A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE II TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PALBOCICLIB IN COMBINATION WITH FULVESTRANT OR LETROZOLE IN PATIENTS WITH ER+/HER2- METASTATIC BREAST CANCER (MBC).

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BACKGROUND

Trial design

Palbociclib (P) is a cyclin dependent kinase inhibitor. In the phase II trial PALOMA-1, the combination palbociclib (P) plus endocrine therapy was shown to be superior in terms of progression free survival (PFS) to endocrine therapy alone in endocrine receptor (ER)+/HER2(-), locally advanced (LA) or metastatic breast cancer (MBC) patients. Based on the results of PALOMA-1 trial, the P + Letrozole (L) combination received accelerated approval by FDA in 2015. Phase III trial comparing P+ fulvestrant (F) to F alone (PALOMA-3[1]) in hormonosensitive women who had progressed to a previous endocrine therapy showed improvement in PFS in the combination arm. Accordingly, the FDA has expanded the indication for P, to be used in combination with F in these patients.

In the phase II FIRST[2] trial, high dose F (HDF) was shown to double PFS compared to anastrozole (A) as first line therapy for ER+ MBC patients. A registration phase III trial (FALCON study[3]) has recently completed accrual.

With two new (L+P and HDF) standards of care shaping up as first line of advance endocrine therapy for hormone-sensitive HER2 (-) women, exploring the combination of P+HDF in the first line setting seems mandatory.

METHODS

The PARSIFAL study is an open-label, randomized, controlled, multicenter phase II clinical trial. We recruit women with ER(+)/HER2(-) LA or MBC in first line therapy for advance disease **(Table 1)**.

Participants are randomly assigned 1:1 using an interactive web-based randomization system, stratified by disease site and onset of metastatic disease diagnose to receive palbociclib plus fulvestrant (Arm A) or palbociclib plus letrozole (Arm B). Patients continue treatment until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first **(Figure 1)**. Patients discontinuing the active treatment phase enter a treatment follow-up period during which survival and new anti-cancer therapy information is collected every 6 months from the last dose of investigational product. The treatment follow-up period continues up to 12 months after last included patient has been randomized into the study **(Figure 2)**. The protocol approval was obtained at participating sites from institutional review board/independent ethics committee. Sites are located in 8 countries in Europe and middle East **(Figure 3)**.

The primary endpoint is 1 year-progression free survival (1y-PFS) according to RECIST (version 1.1). The primary efficacy analysis is to compare the efficacy of arm A against arm B. We assumed exponential survival functions. The analysis will be performed with two-sided Log-Rank test. The investigator hypothesis (H1) is that 1y-PFS rate in arm A (85%) is higher than 1y-PFS rate in arm B (70%).

We estimated a dropout rate of 15%. We plan one interim analysis after half of all expected patients have completed one year of follow-up or has been discontinued. The Haybittle–Peto significance level for testing the null-hypothesis within the interim and final analysis are 0.001 and 0.0495, respectively. The sample size is 304 patients. This design yield an overall type I error of 5% and a power of 85%. We will use Cox proportional hazard models adjusting for stratified randomization variables. The main secondary endpoints are safety and tolerability related outcomes, time to progression, overall survival, overall response rate and clinical benefit. A series of prospective translational studies are planned in order to identify potential biomarkers and mechanism of resistance to palbociclib combined with endocrine therapy **(Figure 4)**.

Currently, 131 patients **(Figure 5)** from 5 countries have been recruited for the trial since study start in August 2015. The expected end of accrual will be in Q2 2017.

Trial registration number: NCT02491983; EudraCT: 2014-004698-17

Table 1. Eligibility criteria

A) Inclusion Criteria:	B) Exclusion Criteria:
1. Women aged 18 years or older with metastatic or locally advanced disease, not amenable to curative therapy	**1.** Confirmed diagnosis of HER2 positive disease
2. Confirmed diagnosis of HR+/HER2- breast cancer	**2.** Patients with rapidly progressive visceral disease or visceral crisis.
3. Post-menopausal status	**3.** Locally advanced breast cancer candidate for a radical treatment.
4. Premenopausal women receiving an LHRH agonist	**4.** Prior (neo)adjuvant endocrine treatment with DFI ≤ 12-months from completion of treatment.
5. No prior chemotherapy line in the metastatic setting	**5.** Major surgery within 4 weeks of start of study drug
6. Measurable disease defined by RECIST version 1.1, or non-measurable disease	**6.** Serious concomitant systemic disorder incompatible with the study
7. Eastern Cooperative Oncology Group (ECOG) PS 0-2	**7.** Known active uncontrolled or symptomatic CNS metastases
8. Adequate organ and marrow function, resolution of all toxic effects of prior therapy or surgical procedures	

Figure 1. Study Schedule

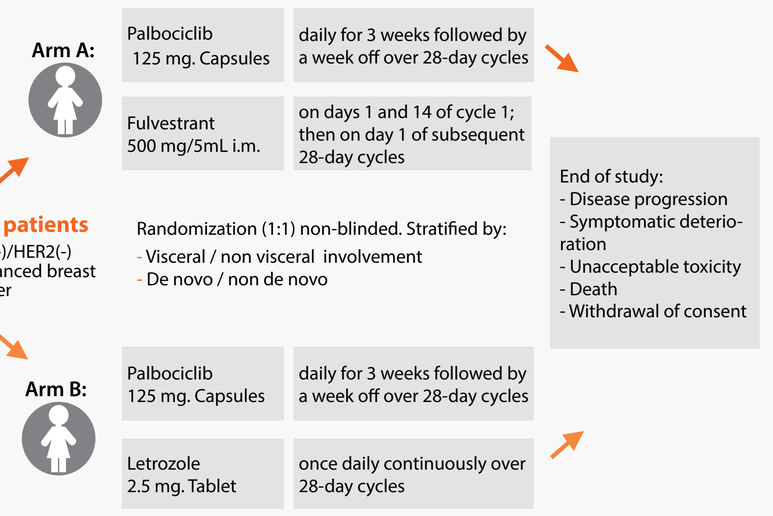


Figure 2. Summary of dose modifications during the study

Palbociclib

Hematological toxicities

CTCAE grade v 4.0	Dose Modifications
Grade 1 or 2	No dose interruption. No dose adjustment required.
Grade 3	No dose adjustment is required. Blood count monitoring one week later. Withhold dose of until recovery to Grade ≤2.
Grade 3 ANC + fever ≥38.5°C and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2 (≥1000/mm³). Resume at next lower dose.
Grade 4	Withhold palbociclib until recovery to Grade ≤2. Resume at next lower dose.

Non-hematological toxicities

CTCAE grade v 4.0	Dose Modifications
Grade 1 or 2	No dose interruption. No dose adjustment required.
Grade ≥3 (if persisting despite medical treatment)	Withhold palbociclib until recovery to Grade ≤1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient). Resume at next lower dose.
Grade 3 QTc prolongation (no reversible cause)	Withhold palbociclib until recovery to Grade ≤2. Resume at next lower dose.
Grade 4 QTc prolongation	Permanently discontinue.

Dose level — Palbociclib for 3 out of 4 weeks (3/1 schedule) → Starting dose → 125 mg/day; 1st dose reduction → 100 mg/day; 2nd dose reduction* → 75 mg/day

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Letrozole → Dose modifications for letrozole will be aligned to the summary of product characteristics approved locally.

Fulvestrant → Dose delays according with investigator's criteria. No dose adjustment for fulvestrant is permitted but dosing interruptions are allowed.

Figure 4. Objectives, predictive factors and outcomes of prospective translational studies

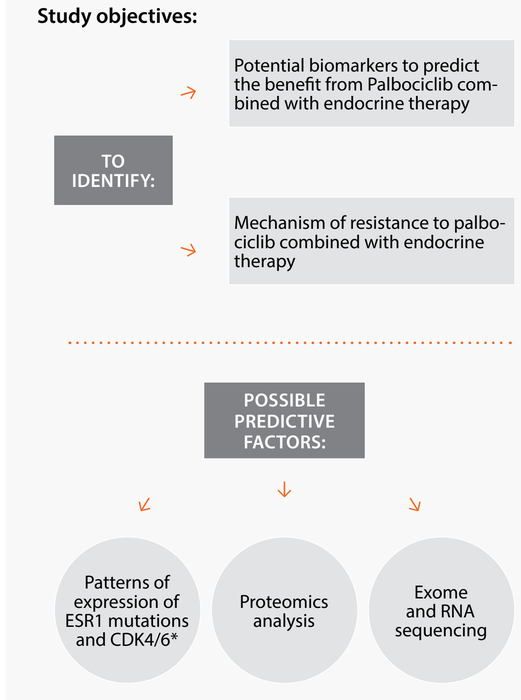


Figure 3. Participant countries and cities in Europe and middle east

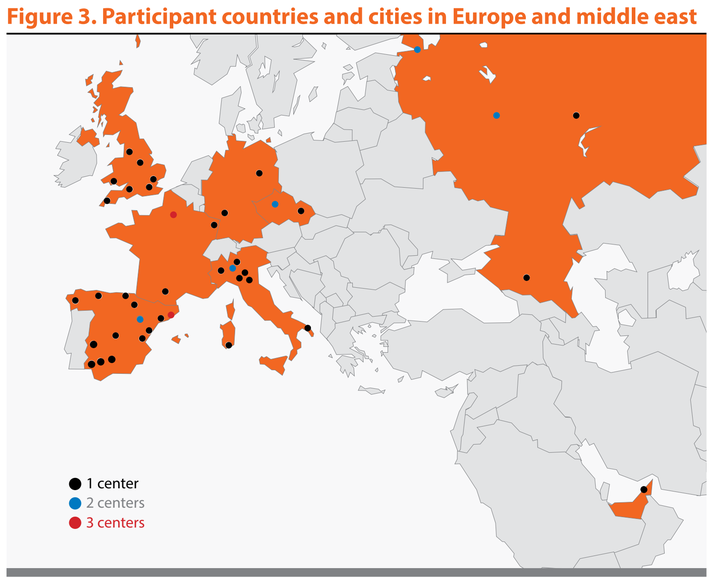
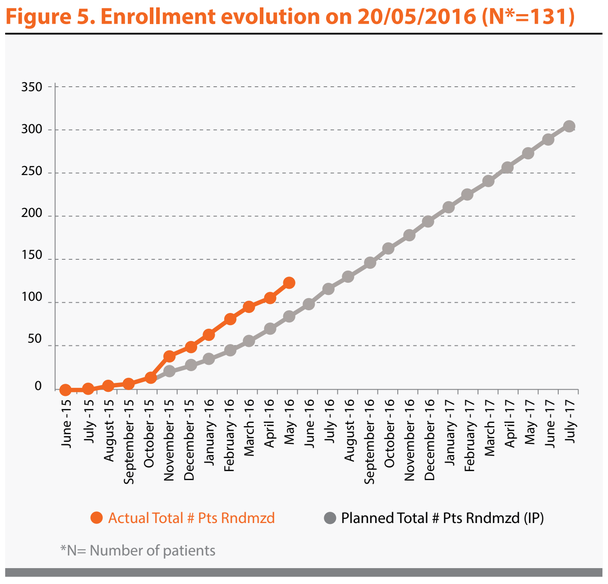


Figure 5. Enrollment evolution on 20/05/2016 (N*=131)



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[3] Clinical Trials ID: NCT01602380 (FALCON)