PRECYCLE: Multicenter, Randomized Phase IV Intergroup Trial to Evaluate the Impact of E Health-Based Patient Reported Outcome (PRO) Assessment on Quality of Life in Patients with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Treated with Palbociclib and an Aromatase Inhibitor- or Palbociclib and Fulvestrant

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Study protocol

Keywords: metastatic breast cancer, eHealth, patient reported outcome, Quality of life, CDK 4/6 inhibitor, endocrine therapy

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Abstract

Background: Efficacy and quality of life (QoL) are key when selecting a therapy for metastatic breast cancer (MBC) patients. In hormone receptor positive (HR+) human epidermal growth factor receptor 2 minus (HER2-) MBC, addition of targeted oral agents such as everolimus or a cycline-dependent kinase 4/6 (CDK 4/6) inhibitor (e.g. palbociclib, ribociclib, abemaciclib) to endocrine therapy substantially prolongs progression-free survival and in the case of a CDK 4/6i also overall survival. Prerequiste for obtaining such benefit is adherence to therapy over the whole treatment duration. Adherence, maintaining patients' satisfaction, early detection and management of side effects have thus become important challenges, in particular with these new oral drugs and new ways of continuous support for oncological patients are needed. An eHealth-based platform can help to support therapy management and physician-patient interaction.

Methods: PreCycle is a multicenter, randomized, phase IV trial in HR+ HER2+ MBC. All patients (n=960) receive the CDK 4/6 inhibitor palbociclib either in first (62.5%) or later line (37.5%) together with endocrine therapy (AI, fulvestrant) according to national guidelines. PreCycle evaluates the time to deterioration (TTD) of QoL in patients supported by eHealth systems with substantially different functionality: CANKADO active vs. inform. CANKADO active is the fully functional CANKADO-based eHealth treatment support system. CANKADO inform is a CANKADO-based eHealth service with a personal login, documentation of daily drug intake, but no further functions. To evaluate QoL, the FACT-B questionnaire is completed at every visit. As little is known about relationships between behavior (e.g. adherence), genetic background, and drug efficacy, the trial includes both patient reported outcome and biomarker screening for discovery of forecast models for adherence, symptoms, QoL, progression free survival (PFS), and overall survival (OS).

Discussion: The primary objective of PreCycle is to test the hypothesis of superiority for time to deterioration (TTD) in terms of DQoL = "Deterioration of quality of life" (FACT-G scale) in patients supported by an eHealth therapy management system (CANKADO active) versus in patients merely receiving eHealth-based information (CANKADO inform).

EudraCT Number: 2016-004191-22

Background

Despite treatment improvements in hormone receptor positive (HR+) HER2- breast cancer, a large number of patients still progresses to the metastatic stage. Not only efficacy, but also quality of life (QoL) is in the focus when planning a therapy or therapy sequence for metastatic breast cancer (MBC) patients. Recently, some therapies have been approved for MBC to overcome hormone resistance such as everolimus or CDK 4/6 inhibitors (e.g. palbociclib, ribociclib, abemaciclib) which are administered orally.

Palbociclib is the first inhibitor of cyclin-dependent kinases (CDK) 4 and 6 that was approved in breast cancer. In vitro, palbociclib reduced cellular proliferation of ER-positive breast cancer cell lines by blocking

progression of cells from G1 into S phase of the cell cycle. Based on the three large studies Paloma 1, 2 and 3 palbociclib was approved for pre- and postmenopausal patients with advanced/metastatic breast cancer who are candidates for aromatase inhibitor or fulvestrant.

The steady increase of oral drugs in anticancer treatment requires changes in patient management. Despite several advantages of an oral treatment compared to intravenous application of antineoplastic medications such as more flexibility and less time waste and effort, patients are increasingly self-responsible and there is a loss of physicians assistance and control over the treatment. Therefore, adherence, patient' satisfaction and management of side effects are important challenges and new ways of supporting oncological patients are strongly needed. Not only efficacy, but also quality of life (QoL) is in the focus when planning a therapy for metastatic breast cancer (MBC) patients. An eHealth based platform like CANKADO can help to support therapy management.

QoL combines different aspects of personal health status of the individual ([1]). It represents a multi-domain concept, which includes the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.

For cancer patients, it is important to determine further aspects such as economic burden, home management problems or lack of emotional well-being - all of which can adversely affect quality of life ([2]). An important role of patient reported outcome (PRO) measurement in cancer care is the determination of negative effects or the identification of needs for supportive care ([3]).

All these aspects are well covered in the FACT-G scale. The FACT-G as a part of the breast cancer questionnaire FACT-B is multidimensional, consisting of subscales assessing Physical Well-Being (PWB), Emotional Well-Being (EWB), Social Well-Being (SWB), Functional Well-Being (FWB). The FACT-G yields a total score, as well as individual subscale scores, with higher scores reflecting better QoL ([4] and [5]). A change from baseline of 5 points or greater is considered a minimally important difference (MID) ([6]).

Having a continuous PRO feedback can heighten physicians' awareness of their patients' QoL ([7]). A simplified PRO like a pain scale is feasible for daily documentation and is suited to improve communication between patients and healthcare professionals ([8]).

Moreover, uncertainty is a known factor that influences outpatient communication ([9]). Patient's uncertainty and anxieties related to the physician can lead to clinical symptoms like 'white-coat hypertension'. They mostly effect women above 50 years ([10] and [11]). Concerning clinical symptoms, patients quite often try to please their physician and may not report symptoms or discomfort in their entirety. eHealth can be used to empower patients, to overcome uncertainty, and to obtain complete patient reports ([3], [12]).

The "ISPOR ePRO Good Research Practices Task Force" summarized in their report that an electronic PRO (ePRO) questionnaire that has been adapted from a paper-based questionnaire is equivalent or superior

(e.g., higher reliability) to the information produced from the original paper version ([13]). ePROs avoid data entry errors, give immediate access to data, enable triggering alerts/notifications, reduce missing data as compared to paper-based PRO, and increase patient's willingness to report sensitive information. In addition, data obtained from ePRO provides real-time tracking of survey compliance ([3]). Moreover, Basch et al, were able to show that patient ePRO documentation are associated with improved overall survival compared to routine care in cancer patients ([14]).

Giving patients the opportunity to document complains and QoL continuously at home provides a more detailed overview about their progress and can be used for directed questions from the physician. It also facilitates a more granular and reliable longitudinal overview. Such reports can improve the understanding of QoL of cancer patients receiving oral therapies.

The PreCycle trial was designed to evaluate the impact of ePROs in MBC using CANKADO ([15]). CANKADO is designed as an eHealth portal aimed to support therapy management and physician-patient interaction ([16]). Within PreCycle, CANKADO will allow drug intake documentation, support collection of electronic Patient Reported Outcome (ePRO) measure in a highly standardized manner, and provide overview reports to the investigators.

Material/Methods

Study Design

PreCycle is a multicenter, randomized, parallel-group, Phase IV clinical trial with the primary objective of testing the hypothesis of superiority for time to deterioration (TTD) in patients using the ePRO system „CANKADO active“ over „CANKADO inform“ version. „CANKADO active“ is the fully functional CANKADO-based eHealth treatment support service, including documentation of daily drug intake, daily documentation of QoL, feedback functions (PRO-React) and On-site surveys. „CANKADO inform“ stands for a CANKADO-based eHealth service with a personal login. On-site surveys without feedback functions for the patient and documentation of daily drug intake will be available.

See Figure 1 and Figure 2: Precycle study design

Participants

Eligible patients have histologically or cytologically proven diagnosis of HR+ HER2- locally advanced or metastatic breast cancer and are either candidates to receive palbociclib in combination with aromatase inhibitor or candidates to receive palbociclib in combination with fulvestrant for their locally advanced or metastatic disease. All anticancer treatments used in this study are approved drugs and therapy is in accordance to German treatment guidelines ([17]). The trial compares two different ways of eHealth support and documentation of patient reported quality of life data.

For Patients who are candidates for palbociclib in combination with aromatase inhibitor or fulvestrant, one prior line of chemotherapy for locally advanced or metastatic breast cancer is allowed in addition to a maximum of two lines of endocrine therapy. For inclusion and exclusion criteria refer to Table 1.

Patients will be stratified according their eligibility of receiving palbociclib with endocrine therapy (AI or fulvestrant) as first or later lines.

Treatment

Patients allocated to the combination of palbociclib with aromatase inhibitor will receive:

- Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment and
- Aromatase inhibitor, orally once-daily (continuously).
- Pre- or peri-menopausal patients should additionally receive a LHRH-agonist

Patients allocated to the combination of palbociclib with fulvestrant will receive:

- Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment and
- Fulvestrant , 500 mg, intramuscularly on Days 1 and 14 of Cycle 1, every 28 days (± 7 days) thereafter starting.
- Pre- or peri-menopausal patients should additionally receive a LHRH-agonist

Patients of each treatment group (palbociclib / aromatase inhibitor and palbociclib/fulvestrant) will randomized 2:1 in the Intervention Arm A using „CANKADO active“ and in the control Arm B using „CANKADO inform) (see:Figure 2).

Patients will continue to receive study treatment together with the assigned ePRO assessment until investigator assessed disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

Patients discontinuing the active treatment phase will enter a follow-up period phase during survival further progression and new anti-cancer therapy information will be collected once a year up to 48 months after randomization.

In addition, biomarkers will be assessed as a scientific translational program within this study. Tumor material from available primary tumor and/or available biopsies from recurrent disease will be collected. Blood samples will be collected at four time points during the study when also routine blood samples are mandatory (see: Figure 3).

Statistical considerations

The primary objective is to test the hypothesis of superiority of TTD (time to deterioration) in terms of DQoL (deterioration of quality of life) in patients supported by eHealth therapy management using the FACT-G scale. The sample size is estimated as follows. The trial tests the hypothesis of superiority of DQoL in the test collective (with CANKADO active, 2/3 of patients randomized) in comparison to the control collective (CANKADO inform, 1/3 of patients randomized) according to the standard stratified log-rank test (for a discussion see: Schoenfeld, D. A., & Tsiatis, A. A. (1987). A modified log rank test for highly stratified data. Biometrika, 167-175; Kalbfleisch, J. D., & Prentice, R. L. (2002). The statistical analysis of failure time data (2nd Ed.). John Wiley & Sons, p. 224).

Two strata are determined by

1) first-line patients

2) later-line patients.

First-line patients are assumed to comprise about 5/8 (62.5%) of the entire trial population; the remaining patients (3/8, i.e. 37.5%) are assumed to be treated in later lines. See figure 10.1.1 for a visualization of the patient distribution across strata and arms. The test is calibrated with respect to an alternative hypothesis that asserts a hazard ratio of 0.8 between the two arms (lower hazard in CANCADO active).

To estimate a lower bound for the expected number of deterioration events we assume that at least a progress will generate a DQoL. Therefore, the median PFS reported in the PALOMA 1, and 2 trials (first line patients treated with palbociclib and letrozol), as well as PALOMA 3 (2^{nd} line patients treated with palbociclib and fulvestrant) may serve as model for first-line and later-line strata here. Consequently, we used the upper confidence limit for median PFS reported in Paloma 1 (27.5 months) and Paloma 3 (11 months) to compute conservative estimates for the expected number of events in the first-line and later-line stratum respectively.

In first-line patients, the proposed hazard ratio between CANCADO arms of 0.8 corresponds to about 4 months superior TTD for CANCADO active; in later-line patients, it corresponds to about 2 months superior TTD. Such an increase is assumed to have a clinically relevant benefit.

The sample size was estimated using a validated Monte-Carlo simulation implemented in Python 3.5. In all 4 groups (2 arms with 2 strata each) exponential survival was used as parametric sampling distribution with hazard rate computed from median PFS estimates as indicated above. In addition, an independent exponential censoring process was used to simulate loss to follow-up with 48-month probability of censoring calibrated at 10%.

If 960 patients are recruited (assuming 10% loss to follow-up), we can expect to reject the null-hypothesis with 80% **power** if a stratified two-sided test of equal hazards between (CANKADO active) and (CANKADO

inform) is performed at alpha = 0.05. The corresponding expected number of events across groups is 693.

- To show superiority w.r.t. TTD of QoL in CANCADO active vs. CANCADO inform
- Stratified log-rank test, two-sided, $\alpha = 0.05$, $\beta < 0.2$
- Hazard ratio of 0.8 assumed as alternative hypothesis in sample size calculation
- Sample size of n=960 required to reach 80% power, assuming 10% loss to follow-up
- In total, 693 observed events expected
- Expected distribution of patients across strata and treatment arms given in figure below

Discussion

Since metastatic breast cancer (MBC) is a chronic disease, maintaining a good QoL is of foremost importance. Enrolled patients receive an approved therapy (aromatase inhibitor + palbociclib or fulvestrant + palbociclib) in both arms of this randomized study. Potential risks (e.g. toxicity) should be equally distributed between both arms. A theoretical, albeit unlikely, risk might be that an eHealth-based high density observation using CANKADO could have a negative impact on clinical outcome or QoL. Therefore, the primary objective is to demonstrate superiority of time to deterioration (TTD) of quality of life for patients with eHealth-based high-density observation using CANKADO (CANKADO active) versus eHealth-based static observation on site (CANKADO inform).This clear focus on QoL should provide a benefit for all patients enrolled to this trial.

To our knowledge, PreCycle is the largest worl-wide trial evaluation of the benefits of an eHealth therapy support in oncology. This trial should lead to an increased awareness of eHealth tools like CANKADO to monitor QoL under systemic treatment. Continuous PRO documentation may lead to increased patient empowerment in oncology and addresses an urgent need as oral therapies are becoming much more frequent ([18]). ePROs have the potential improving patient-physcian communication while individualizing site visits without compromising patient safety. PreCycle will address the impact on patient QoL of such continued ePRO documentation and thus add to the knowledge-base in the literature. The accompanying translational research program is implemented into the study design to improve our understanding of the mechanisms of resistance to endocrine therapies.

PreCycle started recruitment in mid 2017 and has already recruited almost 470 patients.

Trial status

PreCycle: Multicenter, randomized phase IV intergroup trial to evaluate the impact of e Health-based patient reported outcome (PRO) assessment on quality of life in patients with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer treated with Palbociclib and an aromatase inhibitor- or Palbociclib and Fulvestrant

Protocol Number: PH001PreCycle, Version 2.0

AGOB002 TraFO002-16

EudraCT Number: 2016-004191-22

Testing Objective: eHealth-based Patient Reported Outcome (e PRO)

Study Treatment: Palbociclib in combination with endocrine therapy (aromatase inhibitor or / Fulvestrant combined with a LHRH agonist in pre- or peri-menopausal women)

Sponsor Name and Legal Registered Address:

Palleos healthcare GmbH

Taunusstr. 5a

65183 Wiesbaden

Short Title:

Impact of eHealth-support on Quality of Life in metastatic breast cancer patients treated with Palbociclib and endocrine therapy

The protocol was developed in cooperation with the ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research 2016

Regulatory	Date
Approval of legal authority: Bundesamt für Arzneimittel und Medizinprodukte	05/19/2017
Approval ethics committee	07/06/2017
1st data and safety monitoring board meeting	06/26/2017
1st patient in	08/07/2017
App. end of recruitement	QII/2023
Study duration	48 months of follow-up

Abbreviations

cyclin-dependent kinase (CDK)

Deterioration of quality of life (DQoL)

hormone receptor positive (HR+)

metastatic breast cancer (MBC)

minimally important difference (MID)

overall survival (OS)

patient reported outcome (PRO)

progression free survival (PFS)

time to deterioration (TTD)

quality of life (QoL)

Declarations

Acknowledgements: The protocol was developed in cooperation with the ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research 2016. The authors are grateful for the continued support of the trial conduct by Palleos and iOMEDICO and the financial trial support by Pfizer.

Ethical considerations and approval

This clinical study is being conducted in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical

Sciences international ethical guidelines, and ICH good clinical practice (GCP) guidelines, and applicable German laws and regulations. The trial has been approved by relevant competent authorities and an independent ethics committee and is registered at EudraCT (2016-004191-22).

The study will use a Data Monitoring Committee (DMC). The DMC membership and governance is outlined in a separate charter. The DMC will be responsible for ongoing monitoring of the efficacy safety of patients under the study treatment and randomized PRO procedures.

Consent

All patients will provide written informed consent prior to conducting any study-specific procedures.

Dissemination

The sponsor is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome.

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Tables

Table 1 PreCycle _ inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Post- or pre/peri-menopausal female patients, age ≥18 years	Known hypersensitivity to aromatase inhibitor, fulvestrant, palbociclib or any of its excipients
Patients with metastatic or locally advanced (non-operable) breast cancer disease	Contraindication for aromatase inhibitor, fulvestrant or palbociclib; or LHTH-agonists (if pre-menopausal)
Patients who are appropriate candidates for aromatase inhibitor + palbociclib combination therapy	Prior treatment with any CDK inhibitor
Patients having already received endocrine therapy who are appropriate candidates for fulvestrant+ palbociclib combination therapy	Patients with locally advanced or metastatic, symptomatic, visceral spread, who are at risk of life threatening complications in the short term
One prior line of chemotherapy and/or a maximum of two endocrine therapy lines for locally advanced or metastatic disease is/are allowed	Known active uncontrolled or symptomatic CNS metastases
Peri-/pre-menopausal patients should additionally receive a LHRH-agonist.	Current use of food or drugs known to be potent inhibitors or inducers of CYP3A4.
The tumor must be hormone-receptor positive	High cardiovascular risk, including, but not limited to recent myocardial infarction, severe/unstable angina, or severe cardiac dysrhythmias in the past 6 months of enrollment.
The tumor must be HER2-negative defined as either HER2 immunohistochemistry Score 0 or 1+ or as HER2-negative by ISH.	Diagnosis of any second malignancy within the last 5 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix
Eastern Cooperative Oncology Group (ECOG) performance status 0-2	Participation in other clinical trials involving investigational drug(s) (Phases 1-4) within 2 weeks before the current study begins and/or during study participation.
Tissue of the primary tumor and metastatic lesion for biomarker study if applicable	Lactating women
Adequate organ and marrow function	Life expectancy < 3 months
In case of patients of child bearing potential: negative serum pregnancy test at baseline. Patients must agree to use highly effective non-hormonal contraception	Known infection with HIV, hepatitis B virus, or hepatitis C virus
Resolution of all acute toxic effects of prior therapy, including radiotherapy grade <1 (except toxicities not considered a safety risk for the patient) and recovery from surgical procedures	Concurrent severe, uncontrolled systemic disease, social or psychiatric condition that might interfere with the planned treatment and with the patient's adherence to the protocol

Willingness and capability to use CANKADO	Legal incapacity or limited legal capacity
Availability of hardware: Computer and/or tablet and/or smartphone with internet access	
Signed Written Informed Consent	

Figures

Arm	daily EQ-VAS scale	daily drug intake	triggered questionnaire feedback	Onsite (every 28 days) FACT-B
Arm A: „CANKADO active“	X	X	X	X
Arm B: „CANKADO inform“	-	X	-	X

Figure 1

Schedule of ePRO documentation

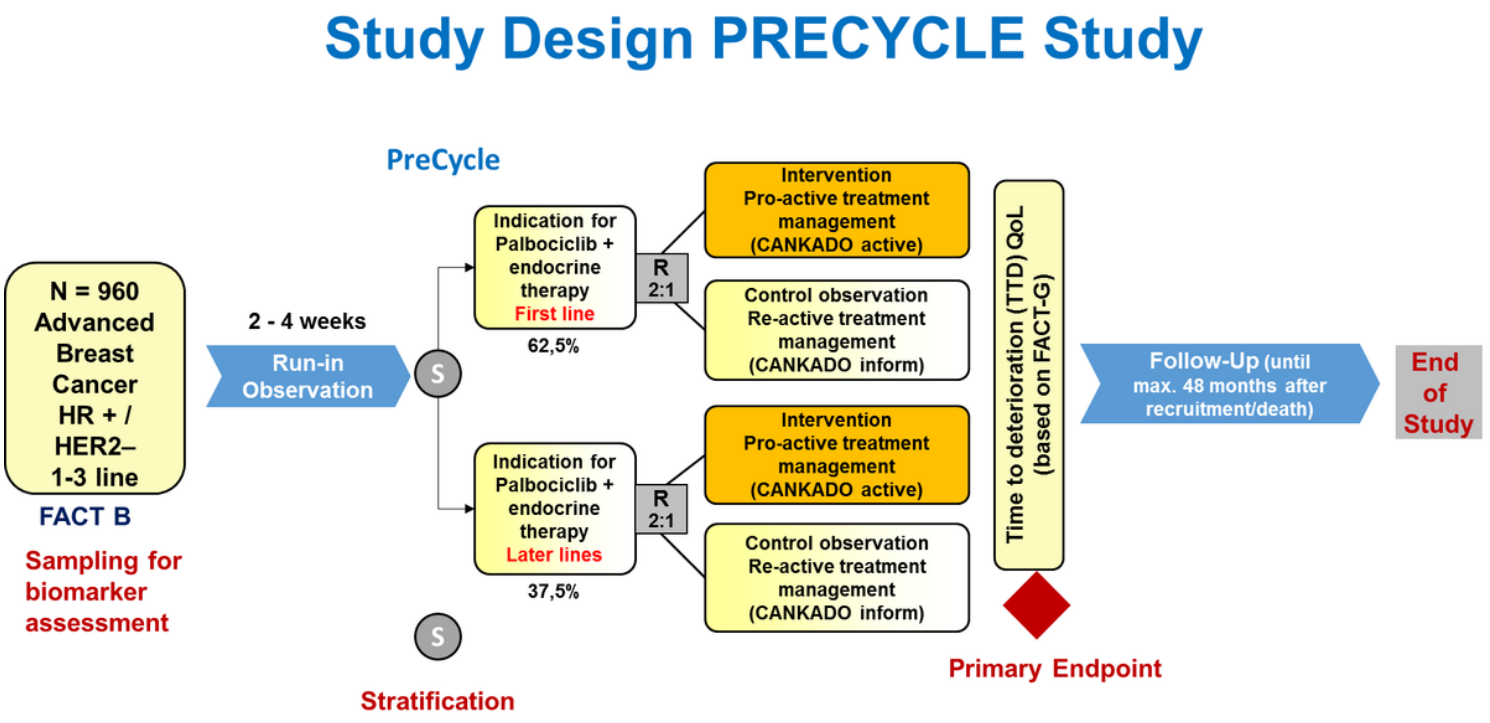

Figure 2

PreCycle - study design

Investigation	Cycle 1 Day 1	Cycle 1 Day 14	Cycle 2 Day 1	Cycle 2 Day 14	Every 4 weeks	discontinu ation
Symptoms AE/SAE	X	X	X	X	X	X
physical examination (ECOG)	X		X		X	X
blood cell count	X	X	X	X	X	X
blood sample for translational program	X	X			Cycle 4 Day1	
tumor tissue		primary tumor and/or biopsy of recurrent disease if available				
ECG (12 chanal)		X			X	
tumorasse- ssment (every 12 weeks)	after physicians choice				X	X

Figure 3

PreCycle - Schedule of investigations

Supplementary Files

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- Graphicalabstract.png