A randomized, open-label, multi-center phase IV study evaluating Palbociclib plus endocrine treatment versus a chemotherapy-based treatment strategy in patients with hormone receptor-positive/HER2-negative metastatic breast cancer in a real world setting (PADMA)

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Background

Although endocrine therapy (ET) is recommended as first-line therapy for hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) up to 50% of patients receive chemotherapy in this setting.[1,2,3] However, data comparing ET with chemotherapy as first-line therapy are scarce and less convincing.[4] Meanwhile, new targeted treatment options for combination with ET have been developed and endocrine-based therapy with palbociclib (CDK4/6 inhibitor) has been shown to improve the median progression-free survival (PFS) of ET alone.[5,6]

The hypothesis of the PADMA trial is that palbociclib + ET is superior to mono-chemotherapy of physician's choice with or without maintenance ET in time-to-treatment failure (TTF). To mirror the general breast cancer population and every-day clinical practice the PADMA trial is planned as a real world, low intervention trial with no rigid inclusion and exclusion criteria, treatment options and study assessments.

Patients and Methods

PADMA will randomize 360 patients in a 1:1 ratio to receive either ET with palbociclib (Arm A) or mono-chemotherapy per investigator's choice with or without maintenance ET (Arm B). In both study arms, treatment will be administered according to the approved label in the respective country and/or supported by guidelines for the treatment of first-line MBC. Treatment will be given until disease progression, unacceptable toxicity, withdrawal of consent of the patient or change of initial treatment plan.

Information regarding sleep and activity will be collected passively via a validated wearable device (Actiwatch) to gauge patient's daily sleep and activity levels. Utilization of healthcare infrastructure will be monitored and is defined by number and duration of phone calls and patient visits to investigator's site.

Stratification factors for randomization will be hormone resistant (relapse on or within 12 months of end of adjuvant endocrine therapy) versus hormone sensitive (relapse beyond 12 months after end of endocrine therapy or de-novo metastatic HR-positive / HER2-negative breast cancer) and symptomatic vs. asymptomatic (as defined by investigator) (Figure 1).

Main Inclusion Criteria:

Females or males ≥18 years with HR-positive, HER2-negative MBC and symptomatic or asymptomatic metastases (≥ 1 liver or ≥ 2 metastatic sites) in which mono-chemotherapy (with or without maintenance ET) deemed to be an appropriate option by the physician. Willingness and ability of the patient to complete collection of data via wearable device and study mobile is required.

Statistical Considerations:

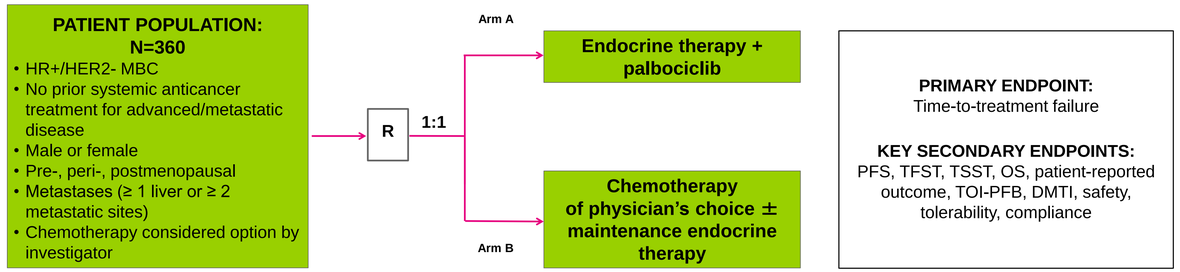
A total of 222 events are required to achieve 85% power to detect a hazard ratio of 0.667 in favor of palbociclib and ET using a two-sided, log-rank test at a significance level of 0.05. Assuming a 15% drop-out rate on either treatment arm and a non-uniform enrolment rate of 30 patients per month at the peak, it was estimated that 360 patients will need to be randomized. The sample size estimation includes one interim analysis planned at 65% (~144) of total TTF events to allow for early stopping of the trial due to futility (non-binding).

Objectives

Primary objective: To compare the TTF for patients randomized to receive pre-defined chemotherapy treatment strategy versus those randomized to receive palbociclib and ET. TTF is defined as time from randomization to discontinuation of treatment due to disease progression, treatment toxicity, patient's preference, or death.

Secondary Objectives: PFS; time to first subsequent treatment (TFST); time to first subsequent chemotherapy (TFSCT); time to second subsequent treatment regimen (TSST); overall survival (OS); safety and tolerability; compliance; sleep and activity levels, patient well-being and health care utilization by daily monitoring treatment impact (DMTI); patient-reported outcome (FACT-B); time-to-deterioration in Trial Outcome Index-Physical/Functional/Breast (TOI-PFB derived from FACT-B). A translational program and exploratory analyses are planned.

Figure 1: Study design of the PADMA trial



STRATIFICATION FACTORS:
- hormone resistant versus hormone sensitive
- symptomatic versus asymptomatic

Investigational Medical Products:

- **Arm A:** Palbociclib in combination with exemestane, letrozole or fulvestrant
- **Arm B:** Epirubicin, paclitaxel, vinorelbine or capecitabine +/- maintenance ET with letrozole, exemestane, fulvestrant or tamoxifen

For pre- or perimenopausal women surgical ovarian ablation or suppression with an GnRH analogue is mandatory, when an aromatase inhibitor or fulvestrant is administered.

Results

Recruitment is planned for approximately 18 months in 130 sites in Germany, Spain, Poland, Italy, UK and Canada.

Conclusions

- The primary aim of PADMA is to demonstrate in a real world setting, that an endocrine-based strategy consisting of ET plus palbociclib is superior to a chemotherapy-based strategy as first-line therapy in women with HR-positive, HER2-negative MBC.
- DMTI and patient-reported outcome will deliver important information on the differences between endocrine-based and chemotherapy-based treatment.

References

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