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Palbociclib rechallenge in Hormone Receptor (HR)[+]/HER2[-] advanced breast cancer PALMIRA Trial

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BACKGROUND

- The combination of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with letrozole (LET) or fulvestrant (FUL) is the most active first–line (1L) treatment for patients (pts) with hormone receptor-positive (HR[+]) and Human Epidermal Growth Factor Receptor 2-negative HER2[-] advanced breast cancer (ABC).[1,2]
- Although endocrine sensitivity persists beyond progression, preliminary findings suggest more adaptive resistance mechanisms to endocrine therapy (ET) than to CDK4/6i.[3]
- At present, there are no data about prolonging CDK4/6 blockade beyond progression on a CDK4/6i. [4]
- The aim of this study is to determine whether palbociclib rechallenge combined with second–line ET upon progression to a prior palbociclib–based therapy will improve progression–free survival (PFS) over ET alone in pts with HR[+]/HER2[-] ABC.

OBJECTIVES

PRIMARY OBJECTIVE

To compare the efficacy –defined as PFS– of continuation of palbociclib treatment combined with second-line ET (LET or FUL) versus ET alone in pre- and post-menopausal women with HR[+]/HER2[-] ABC who have achieved clinical benefit during 1L palbociclib-based treatment.

PRIMARY ENDPOINT

- The primary endpoint is PFS, defined as the time from random assignment to the date of the first documentation of objective progressive disease or death due to any cause, whichever occurs first.

SECONDARY OBJECTIVES

- Objective response rate, duration of response, time to response, clinical benefit rate, time to progression, overall survival, and time to first chemotherapy.
- Health-related quality of life (HRQoL) measured by the European Organization for Research and Treatment of Cancer (EORTC) and EuroQoL 5D (EQ-5D) questionnaires.

SAFETY OBJECTIVES

- Adverse events assessed using the National Cancer Institute´s Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

EXPLORATORY OBJECTIVES

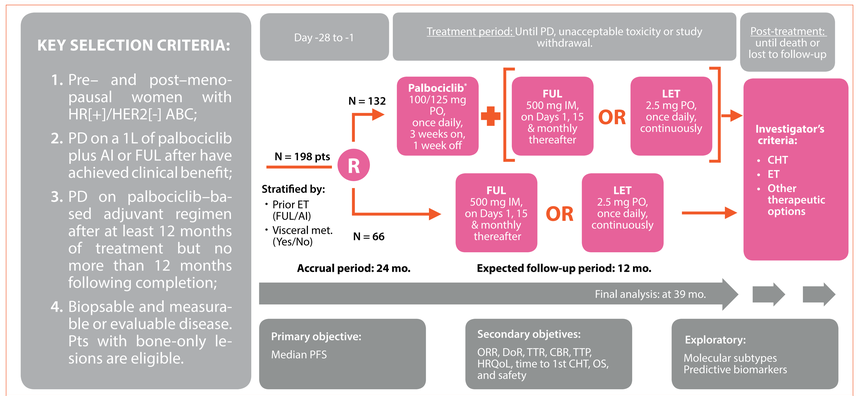
- Correlation between the intrinsic molecular subtypes of HR[+]/HER2[-] ABC and efficacy/safety findings.
- Identification of new predictive markers of sensitivity and resistance to palbociclib in combination with second-line ET.

METHODS

STUDY DESIGN

1. This is an international, multicenter, randomized, open-label, phase II clinical trial (Figure 1).
2. A total of 198 pts will be randomized (2:1) to palbociclib plus ET (LET or FUL) (Arm A) or ET alone (Arm B), until progressive disease or unacceptable toxicity.
3. Pts previously treated with FUL will change to LET treatment, and those previously treated with LET, Anastrozole or Exemestane will switch to FUL treatment.

Figure 1. Study design



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; CBR: Clinical benefit rate; CHT: Chemotherapy; DoR: Duration of response; ET: Endocrine therapy; FUL: Fulvestrant; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; HRQoL: Health-related quality of life; IM: Intramuscular injection; LET: Letrozole; met.: Metastasis; mo: Months; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; pts: Patients; PO: oral administration; PD: Progressive disease; TTP: Time to progression; TTR: Time to response.

* Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.

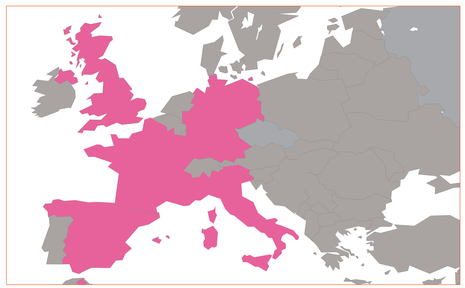
SAMPLE SIZE

- A total of 198 pts will be randomized in a 2:1 ratio (N=132 in Arm A and N=66 in Arm B).
- Sample size calculation is based on two co-primary analyses:
  1. The first co-primary analysis is the estimation of median PFS (mPFS) in palbociclib plus ET arm (H0: mPFS ≤ 4 months; HA: mPFS ≥5.4 months).
  2. If the first analysis meets the significant criterion ($p<0.05$), mPFS will be compared between the two treatment arms.
- The first and second co-primary analyses will be analyzed with maximum likelihood estimation for exponential distribution and stratified log-rank tests, respectively.
- The first and second analyses have an 80% power to detect a 1.4–month (hazard ratio [HR]=0.74) or 2.74–month (HR=0.6) increase over 4–month mPFS for ET arm, respectively.
- We expect a total of 128 PFS events in both arms and 85 PFS events in Arm A.
- The nominal alpha level is 5% for both two-sided survival tests.

TRIAL ENROLLMENT

Currently, the PALMIRA trial is open and recruiting in **France, Spain, and United Kingdom** (Figure 2). The patient recruitment started in April 2019.

Figure 2. Participant countries



BIBLIOGRAPHY

(1) Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925-1936.
(2) Cristofanilli M, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo (…) (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425-439.
(3) Portman N, et al. Overcoming CDK4/6 inhibitor resistance in ER positive breast cancer. Endocr Relat Cancer. 2018 Sep 1. pii: ERC-18-0317.R1. doi: 10.1530/ERC-18-0317.
(4) Pernas S, et al. CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol. 2018 Jul 17;10:1758835918786451. doi: 10.1177/1758835918786451.

Conflicts of interest: https://medsir.org/palmira/

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Trial registration: NCT03809988. **Date of registration:** January 18th, 2019. **First patient included:** April 15th, 2019.

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