PONS Study Synopsis

Title of the Study

"Subtype-Stratified Follow-up Care Study of Breast Cancer Patients with Combined In Vitro and In Vivo Diagnostics Plus Early Target-Oriented Intervention"

Goals

Improve and individualize breast cancer aftercare through a subtype-adapted combination of molecular tissue diagnostics, regular serological biomarker measurements, sensitive whole-body imaging and individualized therapy management.

Rationale

- Tumor biology determines the risk of metastasis and time of metastasis (Kennecke et al. JCO 2010)
- Current guidelines recommend minor follow-up care in general irrespective of particular subtypes (Janni et al. 2009)
- Current follow-up care guidelines are based on data over 25 years old (Rosselli del Turco and GIVIO et al. JAMA 1994)
- Since this time, sensitive and specific diagnostic parameters (tumor markers such as CEA, CA 15-3 and CA 125, and whole body imaging like PET-CT) have benefitted the detection of recurrence (Molina et al. Tumor Biol 2005; Ertl et al., abstract ISOBM 2009; Stieber et al. ASCO 2006; Veit-Haibach et al. Br J Radiol 2007; Radan L et al. Cancer 2006)
- Diagnostic apparatuses are recommended only for symptoms, so that an early detection of relapse is no longer possible
- New loco-regional procedures such as RFA, resection and CyberKnife are rarely used, since the proportion of oligometastatis is < 3% (Tait et al. JCO 2005)
- A delay in starting treatment of > 12 weeks results already in symptomatic metastatic disease in reduced survival (Jung SY et al. BCRT2011)

Study Design

Open, three arm-stratified, non-randomized, prospective, multicentric study

Duration of the Study

Duration of the complete study (from the admission of the first patient until the final patient's exit): 84 months.

Admission period for patients: 24 months.

Duration for an Individual Patient:
The observation period lasts up to 60 months after admission into the study

Number of Patients Planned:

Total: 1000
HER2-neu: 150
Triple-Negative: 150
Luminal: 700

The number of patients planned can be increased by an amendment, if necessary, which would be indicated by a subsequent change.

Primary Objective of the Study:

- **To find a proportion > 20% of oligometastatic patients among all patients detected with metastatic disease during the study.**

Secondary Study Goals:

- **Evaluation of diagnostic sensitivity**:
    - *Serological biomarkers: time and frequency* of disease at detection of the appearance of metastases in the context of a subtype-specific relapse-risk
    - *Whole-body imaging: time, frequency, location, and extent* of disease at detection of the appearance of metastases in the context of a subtype-specific relapse-risk
- **Evaluation of diagnostic specificity**:
    - *Serological biomarkers*: number and description of false-positive findings
    - *Whole-body Imaging*: number and description of false-positive findings
- **Evaluation of subtype specificity**:
    - *Evaluation of the time, location, frequency and magnitude* with relations to the subgroups Luminal A, Luminal B, triple-negative and HER2
- **Evaluation of ECOG-status**:
    - Detection of ECOG status at the time of the first metastasis: average improved ECOG status due to the extension of the lead-time for symptomatic disease and an enlarged range of possible treatment

modalities

- Proportion of patients in whom an imaging and/or biochemical remission can be achieved (curative approach)

- Period of time without symptoms and/or biochemical remission, with respect to the subtype specific behavior of progressive disease

- Length of the interval without treatment after metastasis occured, with respect to subgroup-specific therapeutic options

- **Improved cancer-specific *overall survival:***

    - Detection of cancer-specific overall survival from time of primary diagnosis to death: average improved survival, independent of the "lead time"

- Increased adherence to recommended therapy due to increased awareness about the individual risk for relapse

- Detection of *the frequency*, *timing,* and *extent of use* of alternative and complementary treatments and therapies

- Detection of the frequency, timing, and extent of use of additional diagnostic procedures outside of the study protocol

- Measurement of quality of life by reduction of anxiety and increase of "perceived" security through a proactive and transparent approach to the patient, with regard to her subtype-specific disease during the follow-up (*under the PO-BADO BK-LQ-curve*).

- *Evidence of cost-effectiveness* of a subtype-specific aftercare vs. an uncontrolled "*gray*" aftercare

- Health-economic comparison of costs relating to subtype-specific aftercare study arms

- Effects of subtype-specific aftercare on the practice of the "5-year cure probation" in the Disabilities Act

<u>Evaluation of Safety:</u>
Not applicable

Admission Criteria:

- Fully resected (≥1 mm) histopathologically secure unilateral or bilateral primary breast cancer

- Availability of representative formalin-fixed, paraffin-embedded tissue blocks of the untreated primary tumor (biopsy or resected tissue) to the main pathology department

- Written informed consent prior to the study, authorizing procedures including genetic testing of the primary tumor tissue

- Women with an age at the time of diagnosis ≥18 years

- No evidence of distant metastases after complete diagnostic examinations including PET-CT or PET-MR

- General condition ECOG < 2

- The patient must be accessible for diagnostic follow-up

- In the event of the occurrence of relapse in the period of the study, patients must be controlled by a principle investigator

- The study admission is subgroup specific according to the following scheme:

  - Luminal A > 48 months after primary surgery
  - Luminal B > 18 months after primary surgery
  - HER2-positive < 9 months after primary surgery
  - Triple-negative < 9 months after primary surgery

Exclusion Criteria:

- Inoperable breast cancer

- Any earlier or parallel malignant tumor disease in addition to the non-metastasized primary breast cancer disease

- Known hypersensitivity reactions, or lack of compliance regarding planned diagnostic and logistic processes

Statistical Analyses:

Dr. Christine Windemuth-Kieselbach

Effectiveness:
Increased frequency of oligometastatic lesions in asymptomatic patients due to subtype-specific combination of in vitro and in vivo diagnostics

Description of the primary analysis of efficacy and population:

The following assumptions underlie:

- A 10-year survival is significantly different between the subgroups (Kennecke et al. JCO 2010)

- Luminal A: 70%
- Luminal B: 54.4%
- HER2: 48.1%
- TNT: 62.6%

- Within the subgroups, there are significant differences with respect to the timing of metastases (Kennecke et al. JCO 2010):

  - Luminal B/TNT/HER2 within the first 5 years
  - Luminal A shows a continuous relapse between 5-15 years

- 15% of patients with breast cancer experience a distant metastasis (empirical value of the Munich follow-up study)

- The rate of patients with oligometastatic disease (defined as < 3 lesions limited to one organ except the bones) must be < 3% within the first five years, independent of tumor subtype

- The rate of patients with oligometastatic disease demonstrated by regular serum analyzes within the first three years will be < 10% within the non-subtypical group of all study participants

- The margin of error for a false positive output (alpha) is set to 5% using two-tailed significance tests. The margin of error for a false negative output (beta) is set to 20%, e.g. the study's power is specified as 80% for the differentiation of clinical interest

- The general exponential failure rate is 10%

- Patients will be enrolled in the study for 24 months

- The follow-up period from the end of the admission period until data analysis is 84 months

Assumptions:

- 15% of patients with breast cancer suffer from a distant metastasis
- The rate of patients with oligometastasis is ≤ 10%
- α = 5%, two-sided
- Power = 80%
- Failure rate = 10%
- With the combined method, the rate of patients with oligometastatic disease is ≥ 20%
- Assuming a probability of less than 10% for the early detection of metastases in a oligometastatic state (historical control) and at least 20% using a combined diagnostic approach of molecular testing and serum testing at determined intervals, 78 patients are needed. Of this patient group, 13 must be identified in order to demonstrate the difference of the A'Hern method in a two-sided significance level of 0.05 and a power of 80%. Since only 15% of patients suffer from breast cancer distant metastasis, 572 patients should be admitted in this study on the assumption of a 10% failure rate.

Evaluation of safety
Not applicable

Primary endpoint:
- More than 20% of oligometastatic patients within the patients found with distant metastases during the study

Secondary endpoints:
- Refer to secondary objectives

Sample size calculation:
- To attain reliability: n=573
- Assignation of n: n=1000
- To analyze: n=1000

The number of planned patients may be increased by an amendment.

Control Check-ups

Basic investigations = Admission time (for all patients)

- Molecular analysis (RNA expression profile) with kPCR of an mRNA which was extracted from formalin-fixed and paraffin-embedded tumor tissue
- Entrance PET/CT
- Central lab analysis of tumor marker CEA, CA 15-3, CA 125 (determination of individual base value)

Additional original investigations (only for TNT and HER2):
- Molecular analysis through immune cell testing

Every 8 weeks (for all patients):
- Central lab analysis of tumor markers CEA, CA 15-3, CA-125

Every 3 months (for TN, HER2 and Luminal B)
- Anamnestic and physical examination findings

Every 6 months (for Luminal A)
- Anamnestic and physical examination findings

Every 6 months (for patients with BCS in the first 3 years after primary OP):
- Mammography of the affected side

Every 12 months (also 18, 30 and 42 months after R0-resection of the primary tumor; only for high-risk patient groups: TN + HER2):
- PET/CT

Every 12 months (for all patients):

- Mammography of the healthy side; mammography of the affected side for patients with BCS after the 4th year following primary surgery

In general (for all patients):

- In the case of a reproducible pathological increase of tumor markers according to defined criteria → immediate PET/CT

- In the case of a tumor's detection, individualized therapeutic concept (with serologic follow-up every 4 weeks) as determined by the interdisciplinary tumor board

In the absence of tumor detection: continuation of the tumor marker determination every 4 weeks, repeated whole-body imaging after 3 months

Planned accompanying scientific project:

Circulating tumor cells (Fr. Prof. K. Pachmann)