# PRAEGNANT

## Real world Evidence, Translational Research, Big and Smart Data:
## A prospective academic translational research network for the optimization of the oncologic health care quality in the adjuvant and advanced/metastatic setting

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V. Mueller[1], J. Huober[2], B. Volz[3], F. Overkamp[4], H.-C. Kolberg[5], P. Hadji[6], L. Häberle[3,7], J. Ettl[8], A. Hartkopf[9], M.P. Lux[3], D. Lüftner[10], M. Wallwiener[11], F. Taran[9], M. W. Beckmann[3], E. Belleville[12], P. Wimberger[13], C. Hielscher[14], M. Geberth[15], J. Lermann[16], W. Abenhardt[17], C. Kurbacher[18], R. Wuerstlein[19], C. Thomssen[20], M. Untch[21], W. Janni[2], T. Fehm[22], S. Brucker[9], D. Wallwiener[9], A. Schneeweiss[23], P. Fasching[3], H. Tesch[24]

[1]Department of Gynecology Hamburg-Eppendorf University Medical Center, Hamburg, Germany; [2]Department of Gynecology and Obstetrics Ulm University Hospital, Ulm, Germany, [3]Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany; [4]OncoConsult Hamburg GmbH, Hamburg, Germany; [5]Marienhospital Bottrop gGmbH, Bottrop, Germany; [6]Department of Bone Oncology Nordwest Hospital, Frankfurt, Germany; [7]Biostatistics Unit University Hospital Erlangen, Erlangen-Nuremberg, Germany; [8]Department of Obstetrics and Gynecology Klinikum rechts der Isar Technical University of Munich, Munich, Germany; [9]Department of Obstetrics and Gynecology University of Tuebingen, Tuebingen, Germany; [10]Charité Campus Benjamin Franklin, Berlin, Germany; [11]Department of Obstetrics and Gynecology University of Heidelberg, Heidelberg, Germany; [12]ClinSol GmbH &Co KG, Wuerzburg, Germany; [13]Department of Gynecology and Obstetrics, Carl Gustav Carus University Dresden, TU Dresden, Dresden, Germany; [14]gSUND Gynäkologie Kompetenzzentrum, Stralsund, Germany, [15]Gynäkologische Praxisklinik am Rosengarten, Mannheim, Germany; [16]Department of Gynecology and Obstetrics, Klinikum Bayreuth, Bayreuth, Germany; [17]MVZ Onkologie im Elisenhof, Munich, Germany; [18]Department of Gynecology and Obstetrics Medizinisches Zentrum Bonn, Bonn, Germany; [19]Department of Gynecology and Obstetrics Breast Center and CCC Munich University Hospital, Munich, Germany; [20]Department of Gynecology Martin-Luther-University Halle-Wittenberg, Halle, Germany; [21]Department of Gynecology and Obstetrics Helios Clinics Berlin Buch, Berlin, Germany; [22]Department of Gynecology and Obstetrics University Hospital, Duesseldorf, Germany; [23]National Center for Tumor Diseases and Department of Gynecology and Obstetrics, University Hospital Heidelberg, Heidelberg, Germany; [24]Oncology Practice at Bethanien Hospital, Frankfurt, Germany

## BACKGROUND

Advanced breast cancer (ABC) patients are considered to be the patient group with the worst prognosis. Not only with regard to therapy decisions, but also with regard to quality assured healthcare and health economics this entity remains a challenge.

Novel approaches in breast cancer therapy aim at the targeted therapy of tumor entities and identification of patients for whom the greatest therapy benefit and the least side effects are expected (Lux *et al.*, 2013).

Molecular assessment of the tumor in the metastatic situation is not performed on a routine basis, and in many cases tumor characteristics from the primary tumor are considered reliable enough to also make therapy decisions for metastatic patients. Although molecular reassessment of tumor characteristics from tumor material of the metastasis is recommended in national guidelines (AGO Breast, 2014), only a minority of patients is biopsied, because of the invasiveness of the procedure, even though biopsy related complications are rare.

With modern analytic methods from blood based biomaterials there is an opportunity to correlate blood based tumor assessments with actual characteristics of the tumor. These include i.e. expression analyses, tumor mutation analyses and tumor gene copy number aberrations. One of the main aims of the PRAEGNANT academic research network is to establish an infrastructure for the comprehensive analysis of molecular characteristics of primary tumors and their metastases. Furthermore, health care related outcomes as well as health economics and health care awareness provide novel approaches of patients in the registry and are further aims of the PRAEGNANT study (Fasching *et al.*, 2015).

## STUDY DESIGN

The PRAEGNANT study is conducted as a prospective, diagnostic, translational and multi-centric registry with a central documentation of patient and tumor characteristics and a central biomaterial archive for prospective molecular analyses.

The study network aims at registering 3,500 breast cancer patients with advanced, incurable, metastatic disease.

A patient remains in the study for a maximum of 36 months or until death or withdrawal of consent, whichever occurs first.

Documentation intervals are consistent with clinical routine and are based on the symptoms of the respective patient (Table 1).

The authority to decide for certain diagnostic or therapeutic measures resides with the treating physician. Patients give informed consent to screening for ongoing studies and molecular analyses and consent to that their attending physician is informed about studies, the patient might be eligible for.

Table 1: Documentation schedule (abbreviated)

| | Baseline | Follow Up Documentation: Every 3 months or following a change of a therapy line (event-associated, e.g. after progression) | End of study/ Study completion Month 36 |
|---|---|---|---|
| ICF | X | | |
| Demography/medical history | X | | |
| Status of tumor/relapse/metastasis Survival status | X | X | X |
| Biomarker sampling | X | Only following any change of a therapy line | X |
| ECOG Status | X | X | x |
| Previous/current antineoplastic therapies/diagnostic measures/imaging; Concomitant medication | X | X | X |
| AEs/SAEs | X | X | X |
| Patient Reported Outcomes (quality of life, depression, activity, socioeconomic aspects, nutrition etc.) | At Baseline and every 12 weeks until end of study | | |

## ELIGIBILITY CRITERIA

**Inclusion Criteria**

- Adult patients (age ≥18 years) with metastatic or locally advanced, inoperable breast cancer (ABC), proven by clinical measures (i.e. standard imaging; irrespective of status of BC, e.g. TNM, receptor status etc.),
- Patients, who are able and willing to sign the informed consent form.

**Exclusion Criteria**

- Patients who did not sign the informed consent form,
- Patients who are not eligible for observation due to severe comorbidities or unavailability according to the treating physician.

## STUDY OBJECTIVES

**Primary Objective**

Discovery of biomarkers, which predict progression free survival (PFS). Biomarkers comprise comprehensive molecular analyses of gene expression, gene mutations, serum and tissue biomarkers.

**Secondary Objectives**

- Assessment of overall survival (OS),
- Assessment of breast cancer specific survival (BCSS),
- Objective response,
- Description of therapies used in the metastatic setting,
- Percentage of women, who will receive results of molecular tests undertaken in the context of the scientific objectives of this trial,
- Feasibility and satisfaction regarding receipt of molecular testing results (including hereditary genetic alterations),
- Quality of life,
- Therapy adherence,
- Health economics for women with metastatic and/or locally advanced, inoperable breast cancer.

**Secondary Objectives**

- Influencing factors of depression in patients with metastatic breast cancer,
- Patient reported influencing factors on therapy adherence in patients metastatic and/or locally advanced, inoperable breast cancer,
- Incidence of adverse events, serious adverse events will be reported.

**Exploratory Objectives**

Correlation of…

- …the incidence of depression with germ line genetic variation and therapies and gene expression from leucocytes,
- …gene alterations (mutations and amplifications) and gene expression between primary tumor, metastatic tumor and circulating tumor cells (CTCs),
- …gene alterations (mutations and/or amplifications) between primary tumor, metastatic tumor and circulating tumor DNA,
- …blood protein biomarkers with side effects,
- Prediction of therapy response, prognosis and side effects with germ line single nucleotide polymorphisms (SNPs),
- Identification of risk factors for the development of metastatic disease in healthy women and progression,
- Influencing factors of physical activity, mental factors and nutrition in patients with metastatic breast cancer,
- Time to progression from the beginning of subsequent therapy lines until the next progression,
- Time to death from the beginning of subsequent therapy lines.

## BIOMARKERS

Somatic mutations have been described, which are involved in the pathogenesis of breast cancer. With novel methods of next generation sequencing a high throughput of samples can be sequenced and compared with regard to differences and possible mutations. The Cancer Genome Atlas is one of these projects, which has compared the genetic sequence of breast cancer types and reference DNA from the same individual (The Cancer Genome Atlas, 2012). This comparison revealed several tens of thousands differences of which several dozens are regarded as mutations which could play a pivotal role in breast cancer pathogenesis.

The PRAEGNANT study will use tumor material from the primary tumor, the metastases, circulating tumor cells (if available and possible), and blood samples to identify such somatic genetic alterations (Fasching *et al.*, 2015). This information could be used to provide patients access to modern treatment approaches.

Blood samples are collected at baseline, at any change in therapy and at the end of study (EoS) visit (Table 1). Therapy changes can happen due to progression of disease or patient's wish, an intolerable toxicity or any other reason.

Figure 1 schematically displays the planned analyses from available biomaterials within the core infrastructure as well as within exploratory sub-projects.

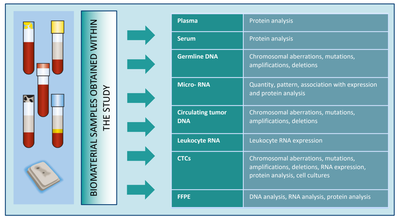


Figure 1: Overview of planned molecular analyses from collected biomaterials (modified from Fasching *et al.*, 2015)

## PARTICIPATING SITES AND RECRUITMENT

Since the beginning of the study in June 2014, 2827 patients (Figure 3) have been recruited. Recruitment aim is a total of 3500 patients.


Figure 2: Nationwide distribution of participating sites

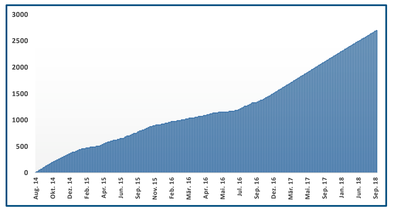


Figure 3: Patient recruitment over time

## STUDY COHORT DESCRIPTION

Basic patients' characteristics are summarized in table 2. Mean age of the patients included was 61 (± 12,81) years and age did not differ greatly among therapy lines, in which the patients were included into the study.

Table 2: Patient baseline characteristics

| | | n (%) or mean |
|---|---|---|
| | | Mean age 61 years (±12.81) |
| **pT documented total** n=2470 | Not available due to no surgery | 444 |
| | pT0 | 69 (3.41%) |
| | pTis | 51 (2.52%) |
| | pT1 | 715 (35.29%) |
| | pT2 | 852 (42.05%) |
| | pT3 | 214 (10.56%) |
| | pT4 | 125 (6.17%) |
| **pN documented total** n=2325 | Not available due to no surgery | 444 |
| | pN0 | 747 (39.71%) |
| | pN1 | 1134 (60.29%) |
| **Laterality documented total** n= 2702 | unilateral | 2372 (87.79%) |
| | bilateral | 330 (12.21%) |
| **cM documented total** n=2590 | cM0 | 1537 (59.34%) |
| | cM1 | 751 (29.00%) |

Most of the patients have been included into the PRAEGNANT study in the first (1st) line of therapy (n=1471; 53,63%) (Figure 4). However, a substantial number of patients (n=210; 7,66%) were included in the 5th line or higher.

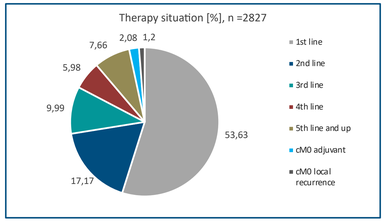


Figure 4: Therapy line at study entry

The distribution of molecular subtypes is shown in table 3, the distribution of molecular subtypes among therapy lines is shown in figure 5. Rarest subtype were patients with a triple negative tumor (n= 309; 14.21%), as assessed at the time of the initial diagnosis, while Luminal A like tumors (n=1036; 47,65%) and HER2 positive tumors (n=572; 26.31%) were the most frequent tumor subtypes. Distribution of molecular subtypes did not differ greatly according to therapy line in which the patients were included into this study.

Table 3: Tumor characteristics at study entry

| | | n (%) |
|---|---|---|
| **G documented total** n=2324 | G1 | 118 (5.08%) |
| | G2 | 1381 (59.42%) |
| | G3 | 825 (35.5%) |
| **ER documented total** n=2381 | ER negative | 431 (18.1%) |
| | ER positive | 1950 (81.9%) |
| **PR documented total** n=2373 | PR negative | 646 (27.22%) |
| | PR positive | 1727 (72.78%) |
| **HER2 documented total** n=2066 | HER2 negative | 1595 (77.2%) |
| | HER2 positive | 471 (22.8%) |
| **Molecular subtype documented total** n=2174 | TNBC | 309 (14.21%) |
| | Luminal A like | 1036 (47.65%) |
| | Luminal B like | 400 (18.4%) |
| | HER2 positive | 572 (26.31%) |

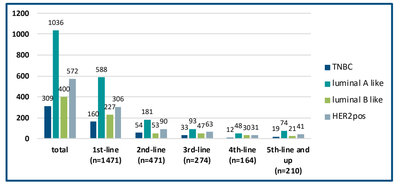


Figure 5: Distribution of molecular subtypes by therapy line at study entry

## CONCLUSION

The PRAEGNANT study network has established an innovative infrastructure to improve the healthcare for patients with advanced breast cancer.

The PRAEGNANT scientific network enables oncological health care quality reporting and the development and maintenance of efficient oncological treatments via the synergistic cooperation of translational research, health care economics and innovative health care research.

Prospectively, the established infrastructure will be employed to monitor and improve health care for breast cancer patients in the (neo)adjuvant setting as well as for cancer patients in other indications.

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