# PROTOCOL CONCEPT SHEET

**(Due on Sunday 23 June 2024 at 12:30)**

**CONCEPT SHEET FOR CLINICAL TRIAL PROTOCOLS - MAXIMUM 3 PAGES!**

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DATE AND TIME: 23.06.2024, 12:30 UHR

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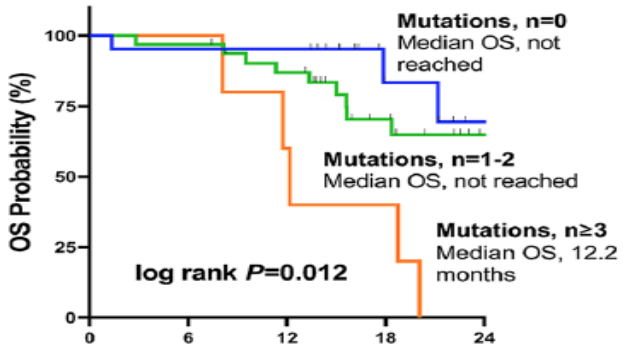
1. **What is the title of the study?**
   Intermittent capecitabine to reduce clonal evolution in patients with luminal B, HR-positive HER2-negative metastatic breast cancer treated with CDK4/6-inhibitors and aromatase-inhibitors.
   Acronym: **RED.CLONE**

2. **What is the main objective of the trial?**
   The primary aim of the trial is to assess the efficacy in patients with metastatic or locally advanced luminal B HR-positive HER2-negative breast cancer undergoing CDK4/6 inhibitor therapy with intermittent capecitabine, compared to those not receiving intermittent capecitabine treatment.

3. **What is the proposed trial design?**
   The proposed trial design is a randomized, two-arm, phase II study. Initially, all patients with luminal B HR-positive, HER2-negative metastatic or locally advanced breast cancer will receive a combination of CDK4/6 inhibitors and aromatase inhibitors (AI). After 6 months of this initial therapy, patients will be randomized in a 2:1 ratio into two groups: the experimental arm and the standard arm. In the experimental arm, patients will receive capecitabine (administered for 7 days followed by a 7-day break) every three months for a total amonth of three months, alternating with CDK4/6 inhibitors and antihormonal therapy for three months. The standard arm will continue with the current therapy.

4. **What is the rationale for performing this trial?**
   CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib and trilaciclib) play a key role in the treatment of locally advanced or metastatic hormone receptor-positive, HER2-negative breast cancer in combination with endocrine therapy [1-3]. However, studies have shown that continuous treatment with CDK4/6 inhibitors in combination with endocrine therapy leads to various resistance mechanisms after a certain period (including an increase in the oestrogen receptor 1 gene (ESR1), mutations in various tumour suppressor genes for example: RB1 mutation, PIK3CA mutation or CCNE1 amplification). This is caused by the selection pressure triggered by CDK4/6 inhibitors and anti-hormonal therapy [4-5]. These resistance mechanisms can be investigated and evaluated using circulating tumor DNA (ctDNA). The ctDNA can be determined in peripheral blood and thus provides a non-invasive method for determining the specific mutation load in the tumour [6].
   HR-positive breast cancer can be classified into subgroups based on characteristic gene activation patterns: luminal A and luminal B. The luminal B subgroup tends to have a more aggressive progression and a higher risk of metastasis. Due to its generally poorer prognosis, the study should focus on patients within this subgroup [7]. In order to be able to use the effect of CDK4/6 inhibitors for as long as possible, it is essential to prolong the time to the occurrence of resistance mechanisms to endocrine therapy, as these are associated with a poorer prognosis [7]. If the selection pressure is reduced by removing the target substance, it is assumed that resistance mechanisms will occur less frequently. This phenomenon is known as "Clonay decay". It is the regression of subclones of mutations as soon as the growth advantage decreases after the removal of the selection pressure by a targeted substance. This concept has been well described in colon carcinoma treated with EGFR antibodies and is already being used clinically [8, 9]. Similar considerations have led to the conception of the SOLE study in breast cancer patients [10, 11]. During the pause of the CDK4/6 inhibitor and ET therapy, a therapy with capecitabine would be used in this study, which could lead to a rapid additional elimination of the ctDNA (and thus the corresponding clones).
   Both the 2021 published study by Bryson et al. in colorectal cancer patients and the recently published 2023 study by J. Khan et al. in metastatic breast cancer patients have shown that a shorter duration of capecitabine (1500 mg twice daily) for 7 days of therapy followed by 7 days off has the same efficacy with less toxicity than the standard regimen. Therefore, the 7-day regimen should be used in this study [12, 13].




Muendlein A *et al*: **Significant impact of circulating tumour DNA mutations on survival in metastatic breast cancer patients**. *Sci Rep* 2021, **11**(1):6761.

## 5. Risk-benefit assessment

a. Please describe the potential risks and benefits of this trial for the participating patients.

| Risks | Benefits |
|---|---|
| -Toxicity of capecitabine<br>- biopsies and blood tests risk factors<br>-disease progression<br>-unanticipated AEs<br>-compliance | -Increase in PFS<br>-decrease in resistance mechanisms<br>-potentially longer use of CDK4/6-Inhibitors in total<br>-personalized treatments in the future<br>-potential biomarkers |

b. Toxicity management: what are your intended supportive and safety measures.
- Physical examination, laboratory evaluation
- Control examinations for Tumor response according to clinical routine
- see technical information of the respective drug

c. Ethical considerations / How do they plan to continue treatment after the end of the study.
-Continuation of therapy after 24 months as decided by the attending physician

## 6. What are the characteristics of the population under study?

Please describe your target population (clinically / epidemiologically)

a) Breast cancer subtype: Patients diagnosed with luminal B hormone receptor (HR)-positive, HER2-negative breast cancer or patients with poor prognosis, particulary those with visceral metastasis or those with endocrine resistance after adjuvant therapy.
b) Disease stage: locoregionally recurrent breast cancer not amenable to surgical resection or radiotherapy with curative intent or metastatic disease.
c) Patients who have previously failed treatment with taxanes and anthracyclines, or for whom further anthracycline treatment is not indicated.
d) CDK4/6-Inhibitors treatment naïve patients are eligible (endocrine therapy in the neoadjuvant therapy or adjuvant setting is permitted if the patient had a disease-free interval > 12 months from the completion of endocrine therapy

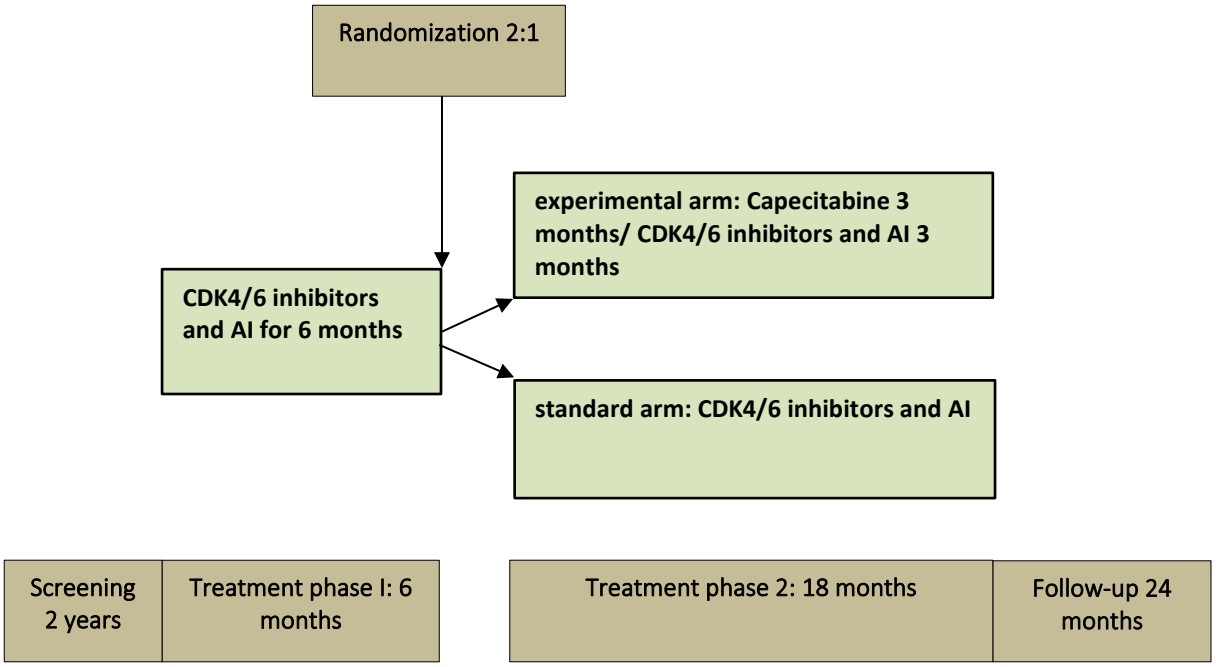
Exclusion criteria:

a) symptomatic CNS metastases
b) prior treatment with Everolimus or a CDK4/6-Inhibitor

## 7. What are the planned trial interventions

All Patients receive CDK4/6-Inhibitors and endocrine therapy.
After 6 month of therapy Patients will be randomized 2:1 to the following arms:

a) *Therapeutic arm:* alternating between capecitabine (7 days therapy followed by 7 days break) for 3 months and ribociclib+ aromatase inhibitor (AI) for 3 months. (In total for 1,5 years after randomization or till progressive disease).
b) *Standard Arm:* continuous CDK 4/6-Inhibitors and AI




8. **What are the endpoints (outcome measures)? Please provide definition to each endpoint**
   Primary endpoint: PFS after 24 months of therapy
   Secondary endpoints:
   1. RR (Response Rate), OS (Overall Survival)
   2. Number of patients who develop new mutations.
   3. Number of mutations in total
   4. Variations of ESR1- Mutations
   5. Correlation between ctDNA analysis in peripheral blood and tumor tissue expression analysis
   6. Potential Biomarkers
   7. Quality of Life
   8. Safety and feasibility of the experimental arm

9. **Study specific assessments**
   -Blood tests (tumor markers and according to physicians' routine)
   - Regular imaging (e.g., CT scans, MRI as decided by the attending physician) and clinical evaluations to determine disease progression or response to treatment.
   - Validated questionnaires (e.g., EORTC QLQ-C30, FACT-B) to assess physical, emotional, and social well-being
   - patient diaries
   -Liquid biopsy every 6 months
   -Tumor tissue analysis (Access to the biopsy performed at progress=Baseline and mandatory at disease progression).

10. **Is the study randomized?** Yes 2:1 randomisation after 6 months of therapy with CDK4/6-I. and AI

11. **Statistical design, hypothesis, and analysis strategy: What are the parameters of the statistical design? As per proposal** to discuss with statistician.

    Open phase II 2:1 randomized study. Primary endpoint is the PFS. Superiority study.
    N= 144 (2/3= 96, 1/3 =48), Power 80%, Delta: 20% recruitment 2 years, follow-up for two years alpha 0.025

    H0: PFS at 24 months (more precisely 1.5 years after randomisation) is shorter or as good as the PFS of the standard arm at 24 months (more precisely 1.5 years after randomisation)

H1: PFS at 24 months (more precisely 1.5 years after randomisation) is better than the PFS of the standard arm at 24 months (more precisely 1.5 years after randomisation)

**12. Trial stopping rules und subject discontinuation rules.**
SAEs, withdrawal of consent, ineligibility. If the patients has a progression the respective practitioner decides how the patient is to be treated further.

**13. Do you have any intention to undertake pharmacokinetic/pharmacodynamics studies?**
No

**14. Do you have any intention to undertake translational research studies?**
ctDNA analysis (detecting new mutations or variations of mutations) every six months per blood test, tumor tissue analysis (Biopsy at baseline and at disease progression).

**15. Do you intend to perform a quality-of-life study? YES**
What is the rationale for including QOL in the study?
Evaluate the impact of the intermittent therapy of Capecitabine and CDK4/6-I+ AI on quality of life.
Which QOL instrument will be used: EORTC QLQ-C30 or FACT-B

**16. Do you have any intention to perform health economics studies? NO**

**17. Feasibility of the study: to be discussed.**
Do you have access to adequate supplies of the drugs under study? Does not apply.
Do you have access to the required number of patients to perform the study? *YES multicenter (at least 20-30 centers)*
*To be discussed:*
Epidemiology (incidence and prevalence)
Analysis of care pathways in Germany (outpatient vs. inpatient) outpatient
Personnel and documentation effort estimation
Retrospective data from the trial centres (registries and certification programmes): No
Patient identification and approach
Study-specific devices and materials
Minimum requirements for the centre

**18. Informed consent process**
Site monitoring, the investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file.

All tests recording the translational research (NGS-analysis with the already exciting tumor tissues, the planned mandatory biopsy at disease progressin and the planned blood tests during therapy for ctDNA analysis are included in the informed consent sheets.

**19. Quality assurance**
What are your plans to assure high data quality? E.g.
SOPs, use of eCRF, Training of personnel, QC

**20. Publication strategy, to be discussed.**
Publication of the trial protocol after the trial being registered. First abstract ESMO 202+, San Antonio 202x, Final Publication 203x…

**Citations**

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