2023 ASCO® ANNUAL MEETING

Second-line endocrine therapy with or without palbociclib maintenance in patients with HR[+]/HER2[-] advanced breast cancer: PALMIRA trial

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Declaration of Interests

Antonio Llombart Cussac

- Research support: Roche, Agendia, Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Gilead, and Daichii-Sanyo
- Consulting or advisory role: Lilly, Roche, Pfizer, and Novartis
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- Travel support: Roche, Pfizer, AstraZeneca
- Stock or other ownership: MEDSIR and Initia-Research.

HR[+]/HER2[-] advanced breast cancer

- The combination of a CDK4/6 inhibitor (CDK4/6i) with letrozole or fulvestrant is the most active first–line (1L) treatment for patients with HR[+] and HER2[-] advanced breast cancer (ABC).[1-6]
- The optimal treatment after progression on 1L CDK4/6i remains undetermined.
- Although endocrine sensitivity persists after CDK4/6i regimens, preliminary findings suggest more adaptive resistance mechanisms to endocrine therapy (ET) than to CDK4/6i.[7-8]
- PALMIRA trial aims to determine whether maintaining palbociclib with an alternative ET improves the antitumor activity of second-line ET in patients with HR[+]/HER2[-] ABC progressing on a 1L palbociclib regimen.

HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive

(1) Finn RS, et al. *N Engl J Med*. 2016 Nov 17;375(20):1925-1936.
(2) Cristofanilli M, et al. *Lancet Oncol*. 2016 Apr;17(4):425-439.
(3) Goetz MP, et al. *J Clin Oncol*. 2017 Nov 10;35(32):3638–46.
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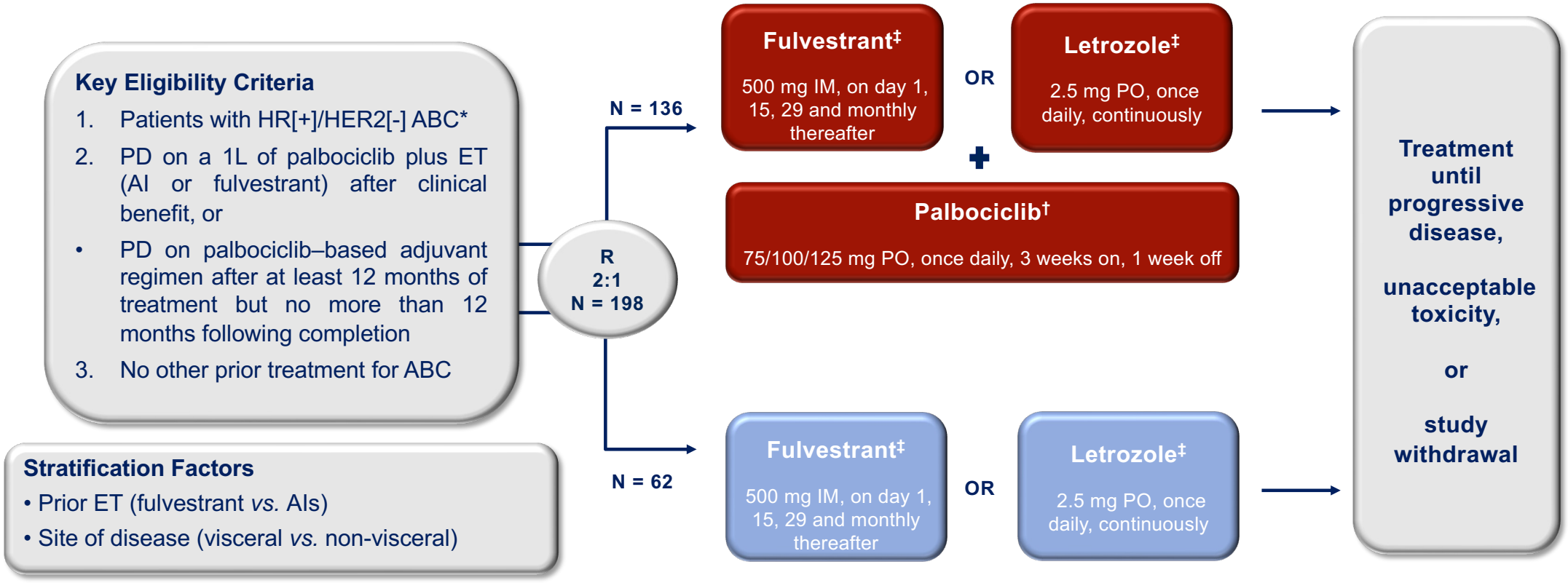
(5) Tripathy D, et al. *Lancet Oncol*. 2018 Jul;19(7):904-915.
(6) Llombart-Cussac A, et al. *JAMA Oncol*. 2021 Dec 1;7(12):1791-1799.
(7) Portman N, et al. *Endocr Relat Cancer*. 2019 Jan;26(1):R1-R30.
(8) Albanell J, et al. *Clin Cancer Res*. 2023 Jan;29(1):67-80.

PALMIRA Study Design (NCT03809988)



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

Key Selection Criteria

Inclusion criteria

1. Premenopausal (with OSF) or postmenopausal women with HR[+]/HER2[-] ABC;
2. Progression on a palbociclib plus ET based regimen
   - 1L ABC with clinical benefit (SD ≥ 24 weeks or partial / complete response) or;
   - Adjuvant palbociclib after at least 12 mo. of treatment but no >12 mo. from completion;
3. Last dose of prior palbociclib regimen within 8 weeks from study entry*;
4. RECIST v.1.1 Measurable or evaluable disease;
5. ECOG PS score 0-1.

Exclusion criteria

1. Visceral crisis;
2. Any previous treatment for ABC out of the 1L palbociclib regimen;
3. Use of a CDK4/6i other than palbociclib;
4. Resistance criteria to both fulvestrant and letrozole.

* Except for patients relapsing on a palbociclib-based regimen in the adjuvant setting

1L: First-line; ABC: Advanced breast cancer; CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; mo: months; OSF: Ovarian suppression function; SD: Stable disease; RECIST v.1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

Study Endpoints

Primary Endpoint

- Investigator-assessed progression-free survival (PFS) determined by RECIST v.1.1

Secondary Endpoints

- Objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS), duration of response (DoR), time to response (TTR), and time to progression (TTP)
- ORR, DoR, TTR, CBR, TTP, OS, and PFS by prior endocrine therapy, site of disease, and HER2 expression status
- Overall change from baseline in patient reported global quality of life (QoL), functioning, symptoms and general health status
- Time to deterioration in global QoL
- Time to deterioration in pain
- Time to first chemotherapy
- Safety and tolerability

Exploratory Endpoints

- Molecular subtypes
- Predictive biomarkers

Statistical Considerations

- Efficacy was assessed in all patients who had undergone randomization. Safety was assessed in all patients who received at least 1 dose of study drug.
- The Kaplan–Meier method was used to estimate PFS. The treatment difference in PFS was assessed with the use of the stratified log-rank test and Cox proportional-hazards models.
- The sample size was based on a superiority test of PFS. We estimated that with an enrollment of 198 patients, the trial would have 80% power to detect a 2.74-month increase in median PFS over a 4-month median PFS for the endocrine therapy group, at a two-sided alpha level of 0.05 (hazard ratio = 0.59).

PFS: Progression-free survival

Summary of Analysis Population

198 patients randomized 2:1 from April 2019 to October 2022
Data cut-off: February 2, 2023

ET + Palbociclib

136 allocated

135 (99.3%) started treatment

24 (17.6%) on treatment

111 (81.6%) discontinued treatment

- 107 (78.7%) disease progression

ET

62 allocated

60 (96.8%) started treatment

8 (12.9%) on treatment

52 (85.5%) discontinued treatment

- 51 (82.3%) disease progression

Analysis Populations

- ITT: N = 136
- Safety-evaluable: N = 135

Analysis Populations

- ITT: N = 62
- Safety-evaluable: N = 60

Median (range) follow-up: 13.2 months (0-41.1)

ET: Endocrine therapy

Three patients (one for ET + Palbociclib and two for ET arms) did not receive the study treatment and were excluded from safety analysis.

Baseline Characteristics (ITT population)

Baseline characteristics, n (%)	ET + Palbociclib (N = 136)	ET (N = 62)
Age in years, Median (Min; Max)	59 (33; 85)	61 (34; 83)
Menopausal status		
Premenopausal	18 (13.2%)	6 (9.7%)
Postmenopausal	118 (86.8%)	56 (90.3%)
ECOG PS score		
0	90 (66.2%)	31 (50.0%)
1*	45 (33.1%)	31 (50.0%)
Measurable disease at baseline		
Yes	94 (69.1%)	44 (71.0%)
No	42 (30.9%)	18 (29.0%)
Visceral involvement		
Yes	84 (61.8%)	37 (59.7%)
No	52 (38.2%)	25 (40.3%)

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

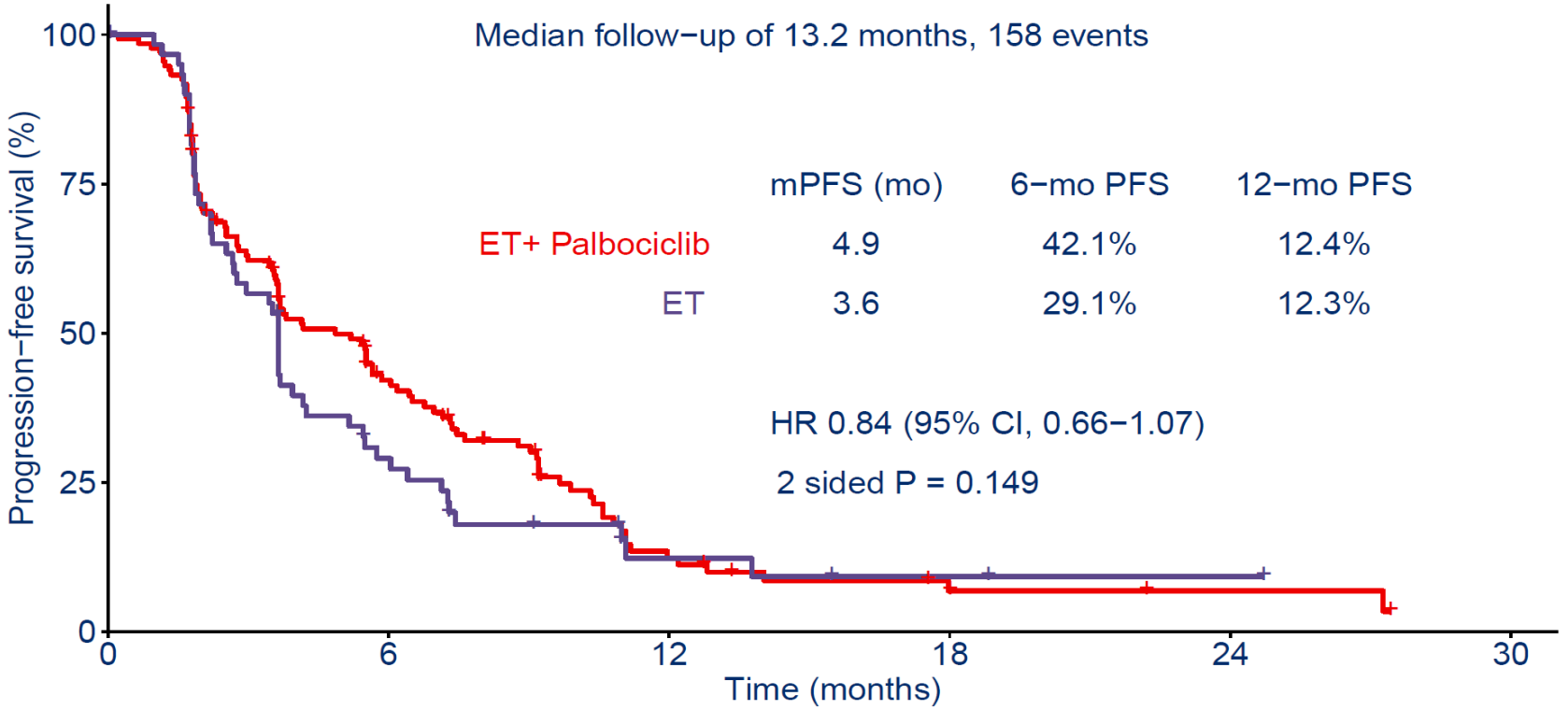
*One patient in ET + Palbociclib group had ECOG 2.

Baseline Characteristics cont. (ITT population)

Baseline characteristics, n (%)	ET + Palbociclib (N = 136)	ET (N = 62)
Number of metastatic sites		
<3	92 (67.6%)	38 (61.3%)
≥3	44 (32.4%)	24 (38.7%)
Prior endocrine therapy used in combination with palbociclib		
Fulvestrant	16 (11.8%)	4 (6.5%)
Aromatase Inhibitor	120 (88.2%)	58 (93.5%)
Duration of first-line palbociclib (6-12; ≥12 months)		
6-12 months	18 (13.2%)	10 (16.1%)
≥ 12 months	118 (86.8%)	52 (83.9%)
Last dose of first-line palbociclib		
125 mg	83 (53.2%)	33 (61.0%)
100 mg	45 (43.5%)	27 (33.1%)
75 mg	8 (3.2%)	2 (5.9%)

ITT: Intention to treat.

Primary Objective: Investigator-assessed PFS (ITT Population)



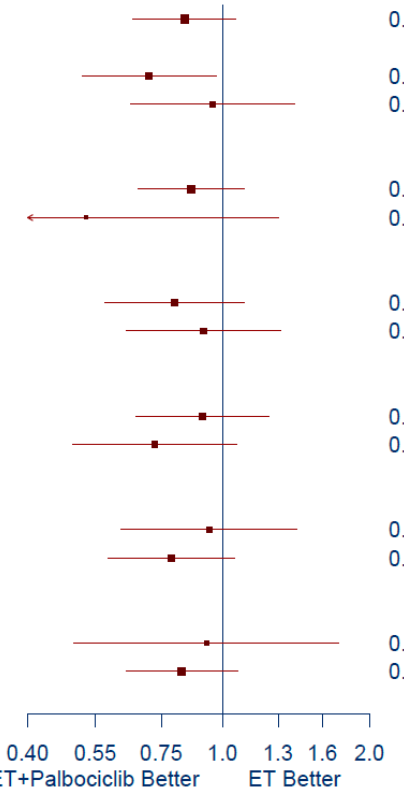
Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

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

Subgroup Analyses of PFS (ITT Population)

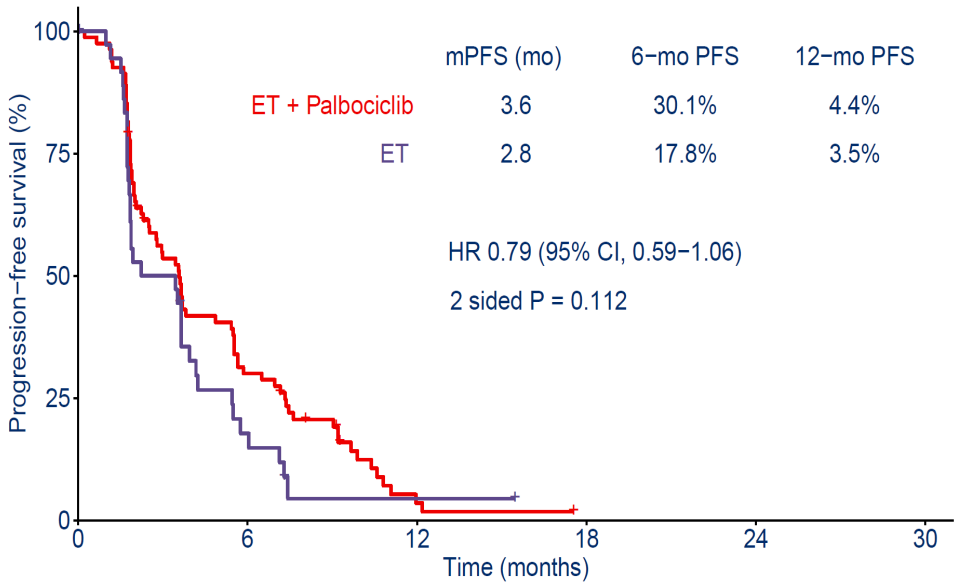
	ET+Palbociclib n=136 events / n(%)	Median PFS (mo) 95% CI	ET n=62 events / n(%)	Median PFS (mo) 95% CI	Adjusted HR 95%CI	Interaction p
All patients	107 / 136 (78.7%)	4.9 (3.6 - 6)	51 / 62 (82.3%)	3.6 (2.5 - 4.2)	0.84 (0.66-1.07)	
Age						
<65 yr	73 / 94 (77.7%)	4.1 (3.5-5.8)	29 / 33 (87.9%)	2.7 (1.9-3.9)	0.71 (0.52-0.97)	0.239
≥65 yr	34 / 42 (81%)	5.5 (2.5-7.6)	22 / 29 (75.9%)	3.6 (3.5-7.1)	0.95 (0.65-1.4)	
Endocrine therapy						
Fulvestrant	96 / 120 (80%)	4.1 (3.5-5.8)	47 / 58 (81%)	3.6 (2.7-4.2)	0.86 (0.67-1.11)	0.313
Letrozole	11 / 16 (68.8%)	6.7 (2.5-14)	4 / 4 (100%)	3.1 (1.6-NA)	0.53 (0.21-1.3)	
ECOG performance status						
0	70 / 90 (77.8%)	4.9 (3.5-6.8)	25 / 31 (80.6%)	3.6 (1.9-7.3)	0.8 (0.58-1.11)	0.581
1 to 2	37 / 46 (80.4%)	4.1 (2.8-5.7)	26 / 31 (83.9%)	3.6 (2.5-5.5)	0.92 (0.64-1.32)	
Metastatic sites						
<3	65 / 92 (70.7%)	5.7 (3.6-7.4)	30 / 38 (78.9%)	3.7 (2.7-7.1)	0.91 (0.67-1.24)	0.374
≥3	42 / 44 (95.5%)	3.5 (2-5.5)	21 / 24 (87.5%)	2.9 (1.8-4.2)	0.73 (0.5-1.07)	
Visceral involvement						
No	34 / 52 (65.4%)	8.8 (4.2-11)	18 / 25 (72%)	4.4 (2.8-11.1)	0.94 (0.62-1.42)	0.239
Yes	73 / 84 (86.9%)	3.6 (2.3-5.4)	33 / 37 (89.2%)	2.8 (1.8-3.9)	0.79 (0.59-1.06)	
Duration of first-line palbociclib						
6-12 months	14 / 18 (77.8%)	1.8 (1.7-12)	8 / 10 (80%)	3.5 (1-NA)	0.93 (0.5-1.73)	0.734
≥12 months	93 / 118 (78.8%)	5.5 (3.6-6.4)	43 / 52 (82.7%)	3.6 (2.5-5.2)	0.83 (0.63-1.07)	



CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ET: Endocrine therapy; HR: Hazard ratio; ITT: Intention to treat; mo: Months;; PFS: Progression-free survival.

PFS by Visceral Disease (ITT Population)

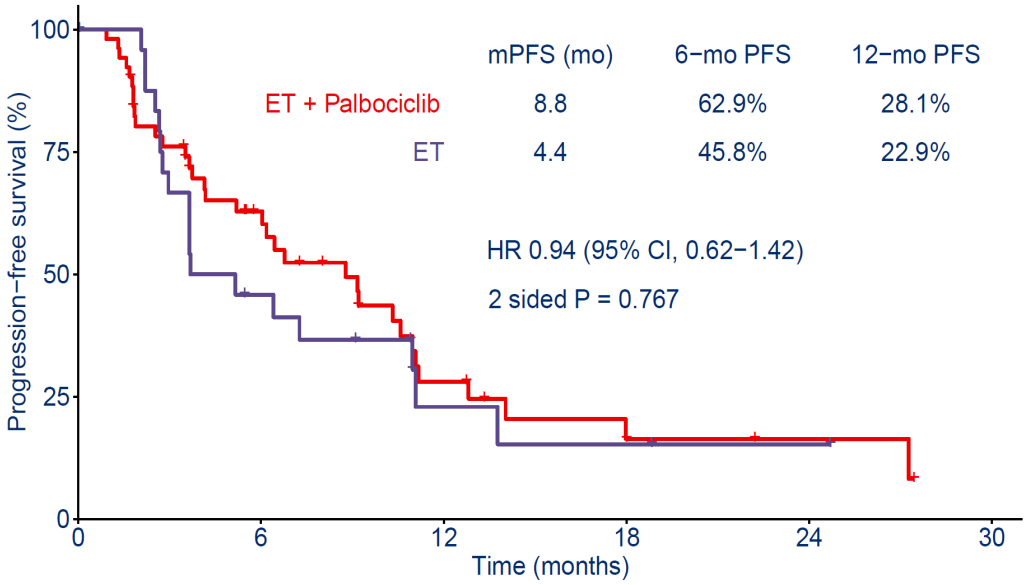
Visceral involvement (N = 121)



Patients at risk, n (%)

ET+Palbociclib	84 (100)	23 (27)	2 (2)	0 (0)	0 (0)	0 (0)
ET	37 (100)	6 (16)	1 (3)	0 (0)	0 (0)	0 (0)

Without visceral involvement (N = 77)



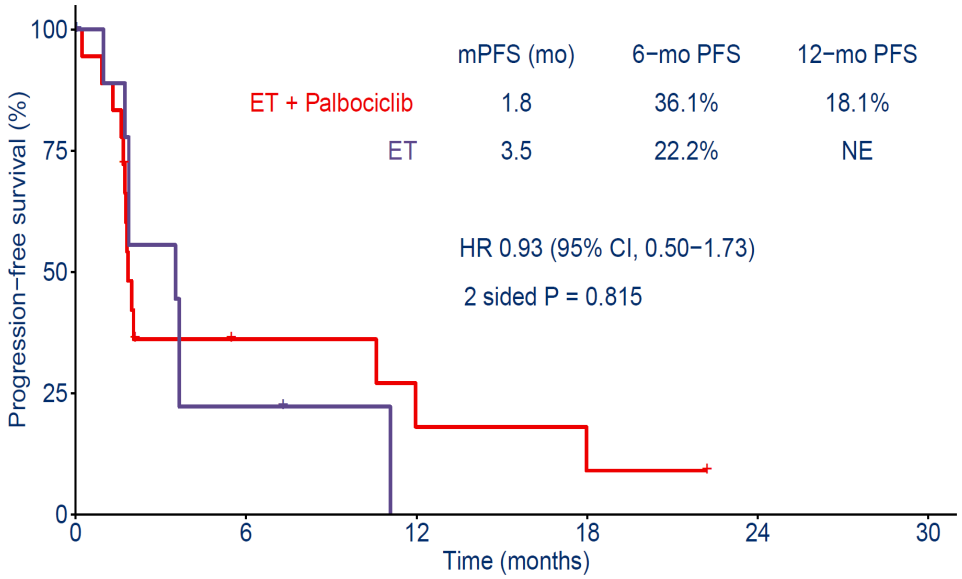
Patients at risk, n (%)

ET+Palbociclib	52 (100)	24 (46)	9 (17)	4 (8)	2 (4)	0 (0)
ET	25 (100)	10 (40)	3 (12)	2 (8)	1 (4)	0 (0)

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

PFS by prior duration of palbociclib treatment (ITT Population)

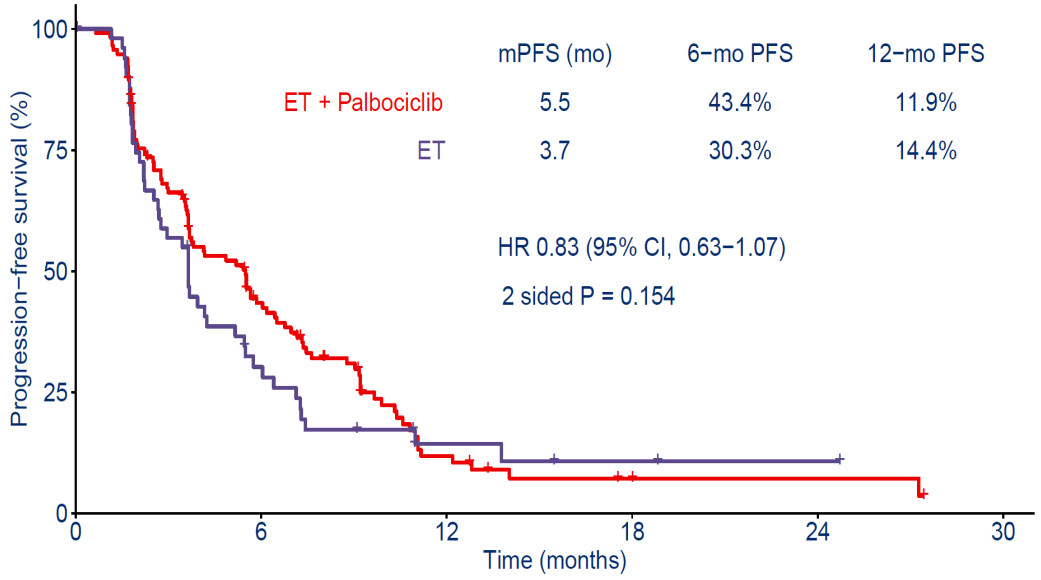
6-12 months (N = 28)



Patients at risk, n (%)

ET+Palbociclib	18 (100)	4 (22)	2 (11)	1 (6)	0 (0)	0 (0)
ET	10 (100)	2 (20)	0 (0)	0 (0)	0 (0)	0 (0)

≥ 12 months (N = 170)



Patients at risk, n (%)

ET+Palbociclib	118 (100)	43 (36)	9 (8)	3 (3)	2 (2)	0 (0)
ET	52 (100)	14 (27)	4 (8)	2 (4)	1 (2)	0 (0)

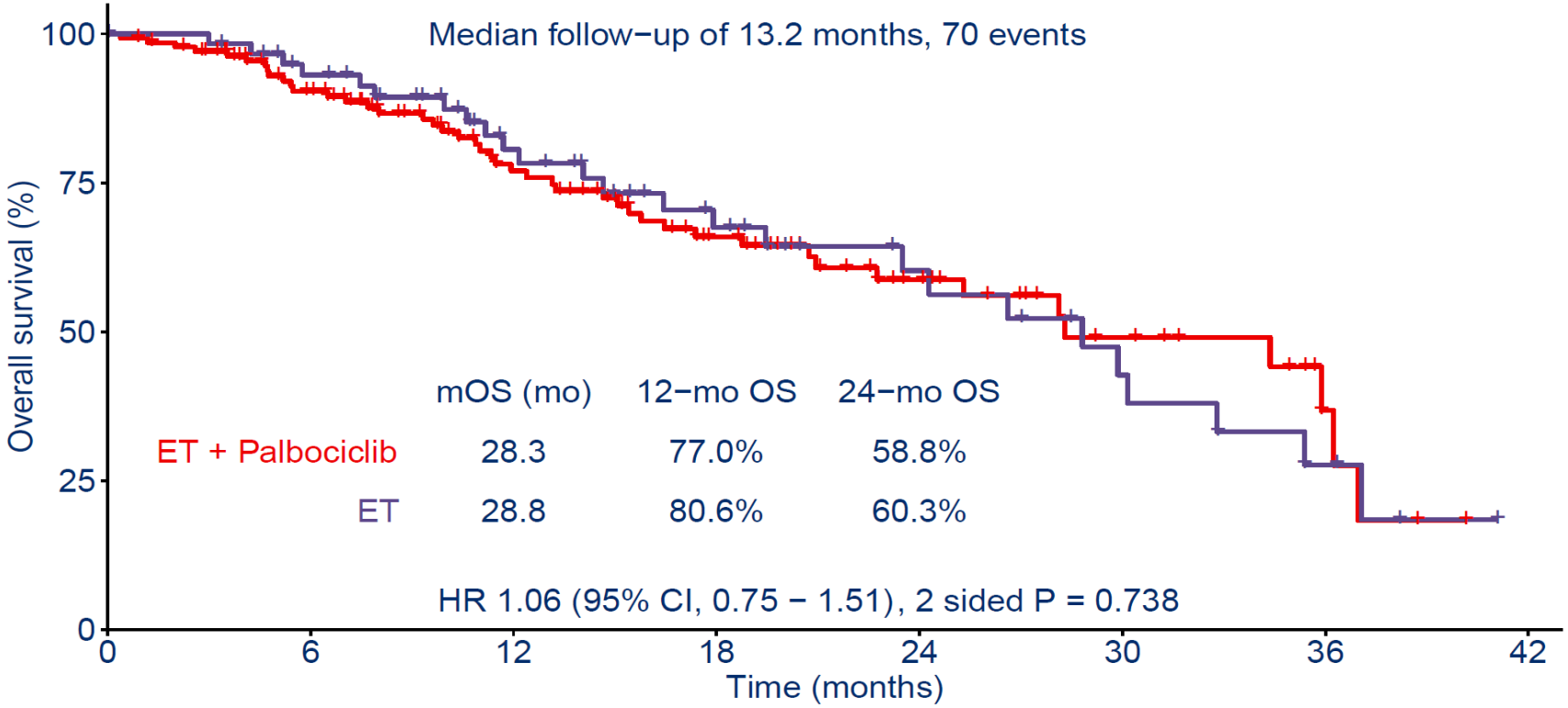
CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Tumor Response by RECIST v1.1 (ITT Population)

Tumor response, n (%)	ET + Palbociclib (N = 136)	ET (N = 62)
Overall Response, *n* (%)		
CR	0 (0.0)	0 (0.0)
PR	6 (4.4)	1 (1.6)
SD	49 (36.0)	22 (35.5)
Non-CR/Non-PD	34 (25.0)	13 (21.0)
PD	39 (28.7)	24 (38.7)
NE	8 (5.9)	2 (3.2)
Objective Response Rate (ORR), *n* (%)		
Yes (95% CI)	6 (4.4%; 1.6-9.4)	1 (1.6%; 0-8.7)
Clinical Benefit Rate (CBR), *n* (%)*		
Yes (95% CI)	57 (41.9%; 33.5-50.7)	17 (27.4%; 16.9-40.2)
Measurable disease, ORR (95%CI)		
Yes (95% CI)	(N = 94) 6 (6.4%; 2.4-13.4)	(N = 44) 1 (2.3%; 0.1-12.0)

CI: Confidence Interval; CR: Complete response; ITT: Intention to treat; NE: Not evaluated; PD: Progressive disease; PR: Partial response; SD: Stable disease.
ORR: CR + PR; CBR: CR + PR + SD or Non-CR/Non-PD ≥ 24w
* CBR in ET + palbociclib group was significantly better than in the ET group (p-value = 0.0442)

Overall Survival (ITT Population)

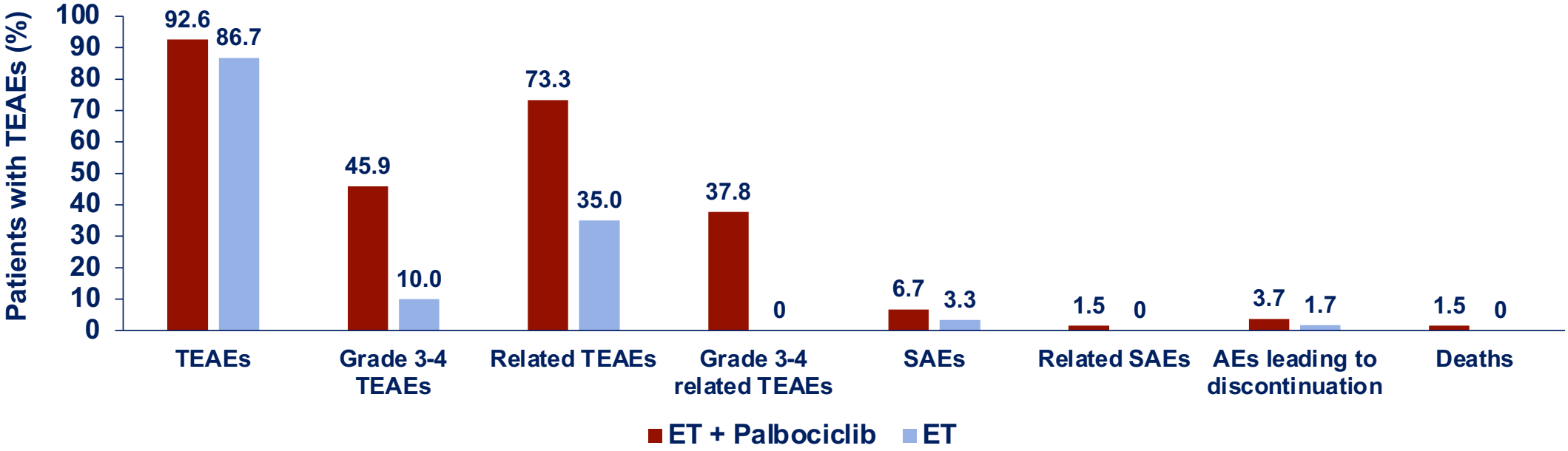


Patients at risk, n (%)

ET+Palbociclib	136 (100)	106 (78)	68 (50)	46 (34)	25 (18)	13 (10)	4 (3)	0 (0)
ET	62 (100)	52 (84)	35 (56)	23 (37)	15 (24)	9 (15)	4 (6)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mOS: median Overall survival.

Safety Analysis



TEAEs: Treatment-emergent adverse events; SAEs: Serious adverse events

No treatment related deaths were reported
Two patients treated with endocrine therapy plus palbociclib died due to unrelated toxicities (Pulmonary hypertension and Thrombotic thrombocytopenic purpura).

TEAEs by maximum severity affecting at least 10% or of grade 4-5 (Safety Analysis)

	ET + Palbociclib (N = 135)			ET (N = 60)		
TEAEs, n (%)	**Any grade**	**Grade 3**	**Grade 4***	**Any grade**	**Grade 3**	**Grade 4**
ANY	**125 (92.6%)**	**54 (40.0%)**	**8 (5.9%)**	**52 (86.7%)**	**6 (10.0%)**	**0 (0%)**
HEMATOLOGICAL	**81 (60%)**	**47 (34.8%)**	**6 (4.4%)**	**8 (13.3%)**	**0 (0%)**	**0 (0%)**
Neutropenia	71 (52.6%)	46 (34.1%)	6 (4.4%)	1 (1.7%)	0 (0%)	0 (0%)
Anaemia	25 (18.5%)	4 (3.0%)	0 (0%)	5 (8.3%)	0 (0%)	0 (0%)
Leukopenia	14 (10.4%)	5 (3.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NON-HEMATOLOGICAL	**109 (80.7%)**	**12 (8.9%)**	**2 (1.5%)**	**50 (83.3%)**	**6 (10.0%)**	**0 (0%)**
Fatigue	37 (27.4%)	0 (0%)	0 (0%)	14 (23.3%)	0 (0%)	0 (0%)
Arthralgia	23 (17.0%)	2 (1.5%)	0 (0%)	7 (11.7%)	0 (0%)	0 (0%)
Nausea	16 (11.9%)	0 (0%)	0 (0%)	7 (11.7%)	0 (0%)	0 (0%)
GGT increased	6 (4.4%)	3 (2.2%)	1 (0.7%)	1 (1.7%)	0 (0%)	0 (0%)
Colitis ischaemic	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)

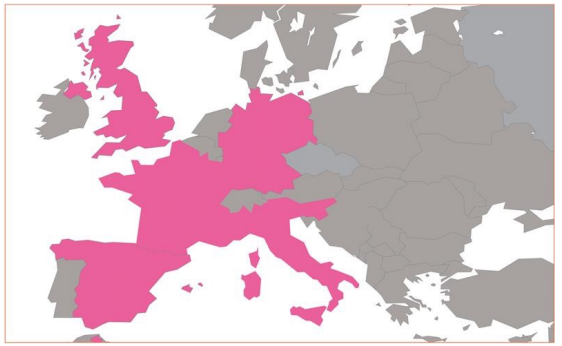
* Two patients died due to unrelated toxicities (Pulmonary hypertension and Thrombotic thrombocytopenic purpura).

GGT: Gamma-glutamylransferase; TEAEs: Treatment-emergent adverse events; SAEs: Serious adverse events.

Conclusions

- Palbociclib maintenance strategy following progression on a first-line palbociclib regimen did not improve PFS compared to standard ET in patients with HR[+]/HER2[-] ABC.
- PFS analyses showed no significant differences across all prespecified subgroups. However, CBR and PFS rates at 6 months, as well as the activity in patients with aggressive disease suggest that a subset of patients may benefit from palbociclib maintenance.
- No unexpected safety signals were identified.
- A vast biomarker study program is underway to identify which patients are most likely to benefit from a CDK4/6i maintenance strategy.

Acknowledgements



Patients and their families.

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Lay Language summary - PALMIRA at ASCO 2023

Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR[+])/human epidermal growth factor receptor 2-negative (HER2[-]) advanced breast cancer (ABC): PALMIRA trial

Patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer are first treated with a combination of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors and endocrine therapy, where CDK4/6 inhibitors work by stopping cancer cells growth and endocrine therapy blocks hormones that stimulate cancer cell growth. However, the best treatment for patients who progress on a CDK4/6 inhibitors therapy remains unknown. Despite ongoing research to determine the optimal treatment strategy for these patients, the best approach remains unclear. Some studies suggest that cancer may become resistant to endocrine therapy more easily than to CDK4/6 inhibitors. To address this gap in knowledge, the PALMIRA trial has been designed to explore if keeping patients on palbociclib (a CDK4/6 inhibitor) but giving a different type of endocrine therapy (with the drugs letrozole or fulvestrant) can improve the effectiveness of second-line treatment in patients with HR[+]/HER2[-] advanced breast cancer.

PALMIRA was an international, randomized, open-label phase II trial across 44 hospitals in 6 countries, that enrolled 198 patients with HR+/HER2- advanced breast cancer who had experienced disease progression after initially responding to treatment with the immediately prior regimen of palbociclib plus endocrine therapy. Patients were randomly allocated to receive either palbociclib plus endocrine therapy or endocrine therapy alone. The choice of endocrine therapy administered during this trial was switched based on the previously administered agent: patients previously treated with fulvestrant changed to letrozole, whereas patients previously treated with letrozole, anastrozole or exemestane were switched to fulvestrant. The primary objective of the study was to determine the amount of time from the start of the treatment until the disease got worse again, also called progression-free survival (PFS).

The results show that, after a median follow-up of 13.2 months, there was no significant difference in the length of time that patients' conditions got worse between the two groups. Median PFS was 4.9 months in the palbociclib plus endocrine therapy group and 3.6 months in the endocrine therapy alone group. However, differences in the median PFS and clinical benefit rates at 6 months were observed between groups, suggesting that a subset of patients may benefit from continuing palbociclib treatment. Several biomarker studies are planned to identify which patients are most likely to benefit from adding CDK4/6 inhibitor to their treatment.