocrine-sensitive scenario.

CDK4/6: Cyclin-dependent kinase 4 and 6.

1. Cardoso F et al. *Ann Oncol* 2017; 28:16-33

2. Finn RS et al. *Lancet Oncol* 2015 16:25-35

3. Finn RS et al. *N Engl J Med* 2016; 375:1925-1936

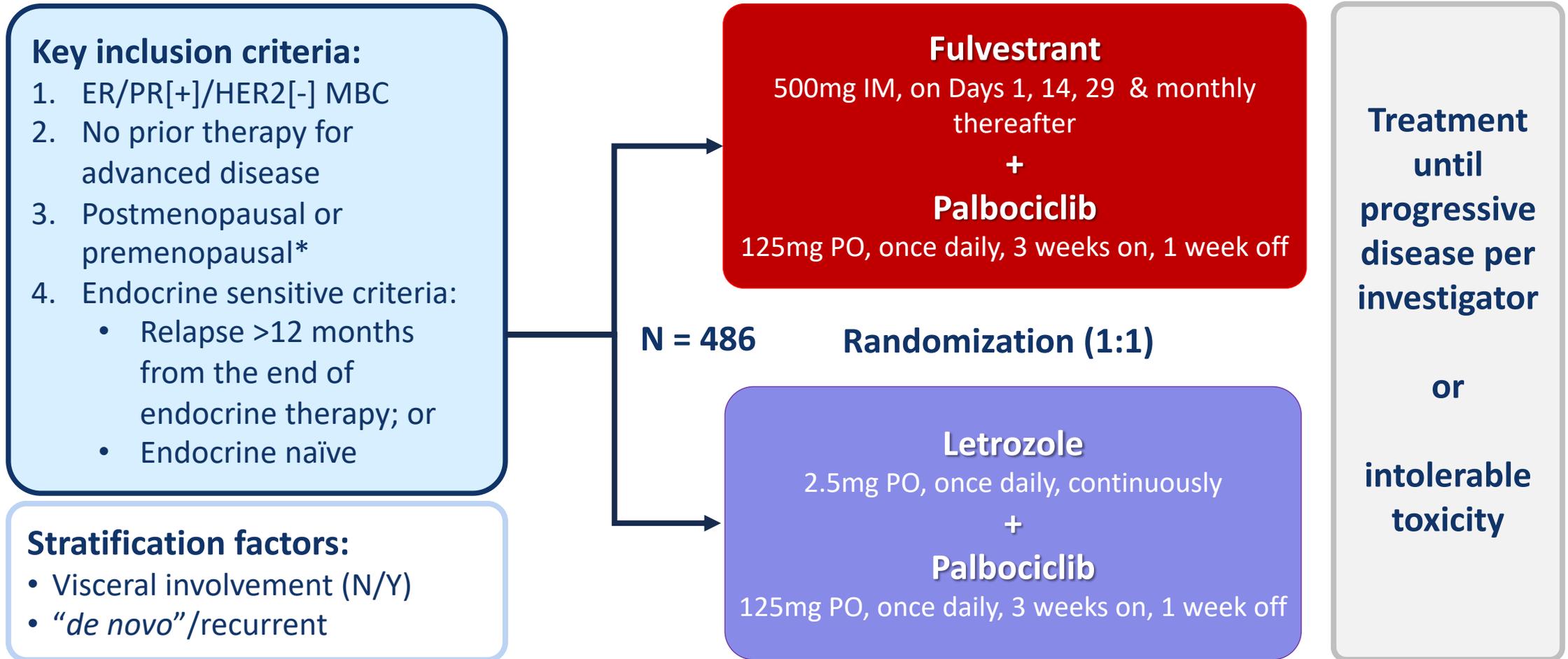
4. Turner NC et al. *N Engl J Med* 2018; 379:1926-1936

5. Slamon, DJ et al. *N Engl J Med* 2020; 382:514-524

6. Sledge GW et al. *JAMA Oncol* 2020; 6:116-124

7. Robertson JFR et al. *Lancet* 2016;388:2997-3005

# PARSIFAL: Study Design



\*If pre-menopausal, an ovarian suppression method was required.

ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; IM: Intramuscular; MBC: Metastatic breast cancer; PO: Oral administration; PR: Progesterone receptor.

# Study Endpoints

## PRIMARY ENDPOINT:

- Investigator-assessed PFS

## SECONDARY ENDPOINTS:

- Prespecified subgroup analyses of PFS
- Overall Survival
- Tumor response and Clinical Benefit Rate by RECIST v1.1
- Toxicity (CTCAE v4.0)

## EXPLORATORY ENDPOINTS:

- Biomarker sub-studies

CTCAE v4.0: Common Terminology Criteria for Adverse Events version 4.0; PFS, Progression-free survival; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1

# Statistical Assumptions

- We assumed a 22-month median PFS for letrozole plus palbociclib arm.
- The two-sided log-rank test had an 80% power to detect a 0.70 hazard ratio (HR) increase in median PFS for fulvestrant plus palbociclib arm (31.3 months). A total of 486 patients to be included with final PFS analyses planned after 254 events.
- If superiority objective was not achieved, we would switch to a non-inferiority analysis. The non-inferiority margin (NIM) defined in terms of HR was 1.21.
- PFS and OS were compared between arms adjusted by stratification factors, based on a Cox model (likelihood ratio test).
- The data cut-off date for the final PFS analysis was on January 31, 2020.

OS, Overall survival; PFS, Progression-free survival.

# Key Selection Criteria

## Inclusion criteria:

- Histologically confirmed ER-/PR-positive, HER2-negative locally advanced or MBC patients.
- Postmenopausal or premenopausal with an ovarian suppression method.
- No prior systemic therapy in the metastatic setting.
- Endocrine-sensitive criteria by ABC3 consensus.
- ECOG PS score 0-2.

## Exclusion criteria:

- Patients with rapidly progressive visceral disease or visceral crisis.
- Locally ABC candidate for a radical treatment.
- Prior (neo)adjuvant endocrine treatment with a DFI  $\leq$  12 months from completion of treatment.

ABC: Advanced Breast Cancer 3; DFI: Disease-free interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; MBC: Metastatic breast cancer; OS: Ovarian suppression method; PR: Progesterone receptor.

# Baseline Characteristics (ITT Population)

Characteristics, n (%)		All patients N=255	Fulvestrant + Palbociclib N=130	Letrozole + Palbociclib N=125
Age, median (range)		64.0 (25.0–90.0)	64.0 (25.0–88.0)	63.0 (39.0–90.0)
ECOG PS score	0	142 (55.7)	78 (60.0)	64 (51.2)
	1	100 (39.2)	46 (35.4)	54 (43.2)
	2	13 (5.1)	6 (4.6)	7 (5.6)
Premenopausal*	No	242 (94.9)	124 (95.4)	118 (94.4)
	Yes	13 (5.1)	6 (4.6)	7 (5.6)
<i>De novo</i>	No	150 (58.8)	71 (54.6)	79 (63.2)
	Yes	105 (41.2)	59 (45.4)	46 (36.8)
Visceral	No	123 (48.2)	61 (46.9)	62 (49.6)
	Yes	132 (51.8)	69 (53.1)	63 (50.4)
Organs	<3	152 (59.6)	77 (59.2)	75 (60.0)
	≥3	103 (40.4)	53 (40.8)	50 (40.0)
Measurable	No	73 (28.6)	34 (26.2)	39 (31.2)
	Yes	182 (71.4)	96 (73.8)	86 (68.8)

\* For pre-menopausal, patients an ovarian suppression method was compulsory

ECOG PS: Eastern Cooperative Oncology Group performance status; ITT: Intention to treat.

# Baseline Characteristics (ITT Population)

Characteristics, n (%)	All patients N=255	Fulvestrant + Palbociclib N=130	Letrozole + Palbociclib N=125
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## Prior therapies in early breast cancer

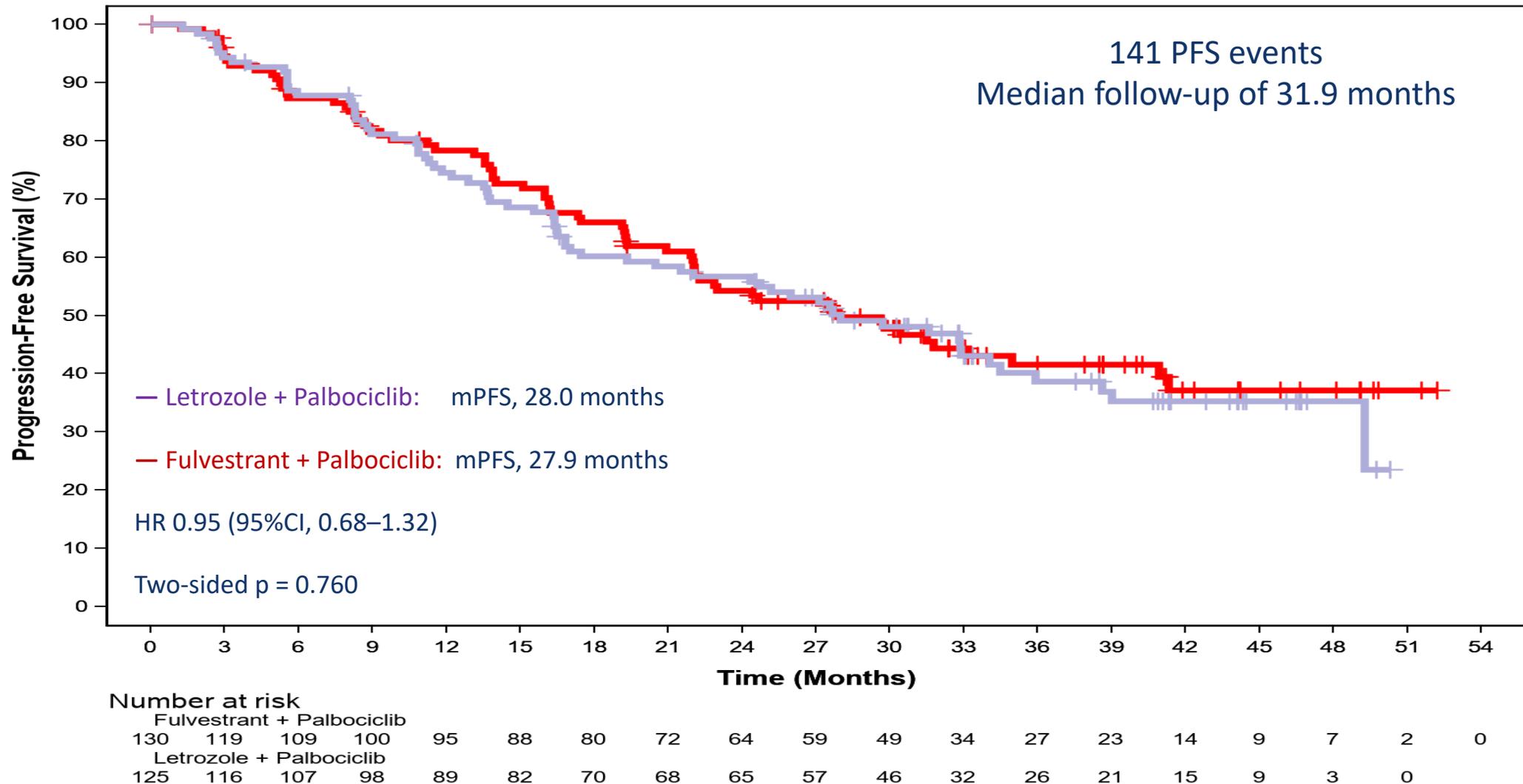
<b>Chemotherapy</b>			
Neoadjuvant	29 (11.4)	14 (10.8)	15 (12.0)
Adjuvant	86 (33.7)	43 (33.1)	43 (34.4)

## Endocrine therapy

Tamoxifen only	48 (18.8)	16 (12.3)	32 (25.6)
Aromatase inhibitors only	29 (11.4)	17 (13.1)	12 (9.6)
Both	41 (16.1)	23 (17.7)	18 (14.4)

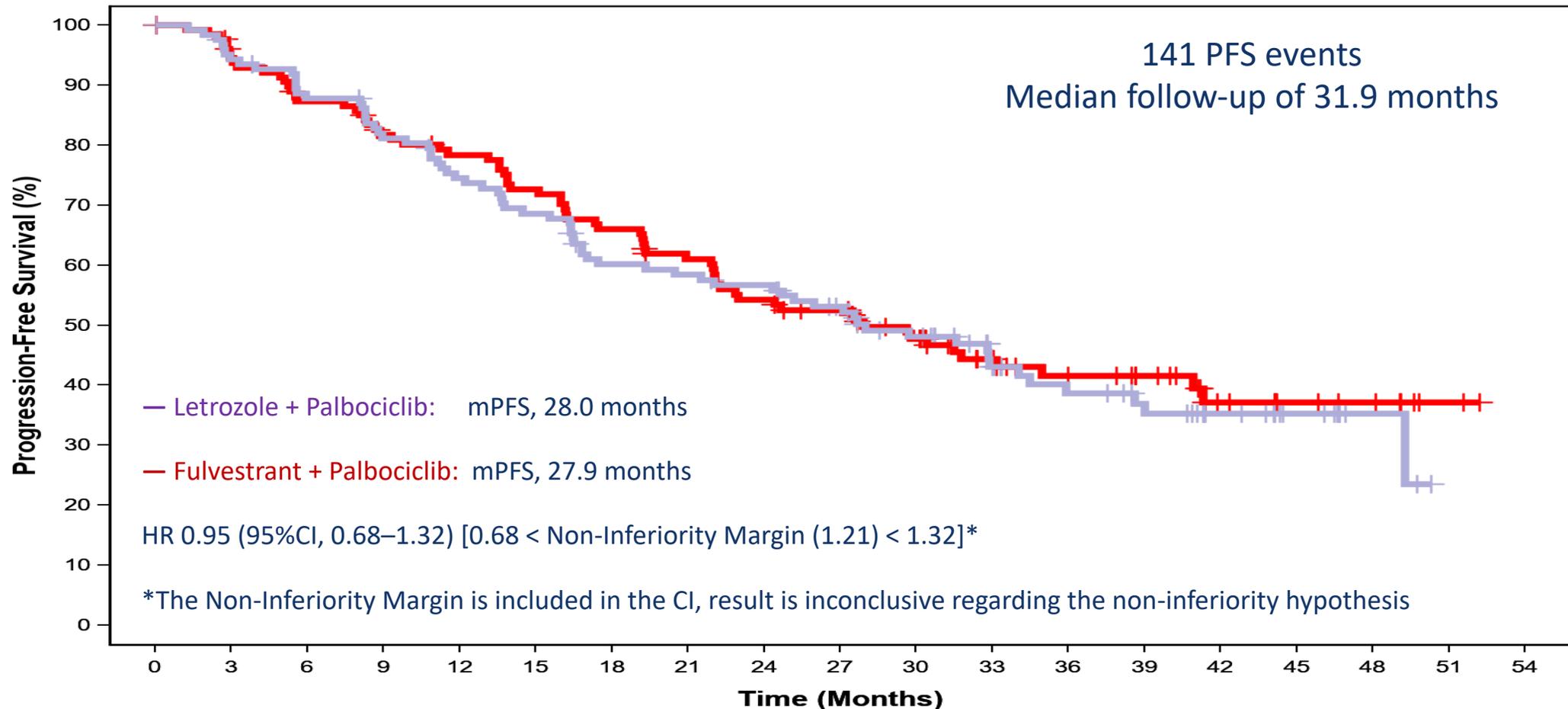
ITT: Intention to treat.

# Primary Objective PFS (ITT Population)



CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mPFS: Median progression-free survival; PFS: Progression-free survival.

# Primary Objective PFS (ITT Population)

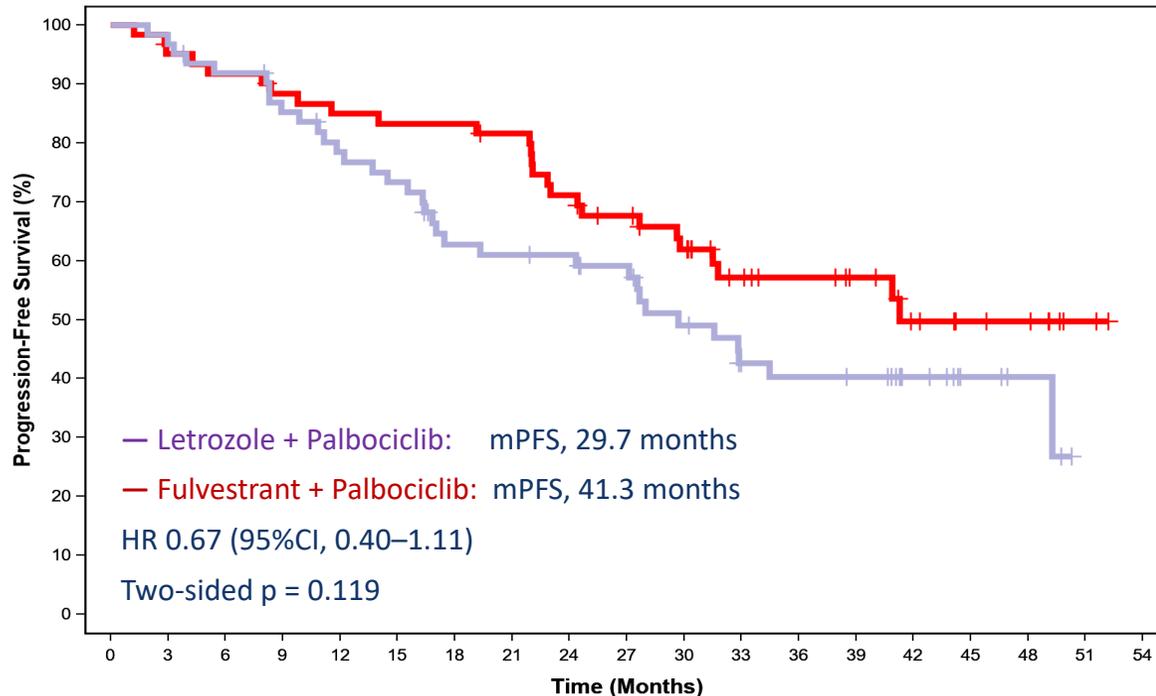


Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Fulvestrant + Palbociclib		130	119	109	100	95	88	80	72	64	59	49	34	27	23	14	9	7	2	0
Letrozole + Palbociclib		125	116	107	98	89	82	70	68	65	57	46	32	26	21	15	9	3	0	0

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mPFS: Median progression-free survival; PFS: Progression-free survival.

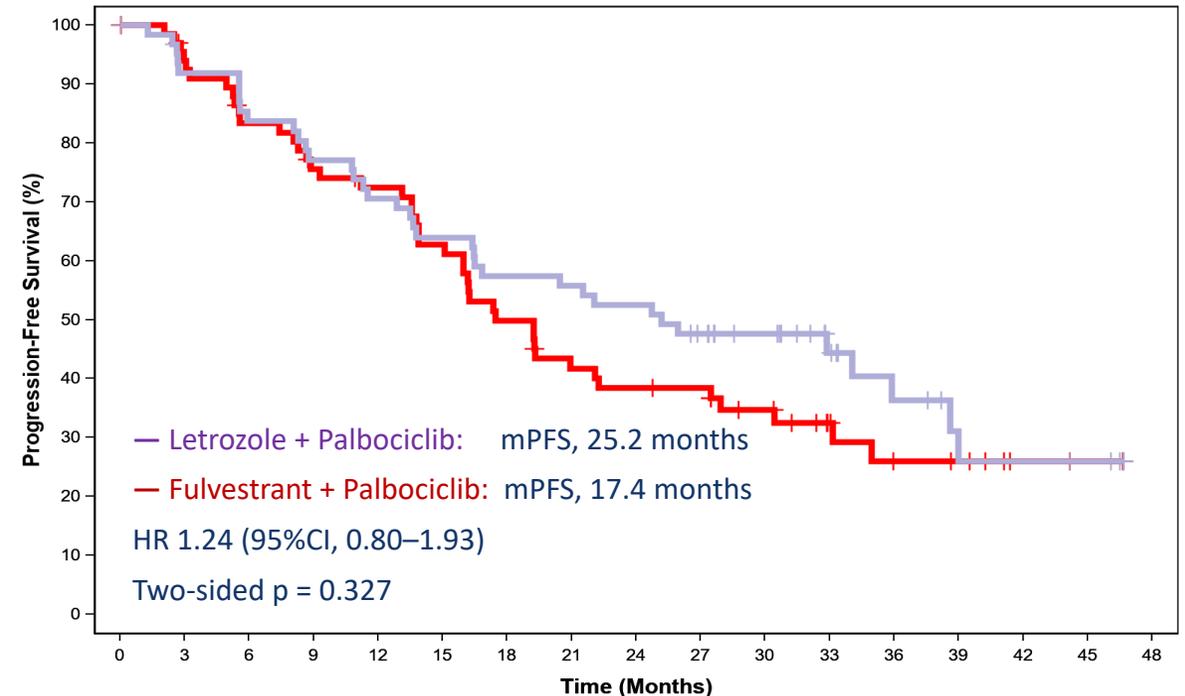
# PFS by Visceral Disease (ITT Population)

## Non-visceral disease



Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Fulvestrant + Palbociclib		61	57	55	52	50	49	49	47	41	37	32	23	20	17	12	8	7	2	0
Letrozole + Palbociclib		62	60	56	51	46	43	35	34	33	30	24	18	17	16	10	5	3	0	

## Visceral disease



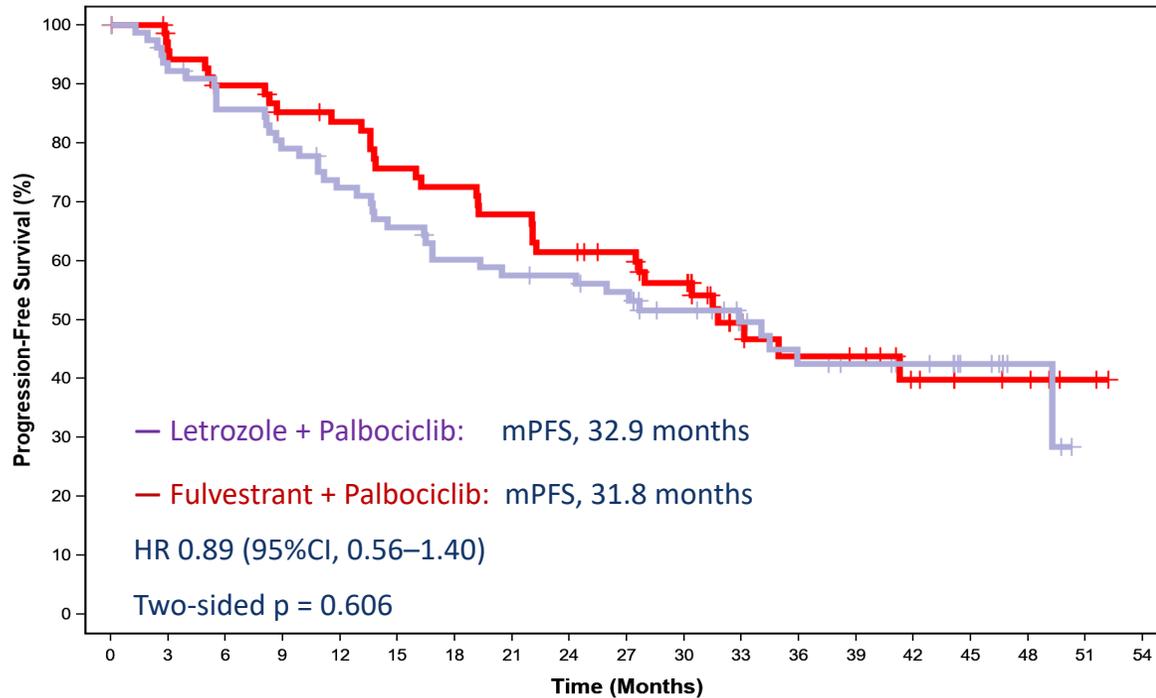
Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Fulvestrant + Palbociclib		69	62	54	48	45	39	31	25	23	22	17	11	7	6	2	1	0
Letrozole + Palbociclib		63	56	51	47	43	39	35	34	32	27	22	14	9	5	5	4	0

Interaction p-value = 0.062

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mPFS, Median progression-free survival; PFS, Progression-free survival.

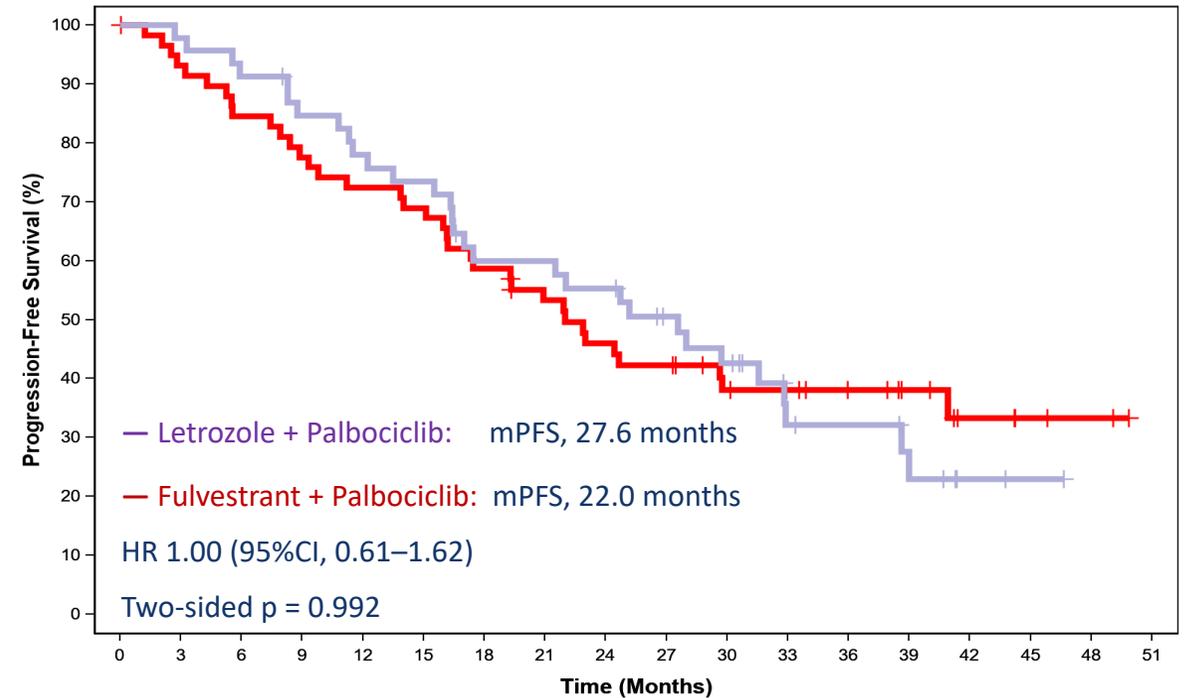
# PFS by Disease Presentation (ITT Population)

## Recurrent



Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Fulvestrant + Palbociclib		71	65	60	55	53	48	46	43	39	36	31	19	15	14	9	6	5	2	0
Letrozole + Palbociclib		79	71	65	60	54	49	44	42	41	38	30	23	18	16	13	8	3	0	

## De novo

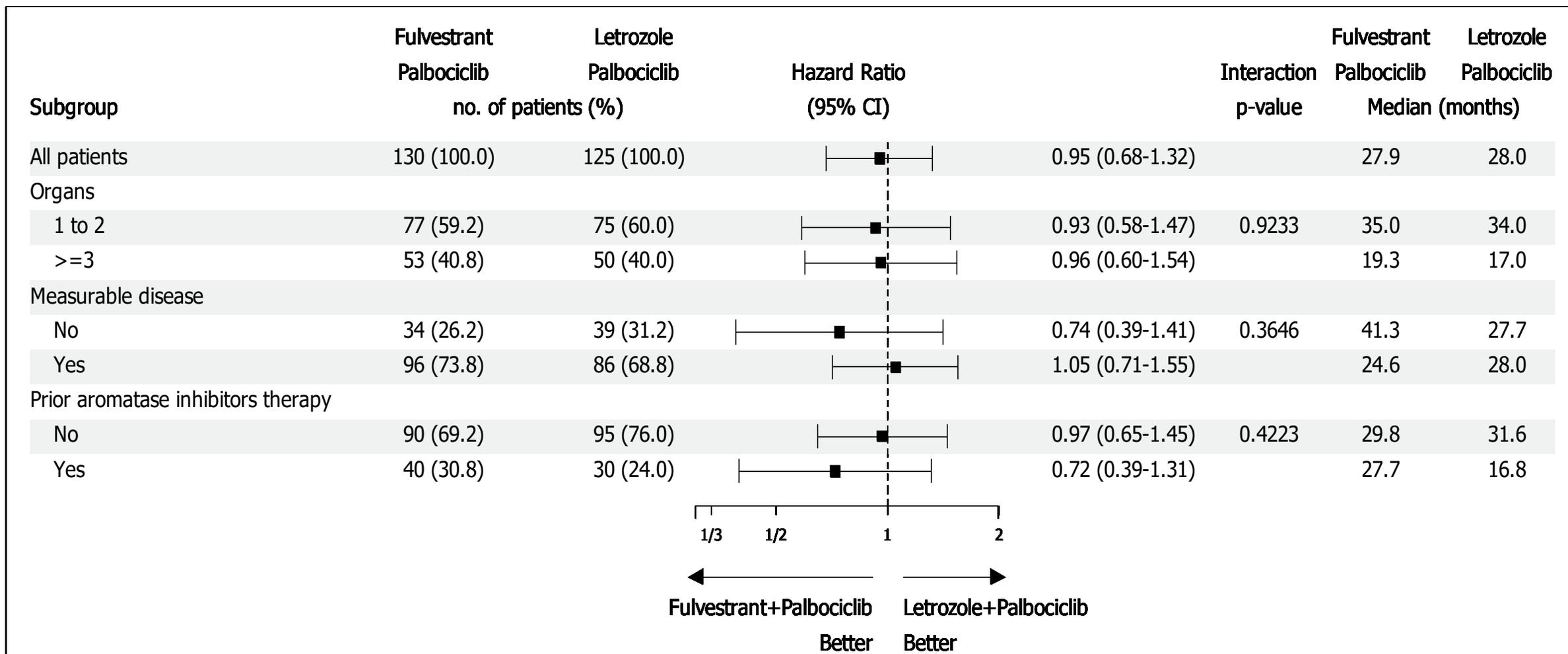


Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Fulvestrant + Palbociclib		59	54	49	45	42	40	34	29	25	23	18	15	12	9	5	3	2	0
Letrozole + Palbociclib		46	45	42	38	35	33	26	26	24	19	16	9	8	5	2	1	0	

**Interaction p-value = 0.737**

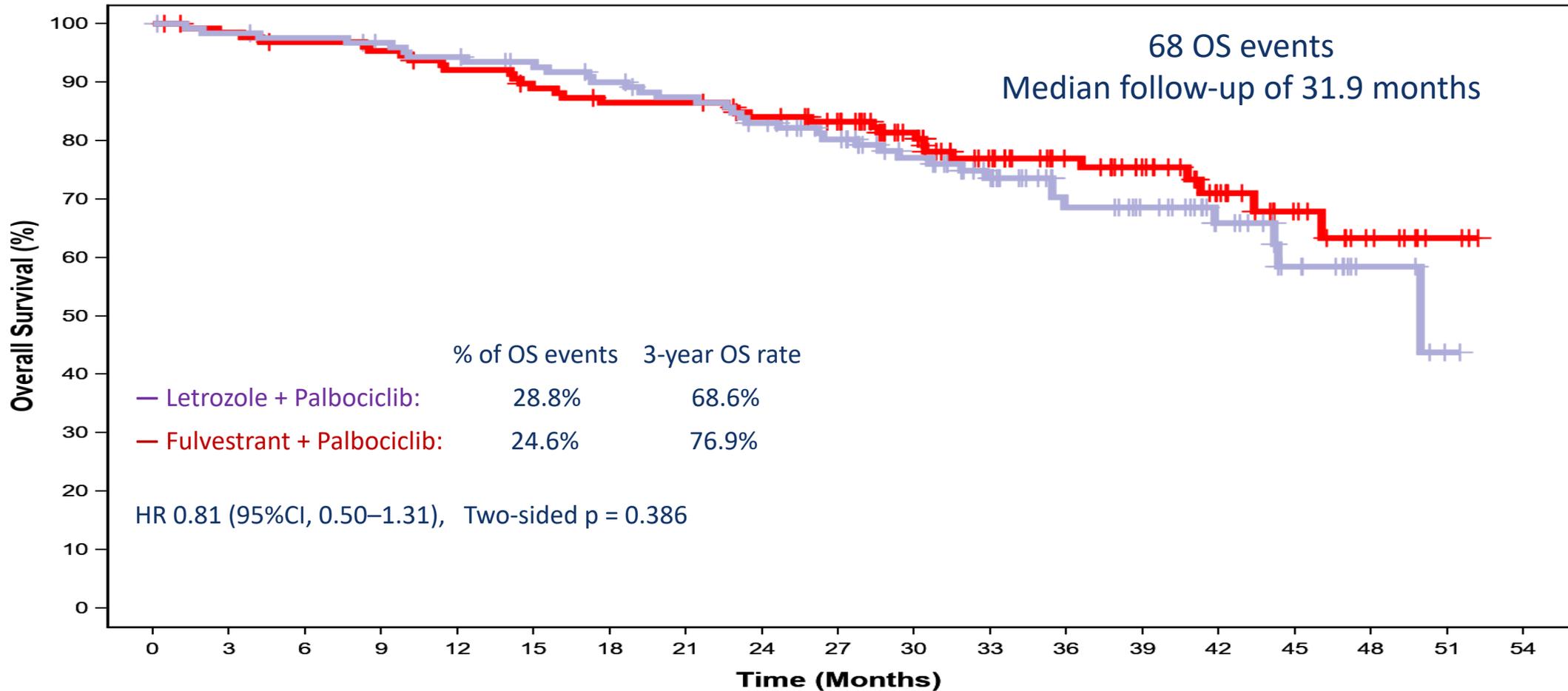
CI, Confidence interval; HR: Hazard ratio; ITT, Intention to treat; mPFS, Median progression-free survival; PFS, Progression-free survival.

# Prespecified Subgroup Analyses of PFS (ITT Population)



CI: Confidence interval; ITT: Intention to treat.

# Overall Survival (ITT Population)



### Number at risk

Fulvestrant + Palbociclib	
130	126
123	121
116	111
107	107
101	95
79	62
50	41
28	17
9	3
0	0

Letrozole + Palbociclib	
125	122
120	117
114	110
105	100
94	85
71	59
41	35
23	13
5	1
0	0

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; OS: Overall survival.

# Tumor Response and Clinical Benefit (ITT Population)

Tumor best response, n(%) [RECIST v1.1 ]	Fulvestrant + Palbociclib N=130	Letrozole + Palbociclib N=125	P value
Complete response	8 (6.2)	5 (4.0)	
Partial response	55 (42.3)	57 (45.6)	
Stable disease*	21 (16.2)	19 (15.2)	
No CR/No PD	27 (20.8)	31 (24.8)	
Progressive disease	13 (10.0)	9 (7.2)	
Not evaluable	6 (4.6)	4 (3.2)	
<b>Objective Response Rate</b> (95% CI)	<b>63 (48.5)</b> 39.6–57.4	<b>62 (49.6)</b> 40.5–58.7	0.901
<b>Clinical Benefit Rate</b> (95%CI)	<b>84 (64.6)</b> 55.8–72.8	<b>81 (64.8)</b> 55.8–73.1	1.000
<b>Measurable disease</b>	N=96	N=86	
<b>Objective Response Rate</b> (95%CI)	60 (62.5) 52.0–72.2	61 (70.9) 60.1–80.2	

\*The minimum criteria for SD duration was 24 weeks. The study includes patients with measurable (N=182) and evaluable disease (N=73).

CI: Confidence interval; ITT: Intention to treat; No CR/No PD: No complete response / no progressive disease in patient without target lesions.

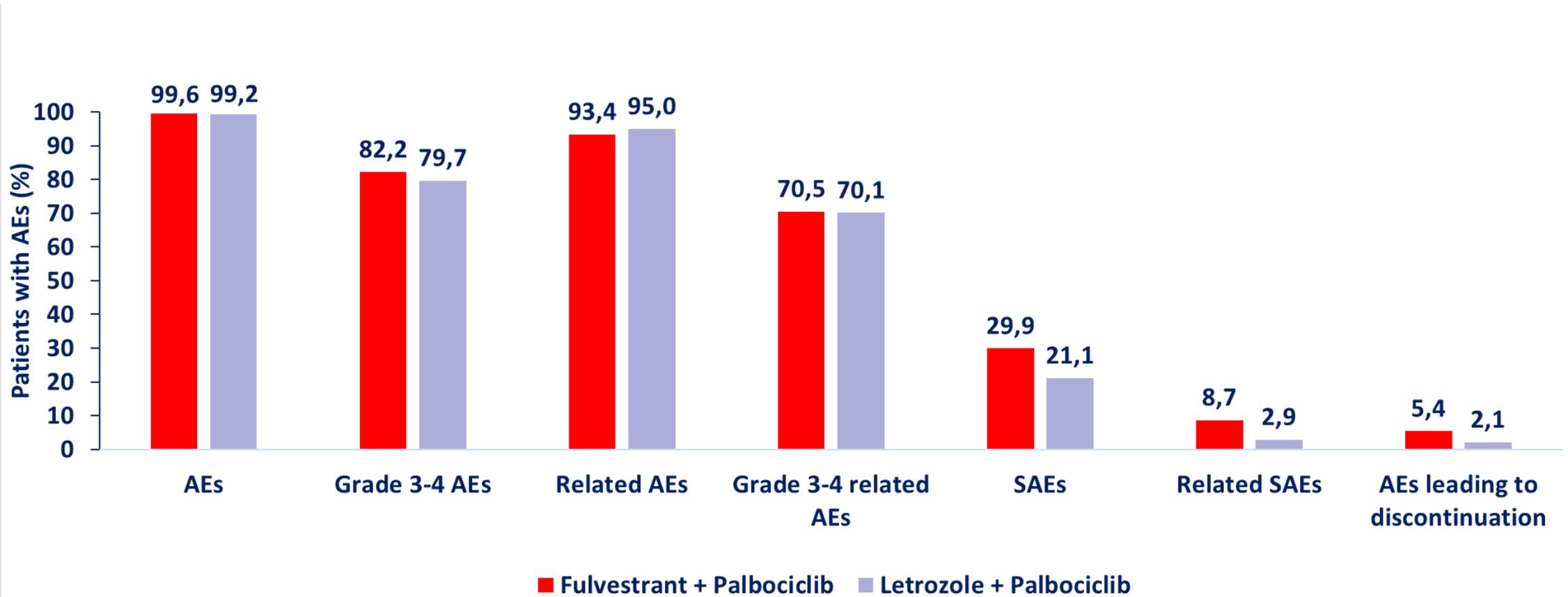
# Relative Dose Intensity and Drug Discontinuation

Characteristics, n (%)	All patients N=255	Fulvestrant + Palbociclib N=130	Letrozole + Palbociclib N=125
<b>Median relative dose intensity</b>		F: 90.9 / P: 99.3	L: 90.2 / P: 99.0
<b>Treatment discontinuation</b>	169 (66.3)	88 (67.7)	81 (64.8)
Disease progression	134 (52.5)	65 (50.0)	69 (55.2)
Patient withdrew consent	9 (3.5)	4 (3.1)	5 (4.0)
Adverse events	7 (2.7)	6 (4.6)	1 (0.8)
Death	7 (2.7)	5 (3.8)	2 (1.6)
Other <sup>a</sup>	12 (4.7)	8 (6.2)	4 (3.2)
<b>Dose reduction, n (%)</b>	104 (40.8)	46 (35.4)	58 (46.4)
<b>Dose delayed, n (%)</b>	118 (46.3)	59 (45.4)	59 (47.2)

<sup>a</sup>Other reasons of discontinuation include Physician's decision, protocol deviations, and loss to follow-up.

F: Fulvestrant; L: Letrozole; P: Palbociclib.

# Safety Analysis



AEs: Adverse events; SAEs: Serious adverse events.

AEs, n (%)	Fulvestrant + Palbociclib (N=129)			Letrozole + Palbociclib (N=126)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
<b>ANY</b>	128 (99.2)	87 (67.4)	15 (11.6)	125 (99.2)	89 (70.6)	10 (7.9)
<b>HAEMATOLOGIC</b>						
Neutropenia	109 (84.5)	74 (57.4)	9 (7.0)	109 (86.5)	78 (61.9)	4 (3.2)
Anemia	27 (20.9)	3 (2.3)	0 (0.0)	32 (25.4)	4 (3.2)	0 (0.0)
Leukopenia	23 (17.8)	6 (4.7)	0 (0.0)	21 (16.7)	3 (2.4)	0 (0.0)
Thrombocytopenia	23 (17.8)	3 (2.3)	0 (0.0)	18 (14.3)	0 (0.0)	0 (0.0)
<b>NON-HAEMATOLOGIC</b>						
Asthenia	66 (51.2)	5 (3.9)	0 (0.0)	59 (46.8)	3 (2.4)	0 (0.0)
Arthralgia	34 (26.4)	0 (0.0)	0 (0.0)	43 (34.1)	0 (0.0)	0 (0.0)
Alopecia	32 (24.8)	0 (0.0)	0 (0.0)	35 (27.8)	0 (0.0)	0 (0.0)
Back pain	33 (25.6)	3 (2.3)	0 (0.0)	32 (25.4)	1 (0.8)	0 (0.0)
Diarrhoea	33 (25.6)	1 (0.8)	0 (0.0)	30 (23.8)	0 (0.0)	0 (0.0)
Stomatitis	31 (24.0)	0 (0.0)	0 (0.0)	31 (24.6)	0 (0.0)	0 (0.0)
Nausea	39 (30.2)	3 (2.3)	0 (0.0)	22 (17.5)	0 (0.0)	0 (0.0)
Fatigue	31 (24.0)	3 (2.3)	0 (0.0)	25 (19.8)	2 (1.6)	0 (0.0)
Cough	29 (22.5)	0 (0.0)	0 (0.0)	23 (18.3)	0 (0.0)	0 (0.0)
Decreased appetite	27 (20.9)	1 (0.8)	0 (0.0)	24 (19.0)	1 (0.8)	0 (0.0)

N=2 patients died due to unrelated AEs, of whom 1 (0.8%) were randomized in fulvestrant plus palbociclib arm and 1 (0.8%) in letrozole plus palbociclib arm.

AEs: Adverse Events

## Adverse Events of Special Interest between Arms (Safety analysis)

Patients with AEs, n(%)	Fulvestrant + Palbociclib (N=241)			Letrozole + Palbociclib (N=242)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Tromboembolic events	14 (5.8)	11 (4.6)	2 (0.8)	11 (4.5)	7 (2.9)	0 (0)
Pulmonary embolism*	12 (5.0)	10 (4.2)	2 (0.8)	6 (2.5)	6 (2.5)	0 (0)
Varicose vein	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0)
Pelvic venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0)
Jugular vein thrombosis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
Ischaemic stroke	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0)
ILD/pneumonitis**	6 (2.5)	2 (0.8)	0 (0.0)	6 (2.5)	3 (1.2)	0 (0)

CTCAE v4.0 criteria

\*One patient died due to unrelated pulmonary embolism in Fulvestrant + Palbociclib arm.

\*\*Interstitial lung disease (ILD)/pneumonitis includes any reported preferred terms that are part of the Standardised MedDRA Query Interstitial Lung Disease.

AEs: Adverse events.

# Conclusions

- PARSIFAL study did not show a statistical superiority in PFS for fulvestrant plus palbociclib over letrozole plus palbociclib in the first-line endocrine sensitive MBC population (HR 1.13, 95%CI 0.89–1.45, p=0.321). The non-inferiority hypothesis was also refused.
- No major efficacy differences were observed by the two stratification factors, visceral disease or “*de novo*” metastatic.
- With a median FU of 32 months and 21% of events, OS was not different between arms (HR 1.00, 95%CI 0.68–1.48, p=0.986).
- No unexpected safety signals were identified.
- PARSIFAL study was inconclusive in establishing superiority between the two endocrine backbone agents when combined with palbociclib. Final treatment decision must balance patients and clinicians' preferences as well as subsequent treatment strategies.

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