

## 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.<sup>1,2,3</sup> However, data comparing ET with chemotherapy as first-line therapy are scarce and less convincing.<sup>4</sup>

Meanwhile new targeted treatment options for combination with ET have been developed and endocrine-based therapy with Palbociclib (CDK4/6 inhibitor) improves the progression free survival (PFS) of ET alone by about 50%.<sup>5</sup>

The hypothesis of 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 PADMA trial is planned as so called 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 or mono-chemotherapy per investigator's choice with or without maintenance ET. In both study arms, treatment will be given until disease progression, unacceptable toxicity, withdrawal of consent of the patient or change of initial treatment plan. Stratification factors for randomization will be hormone resistant versus hormone sensitive and symptomatic vs. asymptomatic (as defined by investigator) (Figure 1).

### Main inclusion criteria:

Females or males  $\geq 18$  yrs with HR-positive, HER2-negative MBC and symptomatic or asymptomatic metastases ( $\geq 1$  liver or  $\geq 2$  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 (HR) 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

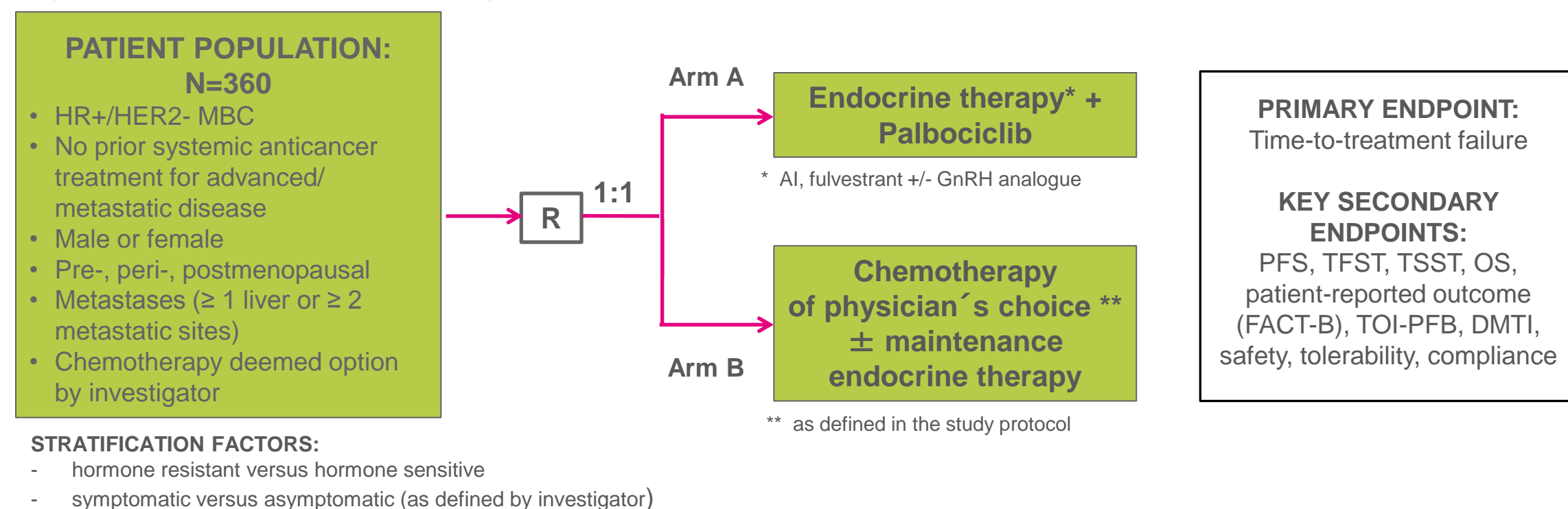
### Primary objective:

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 (36 months after first patient-in); safety and tolerability; compliance; sleep and activity levels, patient well-being and health care utilization (number and duration of phone calls and patient visits to investigator site) by daily monitoring treatment impact (DMTI); patient-reported outcomes (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: PADMA trial design



## Results

Recruitment is planned for approximately 18 months in 100 sites in Germany, Spain, Poland, Italy, France, UK and Canada.

## Conclusions

The 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. Patient-reported outcome is one of the main secondary objectives and will deliver important information on the differences between endocrine-based and chemotherapy-based treatment.

## References

1. Rugo HS, Rumble RB, Macrae E, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016; 34(25):3069-103.
2. Cardoso F, Costa A, Senkus E, et al. ESO-ESMO 3rd international consensus guidelines for advanced breast cancer (ABC3). Annals of Oncology 2017; 28: 16-33.
3. Q4 2015 Ipsos Oncology Monitor Available from: <https://www.ipsos.com/>
4. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.
5. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16(1):25-35.